KRYSTEXXA™ (pegloticase) for intravenous infusion

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Briefing Document for Arthritis Advisory Committee

Division of Anesthesia, Analgesia, and Rheumatology Products

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ACR	American College of Rheumatology
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
ANOVA	Analysis of variance
APTC	Anti-Platelet Trialist Collaborative
ASHD	atherosclerotic heart disease
ASHI	arthritis-specific health index
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical WHO Drug Classification
AUC	area under the concentration-time curve
AUC0-τ	area under the concentration-time curve, time 0 to time t
AUCinf	area under the concentration-time curve, time infinity
AVR	Aortic valve replacement
BLA	Biologics License Application
BMI	body mass index
BP	Bodily pain
BSA	body surface area
BUN	blood urea nitrogen
C1q	complement component 1q
C3	complement component 3
C4	complement component 4
CABG	coronary artery bypass graft
CAD	coronary artery disease
Caverage	average concentration
CCr	calculated creatinine clearance rate
CGA	Clinician's Global Assessment
CH50	total hemolytic complement function
CHF	congestive heart failure
CKD	chronic kidney disease
CL	total body clearance
CLL	B-cell chronic lymphocytic leukemia
Cmax	maximal concentration
Cmin	minimal concentration
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPF	cut-point factor
CR	Complete response
CRF	case report/record form
CRO	contract research organization

CRP	C-reactive protein
CSR	clinical study report
CV	cardiovascular
DB	double-blind
DM	diabetes mellitus
DMC	Data Monitoring Committee
DVT	deep vein thrombosis
EC50	half maximal effective concentration
ECG	electrocardiogram
EF	ejection fraction
ELISA	enzyme-linked immunosorbent assay
Emax	maximum effect
ESR	erythrocyte sedimentation rate
ER	Emergency room
FDA	United States Food and Drug Administration
GERD	gastro
G6PD	glucose-6-phosphate dehydrogenase
GGT	gamma-glutamyl-transferase
GH	general health perceptions
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire-Disability Index
HCPs	healthcare professionals
Hct	hematocrit
Hgb	hemoglobin
H_2O_2	Hydrogen peroxide
HRP	Horseradish peroxidase
HRQOL	health-related quality of life
HTN	hypertension
ICH	International Conference of Harmonization
IgG	Immunoglobulin G
IgM	Immunoglobulin M
i.v.	intravenous(ly)
IVR	Interactive voice response
IR	infusion reaction
ISE	integrated summary of efficacy
ISS	integrated summary of safety
ITT	Intent to treat
KAB	Knowledge, attitude and behavior
kDa	kilodalton
LDH	Lactate dehydrogenase
LOCF	last observation carried forward

LLOQ	lower limit of quantification
LOS	longitudinal observation study
LOQ	Limit of quantification
LV	left ventricle
LVEF	left ventricular ejection fraction
MCID	Minimum clinically important differences
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mental health
MI	myocardial infarction
MRSA	methicillin-resistant Staphylococcus aureus
MSU	Monosodium urate
MTP	metatarsophalangeal
NA	Not Applicable
NCO	Negative Cut-off
NIDDM	non insulin dependent diabetes mellitus
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NSAID	non-steroidal anti-inflammatory drug
NSIR	non-serious infusion reaction
OA	Osteoarthritis
OLE	open-label extension
OMERACT	Outcome measures in rheumatology clinical trials
ORSA	oxacillin-resistant Staphylococcus aureus
PBS	Phosphate buffered saline
PCS	Physical component score
PD	pharmacodynamic
PD	Progressive disease
PEG	polyethylene glycol
PF	Physical functioning
PGA	Physicians Global Assessment
PI	Prescribing information
PK	pharmacokinetic
PPI	proton pump inhibitor
PR	Partial response
PRO	patient-reported outcome
PTCA	percutanerous transluminal coronary angioplasty
PUA	plasma uric acid
QC	Quality control
QoL	Quality of life
QSAP	Quantitative Safety Analysis Plan

RA	Rheumatoid arthritis
RCT	randomized controlled trials
RE	Role limitations due to emotional problems
REMS	Risk Evaluation Management Strategy
RES	reticuloendothelial system
RP	Role physical
s.c.	subcutaneous(ly)
S/P	Status-post
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
Savient	Savient Pharmaceuticals, Inc.
SD	standard deviation
SD	Specialty distributors
SD	Stable disease
SEM	Standard error of the mean
SF	Social functioning
SF-36	Medical Outcomes Survey Short Form-36
SIR	serious infusion reaction
SLE	Systemic lupus erythematosus
SOC	Social role
SPs	Standard operating procedures
SPA	Special Protocol Assessment
SPP	Specialty Pharmacy Providers
SUA	serum uric acid
TEAE	treatment-emergent adverse event
TFG	Treatment Failure Gout
TIA	transient ischemic attack
Tmax	time to maximal concentration
Tmin	time to minimal concentration
U.S.	United States of America
UA	uric acid
ULT	Urate-lowering therapy
VAH	Veteran's Administration Office
VAS	visual analog scale
Vc	volume of distribution
VT	vitality
WHO	World Health Organization

1. EXECUTIVE SUMMARY

Gout is a acute inflammatory and chronically destructive disorder resulting from the formation and deposition in tissues of urate crystals from extracellular fluid saturated for urate, the end product of human purine metabolism Pegloticase is a novel monomethoxy-poly(ethylene glycol) (PEG) modified recombinant mammalian uricase (urate oxidase), which, when administered intravenously, reverses blood urate supersaturation (hyperuricemia) by catalyzing the conversion of urate to allantoin, a water-soluble metabolite readily excreted in the urine. Pegloticase is being developed for the reduction of the hyperuricemia and signs and symptoms of treatment failure gout (TFG), a condition affecting a small subset of gout patients with no alternative therapy available to them. These patients have severe and progressive crystal deposition disease due to failure of or intolerance to currently available urate-lowering therapy (ULT). The severity of TFG is manifested by frequent acute attacks of disabling arthritis, chronic deforming joint disease, destructive masses of urate crystal (tophi), progressive physical disability, and poor health-related quality of life.

TFG effects approximately 50,000 patients or about 1% of the overall population of patients with gout in the US [1,2,3]. FDA granted Orphan Drug designation to pegloticase on 21 February 2001. It is anticipated that only Rheumatologists and a subset of Nephrologists who have experience infusing biologics will adminsiter pegloticase in patients with treatment failure gout following BLA approval.

1.1 What is Treatment Failure Gout?

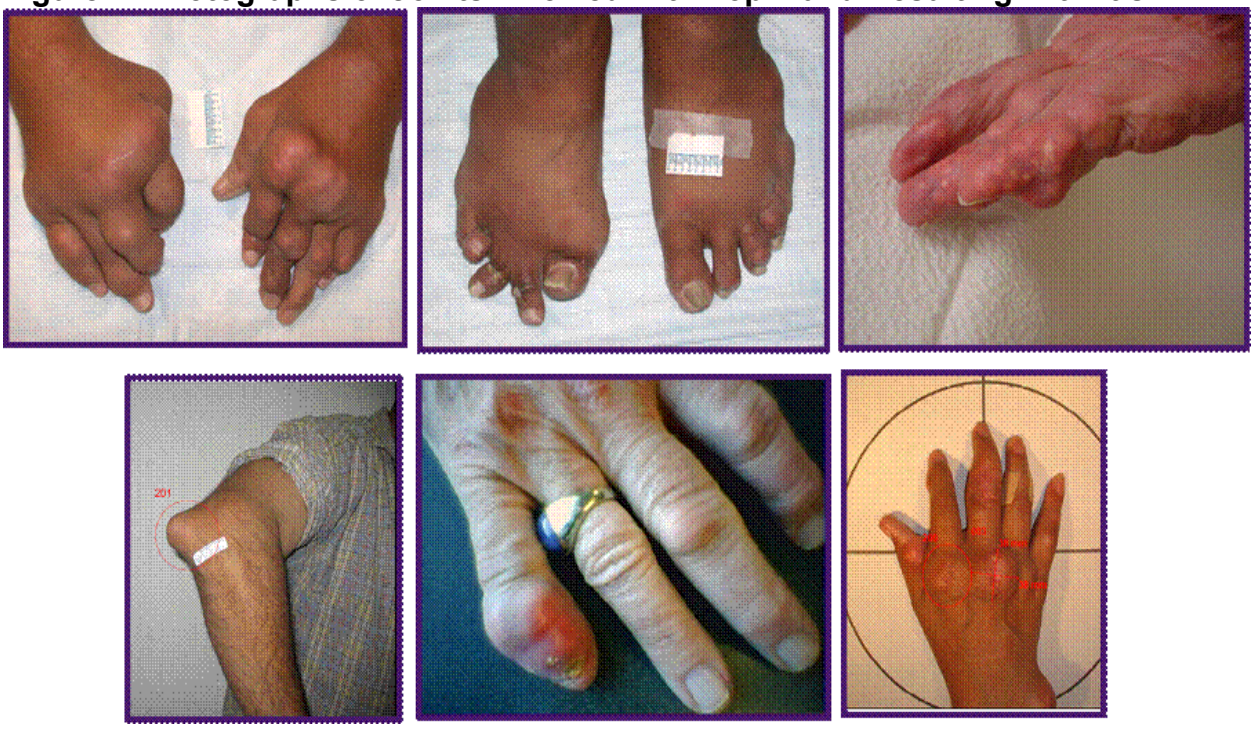
Gout is a chronic disorder of urate metabolism resulting in deposition of monosodium urate crystals in the joints and soft tissues, with accompanying inflammation and eventually, in some patients, destructive, chronic arthropathy. Gout is the most prevalent form of arthritis in men and and is increasing in incidence and prevalence among older persons of both genders. Treatment failure gout (TFG) is an uncommon but severe outcome of progressive gout resulting from demonstrated intolerance of or refractoriness to available therapy to prevent urate crystal deposition by reducing and maintaining serum urate levels in a subsaturating range. TFG is characterized clinically by: painful arthritis and chronic arthropathy; destructive tophi; impaired quality of life; and chronic disability. Hyperuricemia and gout are often accompanied by significant medical co-morbidities including cardiovascular disease, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, and obesity. These associated disorders are especially frequent among patients with TFG. The combination of severe gout and a high burden of cardiovascular and metabolic co-morbidities, often requiring polypharmacy, makes TFG exceptionally difficult to manage.

The severe and advanced nature of TFG manifestions, require modification in the pursuit of the historical goals of medical management of gout: prompt termination of acute flares of gouty arthritis; prophylaxis to reduce recurrent flares; and urate-lowering to prevent and reverse urate crystal deposition, eventually abolishing gouty signs and symptoms. The high prevalence of severe tophaceous gout among TFG patients (Figure 1) makes rapidity in the resolution of tophi an important aim, as do measures to achieve prompt relief of chronic pain and improve physical function and quality of life by accelerated reduction of the total body urate burden. The pegloticase development program has demonstrated the clinical efficacy of this agent in achieving these aims in the TFG population, representing the first evidence for any urate-

lowering regimen in achieving clinical endpoints in gout patients in the course of randomized controlled trials. In this sense, pegloticase is demostrably a disease modifying agent for what is currently a patient group with an unmet medical need.

The personal and societal burden of TFG can be significant, as is apparent from the photos in Figure 1.

Figure 1. Photographs of Joints Involved with Tophi and Resulting Arthritis.



1.2 Comparison of Gout features and co-morbidity rates in patients with gout and with Treatment Failure Gout.

Table 1 compares published clinical study data in patients with TFG to data from the overall gout population. This underscores the increased severity and complexity of the TFG population. While the general gout population is heterogenous in relation to their clinical presentation, the patients with Treatment Failure Gout (TFG) is a more narrowly defined patient population. Table 1 provides data consolidated from 5 studies: two distinct phase 3 trials with febuxostat, one non-interventional natural history study in TFG pre-dating interventional studies with intravenous pegloticase and two replicate phase 3 studies with pegloticase. The comparison of these populations underscores the increased severity and complexity of the treatment failure gout population.

Table 1. Comparison of Baseline & Co-morbid Features from Studies in Gout and Treatment Failure Gout.

	Febuxostat Phase 3 Population[4,5]	Natural History Study[6,7]	Pegloticase Phase 3 Population[8]
Age (mean)	52 years	59 years	55.4 years
Percent reporting flares	40-89%	98%	98%
Mean reported flares/yr	1.6	7	7
Tender, swollen joints	Unusual between flares	Frequent arthropathy	Frequent arthropathy
Percent with tophi	20-24%	70%	73%
Disease duration (mean)	10-12 years	6.9* years	15 years
Prior surgery/hospitalization for gout	Not addressed	Not addressed	22%
Co-morbidities			
CAD/CVD	10-13%	15%	18%
Hypertension	44-49%	71%	72%
Renal impairment	CKD Stg 3: 18% CKD Stg 4: 0%	CKD Stg 3: 47% CKD Stg 4: 10% CKD Stg 5: 2%	CKD Stg 3: 20% CKD Stg 4: 9%
Diabetes	7-10%	14%	23%
Hyperlipidemia	34-38%	N/A	49%
Obesity, mean BMI	32 kg/m^2	32 kg/m^2	32 kg/m^2

Mean interval between confirmation of gout diagnosis and study entry was 6.9 years ± 8.2 (mean ± SD).
N/A = Not assessed

1.3 Pegloticase Development Program

At an FDA Arthritis Advisory Committee meeting in May 2004 agreement was reached that a successful ULT would be defined by achieving serum urate levels < 6.0 mg/dL which is within the solubility limit of ≤ 6.8 mg/dL. Normalization of uric acid to < 6.0 mg/dL was selected for the Pegloticase Development Program as the primary outcome measure to reflect the pharmacodynamic effect of pegloticase. Elevated surm uric acid levels are a clear risk factor for gout. Persistently elevated plasma uric acid (PUA) or serum uric acid (SUA) levels result in deposition of uric acid in joints and soft tissues. As the total body burden of uric acid increases, signs and symptoms of gout result, including arthritis, characterized by recurrent painful gout flares, development of tophi and joint deformities with resultant chronic pain/inflammation and consequent loss of physical function. Based on the pharmacodynamic effect of pegloticase on PUA, it was expected that clinical benefit in the TFG population would be observed by decreases in number of tophi, tender or swollen joints, fewer gout flares over time after an initial increase in flares associated with the initiation of urate-lowering therapy, and improvements in patient reported global assessments of disease activity, pain, physical function (measured by HAQ) and health-related quality of life (HRQOL, by SF-36). These were selected as important secondary outcome measures to demonstrate that sustained lowering of uric acid levels would be associated with clinically meaningful improvements.

The safety and efficacy of pegloticase were evaluated in 6 clinical studies, including two replicate 6-month randomized double-blind, placebo-controlled phase 3 studies (C0405 and C0406) in which 8 mg of pegloticase was administered intravenously every 2 (pegloticase q 2

weeks) or every 4 weeks (pegloticase q 4 weeks). A total of 225 subjects were randomized in phase 3; 212 were dosed, and 157 subjects completed protocol treatment. In the ITT population, all subjects who discontinued were considered "treatment failures" in the primary analysis.

Both randomized controlled trials (RCTs) (Studies C0405 and C0406) were replicates and designed in collaboration with FDA. The Phase 3 protocol C0405 were approved by FDA under a Special Protocol Assessment (SPA).

Subjects who completed either phase 3 pivotal study (C0405 or C0406) were eligible to be enrolled in a long-term Open Label Extension (OLE) Study (C0407). Of 74% of subjects (157 of 212) who completed phase 3 RCTs, 151 of 157 (96%) enrolled in the open label extension (representing 71% [151 of 212] of the ITT population), choosing either pegloticase 8 mg every 2 weeks (82 of 151), pegloticase 8 mg every 4 weeks (67 of 151), or observation (2 of 151). Overall safety exposure of pegloticase-treated subjects was:

- 121 subjects: study duration of approximately 12 months or more,
- 115 subjects: study duration of approximately 15 months or more, and
- 95 subjects: study duration of approximately 18 months or more.

1.4 Results of the Phase 3 Pivotal Studies (C0405 and C0406)

1.4.1 Primary Endpoint

Pegloticase was demonstrated effective in both RCTs (Table 2) using the primary outcome measure of normalization of PUA ≥ 80% of the time during Months 3 and 6. In both phase 3 RCTs, treatment with pegloticase 8 mg q 2 weeks resulted in statisitically significant decreases in PUA compared with placebo, also evident with pegloticase 8 mg dosed every 4 weeks. In the pooled studies, all subjects had rapid normalization of uric acid; in 42 % of subjects receiving pegloticase 8 mg every 2 weeks, normalization of uric acid levels was sustained throughout the 6-month treatment period, compared with 35% with pegloticase q 4 weeks, although results differed between studies (Table 2). In most subjects with transient responses to pegloticase, uric acid levels rose to > 6 mg/dL within 3 months after initiation of treatment.

Table 2. PUA Response in Phase 3 Studies.

Study C0405			
	N	**Persistent PUA responders**	**p-value**
Pegloticase 8 mg q 2 weeks	43	47%	< 0.001
Pegloticase 8 mg q 4 weeks	41	20%	0.044
Placebo	20	0%	-
Study C0406			
	N	**Persistent PUA responders**	**p-value**
Pegloticase 8 mg q 2 weeks	42	38%	< 0.001
Pegloticase 8 mg q 4 weeks	43	49%	< 0.001
Placebo	23	0%	-
Pooled Data			
	N	**Persistent PUA responders**	**p-value**
Pegloticase 8 mg q 2 weeks	85	42%	< 0.001
Pegloticase 8 mg q 4 weeks	84	35%	< 0.001
Placebo	43	0%	-

1.4.2 Secondary Outcomes

Secondary outcomes were analyzed for each of the Phase 3 studies, and pooled across studies, as agreed with FDA. These are presented below.

1.4.2.1 *Tophus Resolution*

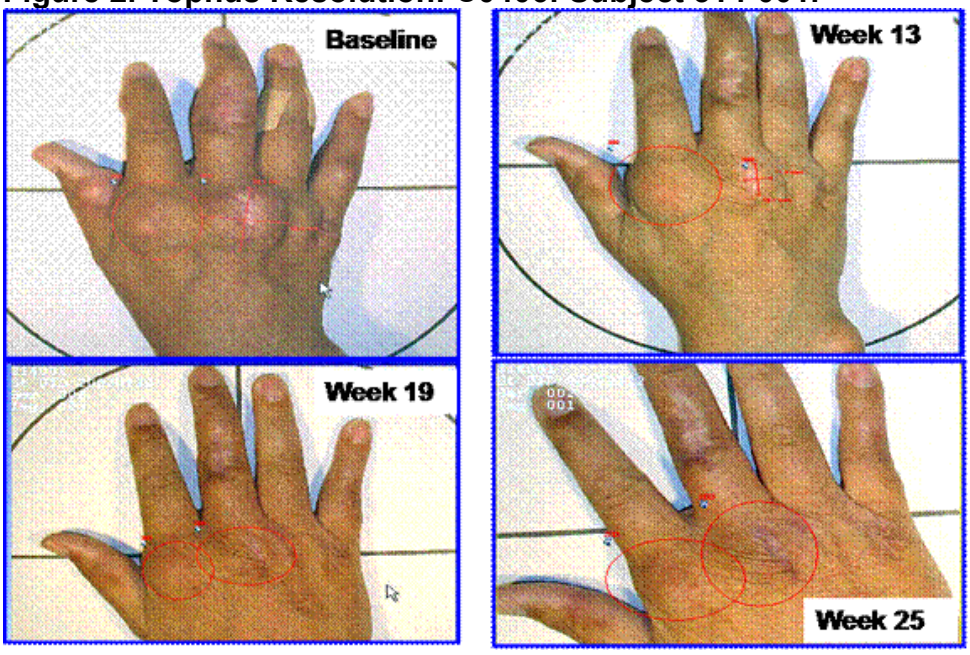
In those subjects with tophi present at baseline (approximately 73% of the overall population), the proportion with complete resolution (defined as 100% resolution of ≥ one target tophus without progression of other tophi or appearance of new tophi) was statistically significantly higher in the pegloticase 8 mg q 2 weeks group at the final visit compared with placebo in each RCT and in the pooled analysis (Table 3).

Table 3. Resolution of Tophi at Final Visit.

Pooled			
	N	**Tophus Complete Resolution**	**p-value**
Pegloticase 8 mg q 2 weeks	52	21 (40%)	p=0.002
Pegloticase 8 mg q 4 weeks	52	11 (21%)	p=NS
Placebo	27	2 (7%)	-
Study C0405			
	N	**Tophus Complete Resolution**	**p-value**
Pegloticase 8 mg q 2 weeks	26	8 (31%)	0.035
Pegloticase 8 mg q 4 weeks	23	5 (22%)	0.136
Placebo	13	0	-
Study C0406			
	N	**Tophus Complete Resolution**	**p-value**
Pegloticase 8 mg q 2 weeks	26	13 (50%)	0.040
Pegloticase 8 mg q 4 weeks	29	6 (21%)	1.000
Placebo	14	2 (14)	-

A representative set of photographs from one subject in the phase 3 Study C0406 that received pegloticase 8 mg q 2 weeks is provided in Figure 2. Each picture represents this patient's hand at different times as noted in each frame after initiation of pegloticase treatment. The metacarpal phalangeal joints of the first and second finger have large tophi. By study week 25 which was the final visit for this patient, the target tophi resolved defining this patient as having a complete tophus resolution.

Figure 2. Tophus Resolution: C0406: Subject 314-001.



1.4.2.2 *Gout Flares*

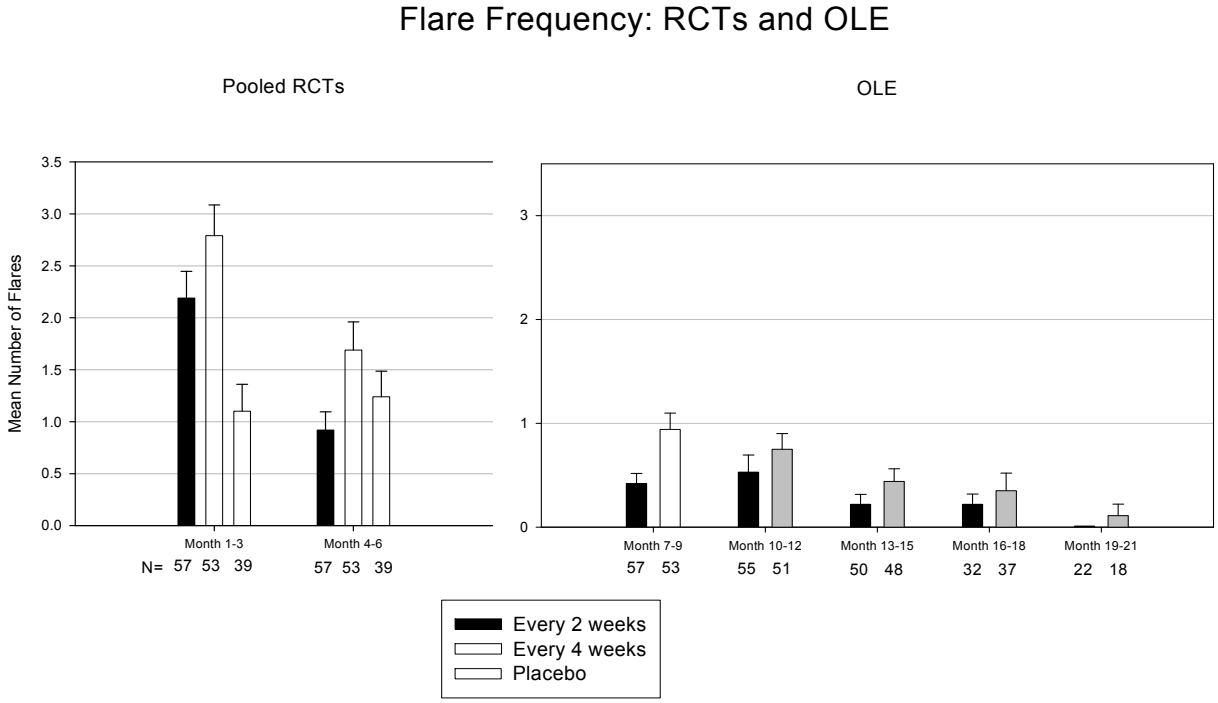
Gout flares are associated with the natural history of the disease, but also may be induced by initiation of uric acid lowering therapy. Thus, reported gout flares may represent lack of therapeutic efficacy, evident in the placebo group, or be secondary to desired pharmacological effects, evident in the active treatment groups, particularly in the first 3 months of treatment. Because of the risk for gout flares, all patients received either colchicine or NSAID prophylaxis to suppress flares. At baseline (study entry), subjects reported a mean of 10 gout flares in the previous 18 months and 63% of patients reported these to be of crippling severity. Following the initiation of pegloticase treatment, the incidence and frequency of gout flares (Table 4) in Months 1-3 increased; as expected as this also occurs with other ULT. In contrast, during Months 4-6, patients administered pegloticase 8 mg q 2 weeks had statistically significant reductions in in the incidence and frequency of gout flares compared with placebo.This was a predefined secondary efficacy outcome.

Table 4. Resolution of Gout Flares.

Treatment Group	Months 1-3			Months 4-6		
	n/N[a]	Incidence	p-value[1]	n/N	Incidence	p-value
Pooled Data						
Pegloticase 8 mg q 2 weeks	64/85	75.3%	0.016	28/69	41%	0.007
Pegloticase 8 mg q 4 weeks	68/84	81.0%	0.002	39/69	57%	0.321
Placebo	23/43	53.5%	-	29/43	67%	-
Study C0405						
Pegloticase 8 mg q 2 weeks	31/43	72.1%	0.390	11/37	29.7%	0.002
Pegloticase 8 mg q 4 weeks	31/41	75.6%	0.242	20/33	60.6%	0.375
Placebo	12/20	60.0%	-	15/20	75.0%	-
Study C0406						
Pegloticase 8 mg q 2 weeks	33/42	78.6%	0.015	17/32	53.1%	0.595
Pegloticase 8 mg q 4 weeks	37/43	86.0%	0.001	19/36	52.8%	0.599
Placebo	11/23	47.8%	-	14/23	60.9%	-

This improvement in the incidence and frequency of gout flares continued in the open label extension over Months 7-21 (Figure 3).

Figure 3. Frequency (mean ± SEM) of Gout Flares over Time (Pooled RCTs and OLE Study).



1.4.2.3 *Other Secondary Outcomes*

For other secondary endpoints, statisitically significant and/or clinically meaningful improvements or trends in improvement were evident.

- Tender or Swollen Joint Counts - Treatment with pegloticase q 2 weeks resulted in statistically significant improvement in the number of tender joints in pooled analysis and one RCT (C0405) compared with placebo. Benefits were maintained with OLE treatment.
- Clinician Global Assessment (CGA) of disease activity - Statistically significant improvements in CGA were reported in both pegloticase q 2 weeks and q 4 weeks dose groups compared with placebo, which were maintained with OLE treatment.
- Patient Reported Outcomes included global assessment of disease activity (PGA), pain, physical function (HAQ DI), and HRQOL (SF-36).
  - PGA: Statistically significant improvements were evident with pegloticase q 2 weeks treatment in pooled analysis and one RCT (C0405) compared to placebo. Fifty-four percent (54%) of subjects reported changes meeting or exceeding the minimum clinically important difference (MCID = 10 mm on a 100 mm VAS scale). Benefits were maintained with OLE treatment.
  - Pain: Statistically significant changes compared to placebo were evident with pegloticase q 2 weeks treatment in pooled analysis. Fifty-five percent (55%) reported improvements ≥ MCID (10 mm). Benefits were maintained with OLE treatment.

  - HAQ DI: Statistically significant improvements were evident with pegloticase q 2 weeks treatment in pooled analysis and one RCT (C0406) compared to placebo; Forty-five percent (45%) reported changes ≥ MCID (-0.22). Benefits were maintained with OLE treatment.
  - SF-36 physical component summary score: Statistically significant improvements were evident with pegloticase q 2 weeks treatment in pooled analysis at endpoint; 64% reported changes ≥ the highest value for MCID (2.5-5.0). Similarly reported improvements in 6 of 8 domains were statistically significant and met or exceeded MCID (5-10).

- In those 36 subjects (42%) receiving pegloticase q 2 weeks who were persistent PUA responders, 23 reported improvements ≥ MCID in two or more patient reported outcomes (HAQ DI, PGA, pain, and PCS); and of those with evaluable tophi (n=25), 18 reported improvements ≥ MCID in two or more patient reported outcomes, associated with complete tophus resolution in nine.

In conclusion, the pharmacodynamic effects of pegloticase 8 mg q 2 weeks administered intravenously resulted in rapid decreases in uric acid levels and resolution of tophi. These changes were associated with decreased tender joint counts, reduction in incidence and frequency of gout flares during months 4-6 and clinically meaningful improvements in global assessment of disease activity, pain, physical function and HRQOL at 6 months.

1.5 Safety

The most common adverse events associated with pegloticase treatment includes gout flares and infusion reactions associated with antibody responses, both generally mild to moderate in severity. An initial increased incidence of gout flares resolved after 3 months of pegloticase therapy. Antibody responses were found in 90% of subjects; those with titers >1:2430 of anti-pegloticase antibodies were most likely to become transient PUA responders with an increased risk of infusion reactions. PUA responses in subjects with titers <1:2430 were largely preserved. Overall safety observations in open label extension (OLE) were consistent with those reported in the phase 3 studies suggesting no cumulative risk with continued exposure to pegloticase.

Because there was a 2:2:1 randomization in the phase 3 RCTs, there were roughly four times as many subjects in active treatment than placebo. Results are therefore presented as percentage and then number within treatment groups. The higher incidence of cardiac SAEs with active treatment may, in part, be attributed to important pre-existing clinical co-morbidities and risk factors in this treatment failure gout population.

1.5.1 All-Cause Mortality

Deaths reported as Serious Adverse Events (SAEs), in the RCTs combined treatment groups, included:

- Pegloticase every 2 weeks: 3.5 % (3 of 85 subjects)

- Study C0405: Subject 203-001: Sudden death; 61 year old male with pre-study coronary artery disease, diabetes mellitus, congestive heart failure, low (~17%) ejection fraction.
- Study C0406: Subject 315-005: Ascribed to arrhythmia; 69 year old male with atherosclerotic heart disease, chronic kidney disease, coronary artery disease, coronary artery bypass graft, carotid endarterectomy .
- Study C0406: Subject 301-003: MRSA Sepsis; 89 year old male with coronary artery disease, diabetes mellitus, chronic kidney disease, aortic valve replacement. Died after voluntary withdrawal of antibiotics 2.5 months after pegloticase treatment.

- Pegloticase every 4 weeks: 1.2 % (1 of 84 subjects)

  - Study C0405: Subject 102-006: Congestive heart failure resolved; 64 year old male with end stage cardiomyopathy, low (~12%) cardiac ejection fraction, diabetes mellitus, developed worsening renal failure and voluntarily discontinued dialysis.

- Placebo: 2.3% (1 of 43 subjects)

  - Study C0406: Subject 301-014: Multiple organ failure in an 84 year old female after randomization and prior to first infusion.

One subject (Study C0405: Subject 122-004) treated with pegloticase q 4 weeks during the RCT and q 2 weeks during the OLE Study C0407 died during the OLE Study from ORSA after voluntary withdrawal from antibiotics. Two patients (C0405: Subject 101-005 and C0406: Subject 311-002) who received placebo in the RCTs died approximately 4 months after their participation in the RCT. Neither enrolled in OLE Study C0407.

1.5.2 Cardiovascular Serious Adverse Events

There was an imbalance in cardiovascular serious adverse events (SAEs) for the pegloticase treatment groups compared to placebo. However, interpretation of the likelihood of a causal relationship of pegloticase is confounded by the relatively low number of events, superimposed on the relatively high incidence of cardiovascular co-morbidity at baseline in the treatment failure gout study population, and the 2:2:1 randomization scheme. The cardiovascular SAEs were disparate, and mostly occurred in isolation without an apparent predominant pattern emerging that might support a causal relationship.

An independent blinded post-hoc Cardiovascular Event Adjudication Committee of experts reviewed these data and similarly an imbalance was confirmed. This report is included in Appendix 6.

1.5.3 Gout Flares

Since giout flares were expected, there was protocol-specified gout flare prophylactic treatment with colchicine or a NSAID before each infusion. While that prophylaxis mitigated the gout flares, they did not stop them from occurring. In some cases the gout flares were reported as SAEs; treatment discontinuation occurred infrequently in all treatment groups:

- Pegloticase 8 mg q 2 weeks: 5% with gout flare SAEs (4 of 85 subjects); four subjects discontinued due to gout flares (one of which was an SAE).
- Pegloticase 8 mg q 4 weeks: 1.2 % with gout flare SAEs (1 of 84 subjects); two subjects discontinued due to gout flares.
- Placebo: 4.7 % with gout flare SAEs (2 of 43 subjects); one subject discontinued due to gout flares.

There was an early increased incidence of gout flares in patients receiving pegloticase. Most flares were mild to moderate in severity and did not result in treatment discontinuation. The increased incidence of gout flares was transient and resolved after three months of therapy.

As noted in the Phase 3 Efficacy Results Section 4, the incidence (40.6% vs. 67.4%) and frequency (0.8 vs 1.31) of gout flares were significantly lower in the pegloticase q 2 week as compared to placebo during Months 4-6 of therapy, ($p = 0.007$ and 0.048, respectively).

1.5.4 Infusion Reactions

An infusion reaction was defined as any adverse event that occurred during or within 2 hours after the pegloticase or placebo infusion. Although there was protocol-specified infusion reaction prophylatic treatment, infusion reactions occurred in 26% of subject treated with pegloticase q 2 weeks and 40% with pegloticase q 4 weeks. In addition to a few (5%) infusion reactions in the placebo group, there were a few infusion reactions that occurred during a placebo infusion in the pegloticase q 4 week group. Most infusion reactions were mild to moderate in severity. Some infusion reactions resolved with: (a) slowing the infusions (b) stopping and restarting the infusion at a slower rate, (c) supportive treatment with i.v. fluids, (d) additional glucocorticoids, (e) antihistamines, and/or (f) discontinuation of the infusion. An infusion reaction caused about 12% of subjects to discontinue pegloticase treatment.

The cause of some infusion reactions were clearly not related to immunogenicity, however, most of these events were related to some form of immune reaponse. The Sponsor recommends that patients who experience a moderate to severe infusion reaction should discontinue further pegloticase therapy.

1.5.5 Immunogenicity

Anti-pegloticase antibodies were observed in about 90% of subjects treated with pegloticase. Antibodies at higher titers (>1:2430) result in increased clearance of pegloticase and loss of pegloticase activity (transient responders). Antibody development follows a predictable pattern, developing soon after initiation of therapy, and not at later time points. The rise in PUA, representing a transient response in the primary outcome, preceeds the evidence of higher titers of antibodies, and predicts the development of both higher titer antibodies along with falling serum CH50 levels in some subjects and many of the infusion reactions. This series of events, higher titer antibodies, falling CH50 levels, and infusion reactions were more common in the q 4 dose of drug than with the q 2 dose of drug. Although those patients who developed higher titer antibodies had a higher incidence of infusion reactions, there was no clear relationship between antibody titer and severity of infusion reactions. Patients who developed high antibody titers (but not lower titers) had a high likelihood of loss of PUA response. The evidence of a transient response was clear in all patients by Month 4 following initiation of therapy. The clinical

effects of immunogenicity are immediate and easily detected by monitoring SUA levels weekly during the first 3-4 months of therapy.

In some patients, although there did not appear to be a rise in IgE levels, tryptase levels did rise in some patients and may have been associated with important IR's.

Few subjects in the RCTs were positive for anti-pegloticase IgE, and in those subjects the titers were so low that they were considered not to be meaningful. The anti-pegloticase IgE did not reveal any association to IRs. IgE was measured one to two weeks after an IR and there was no evidence of IgE spike in any subject.

Serum tryptase has been reported to be elevated in anaphylactic IRs. Tryptase elevations were not associated with a consistent pattern of IR signs and symptoms and therefore did not identify a type of IR associated with mast cell degranulation.

1.6 Conclusion

In conclusion, in the treatment failure gout orphan population, characterized by advanced disease, a high burden of co-morbidity and polypharmacy, pegloticase offers the first effective urate-lowering therapy. Based upon the saety and eficacy data, the Sponsor proposes that pegloticase 8 mg q 2 weeks administered intravenously is the appropriate dose and schedule for treating patients with treatment failure gout.

Pegloticase 8 mg every 2 weeks results in dramatic decreases in uric acid (PUA and SUA), associated with complete resolution of tophi in some subjects, decreased tender joint counts and clinically meaningful improvements in patient reported global assessment of disease activity, pain, physical function and HRQOL at 6 months. Treatment was also associated with a decrease in the incidence and frequency of gout flares after 3 months of therapy compared with placebo, with continued reductions in flare incidence and frequency with long term administration, up to at least 18 months. These benefits occur in patients with severe disease who have no other currently available therapy. Persistent responders are those patients that maintain anti-pegloticase antibody response (titers <1:2430) and who, on or after Month 4, continue to have normal PUA values in response to repeated pegloticase infusions.

A higher incidence of cardiac SAEs with active pegloticase treatment may, in part, be attributed to pre-existing co-morbidities in this treatment failure gout population and the 2:2:1 randomization resulting in a 4:1 pegloticase:placebo exposure. The most commonly reported adverse events were gout flares and infusion reactions related mostly to immunogenicity. Infusion reactions resulted in discontinuations in 12% of subjects without any incidence of anaphylaxis. High titer anti-pegloticase antibodies, observed in 35% of subjects in both pegloticase treatment groups, are associated with a transient PUA response and an increased incidence of infusion reactions. Continued therapy is not recommended in those subjects who have lost uric acid response or have experienced a clinically important infusion reaction.

The benefit/risk profile of pegloticase 8 mg q 2 weeks has been demonstrated to be significantly and importantly beneficial to patients with severe treatment failure gout, a small orphan population with no presently available therapy thus a large unmet medical need. This benefit is

observed in replicate randomized controlled trials as compared with placebo and is in terms of pharmacodynamic measures of plasma uric acid as well as statistically significant relevant clinical outcomes. The proposed Risk Minimization Action Plan will minimize the risk inherent to therapy while ensuring that the correct patient population is treated. Pegloticase therapy can be successfullymanaged with careful clinical monitoring.

2. INTRODUCTION

Pegloticase is a novel, recombinant, mammalian uricase modified by the covalent attachment of monomethoxy-poly(ethylene glycol) (PEG) to lysine residues on the enzyme. Pegloticase reduces levels of urate in the serum (or plasma) by catalyzing conversion of urate to allantoin, a water-soluble metabolite readily excreted in the urine.

The uricase core protein is a homotetramer. A structural model of two views of native uricase showing each of the four identical subunits in different colors, is provided in Figure 4.

A structural model of pegloticase is provided in Figure 5, showing the protein (uricase) core in color and the PEG chains anchored to and surrounding the core, in grey. The PEG chains bound to the protein are intended to shield potentially immunogenic protein epitopes and to block exposure of the uricase core to proteolytic enzymes. In pegloticase each of the four subunits of uricase protein is coupled to an average of 9 ±1 strands of 10 kDa mPEG, for an average 36 strands of PEG per tetramer.

Figure 4. Molecular Model of Native Uricase Viewed from Two Angles, Showing Each Subunit in a Different Color

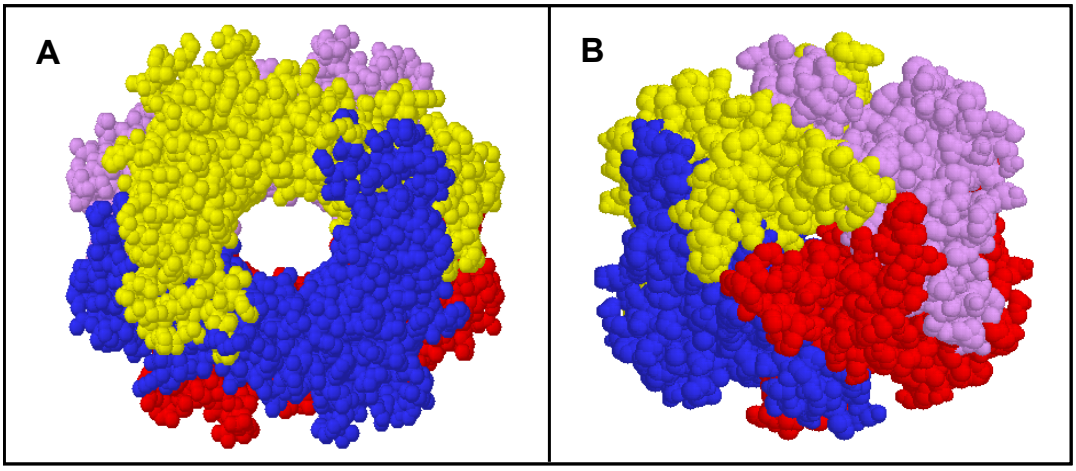
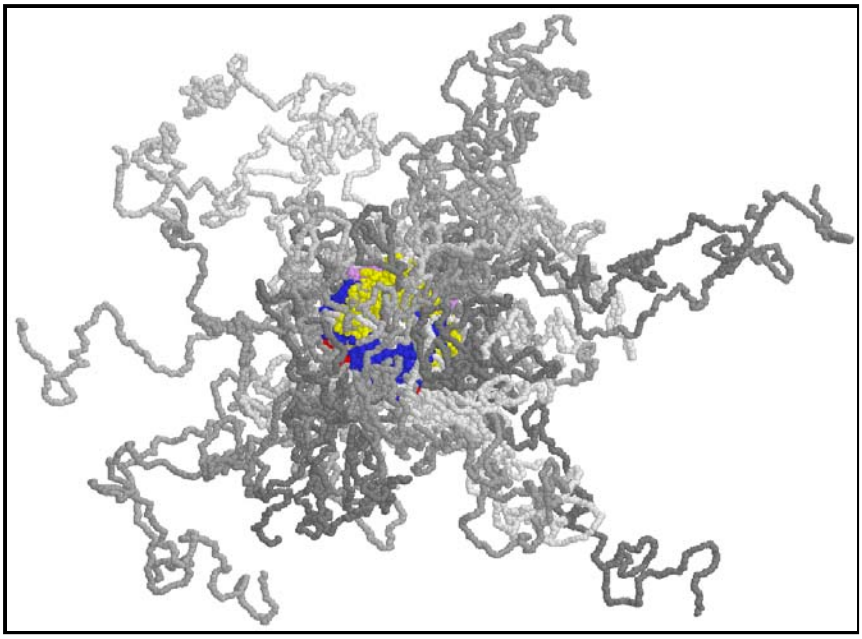


Figure 5. Molecular Model of Pegloticase: The Protein (uricase) Core, a Homotetramer in Color, and the PEG chains Anchored to and Surrounding the Core, in Grey.



Pre-clinical studies identified an optimum number of PEG chains per uricase monomer both to preserve pegloticase enzyme activity and to minimize potential immunogenicity.

Pegloticase is being developed for the treatment of patients with treatment failure gout (TFG) who have no alternative therapies available to them. This is a small subset of patients with severe gout who have failed or are intolerant of currently available urate-lowering therapy (ULT). TFG patients experience a high burden of disease, with a high prevalence of tophi (70%), frequent and often crippling gout flares (averaging 7 per year at baseline), deforming arthropathy, impaired quality of life, and progressive disability.

It is estimated that the term TFG describes approximately 50,000 gout patients, representing aprroximately 1% of the overall gout population in the US. FDA granted Orphan Drug designation to pegloticase on 21 February 2001. It is anticipated that only Rheumatologists and a subset of Nephrologists who have experience infusing biologics will adminsiter pegloticase in patients with treatment failure gout following BLA approval.

2.1 Mechanism of Action and Chemical Class

Gout results from formation and deposition of monosodium urate crystals, usually after a prolonged period of hyperuricemia. In humans, purines are metabolized to uric acid via the intermediates hypoxanthine and xanthine. Conversion of hypoxanthine to xanthine and xanthine to urate is catalyzed by the enzyme xanthine oxidase. The aim of urate-lowering therapy is to reduce circulating levels of urate in symptomatic gout patient to prevent disease progression and reverse prior signs of disease, such as tophi. Allopurinol and febuxostat inhibit xanthine oxidase, thereby reducing uric acid synthesis. Probenecid, and other uricosuric agents, facilitate the renal

excretion of uric acid. Pegloticase was conceived for patients who have failed or cannot use conventional approaches to urate-lowering therapy.

Pegloticase is unique among urate-lowering therapies, converting urate, which is sparingly soluble in extracellular fluids (limit of solubility of urate in serum is 6.8 mg/dL) to allantoin, a more soluble endproduct that is readily excreted by the kidney. Enzymatic elimination of urate by pegloticase achieves much lower serum or plasma urate levels than those attainable with uricosuric agents or xanthine oxidase inhibitors, thereby accelerating mobilization of tissue pools of urate into the blood for conversion to to allantoin, and excretion..

Pegloticase is a recombinant mammalian urate oxidase (uricase) produced in *E. coli;* a tetrameric enzyme, molecular weight approximately 34.2 kDa per subunit and is conjugated to PEG. Pegloticase treatment is designed to reduce and maintain blood concentrations of uric acid below limits of solubility (SUA or PUA <6 mg/dL) to mobilize existing crystal accumulations into solution for enzymatic degradation. Pegloticase catalyzes oxidation of uric acid to 5-hydroxyisourate which spontaneously converts to allantoin. Normally present in humans at very low concentrations resulting from non-enzymatic oxidation of uric acid, allantoin is an inert and highly soluble purine metabolite that is readily eliminated, primarily via the kidney. It is expected that, with use of pegloticase over time, soluble and insoluble (crystalline) extracellular urate pools will decrease as a result of the induced concentration gradient between tissue stores and intravascular urate.

Pegloticase was designed to control hyperuricemia and the clinical consequences of severe gout in patients with TFG, who have failed to normalize serum uric acid and are inadequately controlled with conventional ULT at the maximum medically appropriate dose or for whom these therapies are contraindicated.

2.2 Rationale for Pegloticase Development

An aspergillus-derived recombinant but unmodifieduricase (rasburicase) is approved in the United States for the prevention or treatment of tumor lysis syndrome. The biological half life of the uricase activity of rasburicase is brief, however, and the unmodified protein is antigenic, limiting use of this agent to 5 successive days. Repeated courses of rasburicase therapy have resulted in clinically significant immune adverse events. With the dual aims of lengthening the circulating half-life of the enzymaticially active uricase moiety and lessening immunogenicity in long-term use for TFG therapy, pegloticase has been developed as a recombinant and modified (by PEGylation) uricase.

2.3 Treatment Failure Gout

Gout is an acutely disabling and often chronically destructive disease resulting from responses to the deposition of urate crystals from extracellular fluids containing urate concentrations exceeding the limit of sulubility of urare. Urate crystal deposition often occurs in and around articular structures, intermittently provoking acute inflammation (acute gouty arthritis or bursitis), the most common clinical feature of gout. When urate crystal deposition persists over months to years, due either to failure or unsuccessful attempts to lower and maintain serum urate levels in a sub-saturating range, recurrent and increasingly severe gout flares may occur, often accompanied by progressive joint deformity and the development of deforming and destructive

accumulations of urate crytals (tophi) in joints, bone, cartilage, the skin, and even solid organs. Advanced untreated or treatment failure gout is often accompanied by progressive physical disability and impaired quality of life. When efforts at urate-lowering treatment of progressive gout are unsuccessful, due either to intolerance of or medical circumstances limiting the use of adequate doses of available urate-lowering pharmacotherapy, the outcome is described as treatment failure gout.

Hyperuricemia results from either impaired renal urate excretion or from excessive urate production [10,11], or, occasionally, from a combination of these mechanisms. Impaired renal clearance of urate accounts for hyperuricemia in about 90% of gout patients. Although lifestyle adjustments (changes in diet composition and/or amount, reduction in alcohol intake, weight reduction, dietary supplementation, or change in medication for co-morbid conditions) may contribute to urate-lowering, the effects of these actions are most often inadequate to reverse hyperuricemia, so that urate-lowering pharmacotherapy is often indicated to prevent gout progression. Currently available agents used to control hyperuricemia in gout fall into two categories: xanthine oxidase inhibitors, such as allopurinol and febuxostat, and uricosuric agents, such as probenecid. Probenecid use is restricted to patients with adequate renal function and to patients without a history of nephrolithiasis (probenecid package insert). Because the choice of efficacious uricosuric agents in the US is limited, and renal dysfunction and urate nephrolithiasis are common problems among gout patients, use of probenecid is severely limited and currently comprises less than 5% of all urate-lowering therapy prescribed. In contrast, allopurinol is the most widely used urate-lowering agent, comprising more than 95% of all urate-lowering therapy (ULT) prescriptions (IMS Health National Prescription Audit, 2007).

Acute gout flares are characterized by intense often crippling pain and have been associated with decreased physical functioning, increased hospitalizations and decreased work productivity. Importantly, given the prevalence of renal compromise in patients with gout, the frequent use of high dose NSAIDs with each acute flare may also contribute to the progressive renal compromise seen in these patients. Intermittent and at times frequent gout flares can be triggered by dehydration and circulatory changes as seen with myocardial infarction, trauma, and surgery as well as the more commonly recognised dietary and lifestyle triggers including alcohol and certain medicines that interfere with urate elimination such as low dose aspirin and the immunosuppressant cyclosporine. Initiation of any urate-lowering therapy is strongly associated with an increase in the incidence and frequency of gout flares [12]. It is hypothesized that stored urate crystals that had become encapsulated by proteins or other substances begin to dissolve into smaller crystals as serum urate levels decrease. The smaller crystals might be expected to have exposed reactive pro-inflammatory surfaces that can trigger the inflammatory pathway leading to gout flares [13]. An increase in flares at the onset of therapy is indicative of the pharmacological effect of urate-lowering therapy.

Treatment failure gout (TFG) occurs in patients who fail to normalize SUA and whose signs and symptoms are inadequately controlled (or cannot be controlled due to contraindication to use) with conventional ULT. The population with TFG is characterized by patients with severe gout manifestations including frequent gout flares, chronic painful arthropathy and disability, multiple and often debilitating tophaceous accumulations of MSU crystals. Patients with treatment failure gout experience impacted physical function and health related quality of life [6], and is

associated with an increased risk for cardiovascular events and death [14,15]. Patients with TFG also have a high burden of significant preexisting medical co-morbidities including hypertension, cardiovascular disease, diabetes mellitus, chronic kidney disease, obesity, and hyperlipidemia. The combination of severe gout, cardiovascular disease and high burden of co-morbidities (mean: about eight per patient in the Phase 3 study population), polypharmacy, and lack of urate control by conventional ULT makes management of TFG patients exceptionally challenging.

Elevated serum urate is a hallmark biochemical marker of gout and can reflect a process of continuous deposition of urate crystals that mediate the signs and symptoms associated with the disease. It has been demonstrated that generally the higher the levels, the faster the progression and the greater the severity of the disease and its complications. The converse has also been demonstrated; lower levels achieved with ULT are associated with improved clinical outcomes. Treatment goals for TFG patient population are to eliminate tophi, reduce flares and improve chronic pain by lowering the total urate pool. By maintaining sub-saturating serum urate levels, i.e., <6 .0 mg/dL, frequency of gout flares [16] and presence of tophi [17] can eventually be reduced. Because these reductions are inversely related to the magnitude of SUA reduction, [16,18] it is recognized that subjects with TFG require more substantial lowering of SUA than can typically be achieved with available therapies during randomized controlled trials, including allopurinol, febuxostat, and probenecid.

The photograph (Figure 6) is an example of the manifestations of chronic severe tophaceous gout.

Figure 6. Photograph of the Hands of a Patient with Chronic Tophaceous Gout

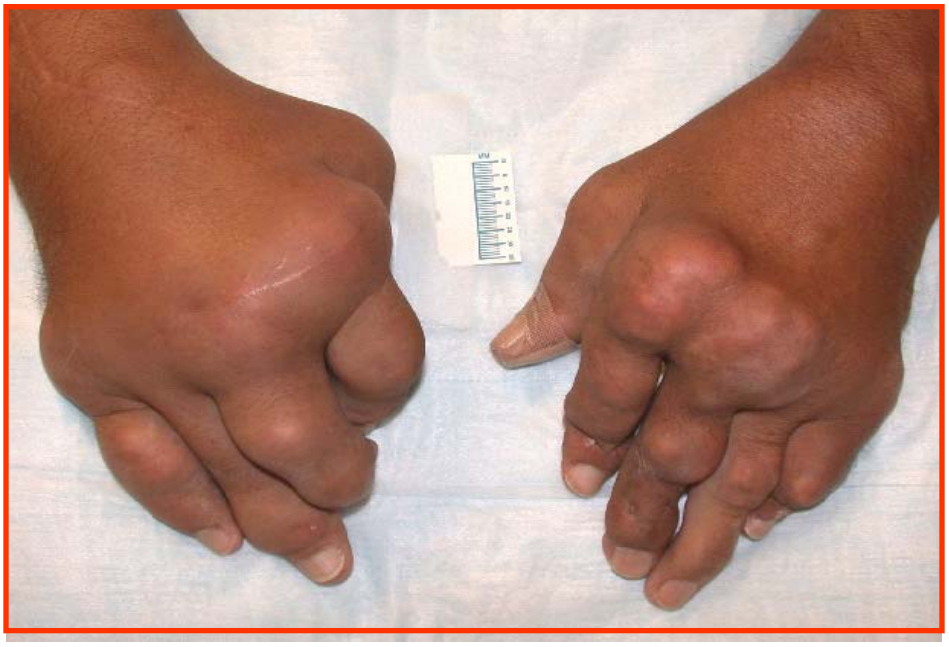


Table 5 compares published clinical study data in patients with TFG to data from the overall gout population.. This underscores the increased severity and complexity of the TFG population. While the general gout population is heterogenous in relation to their clinical presentation, the patients with Treatment Failure Gout (TFG) is a more narrowly defined patient population.

Table 5 provides data consolidated from 5 studies: two distinct phase 3 trials with febuxostat, one non-interventional natural history study in TFG pre-dating interventional studies with intravenous pegloticase and two replicate phase 3 studies with pegloticase. The comparison of these populations underscores the increased severity and complexity of the treatment failure gout population.

Table 5. Comparison of Baseline & Co-morbid Features from Studies in Gout and Treatment Failure Gout.

	Febuxostat Phase 3 Population[4,5]	Natural History Study[6,7]	Pegloticase Phase 3 Population[8]
Age (mean)	52 years	59 years	55.4 years
Percent reporting flares	40-89%	98%	98%
Mean reported flares/yr	1.6	7	7
Tender, swollen joints	Unusual between flares	Frequent arthropathy	Frequent arthropathy
Percent with tophi	20-24%	70%	73%
Disease duration (mean)	10-12 years	6.9* years	15 years
Prior surgery/hospitalization for gout	Not addressed	Not addressed	22%
Co-morbidities			
CAD/CVD	10-13%	15%	18%
Hypertension	44-49%	71%	72%
Renal impairment	CKD Stg 3: 18% CKD Stg 4: 0%	CKD Stg 3: 47% CKD Stg 4: 10% CKD Stg 5: 2%	CKD Stg 3: 20% CKD Stg 4: 9%
Diabetes	7-10%	14%	23%
Hyperlipidemia	34-38%	N/A	49%
Obesity, mean BMI	32 kg/m^2	32 kg/m^2	32 kg/m^2

Mean interval between confirmation of gout diagnosis and study entry was 6.9 years ± 8.2 (mean ± SD).
N/A = Not assessed

In a survey of veterans, those reporting gout were more likely to have medical and other arthritic co-morbidities compared with those without gout (1.5±1.1 medical co-morbid conditions; and 0.6±0.9 arthritic co-morbid conditions). These subjects reported SF-36 scores remarkably similar to those in the longitudinal NHS study, indicating HRQOL was similarly impacted by TFG. Importantly, after 4-12 months, treatment of TFG with currently available therapies in the NHS study failed to improve HRQOL scores by SF-36 [45].

2.4 Rationale for Treating Patients with Treatment Failure Gout

Uric acid (UA) is the end metabolite in the purine catabolic pathway of humans. In nearly all other mammals, with the exception of most great apes, urate oxidase catalyzes the conversion of UA to allantoin, both excreted in the urine. Uric acid is poorly soluble in water. When the serum concentration of UA is above the biochemical limit of solubility, 6.8 mg/dL, monosodium urate crystals may precipitate in tissues. It is hypothesized that after years of persistent hyperuricemia, accumulation of monosodium urate crystals causes symptoms of gout, such as acute inflammation of joints (an acute gout flare), formation of gout tophi, gouty arthritis, and UA nephropathy (including UA renal stones).

The treatment of asymptomatic hyperuricemia is not recommended. However, when patients have experienced repeated occurrences of symptoms, e.g. a third or fourth gout flare, chronic urate-lowering therapy is generally instituted. The principal pharmacologic approach to the treatment of gout is use of xanthine oxidase inhibitors to block urate synthesis. Less often, uricosuric agents are used to enhance the urinary excretion of UA, either as stand alone therapy, or in combination with xanthine oxidase inhibitors such as allopurinol. Although allopurinol is generally well tolerated, many gout patients fail to normalize SUA levels with this therapy, due to several factors: physicians' discomfort in titrating allopurinol to sufficiently high doses to fully normalize SUA levels, incomplete prophylaxis for gout flares after institution of therapy, and lack of patient adherence to chronic treatment, especially when split dosing is required. With the recent availability of febuxostat there is an alternative xanthine oxidase inhibitor. However, the lower approved dose (40 mg) was not superior to allopurinol and neither 40 or 80 mg doses have been demonstrated to result in tophus resolution or have significant impact on patient reported outcomes in randomized controlled studies.

Control of chronic gout cannot be achieved without maintaining normal SUA [19, 21, 22, 23]. Treatment of hyperuricemia with allopurinol is generally effective and well-tolerated [22]. However, approximately 2% of patients treated with allopurinol develop allergic reactions, and a severe hypersensitivity syndrome occurs in about 0.4% of the patients [24, 25]. This "allopurinol hypersensitivity syndrome" can cause acute renal and hepatic failure, and severe skin injury (toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome) and it is often life-threatening, with a mortality rate of 20-30%. Two important drug-drug interactions with allopurinol include azathioprine and 6-mercaptopurine. These drugs are used for immunosuppression in prevention of organ allograft rejection and the latter in the treatment of leukemia. Both conditions can be associated with marked and progressive hyperuricemia, potentially causing threatening renal function, mortality, and flare precipatate or new-onset gout. Also, there are a group of patients who appear to be refractory to such allopurinol therapy and develop chronic tophaceous gout despite aggressive conventional urate-lowering therapy [26, 27, 28, 29].

It is estimated that there are 3 to 6 [1,2] million patients with self-reported gout in the United States, with approximately 2.6 million patients using allopurinol [29]. It is thought that a small portion of this large gout population, estimated at approximately 50,000, who have medical contraindications to allurinol due to allergy/hypersensitivity or who have failed to normalize SUA even at maximum medically appropriate doses of allopurinol. These patients, together with those with an allopurinol allergy, define the orphan population of gout, for which pegloticase treatment was created.

2.5 Summary Pegloticase Nonclinical Studies

The toxicological testing of pegloticase followed the recommendations provided by FDA to support the clinical development program of this biotechnology product. The design of the non-clinical testing program for pegloticase was based also on the ICH S6 guidance for the non-clinical development of biotechnology pharmaceuticals. This testing strategy involved pharmacodynamic studies to evaluate pegloticase activity, pharmacokinetic studies to ascertain systemic disposition and elimination, and toxicology studies to characterize the safety profile. Also included was assessing the immunogenic potential of the PEGylated protein. The toxicity

studies completed with pegloticase have fully characterized the safety profile of this novel biotechnology drug. A summary of the nonclinical pegloticase program is provided in Appendix 1.

3. OVERVIEW OF PEGLOTICASE CLINICAL DEVELOPMENT PROGRAM

The clinical development program for intravenous pegloticase consisted of 6 clinical trials involving 273 patients. Phase 1 and Phase 2 studies established the route of administration, dose and regimen. The Phase 2 study is discussed in detail in Appendix 2. The Phase 3 program was designed to demonstrate that pegloticase is an effective and safe therapeutic agent for the small number of subjects with TFG.

Exposure to pegloticase in clinical studies is summarized in Table 6.

Table 6. Clinical Studies of Pegloticase.

Protocol: Protocol Title	Design	Treatment	Subjects (n)	Duration of Treatment
C0401: An Open-Label, Phase 1 Single-Dose-Escalating Study of the Pharmacokinetic Profile and Effects of Pegloticase in Patients with Symptomatic Gout	Open-label, escalating single dose	Pegloticase; s.c. injection 4 mg 8 mg 12 mg 24 mg	 4 4 4 1	1 day
C0402: A Phase 1 Study to Evaluate the Pharmacokinetic Profile, Tolerability, and Safety of Intravenously Administered Pegloticase	Open-label, escalating single dose	Pegloticase; i.v. infusion; dose escalation in 6 cohorts: 0.5 mg 1 mg 2 mg 4 mg 8 mg 12 mg	 4 4 4 4 4 4	1 day
C0403: A Phase 2 Study of Multiple Doses of Intravenous Pegloticase in Patients with Hyperuricemia and Refractory Gout	Randomized, open-label, parallel group	Pegloticase; i.v. infusion; 4 mg q 2 weeks 8 mg q 2 weeks 8 mg q 4 weeks 12 mg q 4 weeks	 7 8 13 13	12 weeks

Protocol: Protocol Title	Design	Treatment	Subjects (n)	Duration of Treatment
C0405: Randomized, multicenter, double-blind, placebo-controlled efficacy and safety study of 8 mg pegloticase in two dose regimens in hyperuricemic subjects with symptomatic gout	Randomized, double-blind placebo controlled, parallel	Pegloticase; i.v. infusion; 8 mg q 2 weeks 8 mg q 4 weeks Placebo	 43 41 20	26 weeks
C0406: Randomized, multicenter, double-blind, placebo-controlled efficacy and safety study of 8 mg pegloticase in two dose regimens in hyperuricemic subjects with symptomatic gout	Randomized, double-blind placebo controlled, parallel	Pegloticase; i.v. infusion; 8 mg q 2 weeks 8 mg q 4 weeks Placebo	 42 43 23	26 weeks
C0407: Multicenter, open label extension study of 8 mg pegloticase in subjects who completed Protocols C0405 or C0406 for symptomatic gout **Ongoing**	Open-label extension	Pegloticase; i.v. infusion; 8 mg q 2 weeks 8 mg q 4 weeks Observation	 82 67 2	24 months
C0409: Multicenter, Open-Label, 24 week regimen of 8 mg pegloticase i.v. in symptomatic gout subjects who participated in previous studies of pegloticase i.v. **Ongoing**	Open label re-exposure study	Pegloticase; i.v. infusion; 8 mg q 2 weeks 8 mg q 4 weeks	 7	24 weeks

3.1 Phase 1 and 2 Studies: Efficacy and Safety

A summary of the Phase 1 and 2 Studies is provided in Appendix 2.

3.1.1 Phase 1 (Single Subcutaneous Dose Escalation Study) (Study C0401)

An open-label, single center, subcutaneous dose escalation study of the pharmacokinetics and pharmacodynamics of pegloticase in subjects with hyperuricemia and symptomatic gout was conducted [30]. This was designed to test 4, 8, 12, 24 and 48 mg of pegloticase in five cohorts of 4 subjects each. However, only 13 subjects were treated. Four subjects in each of the lower dosing cohorts and one subject in the 24 mg dose cohort were studied before the trial was stopped due to a safety concern about the route of administration. The study was discontinued after two subjects in the 12 mg dose cohort developed generalized urticaria and myalgias 10 days

after dosing. Plasma uric acid (PUA) levels in all subjects in the cohorts > 8 mg became normalized (PUA < 6 mg/dL) with the exception of one subject in the 8 mg group, whose initial PUA level was extremely high, approximately 15 mg/dL. Further development of a subcutaneous route of administration was abandoned.

3.1.2 Phase 1 (Single Intravenous Dose Escalation Study) (Study C0402)

This was an open-label, single center study of pegloticase administered intravenously, in ascending doses ranging from 0.5 – 12 mg to groups of 4 patients (n=24), all of whom manifested severely symptomatic treatment failure gout and hyperuricemia. The pharmacokinetics of pegloticase were measured as uricase enzymatic activity. Plasma uric acid levels were determined in all patients over a 21 day period at an academic non-GLP laboratory.. The presence of immunoreactivity directed against the drug product, pegloticase, and against the poly(ethylene glycol) moiety were determined by ELISA procedures and immunodepletion at the same laboratory [30].

At entry, all patients had baseline hyperuricemia >7.0 mg/dL. Pegloticase administration (at doses > 2.0 mg) normalized PUA in all patients.

A total of 22 patients (92%) had 66 adverse events (AEs) during the study. All AEs were rated mild or moderate in severity. There were no serious adverse reactions. All but one of 21 AEs (knee pain) considered study drug related were gout flares or exacerbation of gout.

Nine patients were found to have antibodies to pegloticase. Seroconversion (defined as a positive antibody finding post-baseline, or an increase in titer post-baseline) was not dose related and observed with all doses except the 8 mg dose.

3.1.3 Phase 2 (Multiple Intravenous Dose Administration) (Study C0403)

An open label, randomized, multi-center 17 week dose ranging safety and efficacy phase 2 study was conducted in hyperuricemic patients (SUA > 8.0 mg/dL) with symptomatic gout who were intolerant of or who had failed to normalize SUA with conventional therapy. This study included a 1 week lead-in (or wash out) period, a 12 week treatment period, and a 4 week follow-up period. The purpose of the study was to select a dose and dose regimen for phase 3 studies as well as further understand about responsiveness and its interrelationship with immunogenicity. Each patient was scheduled to receive either 3 or 6 intravenous infusions of pegloticase, infused over 30 minutes (or one hour, post-Protocol Amendment) in doses of 4 mg every 2 weeks, 8 mg every 2 weeks, 8 mg every 4 weeks, or 12 mg every 4 weeks.

The efficacy results extended the findings of phase 1. Four mg i.v. every two weeks was defined as the minimally effective dose, 8 mg every two or every four weeks was effective, and 12 mg every four weeks did not provide additional benefit beyond that of the 8 mg doses, thereby defining a dose-response plateau. Although the every 2 week and every 4 week 8 mg treatment achieved the same degree of PUA decrease, an every 2 week infusion regimen appeared to offer a more rapid, consistently larger and more prolonged reduction of PUA.

Clinical outcomes, other than normalization of PUA, were not captured as a prospectively planned endpoint in this study because it was believed that a 12 week treatment period would be

too brief to allow for their attainment. However, one investigator provided photographic evidence in two patients before and after treatment showing eradication of gout tophi. The PUA in both of these patients was normalized below 2 mg/dL throughout the study period.

No dose relationship was observed with respect to safety outcomes. There were 13 SAEs in nine subjects. Five of these SAEs were designated by the Investigators as possibly or probably related to pegloticase treatment. There were 24 subjects with any AE that was designated to be possibly or probably related to pegloticase. The incidence of gout flares increased by 39% for the first month of treatment, as compared to the self-reported pre-study rate of gout flare occurrence, but then decreased in each of the next three, one-month observation periods. This increase of gout flare was expected as it had been observed previously with other urate-lowering therapies. However, in the last month of the study, the frequency of gout flares was substantially reduced as compared to pre-study self-reported gout flare rates. For this phase 2 study, subjects not already on a prophylactic regimen of colchicine or a nonsteroidal anti-inflammatory drug (NSAID) to prevent gout flares could be placed on one of these agents at the discretion of the investigator, unless such therapy was contraindicated for the subject.

Twenty-eight of 41 (68%) subjects in the ITT population were categorized as positive for seroconversion to anti-pegloticase antibodies during the study, with a fairly even distribution of these subjects across the 4 treatment regimens. Exploratory analyses of the effect of anti-pegloticase antibody production on pharmacokinetic and efficacy parameters within the 8 mg every 2 week treatment group were conducted. Results indicated that plasma pegloticase concentrations were slightly higher at all post first infusion time points for the non-seroconverted subjects but there was no clinically meaningful difference between seroconverted and non-converted subjects for any of the studied efficacy parameters through 21 days after the last infusion. Furthermore, no clear pattern or increase in infusion reactions or the number of adverse events was discernable between the seroconverted and the non-seroconverted subjects within this treatment regimen.

There were 21 infusion reactions in 18 patients (total 148 infusions) who were administered pegloticase. Twelve of the 18 subjects who experienced an IR were withdrawn from the Study by the Investigators, most often in consultation with the Sponsor due to a high level of caution about the potential risk of anaphylaxis. No anaphylactic reactions were observed. Investigators initiated a treatment intervention in 13 subjects (who had 15 IRs) including prolongation of the duration of the infusion, increased volume of infusion or cessation of the infusion, administration of an oral antihistamine, and/or administration of intravenous corticosteroid. Clinical sequelae requiring interventions beyond the day of infusion were not observed. There were no deaths in the Phase 2 study.The mean (±SEM) for PUA over time for all subjects adminsitered pegloticase 4 or 8 mg every 2 weeks is presented in Figure 7, while Figure 8 contains the mean (± SEM) for PUA over time for all subjects adminsitered pegloticase 8 or 12 mg every 4 weeks. Irrespective of the intial dose (4, 8 or 12 mg) a rapid reduction in PUA occurred such that the mean PUA normalized below 6 mg/dL. It should be noted that the downward shift in Figure 7 and Figure 8 at week 10 in both of the every 2 week group and week 8 in both of the every 4 week group represents the intensive post-infusion sampling for the pharmacokinetic evaluation.

Figure 7. Mean Plasma Uric Acid (± SEM) At Various Times, All Treated Subjects Administered Pegloticase Every 2 Weeks: Study C0403.

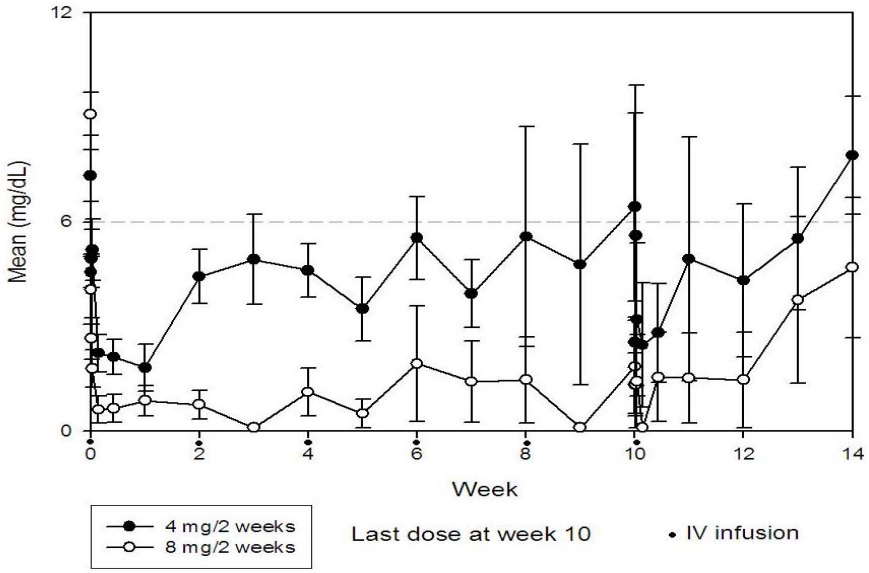
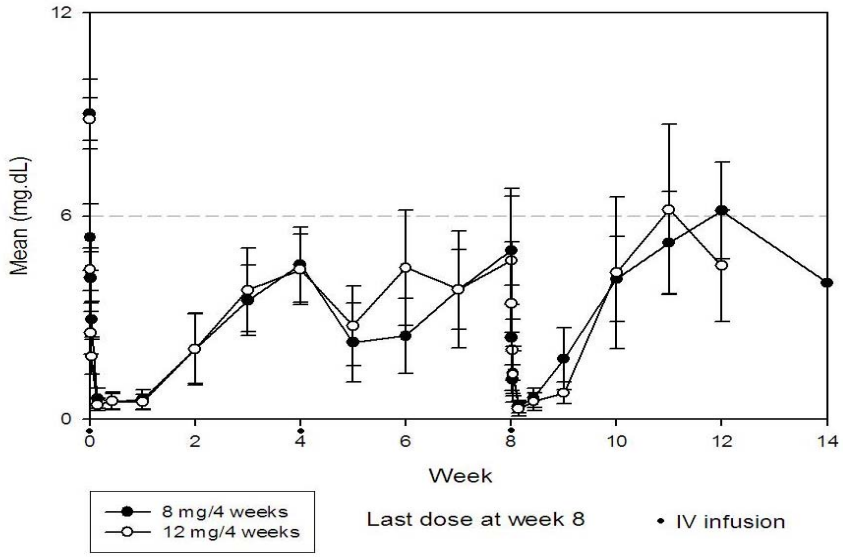


Figure 8. Mean Plasma Uric Acid (±SEM) at Various Times, All Treated Subjects Administered Pegloticase Every 4 Weeks: Study C0403.



While the mean value for all groups remained below 6 mg/dL throughout the 12 week study period, evaluation of individual subjects defined two responder groups for PUA. In each four treatment groups, there were transient responders in which their PUA values returned to values

above 6 mg/dL and there were persistent responders who had a sustained normalizationof PUA (Figures 9-10). Figures 9 and 10 contain the anti-pegloticase antibody titers and demostrate the relationship between PUA and antiibody titer. The persistent responders had a sustained PUA normalization and low titers while the transient responders had higher antibody titers and a return of their PUA values above 6 mg/dL. It is noteworthy that in the transient responders, the first return of PUA to a value >6 mg/dl preceded achievement of the peak antibody titer. The relationship between PUA, transient versus persistent response as measured by PUA or SUA, and anti-pegloticase antibody titer will be discussed further in section 5.6.3 using the more extensive phase 3 database.

This study showed the prompt and persistent efficacy of pegloticase in lowering PUA concentrations in subjects with chronic gout and hyperuricemia who are refractory or intolerant to conventional therapy. All four dose regimens were effective; however the 8 mg and 12 mg groups showed better efficacy in reducing PUA than the 4 mg group. The 12 mg group did not provide additional benefit beyond that of the 8 mg groups.

Figure 9. Mean Plasma Uric Acid and Anti-pegloticase Antibody Titer over Time in Subjects Administered Pegloticase 4 or 8 mg Every Two Weeks

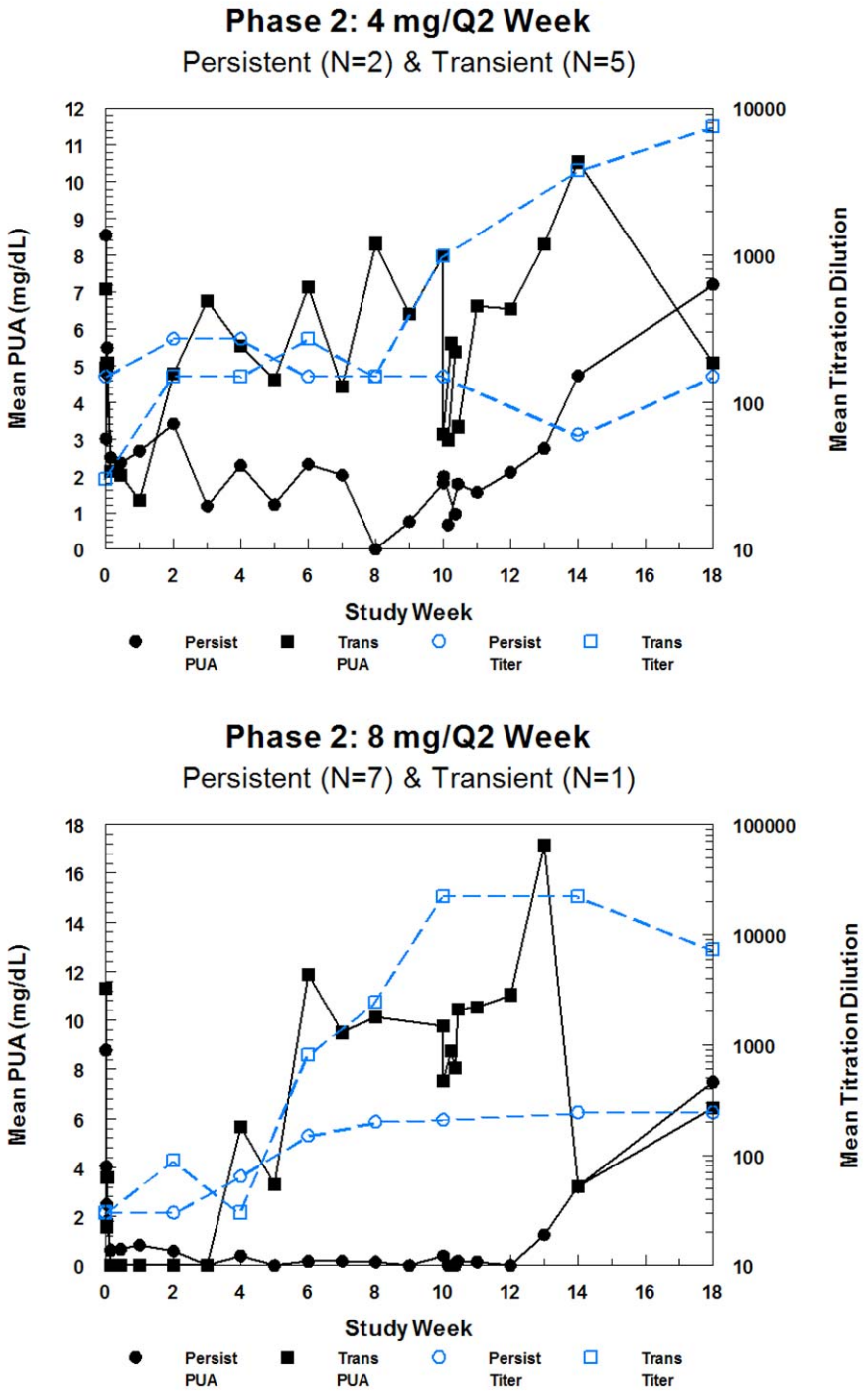
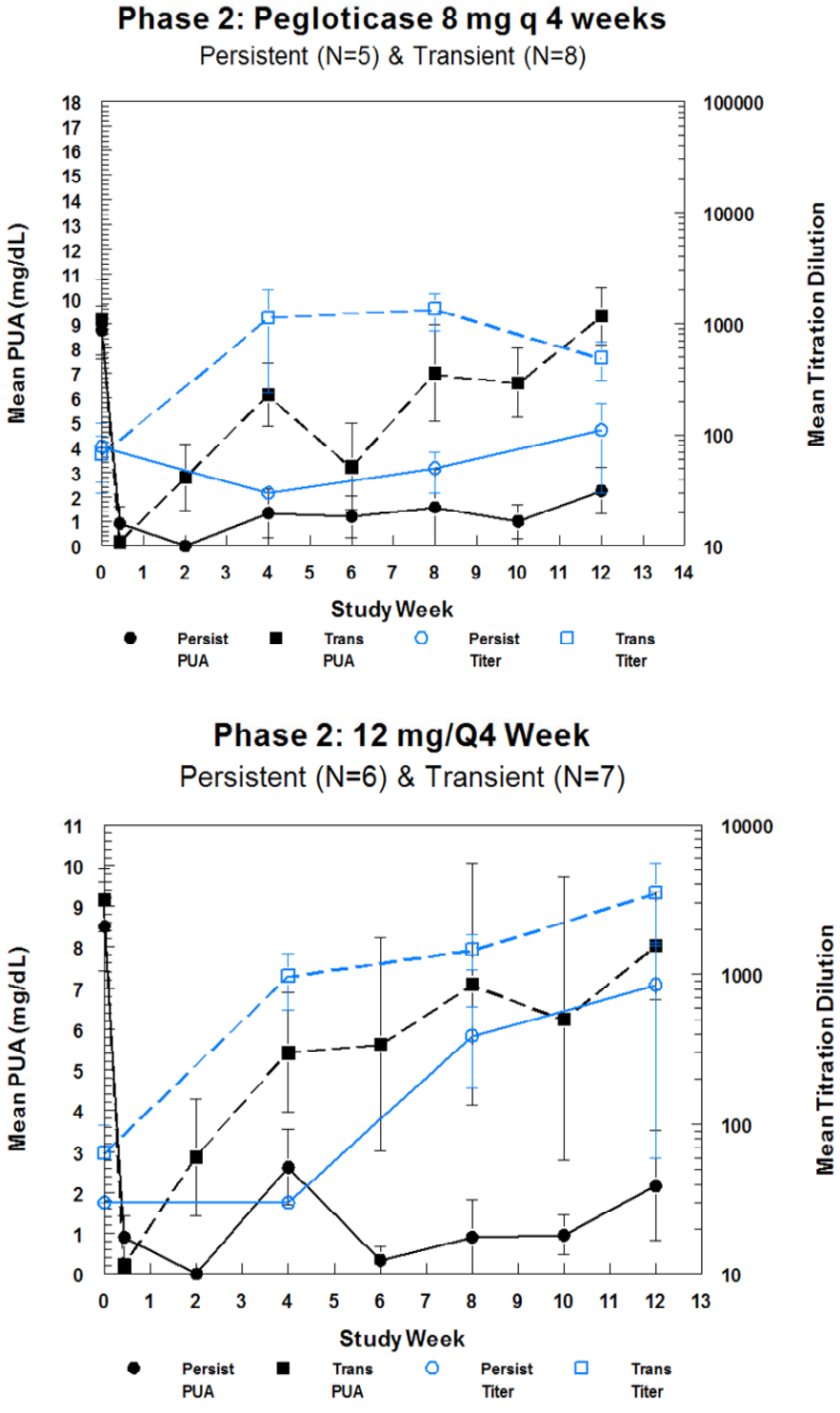
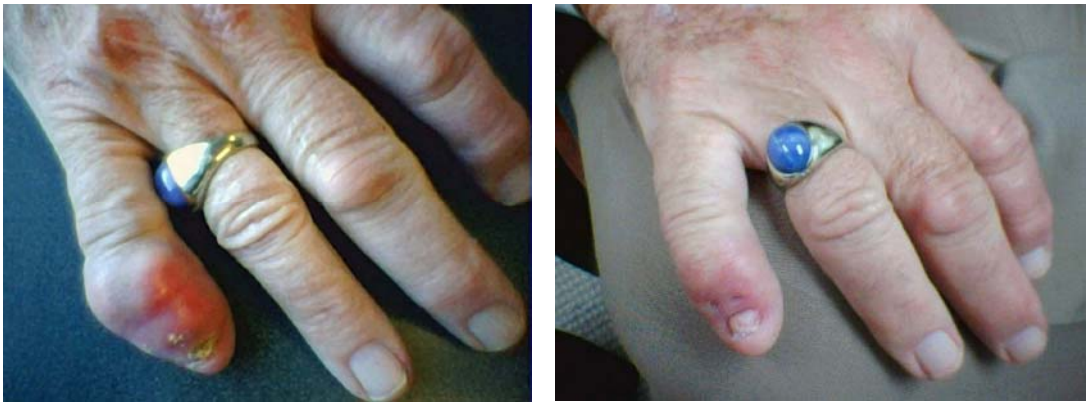


Figure 10. Mean (± SEM) Plasma Uric Acid and Anti-pegloticase Antibody Titer over Time in Subjects Administered Pegloticase 8 or 12 mg Every Four Weeks.



No prospective clinical efficacy endpoints related to reduction of tophi were planned for the Phase 2 study because it was believed that the 3-month treatment period would be too brief to detect change. However, two of the six subjects at one clinical site agreed to have photographs taken before and during the study (Figure 11 and Figure 12).

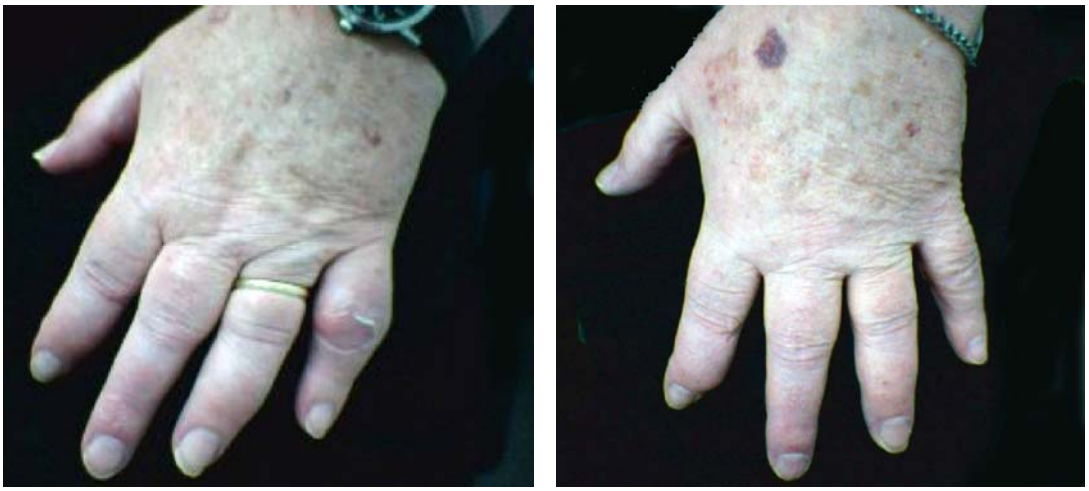
Figure 11. Resolution of a Tophus with Pegloticase Treatment: Study C0403: Subject 001-002.



Before **After**

Subject 001-002: A 70-year-old white male (gout > 25 years) with a history of UA-related nephrolithiasis, multiple tophi at his hands and feet, and an allergy to allopurinol received 8 mg of pegloticase q 2 weeks. Within 24 hrs of the first infusion, UA levels were reduced from SUA 9.3 mg/dl at baseline to PUA <0.1 mg/dL and remained at this level throughout treatment and more than 2 weeks post final infusion. A photograph after 12 weeks (6 doses) shows marked resolution of a large draining tophus at the right fifth distal interphalangeal joint.

Figure 12. Resolution of a Draining Tophus with Pegloticase Treatment: Study C0403: Subject 001-007.



Before **After**

Subject 001-007: A 58-year-old white male (gout diagnosis ~ 1year) with multiple tophi on both hands and an allergy to allopurinol received 12 mg pegloticase q 4 weeks. Uric acid fell from SUA 11.0 mg/dl at baseline to PUA < 0.1 mg/dL and was maintained at this level throughout treatment. After 8 weeks of follow-up it remained at < 0.5 mg/dL. Pre- and post-treatment photographs of a tophus involving the left fifth proximal interphalangeal joint demonstrate marked reduction in tophus size after 12 weeks (3 doses).

For these two subjects, treatment of tophaceous gout with pegloticase resulted in rapid and continuous normalization of PUA and resolution of tophi in 12 weeks documented by photographs. Although anecdotal, these two cases support the undertaking of further study to demonstrate the potential benefit of pegloticase in decreasing the size of monosodium urate crystal deposits in chronic tophaceous gout and the use of measuring tophus dimensions using digital photographs to quantitate those resolutions.

3.1.4 Summary and Conclusion

These data demonstrate that patients treated with pegloticase 8 mg every 2 or 4 weeks had a rapid and sustained reduction in plasma urica acid; 4 mg every 2 weeks was not effective and 12 mg every 4 weeks did not provide additional benefit compared to 8 mg every 4 weeks. A majority of patients developed antibodies to pegloticase; infusion reactions appeared to be associated with the presence of an antibody response. The data also show that these patients can be categorized into two groups based upon their PUA values after repeated pegloticase treatment: (1) persistent responders (previously referred to as completers or responders) who had a sustained reducation in PUA, and (2) transient responders (previously referred to as non-completers or non-responders) who initially had PUA values below 6 mg/ dL but those values increased over time to above 6 mg/dL. While all patients had a response after the first pegloticase administration, those patients who develop antibodies appeared to have transient responsiveness and a higher risk for infusion reactions. On the basis of safety and efficacy results of the Phase 2 study, the pegloticase dose selected for advancement to Phase 3 registration studies was 8 mg administered intravenously (250 mL volume) over 120 minutes every two weeks or every four weeks.

3.2 Randomized Controlled Phase 3 Studies (C0405 and C0406)

Two replicate double-blind, placebo-controlled, studies were performed primarily in the United States (49 sites; 190 subjects) with some investigational sites and subjects (approximately 10%) in Canada (2 sites; 3 subjects) and Mexico (4 sites; 19 subjects). Study C0405 protocol was approved by FDA under a Special Protocol Assessment and feedback was incorporated into the analysis plans for these two identical pivotal studies.

All subjects received an intravenous (i.v.) infusion (pegloticase or placebo) every 2 weeks in order to maintain the blind throughout the study. Subjects were stratified by presence/absence of tophi. Study duration was 26 weeks, including 2 weeks for screening and 24 weeks (6 months) of treatment. After study completion, subjects were offered the option of continuing (or receiving) active treatment or entry into an observation only group for up to an additional 24 months into Study C0407 (OLE Study).

All subjects reported a medical history in which allopurinol therapy was contraindicated (e.g., history of hypersensitivity, intolerance, or toxicity) or had not been effective, defined as failure to normalize SUA with ≥3 months allopurinol treatment at the maximum labeled dose (800 mg/day in the U.S.) or at a medically appropriate lower dose based on toxicity or dose-limiting co-morbidity. In section 4, extensive description of study design is provided. Briefly, the major exclusion criteria at entry included:

- Unstable angina, uncontrolled arrhythmia, non-compensated congestive heart failure, uncontrolled hypertension (above 150/95 mmHg)
- Dialysis
- Organ transplant recipient
- Pregnancy
- G6PD deficiency due to generation of hydrogen peroxide in conversion of uric acid into allantoin and consequent risk of hemolytic anemia and met-hemoglobinemia in G6PD deficient patients, and/or:
- Any medical condition that, in the Investigator's opinion, could create undue risk to the subject or compromise his/her completion of the trial

Subjects discontinued all urate-lowering therapies ≥ one week prior to randomization, and refrained from using such agents throughout the study. Subjects not already receiving prophylactic regimens of colchicine (0.6 qd or bid) or a labeled analgesic dose of a non-steroidal anti-inflammatory drug (NSAID) for gout flares were to initiate such therapy at Screening Visit, unless medically contraindicated. All subjects received prophylaxis for infusion reactions (IR): oral fexofenadine (60 mg evening prior and immediately before infusion), and acetaminophen (1000 mg) and hydrocortisone IV (200 mg) prior to each infusion. Study medication was administered in 250 mL saline over 2 hours although the protocol allowed for slowing the infusion for up to 4 hours total infusion time.

Results of these replicate studies are provided in Sections 4 and 5.

3.3 Other Studies C0407 and C0409

3.3.1 Study C0407

This is an ongoing multi-center, open-label extension (OLE) study for subjects who completed the phase 3 double-blind protocols (Studies C0405 and C0406). Subjects were given the opportunity to participate in this OLE study to evaluate the long-term safety and durability of efficacy of pegloticase (up to 24 months). At entry into the study, blinding to treatment assignment in the completed phase 3 RCTs was maintained. Upon completion of participation in the phase 3 studies, a subject had multiple options: (1) receive pegloticase 8 mg every 2 weeks, (2) receive pegloticase 8 mg every 4 weeks in the OLE study; (3) enroll in the Observational arm of the OLE study; or (4) decline to participate. After 6 months of participation in Study C0407, subjects were allowed to alter the dosing frequency once for the remainder of the study. In addition, at any point, subjects receiving treatment could choose to discontinue treatment and/or enter the Observational arm of the study.

Subjects continued gout flare prophylaxis for 3 months in the OLE study (as prescribed in the RCTs), after which this could be discontinued at discretion of the investigator. Subjects in the Observational arm could receive other urate-lowering therapy at discretion of the Investigator.

The primary objective of the OLE study was to evaluate the long-term safety of pegloticase treatment. Objectives for this safety evaluation were to:

- Describe the safety profile of pegloticase with respect to adverse events, laboratory measurements, physical exam, and EKG
- Determine the incidence of infusion reactions
- Determine the incidence of allergic reactions attributed to pegloticase
- Further characterize the potential for immunogenicity of pegloticase

Additional objectives of the study were to determine the treatment effect of pegloticase in subjects continuing to receive active therapy from the phase 3 RCTs and in those initially randomized to placebo, and duration of benefit with respect to the following parameters:

- Plasma uric acid (PUA)
- Tophus response assessed by image analysis
- Incidence and frequency of gout flares
- Tender and/or swollen joint count
- Clinician Global Assessment (CGA) of disease activity
- Patient-reported outcomes (PROs):
  - Patients Global Assessment
  - Pain
  - Physical function by Health Assessment Questionnaire (HAQ-DI)
  - Health related quality of life by SF-36

As in the phase 3 RCTs, the efficacy of pegloticase in normalizing and maintaining PUA to < 6 mg/dL for ≥ 80% of the time Months 3 to 6 combined was evaluated.

Of 74% of subjects (157 of 212 subjects) who completed the phase 3 trials, 96% (151 of 157 subjects) elected to enroll in the OLE. Seventy-one percent (71%) of subjects in the ITT population (of phase 3 RCTs) chose to receive treatment with pegloticase 8 mg either every 2 weeks (82 of 151 subjects) or every 4 weeks (67 of 151 subjects), or to be followed in the observation arm (2 of 151 subjects) of the protocol.

The BLA submission contained data on 101 subjects from this ongoing study with ≥12 months continuous pegloticase exposure (RCTs and OLE). The 120-day safety update reported on 121 subjects with treatment duration of at least 12 months (≥ 365 days).

Results of Study C0407 are provided in Sections 4 and 5.

3.3.2 Study C0409

Study C0409 is an ongoing open-label study to evaluate the safety and clinical effect of re-exposure to pegloticase 8 mg every 2 weeks intravenously over 24 weeks in subjects with

symptomatic gout whose last exposure to pegloticase was > one year prior to study entry. Mandatory prophylaxis for gout flares and infusion reactions as in the phase RCTs. This ongoing study enrolled seven symptomatic gout patients, age 45 – 75 years, previously enrolled in pegloticase phase 1 or 2 studies that had a pegloticase drug-free interval of > 3 years. Six subjects were male; 4 completed the study; one discontinued treatment due to an infusion reaction and 2 for lack of efficacy. Four of 7 (57%) experienced an IR; all were subsequently re-exposed to pegloticase; and 2 subjects had subsequent IRs. Other AEs that were reported in >1 subject included gout flares (5 subjects) and arthralgia (3 subjects).

3.4 Pharmacokinetics

3.4.1 Assay Methodology

The serum pegloticase assay used in phase 3 is a coupled enzymatic/fluorescent based assay which measures the activity of pegloticase in the serum relative to the amount of pegloticase required to produce that activity. In this assay, pegloticase catalyzes the oxidation of uric acid in the presence of oxygen to allantoin, hydrogen peroxide (H_2O_2) and carbon dioxide. In the presence of horseradish peroxidase (HRP), H_2O_2 reacts with a 1:1 stoichiometry with the Amplex Red reagent to generate the red-fluorescence oxidation product, resorufin. The measured fluorescent response is proportional to the concentration of pegloticase present in the study samples. The pegloticase used in the phase 3 clinical trial had an activity of 6.7 U/mg.

3.4.2 Phase 3 Pharmacokinetics Data

Each subject received 8 mg pegloticase IV every 2 weeks or 8 mg pegloticase IV every 4 weeks (alternating with placebo infusion every 2 weeks) or matching placebo control. Treatment was administered for 24 weeks.

Samples for safety, pharmacokinetic analysis were collected at various time points throughout the conduct of the study. Samples for PK analysis were collected before each dose administration, as well as 2 and 24 hours after the end of dose administration following Doses 1 (Week 1), 5 (Week 9) and 11 (Week 21). Additional samples were also collected 7 days after the end of dose administration following Doses 5 and 11, 2 hours and 7 days after the end of dose administration following Doses 6 and 12, and 14 days after the end of dose administration following Dose 12. In the event of an early termination, a sample was also collected at this time.

Samples for analysis of antibodies to pegloticase and PEG were collected pre-dose before Dose 1 (Week 1), Dose 2 (Week 3), Dose 3 (Week 5), Dose 5 (Week 9), Dose 7 (Week 13), Dose 9 (Week 17), Dose 11 (Week 21) and approximately 14 days after Dose 12 (Week 25).

A population PK analysis was performed using NONMEM VI in order to robustly characterize the pharmacokinetics of pegloticase. A total of 163 subjects (131 men and 32 women) from both protocols were included in the pharmacokinetic analysis. Only subjects who received active drug and who had at least one detectable pegloticase concentration were included in the population PK analysis. The volume of distribution (Vc) and clearance (CL) were increased for subjects with anti-pegloticase antibodies compared with subjects without anti-pegloticase antibodies (Table 7).

Table 7. Population Pharmacokinetic Parameters of Pegloticase.

Parameter	Mean Value	Coefficient Variation (%)	
		Inter-subject	Intra-subject
Vc if no increase in anti-pegloticase (L)	4.73	24.7	18.2
Vc if increase in anti-pegloticase (L)	5.93		
CL if no increase in anti-pegloticase (L/h)	0.0145	39.6	17.0
CL if increase in anti-pegloticase (L/h)	0.0191		
Residual variability (%)	30.8		

The mean half-life for the population of subjects was approximately 221 hours (ranging from 123 to 452 hours with a median value of 217 hours). There was a profound effect on the pharmacodynamics of pegloticase in subjects who exhibited high anti-pegloticase antibody titers. Further information and descriptions regarding the relationship retween pharmacokinetics, pharmacodynamics and anti-pegloticase antibody titers is presented in section 5.6.3.

4. PHASE 3 EFFICACY RESULTS

The primary objective of these replicate studies was to demonstrate statistical signficance in the number of subjects receiving pegloticase compared with those receiving placebo in achieving PUA concentrations <6 mg/dL for at least 80% of the time during months 3 and 6. Secondary outcomes included reductions in tophus burden and incidence/frequency of gout flares months 4 to 6; tender or swollen joint counts; clinical global assessment of disease activity and patient reported outcomes: global assessment of disease activity, pain, physical function and HRQOL. Based on discussion with the FDA, pooled analyses of secondary outcomes from the two identical phase 3 RCTs (Studies C0405 and C0406) were performed.

4.1 Statistical Methods for Phase 3

The statisitcal analysis plan was developed in parallel with protocol development and provided to FDA for comment before completion of the phase 3 studies. Key elements are provided in this section.

4.1.1 Key Design Aspects

These were two, replicate randomized, multi-center, double-blind, 3-arm parallel treatment group, placebo-controlled trails of pegloticase, administered via intravenous infusion, in subjects with hyperuricemia and symptomatic gout in whom conventional therapy was contraindicated or has been ineffective. Subjects must have discontinued any uric acid-lowering agents for at least one week prior to receiving study drug, and refrain from using such agents throughout the study. Subjects not already receiving prophylactic regimens of colchicine or non-steroidal anti-inflammatory drug (NSAID) to prevent gout flares initiated such treatment at screening visit, unless medically contraindicated. After completing the study, subjects had the option (and were encouraged) to continue active treatment for up to another 24 months by entering an Open Label Extension (OLE) protocol (Study C0407). A schematic diagram of the replicate Phase 3 RCTs is presented in Figure 13.

Figure 13. Schematic Diagram of the Design of the Phase 3 Studies.

Screening and Wash-out period	**RANDOMIZATION**	**24 week double blind treatment period**
Days -14 to -1		Randomized treatment: Dosing by i.v. infusion every 2 weeks Three study groups (2:2:1 ratio), stratified by presence or absence of tophi – Group 1: Pegloticase 8 mg every 2 weeks – Group 2: Pegloticase 8 mg every 4 weeks (alternating with placebo) – Group 3: Placebo every 2 weeks

All subjects received an intravenous infusion (pegloticase or placebo) every two weeks in order to maintain the blind throughout the study.
Sample size calculations for the replicate phase 3 RCTs were based on efficacy and safety results from completed phase 1 and 2 studies, and the Natural History Study [6]. From earlier phase 1

and 2 studies, response rates for 8 mg every 2 weeks and every 4 weeks groups were estimated to be ≥35%; without responses in placebo expected. Therefore, each study with 40 subjects (Pegloticase 8 mg q 2 weeks): 40 subjects (Pegloticase 8 mg q 4 weeks): 20 subejcts (Placebo) was estimated to have sufficient power (>80%) to detect a treatment difference of 35% vs. 5% in response rates over 6 months treatment with a significance level of p=0.05 for each comparison.

No interim analysis was performed. As specified in the protocols, after approximately 60 subjects had been randomized drop-out rates were estimated to be <20%. Thus, the enrolment goals were not adjusted during conduct of the studies.

4.1.2 Primary Efficacy Endpoint and Secondary Efficacy Endpoints

The primary efficacy endpoint was normalization of plasma uric acid (PUA) concentration to < 6 mg/dL; using a predefined responder analysis, i.e., the proportion of patients with plasma uric acid (PUA) concentrations < 6 mg/dL for ≥ 80% of the time during treatment Months 3 and 6. It should be noted that these subjects with persistent response were referred to as "responders" in the protocol; likewise, the other subjects that had a transient response were referred to in the protocol as "non-responders".

In addition, proportion of time PUA levels were < 6 mg/dL, mean PUA levels and reductions in mean PUA levels from baseline were analyzed.

Based on a predefined pooled analysis of both identical phase 3 RCTs, the following secondary efficacy endpoints were assessed:

- Reduction in tophus burden, using digital photography, in subjects with evaluable tophi, e.g. "tophus evaluable population"
- Incidence and frequency of gout flares during Months 4 to 6 of treatment
- Tender and/or swollen joint counts
- Clinician global assessment of disease activity
- Patient reported outcomes (PROs):
- Patient global assessment of disease activity (by VAS)
- Pain (by VAS)
- Physical function (by HAQ DI)
- HRQOL by SF-36

4.1.2.1 *Analysis Populations*

The ITT population was defined as all randomized subjects who received at least one dose of study medication. The per-protocol analysis set was the subset of the ITT population of all subjects with no major protocol deviations who completed 6 months study treatment.

4.1.2.2 *Analysis of the Primary Efficacy Endpoint in Individual Studies*

A responder was defined as a subject in whom plasma uric acid (PUA) levels remained < 6 mg/dL for ≥ 80% of the time during treatment months 3 and 6. At an FDA Arthritis Advisory Committee meeting in May 2004 agreement was reached that a successful ULT would be defined by achieving serum uric acid values < 6.0 mg/dL. Normalization of uric acid values to < 6.0 mg/dL was selected for phase 3 studies as the primary outcome. Plasma, rather than serum

uric acid levels, were selected because pegloticase is active during serum processing and could cause enzymatic degradation of the uric acid in blood samples left at room temperature, resulting in spuriously low uric acid levels. Therefore, measurements of uric acid from blood samples in subjects treated with pegloticase were made in plasma processed under cold conditions (ice-salt-water bath, low temperature centrifugation) followed by acidification, protein precipitation, and centrifugation and then shipped and stored under frozen conditions until analysis. These conditions attenuated the activity of pegloticase during the processing of the plasma.

The primary efficacy analysis was a comparison of the proportion of responders between subjects receiving pegloticase to those receiving placebo (i.e. 8 mg pegloticase every 2 weeks, 8 mg pegloticase every 4 weeks vs. placebo). The analysis was conducted based on Fisher's exact test. In addition, 95% confidence intervals for treatment differences of primary endpoint between pegloticase treatment and placebo groups was computed. If any subject withdrew from the study before month 6, they were considered non-responders for the primary efficacy endpoint, in the ITT population.

A time curve was used to estimate the proportion of time that PUA levels were < 6 mg/dL. Based on frequent plasma samples collected during Months 3 and 6, a robust estimate of the time PUA values remained < 6 mg/dL could be determined by connecting neighboring data points with a straight line. If PUA levels exceeded 6 mg/dL, linear interpolation was utilized to estimate the point in time when the PUA value intersected the 6 mg/dL line. Time points included in the analysis over months 3 and 6 were:

- Month 3: samples collected at Visit 6 (both pre-dose 5 and 2 hours post-dose), Visit 7 (24 hours post-dose 5), Visit 8 (7 days post-dose 5), Visit 9 (both pre-dose 6 and 2 hours post-dose 6), Visit 10 (7 days post dose 6) and Visit 11 (pre-dose 7).

- Month 6: samples collected at Visit 15 (both pre-dose 11 and 2 hours post-dose 11), Visit 16 (24 hours post-dose 11), Visit 17 (7 days post-dose 11), Visit 18 (both pre-dose 12 and 2 hours post-dose 12), Visit 19 (7 days post-dose 12) and Visit 20 (14 days post-dose 12).

If T1 is the total time interval in hours over month 3 and W1 hours is the time interval during which PUA levels remained below 6 mg/dL, and, similarly, T2 and W2 correspond to the same values over month 6, then the proportion of time that the PUA level is <6 mg/dL, i.e., percentage of non-hyperuricemic time, is mathematically calculated using:

$$\text{Proportion} = \frac{W1 + W2}{T1 + T2} * 100$$

If PUA levels were missing at Visits 6 (predose), 11, 15 (predose) or 20, baseline PUA levels for that subject were used for calculation. Analyses were carried out on observed values; without imputation for other missing PUA values. Statistical approaches described above for the primary endpoint were repeated for the per-protocol population.

Mean PUA and Reduction in Mean PUA

- Mean PUA level was defined as the area under the PUA time curve divided by the corresponding time interval. Area under the PUA time curve can be computed using the linear trapezoidal rule during months 3 and 6.
- Reduction in mean PUA was computed by subtracting baseline PUA level (pre-dose 1 PUA level) from mean PUA during months 3 and 6.
- Percent reduction in the mean PUA from baseline was computed as the mean PUA level during months 3 and 6 minus baseline PUA level divided by baseline PUA level multiplied by 100, i.e.

$$\text{Percent Reduction in mean PUA} = \frac{\text{Mean PUA during months 3 and 6} - \text{Baseline PUA}}{\text{Baseline PUA}} * 100$$

Mean PUA, reduction in mean PUA and percent reduction in the mean PUA from baseline during month 3 and month 6 are defined using the same approach. Pair-wise comparisons of percentage of non-hyperuricemic time, mean PUA, reduction in mean PUA and percent reduction in the mean PUA from baseline between pegloticase treatment groups (8 mg pegloticase every 2 weeks or 8 mg pegloticase every 4 weeks) versus placebo group were carried out using two sample t-test (assuming normality assumption is satisfied). Otherwise, analogous non-parametric techniques were used.

4.1.2.3 *Analysis of the Secondary Efficacy Endpoints in Individual and Pooled Analyses*

4.1.2.3.1 Resolution of Tophi

As the serum becomes supersaturated with urate, the material begins to deposit in the tissues. With some patients this not only leads to increased tissue stores of urate, but may lead to recurrent gout flares; however, in others this might lead to extensive tissue deposition which could lead to the development of a tophus (tophi) sitting in the periarticular tissues, on extensor surfaces, in the subperiorsteal space, in bursae, around the ear, or more rarely in the spinal cord, brain, or in organs. The resolution of these tophi has not been demonstrated with available urate-lowering therapies alone or in combination with urate-lowering therapies with a uricosuric in randomized controlled trials. This is thought to be through the resolubilization of uric acid from the tophus into blood as the serum uric acid levels are lowered by the therapy.

Baseline photographs of the hands and feet and other sites of tophaceous deposits were obtained in each subject prior to initial study drug administration in a standardized manner were submitted to the digital imaging vendor. Up to 5 measurable tophi, ≥ 5 mm at baseline in the longest dimension, with distinguishable borders in photographs were chosen by the central reader for assessment over the course of therapy. Up to 2 tophi representative of tophus burden which could not be precisely measured (e.g. due to location, shape or other factors) were also followed during the study – these globally measured tophi must have been approximately ≥10 mm at baseline to allow reliable assessment of change in size.

Follow-up photographs were obtained for tophi at weeks 13, 19 and 25, final visit or early termination. At each timepoint, these were assessed by the blinded central reader and compared

to baseline, including new appearance of a tophus not evident at baseline. Photographs were read in "sequential locked read" format, programmatically controlled by software that prohibited the reader from changing the previous evaluation. Most tophi were precisely assessed bi-dimensionally (using longest diameter and longest perpendicular to that diameter) and response of each individual tophus categorized according to change from baseline in area of each tophus at each visit. Some tophi were unable to be precisely quantified as their margins could not be precisely defined. These tophi were assessed for global change. Determinations of each indiviual tophus were based on the following criteria (Table 8).

Table 8. Definition of Individual Tophus Response.

Assessments	Precisely Measured Tophus*	Globally Measured Tophus**
Complete Response (CR)	100% decrease in area of tophus	Disappearance of tophus
Marked Response (MR)	≥75% decrease in area of tophus	
Improved (I)		≥50% reduction in size of tophus
Partial Response (PR)	≥50% decrease in area of tophus	
Stable Disease (SD)	Neither 50% decrease nor 25% increase in area of tophus	Neither improvement nor progression from baseline
Progressive Disease (PD)	≥25% increase in area of tophus	≥50% increase in area of tophus
Unable to Evaluate (UE)	tophus cannot be accurately measured at any time point	Tophus cannot be assessed for any reason at any time point

*Referred to in the BLA submission as "Measurable".
** Referred to in the BLA submission as "Unmeasured".

Overall response for a subject was based upon the best response among all tophi (precisely measured and globally measured) for that subject and categorized as presented in (Table 9). Individual and overall tophi responses were sumarized by visit; number of subjects with resolution of any tophus and time to tophus resolution were summarized by treatment group.

Table 9. Definition of Tophus Response in Individual Patients.

Overall Assessment	Determination of Overall Assessment
Complete Responder (CR)	If CR (no PD) for either precisely measured or globally measured tophus
Partial Responder (PR)	If MR or PR (no CR, PD) for precisely measured or improved for globally measured tophus
Stable Disease (SD)	If SD (no CR, PR, PD) for either precisely measured or globally measured tophus
Progressive Disease (PD)	If PD for any precisely measured or globally measured tophus, or if any new tophus appears during study treatment
Unable to Evaluate (UE)	If UE for all precisely measured or globally measured tophus

Numbers of subjects with an overall tophi response of CR (i.e., responder) were compared between each of the pegloticase dose groups against the placebo group using the Fisher's exact test. In addition, the overall tophi response such as CR, PR, SD, or PD were assigned an ordinal

score of 1, 2, 3, or 4, and the two-sample Wilcoxon test were used to compare each of the pegloticase dose groups against the placebo group for the tophus assessment.

Time to tophus resolution was defined as the earliest time at which a complete resolution was demonstrated in one target tophus. Subjects without tophus resolution were excluded from this analysis. Kaplan-Meier plots were presented by treatment for the time point stated above.

4.1.2.3.2 Incidence and Frequency of Gout Flares

The phase 3 protocols required self-reported gout flares to be investigator-confirmed through questioning or direct observation if feasible. Some flares may have been completely resolved before physician's examination. The occurrence, severity and duration of each confirmed flare were captured in order to allow an analysis of the flare activities by month between the three treatment arms.

The number of gout flares reported each month during the study were summarized by treatment groups. It was expected that subjects treated with pegloticase may experience more flares during the first 3 months, in spite of mandated gout flare prophylaxis, and the flare incidences will decrease during the second 3 months. Therefore the number of gout flares during the first 3 and second 3 months were analyzed separately for treatment differences using the two-sample t-test comparing each of the pegloticase groups to placebo. The number of subjects reporting flares were compared between each of the pegloticase dose groups against the placebo group using the Fisher's exact test. Furthermore, within-group comparisons for each treatment group between the numbers of gout flares during the first 3 and second 3 months were carried out using the one sample paired t-test.

4.1.2.3.3 Tender or Swollen Joint Counts

Assessing the number of tender or swollen joints is a clinical method of quantifying the amount of inflamed synovial tissue. As joint swelling and tenderness vary from case to case and time to time in the same patient, both were analyzed separately and together. Number of tender or swollen joints were summarized using descriptive statistics (number of observations, mean, median, standard deviation, minimum and maximum values) at baseline and at weeks 13, 19 and 25.

4.1.2.3.4 Clinician Global Assessment of Disease Activity

The Clinician Global Assessment (CGA) of disease activity was quantified using a 100-mm visual analogue scale (VAS), from 0 (very good) to 100 (very bad) in response to the query: "Considering disease activity alone, mark on the line below how well the subject is doing". Clinician global assessment was summarized using descriptive statistics (number of observations, mean, median, standard deviation, minimum and maximum values) at baseline, at weeks 13, 19 and 25.

Pair-wise comparisons of physician global assessment, and the mean number of tender or swollen joints between pegloticase treatment groups (8 mg pegloticase every 2 weeks or 8 mg pegloticase every 4 weeks) to placebo used two sample t-test. In addition, changes from baseline at weeks 13, 19 and 25 were analysed using the linear model where treatment was considered as

a fixed factor and baseline values as a covariate. Furthermore, within group comparisons for each treatment group used one sample paired t-tests.

4.1.2.3.5 Patient Reported Outcomes

Patient reported outcomes, including global assessment of disease activity, pain, physical function by Health Assessment Questionnaire Disability Index (HAQ DI) and HRQOL or multi-dimensional function by SF-36 were scored at baseline at weeks 13, 19 and 25. The SAP pre-specified a pooled analysis of treatment groups across both phase 3 RCTs, using an ITT-LOCF approach. Results for SF-36 are presented using available data from those patients with data at baseline, and Weeks 13, 19 and 25.

4.1.2.3.6 Patient Global Assessment of Disease Activity (by VAS)

Patient Global Assessment of Disease Activity (PGA) was queried by: "in all the ways your disease affects you today, how are you doing?" using a 100-mm VAS scale, where 0 = very well and 100 = very poorly. A 10 mm improvement in VAS scores is considered to represent minimum clinically important difference (MCID), eg, improvement perceptible to patients [31, 33]. The proportion of subjects reporting improvements meeting or exceeding MCID was analyzed.

4.1.2.3.7 Patient Reported Pain (by VAS)

Patient assessment of pain used a 100-mm VAS scale (0 = no pain to 100 = severe pain). A 10 mm improvement in VAS scores is generally considered to represent MCID.[33, 34] The proportion of subjects reporting improvements ≥MCID was analyzed.

4.1.2.3.8 Physical Function – by HAQ DI

The Health Assessment Questionnaire Disability Index (HAQ DI) is well-validated and has been extensively used in RCTs and longitudinal observational studies (LOS) in patients with rheumatoid arthritis and other rheumatologic conditions, and demonstrated to fulfill the OMERACT filter in gout [35-38]. The HAQ DI queries patients' ability to perform activities of daily living as well as the need for help or use of functional aids. 20 questions assess 8 domains: dressing, arising, eating, walking, hygiene, reach, grip, and activities, from "0" no impairment to "3" unable to do. The highest scores for each of domain are summed (range from 0 to 24) and divided by 8 to yield, on a continuous scale, a Disability Index with a range from 0 to 3. An improvement of -0.22 is considered to represent MCID [33, 39, 40]. The proportion of subjects reporting improvements ≥MCID was analyzed.

Pair-wise comparisons of patient global assessment, pain and HAQ DI scores between pegloticase treatment groups versus placebo used two sample t-test. Changes from baseline in PGA, pain and HAQ DI were summarized using descriptive statistics. In addition, changes from baseline were analyzed using a linear model where treatment is considered as a fixed factor and baseline value as a covariate. Furthermore, within-group comparison at different visits were carried out using one sample t-test. Subjects reporting improvements ≥MCID, eg ≥ 10 in PGA, ≥ 10 in Pain and/or ≥ - 0.22 in HAQ DI scores were considered "responders". Fisher's exact test compared treatment differences in responder rates for each and combined patient reported outcomes.

4.1.2.3.9 Health Related Quality of Life (HRQOL) – by Medical Outcomes Survey Short Form 36 (SF-36)

The Short Form-36 (SF-36) is a well-validated measure of HRQOL, or "multidimensional function" and has been extensively used in RCTs and LOS of a variety of medical conditions including hypertension, cardiovascular disease, diabetes[41] as well as rheumatoid arthritis [35, 39], osteoarthritis [23, 24] systemic lupus erythematosus [44], psoriatic arthritis[37], systemic sclerosis [37], and most recently gout [45, 6]. SF-36 comprises 8 domains: Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GHP), Vitality (VT), Social Functioning (SF), Role Emotional (RE), and Mental Health (MHI), which are aggregated into two summary scores - Physical Component Summary (PCS), and Mental Component Summary (MCS) scores. The PCS score positively weights the 4 "physical domains": PFI, RP, BP and GHP, as well as VT; negatively weighting the remaining mental domains. The MCS score positively weights the 4 mental domains: VT, RE, SF amd MHI and negatively weights the physical domains.

A common approach in establishing an MCID is to anchor the measure of interest (e.g. PCS) to actual patient ratings of improvement in the disease population of interest. Values for MCID in domain and summary scores (PCS and MCS) of SF-36 have been derived in rheumatoid arthritis, osteoarthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, fibromyalgia syndrome and gout, based on correlations with patient reported improvements in global disease activity or condition, on an individual patient basis. Improvements of 5 to 10 in domain scores and 2.5 to 5 in PCS and MCS summary scores can be considered to represent MCID in rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and gout, based on correlations with patient global assessments of disease activity and/or Guyatt 'feeling thermometer'[32, 36, 39, 42, 43, 46, 47]. The proportion of subjects reporting improvements ≥ MCID was analyzed.

Pair-wise comparisons of PCS, MCS and domain scores between pegloticase treatment groups versus placebo used two sample t-test. Mean changes from baseline were analyzed using the linear model where treatment is considered as a fixed factor and baseline value as a covariate. Furthermore, within-group comparison at different visits were carried out using one sample t-test.

4.1.2.4 *Statistical Analyses of Phase 3 Data and Pooled Analysis*

Demographic and baseline characteristics by treatment group are descriptively summarized in ITT and per-protocol populations. For continuous variables, descriptive statistics will include: number of observations, mean, standard deviation, median, minimum and maximum values; and by analysis of variance (ANOVA) to compare all three groups. Categorical variables were summarized by frequency count, percentages of each possible response and comparison of treatment groups by Chi-square test. Hypotheses testing utilized a Type I error rate of 0.05. All statistical tests were performed as two-sided tests, unless explicitly described otherwise.

SAS programs and log files, tables, listings, figures and derived data set were validated by an independent Biostatistician or Statistical Programmer. All statistical analyses were performed using SAS version 8.2 (or higher) statistical package.

4.2 Phase 3 Efficacy Results

Data will be presented in two different formats. For the primary efficacy outcome, the data are presented by individual study outcomes and in a pooled analysis. For the secondary outcomes, the data is pooled as pre-defined in the SAP and in agreement with FDA. These data are presented pooled by treatment group across studies; individual study data are provided in the same tables. While all data are presented, the focus of the discussion in this section will be on the pegloticase 8 mg every 2 weeks group in comparison to the placebo group as the benefit to risk ratio favors that dose of pegloticase.

4.2.1 Patient Population

In the phase 3 studies, 225 subjects were randomized and 212 subjects with treatment failure gout were treated with either:

- 8 mg pegloticase every 2 weeks: 85 subjects;
- 8 mg pegloticase every 4 weeks: 84 subjects;
- Placebo: 43 subjects

The demographic and baseline characterisitics of the Phase 3 study populations are shown in Tables 9, 10 and 11. These data are shown for the combined groups. Active and placebo treatment groups were well balanced with respect to demographic and baseline characteristics in the safety, intent to treat and per protocol populations and for the individual studies and pooled analyses.

4.2.1.1 *Baseline Demographics and Physical Characteristics*

Baseline demographics are shown in Table 10.

Table 10. Baseline Demographics for Pooled RCTs and Individual Studies.

	Pegloticase		Placebo
	8 mg q 2 weeks	8 mg q 4 weeks	
Pooled RCTs			
	N=85	N=84	N=43
Age (years), mean	56.3	54.5	55.4
Ethnic origin, White	54 (64%)	59 (70%)	30 (70%)
Gender, male	68 (80%)	69 (82%)	36 (84%)
BMI (kg/m2), mean	33	33	32
Study C0405			
	N=43	N=41	N=20
Age (years), mean	58.2	55.1	57.2
Ethnic origin, White	32 (74%)	32 (78%)	14 (70%)
Gender, male	30 (70%)	35 (85%)	15 (75%)
BMI (kg/m^2), mean	35	34	33
Study C0406			
	N=42	N=43	N=23
Age (years), mean	54.3	53.9	53.8
Ethnic origin, White	22 (52%)	27 (63%)	16 (70%)
Gender, male	38 (91%)	34 (79%)	21 (91%)
BMI (kg/m2), mean	31	32	31

The burden of gout symptoms in subjects enrolled in the phase 3 RCTs was very severe. Subjects reported on average approximately 10 acute gout flares over the 18 months prior to study entry; 73% the presence of tophi; 63% considered their gout flares to be “crippling”; and 58% suffered from chronic pain and synovitis/arthropathy. Baseline gout characteristics are shown in Table 11.

There were differences between the individual studies with regard to baseline disease characteristics and the groups became balanced in the pooled analyses. These between study differences were noteable for HAQ DI, subjects failing allopurinol and crippling flares.

Table 11. Baseline Gout Characteristics in the Pooled RCTs and Individual Studies.

	Pegloticase		Placebo
	8 mg q 2 weeks	8 mg q 4 weeks	
Pooled RCTs			
	N = 85	**N = 84**	**N = 43**
Allopurinol contraindication	81%	80%	88%
Allopurinol ineffective	19%	20%	12%
Mean time since gout diagnosis	15 years	16 years	13 years
Mean # of tender joints	11.7	11.1	14.2
Mean # of swollen joints	8.9	10.1	13.3
HAQ DI	1.10	1.21	1.24
Mean # of acute flares in 12 months	6.5	6.4	6.8
Subjects reporting "crippling flares"	63%	66%	57%
Tophi present	73%	76%	67%
Chronic synovitis/arthropathy	59%	56%	61%
Study C0405			
	N = 43	**N = 41**	**N = 20**
Allopurinol contraindication	93%	83%	90%
Allopurinol ineffective	7%	17%	10%
Mean time since gout diagnosis	16 years	16 years	12 years
Mean # of tender joints	13	12	15
Mean # of swollen joints	9	11	14
HAQ DI	1.08	1.38	1.66
Mean # of acute flares in 12 months	7	7	9
Subjects reporting "crippling flares"	72%	70%	63%
Tophi present	67%	76%	70%
Chronic synovitis/arthropathy	63%	56%	65%
Study C0406			
	N = 42	**N = 43**	**N = 23**
Allopurinol contraindication	69%	77%	87%
Allopurinol ineffective	31%	23%	13%
Mean time since gout diagnosis	15 years	16 years	15 years
Mean # of tender joints	11	10	13
Mean # of swollen joints	8.5	9	12
HAQ DI	1.13	1.05	0.87
Mean # of acute flares in 12 months	6	6	5
Subjects reporting "crippling flares"	54%	62%	50%
Tophi present	79%	77%	65%
Chronic synovitis/arthropathy	55%	56%	57%

This TFG population was also characterized by a very high prevalence of medical co-morbidities. Baseline pre-exisiting co-morbidities are shown in Table 12. There were eleven subjects who reported having pre-existing myocardial infarction (three subjects in the pegloticase q 2 weeks group, four subjects in the pegloticase q 4 weeks group, four subjects in placebo

group) and four subjects with cerebral vascular accident (two subjects in the pegloticase q 2 weeks group, one subject in the pegloticase q 4 weeks group, one subject in placebo group).

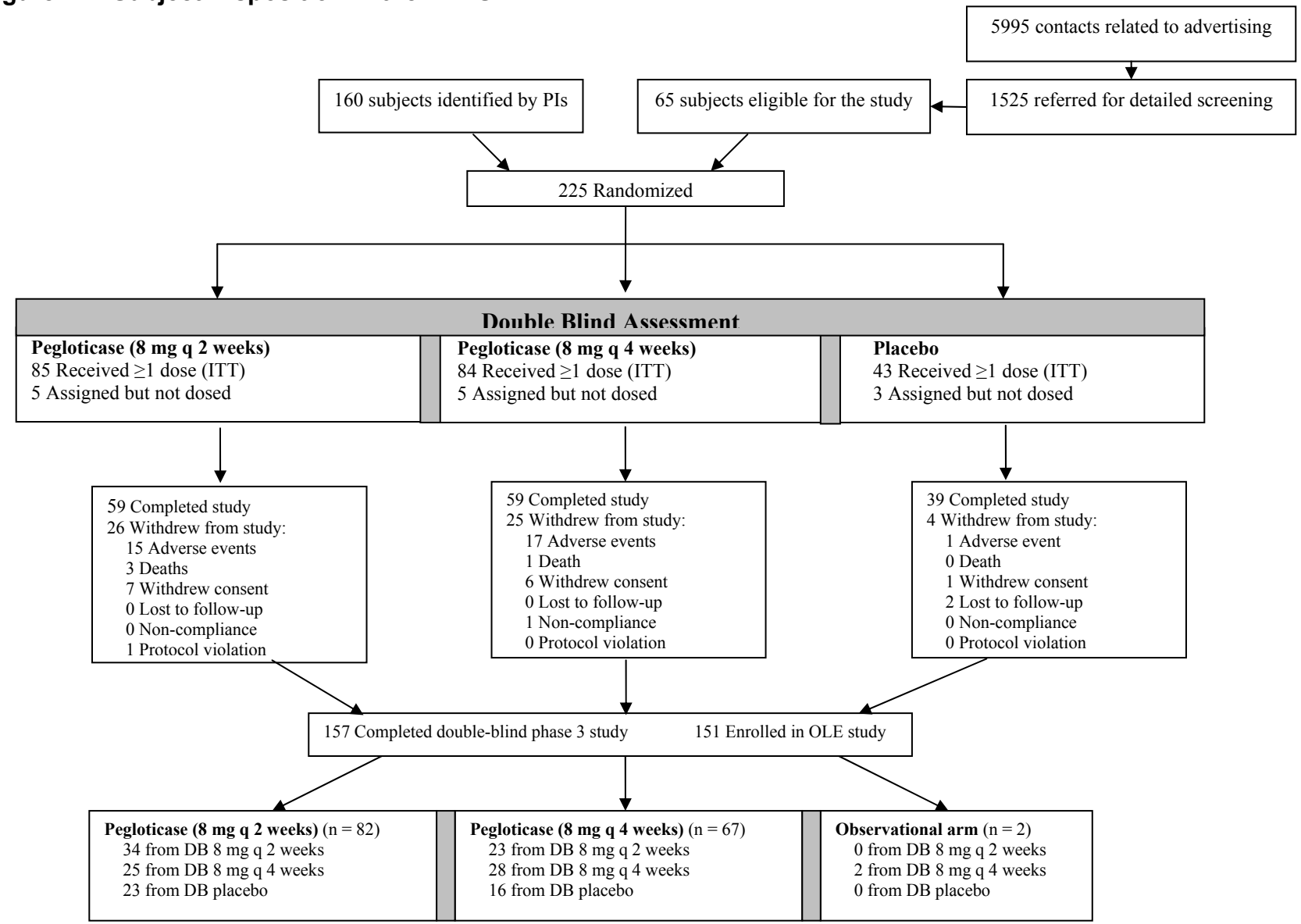
Table 12. Baseline Co-morbidities in Pooled RCTs.

Medical Condition	Pegloticase		Placebo	Total
	8 mg q 2 weeks N=85 n (%)	8 mg q 4 weeks N=84 n (%)	N=43 n (%)	N= 212 n (%)
Subject having at least one of the following cardiovascular conditions or risk factors	72 (85%)	71 (85%)	35 (81%)	178 (84%)
Hypertension	62 (73%)	60 (74%)	31 (72%)	153 (72%)
Dyslipidemia	42 (49%)	41 (49%)	20 (46%)	103 (49%)
Diabetes	24 (28%)	18 (21%)	8 (19%)	50 (24%)
Cardiac arrhythmias	19 (22%)	8 (9%)	7 (16%)	34 (16%)
Coronary artery disease	14 (16%)	16 (19%)	9 (21%)	39 (18%)
Cardiac failure/ LV dysfunction	12 (14%)	8 (9%)	6 (14%)	26 (12%)
Peripheral vascular disease	7 (8%)	6 (7%)	3 (7%)	16 (8%)
Cerebrovascular disease	4 (5%)	3 (4%)	1 (2%)	8 (4%)
Obesity (BMI ≥ 30)	50 (59%)	55 (65%)	24 (59%)	129 (61%)
Osteoarthritis	29 (34%)	23 (27%)	16 (37%)	68 (32%)
Chronic kidney disease (calculated CrCL < 60 mL/min)	26 (30%)	25 (30%)	9 (21%)	60 (28%)
Sleep apnea	8 (9%)	9 (11%)	6 (14%)	23 (11%)
Venous thromboembolic disease	3 (3%)	2 (2%)	2 (5%)	7 (3%)

4.2.1.2 *Phase 3 Disposition*

Subject disposition is presented in Figure 14.

Figure 14. Subject Disposition in the RCTS.



4.3 Primary Outcome: Responders by PUA <6.0 mg/dL ≥80% of the time during Months 3 and 6.

Pegloticase was shown effective in both phase 3 RCTs and in the pooled analysis (Table 13). Significantly more subjects in both pegloticase q 2 weeks and q 4 weeks treatment groups were persistent responders compared with placebo.

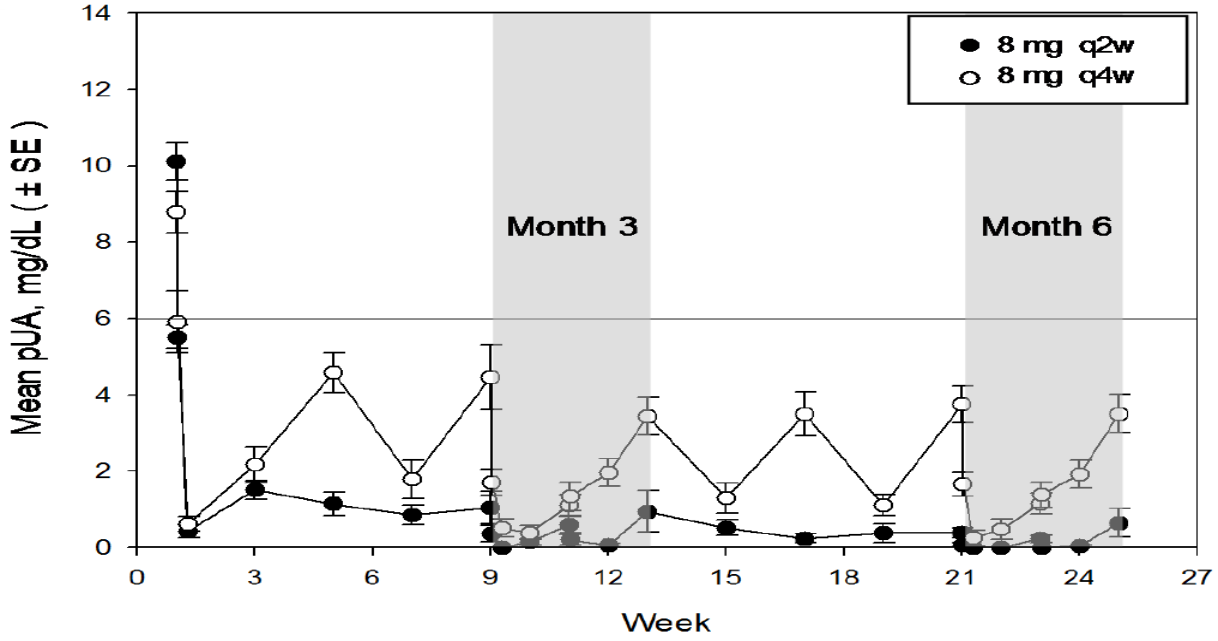
Table 13. PUA Response in Phase 3 Studies.

Study C0405			
	N	**Persistent PUA responders**	**p-value**
Pegloticase 8 mg q 2 weeks	43	47%	< 0.001
Pegloticase 8 mg q 4 weeks	41	20%	0.044
Placebo	20	0%	
Study C0406			
	N	**Persistent PUA responders**	**p-value**
Pegloticase 8 mg q 2 weeks	42	38%	< 0.001
Pegloticase 8 mg q 4 weeks	43	49%	< 0.001
Placebo	23	0%	
Pooled Data			
	N	**Persistent PUA responders**	**p-value**
Pegloticase 8 mg q 2 weeks	85	42%	< 0.001
Pegloticase 8 mg q 4 weeks	84	35%	< 0.001
Placebo	43	0%	

In all subjects administered pegloticase, rapid reductions resulted in normalization of PUA levels in the first day (Figures 15 and 16). There were two groups of responders, referred to as persistent responders and transient responders. In persistent responders PUA values decreased rapidly and were sustained and maintained < 6 mg/dL for 80% of the 6-month study period (Figure 15). In transient responders, initial rapid reductions in PUA levels were followed by increases on or after Week 3 in those receiving pegloticase q 4 weeks compared with Week 10 in subjects receiving pegloticase q 2 weeks. Loss of PUA response is attributable to more rapid clearance of drug due to the presence of anti-pegloticase antibodies (see Immunogenicity section 5.6.3).

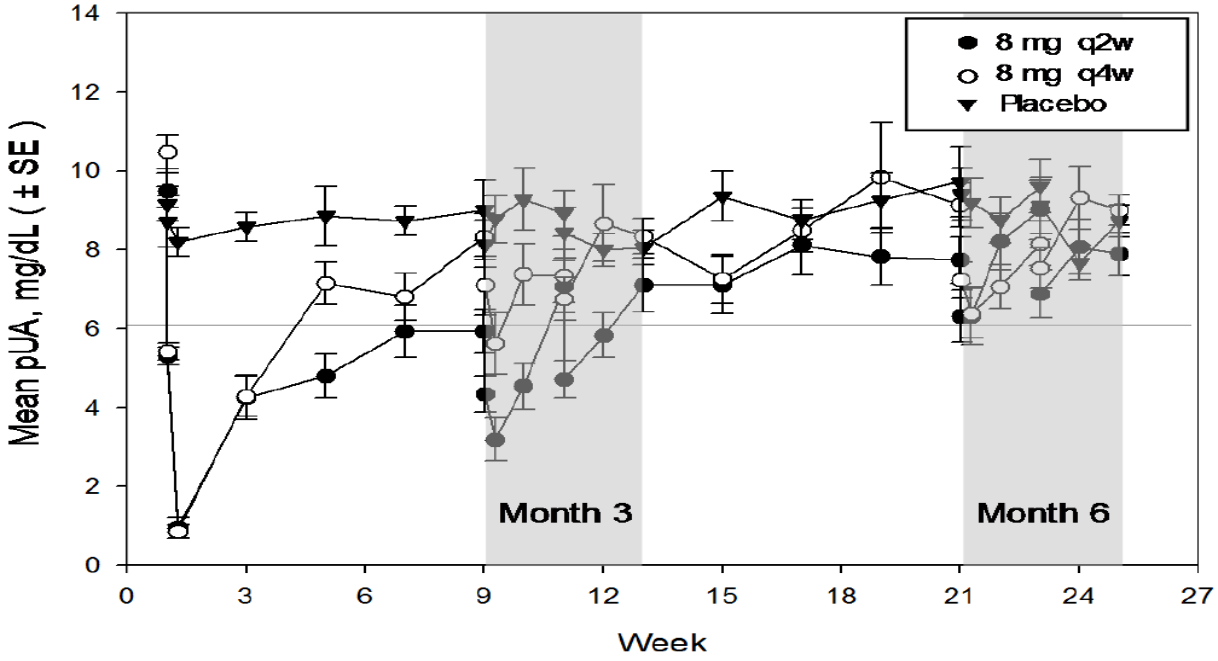
In comparison (Figure 16), mean PUA levels in placebo subjects never normalized.

Figure 15. Mean (± SEM) PUA: Persistent Responders in Phase 3 Studies.



Subjects per group: Pegloticase 8 mg q 2 weeks, n=36, Pegloticase 8 mg q 4 weeks, n=29

Figure 16. Mean (± SEM) PUA: Transient Responders in the Phase 3 Studies.



Subjects per group: Pegloticase 8 mg q 2 weeks, n=23; Pegloticase 8 mg q 4 weeks, n=30; Placebo, n=39

A majority (151 of 157) of subjects that completed the RCT enrolled into the OLE.

All thirty-nine subjects that received placebo in the RCT and completed the study enrolled into the OLE Study. Twenty-three sujects elected to receive pegloticase 8 mg q 2 weeks while 16 subjects elected to receive pegloticase 8 mg q 4 weeks. Figures 17 and 18 provide the mean data

from those subjects. Although fewer samples were obtained, as per protocol, in the OLE Study, these patterns of PUA response to pegloticase every 2 or 4 weeks appear to be similar to those subjects that received pegloticase at these dosing schedules in the RCTs.

Figure 17. Mean (± SEM) PUA: Subjects That Received Placebo in RCTs and Pegloticase 8 mg Every 2 Weeks in the OLE Study.

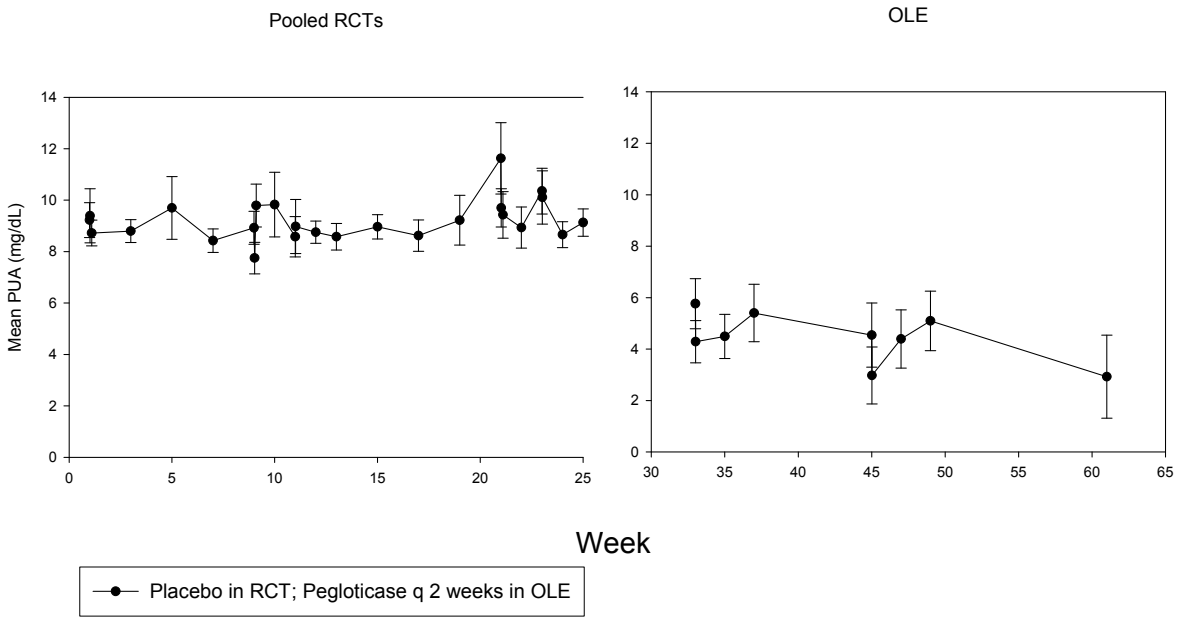
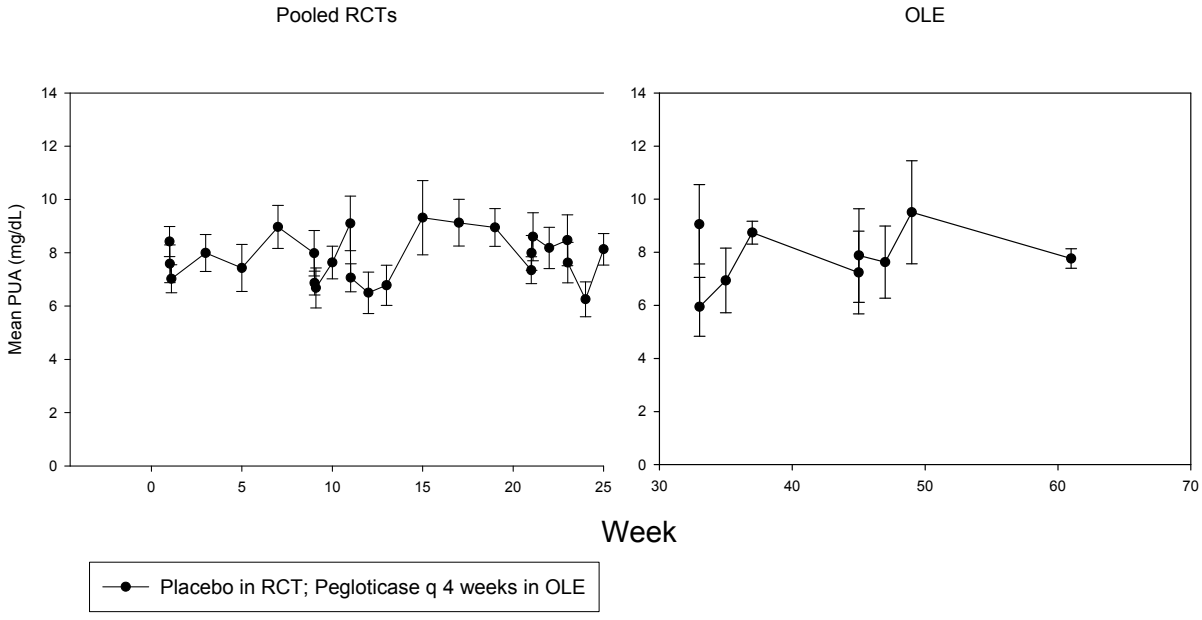


Figure 18. Mean (± SEM) PUA Subjects That Received Placebo in RCTs and Pegloticase 8 mg Every 4 Weeks in the OLE Study.



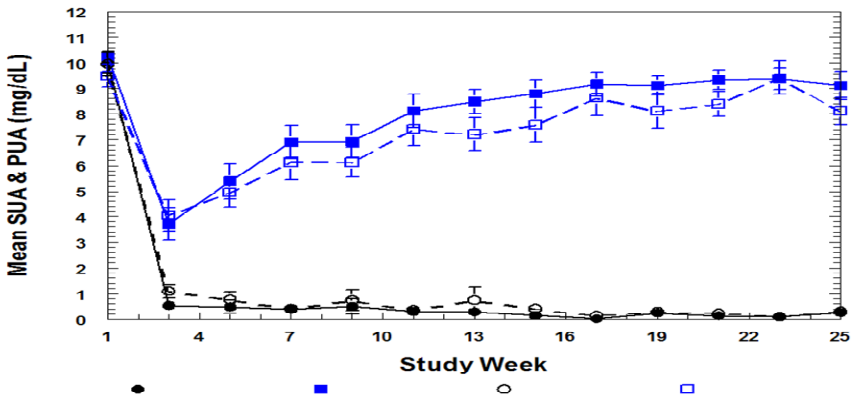
4.3.1 Relationship between Plasma and Serum Uric Acid Values

The relationship between measured plasma uric acid (PUA) and serum uric acid (SUA) values was evaluated from serial samples from all subjects in both pivotal phase 3 studies and in the OLE Study C0407 which was the open label extension. The rationale for this evaluation related to the use of PUA as the measure for the primary endpoint for all pegloticase trials while SUA is used in clinical practice. The handling and processing of samples for PUA determination is much more involved, and this processing was performed at low temperature and utilized trichloroacetic acid to inactivate and precipitate pegloticase so the drug did not continue to oxidize uric acid. In the OLE Study, the serum samples were treated as they normally are in the clinical setting. In addition, another set of serum samples were frozen after processing and remained frozen until analysis.

Figure 19 contains the mean (± SEM) values at various times for both SUA and PUA determinations in subjects that were persistent or transient responders. There was a close correlation between both uric acid values at all time points and irrespective of the uric acid values. The relationship between the two parameters is close, as presented in Figures 20 and 21. The correlation between the two uric acid determinations (PUA and SUA) is $r^2 = 0.65$ (phase 3) and $r^2 = 0.88$ (OLE Study). The rate at which false positives (i.e. subjects that has a PUA > 6 mg/dL and a SUA < 6 mg/dL) is rare (1%).

Importantly, the handling of samples for the determination of SUA in study C0407 (Figure 21) closely mimics the clinical situation in which ambient serum samples were analyzed for SUA. These data support the use of SUA in clinical practice when making decisions regarding pegloticase use.

Figure 19. Relationship Between PUA and SUA Levels (Mean ± SEM) in Persistent and Transient Responders in Pegloticase 8 mg Every 2 Weeks Treatment Group in Pooled Phase 3 RCTs.



Legend:
PUA values: Open circles and Boxes
SUA values: Solid circles and Boxes
Persistent Responders: Circles
Transient Responders: Boxes

Figure 20. Relationship Between PUA and SUA Values in Subjects (n=2352 samples) in all Treatment Groups in Phase 3 RCTs.

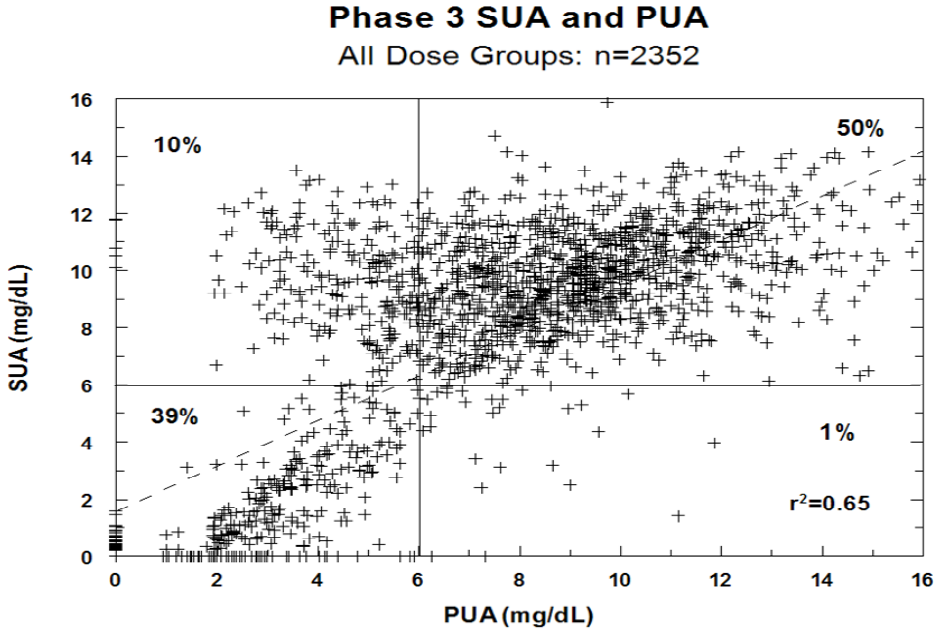
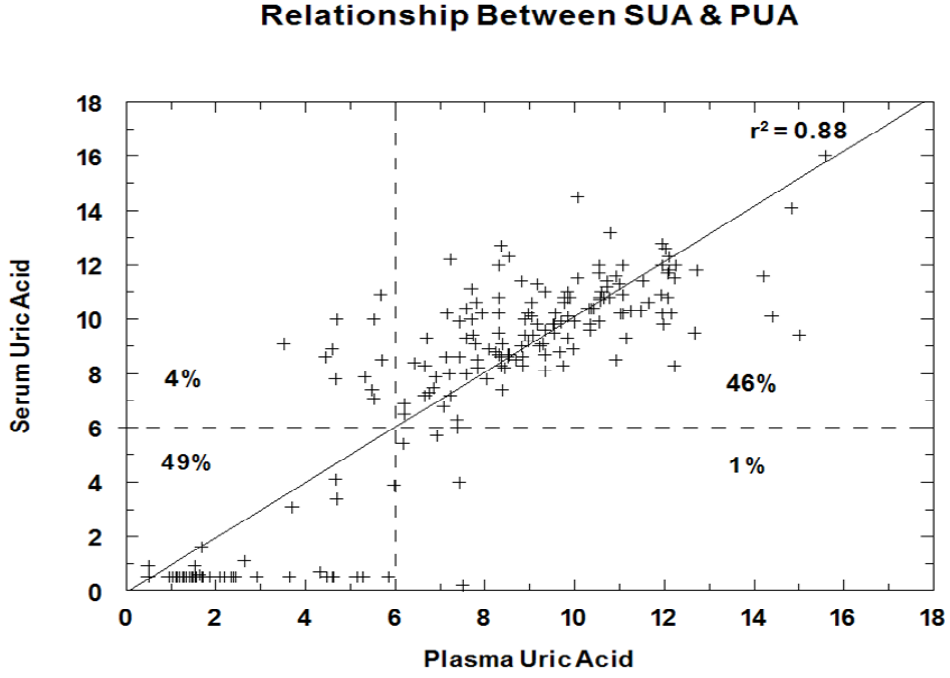


Figure 21. Relationship Between PUA and SUA Values in Subjects (n=247 samples) in all Treatment Groups in Open Label Extension Study C0407.



4.3.2 Durability of PUA Responses

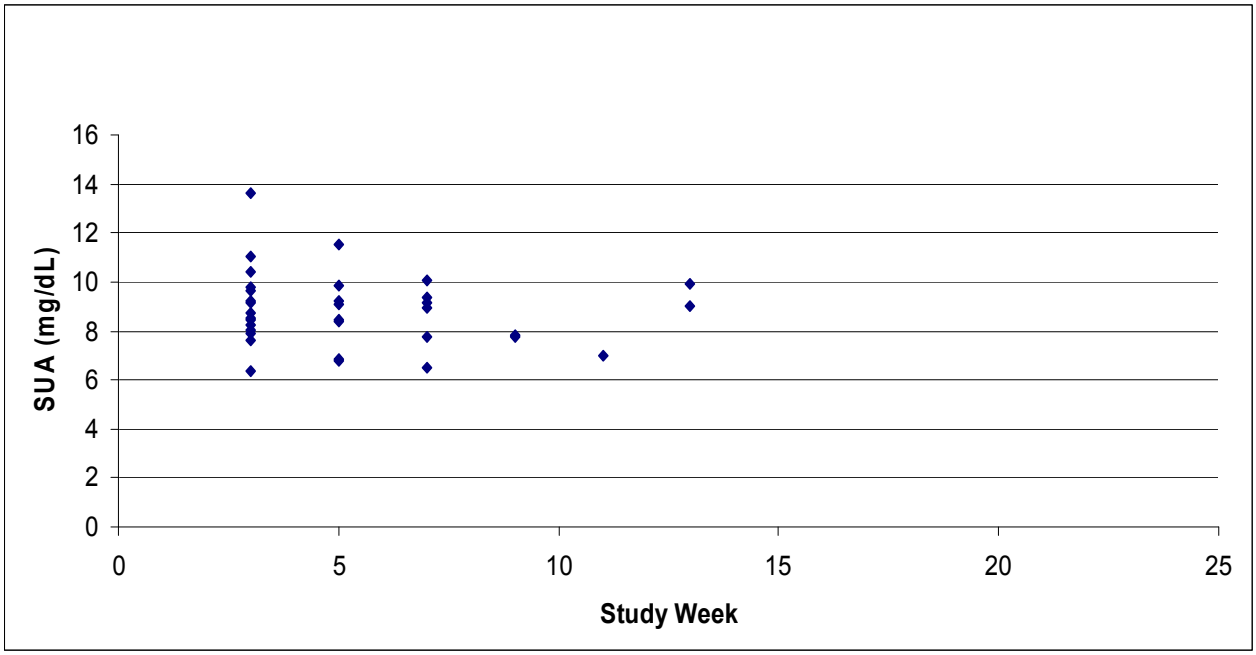
Most (43 of 48 subjects) persistent responders in the RCTs maintained PUA levels < 6 mg/dL during OLE treatment; 5 of 48 subjects did not: one (4.3%) subject who received pegloticase q 2 weeks in both RCT and OLE Study; 2 (11.1%) who switched from pegloticase q 2 weeks to pegloticase q 4 weeks, and two (8.7%) who received pegloticase q 4 weeks in both.

4.3.3 Clinical Guidance Regarding Pegloticase Treatment

Although all patients have a first dose response to pegloticase, in those subjects with transient responses to pegloticase, loss of response occurs within 3 months. In subjects who are transient responders, many have PUA levels > 6 mg/dL within the first 3 months (Figures 22 and 23). Therefore, in labeling we propose that SUA levels be assessed prior to each infusion, and if > 6 mg/dL, pegloticase treatment should be discontinued. Frequent monitoring of SUA is recommended over the first 3 months following initiation of pegloticase treatment.

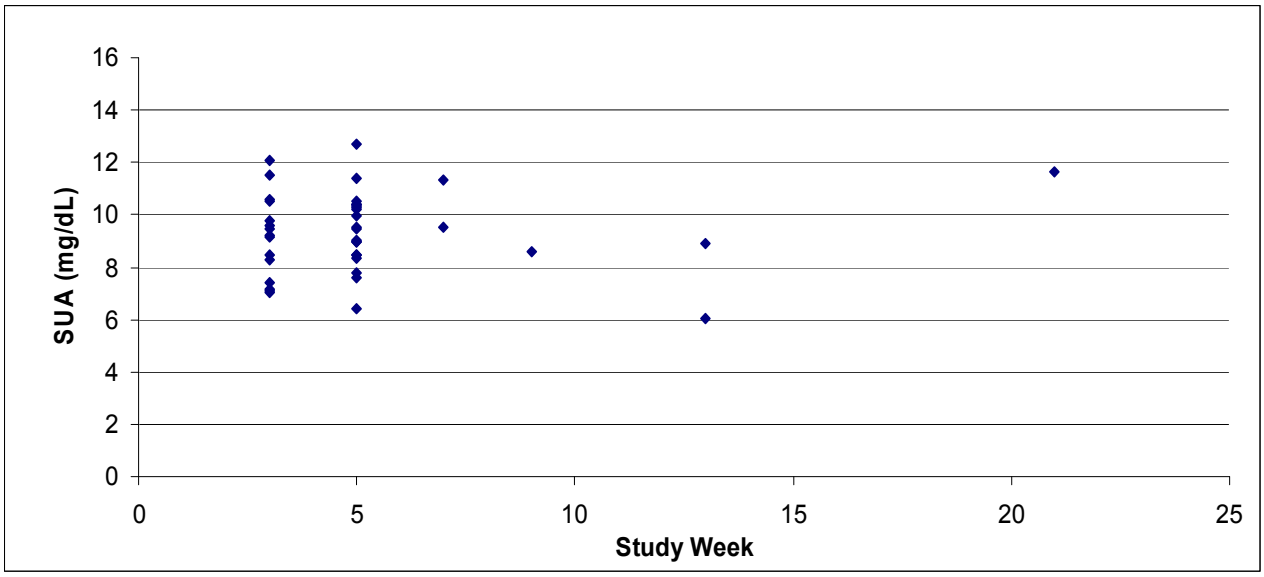
Furthermore, pegloticase 8 mg should be adminsitered every 2 weeks. The relationship between uric acid values, infusion reactions and anti-pegloticase antibodies will be discussed in more detail in the sections that follow.

Figure 22. Transient Responders to Pegloticase 8 mg every 2 weeks in RCTs: First Incidence when SUA levels > 6 mg/dL.



Each point represents an individual transient responder.

Figure 23. Transient Responders to Pegloticase 8 mg every 4 weeks in RCTs: First Incidence when SUA levels > 6 mg/dL.



Each point represents an individual transient responder.

4.3.4 Conclusions Regarding Normalization of PUA Levels

Normalization of PUA levels over 6 months treatment occurred in both pegloticase q 2 weeks and pegloticase q 4 weeks treatment groups, in a population with whom hyperuricemia was not controlled with conventional ULT. Importantly, there were no subjects in the placebo group with a PUA response providing evidence that this measure is reliable and specific to the effect of pegloticase administration.

4.4 Secondary Endpoint: Tophi

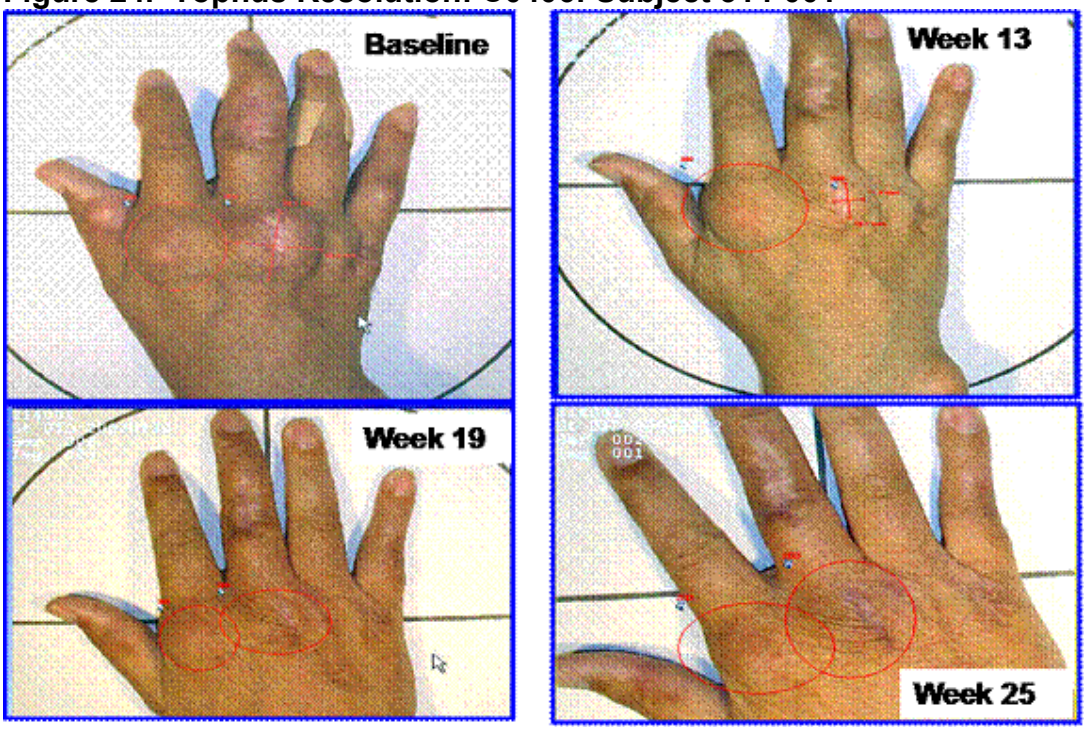
4.4.1 Tophus Resolution

In those subjects with tophi at baseline, the proportion with complete resolution of ≥ one tophus (without progression or appearance of any new tophus) at final visit was highly significant for pegloticase 8 mg q 2 weeks compared to placebo (Table 14). Figure 24 exemplifies a patient who received pegloticase q 2 weeks with a complete tophus resolution.

Table 14. Tophus Resolution (Individual RCTs and Pooled Analysis).

Pooled			
	N	**Tophus Complete Resolution**	**p-value**
Pegloticase 8 mg q 2 weeks	52	21 (40%)	0.002
Pegloticase 8 mg q 4 weeks	52	11 (21%)	0.200
Placebo	27	2 (7%)	-
Study C0405			
	N	**Tophus Complete Resolution**	**p-value**
Pegloticase 8 mg q 2 weeks	26	8 (31%)	0.035
Pegloticase 8 mg q 4 weeks	23	5 (22%)	0.136
Placebo	13	0	-
Study C0406			
	N	**Tophus Complete Resolution**	**p-value**
Pegloticase 8 mg q 2 weeks	26	13 (50%)	0.040
Pegloticase 8 mg q 4 weeks	29	6 (21%)	1.000
Placebo	14	2 (14)	-

Figure 24. Tophus Resolution: C0406: Subject 314-001



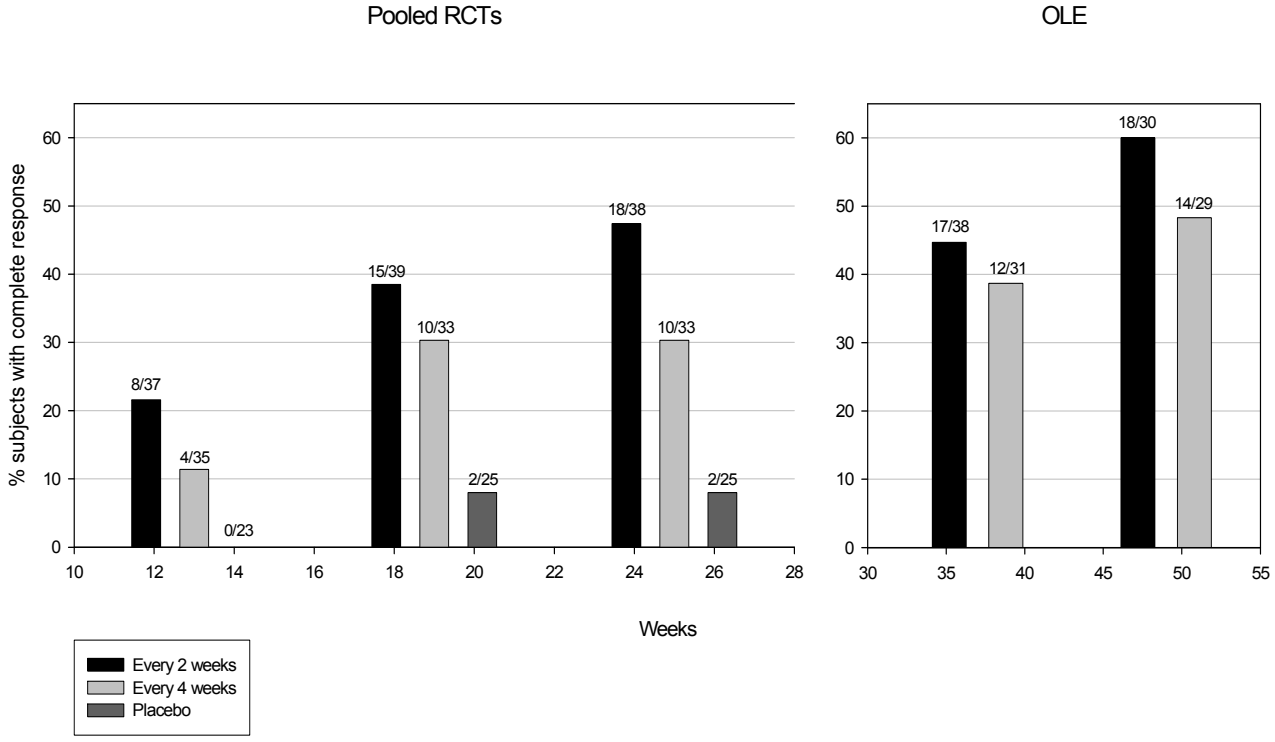
4.4.2 Durability of Tophus Resolution

With continued pegloticase treatment in the OLE, further resolution of tophi was documented. Upon continued treatment with pegloticase in the OLE Study, an addditional 12 subjects that

received pegloticase and completed the RCTs and enrolled into the OLE demonstrated a CR in Overall Tophus Response for the first time in the OLE Study.

Among the previously placebo-treated subjects who switched to pegloticase treatment in the OLE Study, there were eight subjects that demonstrated an Overall Tophus Response of CR (Figure 25). In 3 subjects tophi worsened in OLE treatment: one subject who continuously receiving treatment with pegloticase q 2 weeks, and two initially treated with pegloticase q 4 weeks and subsequently switched to q 2 weeks administration.

Figure 25. Proportion of Subjects with Complete Tophus Resolution during RCTs Who Continued To Receive Pegloticase in the OLE Study.



Treatment group assignment by initial randomization
n/N = Number of subjects with complete tophus resolution/Number of subjects with measurement

4.4.3 Conclusions: Tophus Resolution

Treatment with pegloticase q 2 weeks was associated with statistically significantly more complete responders of tophi in pooled analysis and both RCTs compared with placebo.

4.5 Secondary Endpoint: Gout Flares

4.5.1 Gout Flare Incidence and Frequency

At baseline, subjects reported a mean of 10 gout flares over the prior 18 months and 63% reported these to be of crippling severity. During Months 1-3, as with use of other urate-lowering drugs, the incidence (Table 15) and frequency (Table 16) of gout flares significantly increased in both pegloticase dose groups relative to placebo. Over Months 4-6, treatment with pegloticase q

2 weeks resulted in a significant decrease in both incidence and fequency of flares compared with placebo in combined analysis and in one (C0405) study.

Table 15. Incidence of Gout Flares During Months 1-3 and Months 4-6 in Pooled RCTs and Individual Studies.

	Months 1-3			Months 4-6		
	n/N[a]	Incidence	p-value[1]	n/N	Incidence	p-value
Pooled Data						
Pegloticase 8 mg q 2 weeks	64/85	75%	0.016	28/69	41%	0.007
Pegloticase 8 mg q 4 weeks	68/84	81%	0.002	39/69	57%	0.321
Placebo	23/43	54%	-	29/43	67%	-
C0405						
Pegloticase 8 mg q 2 weeks	31/43	72%	0.390	11/37	30%	0.002
Pegloticase 8 mg q 4 weeks	31/41	76%	0.242	20/33	61%	0.375
Placebo	12/20	60%	-	15/20	75%	-
C0406						
Pegloticase 8 mg q 2 weeks	33/42	79%	0.015	17/32	53%	0.595
Pegloticase 8 mg q 4 weeks	37/43	86%	0.001	19/36	53%	0.599
Placebo	11/23	48%	-	14/23	61%	-

[a] n represents number of subjects who experienced flares during the 3 month period. N represents number of subjects with office visits during the period.
[1] P-value from Fisher's exact test to compare number of subjects reporting flares to placebo.

Table 16. Frequency of Gout Flares per Subject in Pooled RCTs and Individual Studies.

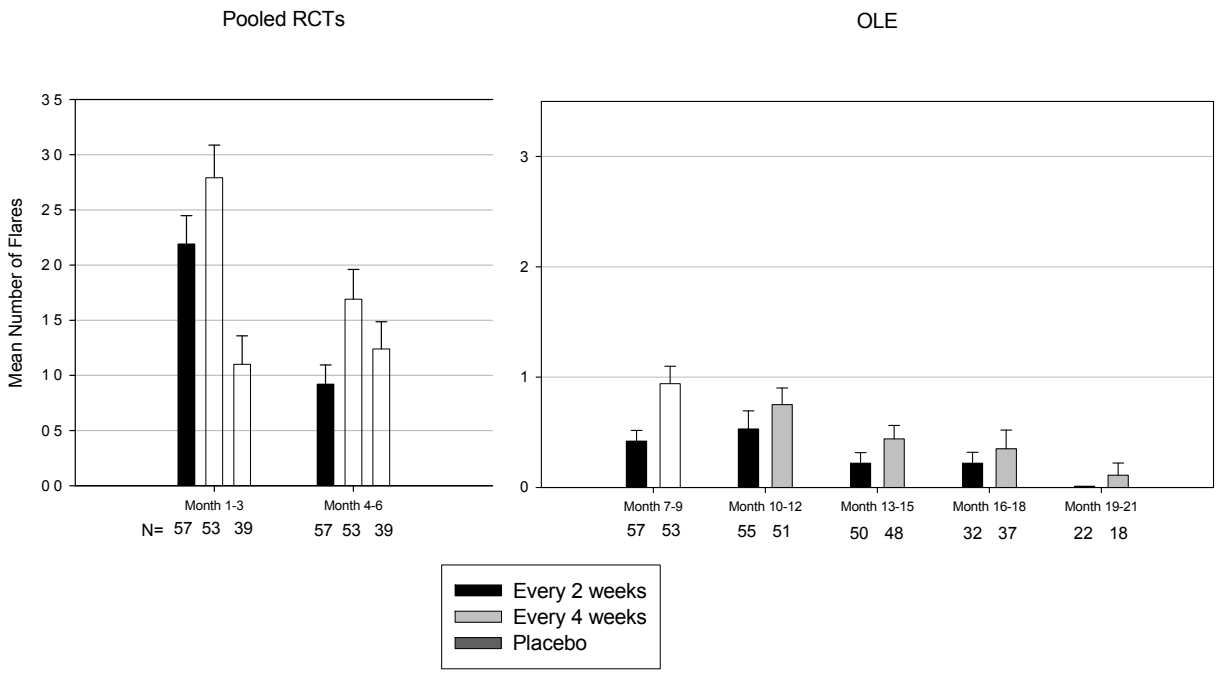
	Pegloticase		Placebo
	8 mg q 2 weeks	8 mg q 4 weeks	
Pooled Data			
Month 1 To Month 3			
N	85	84	43
Mean (SD)	2.3 (2.09)	2.7 (2.43)	1.2 (1.62)
p-value[1]	0.002	<0.001	
Month 4 To Month 6			
N	69	69	43
Mean (SD)	0.8 (1.24)	1.5 (1.99)	1.31 (1.49)
p-value	0.048	0.477	
Study C0405			
Month 1 To Month 3			
N	43	41	20
Mean (SD)	2.0 (1.77)	2.2 (1.92)	1.1 (1.45)
p-value	0.061	0.032	
Month 4 To Month 6			
N	37	33	20
Mean (SD)	0.4 (0.77)	1.4 (1.60)	1.7 (1.73)
p-value	<0.001	0.523	
Study C0406			
Month 1 To Month 3			
N	42	43	23
Mean (SD)	2.6 (2.35)	3.2 (2.77)	1.2 (1.78)
p-value	0.014	0.003	
Month 4 To Month 6			
N	32	36	23
Mean (SD)	1.2 (1.54)	1.7 (2.30)	0.9 (1.15)
p-value	0.525	0.160	

P-value from Fisher's exact test to compare mean number of flares to placebo.

4.5.2 Durability of Gout Flare Reduction

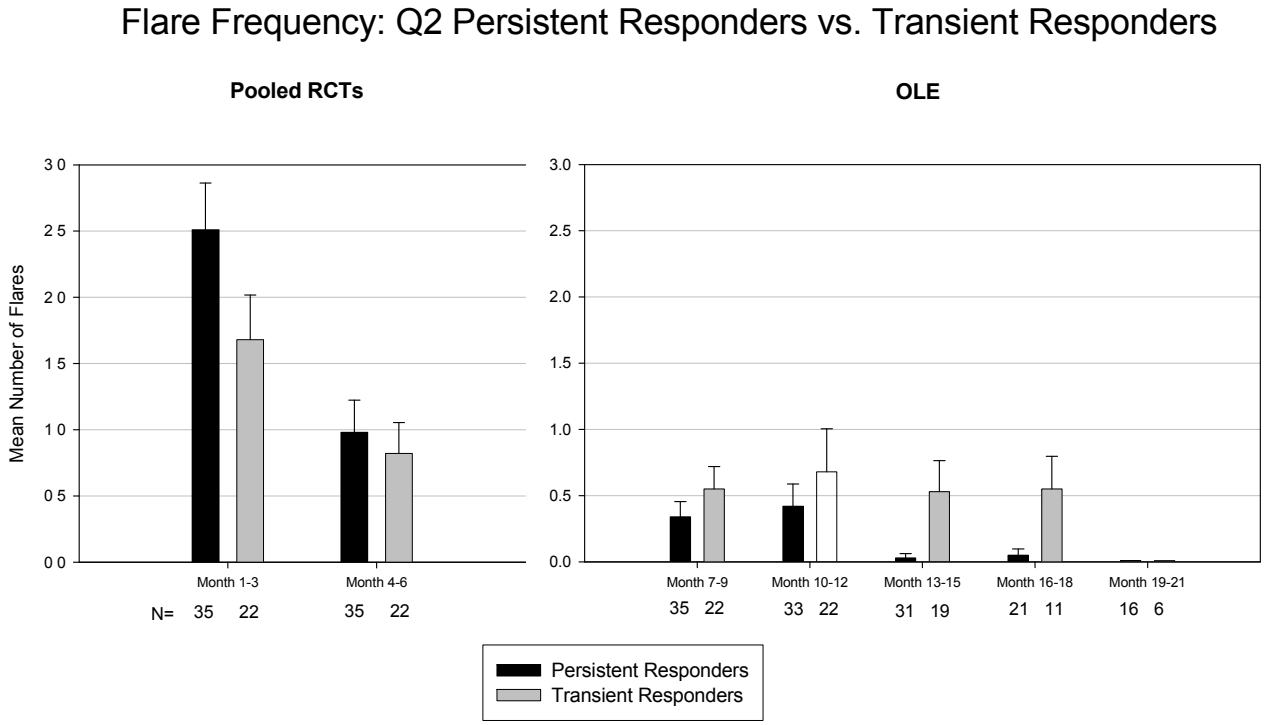
Figures 26 and 27 present gout flare frequency data for those subjects that received pegloticase q 2 week and completed the RCT and continued to receive pegloticase during the OLE Study. With continued active treatment in the OLE study, the incidence and frequency (Figure 26; right panel) of gout flares continued to decrease, most evident in those receiving pegloticase q 2 weeks treatment. Figure 27 (right panel) contains the frequency of gout flares in the peristent and transient responders that received pegloticase 8 mg every 2 weeks in the OLE Study. Importantly, there were few gout flares in those subjects that received pegloticase q 2 weeks during the OLE Study that were persistent responders during the RCT.

Figure 26. Mean (± SEM) Number of Flares per Subject in Pooled RCTs and OLE Study.



Treatment group assignment by initial randomization
N = Number of subjects in each group at each time point

Figure 27. Mean (± SEM) Number of Flares per Subject in Pooled Analysis of Persistent and Transient Responders in Pegloticase q 2 weeks Treatment Group in RCTs and OLE Study.



Treatment group assignment by initial randomization
N = Number of subjects

4.5.3 Conclusion: Incidence and Frequency of Gout Flares

An increase in incidence and frequency of gout flares associated with pegloticase treatment was evident over the first 3 months of therapy, consistent with other urate-lowering therapies. Over months 4-6 pegloticase q 2 weeks treatment resulted in statistically significant decreases in incidence and frequency of flares compared with placebo and in comparison to flares reported over months 1-3. This reduction in gout flares was maintained in OLE study.

4.6 Secondary Endpoint: Physician Assessments

4.6.1 Tender or Swollen Joints

Treatment with pegloticase q 2 weeks resulted in significant reduction in the number of tender joints in pooled analysis and in one (Study C0405) RCT compared with placebo (Table 17). Decreases in the number of swollen joints favored active treatment but did not reach statistical significance for either group (Table 18).

Table 17. Mean Change in Number of Tender Joints from Baseline to Final Visit in Pooled RCTs and Individual Studies.

	N[1]	Baseline Visit	Mean change	p-value[2]
Pooled				
Pegloticase 8 mg q 2 weeks	78	11.7	-7.4	0.008
Pegloticase 8 mg q 4 weeks	77	11.1	-6.1	0.024
Placebo	43	14.1	-1.2	-
C0405				
Pegloticase 8 mg q 2 weeks	43	12.6	-8.4	0.018
Pegloticase 8 mg q 4 weeks	41	12.0	-5.9	0.061
Placebo	20	15.0	0.7	-
C0406				
Pegloticase 8 mg q 2 weeks	42	10.7	-6.2	0.220
Pegloticase 8 mg q 4 weeks	43	10.2	-6.3	0.195
Placebo	23	13.4	-2.9	-

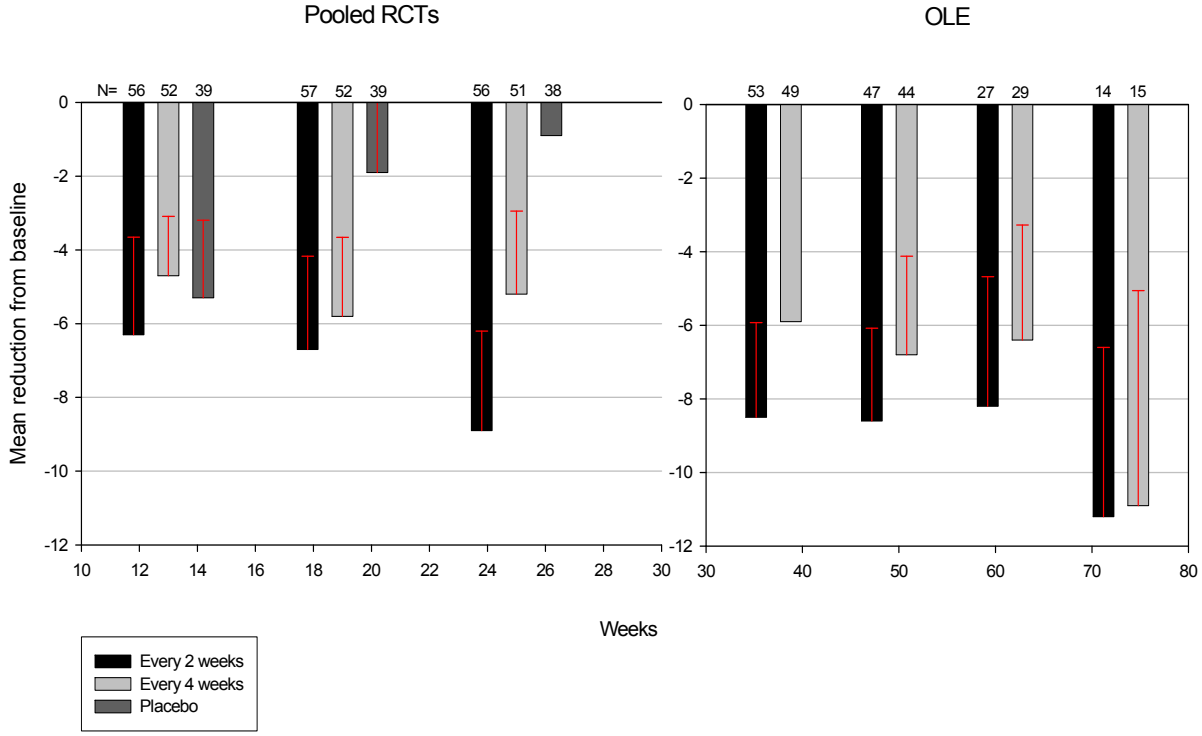
[1] N at Final Visit
[2] P-value based on two sample t-test to compare corresponding pegloticase groups compared to placebo.

Table 18. Mean Change in Number of Swollen Joints from Baseline to Final Visit in Pooled RCTs and Individual Studies.

	N[1]	Baseline Visit	Mean change	p-value[2]
Pooled				
Pegloticase 8 mg q 2 weeks	78	8.9	-5.5	0.166
Pegloticase 8 mg q 4 weeks	77	10.1	-5.1	0.170
Placebo	43	13.2	-2.6	
C0405				
Pegloticase 8 mg q 2 weeks	43	9.2	-5.8	0.185
Pegloticase 8 mg q 4 weeks	41	11.0	-5.5	0.156
Placebo	20	14.3	-1.0	-
C0406				
Pegloticase 8 mg q 2 weeks	42	8.5	-5.2	0.594
Pegloticase 8 mg q 4 weeks	43	9.1	-4.7	0.735
Placebo	23	12.2	-4.1	

[1] N at Final Visit
[2] P-value based on two sample t-test to compare corresponding pegloticase groups compared placebo.

Figure 28. Mean (± SEM) Reduction in Number in Tender or Swollen Joints in Pooled RCTs and OLE Study.



Treatment group assignment by initial randomization
N = Number of subjects

4.6.1.1 *Durability of Response in Reduction in Tender or Swollen Joints*

Reductions in number of tender or swollen joint counts continued or were maintained in OLE treatment (after Week 25) (Figure 28; right panel).

4.6.1.2 *Conclusions: Reduction in Tender or Swollen Joint Counts*

Treatment with pegloticase q 2 weeks resulted in significant improvement in number of tender joints by pooled analysis and in one RCT (C0405) compared with placebo. These benefits were sustained with OLE treatment.

4.6.2 Clinician Global Assessment of Disease Activity

Statistically significant improvements in pooled analysis and in both RCTs were reported with pegloticase q 2 weeks treatment (Table 19 and Figure 29; left panel)

Table 19. Clinician Global Assessment of Disease Activity in Pooled RCTs and Individual Studies.

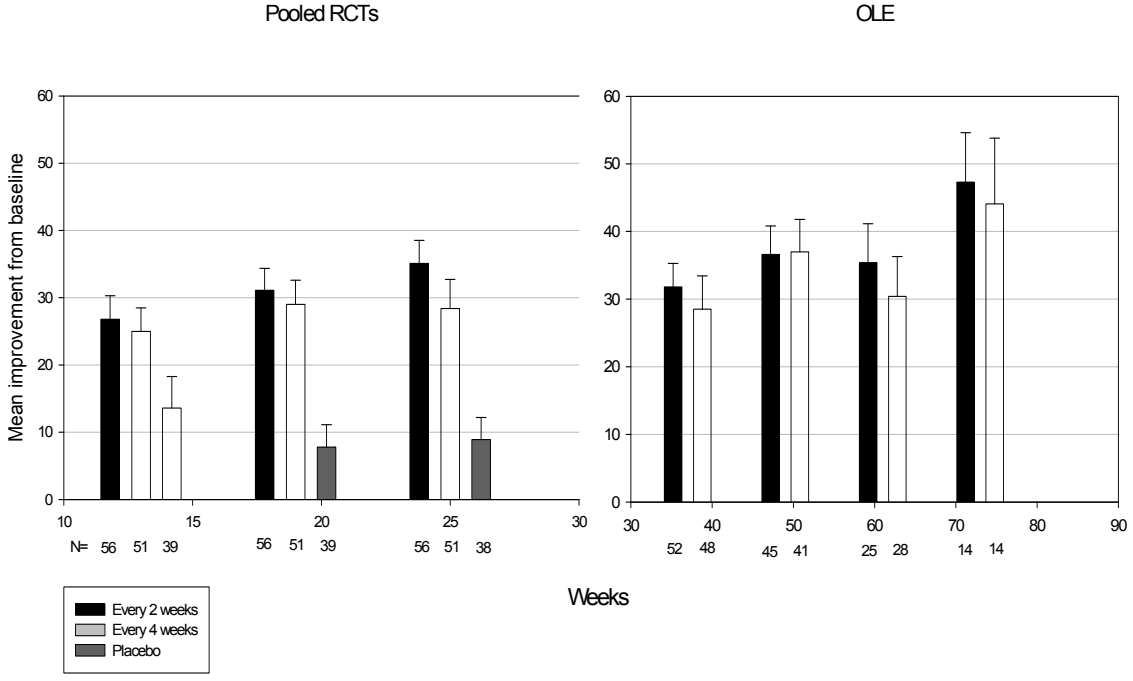
	N[1]	Baseline Visit	Mean change	p-value[2]
Pooled				
Pegloticase 8 mg q 2 weeks	77	47.6	-28.2	<0.001
Pegloticase 8 mg q 4 weeks	77	49.7	-23.6	0.003
Placebo	43	52.6	-8.2	-
C0405				
Pegloticase 8 mg q 2 weeks	40	43.3	-27.8	0.001
Pegloticase 8 mg q 4 weeks	38	46.4	-22.8	0.013
Placebo	20	53.9	-3.8	-
C0406				
Pegloticase 8 mg q 2 weeks	37	52.1	-28.7	0.021
Pegloticase 8 mg q 4 weeks	39	52.9	-24.4	0.095
Placebo	23	51.4	-12.1	-

[1] number of subjects at the final visit
[2] p-value based on two sample t-test to compare corresponding pegloticase groups vs. placebo.

4.6.2.1 *Durability of Improvement in Clinician Global Assessment*

Improvements in CGA in with active treatment were sustained in the OLE study (Figure 29; right panel).

Figure 29. Clinician Global Assessment of Disease Activity: Improvements by Week in Pooled RCTs and OLE Study.



Treatment group assignment by initial randomization
N = Number of subjects

4.6.2.2 *Conclusions: Clinician Global Assessment*

Statistically significant improvements in CGA were reported with pegloticase q 2 weeks treatment in combined and individual RCTs compared with placebo, which were maintained in the OLE study.

4.7 Secondary Endpoint: Patient Reported Outcomes

The pharmacodynamic effects of pegloticase treatment on PUA and tophi were associated with statistically significant and clinically meaningful improvements in patient reported outcomes, including patient global assessment of disease activity, patient reported pain, physical function (HAQ DI) and HRQOL (SF-36). Important descriptive data regarding the SF-36 outcomes is presented as "spydergrams" in Appendix 8.

4.7.1 Patient Global Assessment of Disease Activity

Baseline Patient Global Assessment of Disease Activity (PGA) VAS scores in pegloticase q 2 weeks, pegloticase q 4 weeks and placebo treatment groups were 42, 50 and 52 on a 100 mm VAS scale, indicating their disease considerably affected how they felt.(Table 20 and Figure 30; left panel)

Mean improvements in PGA with pegloticase q 2 weeks treatment were statistically significant and exceeded MCID in combined analysis and one (C0405) RCT. Importantly, PGA scores worsened with placebo treatment.

The percentage of patients reporting improvements ≥ MCID in combined treatment groups were:

- Pegloticase q 2 weeks: 27/50 (54%); p = 0.03
- Pegloticase q 4 weeks: 29/57 (51%); p = ns
- Placebo: 10/35 (29%)

Table 20. Patient Global Assessment of Disease Activity: Mean Changes from Baseline to Final Visit in Pooled RCTs and Individual Studies.

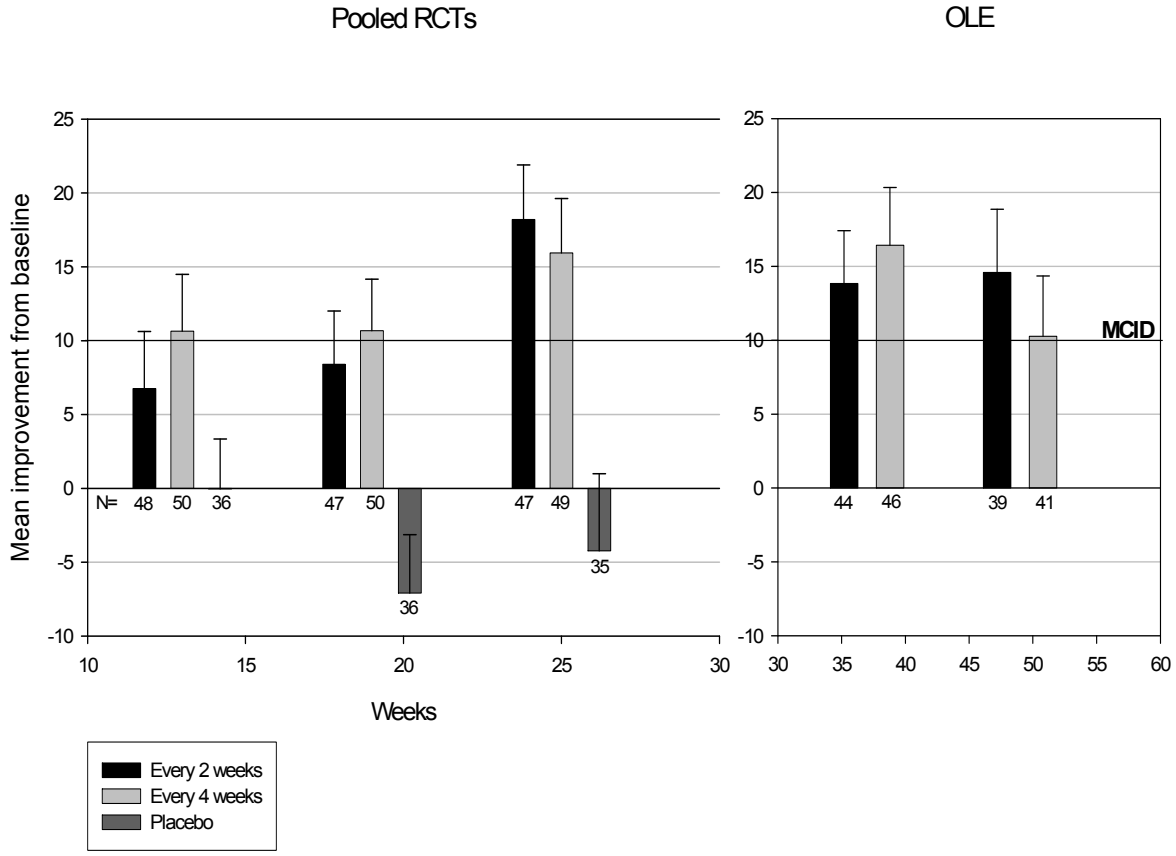
	N[1]	Baseline Visit	Mean change	p-value[2]
Pooled Analysis				
Pegloticase 8 mg q 2 weeks	68	42.44	-11.85	0.02
Pegloticase 8 mg q 4 weeks	72	49.79	-12.64	0.011
Placebo	40	51.58	+0.83	
C0405				
Pegloticase 8 mg q 2 weeks	40	45.67	-17.70	0.011
Pegloticase 8 mg q 4 weeks	37	52.78	-11.65	0.099
Placebo	20	50.75	1.90	-
C0406				
Pegloticase 8 mg q 2 weeks	28	38.06	-3.50	0.668
Pegloticase 8 mg q 4 weeks	35	46.66	-13.69	0.047
Placebo	20	52.40	-0.25	-

[1] N at Final Visit; A global disease activity score was not available in the Spanish version of the questionnaire were not included in this analysis.
[2] P-value from two sample t-test to compare corresponding pegloticase groups to placebo

4.7.1.1 *Durability of Improvement in PGA Scores*

Improvements in PGA scores evident at Week 13 further increased at Week 25 and were maintained during OLE treatment (after Week 25). (Figure 30; right panel)

Figure 30. Improvement in Patient Global Assessment of Disease of Activity by VAS in Pooled RCTs and OLE Study.



Treatment group assignment by initial randomization
N = Number of subjects

4.7.1.2 *Conclusions: Patient Global Assessment of Disease Activity*

In the pre-specified pooled analysis, pegloticase q 2 weeks treatment was associated with statistically significant improvements in PGA, which exceeded MCID of 10 mm. Importantly, mean change in PGA worsened in the placebo group.

4.7.2 Patient Assessment of Pain

Baseline pain VAS scores in pegloticase q 2 weeks, pegloticase q 4 weeks and placebo treatment groups were 44, 45 and 54 on a 100 mm VAS scale, indicating considerable impact of their disease attributable to pain (Table 21 and Figure 28; left panel).

In the pre-specified pooled analysis, pegloticase q 2 weeks treatment was associated with statistically significant mean changes from baseline in pain, which exceeded MCID of 10.0 mm; although not significant in individual RCTs.

The percentage of patients reporting improvements ≥ MCID in combined treatment groups were:

- Pegloticase q 2 weeks: 33/60 (55%) p = 0.01
- Pegloticase q 4 weeks: 27/62 (44%); p = ns
- Placebo: 14/37 (27%)

Table 21. Patient Assessment of Pain: Mean Changes from Baseline to Final Visit in Pooled RCTs and Individual Studies.

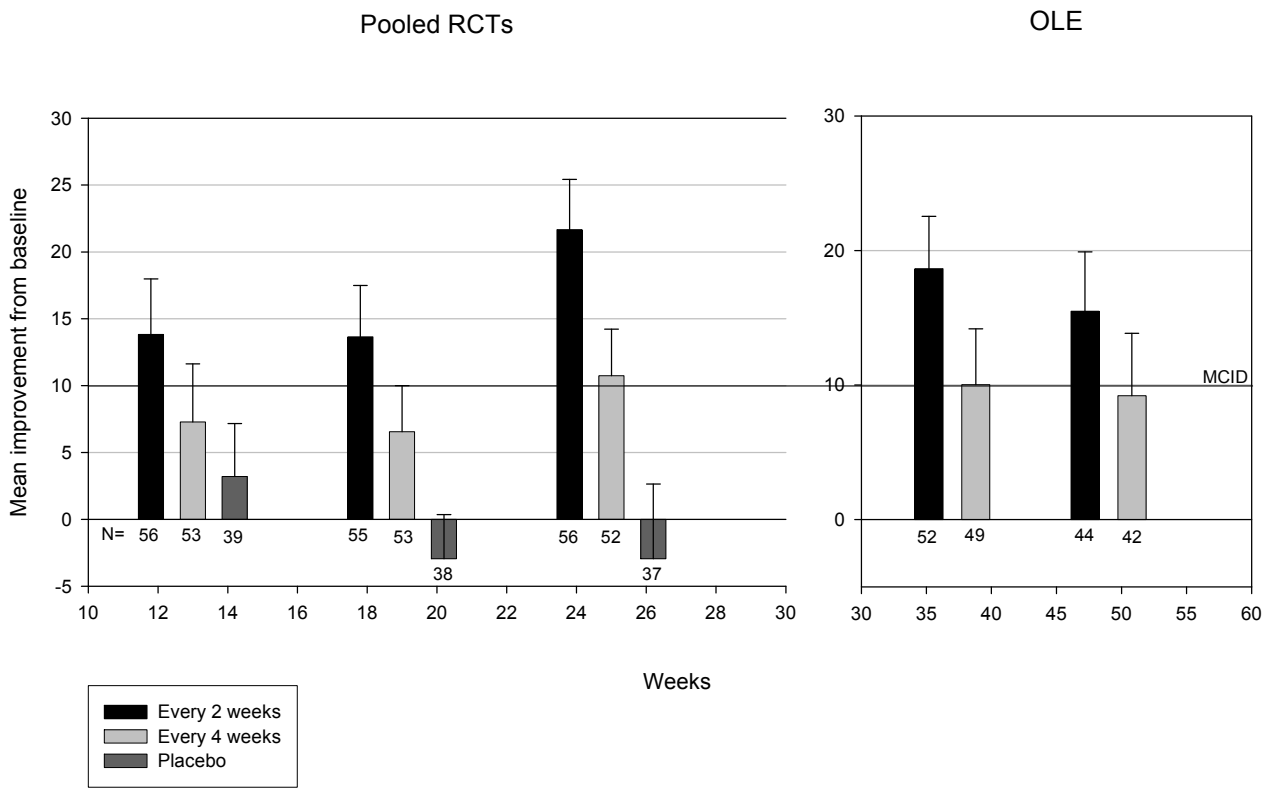
	N[1]	Baseline Visit	Mean change	p-value[2]
Pooled				
Pegloticase 8 mg q 2 weeks	78	44.21	-11.45	0.040
Pegloticase 8 mg q 4 weeks	78	45.06	-6.91	0.124
Placebo	43	53.91	+1.37	
C0405				
Pegloticase 8 mg q 2 weeks	40	45.24	-14.53	0.197
Pegloticase 8 mg q 4 weeks	38	49.07	-3.50	0.969
Placebo	20	62.20	-3.80	-
C0406				
Pegloticase 8 mg q 2 weeks	38	43.19	-8.21	0.132
Pegloticase 8 mg q 4 weeks	40	41.23	-10.15	0.033
Placebo	23	46.70	5.87	-

1 N at Final Visit
2 P-value from two sample t-test used to compare means of the corresponding treatment group to placebo.

4.7.2.1 *Durability of Improvement in Pain VAS Scores*

Improvements in pain VAS scores evident at Week 13 increased at Week 25 and were maintained with OLE treatment (after Week 25) (Figure 31; right panel).

Figure 31. Mean (± SEM) Improvement in Patient Assessment of Pain in Pooled RCTs and OLE Study.



Treatment group assignment by initial randomization
N = Number of subjects

4.7.2.2 *Conclusions: Patient Assessment of Pain*

In the pre-specified pooled analysis, pegloticase q 2 weeks treatment was associated with statistically significant improvement in pain, which exceeded MCID of 10.0 mm, and was sustained during OLE treatment.

4.7.3 Improvement in Physical Function: Health Assessment Questionnaire Disability Index

Baseline HAQ DI scores in pegloticase q 2 weeks, pegloticase q 4 weeks and placebo treatment groups (Table 22) were 1.1, 1.21 and 1.24, respectively, comparable to those reported in patients with longstanding active RA [48]. These indicate considerable impairment in physical function and performance of activities of daily living in TFG subjects enrolled in the phase 3 RCTs.

Pre-specified pooled analyses demonstrated statistically significant improvements with pegloticase q 2 weeks treatment compared with placebo in pooled analysis and one RCT (Study C0406), which ≥ MCID (-0.22). Importantly, little or no improvement was reported with

placebo treatment. The percentage of patients reporting improvements ≥ MCID in combined treatment groups were:

- Pegloticase q 2 weeks: 45% (28/62); p<0.003
- Pegloticase q 4 weeks: 48% (30/63); p<0.001
- Placebo: 16% (6/38)

Table 22. Mean Changes in HAQ DI Scores from Baseline to Final Visit in Pooled RCTs and Individual Studies.

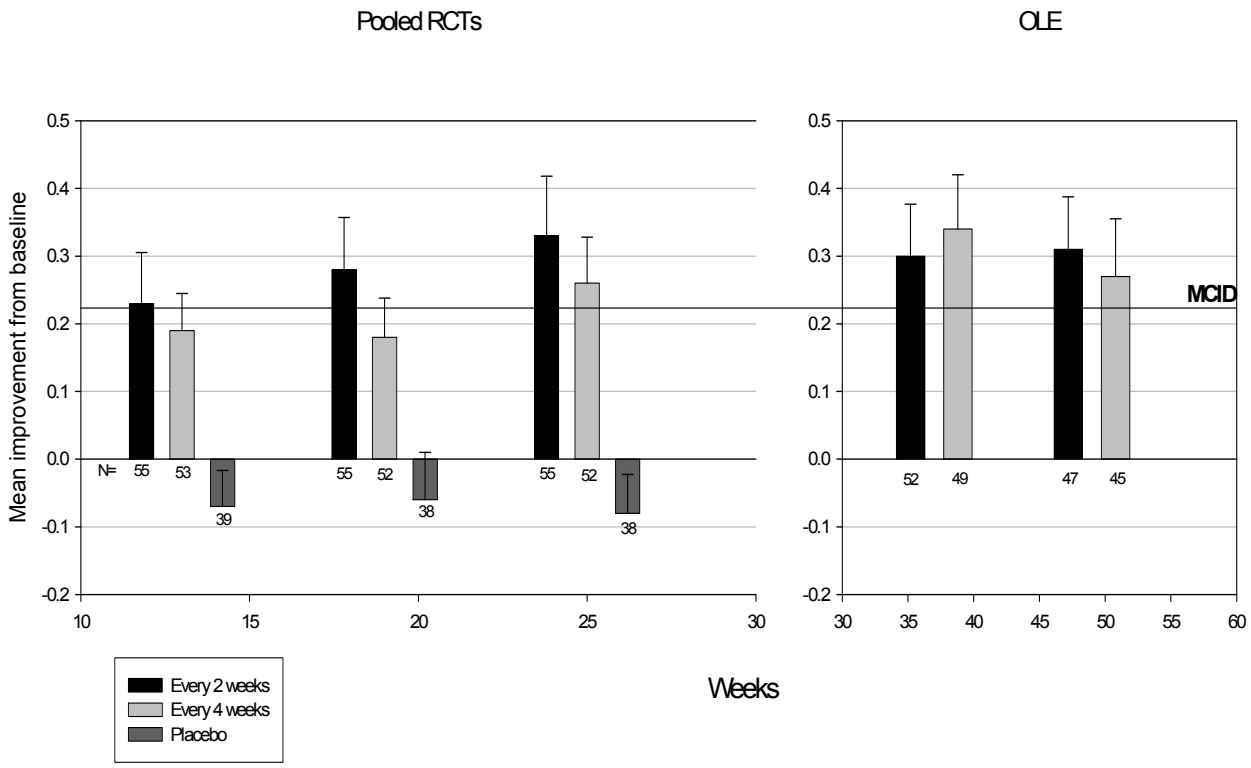
	N[1]	Baseline Visit	Mean change	p-value[2]
Pooled				
Pegloticase 8 mg q 2 weeks	77	1.10	-0.22	0.026
Pegloticase 8 mg q 4 weeks	78	1.21	-0.20	0.025
Placebo	43	1.24	+0.02	
C0405				
Pegloticase 8 mg q 2 weeks	39	1.08	-0.24	0.264
Pegloticase 8 mg q 4 weeks	38	1.38	-0.15	0.503
Placebo	20	1.66	-0.04	-
C0406				
Pegloticase 8 mg q 2 weeks	38	1.13	-0.21	0.041
Pegloticase 8 mg q 4 weeks	40	1.05	-0.25	0.009
Placebo	23	0.87	0.08	-

Note: Scores range from 0 (best) to 3 (worst)
1 p-value from two sample t-test used to compare means of the corresponding treatment group to placebo.

4.7.3.1 *Durability of Improvement in Physical Function (HAQ DI)*

Benefits in performance of daily activities and physical function evident at Week 13 increased at Week 25 and continued with long term treatment in OLE (Figure 32; right panel).

Figure 32. Mean (± SEM) Improvement in HAQ DI in Pooled RCTs and OLE Study.



Treatment group assignment by initial randomization (improvements typically presented as negative changes) are reversed in the above figure to indicate positive change scores
N = Number of subjects

4.7.3.2 *Conclusions: Patient Reported Physical Function (HAQ DI)*

In the pre-specified pooled analysis, subjects receiving pegloticase q 2 weeks weeks reported statistically significant improvements in physical function, ≥ MCID (-0.22); 45% to 48% of subjects reported improvements ≥ MCID, which were sustained during OLE treatment. Subjects receiving placebo reported deterioration in HAQ DI scores.

4.7.4 Health Related Quality of Life by Short Form-36

4.7.4.1 *Physical Component Summary (PCS) Score*

Baseline SF-36 HRQOL scores were low across all treatment groups; PCS scores >1.5 standard deviations below US normative values of 50: (a) 35.2 for the pegloticase q 2 weeks group, (b) 33.3 for the pegloticase q 4 weeks group, and (c) 31.0 for the placebo group. Domain scores, with exception of MHI (mental health) were also 12 to 32 mm lower than age/gender matched normative US population values, reflecting the significant impact of TFG across all domains of HRQOL (Table 23). Decrements were most evident in physical but also mental domains, indicating significant impact of TFG gout not only on physical function, pain and fatigue, but also how a subject feels emotionally and interacts socially.

Of note, baseline scores reported by subjects in the Phase 3 RCTs (Table 23) were very similar to other TFG populations in the NHS study and VAH Survey in veterans with gout and comorbidities [6, 45, 49]. These values are comparable to SF-36 scores at baseline in RCTs in patients with active, longstanding RA as well as severely active SLE [48, 50]. The spydergrams that appear in Appendix 8 demonstrate the similarity between TFG populations, and decrements in comparison to Age/Gender matched norms for each population, as well as US subjects with OA and Hypertension; Angina and Hypertension.

Table 23. Comparison of Baseline SF-36 Domain Scores in Phase 3 RCTs with Age/Gender Matched US Norms, as well as SF-36 Scores in Other TFG Populations.

Domain	PFI	RP	BP	GHP	VIT	SOC	RE	MHI
Pooled Pegloticase RCTs	45.2	47.2	37.4	47.4	47.3	61.9	69.4	68.6
Age/Gender matched norms	77.5	76.7	67.5	67.1	58.8	81.8	84.2	75.0
Decrements jn Baseline scores compared with Age/Gender US norms	32.3	29.5	30.1	19.7	11.5	19.9	14.8	4.4
Comparable TFG Populations								
Domain	**PFI**	**RP**	**BP**	**GHP**	**VIT**	**SOC**	**RE**	**MHI**
NHS Refractory Gout	46.8	35.0	45.6	42.6	45.8	63.2	58.1	67.7
VAH Gout and co-morbidities	37.3	38.3	38.3	43.5	39.5	56.6	58.1	66.6

4.7.4.2 *Results*

In the week 25 analysis, all subjects with data at endpoint reported highly statistically significant improvements in PCS scores with pegloticase q 2 weeks treatment in pooled analysis and individual RCTs (Table 24). Mean changes well exceeded MCID; compared with deterioration reported with placebo. The percentage of subjects reporting improvements ≥MCID were:

- Pegloticase q 2 weeks: 37/58 (64%) $p<0.01$
- Pegloticase q 4 weeks: 38/62 (61%) $p<0.01$
- Placebo: 11/38 (29%)

Table 24. SF-36 Physical Component Summary Score: Mean Changes from Baseline to Week 25 in Pooled RCTs and Individual Studies.

Treatment	N[1]	Baseline Visit	Mean change	p-value[2]
Pooled Data (Week 25)				
Pegloticase q 2 weeks	59	35.16	6.42	< 0.001
Pegloticase q 4 weeks	63	33.26	5.55	< 0.001
Placebo	38	31.01	-8.7	-
C0405 (Week 25)				
Pegloticase q 2 weeks	30	34.84	6.98	0.008
Pegloticase q 4 weeks	28	32.27	4.33	0.067
Placebo	18	29.06	-0.97	-

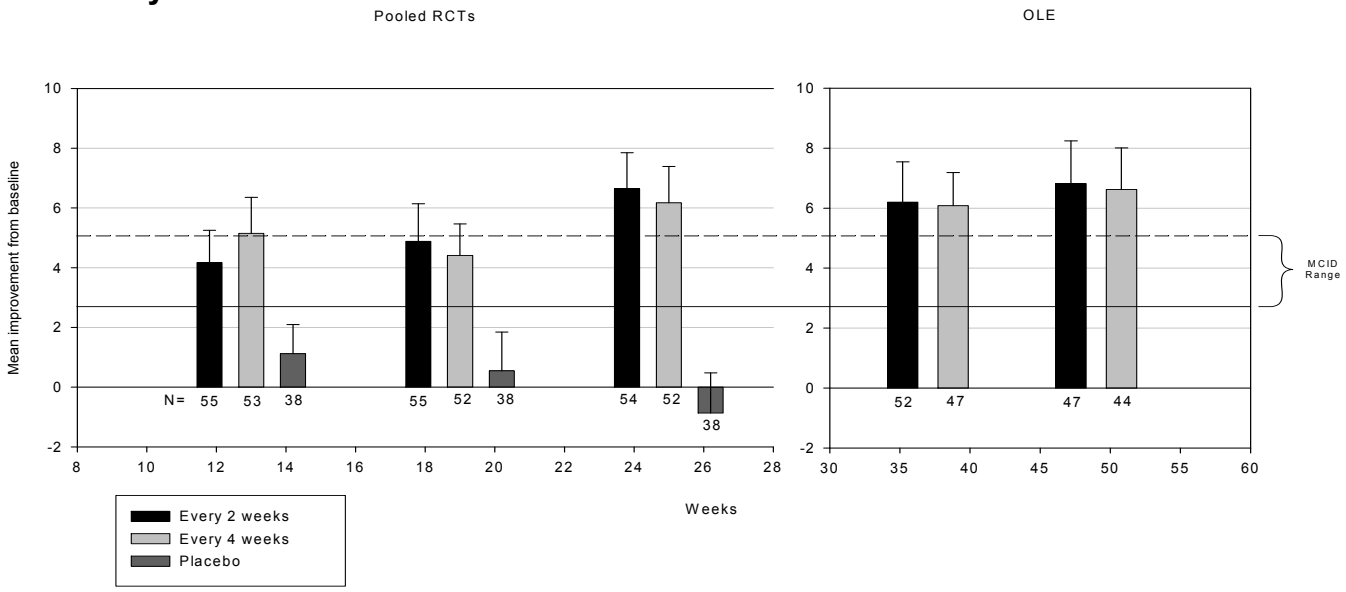
Treatment	N[1]	Baseline Visit	Mean change	p-value[2]
C0406 (Week 25)				
Pegloticase q 2 weeks	29	35.48	5.84	0.004
Pegloticase q 4 weeks	35	34.21	6.52	0.002
Placebo	20	32.70	-0.77	-

[1]N at Week 25
[2]P-value from two sample t-test that was used to compare means of the corresponding treatment group vs. placebo.

4.7.4.2.1 Durability of Improvement in Physical Component Summary

Improvements in mean PCS scores were maintained in OLE treatment after Week 25 (Figure 33).

Figure 33. Mean (± SEM) Improvement in SF-36 PCS by Week in Pooled RCTs and OLE Study.



4.7.5 Mental Component Summary (MCS) Scores

Baseline MCS scores were similar to age/gender matched population norms, and thus little improvement was expected, nor evident.

4.7.5.1 *SF-36 Domain Scores*

In the pooled analysis, with pegloticase q 2 weeks treatment, improvements in 6 of 8 domains were statistically significant (highlighted below, Table 25), were largest in BP, RP, SF and PFI and exceeded MCID in all 8 domains. These changes are reflected in a statistically significant

change in PCS score from baseline (6.42) compared to placebo; this change well exceeded the MCID.

In comparison changes in placebo ranged from worsening [-1.15 in BP] to improvements in RE of 4.6, not meeting MCID.

Table 25. Mean (± SD) Change in SF-36 Domains: Baseline to Week 25 in Pooled RCTs.

Domain	N[1]	PFI	RP	BP	GHP	VT	SF	RE	MHI
Pooled									
Pegloticase 8 mg q 2 weeks	61	11.8* (24.1)	15.4* (27.8)	24.3* (25.5)	7.7* (17.5)	9.9* (20.1)	13.5* (28.9)	8.2 (30.6)	10.1 (19.2)
Pegloticase 8 mg q 4 weeks	63	9.5* (20.3)	10.5* (28.6)	17.9* (24.2)	4.7 (17.2)	4.3 (20.1)	8.9 (26.5)	4.6 (30.3)	1.4 (16.8)
Placebo	38	0.25 (18.97)	1.15 (20.90)	-1.13 (20.77)	0.26 (14.97)	0.33 (15.24)	2.63 (23.99)	4.61 (22.40)	4.3 (18.1)

*** *P*-values < 0.05 are based on independent-groups t-tests of means for treatment groups compared to placebo.**
[1] N is the number of subjects at Week 25

Table 26 shows the proportions of subjects with changes in PCS and domain scores from Baseline to Week 25 ≥ MCID.

Table 26. Number (%) of Subjects with Changes from Baseline at Week 25 ≥ MCID in SF-36 Domain Scores (Pooled RCTs).

		Pegloticase		Placebo
		8 mg q 2 weeks	8 mg q 4 weeks	
n (%) with change ≥2.5 in PCS Score	N	58	62	38
	N (%)	37 (64%)	38 (61%)	11 (29%)
	p-value (vs. Placebo)	< 0.01	< 0.01	
n (%) with change ≥ 5 in PF	N	60	62	38
	N (%)	37 (62%)	37 (60%)	18 (47%)
	p-value (vs. Placebo)	0.21	0.30	
n (%) change ≥ 5 in RP	N	60	62	38
	N (%)	37 (62%)	36 (58%)	19 (50%)
	p-value (vs. Placebo)	0.30	0.54	
n (%) with change ≥ 5 in BP	N	60	62	38
	N (%)	48 (80%)	42 (68%)	15 (40%)
	p-value (vs. Placebo)	< 0.01	< 0.01	
n (%) with change ≥ 5 in GHP	N	60	62	38
	N (%)	32 (53%)	33 (53%)	19 (50%)
	p-value (vs. Placebo)	0.84	0.84	

		Pegloticase		Placebo
		8 mg q 2 weeks	8 mg q 4 weeks	
n (%) with change ≥ 5 in VT	N	58	62	38
	N (%)	37 (64%)	30 (48%)	14 (37%)
	p-value (vs. Placebo)	0.01	0.30	
n (%) with change ≥ 5 in SF	N	60	62	38
	n (%)	31 (52%)	30 (48%)	12 (32%)
	p-value (vs. Placebo)	0.06	0.14	
n (%) with change ≥ 5 in RE	N	60	62	38
	n (%)	25 (42%)	28 (45%)	16 (42%)
	p-value (vs. Placebo)	> 0.99	0.84	
n (%) with change ≥ 5 in MHI	N	58	62	38
	n (%)	38 (66%)	32 (52%)	19 (50%)
	p-value (vs. Placebo)	0.14	> 0.99	

Domain scores at week 25 met or exceeded US Age/Gender matched norms in vitality and MHI, and approach normative values in BP, SOC and RE (Table 25).

4.7.6 Conclusions: Patient Reported HRQOL (SF-36)

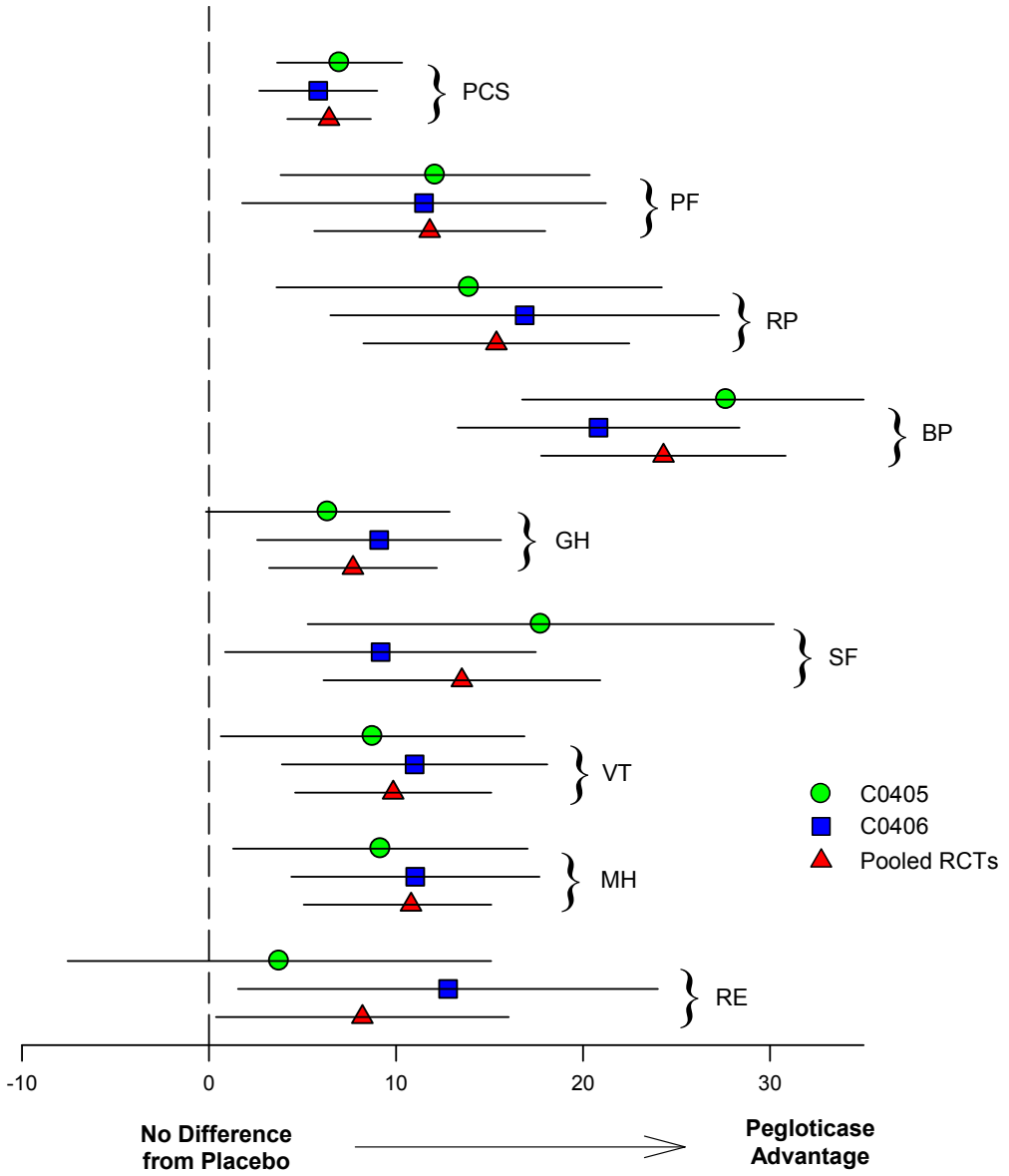
In the pre-specified week 25 pooled analysis, all subjects with data at endpoint reported highly statistically significant improvements in PCS scores with active treatment: 6 of 8 domains with pegloticase q 2 weeks and 3 of 8 domains with pegloticase q 4 weeks treatment. All well exceeded MCID compared with deterioration reported by placebo subjects. It is clear that further improvements accrued with continued treatment through week 25 in both active treatment groups.

These data indicate that pegloticase treatment results in important improvements not only in physical functioning and bodily pain but also fatigue and how subjects feel emotionally and interact socially, and that these changes are clinically meaningful.

4.7.7 Clinically Meaningful Improvements in Patient Reported Outcomes: An Integrated Analysis

As is evident in the analyses of the individual patient reported outcomes, there is a consistent benefit of pegloticase q 2 weeks treatment on global assessment of disease activity, pain, physical function, and HRQOL or “multidimensional function”. Figure 34 contains the Forest plots for HRQOL in the pooled and indvidual studies demonstrating a positive benefit for subjects treated in the pegloticase 8 mg every 2 weeks group compared to placebo with each of these parameters.

Figure 34. Comparison of Pegloticase Every 2 Weeks Group Compared to Placebo Group Changes From Baseline to Week 25 For HRQOL in Pooled RCTs and Individual Studies.



To better understand the relationship between the pharmacodynamic effects of pegloticase and clinically important improvements, persistent responders receiving pegloticase q 2 weeks were analyzed according to how many outcomes they reported improvements ≥ MCID (Table 27). The four PRO parameters for this purpose were HAQ DI, patient global assessment, patient pain assessment and SF-36 Physical Component Score which were the four most important parameters in relation to patients overall quality of life and disability. This data in persistent responders that received pegloticase 8 mg q 2 weeks demonstrated that over 64 % of subjects had at least 2 parameters that exceeded clinically meaningful improvements.

Table 27. Pegloticase 8 mg Every 2 weeks Persistent Responders: Number of Subjects with Improvements in 1, 2, 3 or 4 Patient Reported Outcomes ≥ MCID.

	N = 36 Persistent Responders (%)
Subjects with improvements in ≥ 1 of 4 parameters	31 (86%)
Subjects with improvements in ≥ 2 of 4 parameters	23 (64%)
Subjects with improvements in ≥ 3 of 4 parameters	15 (42%)
Subjects with improvements in all 4 parameters	8 (22%)

Another measure of the relationship between PROs and clinical benefit is a Number Needed to Treat (NNT) analysis. NNT is the number of subjects who need to be treated with a therapy to result in a "good" or "desired" outcome; or to prevent a bad outcome from occurring [51]. Values for NNT range from 1 to infinity; therapies with lower NNTs are more effective. NNT's may be used to illustrate the benefit of a therapy in terms of clinically relevant outcomes, such as the NNT to reach an ACR20% or 50% response.

Table 28. Pegloticase 8 mg Every 2 weeks Persistent Responders: Number of Subjects with Improvements in 1, 2, 3 or 4 Patient Reported Outcomes ≥ MCID: Number Needed to Treat Based Upon Patient Reported Outcome Responders

	NNT (95% LCL, 95% UCL)
	Pegloticase 8 mg q 2 weeks
Subjects with improvements in ≥ 1 of 4 parameters	1.2 (1.1, 1.4)
Subjects with improvements in ≥ 2 of 4 parameters	1.6 (1.3, 2.2)
Subjects with improvements in ≥ 3 of 4 parameters	2.4 (1.7, 3.9)
Subjects with improvements in all 4 parameters	4.5 (2.6, 9.9)

Therapies with lower NNTs may be preferable than those with higher NNTs; although the outcome selected is relevant to this assessment. For example if the NNTs are based on outcomes meaningful to patients, or the bad outcome prevented is "serious" such as death or myocardial infarction, then treatments with higher NNTs may still be considered acceptable.

NNTs were calculated from the combined analysis of phase 3 RCTs for pegloticase q 2 weeks administration, based on those persistent responders in the ITT population who reported clinically meaningful [51], eg improvements ≥MCID in patient global assessment of disease activity, pain, physical function (HAQ DI) and HRQOL or "multidimensional function" (SF-36) PCS scores. The values of the NNTs and their 95% CLs are shown in Table 28 indicating that in persistent responders between 1.2 and 2.4 subjects would need to be treated to achieve clinically meaningful improvements in ≥1 to 3 PROs simultaneously. This is another way to convey that the pharmacodynamic benefit of pegloticase administration is associated with improvements in multiple domains that are meaningful to patients

4.8 Efficacy Conclusions

Pegloticase treatment is associated with significant and durable benefits in patients with treatment failure, a subpopulation with an important unmet need. Rapid normalization of PUA and SUA values and reductions in tophus burden are associated with reductions in gout flares, improvements in global assessment of disease activity, pain, physical function and health-related quality of life, or multidimensional function. Therefore, these data from the replicate pivotal phase 3 studies demonstrate that pegloticase 8 mg every 2 weeks provides a dramatic reduction

in serum urate which manifests in robust clinically meaningful important benefits for those patients with treatment failure gout who are sustained, persistent responders.

5. SAFETY OF PEGLOTICASE

5.1 Introduction

The Pegloticase Clinical Development Program patient population consisted of 273 subjects (Phase 1, 2 and 3). Of these, 169 received their first exposure to pegloticase in two randomized, placebo controlled double-blind, Phase 3 studies in which patients were randomized in a 2:2:1 ratio (pegloticase q 2 weeks, pegloticase q 4 weeks, and placebo, respectively). Overall safety exposure of pegloticase-treated subjects was:

- 121 subjects: study duration of approximately 12 months or more,
- 115 subjects: study duration of approximately 15 months or more, and
- 95 subjects: study duration of approximately 18 months or more.

The median study duration for subjects in the pegloticase 8 mg every 2 weeks and pegloticase 8 mg every 4 weeks groups was about 18 months.

This section describes the safety profile for subjects treated with pegloticase in the RCTs, and includes their experience in the OLE. It does not describe patients who received placebo in the RCTs and switched to pegloticase in the OLE, except where noted. It is important to note that a small population is adequate to detect frequently occurring adverse events but is not adequate to estimate the frequency of rare events.

Exposure to pegloticase from the RCT is shown in Table 29, and for the OLE in Table 30.

Table 29. Safety Exposure in RCTs.

	Pegloticase 8 mg q 2 weeks		Pegloticase 8 mg q 4 weeks		Total	
Duration of Exposure[1]	**Persons**	**Person-Months**	**Persons**	**Person-Months**	**Persons**	**Person-Months**
Up to 1 month	5	3.5	5	4.0	10	7.5
1 - 2 months	5	8.4	4	6.5	9	14.9
2 - 3 months	5	12.7	6	15.2	11	27.9
3 - 4 months	2	6.5	5	18.1	7	24.6
4 - 5 months	6	27.5	2	10.0	8	37.5
5 - 6 months	31	185.4	28	166.4	59	351.8
6 - 7 months	29	182.8	31	194.8	60	377.6
7 - 8 months	2	15.0	3	22.1	5	37.2
Total	**85**	**441.8**	**84**	**437.1**	**169**	**878.9**

[1] **Duration of Exposure = date of last infusion - date of first infusion + 14**

Table 30. Safety Exposure in RCTs and OLE Study

	Pegloticase 8 mg q 2 weeks		Pegloticase 8 mg q 4 weeks		Total	
Duration of Exposure[1]	**Persons**	**Person-Months**	**Persons**	**Person-Months**	**Persons**	**Person-Months**
Up to 1 month	5	3.5	7	5.0	12	8.5
1 - 2 months	7	11.5	5	8.0	12	19.4
2 - 3 months	7	17.8	7	17.7	14	35.4
3 - 4 months	4	13.9	7	24.9	11	38.7
4 - 5 months	7	32.0	4	19.3	11	51.3
5 - 7 months	8	50.0	13	78.4	21	128.4
7 - 9 months	9	70.1	4	29.8	13	99.9
9 - 11 months	6	60.1	6	61.8	12	121.9
11 - 13 months	15	185.2	8	97.5	23	282.7
13 -16 months	16	225.1	16	231.8	32	456.8
16 - 19 months	23	410.3	23	413.1	46	823.4
> 19 months	1	20.3	0	0	1	20.3
Total	108	1099.6	100	987	208	2086.6

[1] **Duration of Exposure = date of last infusion - date of first infusion + 14**

Subject disposition is shown in Figure 14.

The concomitant medications during the RCTs, pooled across both studies, are presented in Table 31.

Table 31. Concomitant Medications in ≥15% Subjects (Pooled RCTs).

WHO-Drug Medication ATC Level 2 [1]	Pegloticase		Placebo
	8 mg q 2 weeks (N = 85) n (%)	8 mg q 4 weeks (N = 84) n (%)	(N = 43) n (%)
Anti-gout preparations	55 (65%)	49 (58%)	27 (63%)
Analgesics	49 (58%)	52 (62%)	25 (58%)
Agents acting on the renin-angiotensin system	49 (58%)	44 (52%)	21 (49%)
Drugs for acid-related disorders	47 (55%)	41 (49%)	23 (54%)
Beta blocking agents, selective	38 (45%)	42 (50%)	20 (47%)
Serum lipid reducing agents	46 (54%)	31 (37%)	15 (35%)
Corticosteroids for systemic use	37 (44%)	38 (45%)	13 (30%)
Diuretics	38 (45%)	31 (37%)	18 (42%)
Anti-inflammatory and Anti-rheumatic products	32 (38%)	33 (39%)	21 (49%)
Antibacterials for systemic use	28 (33%)	32 (38%)	16 (37%)
Antithrombotic agents	32 (38%)	27 (32%)	15 (35%)
Calcium channel blockers	19 (22%)	28 (33%)	11 (26%)
Antihistamines for systemic use	12 (14%)	31 (37%)	7 (16%)
Vitamins	21 (25%)	17 (20%)	11 (26%)

Mineral supplements	22 (26%)	11 (13%)	12 (28%)
Drugs used in diabetes	21 (25%)	15 (18%)	8 (19%)
Psychoanaleptics	14 (17%)	16 (19%)	10 (23%)
Psycholeptics	15 (18%)	14 (17%)	7 (16%)
Antianemic preparations	14 (17%)	13 (16%)	8 (19%)
Cardiac therapy	10 (12%)	16 (19%)	8 (19%)
Cough and cold preparations	9 (11%)	9 (11%)	10 (23%)

Note: Prior medications were coded using WHO Drug (2005Q3).
1 Anatomical Therapeutic Chemical (ATC) Classification Level 2 is the therapeutic main group from WHO Drug.

5.2 Summary of Treatment-Emergent Adverse Events

An overall summary of the TEAEs by treatment, including infusion reactions and gout flares in the pooled RCTs is presented in Table 32. Greater than 90% of subjects in each treatment group experienced an AE: 94% in the pegloticase q 2 weeks group, 100% in the pegloticase q 4 weeks group, and 95% in the placebo group.

Of 34 subjects who were discontinued from treatment due to an AE, 16 (19%) were in the pegloticase q 2 weeks group, 17 (20%) were in the pegloticase q 4 weeks group, and 1 (2%) was in the placebo group.

Table 32. Summary of Treatment-Emergent Adverse Events (Pooled RCTs).

	Pegloticase		**Placebo**
	8 mg q 2 weeks N=85	**8 mg q 4 weeks N=84**	**N=43**
Number of adverse events (AEs)	693	870	370
	n (%)	**n (%)**	**n (%)**
Subjects with serious adverse events (SAEs)	20 (24%)	19 (23%)	5 (12%)
Subjects with treatment discontinued due to SAE	9 (11%)	7 (8%)	0
Subjects with AEs	80 (94%)	84 (100%)	41 (95%)
Subjects with treatment discontinued due to AE	16 (19%)	17 (20%)	1 (2%)

Note: Except for the "Number of AEs", subjects are counted only once in each row.

5.3 Deaths

5.3.1 Deaths in RCTs

There were 5 deaths in subjects who were randomized in the RCTs: three in the pegloticase q 2 weeks group; one in the pegloticase q 4 weeks group; and one in the placebo group. None of these deaths were reported as related to drug by the site investigator caring for the patients. There was no censoring rule for reporting of deaths. Brief descriptions of these deaths are described in Table 33. Patient narratives are in Appendix 3.

Table 33. Deaths in the Pegloticase RCTs.

Study: Subject number	Dose Group	Age Sex	Event	Medical History	Time from Last Infusion	Most Recent PUA	Antibody Titer
C0406: 301-014	Placebo	85 y/o female	Multiple organ failure including MRSA sepsis and renal failure in hospital	Breast cancer, CKD, prosthetic mitral valve.	Randomized, but never dosed	N/A	N/A
C0406: 301-003	Pegloticase 8 mg q 2 weeks	89 y/o male	MRSA sepsis originating from decubitus ulcer. Following lack of response to antibiotics, patient and family asked for voluntary withdrawal of treatment.	CAD, DM, CKD, prosthetic aortic valve, pacemaker, bladder cancer, peri-anal decubitus ulcer.	Died 10 weeks after pegloticase dose 12	PUA < 6 mg/dL	1:7290
C0405: 203-001	Pegloticase 8 mg q 2 weeks	61 y/o male	Sudden death after heavy exertion unloading a wood splitter.	LVEF = 17%; CAD, CHF, HTN, DM, asthma	Died 4 weeks after pegloticase dose 7	PUA > 6 mg/dL	1:7290
C0406: 315-005	Pegloticase 8 mg q 2 weeks	69 y/o male	Reported cause was cardiac arrhythmia. Died suddenly while en- route to ER, after feeling weak for several days.	ASHD, CABG, CKD, DM	Died 12 days after pegloticase dose 9	PUA < 6 mg/dL	1:810
C0405: 102-006	Pegloticase 8 mg q 4 weeks	64 y/o male	Hospitalized for dyspnea secondary to CHF. Following successful treatment of heart failure, patient developed progressive renal failure; subsequently voluntarily withdrew from dialysis and died shortly thereafter	LVEF = 12%; end stage cardiomyopathy, 5 stents, CHF, HTN, CKD	3 weeks after last pegloticase dose	PUA > 6 mg/dL	1:65610

5.3.2 Deaths with Longer Term Treatment

There were three deaths reported in the OLE (Table 34). Patient narratives are in Appendix 3.

Table 34. Deaths in the OLE Study.

Study: Subject number	Dose Group	Age Sex	Event	Medical History	Time from Last Infusion	Most Recent PUA	Antibody Titer
C0405: 122-004	q 4 weeks to q 2 weeks	54 y/o female	Oxacillin-resistant staphylococcal aureus (ORSA) sepsis. Voluntary withdrawal from antibiotics	CKD, HTN, hypercholesterolemia During DB study hospitalized for pancreatitis, hip fracture; bilateral DVT; osteomyelitis, worsening CKD	Received 4 doses of pegloticase in OLE; died 21 days after last dose	PUA > 6 mg/dL	1:810
C0406: 301-002*	q 2 weeks to q 4 weeks	54 y/o male	Pneumonia	HIV-2 infection, HTN, azotenia, gastroesophageal reflex disease, anemia, jaundice, cryptosporidium, atrial fibrillation, chronic renal disease, diverticulitis, H pylori, cholelithiasis, Kaposi's sarcoma skin lesion, candida esophagitis, diabetes mellitus non-insulin-dependent, gynecomastia, bilateral lower extremity weakness, right eye conjunctiva infection, hyperkalemia, dehydration, weight loss, urinary frequency, nocturia, insomnia, and right eye worsening cataract	Received 20 doses in OLE; died 3 months after last dose	PUA < 6 mg/dL	undetectable
C406: 325-001*	q 4 weeks to q 2 weeks	63 y/o male	Necrotizing skin lesions on face and hands (cellulitis gangrenous)	CHF, dilated cardiomyopathy, ventricular tachychardia, hyperclolesterolemia, umbilical hernia and right inguinal hernia. Moderate skin blisters during the OLE	Received 51 doses in OLE ; died 5 weeks after last dose	PUA < 6 mg/dL	1:810

*** These events occurred after the 120-day safety update database cut off**

5.3.3 Deaths After Study Participation

There were two subjects in the RCTs who received placebo that died after study participation. These subjects did not enroll in the OLE. Brief descriptions are provided in Table 35.

Table 35. Deaths After Study Participation.

Study: Subject number	Dose Group	Age Sex	Event	Medical History	Timing	Most Recent PUA	Antibody Titer
C0405: 101-005	Placebo	67 y/o male	Suspected CV event, but insufficient data to adjudicate.	CAD, CHF, MI, coronary stents, DM. During RCT had acute pancreatitis and CHF.	4 months after RCT	PUA > 6 mg/dL	undetectable
C0406: 311-002	Placebo	80 y/o male	Chronic lymphocytic leukemia (CLL)	CLL stable at time of enrollment but recurred during Month 4.	4 months after withdrawal from study	PUA > 6 mg/dL	undetectable

5.4 Serious Adverse Events

Adverse events, including infusion reactions, reported as SAEs included the category of a medically significant event that may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes that categorizes an SAE (e.g., death, hospitalization).

Serious AEs are summarized by system organ class for the pooled RCTs in Table 36. Forty-four (44) subjects experienced a total of 78 SAEs: 20 (23.5 %) subjects were in the pegloticase q 2 weeks group, 19 (22.6 %) subjects were in the pegloticase q 4 weeks group, and 5 (11.6 %) subjects were in the placebo group. Serious AEs typically occurred in single subjects except for infusion reactions (most common SAE) and gout flares (second most common SAE). Serious infusion reactions occurred in four subjects in the pegloticase q 2 weeks group, 7 in the q 4 weeks group and 0 in the placebo group. Serious gout flares occurred in four subjects in the pegloticase q 2 weeks group and one in the q 4 weeks group, and two in the placebo group. Arrhythmia and gastrooesophageal reflux each occurred in two subjects in the pegloticase q 2 weeks group.

Table 36. Serious Adverse Events by System Organ Class and Preferred Term.

	Pegloticase		Placebo
	8 mg q 2 weeks (N = 85)	8 mg q 4 weeks (N = 84)	(N = 43)
Number of Serious Adverse Events	34	30	14
Number (%) of Subjects with Serious Adverse Events	20 (23.5 %)	19 (22.6%)	5 (11.6%)
System Organ Class: Preferred Term	**n (%)**	**n (%)**	**n (%)**
General Disorders and Administration Site Conditions	**7 (8.2)**	**7 (8.3%)**	**0**
Infusion Related Reaction	4 (4.7%)	7 (8.3%)	0
Chest Pain	1 (1.2%)	0	0
Oedema Peripheral	1 (1.2%)	0	0
Pyrexia	1 (1.2%)	0	0
Infections and Infestations	**3 (3.5%)**	**5 (6.0%)**	**4 (9.3%)**
Pneumonia	1 (1.2%)	1 (1.2%)	1 (2.3%)
Cellulitis	1 (1.2%)	1 (1.2%)	0
Arthritis Bacterial	0	0	1 (2.3%)
Cellulitis Staphylococcal	0	1 (1.2%)	0
Herpes Zoster	0	0	1 (2.3%)
Localised Infection	0	1 (1.2%)	0
Necrotising Fasciitis	0	1 (1.2%)	0
Perianal Abscess	0	0	1 (2.3%)
Pyelonephritis	1 (1.2%)	0	0
Sepsis	1 (1.2%)	0	0
Staphylococcal Sepsis	1 (1.2%)	0	0
Musculoskeletal and Connective Tissue Disorders	**7 (8.2%)**	**2 (2.4%)**	**2 (4.7%)**
Gout	4 (4.7%)	1 (1.2%)	2 (4.7%)
Fistula	0	1 (1.2%)	0
Haemarthrosis	1 (1.2%)	0	0
Myopathy Steroid	1 (1.2%)	0	0
Osteoarthritis	1 (1.2%)	0	0
Synovial Cyst	1 (1.2%)	0	0
Cardiac Disorders	**4 (4.7%)**	**3 (3.6%)**	**0**
Arrhythmia	2 (2.4%)	0	0
Angina Pectoris	0	1 (1.2%)	0
Cardiac Arrest	1 (1.2%)	0	0
Cardiac Failure Congestive	1 (1.2%)	0	0
Myocardial Infarction	0	1 (1.2%)	0
Tachycardia	0	1 (1.2%)	0
Gastrointestinal Disorders	**3 (3.5%)**	**1 (1.2%)**	**2 (4.7%)**
Gastrooesophageal Reflux Disease	2 (2.4%)	0	0
Pancreatitis	0	1 (1.2%)	1 (2.3%)
Barrett's Esophagus	1 (1.2%)	0	0
Gastritis Erosive	1 (1.2%)	0	0
Inguinal Hernia, Obstructive	0	0	1 (2.3%)
Renal and Urinary Disorders	**0**	**2 (2.4%)**	**2 (4.7%)**
Renal Failure Acute	0	1 (1.2%)	1 (2.3%)
Haematuria	0	0	1 (2.3%)
Renal Failure	0	1 (1.2%)	0

	Pegloticase		Placebo
	8 mg q 2 weeks (N = 85)	8 mg q 4 weeks (N = 84)	(N = 43)
Metabolism and Nutrition Disorders	**1 (1.2%)**	**1 (1.2%)**	**1 (2.3%)**
Hyperkalaemia	1 (1.2%)	1 (1.2%)	0
Hypoglycaemia	0	0	1 (2.3%)
Nervous System Disorders	**0**	**2 (2.4%)**	**1 (2.3%)**
Convulsion	0	1 (1.2%)	0
Syncope	0	0	1 (2.3%)
Transient Ischaemic Attack	0	1 (1.2%)	0
Injury, Poisoning and Procedural Complications	**2 (2.4%)**	**0**	**0**
Facial Bones Fracture	1 (1.2%)	0	0
Injury	1 (1.2%)	0	0
Muscle Rupture	1 (1.2%)	0	0
Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps)	**0**	**1 (1.2%)**	**1 (2.3%)**
Chronic Lymphocytic Leukaemia Recurrent	0	0	1 (2.3%)
Malignant Melanoma	0	1 (1.2) [1]	0
Respiratory, Thoracic, and Mediastinal Disorders	**1 (1.2%)**	**1 (1.2)**	**0**
Dyspnoea	1 (1.2%)	0	0
Dyspnoea Exacerbated	0	1 (1.2)	0
Blood and Lymphatic System Disorders	**0**	**0**	**1 (2.3%)**
Febrile Neutropenia	0	0	1 (2.3%)
Hepatobiliary Disorders	**0**	**1 (1.2)**	**0**
Cholecystitis	0	1 (1.2)	0
Skin and Subcutaneous Tissue Disorders	**0**	**1 (1.2)**	**0**
Angioneurotic Edema	0	1 (1.2)	0
Urticaria	0	1 (1.2)	0
Vascular Disorders	**0**	**1 (1.2)**	**0**
Deep Vein Thrombosis	0	1 (1.2)	0

[1] **If the same subject in a given treatment had more than one occurrence in the same preferred term event category, the subject was counted only once.**

5.4.1 Serious Adverse Events Leading to Discontinuation

Serious adverse events that led to discontinuation are shown in Table 37. Infusion reactions were the most common serious adverse event leading to discontinuation.

Table 37. Serious Adverse Events, Excluding Deaths That Led to Discontinuation (Individual RCTs).

Study	Preferred Term	Outcome
Pegloticase 8 mg q 2 weeks		
C0405	Infusion Related Reaction	Resolved
	Infusion Related Reaction	Resolved
	Gastritis Erosive	Resolved
	Infusion Related Reaction	Resolved
C0406	Infusion Related Reaction	Resolved
	Gout	Resolved
Pegloticase 8 mg q 4 weeks		
C0405	Fistula	Unknown
	Infusion Related Reaction	Resolved
	Infusion Related Reaction	Resolved
C0406	Infusion Related Reaction	Resolved
	Angioneurotic Edema	Resolved
	Urticaria	Resolved
	Infusion Related Reaction	Resolved

5.4.2 Serious Adverse Events with Longer Term Treatment in OLE Study

Overall, there was no change in the type, incidence or frequency of serious adverse events reported in the OLE.

5.4.3 Serious Adverse Events Leading to Discontinuation of Study Drug with Longer Term Treatment

There were four subjects previously treated with pegloticase in the RCTs who reported SAEs that led to discontinuation. One subject treated with pegloticase q 2 weeks to q 2 weeks with CHF; two subjects treated with q 2 weeks to q 4 weeks with lung infiltration and depression, respectively. One subject treated with q 4 weeks to q 2 weeks that had an infusion reaction SAE. There were eight subjects who were previously treated with placebo who discontinued pegloticase in the OLE. Three subjects in the pegloticase q 2 weeks with infusion reactions and five subjects in the pegloticase q 4 weeks; three infusion reactions, one pyelonephritis/acute renal failure and one MRSA abscess.

5.5 Treatment Emergent Adverse Events

Table 38 below lists all other adverse events occurring in 2 or more subjects and at least 1% more frequently in patients receiving pegloticase when compared to placebo, excluding gout flares and infusion reactions.

Table 38. Adverse Events Occurring in ≥ 2 Subjects and ≥ 1% More Frequently in Pegloticase Treated Patients Compared to Placebo, Excluding Gout Flares and Infusion Reactions.

Adverse Event (Preferred Term)	Pegloticase		Placebo
	8 mg q 2 weeks	8 mg q 4 weeks	
	N=85 n (%)	N=84 n (%)	N=43 n (%)
Nasopharyngitis	6 (7%)	4 (5%)	1 (2%)
Bronchitis	2 (2%)	3 (4%)	1 (2%)
Cellulitis	4 (5%)	2 (2%)	0
Sinusitis	1 (1%)	2 (2%)	0
Staphylococcal Infection	1 (1%)	2 (2%)	0
Dental Caries	0	2 (2%)	0
Back Pain	3 (4%)	7 (8%)	2 (5%)
Osteoarthritis	3 (4%)	3 (4%)	0
Musculoskeletal Pain	1 (1%)	4 (5%)	0
Joint Swelling	4 (5%)	0	0
Bursitis	2 (2%)	0	0
Muscle Fatigue	2 (2%)	0	0
Pain in Jaw	0	2 (2%)	0
Nausea	10 (12%)	6 (7%)	1 (2%)
Vomiting	4 (5%)	5 (6%)	1 (2%)
Constipation	5 (6%)	2 (2%)	2 (5%)
Dyspepsia	2 (2%)	2 (2%)	0
Gastrooesophageal Reflux Disease	3 (4%)	1 (1%)	0
Stomatitis	0	3 (4%)	1 (2%)
Umbilical Hernia	3 (4%)	0	0
Diverticulum	2 (2%)	0	0
Chest Pain	5 (6%)	4 (5%)	1 (2%)
Pyrexia	2 (2%)	5 (6%)	1 (2%)
Asthenia	2 (2%)	4 (5%)	0
Chills	3 (4%)	3 (4%)	0
Chest Discomfort	0	3 (4%)	0
Influenza Like Illness	2 (2%)	1 (1%)	0
Pruritus	3 (4%)	5 (6%)	0
Urticaria	2 (2%)	2 (2%)	0
Alopecia	3 (4%)	0	0
Dermatitis	1 (1%)	2 (2%)	0
Dry Skin	3 (4%)	0	0
Skin Lesion	2 (2%)	1 (1%)	0
Skin Ulcer	2 (2%)	1 (1%)	0
Erythema	0	2 (2%)	0
Headache	8 (9%)	9 (11%)	4 (9%)
Somnolence	2 (2%)	1 (1%)	0

Adverse Event (Preferred Term)	Pegloticase		Placebo
	8 mg q 2 weeks	8 mg q 4 weeks	
	N=85 n (%)	N=84 n (%)	N=43 n (%)
Migraine	2 (2%)	0	0
Dyspnoea	4 (5%)	5 (6%)	2 (5%)
Pharyngolaryngeal pain	4 (5%)	2 (2%)	0
Sinus Congestion	3 (4%)	2 (2%)	1 (2%)
Cough	0	3 (4%)	1 (2%)
Epistaxis	1 (1%)	2 (2%)	0
Respiratory Tract Congestion	3 (4%)	0	0
Wheezing	0	3 (4%)	0
Nasal Congestion	0	2 (2%)	0
Dehydration	4 (5%)	1 (1%)	1 (2%)
Hyperglycaemia	4 (5%)	1 (1%)	1 (2%)
Hyperkalemia	3 (4%)	2 (2%)	0
Hypokalemia	3 (4%)	0	1 (2%)
Hyperlipidaemia	0	2 (2%)	0
Hypocalcaemia	2 (2%)	0	0
Contusion	7 (8%)	0	1 (2%)
Skin Laceration	1 (1%)	3 (4%)	1 (2%)
Muscle Strain	0	2 (2%)	0
Spinal Compression Fracture	2 (2%)	0	0
Blood Glucose Increased	4 (5%)	2 (2%)	1 (2%)
Blood Pressure Increased	0	6 (7%)	0
Blood Creatinine Increased	2 (2%)	2 (2%)	0
Haemoglobin Decreased	1 (1%)	2 (2%)	0
Weight Decreased	2 (2%)	0	0
Dysuria	1 (1%)	3 (4%)	1 (2%)
Hypotension	3 (4%)	0	1 (2%)
Haematoma	2 (2%)	0	0
Tachycardia	1 (1%)	4 (5%)	0
Blood Urea Nitrogen	2 (2%)	2 (2%)	0
Angina Pectoris	0	2 (2%)	0
Arrhythmia	2 (2%)	0	0
Atrial Fibrillation	0	2 (2%)	0
Conjunctivitis	1 (1%)	2 (2%)	0
Conjunctival Haemorrhage	2 (2%)	0	0
Seasonal Allergy	0	3 (4%)	0

[a] If the same subject in a given treatment had more than one occurrence in the same preferred term event category, the subject was counted only once

5.5.1 Renal, Hepatic and Hematologic, Physical Exams and Vital Signs

In the clinical studies, review of renal, hepatic and hematologic function clinical laboratory parameters in the pegloticase dose groups and placebo over time did not show consistent or sustained changes from baseline.

5.6 Adverse Events of Special Interest

This section contains detailed information related to five topics of special interest. These topics are: cardiovascular events, infusion reactions, immunogenicity, gout flares and infections. These topics were chosen for more further analysis to better characterize the safety profile of pegloticase as there was an imbalance in cardiac SAEs in the RCTs, 90% of subjects developed anti-pegloticase antibodies, and the most frequent adverse events associated with pegloticase adminsitration were infusion reactions and gout flares.

5.6.1 Cardiac Serious Adverse Events

In the RCTs there were 7 cardiac SAEs reported: four in the q 2 weeks group; three in the q 4 weeks group and none for placebo. There were six different types of cardiac diagnoses among these 8 SAEs (Table 39). Two of the 7 events (arrhythmia and cardiac arrest) were fatal..

Table 39. Cardiac SAEs in RCTs.

System Organ Class: Preferred Term	Pegloticase		Placebo
	8 mg q 2 weeks N=85 n (%)	8 mg q 4 weeks N=84 n (%)	N=43 n (%)
Cardiac Disorders	**4 (4.7%)**	**3 (3.6%)**	**0**
Arrhythmia	2 (2.4%)	0	0
Angina Pectoris	0	1 (1.2%)	0
Cardiac Arrest	1 (1.2%)	0	0
Cardiac Failure Congestive	1 (1.2%)	0	0
Myocardial Infarction	0	1 (1.2%)	0
Tachycardia	0	1 (1.2%)	0

5.6.1.1 *Cardiovascular SAEs and All-Cause Death Evaluation and Adjudication*

Because of the imbalance in the system organ class (SOC) of cardiac serious adverse events among the three treatment groups as shown in Table 39, the Sponsor performed additional analyses to further investigate these events. To expand the scope of the investigation and ensure evaluation of all relevant adverse events in this area, the Sponsor reviewed all cardiovascular events and deaths across Phase 2, Phase 3 and OLE studies. For this purpose, an independent Cardiovascular Event Adjudication Committee comprised of three outside expert clinicians was established. The Committee performed an ad hoc independent and comprehensive review of all potential cardiovascular SAEs. Initially, the Committee Chairman selected events of interest from blinded SAE listings that included both verbatim and preferred terms (Medical Dictionary for Regulatory Activities version 9.0). Prior to and during the adjudication process, the Committee members were blinded to treatment group and study outcomes. Infusion reactions were not included in the initial adjudication of the events in the RCTs to protect the blind, but were reviewed by the committee chairman after completion of the blinded adjudication. Prior to

initiating their process of evaluation of the potential serious cardiovascular events in the pegloticase studies, the Committee developed a Charter to define their responsibilities and definitions of the various endpoints. The complete methods and reports are provided in Appendix 6.

For adjudicated diagnoses of a cardiovascular (CV) event, the following definitions were used:

Anti-Platelet Trialist Collaborative (APTC) Events

- Cardiovascular Death
- Non-fatal myocardial infarction
- Non-fatal stroke

Non-APTC Major Cardiovascular Adverse Events

- Unstable Angina (includes acute coronary syndrome)
- Coronary revascularization
- Transient ischemic attacks
- Venous and peripheral arterial vascular thrombotic and embolic events
- Congestive heart failure
- Arrhythmia with no evidence of ischemia
- Cerebral revascularization

5.6.1.2 *Cardiovascular Risk in the Study Population*

The cardiovascular (CV) risk profile of the Phase 3 population was further characterized by assessing the prevalence of underlying cardiovascular diseases and risk factors at baseline (Table 40) according to treatment group. A high pre-existing prevalence of CV disease at baseline was present in the phase 3 population.

Table 40. Pre-existing Cardiovascular Conditions and Cardiovascular Risk Factors in the RCTs.

	Pegloticase		Placebo
	8 mg q 2 weeks N=85	8 mg q 4 weeks N=84	N=43
	n (%)	n (%)	n (%)
One or more of the following CV conditions/risk factors	**73 (88%)**	**71 (85%)**	**35 (81%)**
Cardiac arrhythmias	19 (22%)	8 (10%)	7 (16%)
Cardiac failure/ LV dysfunction	12 (14%)	8 (10%)	6 (14%)
Cerebrovascular disease	4 (5%)	3 (4%)	1 (2%)
Coronary disease	14 (17%)	16 (19%)	9 (21%)
Diabetes	24 (28%)	18 (21%)	8 (19%)
Dyslipidemia	42 (49%)	41 (49%)	20 (47%)
Hypertension	62 (73%)	60 (71%)	31 (72%)
Vascular disease, peripheral	7 (8%)	6 (7%)	3 (7%)

Similarly, important cardiovascular risk factors, such as diabetes, hypertension, hyperlipidemia were very common in the RCTs (Table 40). Smoking (data not collected in the study) and

obesity (not considered a strong risk factor) were not included in the risk assessment. The number of cardiovascular risk factors in subjects in the RCTs is show in Table 41.

Table 41. Number of Cardiovascular Risk Factors in the RCTs.

	Pegloticase		Placebo
	8 mg q 2 weeks N=85	8 mg q 4 weeks N=84	N=43
Number of Risk Factors	n (%)	n (%)	n (%)
0	12 (14%)	13 (15%)	8 (19%)
Subjects with ≥ 1 CV Risk Factor	73 (86%)	71 (85%)	35 (81%)
1	23 (27%)	24 (29%)	11 (26%)
2	16 (19%)	20 (24%)	9 (21%)
3	16 (19%)	14 (17%)	7 (16%)
4	9 (11%)	10 (12%)	4 (9)%
5	6 (7%)	2 (2%)	3 (7%)
6	3 (4%)	1 (1%)	1 (2%)

5.6.1.3 *Changes in Blood Pressure, Glucose, Cholesterol and Body Mass Index*

The post-hoc Cardiovascular Adjudication Committee evaluated changes in four biological parameters that are potentially associated with cardiovascular risk or disease were explored during the course of the RCTs.

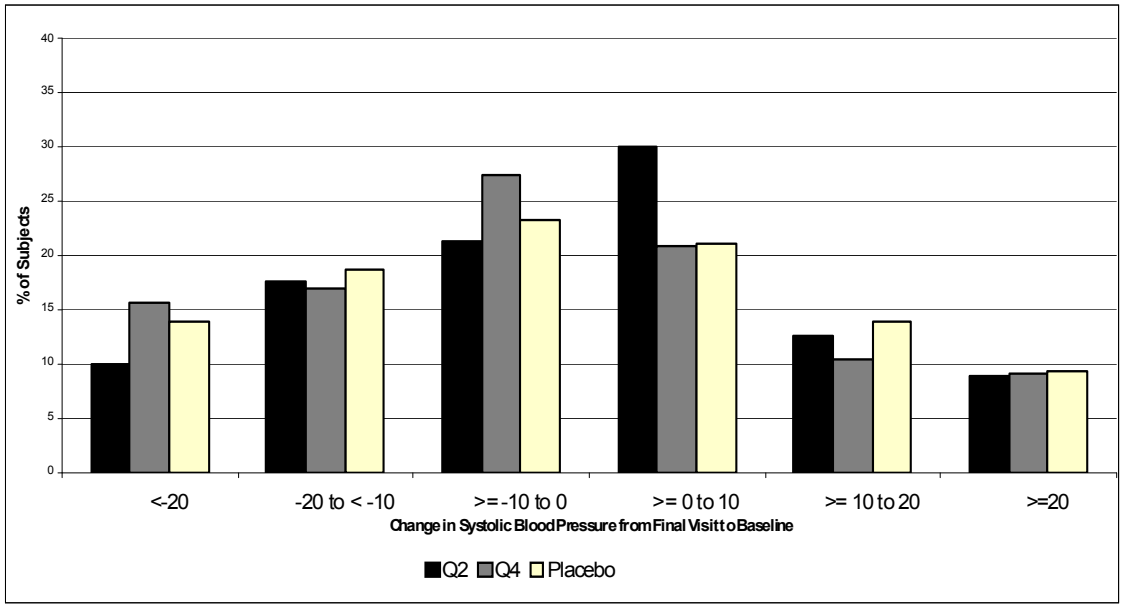
High systolic blood pressure is a potent cardiovascular risk factor. Mean changes in systolic blood pressure from baseline to final visit were -1.3, -4.8 and -2.4 mmHg for pegloticase q 2 weeks, pegloticase q 4 weeks and placebo, respectively. The histogram of change in systolic blood pressure change from beginning to end of the Phase 3 studies shows no clinically significant changes over time, and no differences among the three treatment arms (Figure 35).

The mean changes in serum glucose from baseline to Final Visit were 27.6, 9.3 and 14.7 mg/dL for pegloticase q 2 weeks, pegloticase q 4 weeks and placebo, respectively. The assessment of serum glucose shows an increase in glucose of > 20 mg/dL, from beginning to end of the studies, in more than 30% of subjects in each of the three treatment groups. Overall, these results suggest there is no meaningful effect of pegloticase on serum glucose (see Appendix 6).

Mean changes in total cholesterol from baseline to Final Visit was 0.2, -8.3 and 3.0 mg/dL for pegloticase q 2 weeks, pegloticase q 4 weeks and placebo, respectively. There does not appear to be a change in total cholesterol (see Appendix 6) as a function of time, or a difference across treatment groups.

Mean changes in body mass index from baseline to Final Visit were 0.1, 0.5 and 0.1 kg/m^2 for pegloticase q 2 weeks, pegloticase q 4 weeks and placebo, respectively. There does not appear to be a change in body mass index as a function of time, or a difference across treatment groups. (see Appendix 6)

Figure 35. Change in Systolic Blood Pressure During RCTs.



5.6.1.4 *Non-serious Treatment-Emergent Cardiovascular Events*

Non serious treatment-emergent cardiovascular adverse events were not different across treatment groups (Table 42).

Table 42. Non-serious Treatment Emergent Cardiovascular Events Occurring > 2% Rate.

Preferred Term	Pegloticase		Placebo
	8 mg q 2 weeks N = 85 n (%)	8 mg q 4 weeks N = 84 n (%)	N = 43 n (%)
Cardiovascular Type Adverse Event	21 (24.7%)	34 (40.5%)	16 (37.2%)
Edema, Peripheral	10 (11.8%)	11 (13.1%)	6 (14.0%)
Dizziness	3 (3.5%)	7 (8.3%)	4 (9.3%)
Dyspnea	3 (3.5%)	5 (6.0%)	2 (4.7%)
Hypertension	2 (2.4%)	5 (6.0%)	2 (4.7%)
Chest Pain	4 (4.7%)	4 (4.8%)	1 (2.3%)
Paraesthesia	0	3 (3.6%)	2 (4.7%)
Bradycardia	1 (1.2%)	1 (1.2%)	2 (4.7%)
Hypotension	3 (3.5%)	0	1 (2.3%)
Tachycardia	1 (1.2%)	3 (3.6%)	0
Chest Discomfort	0	3 (3.6%)	0
Syncope	1 (1.2%)	2 (2.4%)	1 (2.3%)
Atrial Fibrillation	0	2 (2.4%)	0
Atrioventricular Block 1st Degree	1 (1.2%)	0	1 (2.3%)
Dyspnea on Exertion	1 (1.2%)	1 (1.2%)	0
Pleural Effusion	0	1 (1.2%)	1 (2.3%)

5.6.1.5 *Serious Cardiovascular Events by APTC and Non-APTC Definitions*

Table 43 and Table 44 show the overall incidence of cardiovascular events in categories of APTC and Non-APTC events in the RCTs and in the open label studies (OLE and Phase 2 study), respectively. In the RCTs, there were three APTC events in the pegloticase treatment groups, and 9 non-APTC events in the pegloticase treatment groups, and no events in the placebo treatment group.

In the open label Phase 2 and OLE studies (no placebo), there were a total of 3 APTC events and eight non-APTC cardiovascular events.

Table 43. Cardiovascular SAEs by APTC and Non-APTC Events in Pegloticase RCTs.

Treatment	N	APTC	Non-APTC
Phase 3 RCTs			
Pegloticase 8 mg q 2 weeks	85	2	3
Pegloticase 8 mg q 4 weeks	84	1	6
Placebo	43	0	0

Table 44. Cardiovascular SAEs by APTC and Non-APTC Events in Pegloticase Open Label Studies.

Treatment	N	APTC	Non-APTC
OLE			
Pegloticase 8 mg q 2 weeks	59	1	7
Pegloticase 8 mg q 4 weeks	51	1	1
Phase 2			
Pegloticase 12mg q 4 weeks	41	1	0

5.6.1.6 *Frequency of Adjudicated Individual Serious Cardiovascular Events*

Table 45 shows a listing of the various diagnoses made by the Cardiovascular Adjudication Committee. No one diagnosis predominated.

Table 45. Analyses of Subjects with Adjudicated APTC and Non-APTC Serious Cardiovascular Events in the RCTs.

	Pegloticase			Placebo
	8 mg q 2 weeks N=85	8 mg q 4 weeks N=84		N=43
	n =	n =		n =
All APTC	2	1		0
CV Death	2	0		0
Non-fatal MI	0	1		0
All Non-APTC	2*	6		0
CHF	2	1		0
Arrhythmia	1	1		0
DVT	0	1		0

	Pegloticase			Placebo
	8 mg q 2 weeks N=85	8 mg q 4 weeks N=84		N=43
TIA	0	1		0
Angina	0	1		0
Coronary revascularization	0	1		0

***Two subjects had multiple events: Subject C0406: 311-005 had 2 events (CHF and arrhythmia); Subject C0405: 122-003 had both an APTC event (MI) and a non-APTC event (DVT).**

There were 12 serious cardiovascular events in 10 subjects. Brief descriptions of the disposition of the serious cardiovascular events in the RCTs are provided in Table 46. Patient narratives are in Appendix 4.

Table 46. Adjudicated Cardiovascular Events in RCTs.

Study Subject number	RCT Dose Group	Age Sex	Relevant Medical History	Event	Time from Last Pegloticase Dose	Disposition
C0405: 124-001	Pegloticase 8 mg q 2 weeks	76 y/o male	HTN; arrhythmia; CRF	CHF (Resolved)	14 days after dose 9	Completed RCT and entered OLE
CO406: 311-005	Pegloticase 8 mg q 2 weeks	67 y/o male	Implanted defibrillator; cardiomegaly; HTN; CRF	Cardiac arrhythmia (Resolved) CHF (Resolved)	22 days after dose 4 3 days after dose 7	Completed RCT and entered OLE
C0405: 117-001	Pegloticase 8 mg q 4 weeks	60 y/0 male	CAD; stent placement one month before the event; HTN; hypercholesterolemia	Infusion reaction with ECG changes, angina and coronary revascularization (Resolved)	At dose 5	Discontinued after 8 doses
CO405: 122-003	Pegloticase 8 mg q 4 weeks	73 y/o male	CAD; atrial fibrillation; HTN; CRF	Acute myocardial infarction (Resolved) Deep venous thrombosis (Resolved)	13 days after dose 2 5 days after dose 4	Completed RCT and entered OLE
CO406: 301-006	Pegloticase 8 mg q 4 weeks	62 y/o female	HTN; tachycardia; CRF secondary to SLE; hyperlipidemia	Arrythhmia: supraventricular tachycardia; hyperkalemia (Resolved)	11 days after third infusion (after second pegloticase dose)	Completed RCT and entered OLE
CO406: 311-001	Pegloticase 8 mg q 4 weeks	50 y/o male	CAD; HTN; coronary artery PTCA and stent placement; hypercholesterolemia	Angina; Treated with angioplasty; no evidence of myocardial infarction (Resolved)	5 days after second infusion (placebo dose)	Completed RCT and entered OLE.
CO406: 301-012	Pegloticase 8 mg q 4 weeks	78 y/o female	DM; COPD	Transient ischemic attack (Resolved)	35 days after second infusion (placebo dose)	Withdrew consent after dose 2 which was 35 days before event
C0405: 203-001	Pegloticase 8 mg q 2 weeks	61 y/o male	Details in Table 33: Deaths in the pegloticase RCTs			
C0406: 315-005	Pegloticase 8 mg q 2 weeks	69 y/o male	Details in Table 33: Deaths in the pegloticase RCTs			
C0405: 102-006	Pegloticase 8 mg q 4 weeks	64 y/o male	Details in Table 33: Deaths in the pegloticase RCTs			

CAD=coronary artery disease; CHF=congestive heart failure; CRF=chronic renal failure; COPD=chronic obstructive pulmonary disease; HTN=hypertension; LVEF=left ventricular ejection fraction; OLE=open label extension; SLE=systemic lupus erythematosus

5.6.1.7 *Adjudicated Serious Cardiovascular Events with Longer Term Treatment in the OLE Study*

Brief descriptions of serious CV events in open label Phase 2 and OLE studies are described in Table 47. There were a total of 10 CV events in 9 subjects. Patient narratives are in Appendix 4.

Table 47. Adjudicated Cardiovascular Events in Open Label Phase 2 and OLE Studies.

Study: Subject number	Dose Group	Age Sex	Relevant Medical History	Event	Time from Last Pegloticase Dose	Disposition
C0405: 204-001	Placebo to pegloticase 8 mg q 2 weeks	49 y/o male	Hyperlipidemia; obesity	Deep venous thrombosis (Ongoing at data cut-off)	14 days after dose 3	Continued in the study
C0405: 120-001*	Pegloticase 8 mg q 2 weeks to 8 mg q 4 weeks	52 y/o male	Chronic renal insufficiency	Myocardial infarction (Resolved)	1 day after dose 20	Continued in the study
C0405: 122-004	Pegloticase 8 mg q 4 weeks to 8 mg q 2 weeks	54 y/o female	CKD, hypercholerterolemia, HTN, (During RCT: Chronic kidney failure; hip fracture)	Bilateral DVTs (Resolved) Concurrent with osteomyelitis first MTP; toe amputation; ORSA sepsis	12 days after dose 10	Death due to sepsis Details in Table 34: Deaths in the pegloticase OLE Study
C0405: 109-008	Placebo to pegloticase 8 mg q 2 weeks	50 y/o male	CHF; HTN; Ischemic cardiomyopathy; coronary stent placement; polycythemia vera; cirrhosis; pitting edema; rheumatoid arthritis; Non-serious infusion reaction with dose 4	Infusion reaction (Resolved) Hospitalized with acute muscle spasms; abnormal ECG; CHF; polycythemia vera Patient did not take cardiac medications on day of event	Prior to dose 6 infusion	Discontinued
C0405: 130-002*	Placebo to 8 mg pegloticase q 2 weeks	75 y/o male	Angioplasty 1 month prior to event; CAD; MI; hyperlipidemia, HTN; pulmonary emboli, DVT, renal insufficiency, abdominal aortic aneurysm, CKD, obesity	DVT (Resolved)	12 days after dose 19	Continued in the study

Study: Subject number	Dose Group	Age Sex	Relevant Medical History	Event	Time from Last Pegloticase Dose	Disposition
C0405: 130-006*	Pegloticase 8 mg q 4 weeks to pegloticase 8 mg q 4 weeks	73 y/o female	Cerebrovascular disease, HTN; chronic renal insufficiency, bilateral renal artery stenosis and renal stents	Cerebral revascularization Scheduled hospitalization for right carotid endarterectomy due to right carotid stenosis. (Resolved)	21 days after dose 14	Continued in the study
C0406: 307-006*	Pegloticase 8 mg q 2 weeks to pegloticase 8 mg 2 q weeks	59 y/o male	CAD, CABG, pacemaker and defibrillator implanted; CHF; cardiomyopathy; HTN; hypercholesterolemia; COPD; atrial fibrillation; peripheral vascular disease; DM, OA, RA	MI post-operatively after right total knee replacement; acute and chronic renal impairment; seizure (Resolved) CHF (Ongoing)	20 days after dose 36 46 days after dose 36	Discontinued after dose 36
C0406: 311-005**	Pegloticase 8 mg q 2 weeks to pegloticase 8 mg q 2 weeks	68 y/o male	Defibrillator implanted; EF 29-35%; severe TR and moderate MVR; MV repair x 2;	CHF (Resolved)	7 days after dose 38	Discontinued
C0406: 325-002	Pegloticase 8 mg q 2 weeks to pegloticase 8 mg q 2 weeks	67 y/o male	History of PE; multiple DVTs; Factor V Leiden deficiency; bradycardia; CAD; chronic renal insufficiency	DVT (Resolved)	14 days after dose 29	Continued in the study
C0403: 002-003	Pegloticase 12 mg q 4 weeks	77 y/o female	PE; DVT; CKD; DM; COPD; CAD; HTN; hyperlipidemia	Non-fatal stroke (infarct) (Resolved)	27 days after the second infusion	Continued in the study

***Reported in the 120-Day safety update**
****Event occurred after the 120-Day safety cut-off date**
CAD=coronary artery disease; CHF=congestive heart failure; CRF=chronic renal failure; COPD=chronic obstructive pulmonary disease; HTN=hypertension; LVEF=left ventricular ejection fraction; PE=pulmonary embolism; DM=diabetes mellitus; CKD=chronic kidney disease

5.6.1.8 *Time to All-Cause Cardiovascular (APTC and Non-APTC) Events*

The temporal distribution of adjudicated APTC and non-APTC cardiovascular events (combined) over the course of the six month Phase 3 studies is shown in Figure 36. There is no evidence of a cumulative risk of a CV event with continued pegloticase exposure.

Figure 36. Time to Event Analysis: Adjudicated APTC and Non-APTC CV Events in RCTs.

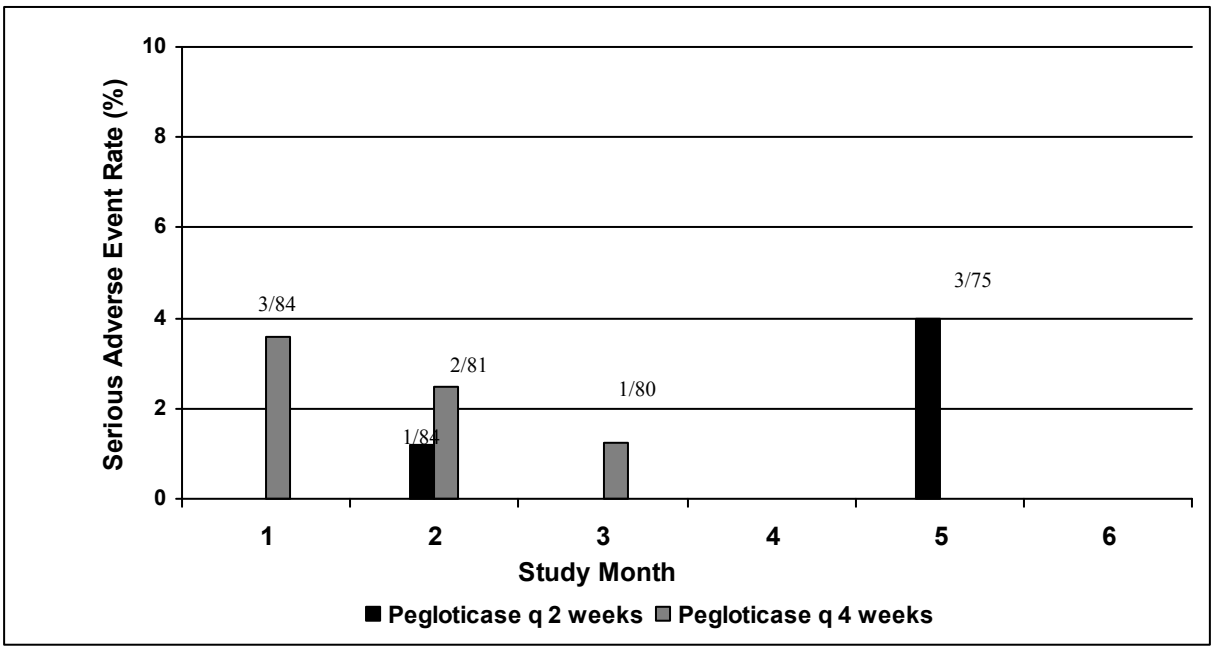
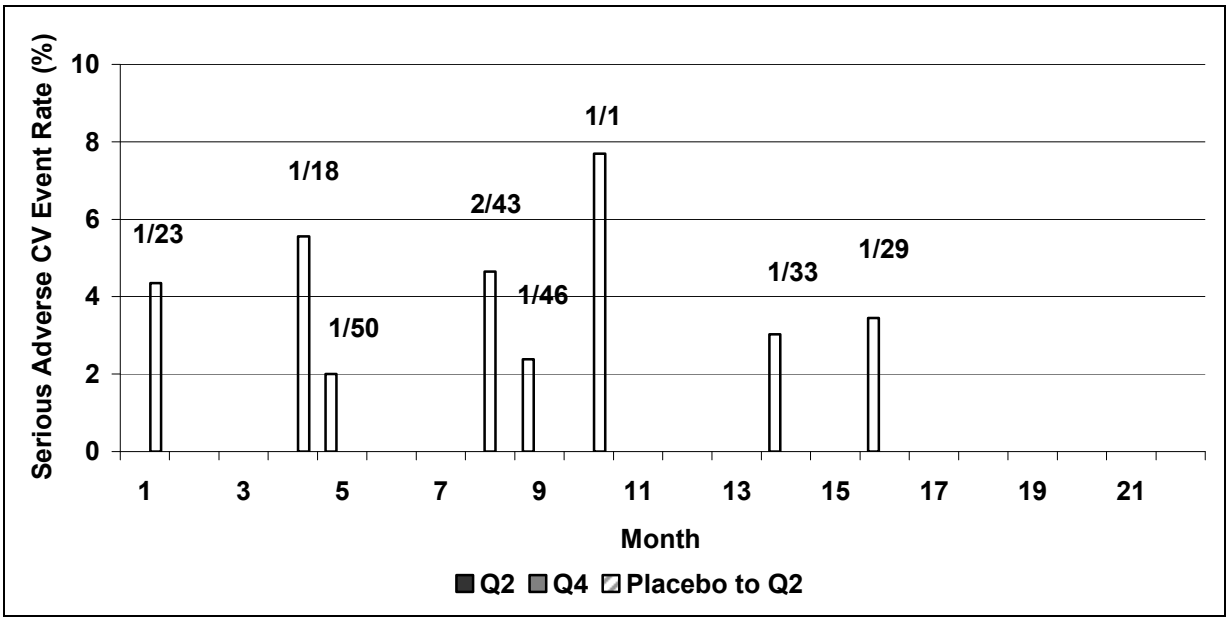


Figure 37 contains the CV event rates for those subjects that continued into the OLE Study. This includes placebo subejcts that received pegloticase in the OLE Study. There was no increasing CV event rate over time with pegloticase treatment.

Figure 37. Time to Event Analysis: Adjudicated APTC and Non-APTC CV Events in OLE Study.



Months represent Time In OLE Study After 6 Months of RCT.
Numerator represents the number of subjects that had a CV event and denominator represents number of subjects that achieved that amount of OLE Study time.

5.6.1.9 *Post-hoc Evaluation of EKGs from the RCTS*

The Sponsor initiated a post-hoc blinded EKG review of all EKGs obtained during the RCTs. Briefly, EKGs were analyzed by two observers blinded to whether the patient received pegloticase or placebo. There was no evidence of QT prolongation associated with pegloticase. The full report of this evaluation is provided in Appendix 7.

5.6.1.10 *Summary for the Cardiovascular Event Assessment during the Pegloticase Studies*

There was an imbalance in cardiovascular events observed for the pegloticase treatment groups compared to placebo. The investigator reported events were confirmed by the results of evaluation by an expert Cardiovascular Adjudication Committee. Interpretation of the likelihood of a causal relationship of pegloticase is confounded by the small number of events, the relatively high number of cardiovascular co-morbidities at baseline in the study population, and the 2:2:1 randomization scheme that led to a 4-fold increase in exposure to pegloticase compared to placebo. No particular cardiovascular event type was prominent, and there was no evidence for a clustering of the timing of events during the randomized controlled trials nor the open-label extension period. Additionally, chronic exposure to pegloticase was not associated with an increase in the cardiovascular event rate.

5.6.2 Infusion Reactions

Infusion reactions were defined as any adverse event that occurred during or within 2 hours after the infusion of blinded study medication. Infusion reactions occurred during the infusion of pegloticase and placebo.

A summary of infusion reactions is presented in Table 48. Most infusion reactions were mild to moderate in severity and did not require specific therapy. The incidence of infusion reactions and the number of serious infusion reactions were fewer in the pegloticase 8 mg every 2 weeks group (26%) compared to the pegloticase 8 mg every 4 weeks group (40%). Of the 34 infusion reactions in the pegloticase 8 mg every 4 weeks group, five subjects had an infusion reaction during placebo infusion. Likewise, there were two placebo subjects that had a total of three mild to moderate infusion reactions when placebo was administered.

Table 48. Infusion Reactions in the RCTs.

Category for infusion related reaction Adverse Events	Pegloticase		Placebo
	8 mg q 2 weeks N=85 n	8 mg q 4 weeks N=84 n	N=43 n
Incidence of Infusion Reaction	**22 (26%)**	**34 (40%)**	**2 (5%)**
Mild	7 (8%)	4 (5%)	0
Moderate	11 (13%)	22 (26%)	2 (5%)
Severe	4 (5%)	8 (10%)	0
SAE	4 (5%)	7 (8%)	0
Infusion Reactions Leading to Discontinuation	9 (11%)	11 (13%)	0

A total of 68 signs and symptoms were recorded for the 113 pegloticase-associated infusion reactions that occurred in the RCTs. The most common signs and symptoms occurring during infusion reactions in the pegloticase q 2 weeks group were: urticaria (11%), dyspnea (7%), erythema (6%), flushing (6%), chills (5%), hyperhidrosis (5%), and hypertension (5%). The most common signs and symptoms occurring during infusion reactions in the pegloticase q 4 weeks group were: chest discomfort (10%), chest pain (10%), pruritis (10%), erythema (10%), flushing (8%), back pain (7%), dyspnea (7%), nausea (7%), pain (7%), rash (7%), and urticaria (7%) (Table 49).

Table 49. Signs and Symptoms of Infusion Reactions (RCTs).

	Pegloticase				Placebo	
	8 mg q 2 weeks (N = 85)		8 mg q 4 weeks (N = 84)		(N = 43)	
Signs and Symptoms	Total Events	n (%)	Total Events	n (%)	Total Events	n (%)
Abdominal discomfort	1	1 (1.2%)	0	0	0	0
Abdominal distension	0	0	1	1 (1.2%)	0	0

	Pegloticase				Placebo	
	8 mg q 2 weeks (N = 85)		8 mg q 4 weeks (N = 84)		(N = 43)	
Signs and Symptoms	Total Events	n (%)	Total Events	n (%)	Total Events	n (%)
Abdominal pain	1	1 (1.2%)	2	2 (2.4%)	0	0
Abdominal pain upper	0	0	1	1 (1.2%)	0	0
Anxiety	0	0	1	1 (1.2%)	0	0
Arthralgia	0	0	1	1 (1.2%)	0	0
Back pain	3	1 (1.2%)	12	6 (7.1%)	0	0
Blood pressure decreased	1	1 (1.2%)	0	0	0	0
Blood pressure increased	0	0	3	3 (3.6%)	0	0
Bradycardia	0	0	1	1 (1.2%)	0	0
Bronchospasm	0	0	1	1 (1.2%)	0	0
Cardiac flutter	0	0	1	1 (1.2%)	0	0
Chest discomfort	7	3 (3.5%)	13	8 (9.5%)	0	0
Chest pain	1	1 (1.2%)	10	8 (9.5%)	0	0
Chills	4	4 (4.7%)	0	0	0	0
Cold sweat	1	1 (1.2%)	0	0	0	0
Conjunctivitis	2	1 (1.2%)	1	1 (1.2%)	0	0
Cough	0	0	1	1 (1.2%)	0	0
Discomfort	1	1 (1.2%)	0	0	0	0
Dizziness	3	3 (3.5%)	1	1 (1.2%)	0	0
Dyspepsia	1	1 (1.2%)	0	0	0	0
Dysphagia	0	0	1	1 (1.2%)	0	0
Dyspnoea	6	6 (7.1%)	8	6 (7.1%)	1	1 (2.3%)
Ear congestion	0	0	1	1 (1.2%)	0	0
Erythema	6	5 (5.9%)	13	8 (9.5%)	0	0
Eye pruritus	0	0	1	1 (1.2%)	0	0
Fatigue	1	1 (1.2%)	0	0	0	0
Feeling hot	3	3 (3.5%)	0	0	0	0
Flushing	6	5 (5.9%)	9	7 (8.3%)	3	1 (2.3%)
Headache	1	1 (1.2%)	5	4 (4.8%)	0	0
Heart rate increased	1	1 (1.2%)	0	0	0	0
Hyperaemia	0	0	1	1 (1.2%)	0	0
Hyperhidrosis	5	4 (4.7%)	2	2 (2.4%)	0	0
Hypertension	6	4 (4.7%)	1	1 (1.2%)	0	0
Hypotension	3	3 (3.5%)	1	1 (1.2%)	0	0
Hypoxia	0	0	1	1 (1.2%)	0	0
Incontinence	1	1 (1.2%)	0	0	0	0
Joint swelling	0	0	1	1 (1.2%)	0	0
Mental status changes	0	0	1	1 (1.2%)	0	0
Muscle spasms	7	2 (2.4%)	4	2 (2.4%)	0	0
Mental status changes	0	0	1	1 (1.2%)	0	0
Muscle spasms	7	2 (2.4%)	4	2 (2.4%)	0	0
Musculoskeletal chest pain	1	1 (1.2%)	0	0	0	0
Musculoskeletal discomfort	0	0	2	1 (1.2%)	0	0
Musculoskeletal stiffness	0	0	1	1 (1.2%)	0	0
Nasal congestion	0	0	2	2 (2.4%)	0	0

	Pegloticase				Placebo	
	8 mg q 2 weeks (N = 85)		8 mg q 4 weeks (N = 84)		(N = 43)	
Signs and Symptoms	**Total Events**	**n (%)**	**Total Events**	**n (%)**	**Total Events**	**n (%)**
Nausea	3	2 (2.4%)	7	6 (7.1%)	0	0
Neck pain	0	0	2	2 (2.4%)	0	0
Ocular hyperaemia	0	0	1	1 (1.2%)	0	0
Oedema	0	0	1	1 (1.2%)	1	1 (2.3%)
Oedema peripheral	0	0	1	1 (1.2%)	0	0
Pain	2	1 (1.2%)	8	6 (7.1%)	0	0
Pallor	1	1 (1.2%)	2	2 (2.4%)	0	0
Pruritus	5	3 (3.5%)	9	8 (9.5%)	0	0
Pulmonary congestion	0	0	1	1 (1.2%)	0	0
Rash	3	3 (3.5%)	7	6 (7.1%)	0	0
Rash macular	1	1 (1.2%)	1	1 (1.2%)	0	0
Sensation of pressure	0	0	1	1 (1.2%)	0	0
Speech disorder	0	0	1	1 (1.2%)	0	0
Swelling	1	1 (1.2%)	1	1 (1.2%)	0	0
Swelling face	0	0	1	1 (1.2%)	0	0
Swollen tongue	0	0	1	1 (1.2%)	0	0
Tachycardia	3	3 (3.5%)	3	3 (3.6%)	0	0
Throat irritation	0	0	1	1 (1.2%)	0	0
Throat tightness	1	1 (1.2%)	3	2 (2.4%)	0	0
Tongue oedema	1	1 (1.2%)	0	0	0	0
Tremor	2	2 (2.4%)	0	0	0	0
Urticaria	9	9 (10.6%)	11	6 (7.1%)	0	0
Vomiting	1	1 (1.2%)	3	3 (3.6%)	0	0
Wheezing	2	2 (2.4%)	2	2 (2.4%)	0	0

We investigated whether there was a grouping of these symptoms that might suggest an anaphylactic reaction to pegloticase. A hierarchical cluster analysis was performed using 16 symptoms including urticaria, chest discomfort, erythema, flushing, dyspnea, nausea, and pain, and eight combination terms formed by grouping physiologically related symptoms. We found 15 distinct groups, each of which was characterized primarily by the presence of a single symptom. The largest (21%) cluster of infusion reactions was characterized by the single symptom, muscle pain. None of the remaining small clusters showed grouping suggestive of symptoms of an allergic reaction..

5.6.2.1 *Serious and Clinically Significant Infusion Reactions*

Signs and symptoms of serious infusion reactions included: dyspnea, hypotension, hypertension, swelling, brochospasm, chest pain, nausea, vomiting and abdominal pain and cramping. One subject in the RCTs received epinephrine. Details of subjects with serious infusion reactions are shown in Table 50. Patient narratives are included in Appendix 5.

Table 50. Brief Descriptions of Serious Infusion Reactions.

Study: Subject number	Pegloticase Dose No.	Disposition	Severity of Infusion Reaction, Symptoms, Anti-pegloticase Antibody Titer, and PUA Response
C0405: 102-003	8 mg q 2 weeks Dose 5	Discontinued	Moderate Infusion Reaction Lingual swelling, dyspnea, and nausea. Anti-pegloticase antibody titer 1:21870. PUA > 6 mg/dL
C0405: 105-001	8 mg q 2 weeks Dose 3	Discontinued	Moderate Infusion Reaction Hypotension, diaphoresis, incontinence, tremor, hyperhidrosis, and feeling hot and confused. The subject developed rigors subsequent to treatment for the IR. Hospitalized overnight for observation. Resolved. Anti-pegloticase antibody titer 1:7290 at dose 3; 1:21,870 at dose 2. PUA > 6 mg/dL
C0405: 117-002	8 mg q 2 weeks Dose 3	Discontinued	Severe Infusion Reaction Throat and chest tightness, shortness of breath, shaking, chills, dizziness, fatigue, diaphoresis, pallor, and gastrointestinal upset. Anti-pegloticase antibody titer 1:2430 PUA > 6 mg/dL
C0406: 308-003	8 mg q 2 weeks Dose 2	Discontinued	Severe Infusion Reaction Severe back and leg cramps, facial flushing and clamminess. Anti-pegloticase antibody titer 1:65610. PUA > 6 mg/dL
C0405: 107-006	8 mg q 4 weeks Dose 4	Discontinued	Moderate Infusion Reaction Bronchospasm, shortness of breath (O_2 saturation of 82%), pallor, blood pressure of 203/68 mmHg, heart rate of 118 bpm, lightheadedness, and flash pulmonary edema. Observed in ER and released on the same day. Resolved. Anti-pegloticase antibody titer 1:7290. PUA > 6 mg/dL
C0405: 113-001	8 mg q 4 weeks Dose 2	Continued	Moderate Infusion Reaction Non-APTC CV event. Chest pain, nausea, vomiting, diaphoresis, and shortness of breath. ECG showed atrial fibrillation with rapid ventricular response. Observed in ER and released on the same day. Resolved. Anti-pegloticase antibody titer 1:2430. PUA > 6 mg/dL

Study: Subject number	Pegloticase Dose No.	Disposition	Severity of Infusion Reaction, Symptoms, Anti-pegloticase Antibody Titer, and PUA Response
C0405: 117-001	8 mg q 4 weeks Dose 3	Continued	Mild Infusion Reaction Non-APTC CV event. Chest tightness, throat tightness, increased blood pressure, and shortness of breath. ECG showed ST-T abnormalities consistent with acute ischemia. Subject underwent angiography revealing right coronary artery lesion and had emergency coronary stent placement. Hospitalized. Resolved. Anti-pegloticase antibody titer 1:2430. PUA > 6 mg/dL
C0405: 129-005	8 mg q 4 weeks Dose 1	Continued	Severe Infusion Reaction Blood pressure was elevated prior to the infusion and continued to increase during the infusion, which was stopped. Subject had a history of HTN. Hospitalized. Resolved. Anti-pegloticase antibody titer 0. PUA > 6 mg/dL
C0405: 133-005	8 mg q 4 weeks Dose 4	Discontinued	Severe Infusion Reaction Chest pain, nausea and abdominal pain, elevated blood pressure, shortness of breath and disorientation to place and date. Subject had a history of cardiomyopathy, cardiac failure congestive, and hypertension. Observed in ER and released on the same day. Resolved. Anti-pegloticase antibody titer 1:810. PUA > 6 mg/dL
C0406: 319-004	8 mg q 4 weeks Dose 2	Discontinued	Severe Infusion Reaction Wheezing, stomach bloating and cramping, pallor, headache and sweating. This was the only subject in the double-blind studies program who received epinephrine. Observed in ER and released on the same day. Resolved. Anti-pegloticase antibody titer 1:270. PUA > 6 mg/dL
C0406: 330-007	8 mg q 4 weeks Dose 3	Discontinued	Moderate Infusion Reaction Flushing, diaphoresis, shortness of breath (with no wheezing on physical examination), light headedness, and rash. Reported as “anaphylactic” by the Investigator. On review of the case, the Sponsor deemed this to be consistent with an anaphylactoid reaction. Resolved with diphenhydramine and prednisone. Anti-pegloticase antibody titer 1:810. PUA > 6 mg/dL

There were 6 infusion reactions that were not reported as SAEs by the Investigator to the Sponsor but which after review by the Sponsor were determined to be clinically significant (Table 51). These AEs were syndromes included stridor, wheezing, peri-oral/lingual edema, rash/urticaria, and/or hemodynamic instability. Patient narratives are in Appendix 5.

Table 51. Descriptions of Clinically Significant Infusion Reactions in RCTs.

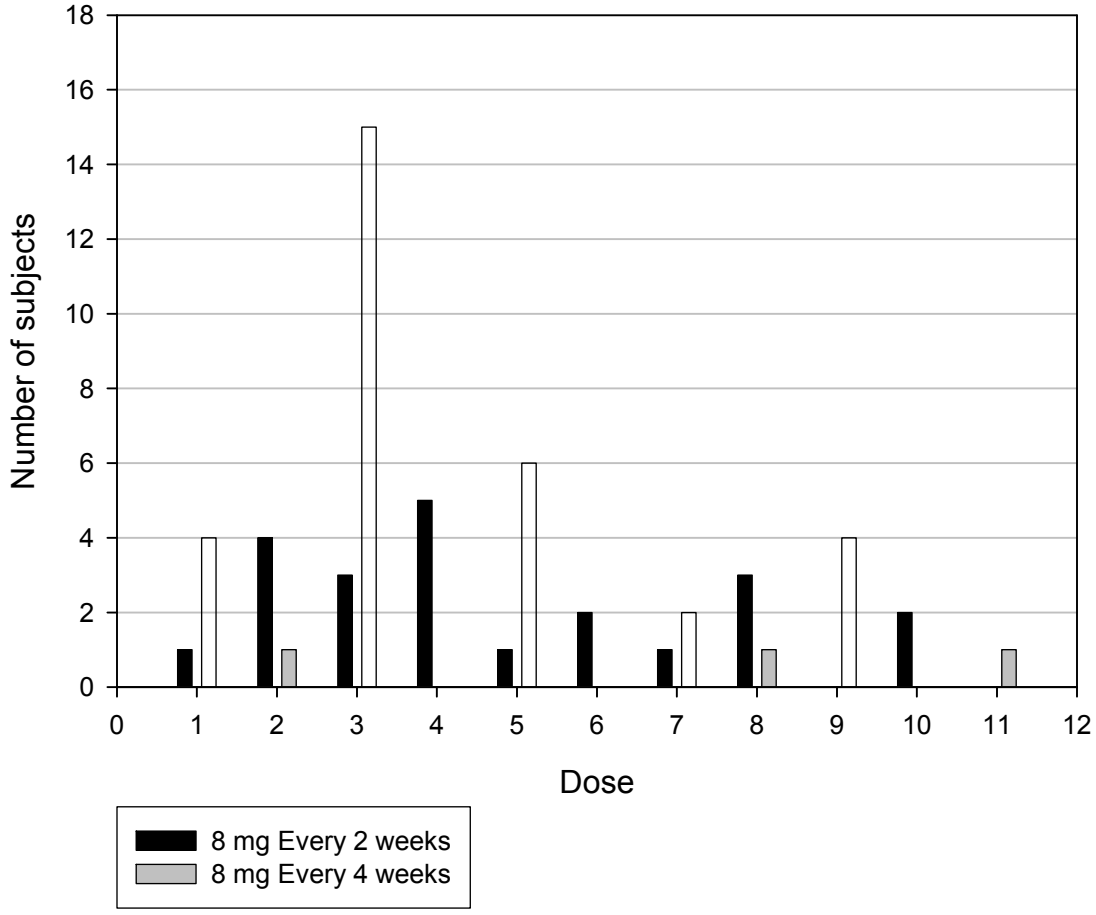
Study: Subject number	Pegloticase Dose No.	Disposition	Severity of infusion reaction, Symptoms, Anti-pegloticase Antibody Titer, and PUA Response
Pegloticase 8 mg q 2 weeks			
C0406: 313-007	Dose 1	Discontinued	Mild infusion reaction Flushing, tachycardia, hypotension, rigors, and urticaria. Subject did not take fexofenadine and acetaminophen pre-infusion, but did receive pre-infusion hydrocortisone. Anti-pegloticase antibody titer 1:90. PUA > 6 mg/dL
Pegloticase 8 mg q 4 weeks			
C0405: 101-004	Dose 3	Discontinued	Moderate infusion reaction Diffuse facial flushing and moderate swelling of the lip and tongue. Anti-pegloticase antibody titer 1:270. PUA > 6 mg/ml
C0405: 103-004	Dose 1	Discontinued	Moderate infusion reaction Chest tightness, wheezing, and muscle spasm in his thoracic and lumbar spine. Anti-pegloticase antibody titer 1:2430. PUA > 6 mg/ml
C0405: 122-010	Dose 3	Discontinued	Moderate infusion reaction Increased blood pressure, dyspnea without wheezing on examination, hypoxia (O_2 saturation of 87%), tachycardia, and urticaria. No anti-pegloticase antibody detected. PUA > 6 mg/ml
C0405: 130-001	Dose 3	Discontinued	Severe infusion reaction Back pain and throat tightness. Anti-pegloticase antibody titer 1:810. PUA > 6 mg/ml
C0406: 401-006	Dose 3 Dose 5	Continued	Moderate infusion reaction Facial hyperemia, facial edema, tachycardia, dyspnea, and back pain. An ECG showed sinus tachycardia Anti-pegloticase antibody titer 1:270 PUA < 6 mg/ml Moderate infusion reaction Dyspnea, facial erythema, and hypotension. Anti-pegloticase antibody titer 1:270 PUA < 6 mg/ml

*** In addition, subject C0406:309-001 had 2 non-serious infusion reactions which were moderate in intensity. The first IR was characterized by dysphagia, speech disorder, and urticaria and the second was characterized by pruritis, rash and a swollen teary eye with conjunctivitis**

5.6.2.2 *Infusion Reaction by Dose*

Figure 38 shows infusion reaction by dose.

Figure 38. First Infusion Reaction by Dose Number in RCT.



5.6.2.3 *Infusion Reaction with Longer Term Treatment*

In Table 52 the incidence of infusion reactions, SAE infusion reactions and those that led to discontinuation in the OLE are shown. There was no increase in the incidence of infusion reactions or in the percentage of infusion reactions that were serious with additional exposure in the OLE.

Table 52. Infusion Reactions in OLE Study.

	Pegloticase 8 mg					
	q 2 wks to q 2 wks	**q 2 wks to q 4 wks**	**q 4 wks to q 2 wks**	**q 4 wks to q 4 wks**	**Placebo to q 2 wks**	**Placebo to q 4 wks**
N	34	23	25	28	23	16
Incidence (n/%)	6 (18%)	4 (17%)	7 (28%)	13 (46%)	12 (52%)	12 (75%)
SAE (n/%)	2 (5%)	0	1 (4%)	0	4 (17%)	3 (19%)
SAE IRs that Led to Discontinuation (n/%)	0	0	1 (4%)	0	2 (9%)	3 (19%)
IRs that Led to Discontinuation (n/%)	1 (3%)	1 (4%)	2 (8%)	2 (7%)	2 (9%)	3 (19%)

Brief descriptions of infusion reactions reported as SAEs in the OLE Study in subjects who received pegloticase in the RCTs are shown in Table 53. All resolved without sequelae. The infusion reaction is C0405:129-001 was related to solu-medrol.

Table 53. Brief Descriptions of Serious Infusion Reaction in OLE Study.

Study: Subject number	**Treatment (q 2 weeks)**	**Pegloticase Dose No.**	**Disposition**	**Severity of infusion reaction, Symptoms, Anti-pegloticase Antibody Titer, and PUA Response**
C0405: 129-001	q 2 weeks to q 2 weeks	Reaction to Solumedrol. Received pegloticase without incident (Dose 22)	Continued	Severe infusion reactions Flushing/facial redness, stomach pain, profuse sweating No anti-pegloticase antibody Experienced no IRs in RCTs PUA < 6 mg/dL
C0405: 129-003	q 2 weeks to q 2 weeks	Dose 16	Continued	Severe infusion reactions Muscle spasms Experienced 7 IRs in the RCTs and 8 IRs in the OLE (as of Dose 33) Anti-pegloticase antibody titer: 1:21870 (Week 13: Dose7) PUA < 6 mg/dL
C0406: 311-001	q 4 weeks to q 2 weeks	Dose 14	Discontinued	Severe infusion reactions Crushing chest pain Experienced 2 IRs (non-serious) in the RCTs Anti-pegloticase antibody titer: 1:7290 (week 13) PUA < 6 mg/dL

The first sampling of uric acid occurred at the beginning of the third month (Week 9) and anti-pegloticase antibodies at the end of the third month (Week 13).

There were two subjects who received pegloticase in the RCTs who experienced a constellation of symptoms that included stridor, wheezing, peri-oral/lingual edema, rash/urticaria, and/or hemodynamic instability (Table 54). There were 12 subjects who were treated with placebo in

the RCTs who experienced this type of infusion reaction in the OLE Study: six subjects in the pegloticase q 2 weeks group and six subjects in the pegloticase q 4 weeks group. Two subjects treated with pegloticase q 2 weeks in the OLE Study who were treated with placebo during the RCTs received epinephrine.

Table 54. Brief Descriptions of Clinically Significant Infusion Reactions in OLE Study.

Study: Subject number	Treatment	Pegloticase Dose	Disposition	Severity of infusion reaction, Symptoms, Anti-Pegloticase Antibody Titer, and PUA Response
C0405: 114-001	q 2 weeks to q 4 weeks	Dose 15	Continued	Moderate infusion reaction Dizziness, flushing, vomiting, hypotension Experienced no IRs in RCTs and 3 IRs in the OLE (as of Dose 30) Anti-pegloticase antibody titer 1:65610 (at end of RCTs ; Week 25) PUA > 6 mg/dL
C0406: 305-001	q 4 weeks to q 4 weeks	Dose 16	Continued	Mild infusion reaction Abdominal discomfort, back pain, chest pain, chest discomfort, flushing, headache, throat tightness Anti-pegloticase antibody titer 1: 21870 (at end of RCTs) PUA > 6 mg/dL

*** Includes RCT and OLE dosing.**

Thirteen subjects who received pegloticase during the RCTs experienced their first infusion reaction during the OLE study (Table 55). Subjects C0405:129-001 and C0405:114-001 are described above in Tables 52 and 53, respectively.

Table 55. Subjects with First Infusion Reaction in OLE Study.

Study: Subject Number	Treatment RCT to OLE	Pegloticase Dose in OLE	End of RCTs PUA response	OLE Study PUA response
C0405: 107-001	q 4 wks to q 4 wks	Dose 6	> 6 mg /dL	> 6 mg /dL
C0405: 107-005	q 4 wks to q 4 wks	Dose 4	> 6 mg /dL	> 6 mg /dL
C0405: 111-005	q 4 wks to q 2 wks	Dose 1	> 6 mg /dL	ND*
C0405: 111-006	q 4 wks to q 2 wks	Dose 9	< 6 mg /dL	> 6 mg /dL
C0405: 117-006	q 4 wks to q 4 wks	Dose 2	< 6 mg /dL	< 6 mg /dL
C0405: 128-002	q 2 wks to q 2 wks	Dose 11	> 6 mg /dL	> 6 mg /dL
C0406: 303-004	q 4 wks to q 2 wks	Dose 32	> 6 mg /dL	> 6 mg /dL
C0406: 305-005	q 4 wks to q 4 wks	Dose 3	< 6 mg /dL	> 6 mg /dL

Study: Subject Number	Treatment RCT to OLE	Pegloticase Dose in OLE	End of RCTs PUA response	OLE Study PUA response
C0406: 307-006	q 2 wks to q 2 wks	Dose 1	> 6 mg /dL	> 6 mg /dL
C0406: 315-002	q 2 wks to q 4 wks	Dose 5	< 6 mg /dL	< 6 mg /dL > 6 mg /dL at week 37
C0406: 330-009	q 2 wks to q 2 wks	Dose 23	< 6 mg /dL	< 6 mg /dL

***ND = not done**

5.6.3 Immunogenicity

5.6.3.1 *Overview*

This section reviews information related to pegloticase associated immune responses from subjects treated in the phase 3 program. This discussion will focus on:

(a) the effect of anti-pegloticase antibodies on the pharmacokinetic properties of pegloticase,
(b) the relationship between anti-pegloticase antibodies and the pharmacodynamic properties of pegloticase with particular emphasis on the loss of the uric acid response, and
(c) the association of anti-pegloticase antibodies and infusion reactions.

These data have provided insights into the safe and effective use of pegloticase in patients with treatment failure gout and provided further clarification on clinical use guidance.

5.6.3.1.1 General Methodology

The qualitative and quantitative ELISA assays used for study sample analysis were validated to GLP following accepted immunology assay guidance [52].

In the phase 3 program, samples for antibody determination using ELISA assays were collected from all subjects at baseline and at Weeks 3, 5, 9, 13, 17, 21 and 25 after initiation of treatment with pegloticase or placebo. The assay development program primarily focused on the detection of total anti-pegloticase antibodies and total anti-PEG antibodies. In addition, IgM, IgG and IgE antibodies to pegloticase were also measured.

During antibody assay method development in the course of Phase 1 investigation, it was determined that the antibodies against pegloticase primarily recognized the PEG moiety of pegloticase [30]. These findings were confirmed in Phase 3 using different methodology. Specifically, the antibodies to pegloticase recognized both: (1) the free PEG (anti-PEG antibodies); and (2) the PEG moiety of intact pegloticase (anti-pegloticase antibodies). Binding of antibodies to PEG was completely inhibited by very low concentrations of soluble pegloticase. Moreover, binding of antibodies to pegloticase could be effectively competed by excess soluble pegylated proteins, including PEG-asparaginase, PEG-catalase, PEG-chymotrypsin, PEG-subtilisin, and PEG-superoxide dismutase, indicating they they were primarily directed to the PEG portion of the molecule.

5.6.3.1.2 Detection of Anti-pegloticase Antibodies

For determination of total anti-pegloticase antibodies, study samples were diluted 1/30 in assay buffer and assayed using microtiter ELISA plate wells coated with either pegloticase or PEG. A human serum containing anti-pegloticase antibodies was used as a positive control for detection of total anti-pegloticase antibody as well as IgM and IgG antibodies. The combination of rabbit anti-human IgM and IgG was used as secondary antibodies, whereas each individually was employed for assay of IgM and IgG anti-pegloticase antibodies, respectively. Horseradish peroxidase-conjugated mouse monoclonal antibody to rabbit IgG was used for detection. Microtiter plate wells coated with purified human IgG and IgM served as immunoglobulin positive controls for the binding of anti-human IgG and anti-human IgM secondary antibodies. The assay sensitivity was determined to be 7.5 µg/mL for the uricase portion of pegloticase and 0.78 ng/mL for the PEG portion of pegloticase. Drug interferance was determined to be 300 µg/mL which is much higher than the measured circulating pegloticase concentration determined in the study samples. Therefore, circulating pegloticase would not be anticipated to interfere with the measurement of antipegloticase antibodies.

Anti-pegloticase IgE potentially present in the sera was assayed by a capture method using a goat anti-human IgE antiserum coated onto the wells of ELISA microtiter plate wells After incubation with test sera, a three step detection procedure was employed that involved pegloticase, rabbit anti-pegloticase anti-serum and a horse radish peroxidase-conjugated murine monoclonal antibody to rabbit IgG, sequentially. Total IgE from a commercial source was used as a reference, since no human IgE anti-pegloticase was available. Total human IgE was determined using a microtiter plate coated with goat anti-human IgE and detected with a horseradish peroxidase-conjugated goat anti-human IgE.

Study samples were first analyzed in a screening assay. Study samples that were positive in the screening assay (above the negative cut-off) were then assayed in the drug competition test to confirm the presence of anti-pegloticase antibodies. Study samples confirmed to be positive in the drug competition test were titrated and the isotype of the antibody was determined.

5.6.3.1.3 Detection of Anti-PEG Antibodies

The anti-PEG antibody analysis methodology parallels the general method for the anti-pegloticase antibody assay except that a surrogate positive control was used for the initial study sample analyses. This positive control consisted of a mixture of mouse monoclonal anti-PEG IgG1 and anti-PEG IgM antibodies, added to pooled human serum, diluted 1/10 in blocker casein in PBS. A human positive control (pool of positive study samples from Studies C0405 and C0406) was introduced in the assay towards the end of the study sample analysis. The assay sensitivity was 500 ng/mL and is also reflected in a false detection rate of 8.6%. Drug interference by PEG occurred at 250 µg/mL and at 5 ng/mL for pegloticase. Since the drug interference level for pegloticase is much below the lover limit of quantitation (LLOQ) (0.6 µg/mL) of pegloticase in sera of treated subjects, study samples from pegloticase-treated subjects may have pegloticase levels that interfere with the assay and may result in false negative determinations.

5.6.3.1.4 Neutralization Assay

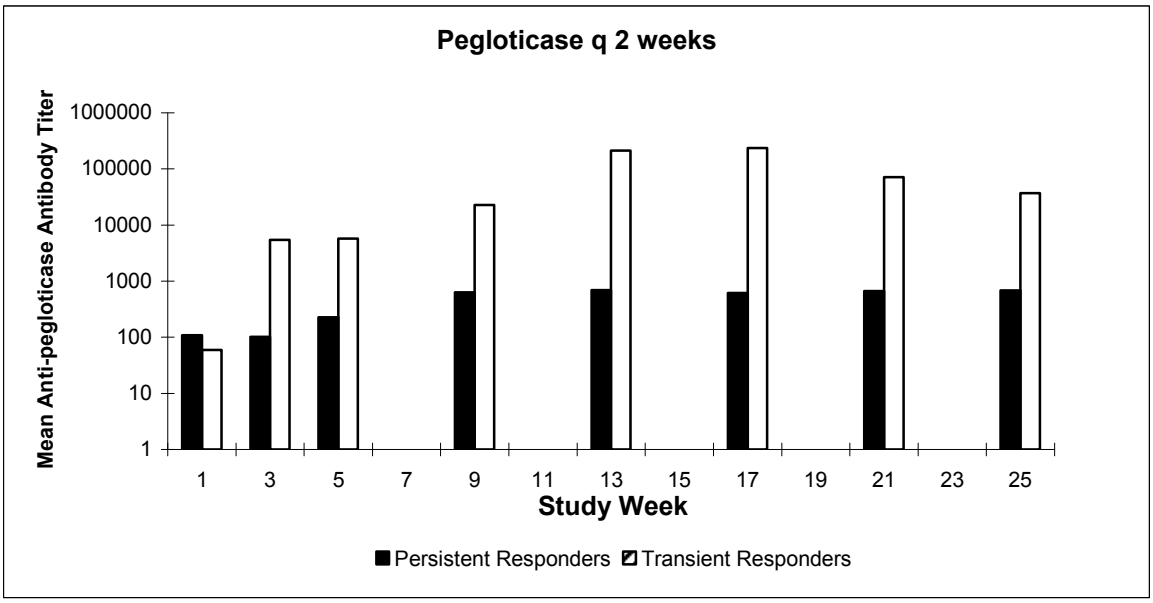
The neutralization assay is a coupled enzymatic/fluorescent based assay. In this assay, pegloticase catalyzes the oxidation of uric acid in the presence of oxygen to allantoin, hydrogen peroxide (H_2O_2) and carbon dioxide. In the presence of horseradish peroxidase (HRP), H_2O_2 reacts with a 1:1 stoichiometry with the Amplex Red reagent to generate the red-fluorescence oxidation product, resorufin. The measured response is proportional to the concentration of pegloticase present in the study samples and inversely proportional to the levels of neutralizing anti-pegloticase antibodies. Study samples confirmed to be positive for the presence of anti-pegloticase IgG and IgM antibodies were tested for the capacity to neutralize pegloticase activity.

5.6.3.2 *Phase 3 RCT Antibody Results*

Anti-pegloticase antibodies were detected in 88% of subjects in the pegloticase 8 mg q 2 weeks and 8 mg q 4 weeks treatment groups of the phase 3 studies and in only 15% of the placebo group. However, only 59% of subjects developed anti-pegloticase antibody titer >1:2430 identified as a subset of subjects in which anti-pegloticase antibody had a potential clinical consequence. (Since antibody titer measurements were not as frequent as PUA or secondary endpoint measurements, at times the antibody data is presented in relation to the most recent antibody titer or the highest titer obtained for each subject.)

At all time points after dosing, the persistent responders in the q 2 week group had mean lower anti-pegloticase antibody titers compared to the transient responders (Figure 39). For example, we observed that subjects with anti-pegloticase antibody titer <1:810 at any time during the RCT was associated with persistent response. Thus, 68% of the q 2 week persistent responders and 67% of q 4 week persistent responders had titers that never exceeded a titer of 1:810. On the other hand, only 23% of the q 2 week transient responders and 22% of the q 4week transient responders had titers < 1:810. Most (93%) subjects had titers <1:810. Therefore, low titer was associated with persistent response.

Figure 39. Mean Anti-pegloticase Antibody Titer by Study Week in Persistent and Transient Responders; Pegloticase 8 mg Every 2 Week Administration.



Anti-PEG antibodies were less commonly detected and were observed at a later time point than the anti-pegloticase antibodies.

Anti-PEG antibodies were less commonly detected (68/214; 32%) than anti-pegloticase antibodies (88%). No placebo patients had anti-PEG antibodies. In general, the titers of antibody to PEG were lower than those to pegloticase. The anti-PEG assay has a reduced sensitivity compared to the anti-pegloticase assay. The nature of the anti-PEG antibodies, including their presence only in subjects with high titer anti-pegloticase antibodies and their development after anti-pegloticase antibodies have been detected suggest that they may represent a sub-set of high avidity anti-pegloticase antibodies that cross-react with PEG with lower avidity. This is substantiated by the capacity of very low concentrations of soluble pegloticase (5 ng/mL) to compete for binding of anti-PEG antibodies compared with the very high concentration of PEG (250 ug/mL) necessary to compete.

Antibodies from only one subject (Pegloticase 8 mg q 4 weeks group) neutralized pegloticase activity only at study weeks 9 and 17.

IgE anti-pegloticase antibodies were also assessed during the RCT. A multi-step ELISA capture assay was used but it was problematic because of the high background which could be related to the need to employ multiple capture antibodies and antisera from different species. Moreover, the absence of a suitable IgE anti-pegloticase positive control precluded the determination of the sensitivity and specificity of the assay. Despite these caveats, detection of IgE anti-pegloticase antibody was infrequent. Of the total number of serum samples analyzed (1493), 90 (6%) obtained from 32 subjects had a positive assay for IgE anti-pegloticase antibodies of > 1:30 (the

background titer). Subjects who had increased titers of IgE anti-pegloticase antibodies tended to have consistent levels throughout the period of sampling. As discussed below, an elevated IgE anti-pegloticase titer was found in only 2 of 14 subjects with an infusion reaction associated with an increase in serum tryptase, and in an additional subject whose tryptase level increased within the normal range during an infusion reaction. Importantly, in each of these circumstances, the SUA had increased above 6 mg/dL before the infusion reaction associated with an increased tryptase had occurred. Because of the difficulties associated with measuring specific IgE antibodies accurately, these results can only be considered preliminary. However, the data provide only minimal evidence for a role of IgE anti-pegloticase antibodies in most infusion reactions. It can not be ruled out that IgE anti-pegloticase antibodies may have contributed to 13 of the 56 infusion reactions (23%). Importantly, in each of these circumstances the few infusion reactions that might be considered IgE-mediated occurred after pegloticase would have been discontinued per the proposed clinical use guidance (e.g. discontinue treatment when SUA > 6.0 mg/dL or after one moderate to severe infusion reaction).

5.6.3.3 *Properties of Anti-pegloticase Antibodies*

5.6.3.3.1 Immunoglobulin Heavy Chain Isotype

In the majority of samples from the phase 3 subjects, the antibody response involved both IgM and IgG antibodies. Isotyping was performed in the 166 subjects that developed anti-pegloticase antibodies: 130 subjects (78%) had both IgM and IgG antibodies, 33 (20%) had only IgM antibodies, and 3 (2%) were positive for IgG only. Subjects with both IgM and IgG antibodies tended to have higher titers and the development of IgM antibody usually preceded the IgG antibody.

5.6.3.3.2 Relationship Between Anti-pegloticase Antibody and Measurements of Total Hemolytic Complement (CH50)

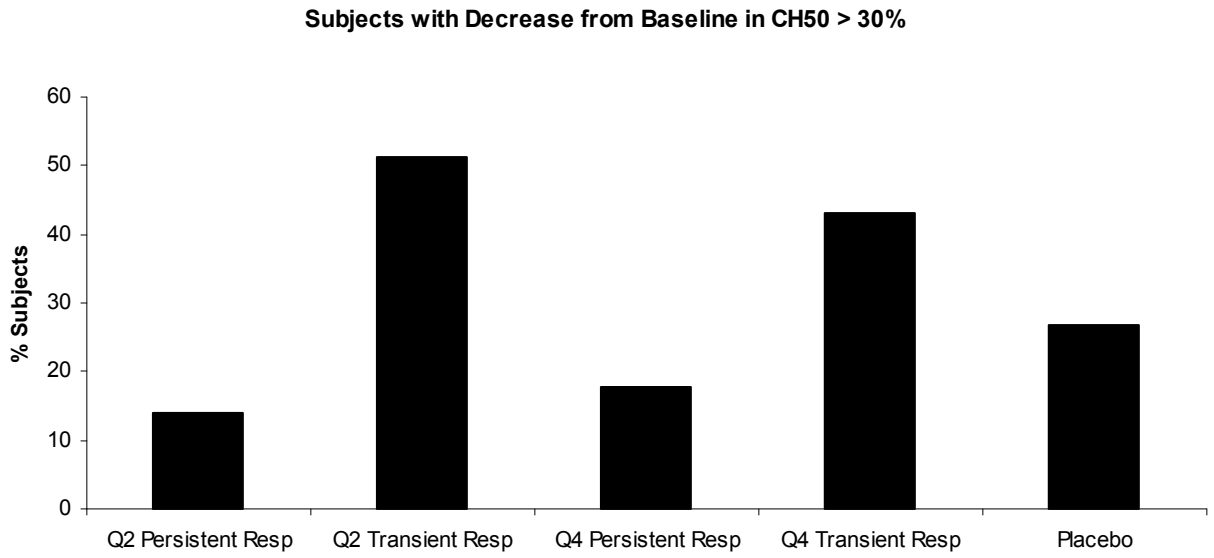
Total serum hemolytic complement levels (CH50) were obtained during the RCTs to determine if anti-pegloticase antibodies resulted in the formation of immune complexes with resultant complement consumption. Samples for the determination of CH50 and antibody titers were obtained at the same time points. In order to determine the minimally meaningul change in CH50, the change from baseline for each placebo observation was used to define the mean and the 95 percentile (referred to here as 95% confidence interval). It was determined that a decrease in CH50 of >30% from the baseline value exceeded the 95% confidence limits and this difference was greater than expected by chance alone.

Approximately 26% of subjects receiving placebo had changes in CH50 that exceeded decreases in CH50 > 30% of baseline at any time during the study (Figure 40). The persistent responders that received pegloticase either every 2 weeks or every 4 weeks were similar to the placebo group in the percentage of subjects with decreases in CH50 that exceeded this limit (q 2 week to placebo, p-value = 0.17; q 4 week to placebo, p-value = 0.39). In contrast, the percentage of subjects with decreases in CH50 > 30% of baseline was higher in subjects who were transient responders (q 2 week to placebo, p-value = 0.04; q 4 week to placebo, p-value = 0.13).

Declines in CH50 were always found in subjects with rising or high titers of anti-pegloticase antibodies. To illustrate this, examples of two individual subjects in the q 2 weeks group who

were transient responders, 403-004 and 109-004 are shown in Figures 53 and 54, respectively. These results indicate that complement consumption, as gauged by a decrease of greater than the 95% confidence interval (30%) in CH50 can be found in association with administration of pegloticase, and is found in those subjects with rising or high titers of anti-pegloticase antibodies, but it is limited to subjects with transient responses to pegloticase. In the persistent reponders, the percentage of subjects experiencing a decline in CH50 is not different than than those subjects receiving placebo.

Figure 40. Proportion of Subjects with Change from Baseline CH50 > 30% At Any Time Point.



5.6.3.4 *Antibodies before first dose*

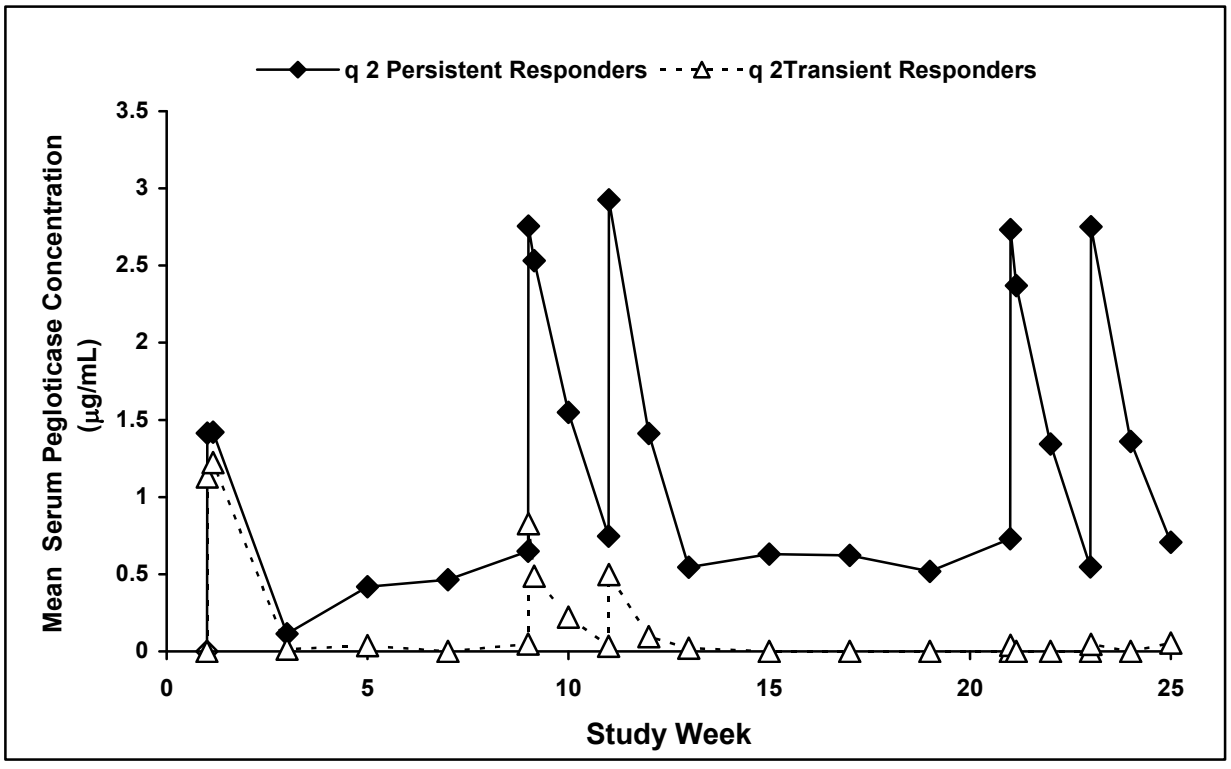
Some individuals may be exposed to PEG in the environment (e.g., shampoos, toothpastes, pharmaceutical preparations) and it has been reported that PEG antibodies were detected in about 15% of individuals [53]. As mentioned previously, the anti-pegloticase antibody cross-reacts with PEG so it was not unexpected to find RCT subjects with antibodies directed at pegloticase at baseline. Anti-pegloticase antibodies were present in samples from all three phase 3 groups; pegloticase 8 mg q 2 weeks group (13 of 85 subjects; 15%), pegloticase 8 mg q 4 weeks (15 of 84 subjects; 18%), and placebo (4 of 43 subjects; 9%). One subject in the pegloticase 8 mg q 4 weeks group also had antibodies to PEG (anti-PEG antibodies) at baseline. All antibodies were of the IgM isotype and most occurred at low titer (93% <1:810). Compared with individuals who did not have baseline anti-pegloticase antibodies, the presence of antibodies at baseline was not associated with subsequent development of higher titer anti-pegloticase antibodies, increased risk of first dose or any dose infusion reactions, or other untoward effects. This will be discussed in more detail below.

5.6.3.5 *Anti-pegloticase Antibody Effects on Pegloticase Pharmacokinetics and Pharmacodynamics*

5.6.3.5.1 Anti-pegloticase antibody effects on pharmacokinetics

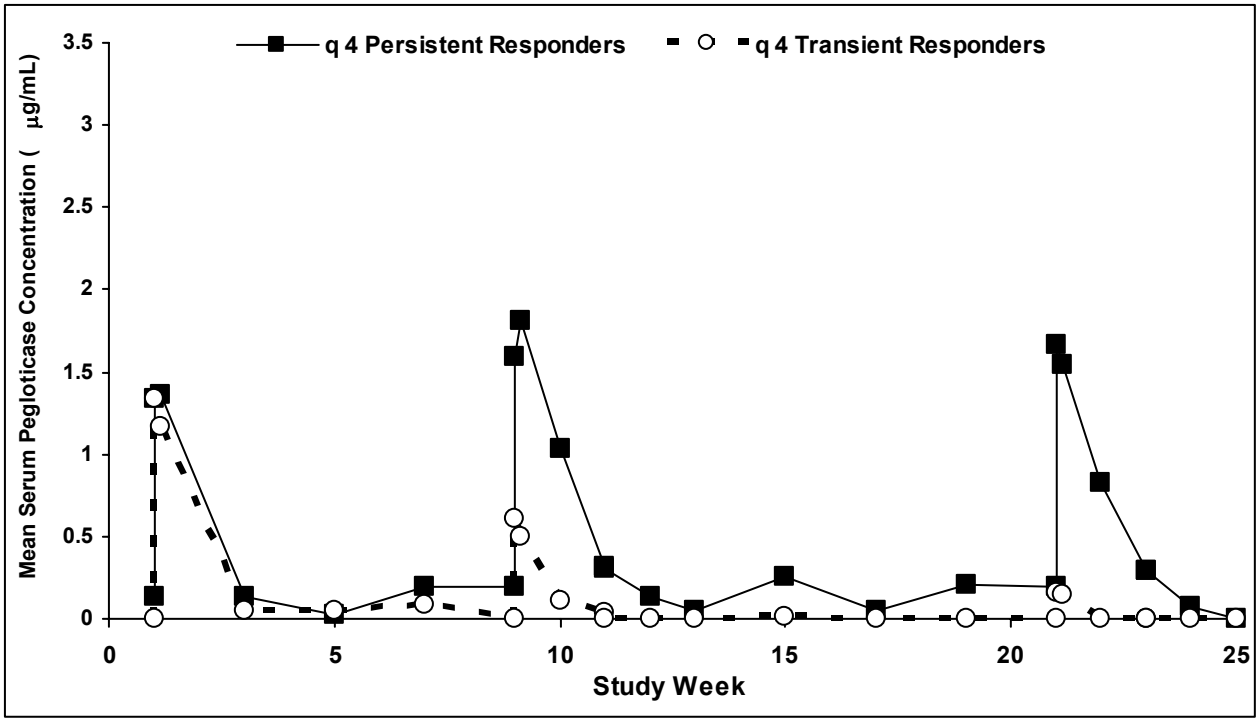
The pharmacokinetics of pegloticase is signficantly influenced by the presence of anti-pegloticase antibodies (Figures 41 and 42). Persistent responders had higher pegloticase peak concentrations (Cmax) in both groups compared to transient responders. The subjects in the q 2 weeks treatment group with a transient response to pegloticase had a mean peak concentration that was approximately 50% lower (0.8 μg/mL) than for persistent responders at study week 9 because of the more rapid clearance associated with higher titer antibodies (Figure 41). By week 15, the transient responders had trough pegloticase concentrations that were below the level of detection (0.6 μg/mL). The persistent responders in the q 2 week group had trough concentrations in the range of 0.5-0.7 μg/mL. Similar effects were observed for the q 4 weeks dosing group (Figure 42).

Figure 41. Comparison of Mean Pegloticase Concentrations Persistent and Transient Responders; Pegloticase 8 mg Every 2 Weeks Group.



NB: peak concentrations of pegloticase following the 1st, 5th, 6th 11th and 12th infusions are shown as these were time points of more intense sampling. The remaining points are taken only at trough levels, i.e., immediately before study drug infusion.

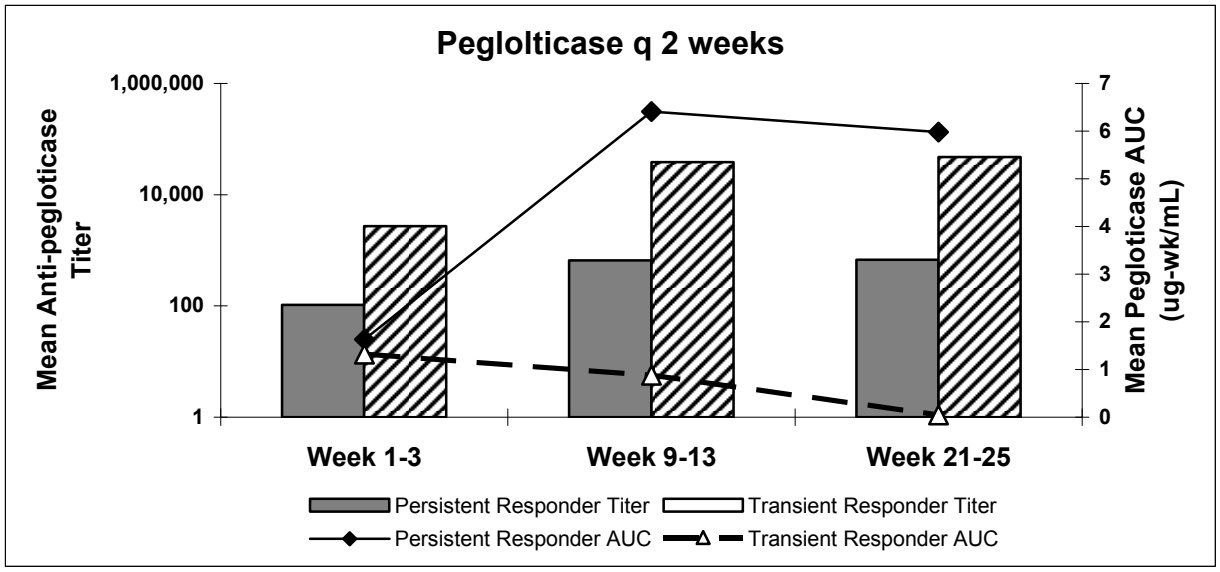
Figure 42. Comparison of Mean Pegloticase Concentrations in Persistent and Transient Responders; Pegloticase 8 mg Every 4 Weeks Group



NB: peak concentrations of pegloticase following the 1st, 5th, 6th 11th and 12th infusions are shown as these were time points of more intense sampling. The remaining points are taken only at trough levels, i.e., immediately before study drug infusion.

Associated with the alterations in pegloticase pharmacokinetics, the transient responders had higher mean anti-pegloticase antibody titers at all time points compared with persistent responders (Figure 43). In the transient responders, the increased anti-pegloticase antibody titers were associated with markedly decreased pegloticase levels as assessed by the area under the time-concentration curve (AUC) compared with the pegloticase levels in the persistent responders. While there is a general association between loss of response and higher anti-pegloticase antibody titers, loss of response could occur contemporaneously or even before the rise in antibody titer, as will be discussed in section 5.6.3.5.3 below.

Figure 43. Relationship between Anti-pegloticase Antibody Titer and Pegloticase AUC in Persistent and Transient Responders Following Pegloticase 8 mg Every 2 weeks Group.

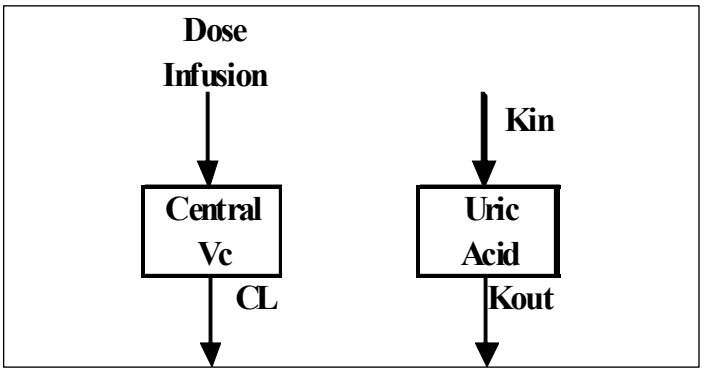


5.6.3.5.2 Effect of anti-pegloticase antibodies on pharmacodynamics (PD)

A pharmacodynamic model was employed to explain the effects of antibodies on clearance of pegloticase and the resultant loss of uric acid response. This model examined PUA levels in response to pegloticase in the presence and absence of anti-pegloticase antibodies. This model also considered the increase in PUA elimination in the presence and absence of pegloticase.

As shown below (Figure 44), Vc is the volume of distribution for pegloticase, CL is the clearance of pegloticase, Kin represents the rate at which urate is presented to the plasma, and Kout represents the endogenous uric acid metabolic rate before pegloticase administration. The effect of pegloticase in this model is to accelerate the elimination of urate (Kout).

Figure 44. PK/PD Model



Using an estimated average serum urate level of 1.5 μg/mL (following intravenous administration of 8 mg pegloticase), PUA elimination was accelerated by 590% of normal endogenous function according to the PD model (Table 56). The level of acceleration was inversely related to the level of circulating antibodies to pegloticase. The reduction in the bioactivity of pegloticase measured as diminished acceleration of urate clearance is indicative of an increased clearance of pegloticase.

Table 56. Effects of Anti-Pegloticase Antibodies on Urate Clearance.

Antibody Titer *	Estimated Acceleration (%)
	1.5 μg/mL
None	590
Low	240
Moderate	87
High	8

***For this analysis, a low titer of anti-pegloticase antibody was 1:90 to 1:810, a moderate titer ranged from 1:2430 to 1:7290, and a high titer antibody titer was > 1:7290).**

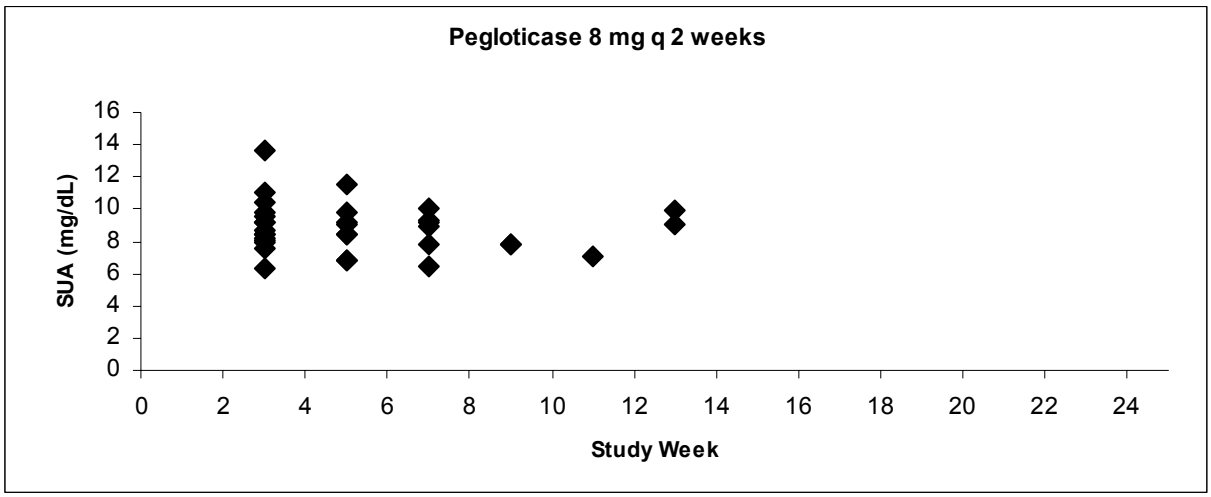
5.6.3.5.3 Anti-pegloticase Antibody Effects on SUA/PUA: SUA/PUA as a Surrogate for Physiologically Relevant Anti-pegloticase Antibodies

The loss of response to pegloticase, as measured by SUA or PUA, occurs at a time when the antibody response is developing, and therefore, anti-pegloticase antibody titers do not correlate with the loss of pegloticase activity. While the loss of the SUA/PUA response (transient response) is found predominantly in subjects who eventually manifest the highest anti-pegloticase titers, at the time the urate level increases > 6 mg/dL, anti-pegloticase antibody titers may be low to absent. Thus, there is no clear relationship between the anti-pegloticase antibody titer and the value of SUA or PUA at the time the uric acid response is lost. As a result, the anti-pegloticase antibody titer cannot be used to distinguish between persistent and transient responders at the time the uric acid response is lost. However, the loss of the uric acid response

can be used reliably to predict the formation of physiologically-relevant anti-pegloticase antibodies.

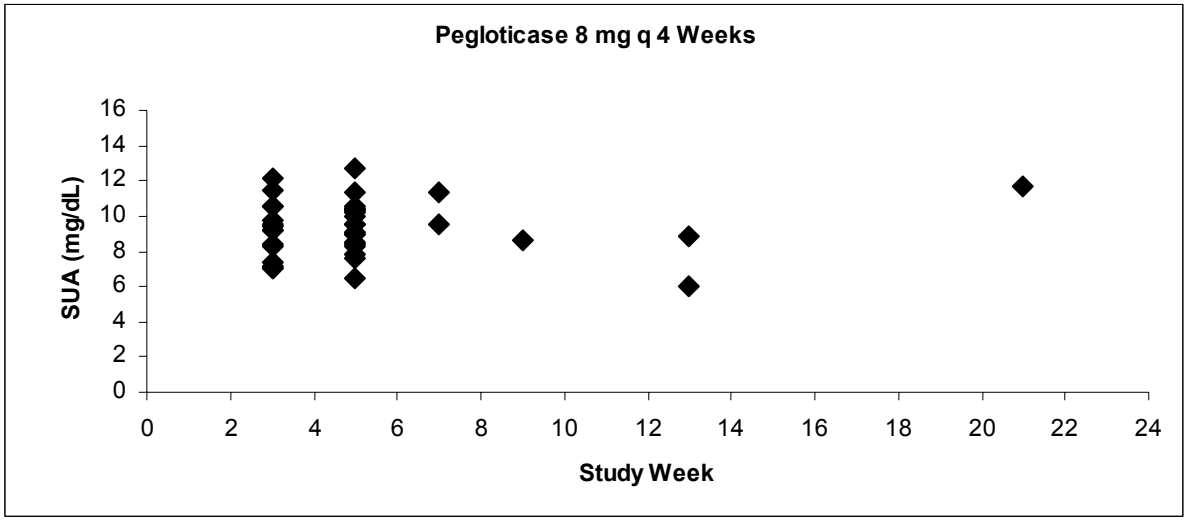
We investigated when the SUA increased above 6 mg/dL in the transient responder group administered pegloticase 8 mg every 2 weeks. Each point in Figure 45 represents an individual transient responders in the q 2 week group when their SUA first increased above 6 mg/dL and the SUA measurement at that time point. Loss of response occurred within the first 2 months of treatment for most (85%) subjects in the q 2 weeks group. The q 4 weeks group also showed a similar pattern, with about 90% of transient responders losing SUA response within the first 2 months of treatment (Figure 46).

Figure 45. Time to SUA > 6 mg/dL; Pegloticase 8 mg Every 2 Weeks Group.



SUA value at first increase above 6 mg/dL is indicated for individual subjects in the RCTs. Each point represents a single patient.

Figure 46. Time to SUA > 6 mg/dL; Pegloticase 8 mg Every 4 Weeks Group.



SU

A level at first increase above 6 mg/dL is indicated for individual subjects in the RCTs. Each point represents a single patient.

At the time of loss of urate response, mean anti-pegloticase antibody titers were 1:3032 for the q 2 weeks group and 1:4440 in the q 4 weeks group (Figure 47), compared to a mean of 1:686 for the q 2 weeks persistent responders and 1:1962 for the q 4 weeks persistent responders . However, in the q 2 weeks group, there were 36 out of 39 subjects and in the q 4 weeks group there were 43 out of 47 subjects whose anti-pegloticase tier was less than 1:2430 at the time of loss of response. Antibody titers began to rise in transient responders at the time of loss of uric acid response and began to plateau after 3 months of treatment (Figure 48). Two examples are provided to indicate the varied nature of the relationship between loss of the SUA response and anti-pegloticase antibody titer. Subjects 109-004 (Figure 49) and 102-009 (Figure 50) were treated with pegloticase q 2 weeks and were both transient responders. In subject 109-004, the SUA response was lost 2 months before a substantial change in anti-pegloticase antibody titer. In subject 102-009, the SUA response was lost between 2 and 3 months of treatment after the anti-pegloticase antibody titer had begun to increase, but before it reached maximal levels. The distribution of antibody titers at the time of loss of SUA response is shown in Figure 51 for the q 2 weeks group.

Figure 47. Mean (± SEM) Anti-pegloticase Antibody Titer at Time of Loss of SUA Response in Transient Responders Compared with Mean Highest Titer in Persistent Responders.

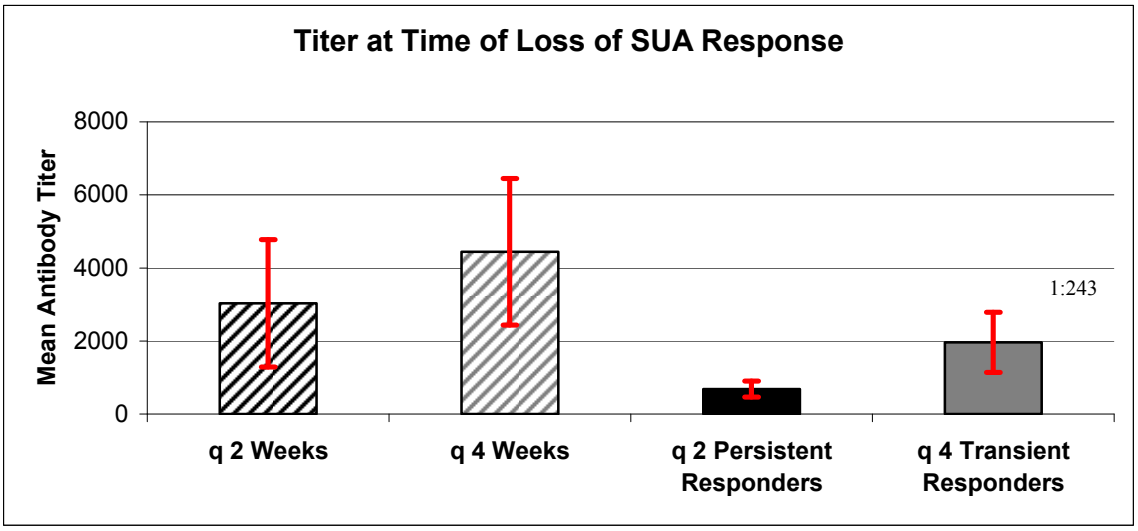


Figure 48. Relationship between Anti-pegloticase Antibody Titer and SUA Comparing Persistent and Transient Responders; Pegloticase 8 mg Every 2 Weeks Group.

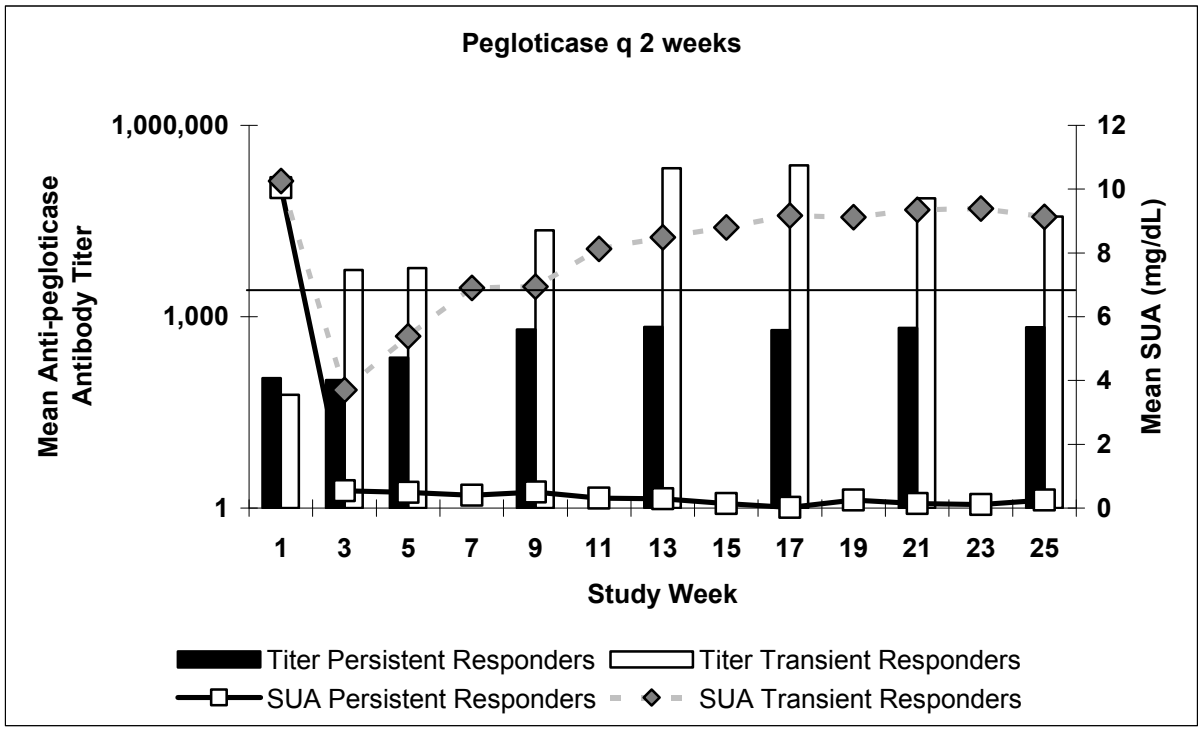


Figure 49. Relationship between Anti-pegloticase Antibody Titer and SUA In a Transient Responder (Subject 109-004) That Received Pegloticase 8 mg Every 2 Weeks.

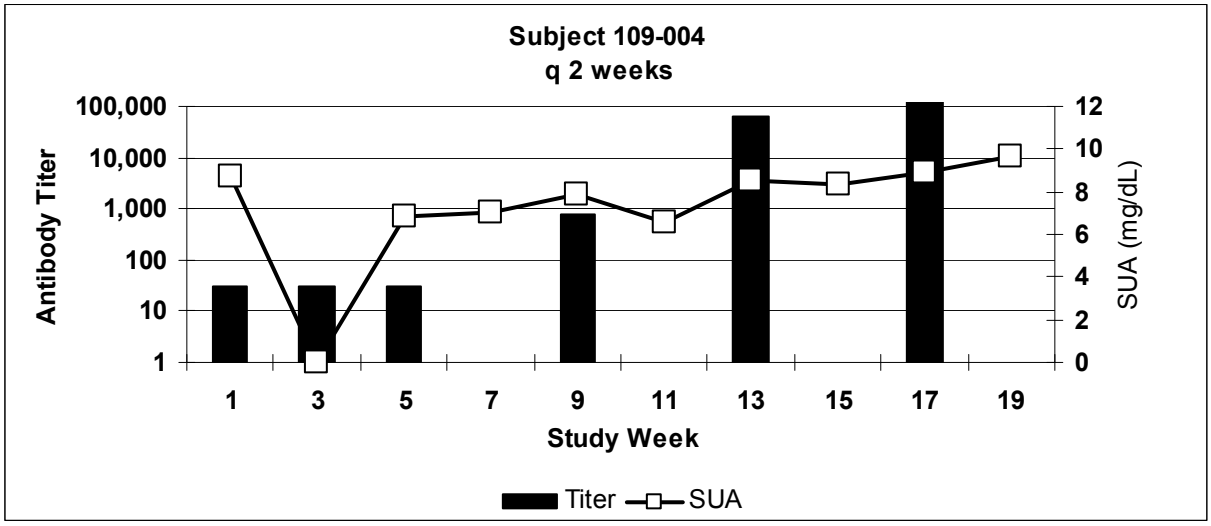


Figure 50. Relationship between Anti-pegloticase Antibody Titer and SUA In a Transient Responder (Subject 102-009) That Received Pegloticase 8 mg Every 2 Weeks.

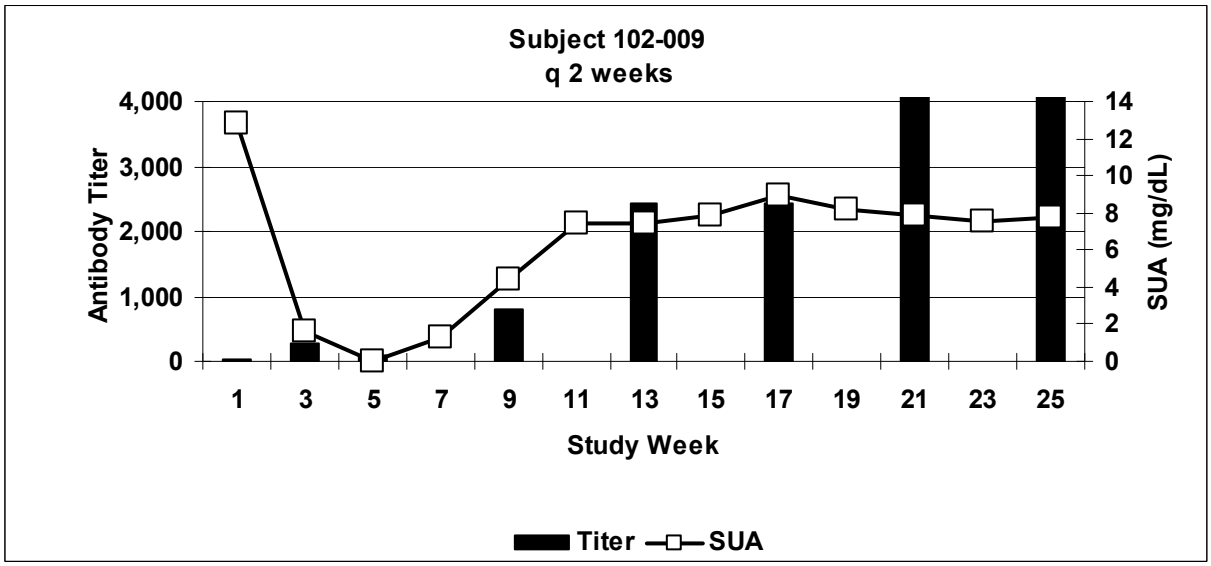
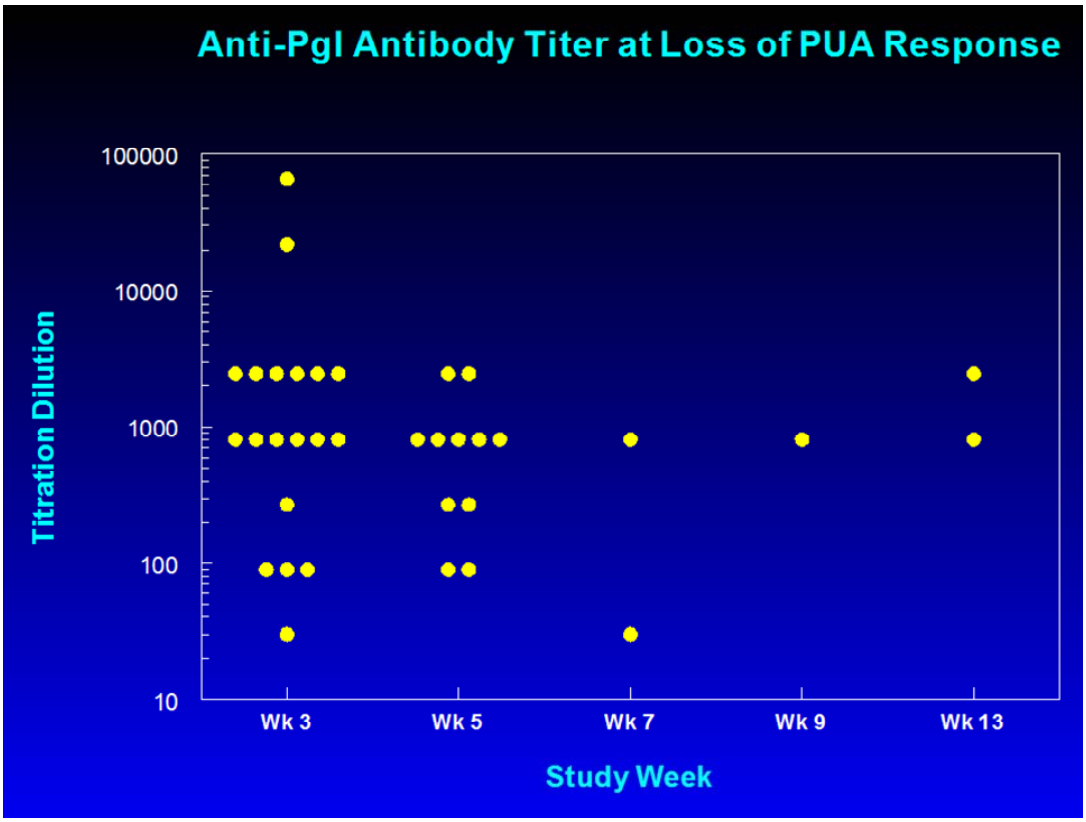


Figure 51. Anti-pegloticase Antibody Titer at Time of Loss of PUA Response; Pegloticase 8 mg Every 2 Weeks Group.



5.6.3.5.4 Conclusions: Anti-pegloticase Antibody Effects on Pegloticase Pharmacokinetics and Pharmacodynamics and the SUA/PUA response

Anti-pegloticase antibodies have direct effects on the pharmacokinetic and pharmacodynamic properties of pegloticase and explain the transient effect of pegloticase in the subjects who develop physiologically-relevant antibodies. Although the increased clearance of pegloticase with the resultant loss of SUA/PUA response is mediated by anti-pegloticase antibodies, the initiation of increased clearance does not correlate with the anti-pegloticase antibody titer. Therefore, measurement of anti-pegloticase antibody titers is not predictive of the loss of the SUA/PUA response, whereas monitoring SUA is a very good surrogate for measuring the development of anti-pegloticase antibodies that cause increased clearance of administered pegloticase. For those transient responders, SUA response is lost (defined as > 6 mg/dL) in 80% of subjects within the first few infusions and most (90%) within the first 9 weeks. Thus, clinical guidance in the label will reflect monitoring of serum uric acid for the first 3 months, indicating that pegloticase treatment should be discontinued when the serum uric acid is no longer normalized below 6 ml/dL. Since the anti-pegloticase antibody titer is not a good predictor of the loss of the SUA/PUA response, measurement of anti-pegloticase antibody is not useful or

necessary for safe and effective pegloticase (8 mg q 2 weeks) treatment of patients with treatment failure gout.

5.6.3.6 *Relationship between Anti-pegloticase Antibody, Infusion Reactions, and SUA/PUA*

Infusion reactions occurred in 26% of subjects in the q 2 group and 40% of subjects in the q 4 group. In general, infusion reactions occurred later during the course of therapy, and usually after the loss of the uric acid response. In the q 2 weeks group, 21 of the 22 subjects with an infusion reaction were transient responders and in the q 4 weeks group, 29 of the 34 subjects were transient responders. There were 2 placebo subjects with an infusion reaction and some infusion reactions occurred when placebo was infused in the q 4 week group.

5.6.3.6.1 Relationship between Infusion Reactions and Anti-Pegloticase Antibody

Of the 22 subjects in the pegloticase 8 mg q 2 weeks group who experienced an infusion reaction, 12 (55%) had elevated anti-pegloticase antibody titers (> 1:2430) (Table 57). Of the 33 subjects in the pegloticase 8 mg q 4 weeks group with available antibody data at the time of an infusion reaction, 32 subjects 12 (36%) subjects had elevated anti-pegloticase antibody titer.

Table 57. Anti-pegloticase Antibody Titer at the Time of The First Infusion Reaction.

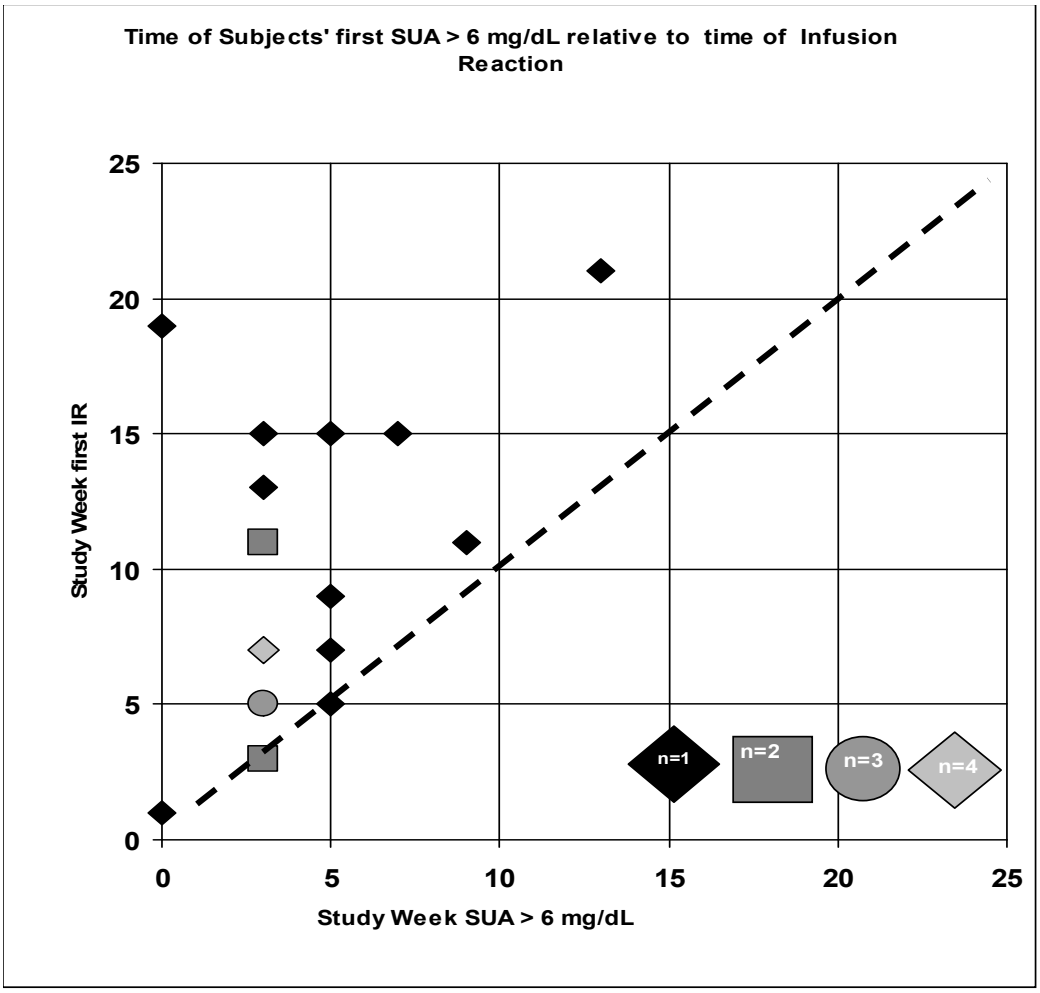
Anti-Pegloticase Antibody Titer	Pegloticase	
	8 mg q 2 weeks N = 22 n (%)	**8 mg q 4 weeks N = 34 n (%)**
0	5 (23%)	4 (12%)
1:30	0	2 (6%)
1:90	1 (5%)	3 (9%)
1:270	1 (5%)	5 (15%)
1:810	3 (14%)	8 (24%)
1:2430	2 (9%)	6 (18%)
1:7290	1 (5%)	2 (6%)
1:21870	4 (18%)	1 (3%)
1:65610	2 (9%)	1 (3%)
1:196830	3(14%)	1 (3%)
No data	0	1 (3%)

5.6.3.6.2 Relationship between Infusion Reactions and Uric Acid Levels

Infusion reactions frequently occurred after the loss of SUA response, as shown for subjects in the q 2 weeks group in Figure 52. In the q 2 weeks group, three subjects had an infusion reaction at the same time their SUA > 6 mg/dL, one subject had an infusion reaction at first dose, and only one subject with an infusion reaction was a persistent responder. The clinical use guidance proposed by the Sponsor is that pegloticase 8 mg q 2 week will be discontinued if their the SUA > 6 mg/dL. Thus, using these criteria, 77% of infusion reactions would have not occurred (been

prevented) as the subject would have been discontinued from therapy once the SUA > 6 mg/dL. In the q 4 weeks group, five subjects with infusion reactions were persistent responders, and only 14 of the 34 subjects had an infusion reaction more than 2 weeks after to loss of SUA response (Table 58).

Figure 52. Time to Subjects' Loss of SUA Response Relative to Time of First Infusion Reaction in the Pegloticase 8 mg Every 2 weeks Dose Group.



The figure shows the time of infusion reaction (study week) on the vertical axis and the time when SUA is first measured > 6 mg/dL for each subject with and infusion reaction in the q 2 weeks group. Black diamonds represent a single patient, grey boxes represent two patients at that data point, grey circles represent three subjects at that data point, and grey diamonds represent four subjects. There was one subject with and infusion reaction at the first dose (no loss of SUA response), one subjects who had an infusion reaction at week 19, but no loss of SUA response. Four patients had an infusion reaction at the time when SUA was first measured > 6 mg/dL Biweekly SUA samples were taken immediately prior to study drug infusion.

Table 58. SUA Category at the Time of First Infusion Reaction.

SUA Status at Time of Infusion Reaction	Pegloticase	
	8 mg q 2 weeks N = 22 % (n)	8 mg q 4 weeks N = 34 % (n)
SUA < 6 mg/dL at time of infusion reaction	1	10
SUA > 6 mg/dL for less than 2 weeks before infusion reaction	4	10
SUA > 6 mg/dL for more than 2 weeks before infusion reaction	17	14

5.6.3.6.3 Infusion Reactions, CH50 and Tryptase

To determine whether immunologic mechanisms explained the majority of infusion reactions, the relationship between these events was explored by examining whether infusion reactions were associated with complement consumption or increases in serum tryptase levels. Of the 21 infusion reactions that occurred in transient responders administered pegloticase q 2 weeks, 11 (53%) had were associated with decreases in CH50 at the time of the infusion reaction, whereas 9/30 (30%) infusion reactions in q4 week transient responders were associated with decreases in CH50 levels. These numbers can be compared to the results of the analysis of the placebo or the persistent responder groups, which demonstrated that at any point in time, less that 4% of subjects had a decrease in CH50 compared to baseline. Even in the transient responders, only about 7% of subjects experienced a decrease in CH50 compared to baseline at a specific point in time.

Samples for tryptase were only obtained at the time of an infusion reaction. In transient responders of the q 2 week group, 4/21 (19%) subjects had tryptase values increased at the time of an infusion reaction, whereas 9/30 (30%) transient responders in the q 4 week group had tryptase increased at the time of an infusion reaction. By contrast, 1/6 (17%) subjects persistent responders who had infusion reactions had an increased tryptase value. Explanation for the increase in serum tryptase in these subjects is uncertain because only 2 subjects with an infusion reaction and increased serum tryptase level manifested an increase in IgE anti-pegloticase antibody.

The CH50 and tryptase activity in the transient and persistent responders for the pegloticase 8 mg q 2 and 4 weeks groups is provided in Table 59. A total of 56 subjects receiving pegloticase experienced infusion reactions, 22 in the q 2 week group and 34 in the q 4 week group. In the q 2 week group, only one (4.5 %) of these subjects was a persistent responder, whereas in the q 4 week group, five (14.6 %) were persistent responders. Of the 50 subjects who were transient responders and experienced an infusion reaction, 29 (58 %) had evidence of either complement consumption or an increase in serum tryptase or both at the time of the infusion reaction. In contrast, of the six subjects who were persistent responders but had infusion reactions, only one subject had increased serum tryptase and none had decreased CH50 levels. These data indicate

that in transient responders, the development of infusion reactions is related to immune responses in that the majority are associated with either complement consumption, mast cell degranulation or both.

Table 59. Summary of Immunologic Activity Associated with Infusion Reactions.

CH50	**Normal**	**Decreased**	**Decreased**	**Normal**
Tryptase	**Normal**	**Normal**	**Increased**	**Increased**
	n =	n =	n =	n =
Pegloticase q 2 wks Persistent responders n = 1	1	0	0	0
Pegloticase q 2 wks Transient responders n = 21	7	10	1	3
Pegloticase q 4 wks Persistent responders n = 5	4	0	0	1
Pegloticase q 4 wks Transient responders n = 29	13	6	3	7
Placebo n = 2	1	0	0	1

5.6.3.7 *Anti-pegloticase antibodies prior to first dose of pegloticase*

Although approximately 15% of subjects had anti-pegloticase antibody present at baseline before the first infusion of pegloticase or placebo, there was no association between the presence or absence of anti-pegloticase antibody at baseline and incidence of infusion reactions (Table 60).

Table 60. Incidence of Infusion Reactions in Subjects with Anti-pegloticase Antibodies before First Dose Administration.

	Pegloticase		**Placebo**
	8 mg q 2 weeks % (n)	**8 mg q 4 weeks** % (n)	% (n)
Anti-pegloticase Antibody Present Before The First Infusion	**15% (13/85)**	**18% (15/84)**	**9% (4/43)**
Number of Subjects who Experienced an Infusion Reaction	8% (1/13)	53% (8/15)	25% (1/4)
Number of Subjects who Discontinued Due To an Infusion Reaction	0% (0/13)	37% (3/8)	0% (0/4)

	Pegloticase		Placebo
	8 mg q 2 weeks % (n)	**8 mg q 4 weeks** % (n)	% (n)
Anti-pegloticase Antibody Negative Before The To First Infusion	**85% (72/85)**	**82% (69/84)**	**91% (39/43)**
Number of Subjects who Experienced an Infusion Reaction	29% (21/72)	38% (26/69)	3% (1/39)
Number of Subjects who Experienced an Infusion Reaction	29% (21/72)	38% (26/69)	3% (1/39)
Number of Subjects who Discontinued Due To an Infusion Reaction	11% (8/72)	12% (8/69)	0% (0/39)

5.6.3.8 *Conclusion: Antibody Effects on Clinical Outcomes*

To illustrate the relationship between loss of PUA response in transient responders and the increase in anti-pegloticase antibody titer, individual subject data is presented in Figure 53 and Figure 54. These two subjects are representative of transient responders from those administered pegloticase 8 mg every 2 weeks. In contrast, titers were lower in persistent responders at all times, as represented by subject C0406: 301-002 (Figure 55). Note that CH50 consumption was not found in all subjects who lost response or in whom an infusion reaction occurred, but was a prominent feature in a substantial number of individual subjects.

Figure 53. Profile of CH50, SUA, and Anti-pegloticase Antibody Titer; Pegloticase 8 mg Every 2 Weeks Transient Responder (Subject 403-004).

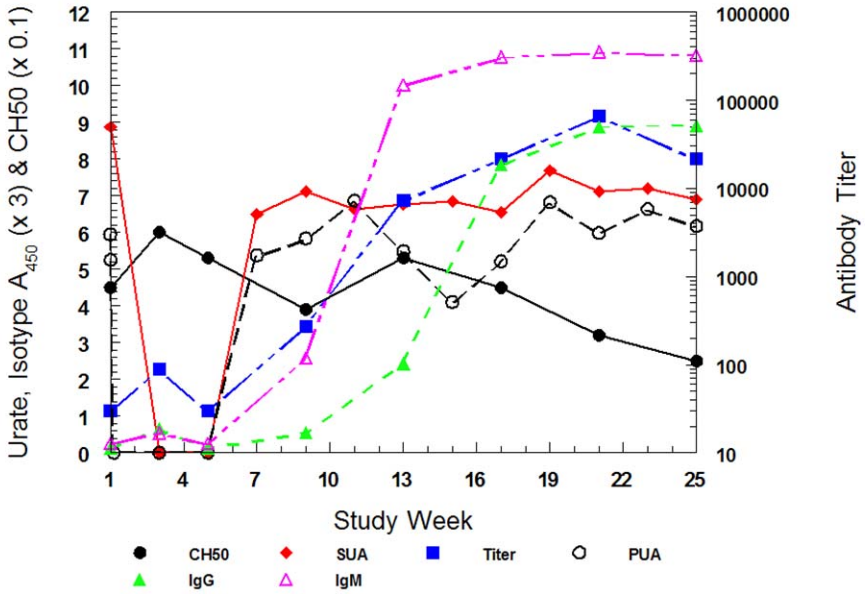


Figure 54. Profile of CH50, SUA, and Anti-pegloticase Antibody Titer; Pegloticase 8 mg Every 2 Weeks Transient Responder (Subject 109-004).

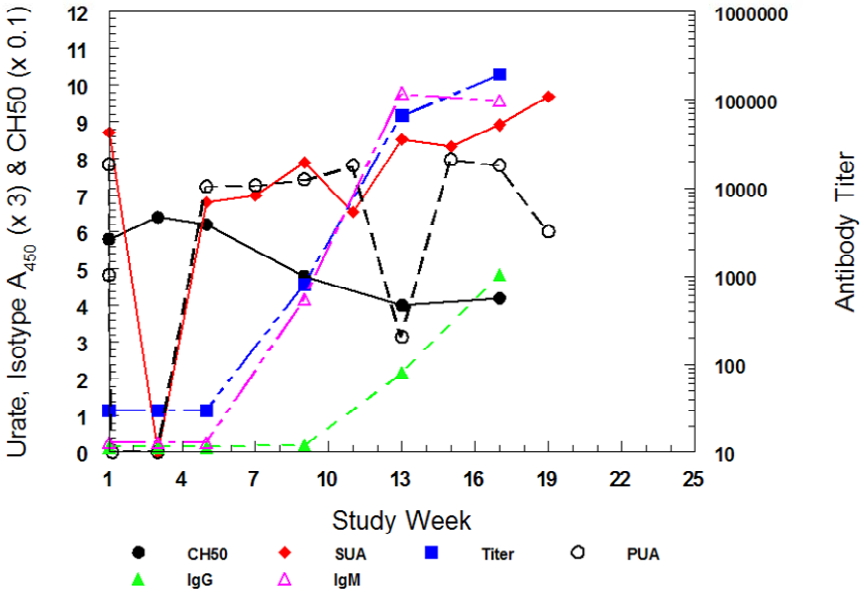
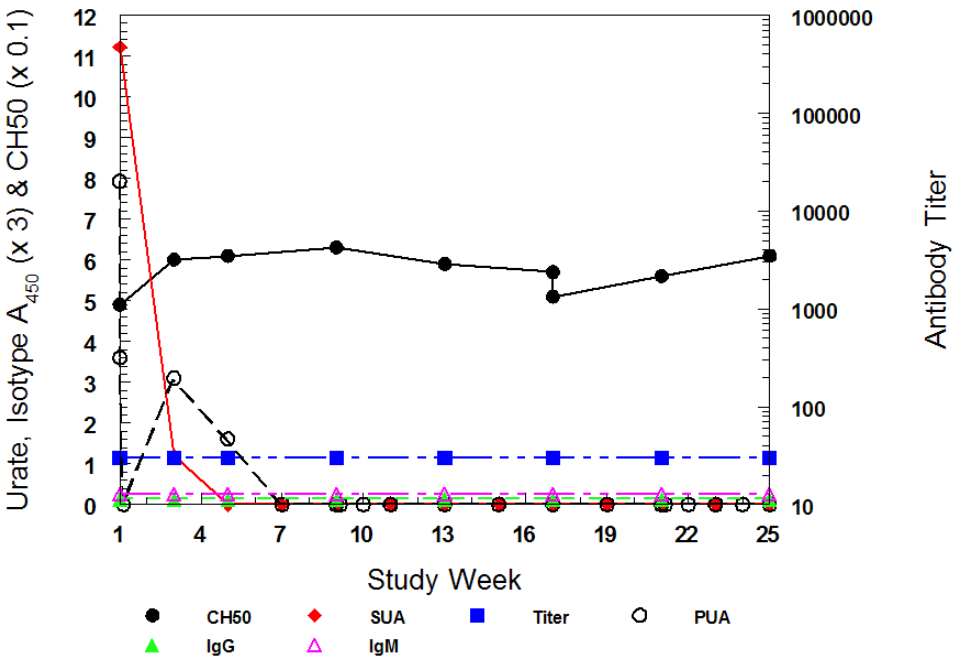


Figure 55. Profile of CH50, SUA, and Anti-pegloticase Antibody Titer; Pegloticase 8 mg Every 2 Weeks Persistent Responder (Subject 301-002)



5.6.3.9 *Conclusions: Immunogenicity*

In conclusion, the development of anti-pegloticase antibody explains the loss of the SUA/PUA response and many of the infusion reactions. Most infusion reactions occur after the loss of SUA/PUA response and, as a result, careful monitoring of SUA can avoid unnecessary dosing and also prevent the majority of infusion reactions. Clinical treatment guidelines in the patient package labeling and the post-approval safety surveillance plan will articulate that a loss of effect with pegloticase, measured as a serum uric acid above 6 mg/dL, should lead the prescriber to discontine pegloticase treatment in order to minimze infusion reactions and their associated safety risks. In addition, discontination of pegloticase treatment after an infusion reaction will also be recommended. The loss of effect in most (80%) transient responders occurs within the first 3-5 weeks, so monitoring serum uric acid during that time period is critical. Finally, the loss of effect of pegloticase occurs during the rise in anti-pegloticase antibody titer, so that there is no correlation between the titer of anti-pegloticase antibody and the loss of a SUA/PUA response. The lack of association between anti-pegloticase antibody titer and the SUA/PUA response confirms the ineffectiveness of monitoring anti-pegloticase antibody titers during pegloticase therapy of patients with treatment failure gout.

5.6.4 Gout Flares

There is a high background incidence of gout flares in the treatment failure gout population. At baseline, patients reported a pre-study mean number of 10 flares during the previous 18 months

and 63% of patients reported their gout flares as being of crippling severity. An initial increase in the occurrence of flares is a well-known phenomenon associated with urate lowering and has been observed with other ULTs. Gout flare prophylaxis with colchicine or a NSAID was used throughout the RCTs and OLE.

Subjects who experienced a gout flare received therapy with a pre-designated: treatment algorithm of any NSAID and a PPI; colchicine; or corticosteroids. If a subject did not experience adequate symptom relief after 5 days of treatment, rapidly progressive polyarticular flare, corticosteroid treatment could be added to the regimen after 48 hours. Narcotic analgesics, acetaminophen, or tramadol, prescribed at the discretion of the Investigator could also be used to attain effective analgesia in conjunction with gout flare treatment at any point in the treatment of an acute gout flare.

5.6.4.1 *Incidence and Frequency of Gout Flares*

Gout flares were the most common adverse event in the RCTs across all three treatment groups: 77%, 83% and 81% of patients treated with pegloticase 8 mg q 2 weeks, pegloticase 8 mg q 4 weeks and placebo, respectively. As stated earlier the increased incidence of flares was transient and resolved after three months of therapy.

The frequency of flares was also decreased in Months 4-6 relative to Months 1-3 and was significantly lower than placebo during Months 4-6. Importantly, only five pegloticase subjects had a serious flare and only six subjects discontinued because of a flare (Table 61).

Gout flares were typically moderate in severity (Table 62). All six pegloticase-treated patients who discontinued due to gout flares did so during the first three months of the study.

Table 61. Serious Gout flares and Flares That Led to Discontinuation in the RCTs.

	Pegloticase		Placebo
	8 mg q 2 weeks N=85 n	8 mg q 4 weeks N=84 n	N=43 n
Serious	4 (5%)	1 (1%)	2 (5%)
Discontinued due to serious gout flares	1	0	0
Discontinued due to any gout flare	4 (5%)	2 (2%)	1 (2%)

Table 62. Incidence of Gout Flares by Severity in the RCTs.

	Pegloticase		Placebo
	8 mg q 2 weeks n (%)	8 mg q 4 weeks n (%)	n (%)
Months 1-3			
	N=85	N=84	N=43
Flare incidence	**63 (85%)**	**68 (81%)**	**22 (51%)**
Mild	7 (8%)	14 (17%)	9 (21%
Moderate	37 (44%)	35 (42%)	11 (26%)
Severe	19 (22%)	19 (23%)	2 (5%)
Months 4-6			
	N=69	N=69	N=43
Flare incidence	**28 (41%)**	**39 (57%)**	**29 (67%)**
Mild	11 (16%)	12 (17%)	8 (19%)
Moderate	12 (17%)	21 (30%)	15 (35%)
Severe	5 (7%)	6 (9%)	6 (14%)

5.6.4.2 *Gout Flares over Time*

The severity, incidence, and frequency of gout flares continued to decrease through the OLE for patients who were already on active treatment at the time of enrollment into the OLE.

5.6.4.3 *Conclusion: Gout Flares*

In patients receiving pegloticase, there was a transient increase in the incidence of gout flares that resolved after three months of therapy. Most flares were mild to moderate in severity and did not result in treatment discontinuation. Gout flares may be mitigated through prophylactic treatment with colchicine or a NSAID.

As noted in the phase 3 Efficacy results (Section 4.5), the incidence and frequency of gout flares were statistically significantly lower in the pegloticase 8 mg q 2 weeks droup during Months 4-6 of therapy when compared to placebo. There was no statisitical difference between the pegloticase 8 mg q 4 weeks group and placebo during the same time period.

5.6.5 Treatment-emergent Infections

The incidence of infections in the RCTs was similar across treatment groups: 35% in the pegloticase 8 mg q 2 weeks group; 48 % in the pegloticase 8 mg q 4 weeks group and 51% in the placebo group.

5.6.5.1 *Serious Infections*

Infections reported as SAEs were similar across the three treatment groups in the RCTs (Table 63). There were 14 subjects with serious infections: 3 subjects (4%) in the pegloticase 8 mg q 2

weeks group; 6 (7%) subjects in the pegloticase 8 mg q 4 weeks group and 5 (12%) subjects in the placebo group. Serious infections were disparate occurring in single subjects within treatment groups.

Table 63. Incidence of Serious Infections in RCTs.

System Organ Class Preferred term	Pegloticase 8 mg		Placebo
	8 mg q 2 weeks N=85	8 mg q 4 weeks N=84	N=43
Subjects with infections	**3 (4%)**	**6 (7%)**	**5 (12%)**
Infections and Infestations			
Pneumonia	1 (1%)	1 (1%)	1 (2%)
Cellulitis	1 (1%)	1 (1%)	0
Arthritis Bacterial	0	0	1 (2%)
Cellulitis Staphylococcal	0	1 (1%)	0
Herpes Zoster	0	0	1 (2%)
Localised Infection	0	1 (1%)	0
Necrotising Fasciitis	0	1 (1%)	0
Perianal Abscess	0	0	1 (2%)
Pyelonephritis	1 (1%)	0	0
Sepsis	1 (1%)	0	0
Staphylococcal Sepsis	1 (1%)	0	0
Renal and Urinary Disorders Hematuria*	0	0	1 (2%)
Hepatobiliary Disorders Cholecystitis	0	1 (1%)	0

Note: If the same subject in a given treatment had more than one occurrence in the same preferred term event category, the subject was counted only once.
***Subject CO405-101-005 was hospitalized with severe hematuria and was diagnosed with urosepsis.**

There were two subjects in the RCTs with methicillin-resistant *Staphylococcus aureus* (MRSA) infection: one subject in the pegloticase 8 mg q 2 weeks group and one subject in the pegloticase 8 mg q 4 weeks group. Subject C0406: 301-003 was an 89 year-old Caucasian male diagnosed with MRSA septicemia, after developing a staphylococcal infection in a stage 1-2 perianal decubitus ulcer. The subject was initially treated in the hospital and subsequently transferred to a skilled nursing care facility to receive a 6-week course of i.v. antibiotics. His condition worsened and was hospitalized for further antibiotic therapy. He subsequently died after voluntarily withdrawing antibiotics. The subject completed the 6-month double-blind study. The subject had multiple co-morbidities including chronic renal failure, a pacemaker, and a prosthetic valve.

Subject C0405:133-005 was a 34 year-old Caucasian male with new onset diabetes who developed a right thigh abscess, that he opened and drained himself, with worsening infection and early necrotizing fasciitis (cultures revealing MRSA) after receiving 4 doses of study drug in the double-blind study. The subject was treated successfully with antibiotics and continued in the study.

5.6.5.2 *Serious Infections with Longer Term Treatment*

There were two subjects who were previously treated with pegloticase in the RCTs who had serious infections in the OLE. Both subjects had antibiotic-resistant staphylococcal infections. In addition, one subject previously treated with placebo in the RCTs had a resistant staphylococcal infection in the OLE.

One subject was a 43 year-old diabetic male in the pegloticase 8 mg q 4 weeks group during the double blind study and in pegloticase 8 mg q 2 weeks group during the OLE study who was diagnosed with MRSA groin abscesses and cellulitis after receiving one dose of pegloticase in the OLE study. The subject had a medical history of MRSA of the right elbow and a 6-month history of a right groin abscess and cellulitis. The subject recovered with antibiotics and continued in the study.

The second subject (C0405: 122-004) was a 54 year-old female with a recent history of hospitalizations, including triple antibiotic treatment of peritonitis due to peritoneal dialysis/catheter, chronic kidney failure, hip fracture, and pancreatitis, who was diagnosed with oxacillin-resistant Staphylococcus aureus (ORSA) sepsis secondary to an osteomyelitis of the right first metatarsophalangeal (MTP) joint due to an infected draining tophus. The subject subsequently died after care was withdrawn. The subject received pegloticase 8 mg q 4 weeks during the double-blind study and received four doses of pegloticase 8 mg q 2 weeks in the OLE study.

Additionally, a 56 year-old female, was diagnosed with a MRSA subcutaneous abscess on her neck following a one-week course of four antibiotics for cellulitis of her neck and upper back. The subject had received one dose of pegloticase in the OLE study. The subject recovered with antibiotics and withdrew from the study. This subject received placebo during the double blind study.

5.7 Safety Conclusions

The principal safety risks associated with pegloticase include infusion reactions, gout flares, and immunogenicity. Infusion reactions were generally mild to moderate in severity. Gout flares were also mostly mild-moderate in intensity and generally tolerated by subjects without resulting in discontinuation of therapy. In addition, the increased incidence was transient, and resolved after 3 months of therapy. This initial increase in gout flares is consistent with other ULT. Immunogenicity was seen in the majority of subjects. Those with high titers of anti-pegloticase antibodies had a strong tendency to lose PUA response as well as an increased risk of infusion reactions. PUA response in subjects with low-moderate titer was largely preserved. There was no clinically meaningful standard laboratory finding observed with pegloticase therapy. Overall safety in the OLE was consistent with that observed in the RCTs.

With respect to cardiovascular events, interpretation of the likelihood of a causal relationship of pegloticase is confounded by the small number of events, the relatively high baseline cardiovascular co-morbidities at baseline in the study population, and the 2:2:1 randomization scheme that led to a 4-fold increase in exposure to pegloticase versus placebo. No particular cardiovascular event type was prominent, and there was no evidence for a clustering of the timing of events during the RCTs nor the OLE. Additionally, chronic exposure to pegloticase was not associated with an increase in the cardiovascular event rate.

6. RISK MINIMIZATION ACTION PLAN

The Sponsor has developed a Educational Outreach Risk Minimization Action Plan assicated with pegloticase administration in the post-approval setting for patients with treatment failure gout. The Sponsor has submitted a proposal to FDA for review and comment. The plan primarily includes a Medication Guide, and a Communication Plan. As pegloticase is an infused biologic, it is anticipated that only infusing specialists in Rheumatology or Nephrology will utilize this therapeutic approach and therefore pegloticase will not be used by non-specialists.

6.1 Goals of the Risk minimization action plan

The plan will include the following four overarching goals:

1. Optimization of patient monitoring and treatment duration through education and outreach to key health care professionals regarding plans for routine monitoring of SUA, and recommendations on discontinuation in the event of loss of SUA or safety adverse events.
2. Optimization of communication of risks and benefits of pegloticase through labeling, issuance of a multi-lingual patient medication guide, letters and educational material to healthcare professionals.
3. Optimization of provider care by recommending the use of pegloticase to prescribers and infusion centers that are registered in the Pegloticase Risk Minimization Plan and have acknowledged understanding of risk through an education and outreach program.
4. Enhanced post-marketing safety surveillance through additional data collection, including initiation of a large post-marketing studies to expand the total pegloticase patient database, and to continue assessment of risks associated with pegloticase in a clinical practice population.

6.2 Goal #1: Optimization of Patient Monitoring and Treatment Duration:

The following educational outreach program will be implemented with prescribers and appropriate infusion center personnel about the correct monitoring of pegloticase administration to patients according to final approved labeling:

- Minimize the risks associated with infusion reactions by providing educational information about:
  - use of infusion reaction prophylaxis
    - fexofenadine 60 mg the night before and the morning of the infusion
    - acetaminophen 1000 mg the morning of the infusion
    - hydrocortisone 200 mg IV immediately prior to the infusion
  - recognizing the signs and symptoms of an infusion reaction
    - most common signs and symptoms of an infusion reaction were urticaria, dyspnea, erythema, flushing, chills, hyperhidrosis, and hypertension
    - signs and symptoms of serious infusion reactions may additionally include dyspnea, hypotension, hypertension, swelling, bronchospasm, chest pain, nausea, vomiting, abdominal pain, and cramping

  - recommended management of infusion reactions
    - discontinue KRYSTEXXA therapy as described in final labeling
    - supportive treatment can include intravenous fluids, glucocorticoids, and/or antihistamines
    - management of severe infusion reactions should be dictated by the signs and symptoms of the reaction

- Alert patients and healthcare providers that gout flares may increase during the first few months of therapy
  - Minimize the risk of gout flares with gout flare prophylaxis
  - prophylaxis with either a colchicine or a non-steroidal anti-inflammatory drug (NSAID) should be initiated at least 1 week prior to initiation of therapy and continued for at least the first three months of therapy (unless medically contraindicated or not tolerated)
- Minimize treatment exposure in transient responders by educating physicians and recommending that therapy should be discontinued in patients who have an moderate to severe infusion reaction or in those who fail to achieve control of serum uric acid (SUA < 6 mg/dL)

6.3 Goal #2: Optimization of Communication of Risks and Benefits of Pegloticase

The communication tools are designed to enhance the awareness of and mitigate the risks associated with the use of the product and to promote informed discussions between prescribers and their patients about the risks and benefits of pegloticase therapy. The FDA-approved label will contain guidelines for the safe use of pegloticase, including the appropriate patient population and recommendations regarding discontinuation of therapy.

6.3.1 Communication Plan

The second key component of the risk minimization action plan is a Communication Plan for education of prescribers and other Heathcare Professionals, including nurses at infusion centers and hospital pharmacists. It is expected that pegloticase will be prescribed primarily by medical specialists (rheumatologists and nephrologists), and because the product is given by intravenous infusion, it will be administered in a controlled healthcare setting providing opportunities for patient education. Since pegloticase is administered in a medical office, hospital, or infusion center setting, the opportunity exists for healthcare providers to regularly reinforce educational messages with patients.

Educational materials will be provided to educate prescribers, relevant infusion center staff and health system pharmacists about the appropriate use of pegloticase. In addition, specialized materials will be provided to aid Heathcare Professionals in discussing pegloticase treatment and in clearly conveying important safety messages to patients. The educational materials in support of this action plan are listed below:

a. Pegloticase Prescribing Information (PI)
b. Pegloticase Medication Guide for Patients
c. Introductory Healthcare Professional Letter

d. Pegloticase Connexxions Prescribing Program - Prescriber Education Form (for Connexxions Risk Minimization System)
e. Pegloticase Connexxions Prescribing Program - Infusion Center Education Form (for Connexxions Risk Minimization System)
f. Pegloticase Connexxions Prescribing Program Guide for Healthcare Professionals
g. Pegloticase Connexxions Prescribing Program Guide for Patients
h. Pegloticase Patient Information Sheet and Acknowledgment

6.3.2 Medication Guide

A Medication Guide for patients will be packaged with every individual dosing unit of pegloticase. The outer package will also include a message to provide the Medication Guide to the patient at every infusion. Healthcare Professionals and infusion centers will be instructed that the Medication Guide must be provided to patients before each administration of the product.

Additional copies of the Medication Guide will be available via sales and/or clinical representatives, the corporate or product website and through the Sponsor toll-free information number.

6.4 Goals #3: Optimization of Provider Education and Outreach Program

6.4.1 Educational Materials for Pegloticase Prescribers and Other Healthcare Professionals

For this Risk Minimization Action Plan, materials have been developed that will provide information for prescribers, infusion nurses, and health system pharmacists consistent with the educational objectives described above. The key risk messages will be based on information that is included in the pegloticase PI.

An introductory letter will be provided to potential prescribers via a direct mail program. This will introduce potential prescribers to the Educational out reach program plan and the requirement that prescribers and infusion centers must be enrolled in the Connexxions risk minimization system in order to use pegloticase. Copies of the educational materials will also be enclosed in the mailing. Because the main prescribers of pegloticase are expected to be rheumatologists and nephrologists, the materials will be sent to all rheumatologist members of the American College of Rheumatology and nephrologist members of the American Society of Nephrology. In order to reach pharmacists at infusion centers, the materials will be distributed to health system pharmacist members of the American Society of Health System Pharmacists. The educational materials will also be available to targeted rheumatologists and nephrologists and nurses at infusion centers from sales representatives and will be available through the Risk Minimization Coordinating Center. The materials will be available for download on the corporate and pegloticase website. In addition, the patient education materials will be delivered by specialty distribution vendors with each vial of pegloticase.

The main educational tool for Healthcare Professionalsis the pegloticase Connexxions Prescribing Program Guide for Healthcare Professionals, which is described below.

6.4.1.1 *Pegloticase Connexxions Prescribing Program Guide for Healthcare Professionals*

An educational brochure will be developed for prescribers, infusion nurses and health system pharmacists, and provides the following information:

- The appropriate target patient population for use of pegloticase is patients with treatment failure gout
- pegloticase is contraindicated in patients with G6PD deficiency
- pegloticase should not be used in patients who have uncompensated congestive heart failure, unstable angina, uncontrolled hypertension or uncontrolled arrhythmia
- The appropriate administration and infusion process for pegloticase (infusion reaction prophylaxis)
- Recognizing the signs and symptoms associated with an infusion reaction
- The appropriate management of infusion reactions
- The recommendation to discontinue pegloticase in patients who have an moderate to severe infusion reaction or in those who fail to achieve control of serum uric acid (SUA < 6 mg/dL) or lose uric acid control (SUA >6 mg/dL)
- The potential for increased gout flares during the first few months of therapy and the need to administer appropriate flare prophylaxis

Preparation and administration instructions are presented in the same document in a more detailed way for ease of reference for the HCP who will prepare and administer pegloticase.

6.4.2 Educational Materials for Patients

In addition to the Medication Guide, a pegloticase Connexxions Prescribing Program Guide for Patients has been developed to use in educating patients about the potential risks of infusion reaction and gout flares, to provide important product information, and to help answer questions about the pegloticase administration process.

6.4.2.1 *Pegloticase Connections Prescribing Program Guide for Patients*

The objective of this safety guide is to educate patients about therapy with pegloticase and the potential risks that may be associated with it. The risk messages will include information about the potential for infusion reactions and the symptoms that may be associated with them, the infusion process (i.e., pre-infusion prophylaxis, duration of the infusion), the risk of an increase in gout flares and the need for gout flare prophylaxis.

This safety guide includes the following information:

- How pegloticase is administered.
- Explains the potential for infusion reactions.
- A description of the potential signs and symptoms associated with an infusion reaction.
- The need for infusion reaction prophylaxis.
- The potential for increased flaring during the first few months of therapy
- The need for gout flare prophylaxis

This safety guide will reach patients via the following channels:

- It will be provided to registered prescribers and infusion centers through the Risk Minimization Coordinating Center, with instructions that it should be provided to patients at the time of administration
- It will be delivered by sales representatives to both targeted rheumatologists and nephrologists likely to infuse pegloticase, with the instruction that the brochure should be given to patients and discussed with them
- It will be available for download from the corporate or pegloticase website
- It will be delivered to the infusion center by distribution vendors with each vial of pegloticase

6.4.3 Education and Outreach to Other Key Audiences

6.4.3.1 *Specialty Distribution*

Pegloticase will be distributed directly to the Healthcare Professionals offices or infusion centers by distribution vendors, predominantly via Specialty Distributors (SDs) and Specialty Pharmacy Providers (SPPs). The Sponsor will establish contracts with pegloticase distribution vendors to ensure that they will make product and educational materials available to patients, prescribers and infusion centers.

6.5 Goal #4: Enhancement of Safety Database through Additional Data Collection

6.5.1 Postmarketing Studies

- The Sponsor will initiate a postmarketing studies, pending review and discussion with the FDA on the appropriate design to further assess the profile of pegloticase in a real-world clinical setting. The first study is expected to begin enrolling subjects approximately one year after FDA approval of the product. Patients receiving pegloticase infusions will be enrolled and followed for at least one year, with additional follow-up after discontinuation of pegloticase.

6.6 Other Relevant Information

6.6.1 Independent Data Safety Monitoring Committee

The Sponsor will establish an independent Data Safety Monitoring Committee. The committee will be constituted prior to product market availability, and will include specialists with expertise in the following disciplines: rheumatology, allergy and immunology, cardiology, epidemiology and biostatistics. The recommendations of the committee will be provided to the Sponsor for review and consideration. It is intended that the Committee will review the Risk minimization action plan as well as postmarketing pharmacovigilance data and adverse events from the pegloticase postmarketing studies. The review will occur at least bi-annually to evaluate new information and determine if there are any unexpected safety signals.

7. BENEFIT-RISK ASSESSMENT OF PEGLOTICASE FOR PATIENTS WITH TREATMENT FAILURE GOUT

In this small orphan population with treatment failure gout, pegloticase offers the first treatment option for this subset of gout patients with advanced progressive and symptomatic disease, a high burden of co-morbidity, and no available alternative therapies.

Pegloticase 8 mg every 2 weeks administered intravenously results in dramatic decreases in uric acid acid values and resolution of tophi in some subjects within the time line of a randomized controlled study. These benefits were also associated with decreases in tender joint counts and statistically and clinically meaningful improvements at 6 months in PROs (pain, global assessment of disease activity, physical function and HRQOL). Pegloticase treatment also resulted in a decrease in the incidence and frequency of gout flares after 3 months of therapy, statistically fewer than placebo treated-patients, and with continued benefit with long term administration. With continued exposure the benefits of pegloticase have been observed to last up to 18 months.

An imbalance in cardiovascular events that was observed with pegloticase administration cannot be clearly attributed to treatment and must be interpreted in the context of the size of the database, imbalance in treatment assignment, and multiple underlying medical co-morbidities of this patient population.

Risks associated with infusion reactions and immunogenicity can be minimized by monitoring serum uric acid regularly during the first 3 months of therapy, and periodically thereafter at the discretion of the physician. If serum uric acid is above 6 mg/dL, pegloticase therapy should be discontinued. This will eliminate many infusion reactions that were observed during the RCTs. Additionally, pegloticase therapy should be discontinued if a subject has a moderate or severe infusion reaction; even if their serum uric acid is below 6.0 mg/dL.

Another important quantitative method to express risk and benefit is the concept of Number Needed to Treat (NNT) in relation to Number Needed to Harm (NNH). NNT (1 to ∞) is the number of subjects who need to be treated with a therapy to result in a "good" or "desired" outcome; or to prevent a bad outcome from occurring. Therapies with lower NNTs are more effective.

NNTs calculations indicate that, in persistent responders, between 1.2 and 2.4 patients would need to be treated to achieve clinically meaningful improvements in $\geq$1 to 3 PROs simultaneously. These compare favorably with the overall incidence of adjudicated APTC cardiovascular events in the pegloticase every 2 weeks treatment group: 2 or 2.4 per 100/patient years [95% CIs: 0.29 - 8.24]. A similar incidence of non-APTC events: 2 or 2.4 per 100/patient years [95% CIs:200.29 - 8.24] again offers a favorable benefit/risk profile for pegloticase every 2 weeks treatment based on the NNT analysis of persistent responders.

In summary, in two replicate phase 3 studies, pegloticase 8 mg every 2 weeks has been demonstrated to be beneficial for patients with severe treatment failure gout, a small orphan population with a large unmet medical need. Importantly, the phase 3 data that supports this

conclusion is based on the first-time demonstration of a clinically meaningful benefit to patients beyond a normalization of serum uric acid. This clinical benefit includes the complete resolution of debilitating and disfiguring tophi that parallels other important physician and PROs.

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APPENDICES:

Appendix 1: Nonclinical Summary

Appendix 2: Phase 1 and 2 Summary

Appendix 3: Narratives for Subjects Who Died

Appendix 4: Narratives for Subjects or Who had Serious Cardiovascular Events

Appendix 5: Narratives for Subjects Who had Serious or Significant Infusion Reactions

Appendix 6: Post-hoc Cardiovascular Adjudication Report

Appendix 7: Post-hoc Evaluation of Phase 3 RCT EKGs

Appendix 8: "Spydergram" SF-36 Scores

SUMMARY OF PEGLOTICASE NONCLINICAL STUDIES

The toxicological testing of pegloticase followed the recommendations provided by FDA to support the clinical development program of this biotechnology product. The design of the non-clinical testing program for pegloticase was based also on the ICH S6 guidance for the non-clinical development of biotechnology pharmaceuticals. This testing strategy involved pharmacodynamic studies to evaluate pegloticase activity, pharmacokinetic studies to ascertain systemic disposition and elimination, and toxicology studies to characterize the safety profile. Also included was assessing the immunogenic potential of the PEGylated protein. The toxicity studies completed with pegloticase have fully characterized the safety profile of this novel biotechnology drug.

In the non-clinical studies, pegloticase was formulated in phosphate buffered saline (PBS), and this vehicle was used in all of the non-clinical studies. The components of PBS are listed as inactive ingredients in the database on FDA approved products. The drug substance used in the toxicology studies was produced and formulated the same as material used in the clinical trials. Thus, any impurities possibly present in the drug substance were tested in the toxicology studies at multiple exposure levels that exceeded those that could be expected with patient exposure.

The results of the acute and chronic toxicity studies did not indicate any toxic or adverse effect of pegloticase administered. The results of these studies revealed no test article related findings at any of the doses or dosing intervals tested, in the following parameters: injection site reactions, morality, clinical observations, body weight, food consumption, ophthalmic and electrocardiographic examinations, Modified Irwin's Behavioral Screening, clinical pathology, organ weights, and macroscopic pathology. The administration of pegloticase injections did not cause any obvious or adverse test article-related effects in any hematology, coagulation, clinical chemistry (except for the expected decreased in uric acid) and urine chemistry or urinalysis tests at any dose or interval.

Four repeated (intermittent) dose toxicity studies were conducted to define the toxicological profile of pegloticase given over 7 - 39 weeks. The repeated (intermittent) dose toxicity studies were designed to identify clinical toxicity, potential target organs, reversibility of any findings, and a No-Observable-Adverse-Effect-Level (NOEL). These studies also were used to identify any parameters that should be monitored during the clinical investigations. Pegloticase was administered to the animals across a spectrum of doses intended to produce adverse effects.

In the repeated (intermittent) dose subcutaneous toxicity studies in rats (q 2 day x 54 day) and dogs (q 4 day x 52 day), subchronic administration of pegloticase was well tolerated. There were no adverse findings. The only treatment-related observation in rats was the microscopic presence of vacuolated macrophages in the spleen at the completion of dosing but not in the recovery group in the 10.2 mg/kg mid-dose group. For the 34 mg/kg high-dose group, vacuoles were found at the completion of dosing and at the end of recovery period. After the recovery period, the splenic siderophage vacuolation at the high-dose remained at a similar incidence but had diminished in degree. The only treatment-related observation in dogs was the microscopic presence of vacuolated macrophages in the spleen and submandibular lymph nodes at the completion of dosing but not in the recovery group in the 5.1 mg/kg mid-dose group. For the 17

mg/kg high-dose group, vacuoles were found at the completion of dosing and at the end of recovery period.

In the repeated (intermittent) dose intravenous toxicity studies, pegloticase was well tolerated by male and female dogs at doses up to 5 mg/kg (high-dose group) on a q 5 day x 12 weeks dosing regimen and at doses up to 10 mg/kg (high-dose group) on a q 7 day x 39 week chronic dosing regimen. There were no adverse findings. The only treatment-related observation was the microscopic presence of vacuolated macrophages predominantly in the spleen and in the 39-week study in the liver and the submucosa of the jejenum and duodenum. Vacuolated cells were present in the basal area of the lamina propria within the duodenum, basal area of the lamina propria within the jejunum, adrenal cortex, hepatic Kupffer cells, and the intimal cells within the aortic outflow area of the heart. An independent re-examination of these tissues disclosed the primary treatment-related effect to be the presence of vacuoles in the cytoplasm of macrophages in the spleen, gastrointestinal tract and the liver (Kupffer cells). In the adrenal and the heart, the vacuoles that were observed were considered to be inconsequential. There were no statistically significant differences in the absolute or relative weights of the adrenal glands from either sex at any dose at the end of the 39-week treatment period or at the end of the 12-week recovery period. The presence of vacuoles in the aortic outflow tract of the heart had no effect upon the electrocardiograms (heart rate, Q-T interval, QTc) of either the males or the females at all doses when evaluated after 12, 24, or 39 weeks of dosing or after a 12-week recovery period. Other than the vacuoles (minimal to slight) noted in the aortic outflow tract of the heart, there were no gross and no other microscopic changes in the heart that would indicate an adverse compound-related effect. There were no deaths in the study. The test-article related vacuolar effects in macrophages in the spleen, intestine and liver (Kupffer cells) as well as the adrenal medulla and the intima of the aorta were interpreted to be the non-adverse effects related to the ingestion of pegloticase. There was no evidence of necrosis in any of the lymphoid organs, including the spleen, and there was no evidence of reduced immune function as would be reflected in an increase in disease in the dosed animals. There were no other clinical or anatomic pathologic findings that would further identify this vacuole observation as adverse.

To determine the contents of the vacuoles seen in the 39-week dog study, an immunohistochemistry study was conducted with antigen immunohistochemical staining for the antigens uricase, PEG and macrophage. Tissues in this study included tissues from the adrenal, spleen, liver, heart, duodenum and jejunum. The stain for macrophages clearly demonstrated qualitatively that macrophages were present in the liver, spleen and lamina propria of the duodenum and jejunum of both dosed and control dogs, and that the cytoplasmic vacuoles noted in the dosed dogs were in macrophages. The absence of positive staining for macrophages in the adrenal cortex and the vascular wall of the aortic outflow tract of the heart suggested that the vacuoles noted in these structures were present in the cytoplasm of cells having phagocytic function but did not contain the markers for macrophages. Numerous cells other than macrophages are known to possess phagocytic activity, and these include endothelial cells. The most striking finding in this immunohistochemical study was the contrast in staining between the end of the dosing and the end of the recovery periods in the 10 mg/kg dose groups. At the end of 39 weeks of dosing, positive staining of cells and vacuoles for both uricase and PEG (pegloticase) occurred in all dogs. There was almost no staining of cells for both uricase and PEG at the end of the recovery period in either sex. In the recovery males, staining for uricase

occurred inconsistently in one or two dogs. There was no staining for PEG. The contrast in the patterns of immunochemical staining between the end of the dosing and the end of the recovery intervals was interpreted to indicate that at the end of the dosing period pegloticase had been taken up by cells and was being sequestered into phagolysosomes to be digested. The markedly reduced or the absence of staining for both uricase and PEG at the end of the recovery period was interpreted to indicate that the cells had metabolized the pegloticase and the intact molecule was no longer present or greatly reduced in the cells or vacuoles.

In the nonclinical studies, the dogs received pegloticase more frequently than was used in the clinical investigations. Despite this exaggerated dosing schedule coupled with high doses, the only treatment-related effect observed was the presence of vacuoles in the cytoplasm of the macrophages, predominantly in the spleen and in the 39-week dog study in the liver and the submucosa of the jejunum and duodenum. The presence of vacuoles in these organs reflected the accumulated removal of injected pegloticase-related (foreign) material from the circulation. There was no evidence of degeneration, inflammation or necrosis associated with the vacuole findings. In addition, there were no other notable findings in the nonclinical studies. Thus, the NOAEL dose in a given study was the high-dose in the study. The 39-week dog study provided a NOAEL exposure (average AUC) ratio of 106 for the Phase 2 clinical 8 mg q 2 week dose and 153 for the Phase 2 clinical 8mg/q 4 w dose.

Weak antibody titers to m-PEG, and pegloticase were detected in most subchronic/chronic studies. The predominant immune response was against uricase. However, following the recovery period, there was a trend towards a general decrease in the titer of anti-uricase antibodies. None of the antibodies were neutralizing antibodies. There were no clinical manifestations associated with the presence of antibodies against the three antigens. Intermittent dosing did not affect immune competence, and in the subchronic intravenous dog study, 4 week intermittent dosing followed by a recovery period and then challenge with pegloticase did not evoke any immune response.

Developmental and reproductive toxicity studies were conducted to determine the potential effects of pegloticase on embryo/fetal development in rats. Pegloticase administered intravenously to pregnant female rats once daily every 2 days at 5, 10, or 40 mg/kg during Gestation Days 6 – 16 was well tolerated. Intrauterine growth and survival were not affected. There were no treatment-related external, visceral, or skeletal malformations, developmental variations, or developmental delays in any of the fetuses in any group. The 40 mg/kg dose was the fetal NOAEL for embryo/fetal developmental toxicity when pegloticase was administered intravenously to pregnant rats during the major period of organogenesis. The fetal NOAEL exposure (total AUC) ratio for the rat embryo/fetal development and the Phase 2 clinical dose of 8 mg given intravenously every two weeks was 22. The fetal NOAEL exposure (total AUC) ratio for the rat embryo/fetal development and the Phase 2 clinical dose of 8 mg given intravenously every four weeks was 35.

No genotoxicity or carcinogenicity studies were conducted in concurrence with the ICH S6 guidance on biotechnology pharmaceutical products and the FDA. There were no findings in the non-clinical studies of mitogenic potential with pegloticase.

In conclusion, non-clinical studies conducted with pegloticase have defined its pharmacology, pharmacokinetic, and toxicology profile. There were no unexpected toxicities encountered in the toxicology program. Results from the toxicology studies also provided adequate and appropriate safety information on risks/benefits relative to immunogenicity and effects on the fetus following exposure to pegloticase. Thus, the non-clinical pharmacology, pharmacokinetic, and toxicology studies support the market registration of pegloticase as safe for the intended clinical indication at the proposed dose of 8 mg on an intermittent dosing schedule of once every 2 weeks.

Special Study in Mice: Urate Oxidase Deficiency in Mice

Animals, except humans and great apes, have an endogenous urate oxidase. A pegloticase proof-of-concept study was performed in an urate oxidase-knock-out mouse model. These animals express no endogenous urate oxidase. They have hyperuricemia and develop UA nephropathy. After intraperitoneal injections of pegloticase every 5 days for two months, the amount of excreted uric acid in urine was greatly reduced, and the renal concentrating ability was significantly improved. Urate levels in serum also were markedly reduced. When urate oxidase administration was begun before weaning, development of nephropathy and diabetes insipidus was prevented.

APPENDIX 2: PHASE 1 AND 2 SUMMARY

PHASE 1 (OPEN-LABEL, SINGLE DOSE STUDY)
An open-label, single center, subcutaneous dose escalation study of the pharmacokinetics and pharmacodynamics of pegloticase in subjects with hyperuricemia and symptomatic gout was conducted [Ganson et al. 2005]. This was designed to test 4, 8, 12, 24 and 48 mg of pegloticase in five cohorts of 4 subjects each. However, only 13 subjects were treated. Four subjects in each of the lower dosing cohorts and one subject in the 24 mg dose cohort were studied before the trial was stopped due to a safety concern about the route of administration. The study was discontinued after two subjects in the 12 mg dose cohort developed generalized urticaria and myalgias 10 days after dosing. Plasma uric acid (PUA) levels in all subjects in the cohorts > 8 mg became normalized (PUA < 6 mg/dL) with the exception of one subject in the 8 mg group, whose initial PUA level was extremely high, approximately 15 mg/dL. Further development of a subcutaneous route of administration was abandoned because of the increased potential for immunogenicity and allergic reactions, and because of injection site reactions thought to be due to the local release of hydrogen peroxide associated with enzymatic conversion of uric acid to allantoin. It was hypothesized that the peroxidase in circulating red blood cells would metabolize any hydrogen peroxide resulting from intravenous pegloticase administration, so this was the route pursued in further development (below).

Phase 1 (Single Intravenous Dose Escalation Study)
This was an open-label, single center study conducted at an academic non-GLP laboratory of pegloticase administered intravenously, in ascending doses ranging from 0.5 – 12 mg to groups of 4 patients (n=24), all of whom manifested severely symptomatic treatment failure gout and hyperuricemia. The pharmacokinetics of pegloticase was measured as uricase enzymatic activity. Plasma uric acid levels were determined in all patients over a 21 day period. The presence of immunoreactivity directed against the drug product, pegloticase, and against the poly(ethylene glycol) moiety were determined by ELISA procedures and immunodepletion.

At entry, all patients had baseline hyperuricemia >7.0 mg/dL. Pegloticase administration (at doses > 2.0 mg) normalized PUA in all patients.

A total of 22 patients (92%) had 66 adverse events (AEs) during the study. All AEs were rated mild or moderate in severity. There were no serious adverse reactions. All but one of 21 AEs (knee pain) considered study drug related were gout flares or exacerbation of gout.

Nine patients were found to have antibodies directed against the drug product, pegloticase, or directed against the PEG moiety on at least two post-treatment test days. Seroconversion (defined as a positive antibody finding post-baseline, or an increase in titer post-baseline) was not dose related and observed with all doses except the 8 mg dose. In 7 of 9 patients with a positive antibody result, antibodies were directed against both PEG and pegloticase. No patient experienced an allergic event.

PHASE 2 (MULTIPLE INTRAVENOUS DOSE ADMINISTRATION)
An open label, randomized, multi-center 18 week dose ranging safety and efficacy phase 2 study was conducted in hyperuricemic patients (SUA > 8.0 mg/dL) with symptomatic gout who were intolerant of or who had failed to normalize SUA with conventional therapy. This study included a 1 week lead-in (or wash out) period, a 12 week treatment period, and a 4 week follow-

up period. The purpose of the study was to select a dose and dose regimen for registration studies for full development as well as further understand about responsiveness and its interrelationship with immunogenicity. Each patient was scheduled to receive either 3 or 6 intravenous infusions of pegloticase, infused over 30 minutes (or one hour, post-Protocol Amendment) in doses of 4 mg every 2 weeks, 8 mg every 2 weeks, 8 mg every 4 weeks, or 12 mg every 4 weeks.

The efficacy results extended the findings of phase 1. Four mg i.v. every two weeks was defined as the minimally effective dose, 8 mg every two or every four weeks was effective, and 12 mg every four weeks did not provide additional benefit beyond that of the 8 mg groups, thereby defining a dose-response plateau. Although the every 2 week and every 4 week 8 mg treatment achieved the same degree of PUA decrease, an every 2 week infusion regimen appeared to offer a more rapid, consistently larger and more prolonged reduction of PUA.

Clinical outcomes, other than normalization of PUA, were not captured as a prospectively planned endpoint in this study because it was believed that a 12 week treatment period would be too brief to allow for their attainment. However, one investigator provided photographic evidence in two patients before and after treatment showing eradication of gout tophi. The PUA in both of these patients was normalized below 2 mg/dL throughout the study period.

No dose relationship was observed with respect to safety outcomes. There were 13 SAEs in nine subjects. Five of these SAEs were designated by the Investigators as possibly or probably related to pegloticase treatment. There were 24 subjects with any AE that was designated to be possibly or probably related to pegloticase. The incidence of gout flares increased by 39% for the first month of treatment, as compared to the self-reported pre-study rate of gout flare occurrence, but then decreased in each of the next three, one-month observation periods. In the last month of observation, the frequency of gout flares was substantially reduced as compared to that predicted from pre-study self-reported gout flare rates. For this phase 2 study, subjects not already on a prophylactic regimen of colchicine or a nonsteroidal anti-inflammatory drug (NSAID) to prevent gout flares could be placed on one of these agents at the discretion of the investigator, unless such therapy was contraindicated for the subject. In phase 3, gout flare prophylaxis was mandatory.

Twenty-eight of 41 (68%) subjects in the ITT population were categorized as positive for seroconversion to anti-pegloticase antibodies during the study, with a fairly even distribution of these subjects across the 4 treatment regimens. The ITT population was all randomized subjects. Exploratory analyses of the effect of anti-pegloticase antibody production on pharmacokinetic and efficacy parameters within the 8 mg 2 week treatment group were conducted. Results indicated that plasma pegloticase concentrations were slightly higher at all post first infusion time points for the non-converted subjects but there was no clinically meaningful difference between seroconverted and non-converted subjects for any of the studied efficacy parameters through 21 days after the last infusion. Furthermore, no clear pattern or increase in infusion reactions or the number of adverse events was discernable between the seroconverted and the non-seroconverted subjects within this treatment regimen.
There were 21 infusion reactions in 18 patients (total 148 infusions) who were administered pegloticase. Twelve of the 18 subjects who experienced an IR were withdrawn from the Study

by the Investigators, most often in consultation with the Sponsor due to a high level of caution about the potential risk of anaphylaxis. No anaphylactic reactions were observed. Investigators initiated a treatment intervention in 13 subjects (who had 15 IRs) including prolongation of the duration of the infusion (dilution) or cessation of the infusion, administration of an oral antihistamine, and/or administration of intravenous corticosteroid. Clinical sequelae requiring interventions beyond the day of infusion were not observed.

The symptoms described by subjects, the evaluation of Investigators at the time of the IRs, the brief duration of IRs, and the observation that signs and symptoms did not recur after the day of infusion led the Sponsor to conclude that these IRs may be interpreted as anaphylactoid type reactions, rather than anaphylaxis. Events with reports of generalized rash or urticaria may be considered more likely as potentially allergic in nature.

On the basis of safety and efficacy results of the Phase 2 study, the pegloticase dose selected for advancement to Phase 3 registration studies was 8 mg administered intravenously (250 mL volume) in 120 minutes every two weeks or every four weeks.

Phase 2 Efficacy
Forty-one subjects were randomized to one of the pegloticase dose groups as follows: seven subjects to the 4 mg every 2 weeks, eight to the 8 mg every 2 weeks, 13 to each of the 8 mg every 4 weeks and 13 mg every 4 weeks dose groups.

At entry, the mean age of the subjects was 58.1 years. Eighty-five percent of the subjects were male and 83% were white. The mean duration of the disease history was 14 years and one or more gout tophi were present in 70% of the subjects.

Phase 2 Efficacy: Uric Acid Measurements
Mean SUA levels at screening by dose group are summarized in Table 1.

Table 1: Mean Serum Uric Acid at Screening: Study C0403.

Serum Uric Acid (mg/dL)	Pegloticase Treatment Regimens (Dose and Frequency)			
	4 mg q 2 weeks N = 7	8 mg q 2 weeks N = 8	8 mg q 4 weeks N = 13	12 mg q 4 weeks N = 13
Mean (SD)	9.39 (0.82)	10.61 (2.75)	10.65 (1.80)	10.19 (1.52)
Median	9.5	9.3	10.3	9.8

Pegloticase is active in serum; therefore, measurements of uric acid from blood samples in patients treated with pegloticase must be made in plasma after denaturation of the protein components. Plasma samples were collected from subjects at defined time-points to determine the PUA levels.

Table 2 presents the mean PUA levels at baseline (drawn immediately prior to first infusion) by dose group.

Table 2: Mean Plasma Uric Acid at Baseline: Study C0403.

Plasma Uric Acid (mg/dL)	Pegloticase Treatment Regimens (Dose and Frequency)			
	4 mg q 2 weeks N = 6*	8 mg q 2 weeks N = 8	8 mg q 4 weeks N = 11*	12 mg q 4 weeks N = 13
Mean (SD)	7.33 (1.81)	9.09 (1.73)	9.01 (3.42)	8.86 (2.26)
Median	6.87	9.55	8.75	8.24
*** Samples for three subjects were unavailable for analysis due to extensive hemolysis.**				

For the primary efficacy analysis, the percentages of treatment success, as defined by the protocol, i.e., subjects whose uric acid values remained below 6 mg/dL during the entire post-infusion period after the last dose, are presented in Table 3.

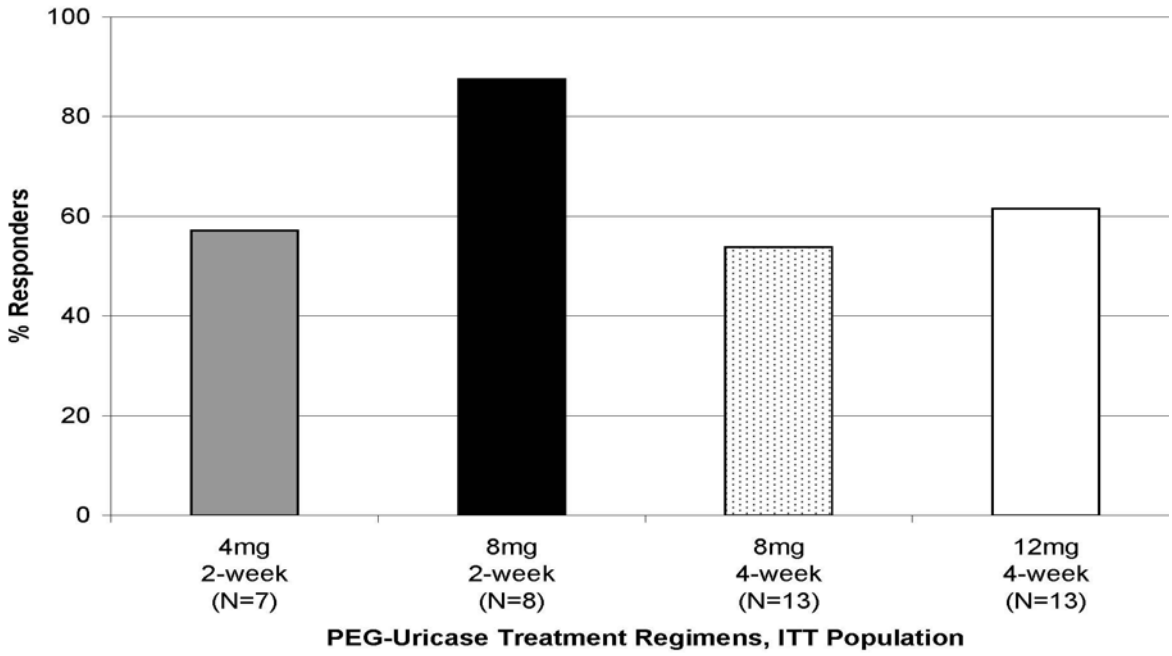
Table 3: Phase 2 Primary Analysis: Treatment Success after the Last Dose.

Population		Pegloticase Treatment Regimens (Dose and Frequency)				Total
		4 mg q 2 weeks n (%)	8 mg q 2 weeks n (%)	8 mg q 4 weeks n (%)	12 mg q 4 weeks n (%)	n (%)
ITT	N	7	8	13	13	41
	Success [1]	1 (14.3)	5 (62.5)	4 (30.8)	3 (23.1)	13 (31.7)
Completer	N	4	8	8	6	26
	Success	1 (25.0)	5 (62.5)	4 (50.0)	3 (50.0)	13 (50.0)
[1] For ITT population, missing data was imputed as failure.						

Persistent Responders

The percentage of treatment (persistent) responders, i.e., subjects whose PUA remained ≤ 6mg/dL for at least 80% of the treatment period within the ITT population for the 8 mg q 2 week regimen was at least 26% higher than for any other treatment regimen in this study (i.e., 4/7 [57%] for the 4 mg q 2 week treatment, 7/8 [88%] for the 8 mg q 2 week regimen, 7/13 [54%] for the 8mg q 4 week regimen, and 8/13 [62%] for the 12 mg q 4 week regimen). See Figure 1**.**

Figure 1. Pegloticase Treatment Regimens. Percentage of Persistent Responders in the ITT Population: Study C0403.



The mean (± SEM) for PUA over time for all subjects administered pegloticase 4 or 8 mg every 2 weeks is presented in Figure 2 while Figure 3 contains the mean (± SEM) for PUA over time for all subjects administered pegloticase 8 or 12 mg every 4 weeks. Irrespective of the initial dose (4, 8 or 12 mg) a rapid reduction in PUA occurred such that the mean PUA normalized below 6 mg/dL. It should be noted that the downward shift in Figure 2 and Figure 3 at week 10 in both of the every 2 week group and week 8 in both of the every 4 week group represents the intensive post-infusion sampling for the pharmacokinetic evaluation.

Figure 2. All Treated Subjects Mean Plasma Uric Acid (± SEM) vs. Time, Every 2 Weeks IV Infusion: Study C0403.

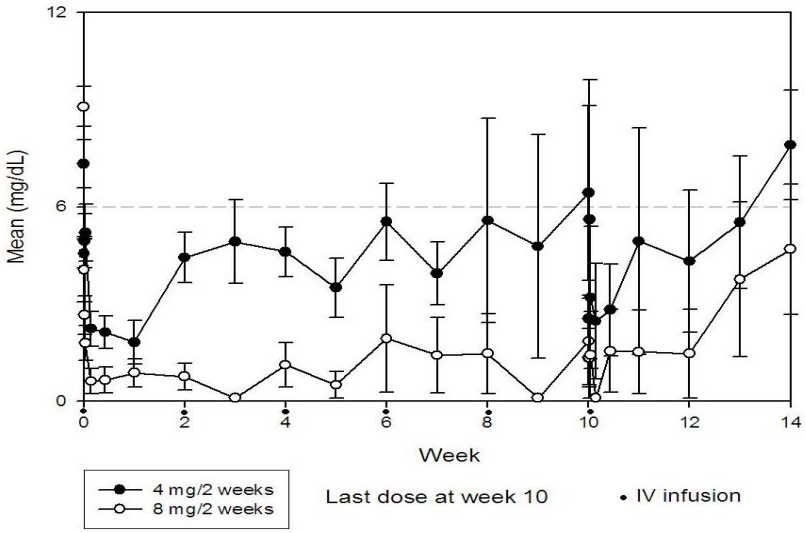
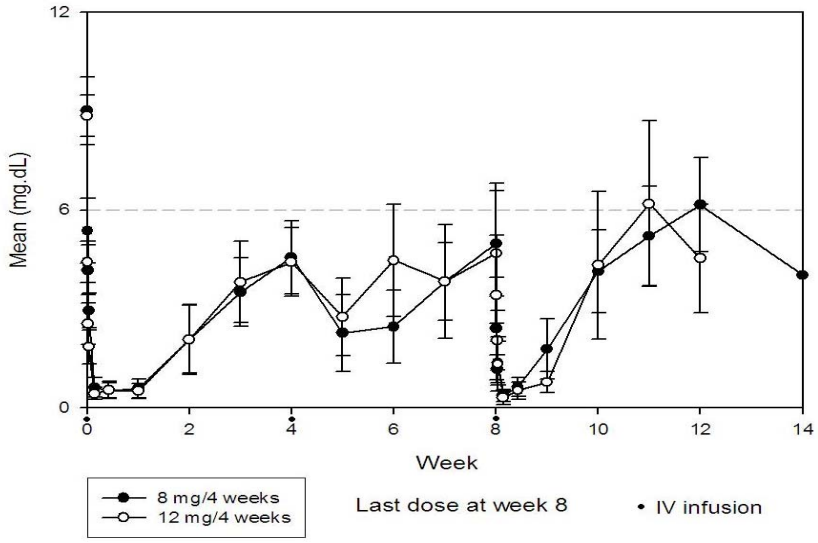


Figure 3. All Treated Subjects Mean Plasma Uric Acid (± SEM) vs. Time, Every 4 Weeks IV Infusion: Study C0403.



While the mean value for all groups remained below 6 mg/dL throughout the 12 week study period, evaluation of individual subjects defined two groups. In all four groups, there were transient responders in which their PUA values returned to values above 6 mg/dL and there were persistent responders who had a sustained normalization of PUA (Figures 4 and 5). Figures 4 and 5 contain the anti-pegloticase antibody titers and demostrate the relationship between PUA and antibody titer. The persistent responders had a sustained PUA normalization and low titers

while the transient responders had higher antibody titers and a return of their PUA values above 6 mg/dL.

Figure 4. Mean (± SEM) Plasma Uric Acid and Anti-pegloticase Antibody Titer over Time in Subjects Administered Pegloticase 4 or 8 mg Every Two Weeks.

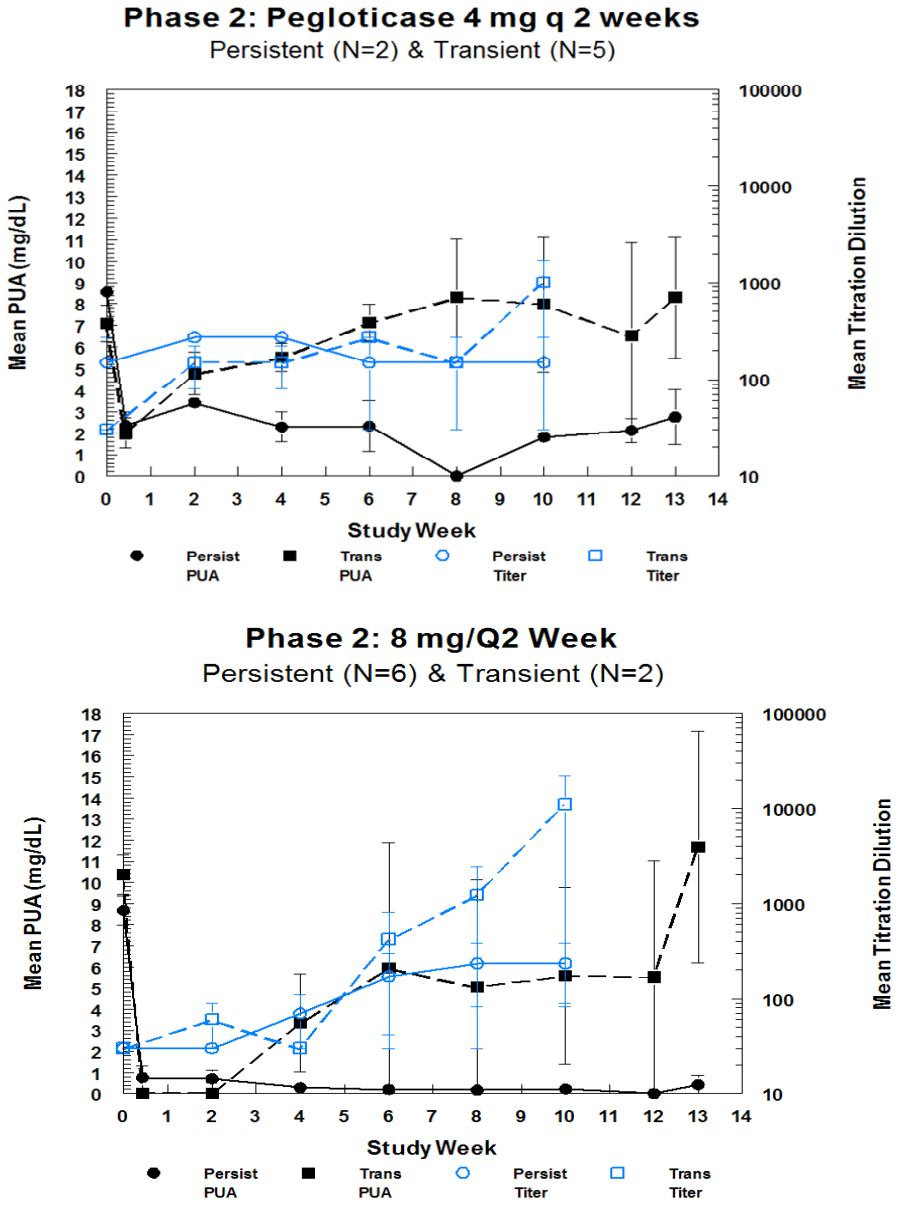
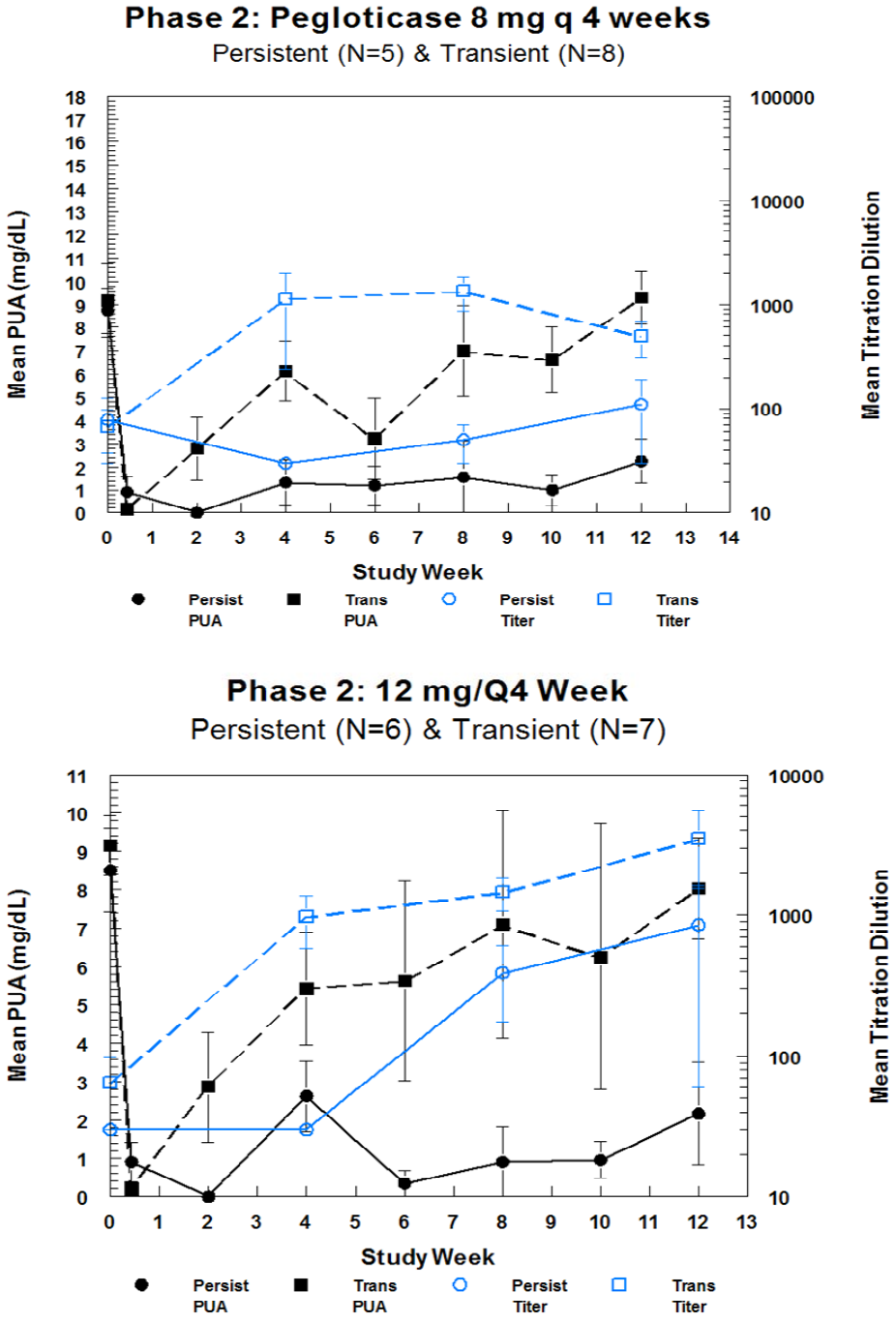


Figure 5. Mean Plasma Uric Acid and Anti-pegloticase Antibody Titer (+/- SEM) over Time in Subjects Administered Pegloticase 8 or 12 mg Every Four Weeks.



The mean PUA levels during treatment and percent of time that PUA level is below 6 mg/dL are summarized below by treatment group in Table 4. The data from Tables 4 and 5 are interesting but the data in Figures 4 and 5 are important in the overall understanding about the pharmacokinetics and pharmacodynamics of pegloticase in subjects with treatment failure gout.

Table 4: Mean Plasma Uric Acid Levels and Time Below 6 mg/dL: Study C0403.

	Pegloticase			
	4 mg q 2 weeks	**8 mg q 2 weeks**	**8 mg q 4 weeks**	**12 mg q 4 weeks**
Mean Plasma Uric Acid (mg/dL) level during Treatment				
N	7	8	13	13
Mean (SD)	4.12 (2.02)	1.42 (2.06)	3.21 (2.26)	3.09 (2.46)
Median	3.85	0.64	3.33	1.77
Percent of time that PUA level is below 6 mg/dL				
Mean (SD)	77% (26)	92% (23)	77% (26)	77% (29)
Median	81%	99%	80%	89%

Table 5: Mean Reduction and Percent Reduction in Plasma Uric Acid Levels: Study C0403.

	Pegloticase			
	4 mg q 2 weeks	**8 mg q 2 weeks**	**8 mg q 4 weeks**	**12 mg q 4 weeks**
Mean Reduction in Plasma Uric Acid (mg/dL) from pre-dose				
N	6*	8	11*	13
Mean (SD)	2.95 (2.61)	7.67 (1.79)	5.76 (3.91)	5.77 (2.03)
Median	2.90	7.77	6.77	6.21
Mean Percent Reduction in Plasma Uric Acid (mg/dL) from pre-dose				
Mean (SD)	38% (31)	86% (18)	58% (36)	67% (22)
Median	36%	92%	67%	74%

*** Baseline samples for three subjects were unavailable for analysis due to extensive hemolysis.**

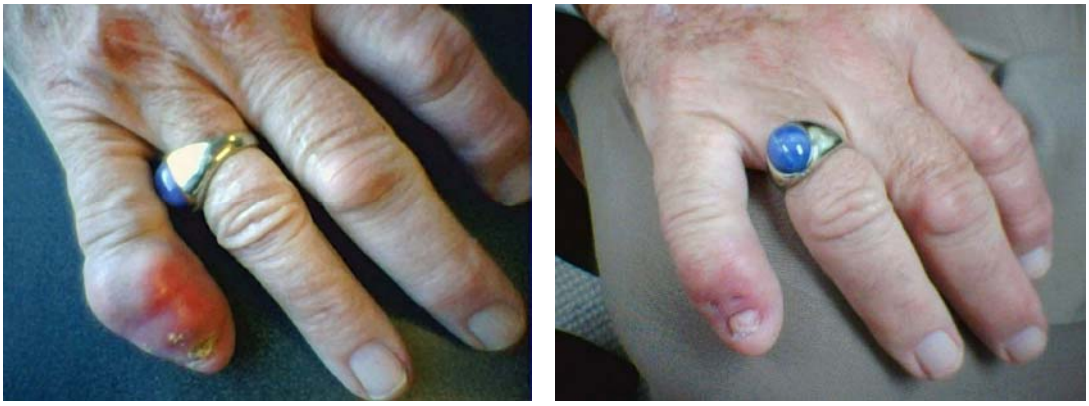
This study showed the prompt and persistent efficacy of pegloticase in lowering PUA concentrations in subjects with chronic gout and hyperuricemia who are refractory or intolerant to conventional therapy. All four dose regimens were effective; however the 8 mg and 12 mg groups showed better efficacy in reducing PUA than the 4 mg group. The 12 mg group did not provide additional benefit beyond that of the 8 mg groups. The efficacy results for the completers are similar to those presented in Table 4 and Table 5.

The percentage of non-hyperuricemic time during the study was highest for the 8mg 2-week regimen (i.e., medians of non-hyperuricemic time for ITT subjects were 80.9% for the 4mg 2-week regimen, 99.9% for the 8mg 2-week regimen, 80.3% for the 8mg 4-week regimen, and 88.9% for the 12mg 4-week regimen).

Phase 2 Efficacy: Tophus Response

No prospective clinical efficacy endpoints related to reduction of tophi were planned for the Phase 2 study because it was believed that the 3-month treatment period would be too brief to detect change. However, two of the six subjects at one clinical site agreed to have photographs taken before and during the study (Figure 6 and Figure 7).

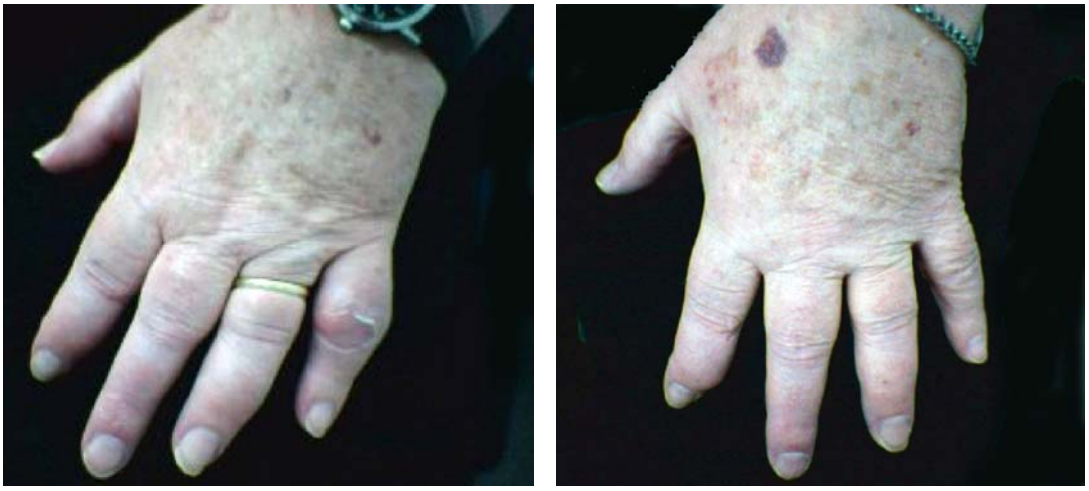
Figure 6. Resolution of a Tophus with Pegloticase Treatment: Study C0403.



Before **After**

Subject 001-002: A 70-year-old white male (gout > 25 years) with a history of UA-related nephrolithiasis, multiple tophi at his hands and feet, and an allergy to allopurinol received 8 mg of pegloticase q 2 weeks. Within 24 hrs of the first infusion, UA levels were reduced from SUA 9.3 mg/dl at baseline to PUA <0.1 mg/dL and remained at this level throughout treatment and more than 2 weeks post final infusion. A photograph after 12 weeks (6 doses) shows marked resolution of a large draining tophus at the right fifth distal interphalangeal joint.

Figure 7. Resolution of a Draining Tophus with pegloticase Treatment: Study C0403.



Before **After**

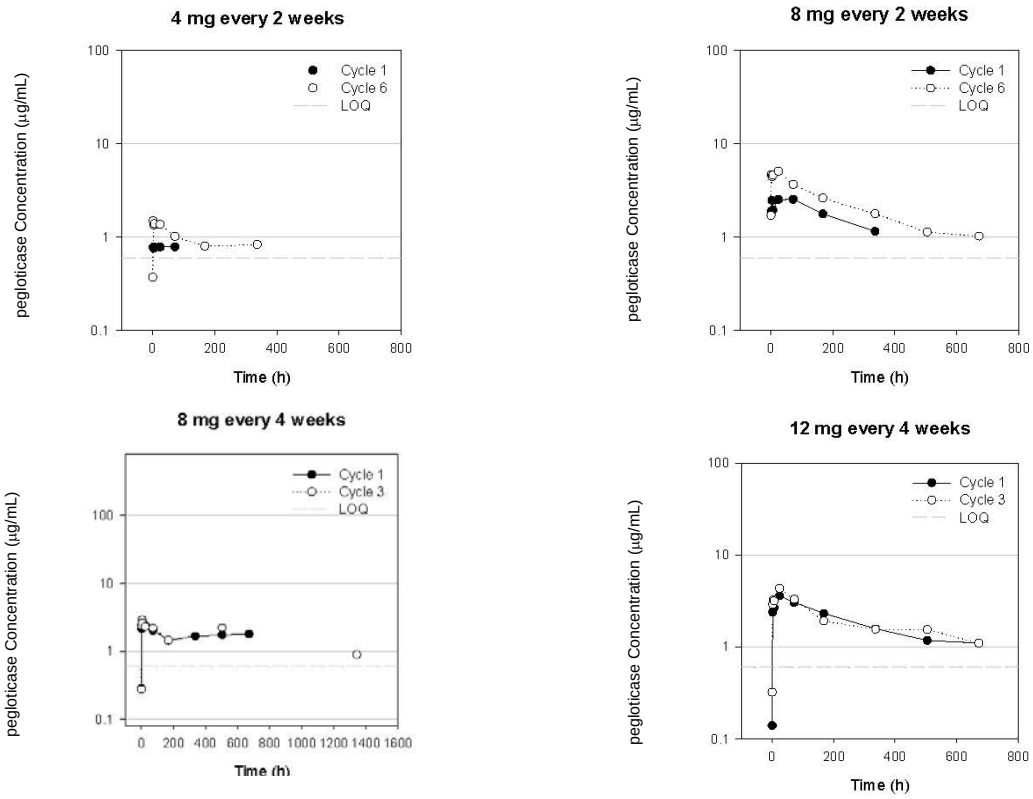
Subject 001-007: A 58-year-old white male (gout diagnosis ~ 1year) with multiple tophi on both hands and an allergy to allopurinol received 12 mg pegloticase q 4 weeks. Uric acid fell from SUA 11.0 mg/dl at baseline to PUA < 0.1 mg/dL and was maintained at this level throughout treatment. After 8 weeks of follow-up it remained at < 0.5 mg/dL. Pre- and post-treatment photographs of a tophus involving the left fifth proximal interphalangeal joint demonstrate marked reduction in tophus size after 12 weeks (3 doses).

For these two subjects, treatment of tophaceous gout with pegloticase resulted in rapid and continuous normalization of PUA and resolution of tophi in 12 weeks documented by photographs. Although anecdotal, these two cases support the undertaking of further study to demonstrate the potential benefit of pegloticase in decreasing the size of monosodium urate crystal deposits in chronic tophaceous gout and the use of measuring tophus dimensions using digital photographs to quantitate those resolutions.

Phase 2: Pharmacokinetics and Pharmacodynamics

From non-compartmental pharmacokinetic analyses, mean PK profiles of pegloticase following the first (Cycle 1) and last (Cycle 3 or 6) intravenous administration of various treatment regimens are presented below (Figure 8). Cycle 1 corresponds to period after the first dose. Cycle 3 or 6 corresponds to the periods after final dose, i.e., the third dose in the q 4 week and q 2 week groups, respectively. Thus, the later time period reflects 12 weeks after initiation of pegloticase in these groups with different schedules of dosing.

Figure 8. Mean Pharmacokinetic Profiles of Pegloticase: Study C0403.



Cycle 1 refers to the period following the first dose of pegloticase. Cycle 6 refers to the period after the sixth pegloticase dose in the q 2 week groups while cycle 3 refers to the period after the third pegloticase dose in the q 4 week groups.

For the 4 mg q 2 weeks dosing regimen, mean serum concentrations of pegloticase were either very close to or below the LOQ of the assay (0.6 µg/mL) in Cycle 1. In Cycle 6, mean serum concentrations were approximately two-fold higher than the LOQ and then fell below the LOQ between 144 and 192 hours.

For the 8 mg q 2 weeks dosing regimen, mean serum concentrations of pegloticase in Cycle 1 and 6 were well characterized over 2 weeks. Mean serum concentrations reached plateau up to 72 hours and then declined in a mono-exponential manner. Mean serum concentrations in Cycle 6 were markedly higher than those observed in Cycle 1, suggesting a degree of accumulation of the drug.

For the 8 and 12 mg every 4 weeks dosing regimens, mean serum concentrations of pegloticase in Cycle 1 and 3 reached plateau up to 72 hours and then declined in a mono-exponential manner. Mean serum concentrations in Cycle 3 were super-imposable to those observed in Cycle 1 for the 8 and 12 mg dose level, suggesting a low degree of accumulation of pegloticase when using a longer dosing interval (4 weeks instead of 2 weeks).

The median values for the pharmacokinetic parameters derived from the analyses of serum samples are summarized in Table 6.

Table 6: Pharmacokinetic Parameters of Pegloticase: Study C0403.

Treatment	Cycle	Median (Range)								
		AUC_{0-24} (mcg·h/ml)	AUC_{0-168} (mcg·h/ml)	AUC_{0-t} (mcg·h/ml)	AUC_{inf} (mcg·h/ml)	C_{max} (mcg/ml)	T_{max} (h)	Half-life (h)	CL (L/h)	Vdss (L)
4 mg q 2 weeks	1	17.0 (15.0-18.9)	NC	18.1 (15.0-170)	NC	0.800 (0.768-1.14)	6.5 (1.58-168)	NC	NC	NC
	6	34.2 (22.7-51.9)	251 (132-369)	132 (97.1-657)	1230 (322-2138)	1.62 (1.51-2.94)	1.60 (1.50-23.5)	414 (210-617)	0.00714 (0.00187-0.0124)	2.73 (1.67-3.79)
8 mg q 2 weeks	1	50.3 (20.5-71.7)	355 (245-489)	608 (264-838)	1090 (568-1494)	2.95 (1.98-4.81)	22.9 (1.50-168)	274 (198-308)	0.00734 (0.00536-0.0141)	2.67 (2.31-3.95)
	6	122 (61.1-186)	710 (326-1034)	1361 (326-2734)	1546 (456-3815)	5.96 (2.87-8.89)	6.00 (1.50-21.9)	160 (95.8-371)	0.00518 (0.00210-0.0176)	1.42 (1.11-2.34)
8 mg q 4 weeks	1	41.4 (15.7-92.9)	269 (151-759)	304 (151-1751)	1337 (579-2549)	2.50 (1.34-5.14)	23.4 (1.67-71.5)	280 (239-296)	0.00896 (0.00449-0.0138)	2.98 (1.88-5.96)
	3	46.5 (25.4-72.8)	403 (231-577)	231 (81.2-3936)	1935 (146-6337)	2.81 (1.92-4.56)	23.2 (1.50-70.9)	399 (61.6-940)	0.0105 (0.00126-0.0548)	3.21 (1.74-4.75)
12 mg q 4 weeks	1	59.6 (30.7-114)	478 (252-765)	1047 (97.6-2574)	1566 (991-3052)	3.52 (1.53-5.79)	23.2 (1.50-71.5)	329 (181-403)	0.00767 (0.00393-0.0121)	3.30 (1.82-4.05)
	3	84.0 (63.5-139)	519 (398-567)	670 (398-1821)	925 (628-2216)	4.64 (3.28-6.18)	14.6 (1.52-23.4)	119 (92.8-282)	0.0130 (0.00542-0.0191)	2.16 (2.00-3.20)

NC: Not calculated; AUC_{0-24}: Area under the serum concentration-time curve, from zero to 24 hours; AUC_{0-168}: Area under the serum concentration-time curve, from zero to 168 hours; AUC_{0-t}: Area under the serum concentration-time curve up to the last measurable point above the lower limit of quantitation (LLOQ); AUC_{int}: Area under the serum concentration-time curve, from zero to infinity; CL: Apparent clearance of pegloticase; C_{max}: Maximum serum pegloticase concentration; T_{max}: Time of maximum measured concentration; Vdss: Apparent volume of distribution.

Immunogenicity

The Phase 2 data set had an extensive immunogenicity evaluation. In the pegloticase 4 mg q 2 weeks group, all subjects had antibodies but one did not seroconvert. That subject along with one subject that seroconverted (1:270) were persistent responders. All transient responders sero-converted as shown in Figure 2. In the 8 mg q 2 week dose, 3 of 6 persistent responders did not sero-convert while all transient responders sero-converted (Figure 2).

Similarly, in the group who received pegloticase 8 mg q 4 week, nine patients developed antibodies and 3 did not, and those three non sero-converters maintained a persistent PUA response (Figure 3). Subjects who received 12 mg q 4 weeks, 6 of the 13 subjects were persistent responders (Figure 3). Most (11 of 12) sero-converted.

A quantitative ELISA assay was developed and validated for the detection of IgG and IgM antibodies directed against pegloticase in human serum. The assay used a surrogate antibody, rabbit anti-pegloticase antiserum, as a positive control. The method validation included negative cut-off, immunodepletion, specificity and recovery, intra- and inter-assay precision, short-term stability (i.e. bench top, at approximately 40°C and after four freeze-thaw cycles at approximately -20°C), long-term stability at approximately -20°C, drug interference and prozone effect.

In the Phase 2 study, a fixed Negative Cut-off (NCO) of 0.218 A_{450} was applied to all plates in the screening assay. This NCO value was based on twenty-five lots of normal human serum (normal population) and 25 lots of serum from gout subjects. The negative cut-off value (NCO) (A_{450}) was determined to be the mean response plus 1.645 standard deviations, which represents the 95^{th} percentile of a normal distribution. Normalization of the plates NCOs (i.e. overall mean of the plate blank multiplied by cut-point factor (CPF) = 1.975) was only used for the titration assays.

There were 196 human serum samples (41 pre-dose and 155 post-dose) collected from the 41 subjects and analyzed for immunoreactivity. Serum samples that were above the negative cut-off value were considered positive and were immunodepleted for confirmation of the presence of anti-pegloticase seropositivity. Positive serum samples confirmed by immunodepletion were titrated. Isotyping (IgG and IgM) also was performed on the positive samples.

Thirty-one of the 41 (76%) subjects in the ITT population had a higher titration dilution value than the pre-dose value at least once following the initial dose, meaning that they had experienced a seroconversion. The distribution of seroconverted subjects was random across the 4 treatment arms. The following numbers and percentages of subjects within each treatment regimen seroconverted during the study: 6/7 (86%) in the 4 mg q 2 week regimen, 5/8 (63%) in the 8 mg q 2 week regimen, 9/13 (69%) in the 8 mg q 4 week regimen, and 11/13 (85%) in the 12 mg q 4 week regimen. Two subjects had only baseline testing, so seroconversion status could not be determined.

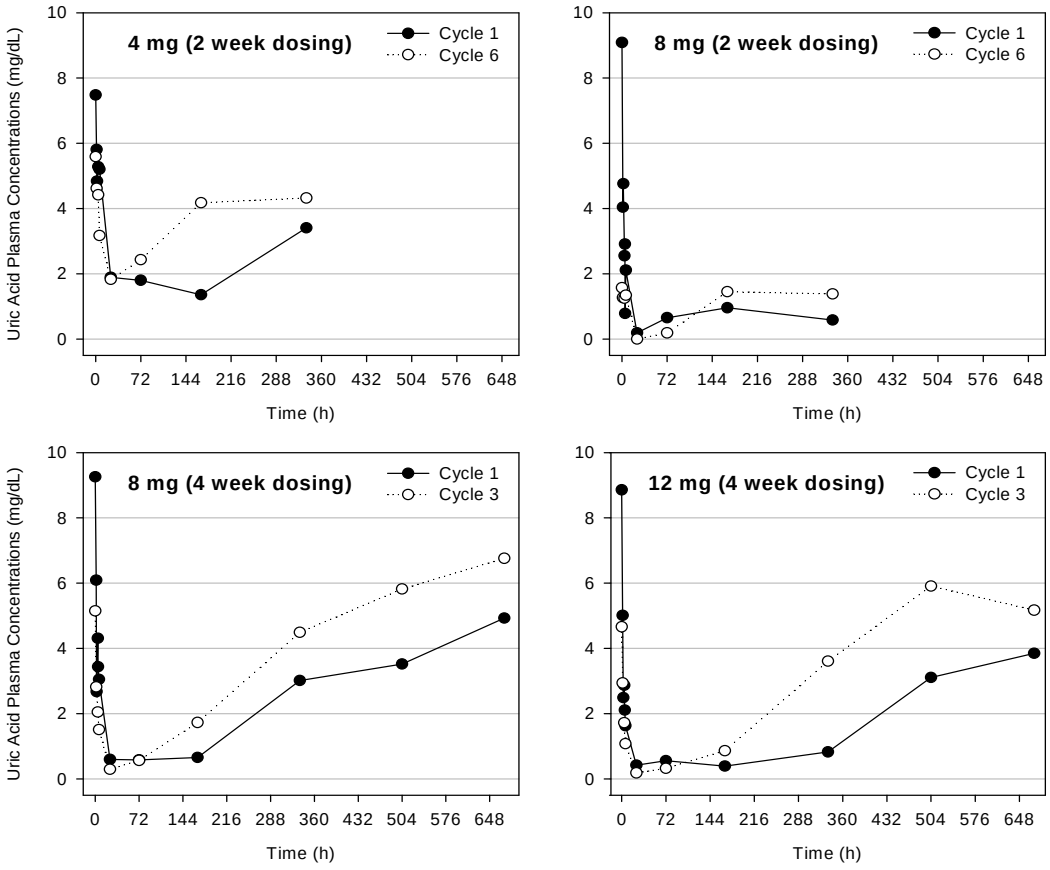
Additional analyses of the effect of anti-pegloticase immunoreactivity on pegloticase and PUA were conducted using PK/PD modeling. Covariates investigated for inclusion in the model for both PK and PD parameters included: age, gender, race, body weight, ideal body weight, and

antibody levels. Although antibody levels were well fitted by an indirect model (with rate of formation [K_{in}] and rate of elimination [K_{out}]) that was a function of pegloticase concentrations, none of the models tested improved the quality of fit of the PK parameters of pegloticase. Therefore, antibody level was not retained in the final model as a covariate.

Nevertheless, it appears that there may have been a loss in effectiveness of pegloticase in some subjects who seroconverted. However, due to the fact that most of the subjects in the study showed some immunoreactivity, that titers were generally low, that the robustness and specificity of the ELISAs are uncertain, and that the sample sizes for each dose regimen were small, it was not possible to make reliable inferences about the impact of antibody formation on the efficacy and safety of treatment with pegloticase in phase 2. Therefore, that was explored in the Phase 3 studies.

Mean concentration values of PUA following intravenous administration of various dose regimens of pegloticase are presented below in Figure 9.

Figure 9. Mean Concentration Values of Plasma Uric Acid: Study C0403.



Cycle 1 refers to the period following the first dose of pegloticase. Cycle 6 refers to the period after the sixth pegloticase dose in the q 2 week groups while cycle 3 refers to the period after the third pegloticase dose in the q 4 week groups.

For all treatment regimens, mean plasma concentration of UA decreased rapidly following pegloticase infusion. Maximal suppression of PUA was observed within 72 hours after intravenous infusion of pegloticase for all treatments with mean concentrations over 2 or 4 week period well below 6 mg/dL.

As shown in Figure 9, an increase in pegloticase led to a decrease in PUA levels with an apparent plateau at 8 mg q 2 week dosing. There did not seem to be a further improvement with 12 mg q 4 weeks but the ideal control is achieved with exposure q 2 weeks but not q 4 weeks every with a larger amount of pegloticase as shown with the 12 mg q 4 week dose. Overall, a strong relationship was observed between concentrations of pegloticase and PUA over the same timeframe.

Phase 2 Safety

The safety results obtained in Phase 2 were consistent with expectations. The emerging safety and tolerability profile supported progression into a larger, longer, and more comprehensive Phase 3 study. The treatment-failure gout population is severely symptomatic, with most subjects having multiple gout flares per year. The majority of these subjects use chronic medications to control their symptoms. Severe gout flares or other gout-related adverse events were expected to occur during the study. However, the study was not designed to make inferences regarding the severity and frequency of gout flares relative to pegloticase infusion.

The procedure for intravenous infusion of pegloticase was changed during the course of the study, when it became apparent that more subjects than expected were reporting Adverse Events associated with infusion. For approximately the first two thirds of the study, pegloticase was infused in a 100 mL volume over 30 minutes. This was changed by Protocol Amendment to 200 mL volume over 60 minutes. Adverse events that might be consistent with infusion reaction or allergic reaction to pegloticase infusion occurred only on the day of dose administration and required no intervention thereafter.

An overall summary of treatment-emergent adverse events is presented in Table 7.

Table 7: Overall Summary of Treatment-Emergent Adverse Events: Study C0403.

	4 mg q 2 weeks (n=7)	8 mg q 2 weeks (n=8)	8 mg q 4 weeks (n=13)	12 mg q 4 weeks (n=13)	Total (n=41)
Subjects with any AE	7 (100%)	6 (75%)	13 (100%)	12 (100%)	38 (93%)
Subjects with SAE	2 (29%)	3 (38%)	2 (15%)	2 (15%)	9 (22%)
Subjects Withdrawal Due to an AE	3 (42.9%)	0 (0.0%)	5 (38.5%)	6 (46.2%)	14 (34.1%)

Deaths

There were no deaths in the Phase 2 study.

Serious Adverse Events

Thirteen SAEs occurred post-randomization in 9 subjects. Of these, one was characterized as allergic in nature (Table 8). Five of these 13 SAEs were assigned causality by the Investigators as possibly or probably related to pegloticase and included infected tophus, allergic reaction, anemia and two subjects with gout flare.

C00403: Subject 001-003: This 34-year-old white male had a 10-year history of gout, which included 35 acute flares over the 12 months prior to study enrollment and 3 hospitalizations due to gout. Two weeks following the first infusion of pegloticase the subject developed a rapidly expanding polyarticular flare necessitating a 2-day hospital admission for fever and uncontrollable pain. The patient continued pegloticase dosing following hospital discharge.

SC0403: Subject 009-004: This 34 year-old white male had an 8-year history of gout, which included 5 acute flares over the 12 months prior to study enrollment and 1 hospitalization due to gout. One day following the first infusion, the subject developed severe polyarticular gout flare and was started on prednisone. After 6 days of continuing flare on prednisone, the subject was hospitalized for three days and treated with intravenous methylprednisolone with resolution of the flare.

C0403: Subject 002-001: This 56 year-old white male had a 15-year history of gout, which included 15 acute flares over the 12 months prior to study enrollment and no hospitalizations due to gout. The subject received his first dose on 17-May-04 (Hgb 14.5 g, Hct 41.3%). On 07-Jul-04, the subject was hospitalized for anemia (Hct 27%).

At the time of hospitalization, the subject's hematocrit had decreased from baseline value of 41% to 27%. The Investigator and hospital staff found no evidence of gastrointestinal bleeding. They considered the possibility that hemolysis may have occurred some time past because of elevated LDH (272U/mL) and haptoglobin (476 mg/dL). Renal ultrasound revealed small kidneys, evidence of chronic renal disease. A bone marrow biopsy done on 15-Sep-04 revealed hypocellularity. The finding of a lack of erythroid hyperplasia in the face of anemia was ascribed to myelosuppressive medication or a non-specific effect of the subject's severe chronic disease. The subject received a transfusion of a single unit of blood on 19-July-04. On 21-July-04, the Hct was 28.2%. The patient was discharged from the hospital on 22-July-04.

Following hospital discharge, the subject asked to continue in the study because he claimed improvement in his gout symptoms. The subject received his final infusion of study drug on 26-Jul-04 and had his end of study visit on 20-Sep-04. On 18-Oct-04, the subject's hematocrit was 36.3%.

Initially, the investigator determined that the SAE relationship to study medication as "unlikely related," but changed this causality assignment to "possibly related" after the subject was discharged from the hospital. Nevertheless, the Investigator administered a final pegloticase dose (a re-challenge) at the subject's request, without mishap or evidence of worsening anemia.

C0403: Subject 006-001: This 55 year-old white male had a 5-year history of gout, which included 3 acute gout flares over the 12 months prior to study enrollment and 2 hospitalizations

due to gout. Two weeks following the first infusion of pegloticase, the subject developed a severe gout flare on the left index finger including drainage of tophaceous material. Cultures of the tophaceous material were positive for a mixed flora. Hospitalization for wound care was undertaken 5-days later with minimal response after 4 days of treatment leading to a decision to amputate the index finger.

C0403: Subject 006-002: This 60-year-old white male had a 10-year history of gout, which included 5 acute flares over the 12 months prior to study enrollment and 1 hospitalization due to gout. Within minutes into the third infusion of pegloticase (to have been administered over 30 minutes), the subject became anxious, diaphoretic, nauseous, and complained of chest heaviness. Additionally, the subject reported a sensation of fullness of the upper lip, itching of the hands and axilla, and erythema of the palms without concomitant report of associated physical findings of perioral edema. A blood pressure of 100/60 and a pulse of 68 were recorded. The infusion was discontinued, Solucortef® and oxygen administered, and the subject was transferred to an emergency room, and then admitted to the hospital for observation and diagnosis. The subject was discharged on 15 June, after ruling out a diagnosis of myocardial infarction. The subject withdrew from the pegloticase study.

Table 8: Serious Adverse Events, Safety Population: Study C0403.

	Pegloticase Treatment Regimens (Dose and Frequency)												**Total**		
	4 mg q 2 weeks (N=7)			**8 mg q 2 weeks (N=8)**			**8 mg q 4 weeks (N=13)**			**12 mg q 4 weeks (N=13)**			**(N=41)**		
	Subjects		AE	Subjects		AE	Subjects		AE	Subjects		AE	Subjects		AE
	#	(%)	#	#	(%)	#	#	(%)	#	#	(%)	#	#	(%)	#
Any SAE	2	28.6%	2	3	37.5%	6	2	15.4%	2	2	15.4%	3	9	22.0%	13
Gout	1	14.3%	1	0	0	0	0	0	0	1	7.7%	1	2	4.9%	2
Angina pectoris	0	0	0	1	12.5%	2	0	0	0	0	0	0	1	2.4%	2
Anemia	0	0	0	1	12.5%	1	0	0	0	0	0	0	1	2.4%	1
Cellulitis	0	0	0	0	0	0	1	7.7%	1	0	0	0	1	2.4%	1
Gouty tophus	0	0	0	0	0	0	1	7.7%	1	0	0	0	1	2.4%	1
Hypersensitivity	1	14.3%	1	0	0	0	0	0	0	0	0	0	1	2.4%	1
Hypoglycemia	0	0	0	1	12.5%	1	0	0	0	0	0	0	1	2.4%	1
Lacunar infarction	0	0	0	0	0	0	0	0	0	1	7.7%	1	1	2.4%	1
Renal colic	0	0	0	1	12.5%	1	0	0	0	0	0	0	1	2.4%	1
Renal insufficiency	0	0	0	1	12.5%	1	0	0	0	0	0	0	1	2.4%	1
Upper respiratory tract infection	0	0	0	0	0	0	0	0	0	1	7.7%	1	1	2.4%	1

Subject #: Number of subjects reporting one or more of the specified adverse event.
AE #: Total number of adverse events

Adverse Events Other Than Gout Flares

Adverse events occurred in all dose groups throughout the study (Table 9). No pattern of dose-relationship or dose-cycle relationship is discernable.

Table 9: Commonly Occurring Adverse Events (> 5% of the Total Population) By Relationship to Treatment, Safety Population: Study C0403.

	Pegloticase Treatment Regimens (Dose and Frequency)												Total		
	4 mg q 2 weeks (N=7)			8 mg q 2 weeks (N=8)			8 mg q 4 weeks (N=13)			12 mg q 4 weeks (N=13)			(N=41)		
	Subjects		AE	Subjects		AE	Subjects		AE	Subjects		AE	Subjects		AE
	#	(%)	#	#	(%)	#	#	(%)	#	#	(%)	#	#	(%)	#
Any AE	7	100.0%	37	6	75.0%	45	13	100.0%	39	12	92.3%	45	38	92.7%	166
Nephrolithiasis	1	14.3%	1	1	12.5%	1	1	7.7%	1	3	23.1%	3	6	14.6%	6
Arthralgia	1	14.3%	1	0	0	0	3	23.1%	4	1	7.7%	1	5	12.2%	6
Anemia	0	0	0	3	37.5%	4	0	0	0	1	7.7%	1	4	9.8%	5
Dyspnoea	1	14.3%	1	0	0	0	3	23.1%	4	0	0	0	4	9.8%	5
Headache	0	0	0	1	12.5%	1	1	7.7%	1	2	15.4%	2	4	9.8%	4
Muscle spasms	1	14.3%	1	1	12.5%	1	1	7.7%	1	1	7.7%	2	4	9.8%	5
Nausea	3	42.9%	5	1	12.5%	1	0	0	0	0	0	0	4	9.8%	6
Pyrexia	1	14.3%	1	0	0	0	2	15.4%	2	1	7.7%	1	4	9.8%	4
Back pain	1	14.3%	1	0	0	0	2	15.4%	3	0	0	0	3	7.3%	4
Diarrhea	1	14.3%	1	1	12.5%	1	1	7.7%	1	0	0	0	3	7.3%	3
Erythema	1	14.3%	1	0	0	0	2	15.4%	3	0	0	0	3	7.3%	4
Fatigue	0	0	0	0	0	0	1	7.7%	1	2	15.4%	2	3	7.3%	3
Hypersensitivity	1	14.3%	1	0	0	0	1	7.7%	1	1	7.7%	1	3	7.3%	3
Pruritus	0	0	0	0	0	0	3	23.1%	3	0	0	0	3	7.3%	3
Rash	2	28.6%	3	0	0	0	0	0	0	1	7.7%	1	3	7.3%	4
Upper respiratory tract infection	0	0	0	0	0	0	0	0	0	3	23.1%	7	3	7.3%	7

Subject #: Number of subjects reporting one or more of the specified adverse event.
AE #: Total number of adverse events.

Gout Flares

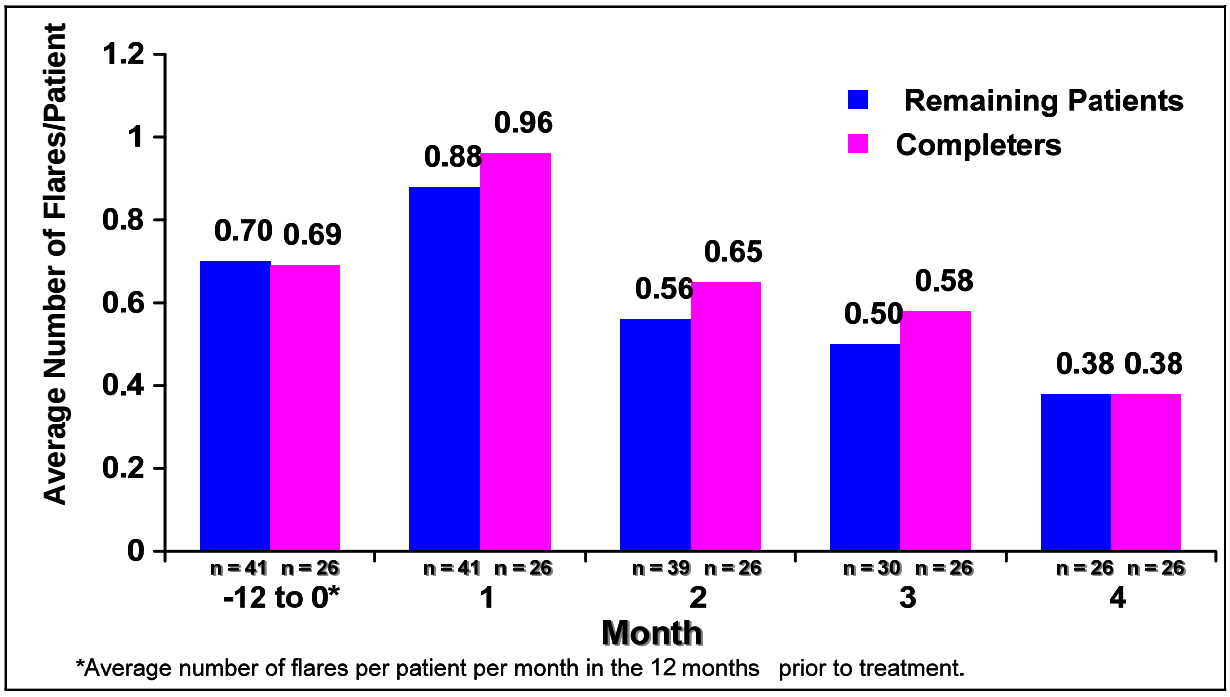
Investigators were instructed to utilize a gout flares specific CRF to capture all subject-reported information about gout flares. No uniform prophylaxis against gout flares was required or implemented.

The self-reported gout flare history of the study population suggested that this was a severely symptomatic group (except for two subjects who reported zero gout flares in the preceding 12 months). The wide variance in the self-reported history may be a reflection of the low reliability of the history, or a reflection of true heterogeneity in the population.

Acute gout flares occurred in all dose groups throughout the 18-week study period with no clear dose relationship emerging from the data. The number of gout flares per month appeared to decrease over the course of the study, as did the percentage of subjects reporting gout flares. The occurrence of gout flares was the reason for discontinuation for one subject.

There is no generally accepted method to document gout flare activity. While gout flare AEs were recorded individually, the majority of them occurred in the context of polyarticular flares. For the purposes of our analysis, all reported gout flare AEs that began within 7 days of each other were considered to be one flare. Flare frequencies are compared to the per-month baseline historical frequency of flare activity in Figures 10 and 11.

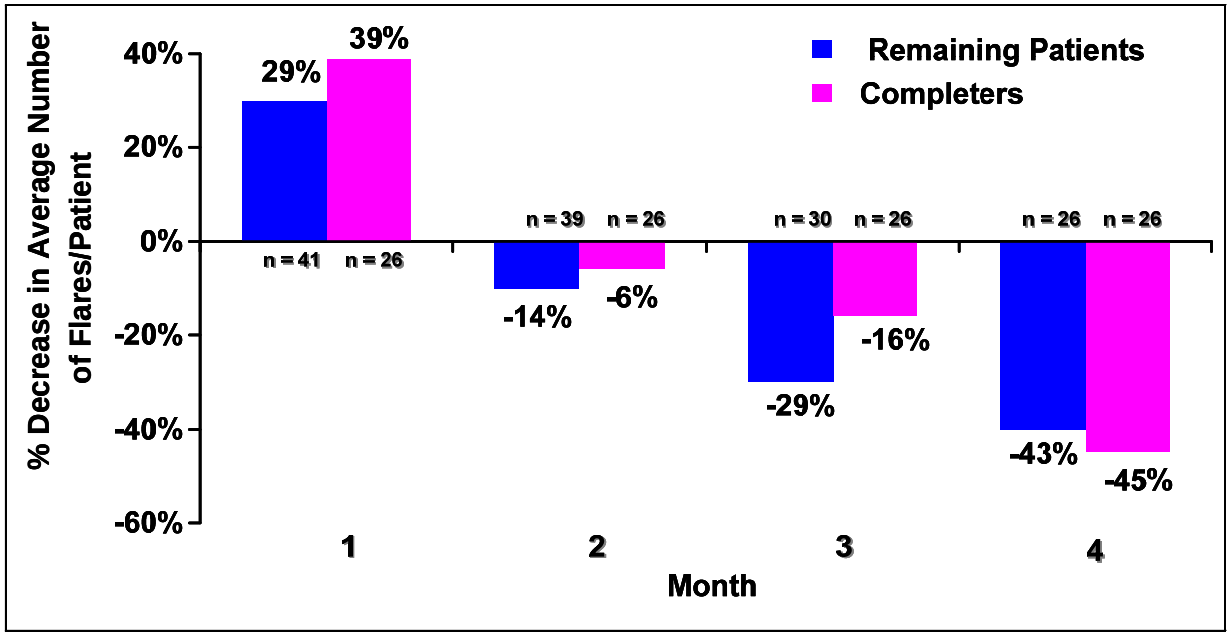
Figure 10. Per-Month Rates of Gout Flares: Pre-Study and During Treatment with Pegloticase: Study C0403.



It is generally accepted that the frequency of gout flares increases initially upon reduction of circulating UA in patients previously uncontrolled. In the Phase 2 pegloticase study the

frequency of gout flares diminished over the course of the study as illustrated by the change in gout flares from pre-treatment values as shown in Figure 11.

Figure 11. Change in Gout Flare Frequency From Pre-Treatment to Treatment with Pegloticase in Completers and Remaining Patients: Study C0403.



Accurate quantitation of self-reported gout flare frequency is problematic. In this population acute gout flares occur in the setting of chronic inflammation. Reporting of monoarticular flares that wax and wane is confounded. The quantitation of "events" in the context of polyarticular flares can be particularly confusing.

Infusion Reactions

Adverse reactions to infused biological agents are a common occurrence. Frequent components of these adverse reactions are chills/rigors, hemodynamic instability, flushing, dyspnea, or cough. Nausea, emesis, wheezing, and angioedema are less frequent. Rare reactions may include anaphylaxis and death. These reactions are believed to sort into two general categories - those that are allergic in nature (generalized rash and urticaria, anaphylaxis) and those that are anaphylactoid in type. Allergic reactions may be prevented (or masked) by pre-treatment with corticosteroids and anti-histamines. Anaphylactoid reactions may be mitigated by pretreatment with corticosteroids and antihistamines, extending the duration of infusion and by increasing the volume of infusion.

Information about Adverse Events occurring on the same day during or after an infusion was captured on Adverse Event Case Report Forms. A specific CRF was not employed to capture these events.

An IR is defined here as an adverse event (AE) or, more typically, a cluster of adverse events that occurred on the same day during or after an infusion and was considered by the Sponsor as conceivably related to infusion, whether or not this causality relationship was the assignment of the Investigator.

Twenty-seven of 41 subjects (148 infusions) experienced 61 AEs on the same day during or after an infusion. Sixteen of 61 AEs were considered by the Sponsor to be highly unlikely to be related to infusions. These 16 AEs (in 11 subjects) were: 7 gout flares, 6 laboratory abnormalities (anemia or increased liver functions), 1 headache, and 2 musculoskeletal events considered to be unrelated to study medication by the Investigators.

Forty-five AEs (or 21 IRs, derived from single or clustered AEs) in 18 subjects were considered by the Sponsor to be conceivably related to the infusion reaction. Thus, infusion reactions occurred in 14% (21/148) of infusions in 44% (18/41) of randomized subjects. Infusion reactions are summarized in Table 10 and Table 11.

Table 10: Infusion Reactions: Study C0403.

Subject No.	Dose Group	Infusion Cycle.	Symptoms (verbatim)	Action Taken
001-003	4 mg q 2 weeks	1 1 1 4 4 4	Nausea Rash Vomiting Chest Pain Nausea Rash	None Drug Withdrawn
006-002	4 mg q 2 weeks	3	Allergic Reaction	Drug Withdrawn
010-003	4 mg q 2 weeks	6 6 6 6	Difficulty Breathing Dizziness Low Back Pain Nausea	Drug Withdrawn
001-002	8 mg q 2 weeks	3	Incr. in Blood Pressure	None
002-001	8 mg q 2 weeks	2 2	Neck Pain Stiffness Neck	None
002-005	8 mg q 2 weeks	6	Back Muscle Spasm	None
002-002	8 mg q 4 weeks	3 3	Flushing Warm Flashes	None
002-006	8 mg q 4 weeks	3	Pruritus	Drug Withdrawn
008-009	8 mg q 4 weeks	3 3 3	Right Hand Itching Right Hand Redness Right Hand Swelling	None
009-001	8 mg q 4 weeks	1	Shortness of Breath	None
010-004	8 mg q 4 weeks	2 2 2 2	Back Spasm Redness in Neck Redness of Head Shortness of Breath	Drug Withdrawn
011-003	8 mg q 4 weeks	2 2 3	Chest Pain Shortness of Breath Shortness of Breath	None Drug Withdrawn
012-002	8 mg q 4 weeks	2	Allergic Reaction (to drug in the infusion)	Drug Withdrawn
001-009	12 mg q 4 weeks	3 3	Angioedema Rash	Drug Withdrawn
005-003	12 mg q 4 weeks	2 2	Red Raised Itchy Rash (on trunk and arms) Stomach Flu	Drug Withdrawn
006-003	12 mg q 4 weeks	2	Allergic Reaction	Drug Withdrawn

Subject No.	Dose Group	Infusion Cycle.	Symptoms (verbatim)	Action Taken
009-004	12 mg q 4 weeks	1 1	Hives Tightness of Chest	Drug Withdrawn
010-001	12 mg q 4 weeks	2 2 2 3 3 3 3	Chest Tightness Flushing (of neck & head) Low Back Spasms Sensation of Burning (ears) Chest Tightness Flushing (of neck & head) Low Back Spasm	None Drug Withdrawn

Table 11: Frequency of Infusion Reactions by Dose Group and by Dose Cycle: Study C0403.

Infusion Cycle	4 mg q 2 weeks (n=3)	8 mg q 2 weeks (n=3)	8 mg q 4 weeks (n=7)	12 mg q 4 weeks (n=5)
1	1	0	1	1
2	0	1	3	3
3	1	1	4	2
4	1	0	NA*	NA
5	0	0	NA	NA
6	1	1	NA	NA
Total	**4**	**3**	**8**	**6**

*** NA = Not Applicable**

Twelve of the 18 subjects who experienced an IR were withdrawn from the Study by the Investigators, often in consultation with the Sponsor due to a high level of caution about the potential risk of anaphylaxis. No anaphylactic reactions were observed.

Investigators initiated a treatment intervention in 13 subjects (who had 15 IRs) including prolongation of the duration of the infusion, administration of an oral antihistamine, and/or administration of intravenous corticosteroid.

Re-exposure After an Infusion Reaction

Five of 18 subjects who experienced an AE on the same day during or after an infusion, and for whom the AE was considered to be an IR by the Investigator or the Sponsor received a subsequent re-exposure to infusion.

Three of the 5 subjects who were re-exposed to a pegloticase infusion after having had an IR experienced another IR, as judged by the Investigator or the Sponsor. All three cases of repeat IR experienced a feeling of chest heaviness and heat or flushing. Two of 5 subjects who were re-exposed did not experience IRs.

Discussion of Infusion Reactions
Investigators were initially instructed to withdraw subjects from the study upon the occurrence of any IRs if medically justified in their opinion. Investigators treated subjects with IRs with cessation of the infusion, administration of anti-histamines and/or corticosteroids acutely. Clinical sequelae requiring interventions beyond the day of infusion were not observed. A great many of these were clearly related to immunogenicity.

The symptoms described by subjects, the evaluation of Investigators at the time of the IRs, the brief duration of IRs, and the observation that signs and symptoms at times did not recur after the day of infusion leads the Sponsor to conclude that these IRs may be interpreted as anaphylactoid reactions, rather than allergic reactions. Events with reports of generalized rash or urticaria may be considered more likely as potentially allergic in nature.

Laboratory Assessments
Laboratory safety assessments included automated hematology and serum chemistry measurements performed at baseline and throughout the study on days 21, 42, 63, and 84. The laboratory safety results do not suggest a clinically important signal for any pegloticase-related abnormality.

Hematology
Hematology assessments included central laboratory analysis of hemoglobin/hematocrit and cell differential. The results were analyzed by the Sponsor as individual listings over time, group means over time, minimum/maximum values, and by shift tables. No clinically meaningful changes were detected in any dose arm, except for decreased hemoglobin and hematocrit values discussed below. Eosinophils and basophils were not observed to be increased during the study.

Eleven subjects of 41 randomized had a baseline hemoglobin value below the sex-adjusted lower limit of normal. In 26 of 41 subjects, a decrease from baseline in hemoglobin was observed. In 6 of the 26 subjects who showed a decrease in hemoglobin below the lower limit of normal at some point in the study, the decrease was not resolved by the end of the study. Three of these 6

subjects had laboratory assessments on only three visits (prior to early discontinuations for reasons unrelated to hematology parameters). Three other subjects in this group of 6 had persistent decreases in hemoglobin through the last Visit (Table 12).

Table 12: Three Subjects with Persistent Decrease in Hemoglobin: Study C0403.

Subject	No. Infusions	Dose Group	Relevant Medical History	Relevant Medications	Hemoglobin (g/dL) Baseline and Final	Hematocrit (g/dL) Baseline and Final	Mean Creatinine Clearance* (ml/min)
009-002	6	8 mg q 2 weeks	Restrictive lung disease CHF Stomach pain Chronic renal failure Dyslipidemia Diabetes Osteoarthritis	Felodipine Chlorthalidone Gemfibrozil Terazosin Metoprolol Furosemide Colchicine Omeprazole Hydralazine NPH insulin Lantus insulin Furosemide Albuterol Aspirin	11.5 9.7	34.6 29.2	67.0
009-001	3	8 mg q 4 weeks	COPD CHF Chronic upset stomach Chronic renal insufficiency Hypogonadism DVT (post warfarin) Hypertension Atrial fibrillation Allergy to: morphine, diphenhydramine, penicillin, allopurinol Smoker	Omeprazole Metolazone Warfarin Theophylline Citalopram Verapamil Colchicine Furosemide Lisinopril Simvastatin	14.7 12.6	44.3 39.5	67.25
005-003	3	12 mg q 4 weeks	CHF Renal failure Diabetes (II) Allergy to allopurinol Kidney stones CAD	Spironolactone Carvedilol Folic acid Aspirin Furosemide Warfarin Benazepril Colchicine Glipizide Digoxin Metolazone Amitriptyline Nitroglycerin	14.1 11.1	42.4 37.2	41.4

***Mean Creatinine Clearance was determined by inclusion of all observations per subject during study.**

Clinical Chemistry

Clinical chemistry assessments included central laboratory analysis of serum samples only. (Urinalysis was performed at baseline only). Clinical chemistry results were analyzed by the Sponsor as individual listings over time, group means over time, minimum/maximum values, and by shift tables.

Assessment of clinical chemistry revealed no clinically meaningful group trends, in change from baseline. Three subjects with normal baseline values exhibited transient transaminase elevations less than 3X upper limit of normal, at some point during the study. All three returned toward baseline prior to study end and no specific cause for transaminases elevation was identified. Information about these three subjects is shown in Table 13.

Table 13: Three Subjects with Transient Increase in Transaminases: Study C0403.

Subject	Number of Infusions	Dose Group	Relevant Medical History	Relevant Medications	Highest Value (U/L)	Mean Creatinine Clearance* (mL/min)
002-006	3	8 mg q 4 weeks	Hypertension, Anemia, Renal insufficiency, Hallux valgus repair, Tophi, Hemiparesis Allopurinol rash Myocardial Ischemia	Metoprolol,Nifedipine Doxazosin,Coated aspirin, Colchicine, Folic acid, PhosLo Alendronate, Erythropoietin, Acetaminophen	AST: 121 ALT: 112	24.04
005-002	6	8 mg q 2 weeks	Diabetes ,CABG, Psoriasis, Hyper-cholesterolemia,	Colchicine, Glyburide, Percocet, Sulindac, Folic acid, Metoprolol, Fosinopril, Simvastatin, Methotrexate, Clopidogrel, Flurazepam, Metformin	AST: 74 ALT:136	48.42
002-003	3	12 mg q 4 weeks	COPD, Pulmonary embolus, GERD, Chronic renal insufficiency, NIDDM, CAD, Osteoarthritis, Hypertension, Hyperlipidemia, Renal mass	Lisinopril, Furosemide, Warfarin, Isosorbide, Mono-nitrate, Pravachol, Prevacid, Diltiazem, Metaglip, Fluticasone, Salmeterol, Clonidine, Omeprazole, Oxygen Tiotropium, Citalopram	AST: 81 ALT: 86	42.16

SUMMARY AND CONCLUSION PHASE 1 AND 2 STUDIES

These data demonstrate that patients treated with pegloticase 8 mg every 2 or 4 weeks had a rapid and sustained reduction in plasma uric acid; 4 mg every 2 weeks was not effective and 12 mg every 4 weeks did not provide additional benefit compared to 8 mg every 4 weeks. A majority of patients developed antibodies to pegloticase; infusion reactions appeared to be associated with the presence of an antibody response.

APPENDIX 3: NARRATIVES FOR SUBJECTS WHO DIED

Appendix 3
Narratives for Subjects Who Died

Study Subject No.	Date of Event	Event Description	Treatment Group	Outcome
Study C0405: Subject 102-006	28 Oct 2006	Acute dyspnea; worsening of kidney disease	Pegloticase 8 mg q 4 weeks RCT	Death
Study C0405: Subject 122-004	19 Aug 2007	Sepsis	Pegloticase 8 mg q 2 weeks OLE; Pegloticase 8 mg q 4 weeks RCT	Death
Study C0405: Subject 122-004	24 Apr 2007	Worsening of chronic kidney disease	Pegloticase 8 mg q 2 weeks OLE; Pegloticase 8mg q 4 weeks RCT	Resolved
Study C0405: Subject 122-004	05 May 2007	Peritonitis	Pegloticase 8 mg q 2 weeks OLE; Pegloticase 8 mg q 4 weeks RCT	Resolved
Study C0405: Subject 122-004	26 May 2007	Right hip fracture	Pegloticase 8 mg q 2 weeks OLE; Pegloticase 8 mg q 4 weeks RCT	Resolved
Study C0405: Subject 122-004	11 Aug 2007	Bilateral lower extremity deep vein thrombosis	Pegloticase 8 mg q 2 weeks OLE; Pegloticase 8 mg q 4 weeks RCT	Resolved
Study C0405: Subject 122-004	11 Aug 2007	Grade 4 anemia	Pegloticase 8 mg q 2 weeks OLE; Pegloticase 8 mg q 4 weeks RCT	Ongoing
Study C0405: Subject 122-004	11 Aug 2007	Osteomyelitis right first MTP	Pegloticase 8 mg q 2 weeks OLE; Pegloticase 8 mg q 4 weeks RCT	Resolved
Study C0405: Subject 203-001	23 Jul 2007	Death attributed to cardiac arrest	Pegloticase 8 mg q 2 weeks RCT	Death
Study C0406: Subject 301-003	05 Jan 2007	Methicillin resistant staphylococcus aureus septicemia	Pegloticase 8 mg q 2 weeks	Resolved withdrawal due to AE
Study C0406: Subject 301-003	12 Mar 2007	Sepsis	Pegloticase 8 mg q 2 weeks	Death
Study C0406: Subject 301-014	17 Feb 2007	Multiple organ failure	Placebo (subject had not dosed yet)	Death
Study C0406: Subject 315-005	05 Apr 2007	Sudden death attributed to cardiac arrhythmia	Pegloticase 8 mg q 2 weeks	Death

Subject No.: C0405 / 102-006	
Manufacturer Report No.: 06US000035	
Double Blind Study Drug:	8 mg PEG-uricase every 4 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	28 Oct 2006
Event:	Acute Dyspnea [Dyspnoea Exacerbated]; Worsening of Kidney Disease [Renal Failure]
Investigator Causality Assignment:	Possible (Dyspnea Exacerbated); Unlikely (Renal failure)
Outcome:	Death

Subject 102-006 was a 64 year-old American Indian/Alaskan Native male with end-stage cardiomyopathy who was hospitalized for shortness of breath that was severe in intensity, one day after receiving his second study drug infusion (which was a placebo infusion). Prior to this event, the subject was also experiencing concurrent adverse events of belching (27 Oct 2006, ongoing), constipation (20 Oct 2006, ongoing), increased dyspnea (27 Oct 2006, resolved 28 Oct 2006), acute bronchitis (28 Oct 2006, ongoing), angina (28 Oct 2006, resolved same day), respiratory alkalosis (28 Oct 2006, resolved 30 Oct 2006), ventricular tachycardia (29 Oct 2006, ongoing), hyponatremia (29 Oct 2006, ongoing), mitral regurgitation (30 Oct 2006, ongoing), pulmonary regurgitation (30 Oct 2006, ongoing), tricuspid regurgitation (30 Oct 2006, ongoing), and hyperglycemia (30 Oct 2006, ongoing). This subject was initially diagnosed with gout in 1997. Unknown to the Investigator at the time of randomization, this subject concealed a medical history that would have precluded his participation in the study. This history included end-stage cardiomyopathy with a profoundly low ejection fraction (10-15%; ongoing 1 year); he had a 10-year history of cardiomyopathy. His other known relevant medical history included multiple coronary arterial stent insertions (ongoing 10 years, ongoing 7 years, and ongoing 1 year), atrial fibrillation (ongoing 1 year), cardiac pacemaker insertion (1 year), chronic kidney failure (ongoing 1 year), hypertension (ongoing 3 years), coronary artery disease (ongoing 10 years), congestive heart failure (CHF) (ongoing 10 years), and hypercholesterolemia (ongoing 10 years). The subject received his first dose of study drug on 13 Oct 2006 and his most recent study drug infusion on 27 Oct 2006 (Dose 2), 1 day before the event.

On 28 Oct 2006, the subject was hospitalized for severe shortness of breath. A directed physical examination the previous day (during Dose 2) revealed no pre- or post-infusion abnormal findings. At the time of hospitalization, the subject reported having had shortness of breath for the previous 5 days, which became severe by the morning of 28 Oct 2006. He was transported to the emergency room where multiple findings were observed including; pedal edema, non-productive cough, chills, constipation, decreased urinary output, chest pressure, nausea, retching, and lightheadedness. On examination, his vital signs were blood pressure (BP) 110/70 mmHg, heart rate (HR) 86 beats per minute (bpm), respiratory rate (RR) 24 breaths per minute (bpm), and temperature 97.2°F. Arterial blood gases revealed pH 7.55, PaO_2 88 mmHg, and $PaCO_2$ 16.8. Laboratory results revealed white blood cells 16,000, hemoglobin 14.8, hematocrit 43, platelets 285,000, sodium 132, potassium 3.7, chloride 89, glucose 156, blood urea nitrogen 82, creatinine 2.6, albumin 4, calcium 43.6, B-type natriuretic peptide 1,850, creatine phosphokinase (CPK) 73, CK-MB 5.1, and troponin < 0.05. A lung perfusion scan was negative for pulmonary embolus. Electrocardiogram (ECG) results showed sinus tachycardia with HR 122 bpm and incomplete left bundle branch block. A second ECG showed atrial fibrillation. The subject's baseline ECG (27 Sep 2006) also showed atrial fibrillation, together with indeterminate or old myocardial infarction, left axis deviation, and left ventricular hypertrophy. A chest X-ray on 28 Oct 2006 revealed no change in the positioning of his

pacemaker leads, and revealed cardiomegaly and bilateral pulmonary congestion, which were unchanged from the year previous.

The subject was admitted to hospital with a diagnosis of acute dyspnea secondary to CHF. He was administered Lasix (furosemide) intravenously and placed on oxygen therapy. His symptoms improved. The subject was also treated with Levaquin (levofloxacin) 250 mg daily. He recovered from the event of acute dyspnea the same day 28 Oct 2006.

During his period of hospitalization, the subject developed severe acute kidney failure (30 Oct 2006) and was started on dialysis on 31 Oct 2006. He also had elevated liver enzymes (cause unknown). The subject decided that he did not want to continue with dialysis, in view of his terminal prognosis of the underlying cardiomyopathy. Dialysis was discontinued after 2 treatments. On 07 Nov 2006, the subject was discharged from the hospital and transferred to a hospice care unit with a diagnosis of acute renal failure, chronic kidney disease, end-stage cardiomyopathy, CHF, acute bronchitis, CAD, anemia, and history of gout and atrial fibrillation. The subject died on 13 Nov 2006 due to kidney failure.

Study drug was discontinued the same day, 28 Oct 2006. The subject elected to be transferred to a hospice care unit and died on 13 Nov 2006.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), digoxin, Plavix (clopidogrel), Prevacid (lansoprazole), Lasix (furosemide), Coreg (carvedilol), Altace (ramipril), folic acid, Vitamin B12 (cyanocobalamin), potassium, Xanax (alprazolam), aspirin (acetylsalicylic acid), Levaquin (levofloxacin), Vitamin B complex (nicotinamide with pyridoxine hydrochloride, riboflavin, thiamine hydrochloride), glyceryl trinitrate, Propacet, metoprolol tartrate, Oxycocet, pantoprazole amiodarone, temazepam, and Viagra (sildenafil).

The event of acute dyspnea and kidney failure resulted in the subject's hospitalization and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that the event of acute dyspnea was possibly related to the study drug and that the kidney failure was unlikely related to the study drug.

His medical history also included presbyopia (ongoing 15 years), joint contractures (ongoing 5 years), hypokalemia (ongoing 5 years), Vitamin B12 deficiency (ongoing 5 years), abdominal discomfort (ongoing 5 years), anxiety (ongoing 3 years), drug hypersensitivity to penicillin (ongoing 30 years), urine output decreased (ongoing 2 months), neuropathy peripheral (ongoing 1 year), dyspnea (ongoing 10 years), insomnia (ongoing 6 months), leukocytosis (ongoing 6 months), hyperparathyroidism (ongoing 6 months), and joint crepitation (ongoing 1 month).

Subject No.: C0405 / 122-004	
Manufacturer Report No.: 07US000220	
Open Label Study Drug:	8 mg pegloticase every 2 weeks, intravenously
Double Blind Study Drug:	8 mg pegloticase every 4 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	19 Aug 2007
Event:	Sepsis [Sepsis]
Investigator Causality Assignment:	Unlikely
Outcome:	Death

Subject 122-004 was a 53 year-old African American female with a history of focal segmental glomerulonephritis (ongoing 5 years) and previous hospitalizations during the study due to pancreatitis; chronic kidney failure; peritonitis; hip fracture; and bilateral lower extremity deep vein thrombosis (DVT), Grade 4 anemia, and osteomyelitis right first metatarsophalangeal (MTP) on 11 Aug 2007. She subsequently developed severe sepsis 8 days after the event of DVT and died. This subject was initially diagnosed with gout in 2002. Her other relevant medical history included chronic kidney disease (ongoing 5 years), hypercholesterolemia (ongoing 5 years), and hypertension (ongoing 10 years). The subject had experienced serious adverse events of pancreatitis on 02 Feb 2007 (refer to Narrative 07US000097) while participating in double-blind study C0405; worsening chronic kidney failure on 24 Apr 2007 (refer to Narrative 07US000161); peritonitis related to peritoneal dialysis on 05 May 2007 (refer to Narrative 07US000176); right hip fracture on 26 May 2007 (refer to Narrative 07US000182); and bilateral lower extremity DVT (refer to Narrative 07US000215), Grade 4 anemia (refer to Narrative 07US000216), and osteomyelitis (refer to Narrative 07US000217) on 11 Aug 2007. The subject received her first dose of open-label study drug (8 mg pegloticase every 2 weeks) on 12 Apr 2007 and 3 additional dose administrations prior to this event. She received her most recent study drug infusion on 30 Jul 2007 (Dose 4).

On 19 Aug 2007, while hospitalized for bilateral lower extremity DVT, the subject developed severe sepsis. She died the next day, 20 Aug 2007.

On 11 Aug 2007, the subject had been admitted to the hospital for treatment of DVT, at which time she was also diagnosed with osteomyelitis right first MTP and Grade 4 anemia. Her toe was amputated on 14 Aug 2007 and cultures from the wound grew oxacillin resistant Staphylococcus aureus for which she was prescribed vancomycin. The subject also received multiple blood transfusions due to Grade 4 anemia. Following her toe amputation, the subject was prescribed a patient-controlled analgesia pump for pain control. Her blood pressure (BP) subsequently fell to 60/30 mmHg, which was thought to be secondary to her prescribed narcotics. Following the drop in her BP, the subject experienced altered mental status. Neurologic evaluation suggested a possible watershed infarct; a computed tomography scan on 14 Aug 2007 was normal and a later magnetic resonance imaging test (date unspecified) revealed a left precentral gyrus infarct. Aggressive fluid resuscitation was administered to maintain her mean arterial pressure above 60 mmHg.

On 15 Aug 2007, the subject experienced atrial flutter that did not resolve with diltiazem and metoprolol. She was started on a loading dose of amiodarone, which was unsuccessful in re-establishing normal sinus rhythm. She was subsequently taken to the Intensive Care Unit where she remained hypotensive despite having a normal sinus rhythm by this time. The subject's hypotensive condition was considered secondary

to worsening sepsis due to her ORSA infection. Peritoneal fluid cultures revealed enterococcal bacteria. She was started on daptomycin and tigecycline for possible vancomycin-resistant enterococcus, and micafungin for fungal coverage of her peritonitis.

On 19 Aug 2007, the subject was taking 4 vasopressor agents but continued to experience worsening hypotension. The subject's pupils were fixed and dilated, and she had no bowel sounds and no reflexes; however, the subject continued to breathe over the ventilator. Given the subject's lack of reflexes, the family decided to withdraw care. Care was withdrawn on 20 Aug 2007. The subject died on 20 Aug 2007 at 14:40.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), metronidazole, vancomycin, sevelamer hydrochloride, aztreonam, metoprolol, and amiodarone.

The event of sepsis led to the subject's death. The Investigator and Clinical Research Physician at Savient felt that the event was unlikely related to the study drug.

Her medical history also included drug hypersensitivity to Lipitor (ongoing unknown duration), allopurinol (ongoing 3 years) and amoxicillin (ongoing 1 year); carpal tunnel syndrome (ongoing 2 years); hip fracture (1 year); osteoporosis (ongoing 4 years); and pneumonia (1 year).

Subject No.: C0405 / 122-004	
Manufacturer Report No.: 07US000161	
Open Label Study Drug:	8 mg pegloticase every 2 weeks, intravenously
Double Blind Study Drug:	8 mg pegloticase every 4 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	24 Apr 2007
Event:	Worsening of Chronic Kidney Disease [Renal Failure Chronic]
Investigator Causality Assignment:	Unlikely
Outcome:	Resolved

Subject 122-004 was a 53 year-old African-American female with a history of focal segmental glomerulonephritis (ongoing 5 years) who was hospitalized with worsening kidney disease of severe intensity. This subject was initially diagnosed with gout in 2002. Her other relevant medical history included chronic kidney disease (ongoing 5 years), hypercholesterolemia (ongoing 5 years), and hypertension (ongoing 10 years). She previously experienced a serious adverse event of pancreatitis on 02 Feb 2007 (refer to Narrative 07US000097) while participating in the double-blind study C0405. Her serum creatinine increased from 3.3 mg/dL at screening (03 Aug 2006) to 6.2 mg/dL at Visit 20 (15 Feb 2007). The subject received one dose of open-label study drug (8 mg pegloticase every 2 weeks) on 12 Apr 2007 (Dose 1) prior to the event.

On , the subject was hospitalized with worsening kidney disease of severe intensity. The subject had been scheduled for outpatient dialysis treatment on (b) (6), but required hospitalization and dialysis on . She was admitted to the hospital with worsening end-stage renal disease and for the evaluation of transaminitis with elevated liver function tests and obstructive biliary pattern. At baseline (03 Aug 2006), her liver function tests were total bilirubin 0.2 mg/dL (NR 0.0-1.1), aspartate aminotransferase (AST) 20 U/L (NR 0.0-37.0), aminotransferase (ALT) 9 U/L (NR 0.0-47.0), and alkaline phosphatase 111 U/L (NR40.0-135.0). Laboratory test results at admission revealed urine culture with E. Coli > 100,000 CPU/mL, total bilirubin 6.5, direct bilirubin 6.3, AST 308, ALT 1572, alkaline phosphatase 606, amylase 43, lipase 401, ferritin 4430 and erythrocyte sedimentation rate 50 (normal ranges were not provided by the site).

On (b) (6) 2-view chest x-ray revealed lower left lobe opacities suggestive of subsegmental atelectasis. Evaluation of elevated liver function test results included a magnetic resonance cholangiopancreatography; findings were compatible with acute chronic pancreatitis with enlargement, peripancreatic fluid, and cystic dilatation in the heart of the pancreas. No biliary ductal stricture or obstruction was observed. Extensive fluid and edema involving the left abdominal wall was noted; and an abdominal plain film x-ray was recommended. An autoimmune panel was recommended following consultation (results pending at the time). Upper right quadrant ultrasound revealed hepatomegaly with fatty infiltration, a slightly dilated pancreatic duct, right lower pole renal calculus, and left renal cyst as before, and small amount of ascites. Her treatment included peritoneal dialysis following the confirmation of proper catheter placement.

On (b) (6), a kidney's/ureter/bladder (KUB) x-ray revealed the peritoneal dialysis catheter projecting over the pelvis. A second KUB the next day showed that catheter placement had not changed significantly, and nonspecific bowel gas pattern was present. Her peritoneal dialysis (date unknown) proceeded and was well tolerated.

During her hospitalization (date not specified), the subject experienced significant gout pain. Her treatment included prednisone and colchicine; however, prednisone did not alleviate her gout pain and she was given steroid injections in her left ankle and right big toe. The subject underwent an arthrocentesis of the left ankle on (b) (6), and on (b) (6), she underwent arthrocentesis of the right big toe. Indomethacin was added to her regimen for control of symptomatic gout pain.

On (b) (6), additional evaluation included a transthoracic echocardiogram, which revealed moderately increased left ventricular wall thickness with normal chamber size; an estimated left ventricular ejection fraction 70-75%, and diastolic dysfunction.

Follow up laboratory results on (b) (6) revealed sodium 136, potassium 3.1, chloride 95, bicarbonate 26, blood urea nitrogen 88, creatinine 5.3, glucose 111, calcium 7.9, magnesium 1.7, phosphorus 5.8, total bilirubin 1.5, AST 40, ALT 98, alkaline phosphatase 381, gamma-glutamyl-transferase 1573, white blood cells 28.1, hemoglobin 8.2, hematocrit 27.6, platelet 283, International Normalization Ratio 1.5, antinuclear antibody negative, and free T3 2.1 (normal ranges were provided by the site). Hepatitis serologies were negative, blood cultures showed no growth, and urine culture showed mixed gram-positive flora. The subject was discharged from the hospital on (b) (6) and the event was ongoing at the time.

The study drug regimen was unchanged and the subject continued in the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), Altace (ramipril), calcium with vitamin D, Fosamax (alendronate sodium), Nexium (esomeprazole magnesium), Zetia (ezetimibe), Norvasc (amlodipine), Aranesp (darbepoetin alfa), atenolol, Zocor (simvastatin), Remeron (mirtazapine), and Vicodin (hydrocodone bitartrate, acetaminophen).

The event of worsening of chronic kidney disease resulted in the subject's hospitalization and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that the event was unlikely related to the study drug.

Her medical history also included drug hypersensitivity to Lipitor (ongoing unknown duration), allopurinol (ongoing 3 years) and amoxicillin (ongoing 1 year), carpal tunnel syndrome (ongoing 2 years), hip fracture (1 year), osteoporosis (ongoing 4 years), and pneumonia (1 year).

Subject No.: C0405 / 122-004	
Manufacturer Report No.: 07US000176	
Open Label Study Drug:	8 mg pegloticase every 2 weeks, intravenously
Double Blind Study Drug:	8 mg pegloticase every 4 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Peritonitis [Peritonitis]
Investigator Causality Assignment:	Unlikely
Outcome:	Resolved

Subject 122-004 was a 53 year-old African American female with a history of focal segmental glomerulonephritis (ongoing 5 years) and previous hospitalizations during the study due to pancreatitis and chronic kidney failure, who was hospitalized for a possible infection related to peritoneal dialysis. This subject was initially diagnosed with gout in 2002. Her other relevant medical history included pneumonia (1 year), chronic kidney disease (ongoing 5 years), hypercholesterolemia (ongoing 5 years), and hypertension (ongoing 10 years). This subject had experienced serious adverse events of pancreatitis on (b) (6) (refer to Narrative 07US000097) while participating in double-blind study C0405 and worsening chronic kidney failure on (b) (6) (refer to Narrative 07US000161). The subject received one dose of open-label study drug (8 mg pegloticase every 2 weeks) on 12 Apr 2007 (Dose 1) prior to the event.

On , the subject was hospitalized with peritonitis related to peritoneal dialysis, which was moderate in intensity. The subject presented to the hospital with infected peritoneal dialysis fluid (date not specified). She was diagnosed with peritonitis and admitted to the hospital the same day. The subject was hemodynamically stable and denied fever, but was experiencing abdominal pain. Admission laboratory test results revealed white blood cells (WBC) 29.3 $x10^9$/L(normal range [NR] 4.5-11.0 $x10^9$/L), red blood cells (RBC) 3.24 $x10^{12}$/L (NR 4.00-5.20 $x10^{12}$/L), hemoglobin (Hb) 9.2 g/dL (NR 12.0-16.0 g/dL), hematocrit (Hct) 29.7 (NR 36.0-48.0 %), absolute neutrophils 25.8 $x10^9$/L (2.0-7.5 $x10^9$/L), chloride 95 mmoL/L (NR 98-107 mmoL/L), urea nitrogen 74 mg/dL (NR 7-21 mg/dL), creatinine 4.8 mg/dL (NR 0.7-1.1 mg/dL) and calcium 8.4 μg/dL (NR 8.5-10.2 μg/dL).

A surface swab at the catheter tip site on (b) (6) (prior to hospitalization) grew diphtheroids 4+. Results of a blood culture taken on (b) (6) showed no growth after 5 days. Analysis of the peritoneal dialysis fluid on (b) (6) indicated mesothelial cells were present, fluid was straw colored and cloudy in appearance, and RBC 14/mm3, total nucleated cells 7000/mm3, neutrophils 95%, lymphocytes 1%, monocytes 3%, other 1% with 200 cells counted.

The catheter tip culture on (b) (6) showed mixed gram-positive flora. Laboratory test results the same day revealed potassium 3.1 mmoL/L (NR 3.5-5.0 mmoL/L), chloride 97, urea nitrogen 68, creatinine 5.1, calcium 7.9, phosphorus 4.6 μg/dL (NR 2.4-4.5 μg/dL), albumin 2.5 g/dL (NR 3.5-5.0 g/dL), alanine aminotransferase (ALT) 63 U/L (NR 15-48 U/L), aspartate aminotransferase (AST) 25 U/L (NR 14.38 U/L), alkaline phosphatase 309 U/L (NR 38-126 U/L), gamma glutamyl transferase (GGT) 991 U/L (NR 11-48 U/L), lactic dehydrogenase (LDH) 887 (NR 338-610), WBC 26.6, RBC 2.87, Hb 8.1, and Hct 26.5.

Results of the dialysis fluid gram stain on (b) (6) grew < 4+ polymorphonuclear leukocytes (diphtheroids). No organisms were seen. A repeat analysis the same day revealed degenerating cells,

macrophages, mesothelial cells, and toxic vacuolation. The dialysis fluid was straw colored and clear in appearance, with RBC 2/mm^3, total nucleated cells 30/mm^3, neutrophils 19%, lymphocytes 13%, monocytes 62%, and 8% other cells, with 100 cells counted.

Laboratory test results on (b) (6) were creatine kinase (CK) <20 U/L (NR 45-145 U/L), CK-MB 4.5 ng/mL (NR 0.0-6.0 ng/mL), troponin T 0.180 ng/mL (NR 0.000-0.029 ng/mL) (18:40); CK 24, CK-MB 4.6 and troponin T 0.199 (22:25); and CK <20 U/L, CK-MB 3.6 and troponin T 0.196 (03:56 on (b) (6)). No further information was provided by the site as to why these tests were performed.

The subject's treatment included intraperitoneal cefazolin (1 g) and ceftazidime (1 g). The dialysate cleared up with daily dwelling (date not specified). Leakage of fluid around the peritoneal dialysis catheter site was noted and 1 month of time was prescribed for maturation around the catheter site; hemodialysis was performed as a temporary measure and was well tolerated. The subject was also started on Ancef 1.5 g for treatment of her ongoing peritonitis.

Also during her hospitalization, the subject experienced pain secondary to gout and was administered indomethacin for pain control. She was taking prednisone and colchicine daily for gout flare prophylaxis; however, the colchicine was thought to be aggravating her gout pain secondary to worsening renal function and was held. The subject recovered and was discharged from the hospital on (b) (6) with prescribed erythropoietin 20,000 U at dialysis and Ancef 1.5 g at each dialysis for the next 10 days.

The study drug regimen was unchanged and the subject continued in the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), Altace (ramipril), calcium with vitamin D, Fosamax (alendronate sodium), Nexium (esomeprazole magnesium), prednisone, Zetia (ezetimibe), Norvasc (amlodipine), Aranesp (darbepoetin alfa), atenolol, Zocor (simvastatin), Remeron (mirtazapine), and Vicodin (hydrocodone bitartrate, acetaminophen).

The event of peritonitis resulted in the subject's hospitalization and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that this event was unlikely related to the study drug.

Her medical history also included drug hypersensitivity to Lipitor (ongoing unknown duration), allopurinol (ongoing 3 years) and amoxicillin (ongoing 1 year), carpal tunnel syndrome (ongoing 2 years), hip fracture (1 year), and osteoporosis (ongoing 4 years).

Subject No.: C0405 / 122-004	
Manufacturer Report No.: 07US000182	
Open Label Study Drug:	8 mg pegloticase every 2 weeks, intravenously
Double Blind Study Drug:	8 mg pegloticase every 4 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Right Hip Fracture [Hip Fracture]
Investigator Causality Assignment:	Unlikely
Outcome:	Resolved

Subject 122-004 was a 53 year-old African-American female with a history of left hip fracture (1 year) who was hospitalized for right hip fracture. This subject was initially diagnosed with gout in 2002. She had a relevant medical history of osteoporosis (ongoing 4 years). This subject had previously experienced serious adverse events of pancreatitis on (b) (6) (refer to Narrative 07US000097) while participating in double-blind study C0405, worsening chronic kidney failure on (b) (6) (refer to Narrative 07US000161), and possible infection related to peritoneal dialysis on (b) (6) (refer to Narrative 07US000176). The subject received one dose of open-label study drug (8 mg pegloticase every 2 weeks) on 12 Apr 2007 (Dose 1) prior to the event.

On , the subject was hospitalized with a right hip fracture of moderate intensity, after falling. She was seen in the emergency room where x-ray revealed a right subcapital femoral neck fracture, and was admitted to the hospital for hip arthroplasty. The subject developed a fever and her surgery was postponed. Blood and urine cultures were negative. She was administered vancomycin and levofloxacin, which were discontinued after her surgery because cultures remained negative and the subject was afebrile. Surgery proceeded without complications; an epidural was used for pain control with transition to OxyContin and morphine as needed. Once her post-surgical pain had resolved, the subject began physical therapy (PT). She then experienced an acute gout flare in her knee, which was treated with an increase of her prednisone dose to 60 mg and a Lidoderm patch. Cortisol injection to her knee was recommended for acute pain relief, allowing the subject to continue with PT. The subject recovered on (b) (6) and was discharged from the hospital on .

The study drug regimen was unchanged and the subject continued in the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), Altace (ramipril), calcium with vitamin D, Fosamax (alendronate sodium), Nexium (esomeprazole magnesium), prednisone, Zetia (ezetimibe), Norvasc (amlodipine), Aranesp (darbepoetin alfa), atenolol, Zocor (simvastatin), Remeron (mirtazapine), Vicodin (hydrocodone bitartrate, acetaminophen) and Cinacalcet.

The event of right hip fracture resulted in the subject's hospitalization and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that the event was unlikely related to the study drug.

Her medical history also included drug hypersensitivity to Lipitor (ongoing unknown duration), allopurinol (ongoing 3 years) and amoxicillin (ongoing 1 year), carpal tunnel syndrome (ongoing 2 years), pneumonia

(1 year), glomerulonephritis (ongoing 5 years), chronic kidney disease (ongoing 5 years), hypercholesterolemia (ongoing 5 years), and hypertension (ongoing 10 years).

Subject No.: C0405 / 122-004	
Manufacturer Report No.: 07US000215	
Open Label Study Drug:	8 mg pegloticase every 2 weeks, intravenously
Double Blind Study Drug:	8 mg pegloticase every 4 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Bilateral Lower Extremity Deep Vein Thrombosis [Deep Vein Thrombosis]
Investigator Causality Assignment:	Unlikely
Outcome:	Resolved

Subject 122-004 was a 53 year-old African American female with a history of focal segmental glomerulonephritis (ongoing 5 years) and previous hospitalizations during the study due to pancreatitis, chronic kidney failure, peritonitis, and hip fracture, who was hospitalized with bilateral lower extremity deep vein thrombosis (DVT). This subject was initially diagnosed with gout in 2002. Her other relevant medical history included chronic kidney disease (ongoing 5 years), hypercholesterolemia (ongoing 5 years), and hypertension (ongoing 10 years). The subject had experienced serious adverse events of pancreatitis on (b) (6) (refer to Narrative 07US000097) while participating in double-blind study C0405, worsening chronic kidney failure on (b) (6) (refer to Narrative 07US000161), peritonitis on (b) (6) (refer to Narrative 07US000176), and hip fracture (refer to Narrative 07US000182). Concurrent to this present event, the subject experienced serious adverse events of Grade 4 anemia (refer to Narrative 07US000216) and osteomyelitis right first MTP (refer to Narrative 07US000217). She received her first dose of open-label study drug (8 mg pegloticase every 2 weeks) on 12 Apr 2007 and 3 additional dose administrations prior to this event. She received her most recent study drug infusion on 30 Jul 2007 (Dose 4).

On (b) (6), the subject was hospitalized with bilateral lower extremity DVT that was severe in intensity. She was unable to walk due to weakness and pain in her legs, and was taken to the emergency room (date not specified) and admitted to the hospital on (b) (6) for bilateral lower extremity DVT. An inferior vena cava (IVC) filter was inserted (date unknown). The event remained ongoing at the time of the report.

The subject was also diagnosed with worsening (Grade 4) anemia (refer to Narrative 07US000216) and treated with 2 units packed red blood cells. On the same day, (b) (6), she was also diagnosed with osteomyelitis in her right first MTP (infected draining tophus of her right toe; refer to Narrative 07US000217) and was treated with antibiotics.

The study drug regimen was unchanged and the subject continued in the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), Altace (ramipril), calcium with vitamin D, Fosamax (alendronate sodium), Nexium (esomeprazole magnesium), prednisone, Zetia (ezetimibe), Norvasc (amlodipine), Aranesp (darbepoetin alfa), atenolol, Zocor (simvastatin), Remeron (mirtazapine), Vicodin (hydrocodone bitartrate, acetaminophen), ASA, cinacalcet, enalapril, Colace (docusate sodium), furosemide, OxyContin (oxycodone hydrochloride), indomethacin, sevelamer hydrochloride, erythropoietin alpha (erythropoietin human) and Lidoderm (lidocaine).

The event of bilateral lower extremity DVT resulted in the subject's hospitalization and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that this event was unlikely related to the study drug.

Her medical history also included drug hypersensitivity to Lipitor (ongoing unknown duration), allopurinol (ongoing 3 years) and amoxicillin (ongoing 1 year), carpal tunnel syndrome (ongoing 2 years), hip fracture (1 year), osteoporosis (ongoing 4 years), and pneumonia (1 year).

Subject No.: C0405 / 122-004	
Manufacturer Report No.: 07US000216	
Open Label Study Drug:	8 mg pegloticase every 2 weeks, intravenously
Double Blind Study Drug:	8 mg pegloticase every 4 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Grade 4 Anemia [Anaemia]
Investigator Causality Assignment:	Unlikely
Outcome:	Ongoing

Subject 122-004 was a 53 year-old African American female with a history of focal segmental glomerulonephritis (ongoing 5 years) and previous hospitalizations during the study due to pancreatitis, chronic kidney failure, peritonitis, and hip fracture, who was hospitalized with bilateral lower extremity deep vein thrombosis (DVT) (refer to Narrative 07US000215) and diagnosed with worsening (Grade 4) anemia on the same day. This subject was initially diagnosed with gout in 2002. Her other relevant medical history included chronic kidney disease (ongoing 5 years), hypercholesterolemia (ongoing 5 years), and hypertension (ongoing 10 years). The subject had experienced serious adverse events of pancreatitis on (b) (6) (refer to Narrative 07US000097) while participating in double-blind study C0405, worsening chronic kidney failure on (refer to Narrative 07US000161), peritonitis on (b) (6) (refer to Narrative 07US000176), and hip fracture (refer to Narrative 07US000182). Concurrent to this present event, the subject experienced serious adverse events of bilateral lower extremity DVT (refer to Narrative 07US000215) and osteomyelitis right first MTP (refer to Narrative 07US000217). She received her first dose of open-label study drug (8 mg pegloticase every 2 weeks) on 12 Apr 2007 and 3 additional dose administrations prior to this event. She received her most recent study drug infusion on 30 Jul 2007 (Dose 4).

On , while the subject was hospitalized for severe bilateral lower extremity DVT for which an inferior vena cava filter was inserted (refer to Narrative 07US000215), the subject was found to have Grade 4 anemia of severe intensity. She passed large amounts of maroon-colored stool and required multiple blood transfusions. Gastroenterology evaluation revealed a clean-based duodenal ulcer, which was treated with a sclerosing agent(s). Laboratory results revealed hemoglobin 5.5 g/dL (normal range [NR] not specified). Treatment included 2 units packed red blood cells the same day, (b) (6). The event was ongoing at the time of the subject's death from sepsis on (b) (6).

The subject received her final dose of study drug on 30 Jul 2007.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), Altace (ramipril), calcium with vitamin D, Fosamax (alendronate sodium), Nexium (esomeprazole magnesium), prednisone, Zetia (ezetimibe), Norvasc (amlodipine), Aranesp (darbepoetin alfa), atenolol, Zocor (simvastatin), Remeron (mirtazapine), Vicodin (hydrocodone bitartrate, acetaminophen), ASA, cinacalcet, enalapril, Colace (docusate sodium), furosemide, OxyContin (oxycodone), indomethacin, sevelamer hydrochloride, erythropoietin alpha (erythropoietin human), and Lidoderm (lidocaine).

The event of Grade 4 anemia was discovered during the subject's hospitalization for bilateral lower extremity DVT and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that this event was unlikely related to the study drug.

Her medical history also included drug hypersensitivity to Lipitor (ongoing unknown duration), allopurinol (ongoing 3 years) and amoxicillin (ongoing 1 year); carpal tunnel syndrome (ongoing 2 years); hip fracture (1 year); osteoporosis (ongoing 4 years); and pneumonia (1 year).

Subject No.: C0405 / 122-004	
Manufacturer Report No.: 07US000217	
Open Label Study Drug:	8 mg pegloticase every 2 weeks, intravenously
Double Blind Study Drug:	8 mg pegloticase every 4 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Osteomyelitis Right First MTP [Osteomyelitis]
Investigator Causality Assignment:	Unlikely
Outcome:	Resolved

Subject 122-004 was a 53 year-old African American female with a history of focal segmental glomerulonephritis (ongoing 5 years) and previous hospitalizations during the study due to pancreatitis, chronic kidney failure, peritonitis, and hip fracture, who was hospitalized with bilateral lower extremity deep vein thrombosis (DVT) (refer to Narrative 07US000215) and diagnosed with severe osteomyelitis of her right first metatarsophalangeal (MTP) on the same day. This subject was initially diagnosed with gout in 2002. Her other relevant medical history included osteoporosis (ongoing 4 years), chronic kidney disease (ongoing 5 years), hypercholesterolemia (ongoing 5 years), and hypertension (ongoing 10 years). The subject had experienced serious adverse events of pancreatitis on (b) (6) (refer to Narrative 07US000097) while participating in double-blind study C0405, worsening chronic kidney failure on (refer to Narrative 07US000161), peritonitis on (b) (6) (refer to Narrative 07US000176), and hip fracture on (refer to Narrative 07US000182). Concurrent to this present event, the subject experienced serious adverse events of bilateral lower extremity DVT (refer to Narrative 07US000215) and Grade 4 anemia (refer to Narrative 07US000216). She received her first dose of open-label study drug (8 mg pegloticase every 2 weeks) on 12 Apr 2007 and 3 additional dose administrations prior to this event. She received her most recent study drug infusion on 30 Jul 2007 (Dose 4).

On (b) (6), while the subject was hospitalized for severe bilateral lower extremity DVT (refer to Narrative 07US000215), she was diagnosed with osteomyelitis of the right first MTP after being treated for an infected, draining tophus of the right first metatarsophalangeal (treatment not specified). A computed tomography scan of her right foot revealed osteomyelitis of the right great toe (date not specified). Her toe was amputated on (b) (6); cultures of the toe wound grew oxacillin resistant Staphylococcus aureus and the subject was treated with vancomycin. The operative report indicated the presence of purulent drainage with extensive bone involvement, and extension of purulence onto the top of the foot. The subject was provided with a patient-controlled analgesia (PCA) pump post-operatively for pain control. Her BP subsequently fell to 60/30 mmHg, which was thought to be secondary to her PCA narcotics. There is no information on whether the subject's PCA was stopped to treat her drop in BP. The subject recovered from the event of osteomyelitis on 13 Aug 2007; however, she remained hospitalized died from sepsis on (b) (6).

Additionally during this hospitalization, the subject was diagnosed with Grade 4 anemia (refer to Narrative 07US000216).

The subject received her final dose of study drug on 30 Jul 2007.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), Altace (ramipril), calcium with vitamin D, Fosamax (alendronate sodium), Nexium (esomeprazole magnesium), prednisone, Zetia (ezetimibe), Norvasc (amlodipine), Aranesp (darbepoetin alfa), atenolol, Zocor (simvastatin), Remeron (mirtazapine), Vicodin (hydrocodone bitartrate, acetaminophen), ASA, cinacalcet, enalapril, Colace (docusate sodium), furosemide, OxyContin (oxycodone), indomethacin (indomethacin), sevelamer hydrochloride, erythropoietin alpha (erythropoietin human), and Lidoderm (lidocaine).

The event of osteomyelitis right first MTP was discovered during the subject's hospitalization for bilateral lower extremity DVT and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that this event was unlikely related to the study drug.

Her medical history also included drug hypersensitivity to Lipitor (ongoing unknown duration), allopurinol (ongoing 3 years) and amoxicillin (ongoing 1 year); carpal tunnel syndrome (ongoing 2 years); hip fracture (1 year); and pneumonia (1 year).

Subject No.: C0405 / 203-001	
Manufacturer Report No.: 07CA000212	
Double Blind Study Drug:	8 mg PEG-uricase every 2 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Death Attributed to Cardiac Arrest [Cardiac Arrest]
Investigator Causality Assignment:	Unlikely
Outcome:	Death

Subject 203-001 was a 61 year-old Caucasian male with a history of congestive heart failure (ongoing 6 years) and hypertension (ongoing 6 years) who died at home; the death was subsequently considered "cardiac arrest" after arriving at the emergency room 45 minutes later in asystole. The subject had also experienced a concurrent adverse event of worsening of non-insulin-dependent diabetes mellitus (07 May 2007, resolution unknown). This subject was initially diagnosed with gout in 2002. His other relevant medical history included angina pectoris (ongoing 6 years) and diabetes mellitus non-insulin-dependent (ongoing 15 years). This subject had previously experienced a non-serious non-severe (mild) infusion-related reaction on 25 Apr 2007 during Dose 3 of study drug, and a serious adverse event of acute gout attack on 11 May 2007 (refer to Narrative 07CA000177). The subject received his first dose of study drug on 28 Mar 2007 and 5 more scheduled doses prior to this event; he did not receive Dose 6 on 06 Jun 2006 (study drug interrupted) because of hypotension. He received his most recent study drug infusion on 20 Jun 2007 (Dose 7). He had been scheduled to receive Dose 8 on 09 Jul 2007; however, he had experienced a reaction to hydrocortisone pretreatment and consequently, did not receive Dose 8.

On (b) (6), the subject unloaded a wood splitter with his wife and son, and had said he was feeling unwell. About 10 minutes later he was found slumped over, unresponsive. Cardiac pulmonary resuscitation was administered and the subject was transported to the emergency room, arriving 45 minutes later and was in asystole. He was treated with epinephrine and atropine but could not be resuscitated. He was pronounced dead on (b) (6). The attending physician at the resuscitation effort reported the cause of death as cardiac arrest. The subject's screening electrocardiogram had revealed 1st degree AV block (14 Feb 2007). The Investigator reported that his information about the subject indicated that subject's ejection fraction was 17% prior to entry into the study, but no documentation was available. Information from 17 May 2007 was also available at the site indicating an ejection fraction of 28%. An autopsy was not performed and no additional information was available.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), furosemide, spironolactone, metoprolol, Zestril (lisinopril), simvastatin, nitroglycerin (glyceryl trinitrate), Imdur (isosorbide mononitrate), Bricanyl Turbohaler (terbutaline sulfate), Pulmicort (budesonide), Glyburide (glibenclamide), trazodone, Celebrex (celecoxib), Tylenol with codeine #3 (codeine phosphate, paracetamol), and Avandia (rosiglitazone maleate) (13 May 2007 to 23 May 2007).

The event cardiac arrest was reported as serious, and lead to the subject's death. The Investigator and Clinical Research Physician at Savient felt that the event was unlikely related to the study drug.

His medical history also included drug hypersensitivity to allopurinol (ongoing 4 years) and to intravenous pyelogram (IVP) dye (ongoing 10 years), prostate examination abnormal (ongoing 10 years), occasional headaches (ongoing 20 years), angina pectoris (ongoing 6 years), insomnia (ongoing 5 years), and asthma (ongoing 24 years).

Subject No.: C0406 / 301-003	
Manufacturer Report No.: 07US000083	
Double Blind Study Drug:	8 mg PEG-uricase every 2 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Methicillin Resistant Staphylococcus aureus Septicemia [Staphylococcal Sepsis]
Investigator Causality Assignment:	Unlikely
Outcome:	Resolved; Withdrawal Due to Adverse Event

Subject 301-003 was an 89 year-old Caucasian male who developed Staphylococcus aureus septicemia thought to be due to a stage 1-2 perianal decubitus. This subject was initially diagnosed with gout in 1983. His relevant medical history included cardiac arrhythmia with pacemaker (ongoing 9 years), stasis dermatitis (ongoing 10 years), cardiac valve prosthesis user (ongoing 10 years), cardiac murmur (ongoing unknown duration), coronary artery disease (ongoing unknown duration), atrial fibrillation (ongoing unknown duration), chronic kidney failure (ongoing unknown duration), peripheral vascular disorder (ongoing unknown duration), wheezing (ongoing 3 years), dyslipidemia (ongoing 3 years), hypothyroidism (ongoing 30 years), and hypertension (ongoing 54 years). The subject received his first dose of study drug on 02 Aug 2006 and 11 additional dose administrations prior to this event. The subject received his most recent study drug infusion on 03 Jan 2007 (Dose 12).

On , the subject was found to be unresponsive and was taken to the emergency room. He was diagnosed with rhabdomyolysis, was dehydrated and hypotensive, and had elevated white blood cells (WBC, 13.6 $x10^3/\mu L$, normal range 3.7 - 10.3 $x10^3/\mu L$). The subject was treated in the intensive care unit with Zosyn (piperacillin sodium, tazobactam sodium) intravenously (IV) and vancomycin, and transferred to the telemetry unit 3 days later (b) (6)). He was oriented and comfortable. An echocardiogram the next day (b) (6) revealed that he had left ventricular hypertrophy with low-normal systolic function, a dilated left atrium, and high systolic pressure in his right ventricle. His prosthetic aortic valve showed moderate stenosis; densely calcified aortic root; and moderate tricuspid and mild aortic, mitral, and pulmonic valve regurgitation. A transesophageal echocardiogram (TEE) performed on (b) (6) confirmed these findings, together with mild tricuspid regurgitation. No vegetations were noted on the mitral or prosthetic aortic valve. Blood cultures revealed methicillin resistant Staphylococcus aureus (MRSA) infection, which was attributed to a stage 1-2 perianal decubitus. During his period of hospitalization, the subject was also found to have mildly-elevated blood glucose levels and was treated with Humulin-R (human insulin).

The subject recovered from the event of Staphylococcus sepsis on (b) (6) and was discharged from the hospital the same day to a Skilled Nursing Facility for long term intravenous antibiotic treatment and rehabilitation. He was given a 6-week course of antibiotic treatment, vancomycin 1 g IV and piperacillin/tazobactam, and discharged to his home.

The full course of study drug was completed on 03 Jan 2007; however, the subject did not complete the follow-up visits following his last dose of study drug due to the adverse event of Staphylococcus aureus septicemia on 05 Jan 2007. The subject was reported as withdrawn from the study on 22 Jan 2007.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis

(colchicine), albuterol, furosemide, quinapril, levothyroxine sodium, atorvastatin, montelukast, metoprolol, methocarbamol, multivitamins and iron, calcium, alfuzosin hydrochloride, Neosporin (bacitracin, neomycin sulfate, polymyxin B sulfate), labetalol, aspirin, fish oil, and warfarin.

The event of Staphylococcal sepsis resulted in the subject's hospitalization and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that this event was unlikely related to the study drug.

His medical history also included drug hypersensitivity to allopurinol (ongoing 7 years), thrombocytopenia / idiosyncratic reaction to allopurinol (1 year), and benign prostatic hyperplasia (ongoing unknown duration). The subject underwent a cardiac catheterization on (b) (6),

Subject No.: C0406 / 301-003	
Manufacturer Report No.: 07US000125	
Double Blind Study Drug:	8 mg PEG-uricase every 2 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Sepsis [Sepsis]
Investigator Causality Assignment:	Unlikely
Outcome:	Death

Subject 301-003 was an 89 year-old Caucasian male who died of sepsis due to a methicillin-resistant Staphylococcus aureus (MRSA) infection initially diagnosed on (b) (6). The subject had been diagnosed with Staphylococcus aureus septicemia, attributed to a perianal decubitus ulcer, on (b) (6) (refer to Narrative 07US000083). This subject was initially diagnosed with gout in 1983. His relevant medical history included cardiac arrhythmia with pacemaker (ongoing 9 years), cardiac valve prosthesis user (ongoing 10 years), cardiac murmur (ongoing unknown duration), coronary artery disease (ongoing unknown duration), atrial fibrillation (ongoing unknown duration), chronic kidney failure (ongoing unknown duration), peripheral vascular disorder (ongoing unknown duration), wheezing (ongoing 3 years), dyslipidemia (ongoing 3 years), hypothyroidism (ongoing 30 years), and hypertension (ongoing 54 years). The subject received his first dose of study drug on 02 Aug 2006 and 11 additional dose administrations prior to this event. The subject received his most recent study drug infusion on 03 Jan 2007 (Dose 12).

On (b) (6) the subject collapsed at home and was brought to the emergency room. He was admitted to the intensive care unit (ICU) for the treatment of sepsis due to an ongoing MRSA infection, which had been ineffectively treated from (b) (6) in a Skilled Nursing Facility. Prescribed treatment for his Staphylococcus aureus septicemia on (b) (6) included a 6-week course of vancomycin 1 g intravenously (from (b) (6) and piperacillin/tazobactam (from (b) (6) to (b) (6) Following his admission to the ICU from the Emergency Room on (b) (6), pacemaker lead extraction was recommended and the subject was transferred to another facility on (b) (6) for the procedure. However, his international normalized ratio (INR) was prohibitively high and the procedure was postponed. During the period of postponement, the subject opted to forgo additional intervention, electing to receive comfort care only. On (b) (6), the subject was transferred to a hospice-type setting. The subject died (b) (6). No autopsy was performed and the presumed cause of death was MRSA sepsis.

The full course of study drug was completed on 03 Jan 2007; however, the subject did not complete the follow-up visits following his last dose of study drug due to the adverse event of Staphylococcus aureus septicemia on (b) (6). The subject was reported as withdrawn from the study on 22 Jan 2007.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), quinapril arginine, Coreg, dopamine, esomeprazole, heparin sodium, Humulin, Lasix (furosemide), levothyroxine sodium, metoprolol, Micro-K, multivitamins and iron, Mucinex, simvastatin, tamsulosin, vitamin C, warfarin, zinc sulfate, Zocor, and Zosyn.

The event of sepsis was life-threatening, required inpatient hospitalization, and resulted in the subject's death. The Investigator and Clinical Research Physician at Savient felt that this event was unlikely related to the study drug.

His medical history also included drug hypersensitivity to allopurinol (ongoing 7 years), thrombocytopenia / idiosyncratic reaction to allopurinol (1 year), stasis dermatitis (ongoing 10 years), and benign prostatic hyperplasia (ongoing unknown duration). It was also reported the subject underwent a cardiac catheterization on (b) (6).

Subject No.: C0406 / 301-014	
Manufacturer Report No.: 07US000105	
Double Blind Study Drug:	Placebo, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6); Had Not Commenced Trial Medication
Event:	Multiple Organ Failure [Multi-Organ Failure]
Investigator Causality Assignment:	Unlikely
Outcome:	Death

Subject 301-014 was an 84 year-old Caucasian female who had been screened and randomized (placebo) into the study, who developed multiple organ failure resulting in her death on (b) (6) before commencing trial medication. This subject was initially diagnosed with gout in 1998. Her medical history included breast cancer (1 year), mitral valve replacement (9 years), vertigo (6 years), left leg open wound (ongoing 5 months), azotemia (ongoing 5 months), lumbar spinal stenosis (ongoing 7 years), osteoarthritis (ongoing 9 years), atrial fibrillation (ongoing 10 years), hypercholesterolemia (ongoing 11 years), hypertension (ongoing 11 years), drug hypersensitivity to allopurinol and probenecid (ongoing 3 years and 2 years 7 months, respectively), cardiac murmur (ongoing unknown duration), as well as ongoing lymphedema, cellulitis, renal impairment, sensory disturbance, elevated liver function tests, left bundle branch block, and urinary tract infection (unknown duration).

The subject had completed her screening visit on 03 Jan 2007 and her baseline visit had been scheduled for 15 Feb 2007. The subject's daughter contacted the investigational site to report that the subject had been hospitalized (date unknown) and would not be participating in the study. The subject died of multiple organ failure on . Additional information was requested and no further details were made available for this case.

The Investigator and Clinical Research Physician at Savient felt that this event was unlikely related to the study drug.

Medications being taken by the subject at the time of her screening visit included Vasotec (enalapril maleate), metoprolol, digoxin, aspirin, Klor-Con (potassium chloride), Zocor (simvastatin), Coumadin (warfarin sodium), furosemide, Diovan (valsartan), Meclizine (Meclozine), Zaroxolyn (metolazone), multivitamin, verapamil, folic acid, prednisone, and colchicine.

The subject had no other reported medical history.

Subject No.: C0406 / 315-005	
Manufacturer Report No.: 07US000147	
Double Blind Study Drug:	8 mg PEG-uricase every 2 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Sudden Death Attributed to Cardiac Arrhythmia [Arrhythmia]
Investigator Causality Assignment:	Unlikely
Outcome:	Death

Subject 315-005 was a 69 year-old Caucasian male who experienced sudden death ascribed post mortem to cardiac arrhythmia, in the context of a long history of cardiac disease. This subject was initially diagnosed with gout in 2000. His medical history relevant to the event included bradycardia (ongoing 1 month), coronary artery disease (ongoing 16 years), coronary artery bypass graft (x3; 16 years), peripheral vascular disorder (ongoing 16 years), cardiac murmur (ongoing 1 month), hypercholesterolemia (ongoing 16 years), left carotid artery occlusion (ongoing 10 years), right carotid endarterectomy (3 years), bilateral lower extremity edema (ongoing 16 years), diabetic neuropathy (ongoing 36 years), diabetes mellitus (ongoing 38 years), hypertension (ongoing 38 years), obesity (ongoing unknown duration), and hyperkalemia (ongoing unknown duration), chronic kidney failure (ongoing 8 years), and renal artery stent placement (4 years). The subject received his first dose of study drug on 29 Nov 2006 and 8 more scheduled doses prior to this event. The subject received his most recent study drug infusion on 27 Mar 2007 (Dose 9).

On , the subject complained of weakness. The next day, (b) (6), he was taken to his primary care physician by his wife who noted that the subject had not felt well the past few days. The subject was weak, achy, and had no appetite; but no specific findings were noted by the physician. Muscle weakness due to Pravachol was considered. He denied vomiting or fever. His BP was 100/62 mmHg, and his cardiac examination was 'regular'. He presented with less edema than observed previously.

Blood drawn on (b) (6) revealed alanine aminotransferase 28 IU/L (normal range [NR] 0 – 55 IU/L), elevated aspartate aminotransferase 54 IU/L (NR 5 - 34 IU/L), blood urea nitrogen (BUN) 114 mg/dL (NR 8 – 26 mg/dL) and creatinine 4.1 mg/dL (NR 0.7 - 1.3 mg/dL). Results also revealed glomerular filtration rate estimated 15 mL/min, calcium 11.7 mg/dL (NR 8.8 - 10.0 mg/dL), total creatinine kinase 194 IU/L (NR 30 - 200 IU/L), bicarbonate 22 mEq/L (NR 23 - 31 mEq/L), glucose 231 mg/dL (NR 80 - 115 mg/dL), potassium 4.8 mmol/L (NR 3.5 - 5.1 mmol/L), sodium 138 mEq/L (NR 136 - 145 mEq/L), white blood cells 7.5 $x10^3/\mu L$ (NR 3.1 - 8.5 $x10^3/\mu L$), POLY 79% (NR 25 - 62%), lymphocytes 10% (NR 22 - 39%), monocytes 11 (NR 2 - 10), hemoglobin (Hb) 12.0 g/dL (NR 14.0 - 18.0 g/dL), hematocrit (Hct) 34% (NR 40 - 54%), platelets 166 $x10^3/\mu L$ (NR 140 - 440 $x10^3/\mu L$), and erythrocyte sedimentation rate 59 mm/hr (NR 0 - 20 mm/hr).

Laboratory results at screening (b) (6) revealed creatinine 3.0 mg/dL (NR 0.6 - 1.4 mg/dL), BUN 78 mg/mL (NR 9 – 24 mg/mL), potassium 5.4 mEq/L (NR 3.6 - 5.2 mEq/L), creatinine clearance 43 mL/min, Hb 11.9 g/dL (NR 13.2 – 17 g/dL), and Hct 35.1% (NR 40 - 54%). Laboratory results at Dose 7 (b) (6)), revealed creatinine 3.2 mg/dL, BUN 70 mg/mL, potassium 5.3 mEq/L, creatinine clearance 40 mL/min, Hb 11.2 g/dL, and Hct 33.3%. There is no documentation from the patient's local physician as to whether or not the elevated potassium was noted or considered to be a risk.

The subject felt worse on (b) (6) and was driven to the hospital by his wife. The subject died on (b) (6) while on the way to the hospital. The cause of death was reported as cardiac arrhythmia (without electrocardiographic evidence).

Study drug was discontinued permanently on 05 Apr 2007. The subject died on (b) (6).

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), omeprazole, PhosLo, Nephro Caps (folic acid, vitamins), clonidine hydrochloride, Pravachol (pravastatin sodium) , Cardizem (diltiazem extended release) , furosemide, Micardis (telmisartan, magnesium oxide), metolazone, prednisone, citalopram, iron, aspirin, stool softener, Kayexalate (sodium polystyrene sulfonate), Humulin N (insulin injection, isophane), Humalog (insulin lispro), and Hectorol (doxercalciferol).

The event of cardiac arrhythmia resulted in the subject's death. The Investigator and Clinical Research Physician at Savient felt that this event was unlikely related to the study drug.

His medical history also included skin ulcer right foot (ongoing 2 months), depression (ongoing 2 years), bilateral cataract removal with lens implants (5 years), left foot second toe deformity and amputation (5 years), osteoarthritis (ongoing 6 years), gastroesophageal reflux disease (ongoing 6 years), blisters (ongoing 6 years), and constipation (ongoing 2 years).

APPENDIX 4: NARRATIVES FOR SUBJECTS WHO HAD SERIOUS CARDIOVASCULAR EVENTS

Appendix 4
Narratives for Subjects who had Serious Cardiovascular Events

Study Subject No.	Date of Event	Event Description	Treatment Group	Outcome
Study C0405: Subject 130-004	(b) (6)	Syncope	Pegloticase 8 mg q 2 weeks OLE; Pegloticase 8 mg q 4 weeks RCT	Resolved
Study C0405: Subject 130-006	(b) (6)	Worsening carotid stenosis	Pegloticase 8 mg q 4 weeks OLE; Pegloticase 8 mg q 4 weeks RCT	Resolved
Study C0405: Subject 204-001	(b) (6)	Left leg deep vein thrombosis	Pegloticase 8 mg q 2 weeks OLE; Placebo RCT	Ongoing
Study C0406: Subject 327-002	(b) (6)	Left thoracic chest pain	Pegloticase 8 mg q 4 weeks OLE; Pegloticase 8 mg q 4 weeks RCT	Resolved
Study C0403: Subject 002-003	(b) (6); (b) (6)	Upper respiratory infection resulting in hospitalization; right-sided lacunar stroke	Pegloticase 12 mg q 4 weeks	Resolved
Study C0405: Subject 101-005	(b) (6)	Syncope	Placebo	Resolved
Study C0405: Subject 102-006	(b) (6)	Acute dyspnea; worsening of kidney disease	Pegloticase 8 mg q 4 weeks	Death
Study C0405: Subject 122-003	(b) (6)	Deep vein thrombosis	Pegloticase 8 mg q 4 weeks	Resolved
Study C0405: Subject 122-003		Acute myocardial infarction	Pegloticase 8 mg q 4 weeks	Resolved
Study C0405: Subject 124-001	(b) (6)	Congestive heart failure	Pegloticase 8 mg q 2 weeks	Resolved
Study C0405: Subject 203-001	(b) (6)	Death attributed to cardiac arrest	Pegloticase 8 mg q 2 weeks	Death
Study C0406: Subject 301-006	(b) (6)	Hyperkalemia, re-entry tachycardia	Pegloticase 8 mg q 4 weeks	Resolved
Study C0406: Subject 301-006	(b) (6)	Acute renal failure, hyperkalemia	Pegloticase 8 mg q 4 weeks	Resolved
Study C0406: Subject 301-012	(b) (6)	Transient ischemic attack	Pegloticase 8 mg q 4 weeks	Resolved; subject chose to withdraw study drug 35 days previous
Study C0406: Subject 311-001	(b) (6)	Angina pectoris	Pegloticase 8 mg q 4 weeks	Resolved
Study C0406: Subject 311-005	(b) (6)	Arrhythmia	Pegloticase 8 mg q 2 weeks	Resolved
Study C0406: Subject 311-005	(b) (6)	A Lower extremity edema	Pegloticase 8 mg q 2 weeks	Resolved

Appendix 4
Narratives for Serious Cardiovascular Events (cont'd

Study Subject No.	Date of Event	Event Description	Treatment Group	Outcome
Study C0406: Subject 315-005	(b) (6)	Sudden death attributed to cardiac arrhythmia	Pegloticase 8 mg q 2 weeks	Death

Subject No.: C0405 / 130-004	
Manufacturer Report No.: 08US000254	
Open Label Study Drug:	8 mg pegloticase every 2 weeks, intravenously
Double Blind Study Drug:	8 mg pegloticase every 4 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Syncope [Syncope]
Investigator Causality Assignment:	Unlikely
Outcome:	Resolved

Subject 130-004 was a 61 year-old Caucasian male with a 12-year history of cardiac disease who wears an automatic implantable cardiac defibrillator (AICD), and experienced syncope while in the study. This subject was initially diagnosed with gout in 1993. His relevant medical history included coronary artery disease (ongoing 12 years), right carotid bruit (ongoing 1 year 6 months), angioplasty of coronary artery disease/infarction anterior wall myocardial (unknown), cardiac arrest (unknown), cardiac arrhythmia (ongoing), dyspnea on exertion (ongoing 1 year 5 months), implantable cardiac defibrillator (ongoing), and ischemic cardiomyopathy (ongoing 12 years). The subject received his first dose of open-label study drug (8 mg pegloticase every 4 weeks) on 10 Jul 2007 and 16 additional dose administrations prior to this event. He received his most recent study drug infusion on 19 Feb 2008 (Dose 17).

On , the subject was hospitalized with syncope of moderate intensity. The subject arrived in the emergency room (ER) with complaints of a "near syncopal episode" lasting approximately 20 minutes. He complained of shortness of breath, dizziness, and diaphoresis. Vital signs included blood pressure (BP) 140/palpable, heart rate (HR) 76 beats per minute (bpm). His electrocardiogram (ECG) was unchanged from screening; his screening ECG on 10 Jan 2007 showed sinus bradycardia, left axis deviation, and a T-wave abnormality. His AICD revealed no activity and the subject was admitted to the hospital for observation. Troponin I was <0.1 ng/mL (NR <0.1 ng/mL) (17:06 on (b) (6)); a repeat measure the same day was unchanged (23:00). Laboratory test results revealed digoxin level <0.3 ng/mL (NR 0.8-2.0 ng/mL) and creatinine kinase 77 U/L (NR 0-230 U/L).

On (b) (6), laboratory test results revealed white blood count (WBC) 5.9 x1000/µL (NR 3.9-11.0 x1000/µL), red blood count (RBC) 4.64 mil/µL (NR 4.3-5.8 mil/µL), serum chloride 111 mEq/L(NR 96-110 mEq/L), sodium 141 mEq/L (NR 135-148 mEq/L), potassium 4.2 mEq/L (NR 3.5-5.5 mEq/L), and creatinine kinase 90 U/L (06:10).

No significant plaque was noted on a carotid duplex scan performed on 02 Mar 2008. Doppler showed mild spectral broadening, compatible with less than 29% stenosis in the internal carotid arteries bilaterally. Good flow was seen with color-flow. Computed tomography (CT) scan of the brain the same day showed non-enhancing right frontal hypodensity consistent with infarct (clarification of whether infarct is old or new event is being queried at the time of this writing). Two-dimensional transthoracic echocardiogram performed on (b) (6) showed a moderately reduced left ventricular systolic function with ejection fraction of approximately 30-35%. The septum was thin and akinesis of the anteroseptal, mid to distal anterior wall, apex, distal lateral and distal inferior wall was reported, together with mild mitral regurgitation. The subject received prophylactic lisinopril, furosemide, lorazepam, and atorvastatin calcium; and recovered from the event and was discharged on (b) (6).

The study drug regimen was unchanged and the subject continued in the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), and ASA (acetylsalicylic acid).

The event of syncope was reported as serious (the reason for syncope is being queried at the time of this writing). The Investigator and Clinical Research Physician at Savient felt that the event was unlikely related to the study drug.

His medical history also included alcohol abuse (unknown), alcoholic hepatitis (unknown), allergy to allopurinol (ongoing 5 years, 8 months), bronchitis (unknown), chronic back pain (ongoing), degenerative disc disease (ongoing), degenerative joint disease (ongoing 14 years), depression (unknown), erectile dysfunction (ongoing 4 months), fracture left sixth rib (unknown), fracture fifth metacarpal (4 months), grade II separation left shoulder (unknown), hearing loss bilateral (ongoing 2 months), hyperlipidemia (ongoing 6 years 6 months), peripheral neuropathy (ongoing), skull fracture (unknown), and smoking (ongoing).

Subject No.: C0405 / 130-006	
Manufacturer Report No.: 08US000256	
Open Label Study Drug:	8 mg pegloticase every 4 weeks, intravenously
Double Blind Study Drug:	8 mg pegloticase every 4 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Worsening Carotid Stenosis [Carotid Artery Stenosis]
Investigator Causality Assignment:	Unlikely
Outcome:	Resolved

Subject 130-006 was a 73 year-old Caucasian female with a 6-month history of carotid artery stenosis who was hospitalized to undergo a scheduled endarterectomy. This subject was initially diagnosed with gout in 1991. Her other relevant medical history included hypertension (ongoing 26 years), cerebrovascular disease (ongoing 3 years), chronic renal insufficiency (ongoing 4 years 9 months), bilateral renal stenosis (ongoing 2 years), and renal stents (ongoing). The subject received her first dose of open-label study drug (8 mg pegloticase every 4 weeks) on 02 Aug 2007 and 7 additional dose administrations prior to this event. She received her most recent study drug infusion on 14 Feb 2008 (Dose 8).

On , the subject was hospitalized for a scheduled endarterectomy due to right carotid stenosis of moderate intensity. She had had a consultation with a vascular surgeon on (b) (6) (b, following a carotid Doppler scan on performed because of her history of carotid stenosis). Results revealed severe spectral broadening and velocities compatible with 70% to 99% stenosis in the right internal carotid artery (ICA) and no significant plaque; she had an increased right ICA stenosis from 12 Mar 2001. An exercise tolerance test (pharmacological stress test) on 25 Feb 2008 revealed no symptomatic or electrocardiographic evidence of ischemia. Additionally, a nuclear stress test (date unknown) revealed a medium area of ischemia of the anterior wall of the left ventricle.

Her pre-admission test results on (b) (6) were hematocrit 34.9% (NR 35.0-45.0%), red blood cells (RBC) 3.80 mil/µL (NR 3.80-5.10 mil/µL), and hemoglobin (Hb) 12.1 g/dL (NR 11.7-15.5 g/dL). Urine culture showed 10,000-50,000 CFU/mL enterococcus species, for which she was treated with clindamycin. Postoperatively, she developed anemia and was given one unit of packed RBC (PRBC) (date unknown). Test results (b) (6) showed calcium 7.7 mg/dL (NR 8.5-10.6 mg/dL), blood urea nitrogen (BUN) 32 mg/dL (NR 5-26 mg/dL), creatinine 1.7 mg/dL (NR 0.5-1.5 mg/dL), RBC 2.63 mil/µL (NR 3.70-5.10 mil/µL), Hb 8.2 g/dL (NR 11.0-15.0 g/dL), and hematocrit (Hct) 23.6% (NR 34.0-46.0%). Results on 09 Mar 2008, showed calcium 8.0 mg/dL, BUN 29 mg/dL, creatinine 1.7 mg/dL, sodium 133 mEq/L (NR 135-148 mEq/L), RBC 2.95 mil/µL, Hb 9.1 g/dL, and Hct 26.3%. The subject recovered from the event and was discharged on (b) (6).

The study drug regimen was unchanged and the subject continued in the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), ASA (acetylsalicylic acid), Plavix (clopidogrel), Cozaar (losartan), metoprolol, ranitidine, insulin, Norvasc (amlodipine), Levothroid (levothyroxine), trimethoprim, and pravastatin.

The event of worsening carotid stenosis involved scheduled hospitalization and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that the event was unlikely related to the study drug.

Her medical history also included angular cheilitis (ongoing 2 months), chronic serous left otitis media (ongoing 6 months), diabetic neuropathy (ongoing 4 years 4 months), elevated creatine phosphokinase (1 year 6 months), elevated lipase (ongoing 2 months), exertional dyspnea (ongoing 1 year), gastroesophageal reflux disease (ongoing 2 years 10 months), glaucoma (ongoing 9 years), hemorrhoids (ongoing 1 year), hiatal hernia (ongoing 1 month), hyperlipidemia (ongoing 4 years 8 months), hypothyroid (ongoing 2 years 11 months), insulin dependent diabetes (ongoing 10 years), mixed hearing loss left ear (ongoing 9 months), obesity (ongoing 20 years), osteoarthritis of hands (ongoing 23 years), recurrent urinary tract infection (6 months), rotator cuff tenderness (ongoing 2 months), seborrheic keratosis (3 years), sigmoid diverticulosis (ongoing 1 month), tinea corporis (ongoing 1 year 2 months), left middle ear fluid (unknown), right hip greater trochanteric bursitis (unknown), and allergies to allopurinol (ongoing 13 years), Ciprofloxacin (ongoing 8 years), latex (ongoing 4 years 8 months), Lipitor (ongoing 8 years), penicillin (ongoing 8 years), probenecid (ongoing 8 years), and Zyloprim (ongoing 8 years)

Subject No.: C0405 / 204-001	
Manufacturer Report No.: 07CA000221	
Open Label Study Drug:	8 mg pegloticase every 2 weeks, intravenously
Double Blind Study Drug:	Placebo
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Left Leg Deep Vein Thrombosis [Deep Vein Thrombosis]
Investigator Causality Assignment:	Unlikely
Outcome:	Ongoing

Subject 204-001 was a 49 year-old Caucasian male who developed left leg deep vein thrombosis (DVT) that was moderate in intensity. This subject was initially diagnosed with gout in 1983. His relevant medical history included hyperlipidemia (ongoing 3 months), and obesity (ongoing 8 years). He previously experienced a serious adverse event of rectal perianal abscess right buttock on 29 Jan 2007 (refer to Narrative 07CA000094) while participating in the double-blind study C0405 and a serious infusion reaction on (b) (6) at Dose 1 (refer to Narrative 07CA000208) while participating in this present study. The subject received his first dose of open-label study drug (8 mg pegloticase every 2 weeks) on 11 Jul 2007 and 2 additional dose administrations prior to this event. He received his most recent study drug infusion on 08 Aug2007 (Dose 3).

On , the subject developed a DVT in his left leg that was moderate in intensity, medically significant and secondary to decreased mobility and inactivity. The subject arrived at the clinical site for his Week 7 visit (Dose 4) with complaints of left lower leg pain and swelling. A Doppler ultrasound of the left leg revealed at least a partially occlusive thrombus from the proximal aspect of the superficial femoral vein to the popliteal vein. The infusion was not started and the subject was sent to the emergency room (ER) where he was treated with Enoxaparin (dalteparin sodium) 25,000 IU subcutaneously and warfarin 10 mg orally. At time of this report, the outcome remained ongoing, not yet recovered. No further information regarding event resolution was available.

The study drug regimen was unchanged and the subject continued in the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine, indomethacin), rabeprazole sodium, Codeine Contin (codeine/codeine sulfate), atorvastatin, ASA (acetylsalicylic acid), Percocet (oxycodone hydrochloride), zopiclone, Flamazine (sulfadiazine silver) 1% cream, and diphenhydramine.

The event of DVT was reported as serious. The Investigator and Clinical Research Physician at Savient felt that the event was unlikely related to the study drug.

His medical history also included chronic kidney failure (ongoing unknown duration), gout pain (ongoing unknown duration), hypertension (ongoing 7 months), intermittent bleeding on both feet (ongoing 1 month) following removal of tophi (ongoing unknown duration), and kidney stones (ongoing 16 years).

Subject No.: C0406 / 327-002	
Manufacturer Report No.: 07US000230	
Open Label Study Drug:	8 mg pegloticase every 4 weeks, intravenously
Double Blind Study Drug:	8 mg pegloticase every 4 weeks
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Left Thoracic Chest Pain [Chest Pain]
Investigator Causality Assignment:	Unlikely
Outcome:	Resolved

Subject 327-002 was a 72 year-old Caucasian male with a history of cardiovascular disease who experienced left thoracic chest pain of mild intensity. This subject was initially diagnosed with gout in 1996. His medical history included peripheral edema (ongoing 3 months), hypercholesterolemia (ongoing 1 year 6 months), hypertension (ongoing 3 years 2 months), angioplasty (3 years), stent placement (4 years), and cerebrovascular accident (6 years). This subject had also experienced a non-serious non-severe infusion reaction on 16 Nov 2006 (Dose 5), while participating in double-blind study C0406. The subject received one dose of open-label study drug (8 mg pegloticase every 4 weeks) on 20 Aug 2007 before this event (Dose 1).

On , the subject was hospitalized with left thoracic chest pain of mild intensity. The subject reported having chest pain twinges for some time prior to his hospitalization and on (b) (6), experienced pain lasting longer than 5 seconds. He was admitted to the hospital on (b) (6) to rule out myocardial infarction. Physical examination revealed clear lungs, and regular heart rate and rhythm with 'distant sounds'. Vital signs revealed blood pressure (BP) 134/75 mmHg, heart rate (HR) 72 beats per minute (bpm), respiratory rate (RR) 16 breaths per minute (bpm), and temperature 97.3°F. The subject's troponin level was 0.020 and ejection fraction was 49 (unknown date and time). Other laboratory results revealed normal complete blood count, normal basic metabolic panel, magnesium 2.1, total creatine kinase (CK) 95, glucose 115, potassium 3.2, CO_2 29, blood urea nitrogen 24, creatinine 1.5, International Normalization Ratio 0.9, and partial thromboplastin time 29.6 (normal ranges [NR] not given).

Serial creatine kinases were within normal limits. Three serial electrocardiograms (ECG) revealed: normal results (first ECG); some questionable changes, where anterior infarct could not be ruled out (second ECG); and normal results on the repeat ECG (third ECG). The subject's screening ECG was normal.

The subject was treated with Imdur (isosorbide mononitrate) 30 mg once daily by mouth, and nitroglycerin sublingually as needed for chest discomfort.

On (b) (6) laboratory results were CK 106 IU/L (NR 38-174 IU/L), CK-MB 1.4 ng/mL (NR 0.5-6.3 ng/mL), CK-MB index 1.3% (NR 0.0-0.0%), potassium 3.6 (NR 3.5-5.1), and troponin I 0.010 ng/mL (NR 0.000-0.040 ng/mL). The subject's BP was 123/70 mmHg and no findings were reported on physical examination. He recovered and was discharged from the hospital on (b) (6) with instructions to follow-up with the cardiologist. A stress echocardiogram performed on (b) (6) was negative (5 METS) and chest X-ray (date not given) was normal.

The study drug regimen was unchanged and the subject continued in the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), Lasix (furosemide), AcipHex (rabeprazole sodium), Plavix (clopidogrel), Norvasc (amlodipine), Toprol XL (metoprolol succinate), Crestor (rosuvastatin), ASA, clonidine, tramadol, Tylenol (paracetamol), Mucinex (Guaifenesin), Seretide, albuterol (salbutamol), and senna (senna alexandrina).

The event of left thoracic chest pain resulted in the subject's hospitalization and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that the event was unlikely related to the study drug.

His medical history also included increased tendency to bruise (ongoing 6 years), chronic bronchitis (12 years), chronic obstructive pulmonary disease (ongoing 12 years), emphysema (ongoing 12 years), denture wearer (ongoing 10 years), gastroesophageal reflux disease (ongoing 6 years), hard of hearing and hearing aid user (ongoing 4 years), left elbow bursitis (1 month), left elbow bursa infection (ongoing1 month), left rib area pain (ongoing 7 months), leg cramps (ongoing 5 years), occasional constipation (ongoing 1 year), osteoarthritis (ongoing 10 years), arthralgia (ongoing 10 years), fall (7 months), drug hypersensitivity to penicillin (ongoing 70 years), kidney failure (ongoing 2 months), rib fracture (7 months), right side endarterectomy (6 years), and ruptured colon-diverticulum (12 years).

002-003: Lacunar Stroke

Subject 002003: Severe Upper Respiratory Infection, Moderate Lacunar Stroke
Randomized Treatment: 12mg every 4 weeks, PEG-uricase

Serious Adverse Event: (1) Severe upper respiratory infection
(2) Moderate right-sided lacunar stroke
Days between onset and last infusion: (1) 26 days after the first infusion
(2) 27 days after the second infusion
Investigator-assessed relationship: Unrelated (both events)
Action taken regarding study medication: Dose not changed (both events)

Subject Narrative: This 77 year-old Black female had an 8-year history of gout, which included 5 acute flares over the 12 months prior to study enrollment and 1 hospitalization due to gout. The subject's refractory category for enrollment to the study was "inadequate response and intolerance to conventional therapy." At screening, this subject had tophi at the right and left elbows. The subject had no history of uric acid kidney stones and was not taking uric acid lowering agents at the time of study entry. Resolved medical histories included: pulmonary embolus and deep vein thrombosis. Ongoing conditions at the time of study entry included: chronic obstructive airway disease, gastro-esophageal reflux disease, chronic renal insufficiency, non-insulin-dependent diabetes mellitus, osteoarthritis, depression, coronary artery disease, renal cyst, renal mass, hypertension, hyperlipidemia. Drug allergies included codeine and allopurinol.
The subject received the first infusion on 17 May 2006. On 04 June 2004, the subject showed signs of a mild upper respiratory tract infection and was started on levofloxacin. Study No. C0403 Page 128 of 1494

002-003: Lacunar Stroke

Worsening of symptoms resulted in hospitalization for severe upper respiratory tract infection on (b) (6) Concomitant medications at the time of this event included salbutamol, clonidine, anticholinergics, warfarin, isosorbide mononitrate, lansoprazole, pravastatin sodium, lisnopril, furosemide, diltiazem, and medication for diabetes (exact medication was not recorded). This event resolved on 25 June 2004 and the subject continued on study.

The second infusion was administered on 28 June 2004. On (b) (6) days after the second infusion the subject was hospitalized for left upper extremity weakness. An MRI of the brain revealed evidence of chronic small vessel ischemic disease and a CT revealed an old cerebellar infarct. The subject's weakness improved over the course of the hospitalization and was diagnosed as a moderate case of suspected lacunar infarct. The subject was discharged in stable condition on (b) (6) at which time the event was considered resolved. The subject continued on study and received the third and final infusion on 28 July 2004. The follow up visit for this subject was on 21 September 2004.

PEG-uricase concentration at the last visit prior to the first hospitalization (ie, Day (b) (6) (b) was 3.558µg/mL; and at the last visit prior to the second hospitalization (ie, Day (b) (6) (b) (6) the PEG-uricase concentration was 2.020µg/mL. PUA concentrations remained well below the 6mg/dL level throughout the study period with below quantifiable limits at all time points starting 4 hours after the first infusion. Urine uric acid concentrations remained below quantifiable limits during the study period.

All data from this subject were included in the ITT and completer efficacy analyses and in the safety analyses. In terms of efficacy outcomes, the subject was classified as a treatment responder (the percentage time non-hyperuricemic was 99.98%), mean PUA concentration was 0.16mg/dL, PUA reduction from baseline was 6.6mg/dL (97.60%), and time to PUA normalization was 14hrs.

Subject No.: C0405 / 101-005	
Manufacturer Report No.: 06US000039	
Double Blind Study Drug:	Placebo
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Syncope [Syncope]
Investigator Causality Assignment:	Unlikely
Outcome:	Resolved

Subject 101-005 was a 67 year-old African-American male who experienced syncope, which was severe in intensity. The subject had no concurrent adverse events. This subject was initially diagnosed with gout in 1977. His relevant medical history included peripheral neuropathy (ongoing 3 years 6 months), hypertension (HTN) (ongoing 30 years), diabetes mellitus (ongoing unknown duration), dyslipidemia (ongoing unknown duration), and coronary artery disease (CAD) (ongoing unknown duration) with stent placement (2 years ago). The subject received his first dose of study drug on 10 Oct 2006 and 2 additional dose administrations prior to this event. The subject received his most recent study drug infusion on 07 Nov 2006 (Dose 3), (b) days before the onset of the event.

On (b) (6) the subject lost consciousness for approximately 1 minute, unaccompanied by other symptoms, and was taken to the emergency room (ER) following a second syncopal episode. In the ER, he complained of mild localized retrosternal chest pain, which resolved spontaneously. He had a fever (102.1°F), became hypotensive (blood pressure [BP] 50's /40's, and had low oxygen saturation (80's). He responded well to fluids and his BP stabilized (100/70 mmHg) with O_2 saturation of approximately 95% (on room air), and he was admitted to the hospital with a preliminary diagnosis of hypotension, fever, and stiff swollen bilateral knee and right elbow. The subject was found to have a "troponin leak," which was described as heart muscle damage not caused by an acute coronary syndrome but thought to be due to his past medical history of CAD. A cardiology consultation was ordered but the results of the consultation were unavailable. Electrocardiogram results showed no change and the subject's troponin stabilized. An echocardiogram revealed normal systolic function, a small thin hypokinetic segment in the basal inferior wall consistent with a small old infarction, and grade 1 diastolic dysfunction.

During the subject's hospitalization, he developed severe left knee pain and swelling, and right elbow pain and swelling, which was exquisitely tender with some skin breakdown and drainage of white chalky material. A rheumatologist was consulted (results unavailable). The subject was treated with prednisone 30 mg and corticosteroid injection intra-articularly, together with the removal of 50 mL synovial fluid, which gave the subject some relief. Of note, when the subject started the study, he was taking prednisone 10 mg once daily (qd). At some point during the study, the subject's prednisone was increased to 20 mg qd (date unknown), which he was taking at the time of his syncopal episode. He recovered and was discharged from the hospital on (b) (6).

Study drug was unchanged and the subject continued in the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (prednisone), pantoprazole, hydrochlorothiazide, Zocor (simvastatin), Toprol XL (metoprolol), nifedipine, clopidogrel, aspirin (ASA), fluticasone, Novolin 70/30 (insulin), Augmentin (amoxicillin/clavulanate), Tylenol No.3 (acetaminophen/codeine), amoxicillin, acetaminophen, enalapril, and gabapentin.

The event of syncope resulted in the subject's hospitalization and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that this event was unlikely related to the study drug.

His medical history also included gastroesophageal reflux disease (ongoing unknown duration), and drug hypersensitivity to colchicine with a reaction of neuropathy (ongoing unknown duration), hyperkalemia (unknown duration), hypercholesterolemia (unknown duration), post-herpetic neuralgia (unknown duration), hoarseness (ongoing 6 months), and benign prostatic hyperplasia (ongoing 1 year), and left orchiectomy and epididymitis (1 year).

Subject No.: C0405 / 102-006	
Manufacturer Report No.: 06US000035	
Double Blind Study Drug:	8 mg PEG-uricase every 4 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Acute Dyspnea [Dyspnoea Exacerbated]; Worsening of Kidney Disease [Renal Failure]
Investigator Causality Assignment:	Possible (Dyspnea Exacerbated); Unlikely (Renal failure)
Outcome:	Death

Subject 102-006 was a 64 year-old American Indian/Alaskan Native male with end-stage cardiomyopathy who was hospitalized for shortness of breath that was severe in intensity, one day after receiving his second study drug infusion (which was a placebo infusion). Prior to this event, the subject was also experiencing concurrent adverse events of belching (27 Oct 2006, ongoing), constipation (20 Oct 2006, ongoing), increased dyspnea (27 Oct 2006, resolved 28 Oct 2006), acute bronchitis (28 Oct 2006, ongoing), angina (28 Oct 2006, resolved same day), respiratory alkalosis (28 Oct 2006, resolved 30 Oct 2006), ventricular tachycardia (29 Oct 2006, ongoing), hyponatremia (29 Oct 2006, ongoing), mitral regurgitation (30 Oct 2006, ongoing), pulmonary regurgitation (30 Oct 2006, ongoing), tricuspid regurgitation (30 Oct 2006, ongoing), and hyperglycemia (30 Oct 2006, ongoing). This subject was initially diagnosed with gout in 1997. Unknown to the Investigator at the time of randomization, this subject concealed a medical history that would have precluded his participation in the study. This history included end-stage cardiomyopathy with a profoundly low ejection fraction (10-15%; ongoing 1 year); he had a 10-year history of cardiomyopathy. His other known relevant medical history included multiple coronary arterial stent insertions (ongoing 10 years, ongoing 7 years, and ongoing 1 year), atrial fibrillation (ongoing 1 year), cardiac pacemaker insertion (1 year), chronic kidney failure (ongoing 1 year), hypertension (ongoing 3 years), coronary artery disease (ongoing 10 years), congestive heart failure (CHF) (ongoing 10 years), and hypercholesterolemia (ongoing 10 years). The subject received his first dose of study drug on 13 Oct 2006 and his most recent study drug infusion on 27 Oct 2006 (Dose 2), 1 day before the event.

On , the subject was hospitalized for severe shortness of breath. A directed physical examination the previous day (during Dose 2) revealed no pre- or post-infusion abnormal findings. At the time of hospitalization, the subject reported having had shortness of breath for the previous 5 days, which became severe by the morning of (b) (6). He was transported to the emergency room where multiple findings were observed including; pedal edema, non-productive cough, chills, constipation, decreased urinary output, chest pressure, nausea, retching, and lightheadedness. On examination, his vital signs were blood pressure (BP) 110/70 mmHg, heart rate (HR) 86 beats per minute (bpm), respiratory rate (RR) 24 breaths per minute (bpm), and temperature 97.2°F. Arterial blood gases revealed pH 7.55, PaO_2 88 mmHg, and $PaCO_2$ 16.8. Laboratory results revealed white blood cells 16,000, hemoglobin 14.8, hematocrit 43, platelets 285,000, sodium 132, potassium 3.7, chloride 89, glucose 156, blood urea nitrogen 82, creatinine 2.6, albumin 4, calcium 43.6, B-type natriuretic peptide 1,850, creatine phosphokinase (CPK) 73, CK-MB 5.1, and troponin < 0.05. A lung perfusion scan was negative for pulmonary embolus. Electrocardiogram (ECG) results showed sinus tachycardia with HR 122 bpm and incomplete left bundle branch block. A second ECG showed atrial fibrillation. The subject's baseline ECG (b) (6) also showed atrial fibrillation, together with indeterminate or old myocardial infarction, left axis deviation, and left ventricular hypertrophy. A chest X-ray on (b) (6) revealed no change in the positioning of his

pacemaker leads, and revealed cardiomegaly and bilateral pulmonary congestion, which were unchanged from the year previous.

The subject was admitted to hospital with a diagnosis of acute dyspnea secondary to CHF. He was administered Lasix (furosemide) intravenously and placed on oxygen therapy. His symptoms improved. The subject was also treated with Levaquin (levofloxacin) 250 mg daily. He recovered from the event of acute dyspnea the same day (b) (6).

During his period of hospitalization, the subject developed severe acute kidney failure (b) (6)) and was started on dialysis on (b) (6). He also had elevated liver enzymes (cause unknown). The subject decided that he did not want to continue with dialysis, in view of his terminal prognosis of the underlying cardiomyopathy. Dialysis was discontinued after 2 treatments. On (b) (6), the subject was discharged from the hospital and transferred to a hospice care unit with a diagnosis of acute renal failure, chronic kidney disease, end-stage cardiomyopathy, CHF, acute bronchitis, CAD, anemia, and history of gout and atrial fibrillation. The subject died on (b) (6) due to kidney failure.

Study drug was discontinued the same day, 28 Oct 2006. The subject elected to be transferred to a hospice care unit and died on (b) (6).

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), digoxin, Plavix (clopidogrel), Prevacid (lansoprazole), Lasix (furosemide), Coreg (carvedilol), Altace (ramipril), folic acid, Vitamin B12 (cyanocobalamin), potassium, Xanax (alprazolam), aspirin (acetylsalicylic acid), Levaquin (levofloxacin), Vitamin B complex (nicotinamide with pyridoxine hydrochloride, riboflavin, thiamine hydrochloride), glyceryl trinitrate, Propacet, metoprolol tartrate, Oxycocet, pantoprazole amiodarone, temazepam, and Viagra (sildenafil).

The event of acute dyspnea and kidney failure resulted in the subject's hospitalization and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that the event of acute dyspnea was possibly related to the study drug and that the kidney failure was unlikely related to the study drug.

His medical history also included presbyopia (ongoing 15 years), joint contractures (ongoing 5 years), hypokalemia (ongoing 5 years), Vitamin B12 deficiency (ongoing 5 years), abdominal discomfort (ongoing 5 years), anxiety (ongoing 3 years), drug hypersensitivity to penicillin (ongoing 30 years), urine output decreased (ongoing 2 months), neuropathy peripheral (ongoing 1 year), dyspnea (ongoing 10 years), insomnia (ongoing 6 months), leukocytosis (ongoing 6 months), hyperparathyroidism (ongoing 6 months), and joint crepitation (ongoing 1 month).

Subject No.: C0405 / 122-003	
Manufacturer Report No.: 06US000025	
Double Blind Study Drug:	8 mg PEG-uricase every 4 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Deep Vein Thrombosis [Deep Vein Thrombosis]
Investigator Causality Assignment:	Unlikely
Outcome:	Resolved

Subject 122-003 was a 73 year-old Caucasian male with a history of coronary artery disease (ongoing 21 years) who developed deep vein thrombosis (DVT). The subject also experienced concurrent adverse events of chills (Oct 2006, resolved), dizziness (unknown day Oct 2006, resolved), dyspnea (unknown day Oct 2006, resolved), epistaxis (unknown day Oct 2006, resolved), diaphoresis (unknown day Oct 2006, resolved), left ear skin lesion (unknown day Aug 2006, resolved 02 Mar 2007), and bronchitis (30 Aug 2006, resolved 14 Feb 2007). This subject was initially diagnosed with gout in 1975. His relevant medical history included paroxysmal atrial fibrillation (ongoing 1 month), hyperkalemia (ongoing 2 years), polycythemia vera (ongoing 11 years), hypertension (ongoing 21 years), and chronic kidney failure (ongoing 5 years). Previously, the subject reported a serious adverse event of acute myocardial infarction (MI) on (b) (6) (refer to Narrative 06US000010). The subject received his first dose of study drug on 03 Aug 2006 and 3 more scheduled doses prior to this event. The subject received his most recent study drug infusion on 28 Sep 2006 (Dose 4).

On (b) (6), the subject was admitted to the hospital due to DVT. Approximately 5 days prior to this event, the subject had begun complaining of increasing calf pain in his right leg. He had just restarted his Coumadin (warfarin sodium) therapy (29 Sep 2006), 30 days following stent placement for the treatment of a myocardial infarction on (b) (6). During a visit to his cardiologist on (b) (6), a venous Doppler study was performed and the subject was diagnosed with a DVT in the femoral vein system, extending from his right proximal femoral vein down to the trifurcation. The subject was admitted to the hospital on (b) (6) for heparin therapy at 1,000 units/hour intravenously. His International Normalized Ratio was 2.0. The subject recovered and was discharged from the hospital on (b) (6). At the time of discharge, the subject remained on Coumadin 5 mg by mouth every night.

Study drug was unchanged and the subject continued in the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), aspirin (ASA), atenolol, prednisone, Cozaar (losartan potassium), hydroxyurea (hydroxycarbamide), glucosamine, chondroitin sulfate, Kayexalate (sodium polystyrene sulfonate), Nexium (esomeprazole magnesium), Lasix (furosemide), Levaquin (levofloxacin), warfarin, atorvastatin, celery seed extract (apium graveolens seed extract), oxycodone, metoprolol, and Nitroglycerin (glyceryl trinitrate).

The event of DVT resulted in the subject's hospitalization and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that the event was unlikely related to the study drug.

The subject's medical history also included gastroesophageal reflux disease (ongoing 1 year), intervertebral disc degeneration (ongoing 11 years), and drug hypersensitivity to angiotensin-converting enzyme inhibitor (ongoing unknown duration).

Subject No.: C0405 / 122-003	
Manufacturer Report No.: 06US000010	
Double Blind Study Drug:	8 mg PEG-uricase every 4 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Acute Myocardial Infarction [Myocardial Infarction]
Investigator Causality Assignment:	Unlikely
Outcome:	Resolved

Subject 122-003 was a 73 year-old Caucasian male with a history of coronary artery disease (ongoing 21 years) who experienced an acute myocardial infarction (MI) that was severe in intensity. The subject also experienced concurrent adverse events of left ear skin lesion (Aug 2006, resolved 02 Mar 2007) and bronchitis (30 Aug 2006, resolved 14 Feb 2007). This subject was initially diagnosed with gout in 1975. His relevant medical history included paroxysmal atrial fibrillation (ongoing 1 month), hyperkalemia (ongoing 2 years), polycythemia vera (ongoing 11 years), hypertension (HTN) (ongoing 21 years), and chronic kidney disease (ongoing 5 years). The subject received his first dose of study drug on 03 Aug 2006 and one more scheduled dose prior to this event. The subject received his most recent study drug infusion on 17 Aug 2006 (Dose 2, placebo).

On (b) (6) at approximately 06:00, the subject experienced an acute MI (b) (6) days after receiving pegloticase). The subject reported acute chest tightness and left arm pain. He had elevated blood pressure and increased heart rate. He presented to the emergency room (ER) at approximately 09:00 by ambulance. Assessment in the ER revealed that the subject had experienced an acute ST elevation MI in leads II, III, aVF, and V5 through V6. A transthoracic echocardiogram performed on the same day (b) (6)), was noteworthy for left ventricular ejection fraction 35%, with hypocontractility in the lateral septal posterior walls and akinesis in the inferior wall. He had moderate left ventricular hypertrophy, mild mitral regurgitation, and mild tricuspid regurgitation. He was sent to the cardiac catheterization laboratory, where 2 bare metal stents were placed in the left circumflex artery due to 95% stenosis. Treatment included Vitamin K (phytonadione), ReoPro (abciximab), Normal Saline, Ecotrin (ASA), and acetylcysteine. The subject recovered in the cardiac care unit. His chemistry laboratory results on 01 Sep 2006 were noteworthy for creatinine 2.5 mg/dL, blood urea nitrogen 66 mg/dL, and potassium 5.4 mmol/L; his creatinine and calculated creatinine clearance at screening (27 Jul 2006) were 1.9 mg/dL (normal range [NR]: 0.6-1.4 mg/dL) and 54 mL/min (NR: 80.0-120.0 mL/min), respectively. Serial electrocardiograms showed resolution of his ST segment elevation, and nonspecific T abnormalities in the lateral leads, and atrial fibrillation. The subject recovered and was discharged from the hospital on (b) (6).

Study drug was unchanged and the subject continued in the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), aspirin (ASA), prednisone, Cozaar (losartan potassium), hydroxyurea (hydroxycarbamide), glucosamine, chondroitin sulfate, Kayexalate (sodium polystyrene sulfonate), Nexium (esomeprazole magnesium), warfarin, Lasix (furosemide), celery seed extract (apium graveolens seed extract), oxycodone, and metoprolol.

The event of acute MI resulted in the subject's hospitalization and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that the event was unlikely related to the study drug.

The subject's medical history also included gastroesophageal reflux disease (ongoing 1 year), intervertebral disc degeneration (ongoing 11 years), and drug hypersensitivity to angiotensin-converting enzyme inhibitor (ongoing unknown duration).

Subject No.: C0405 / 124-001	
Manufacturer Report No.: 07US000122	
Double Blind Study Drug:	8 mg PEG-uricase every 2 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Congestive Heart Failure [Cardiac Failure Congestive]
Investigator Causality Assignment:	Unlikely
Outcome:	Resolved

Subject 124-001 was a 76 year-old African American male with a history of hypertension (ongoing 26 years) who experienced signs and symptoms of cardiac failure congestive immediately before a scheduled study drug infusion, characterized by shortness of breath and coughing. This subject was initially diagnosed with gout in 1991. His other relevant medical history included intermittent hyperphosphatemia secondary to kidney failure (ongoing 6 months), secondary hyperparathyroidism secondary (ongoing 4 months), intermittent hyperkalemia secondary to kidney failure (ongoing 1 year 11 months), kidney failure (ongoing 2 years 1 month), cardiac arrhythmia (ongoing 10 years 1 month), renal papillary necrosis (ongoing 14 years 4 months), and peripheral edema peripheral (ongoing unknown duration). This subject had previously experienced a serious adverse event of steroid myopathy on (b) (6) (refer to Narrative 07US000121). He received his first dose of study drug on 18 Oct 2006 and 8 more scheduled doses prior to this event. The subject received his most recent study drug infusion on 14 Feb 2007 (Dose 9) and was scheduled for Dose 10 .

On (b) (6), the subject developed shortness of breath and coughing before his scheduled study drug infusion that day. He presented to the rheumatology clinic with complaints of coughing and shortness of breath (on exertion and while laying flat) for the past 24 hours, and was subsequently hospitalized. He denied any history of similar symptoms, coronary artery disease, congestive heart failure (CHF), or other pulmonary disease. He denied chest pain, lower extremity edema, sore throat, or runny nose. On admission, his vital signs were blood pressure 171/80 mmHg, respiratory rate 26 breaths per minute (bpm), O_2 saturation 97% (on 2L per nasal canula), heart rate 59 beats per minute (bpm), and temperature 36.9ºC. He had decreased breath sounds bilaterally and diffuse crackles on auscultation, which worsened. The subject was given an initial diagnosis of CHF, based on these physical examination results, and was treated with Lasix (furosemide) for diuresis. Following aggressive diuresis, his renal function worsened, revealing a blood urea nitrogen/creatinine ratio highly suggestive of pre-renal azotemia. His Lasix treatment was held and his renal function improved gradually.

A 2-dimensional echocardiogram performed on 02 Mar 2007 revealed an above average ejection fraction. A repeat echocardiogram on 07 Mar 2007 revealed normal left ventricular systolic function, without clear regional wall motion abnormalities. His shortness of breath and pulmonary edema were considered likely due to fluid overload and consequently, CHF was ruled out. No significant valvular abnormalities were identified. Pulmonary function tests showed moderate to severe restrictive pulmonary disease with evidence of obstruction.

The subject was maintained on bronchodilators (nebulizer albuterol, ipratropium, and Pulmicort (budesonide), which improved his symptoms. With ambulation, his O saturation was 88 to 92% (on room air) and 93 to 95% prior to exertion. He was discharged on (b) (6). The subject recovered, with a reported event end date of (b) (6).

Study drug was unchanged and the subject continued in the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), calcitriol, felodipine, aspirin, dexamethasone, quinine sulfate, Cosopt (dorzolamide hydrochloride, timolol maleate), travoprost, Tums (calcium carbonate), metoprolol tartrate, lansoprazole, furosemide, darbepoetin alfa, and ferrous sulfate.

The event of (signs and symptoms of) CHF (CHF was later ruled out) resulted in the subject's hospitalization and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that this event was unlikely related to the study medication.

His medical history also included anemia (3 months), bilateral carpal tunnel syndrome (ongoing 1 year), left eye glaucoma (ongoing 2 years), arm rash due to allopurinol drug allergy (3 months), muscle spasms (ongoing 15 years), osteoarthritis in hands (ongoing 15 years), hemorrhagic diverticulum (unknown duration), and congenital umbilical hernia (ongoing 76 years 2 months).

Subject No.: C0405 / 203-001	
Manufacturer Report No.: 07CA000212	
Double Blind Study Drug:	8 mg PEG-uricase every 2 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Death Attributed to Cardiac Arrest [Cardiac Arrest]
Investigator Causality Assignment:	Unlikely
Outcome:	Death

Subject 203-001 was a 61 year-old Caucasian male with a history of congestive heart failure (ongoing 6 years) and hypertension (ongoing 6 years) who died at home; the death was subsequently considered "cardiac arrest" after arriving at the emergency room 45 minutes later in asystole. The subject had also experienced a concurrent adverse event of worsening of non-insulin-dependent diabetes mellitus ((b) (6), resolution unknown). This subject was initially diagnosed with gout in 2002. His other relevant medical history included angina pectoris (ongoing 6 years) and diabetes mellitus non-insulin-dependent (ongoing 15 years). This subject had previously experienced a non-serious non-severe (mild) infusion-related reaction on 25 Apr 2007 during Dose 3 of study drug, and a serious adverse event of acute gout attack on (refer to Narrative 07CA000177). The subject received his first dose of study drug on 28 Mar 2007 and 5 more scheduled doses prior to this event; he did not receive Dose 6 on 06 Jun 2006 (study drug interrupted) because of hypotension. He received his most recent study drug infusion on 20 Jun 2007 (Dose 7). He had been scheduled to receive Dose 8 on 09 Jul 2007; however, he had experienced a reaction to hydrocortisone pretreatment and consequently, did not receive Dose 8.

On (b) (6), the subject unloaded a wood splitter with his wife and son, and had said he was feeling unwell. About 10 minutes later he was found slumped over, unresponsive. Cardiac pulmonary resuscitation was administered and the subject was transported to the emergency room, arriving 45 minutes later and was in asystole. He was treated with epinephrine and atropine but could not be resuscitated. He was pronounced dead on (b) (6) The attending physician at the resuscitation effort reported the cause of death as cardiac arrest. The subject's screening electrocardiogram had revealed 1st degree AV block (14 Feb 2007). The Investigator reported that his information about the subject indicated that subject's ejection fraction was 17% prior to entry into the study, but no documentation was available. Information from 17 May 2007 was also available at the site indicating an ejection fraction of 28%. An autopsy was not performed and no additional information was available.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), furosemide, spironolactone, metoprolol, Zestril (lisinopril), simvastatin, nitroglycerin (glyceryl trinitrate), Imdur (isosorbide mononitrate), Bricanyl Turbohaler (terbutaline sulfate), Pulmicort (budesonide), Glyburide (glibenclamide), trazodone, Celebrex (celecoxib), Tylenol with codeine #3 (codeine phosphate, paracetamol), and Avandia (rosiglitazone maleate) (13 May 2007 to 23 May 2007).

The event cardiac arrest was reported as serious, and lead to the subject's death. The Investigator and Clinical Research Physician at Savient felt that the event was unlikely related to the study drug.

His medical history also included drug hypersensitivity to allopurinol (ongoing 4 years) and to intravenous pyelogram (IVP) dye (ongoing 10 years), prostate examination abnormal (ongoing 10 years), occasional headaches (ongoing 20 years), angina pectoris (ongoing 6 years), insomnia (ongoing 5 years), and asthma (ongoing 24 years).

Subject No.: C0406 / 301-006	
Manufacturer Report No.: 06US000034	
Double Blind Study Drug:	8 mg PEG-uricase every 4 weeks
Classification of the Events:	Serious Adverse Events
Date of Events:	(b) (6)
Events:	Hyperkalemia [Hyperkalemia], Re-entry Tachycardia [Tachycardia]
Investigator Causality Assignment:	Unlikely
Outcome:	Resolved

Subject 301-006 was a 62 year-old African American female developed hyperkalemia and tachycardia. The subject had previously experienced serious adverse events of renal failure acute and hyperkalemia on 02 Oct 2006 (refer to Narrative 06US000021). This subject was initially diagnosed with gout in 2005. Her relevant medical history included hyperlipidemia (ongoing 16 years), chronic kidney failure (ongoing 1 year), hypertension (ongoing 16 years), and systemic lupus erythematosus (ongoing 18 years). The subject received her first dose of study drug on 31 Aug 2006 and 2 additional dose administrations prior to this event. The subject had received her most recent study drug infusion prior to these SAEs on 16 Oct 2006 (Dose 3).

On (b) (6), the subject developed hyperkalemia and re-entry tachycardia. She had been scheduled to receive study drug Dose 4 on this day, but was noted to be tachycardic (heart rate 150 beats per minute [bpm]). Results from two separate electrocardiograms revealed sinus tachycardia and atrial fibrillation, interpreted as re-entry tachycardia by the consulting cardiologist. A complete blood count and metabolic panel were processed immediately and revealed elevated potassium 6.0 mmol/L (normal range [NR] 3.6 - 5.2 mmol/L), blood urea nitrogen 71 mg/dL (NR 7 - 18 mg/dL), and creatinine 3.0 mg/dL (NR 0.6 - 1.3 mg/dL). She was admitted to the hospital the same day, and was treated with adenosine and atenolol for supraventricular tachycardia, which resolved. Thereafter, her atenolol was replaced with prescribed metoprolol succinate. The subject's fourth study drug infusion was postponed. The subject recovered from the event of tachycardia on (b) (6) and from the event of hyperkalemia on (b) (6) and was discharged from the hospital the same day.

Study drug was interrupted and the subject continued in the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (prednisone), adenosine, atenolol, Diflucan, warfarin, FolTx (folic acid plus vitamins B6, B12), furosemide, Benadryl, Protonix, pantoprazole, alendronate sodium, fluvastatin, nystatin, Toprol XL, lidocaine viscous, and multivitamins (plain).

The event of hyperkalemia and tachycardia resulted in the subject's hospitalization and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that the event was unlikely related to the study drug.

Her medical history also included osteoporosis (ongoing 1 year 4 months), Vitamin B6 and B12 deficiency (ongoing 1 year 3 months), deep vein thrombosis (ongoing 3 years 8 months), cardiac murmur (ongoing 30 years), lower extremity edema (ongoing 4 months), gastric ulcer (ongoing 3 years 11 months), gastroesophageal reflux disease (ongoing 4 years 1 month), sinus tachycardia (ongoing unknown duration), ventricular extrasystoles (ongoing unknown duration), periodontal disease (ongoing 4 years), bursitis

(ongoing 2 months), and drug hypersensitivity to allopurinol (ongoing 1 year 2 months), ampicillin (ongoing unknown duration), tetracycline (ongoing unknown duration), penicillin (ongoing unknown duration), and sulfa (ongoing unknown duration).

Subject No.: C0406 / 301-006	
Manufacturer Report No.: 06US000021	
Double Blind Study Drug:	8 mg PEG-uricase every 4 weeks
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Acute Renal Failure [Renal Failure Acute], Hyperkalemia [Hyperkalemia]
Investigator Causality Assignment:	Unlikely
Outcome:	Resolved

Subject 301-006 was a 62 year-old African American female with a history of chronic kidney failure (ongoing 1 year) who developed renal failure acute and hyperkalemia. The subject also experienced concurrent adverse events of candidiasis (20 Sep 2006; resolved 03 Nov 2006), pain (22 Sep 2006; resolved 06 Oct 2006), 3 events of blister (22 Sep 2006; resolved 16 Nov 2006), asthenia (22 Sep 2006; resolved 06 Dec 2006), decreased appetite (26 Sep 2006; resolved 28 Oct 2006), pharyngolaryngeal pain (26 Sep 2006; resolved 29 Oct 2006), blood creatinine increased (02 Oct 2006; resolved 06 Oct 2006), blood urea increased (02 Oct 2006; resolved 06 Oct 2006), dehydration (02 Oct 2006; resolved 06 Oct 2006), and anemia (04 Oct 2006; resolved 06 Oct 2006). The subject also experienced a concurrent gout flare (06 Sep 2006; resolved 11 Oct 2006). This subject was initially diagnosed with gout in 2005. Her other relevant medical history included hypertension (ongoing 16 years), hyperlipidemia (ongoing 16 years), and systemic lupus erythematosus (ongoing 18 years). The subject received her first dose of study drug on 31 Aug 2006 and 1 additional dose administration prior to these events. The subject received her most recent study drug infusion prior to these SAEs on 18 Sep 2006 (Dose 2).

On , the subject developed acute renal failure secondary to volume depletion, and hyperkalemia. From 07 Sep 2006 to 12 Sep 2006, and from 14 Sep 2006 to 19 Sep 2006, the subject was taking prednisone as prophylaxis for gout flare (12.5 mg daily as of 17 Aug 2006). The subject arrived at the site on 02 Oct 2006 for a follow-up visit related to a diagnosis of oral thrush made during her scheduled visit on 29 Sep 2006 for study drug Dose 3. She had taken nothing by mouth for the last 6 days (from 02 Oct 2006) due to an oral thrush infection.

A complete blood count and comprehensive metabolic panel revealed elevated potassium 6.4 mmol/L (normal range (NR) 3.5 - 5.2 mmol/L), blood urea nitrogen BUN 156 mg/dL (NR 7 – 18 mg/dL), creatinine 6.4 mg/dL (NR 0.6 - 1.3 mg/dL), and white blood cell (WBC) 14.0 $x10^3/\mu L$ (NR 4.2 - 10.0 $x10^3/\mu L$). Her red blood cell (RBC) was 4.10 (NR 4.2 - 5.4$x10^6$ mm^3, hemoglobin (Hb) 9.9 g/dL (NR 12.0 - 16.0 g/dL), and hematocrit (Hct) 31.0% (NR 37.0 - 47.0%). Results at screening (17 Aug 2006) showed potassium 5.1 mmol/L, BUN 55 mg/dL, creatinine 3.2 mg/dL, and WBC 10.7 $x10^3/\mu L$, and Hct 34.9%.

The event of hyperkalemia was treated with calcium gluconate 1 ampule IV and the subject was admitted to the hospital the same day, (b) (6). Upon hospitalization, her vital signs were blood pressure 69/45 mmHg, heart rate (HR) 121 beats per minute (bpm), respiratory rate 22 breaths per minute (bpm), temperature 99.3°F, and oxygen saturation 97% (on 2L). The subject was in no acute distress and physical examination revealed clear lungs, regular HR and rhythm, and a soft non-tender abdomen. She was also obese. She had no cyanosis, clubbing, or edema of the extremities. She had no focal defects. Laboratory values on (b) (6) revealed WBC 12.6 $x10^3/\mu L$, Hct 31%, platelet 493 $x10^9/L$, sodium 142 mmol/L, potassium 6.3 mEq/L, chloride 106 mmol/L, bicarbonate 20, BUN 143 mg/dL, creatinine 7.3 mg/dL and glucose 183 mg/dL.

She was admitted with a diagnosis of acute renal failure, chronic renal insufficiency with azotemia, macrocytic anemia, hypotension (BP 69/45 mmHg), anemia, thrush, and gout.

Her planned treatment included hydration with IV fluids, and Diflucan and nystatin for her thrush. For her anemia, treatment included transfusion (date unknown).

Her vital signs on (b) (6) were BP 111/46 mmHg and HR 111 bpm. Her BUN (107 mg/dL) and creatinine (4.6 mg/dL) levels had decreased (b) (6)). She continued to improve on (b) (6), with continued decrease in her BUN (54 mg/dL) and creatinine (2.8 mg/dL) levels; however, her Hct (22.9%) had dropped, for which she received a blood transfusion. The event of acute renal failure resolved on 06 Oct 2006. The subject was discharged with BUN 31 mg/dL, creatinine 2.6 mg/dL, INR 3.66, WBC 9.4 $x10^3/\mu L$, and Hct 30.6%.

Study drug was interrupted and the subject continued in the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (prednisone), calcium gluconate, nystatin, Protonix, warfarin, lisinopril, hydrochlorothiazide, fluvastatin, Aranesp, Diflucan, Foltx, multivitamins, Benadryl, lidocaine viscous, oxygen, and acetaminophen.

The event of acute renal failure and hyperkalemia resulted in the subject's hospitalization and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that these events were unlikely related to the study drug.

Her medical history also included osteoporosis (ongoing 1 year 4 months), sinus tachycardia (ongoing unknown duration), cardiac murmur (ongoing 30 years), lower extremity edema (ongoing 4 months), Vitamin B6 and B12 deficiency (ongoing 1 year 3 months), deep vein thrombosis (ongoing 3 years 8 months), gastric ulcer (ongoing 3 years 11 months), gastroesophageal reflux disease (ongoing 4 years 1 month), periodontal disease (ongoing 4 years), bursitis (ongoing 2 months), and drug hypersensitivity to allopurinol (ongoing 1 year 2 months), ampicillin (ongoing unknown duration), tetracycline (ongoing unknown duration), penicillin (ongoing unknown duration), and sulfa (ongoing unknown duration).

Subject No.: C0406 / 301-012	
Manufacturer Report No.: 06US000071	
Double Blind Study Drug:	8 mg PEG-uricase every 4 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Transient Ischemic Attack [Transient Ischaemic Attack]
Investigator Causality Assignment:	Unlikely
Outcome:	Resolved; Subject Chose to Withdraw Study Drug 35 days Previous

Subject 301-012 was a 78 year-old Caucasian female with a history of obesity (ongoing 4 years), hypertension (ongoing 11 years), and hyperlipidemia (ongoing unknown duration), who had a transient ischemic attack (TIA) 35 days after withdrawing from the study. This subject was initially diagnosed with gout in 2000. Her other relevant medical history included diabetes mellitus (ongoing 2 years) and chronic obstructive pulmonary disease (ongoing 6 years). The subject received her first dose of study drug on 26 Oct 2006. The subject received her most recent study drug infusion on 09 Nov 2006 (Dose 2). The subject withdrew consent from the study on the same day.

On (b) (6), the subject experienced a TIA. She awoke that day with difficulty expressing words, which resolved several minutes later. After consulting with the subject's primary care physician, her family took her to the emergency room, where she was admitted the same day for evaluation. A head computerized tomography suggested atrophy of the brain. A bilateral carotid ultrasound revealed an elevated peak systolic velocity within the carotid arteries, suggesting 50-69% stenosis and atherosclerotic plaque within the bilateral carotid bulbs. On , a magnetic resonance imaging and magnetic resonance angiography of the brain revealed moderate generalized atrophy and small vessel disease, with normal results overall. A demyelinating process was ruled out. No new medications were initiated while she was hospitalized. The subject recovered and was discharged on (b) (6).

Study drug had been discontinued prior to this event. The subject withdrew her consent from the study on 09 Nov 2006.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), Cartia XT (diltiazem), Protonix (pantoprazole), Avalide (hydrochlorothiazide, irbesartan), furosemide, spironolactone, multivitamins, Vitamin E (tocopherol), Vitamin B12 (cyanocobalamin), Boniva (ibandronate sodium), Prandin (repaglinide), Duragesic (fentanyl), Senokot (senna alexandrina), metoclopramide, Vitamin D (ergocalciferol), Synthroid (levothyroxine sodium), oxygen, Advair (fluticasone propionate, salmeterol xinafoate), and iron sulfate.

The event of TIA resulted in the subject's hospitalization and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that this event was unlikely related to the study drug.

Her medical history also included osteoarthritis (bilateral knees, ongoing 3 years 10 months; bilateral shoulders, 3 years 4 months), hypothyroidism (ongoing 1 year), visual acuity reduced (ongoing 2 years), drug hypersensitivity to codeine (ongoing unknown duration), allopurinol (ongoing 2 years 3 months), and tramadol (ongoing 2 years 10 months), lumbar spinal stenosis (ongoing 4 years), osteoporosis (ongoing 7 years), gastroesophageal reflux disease (ongoing 15 years), chronic lower back pain (ongoing 16 years),

spinal compression fracture (ongoing 16 years), iron deficiency anemia (ongoing 4 years), aortic calcification (ongoing 2 years 5 months), increased red blood cell sedimentation rate (ongoing 4 years 2 months), constipation (ongoing unknown duration), joint crepitation (ongoing 3 years 10 months), elevated liver function tests (ongoing 2 years 2 months), tachycardia (ongoing 4 years), osteonecrosis (ongoing 3 years 8 months), rotator cuff syndrome (left, ongoing 3 years 4 months; right, ongoing 3 years 10 months), sleep apnea syndrome (ongoing 2 years 8 months), intervertebral disc protrusion (ongoing 2 years 5 months), spinal osteoarthritis (ongoing 3 years 3 months), breast mass (ongoing 3 years 5 months), and vitamin D deficiency (ongoing 3 years 10 months).

Subject No.: C0406 / 311-001	
Manufacturer Report No.: 06US000006	
Double Blind Study Drug:	8 mg PEG-uricase every 4 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Angina Pectoris [Angina Pectoris]
Investigator Causality Assignment:	Unlikely
Outcome:	Resolved

Subject 311-001 was a 50 year-old Caucasian male with a history of coronary artery disease (CAD), who experienced angina pectoris of moderate intensity. This subject was initially diagnosed with gout in 1975. His relevant medical history included CAD (ongoing 5 years), hypertension (ongoing 5 years), hypercholesterolemia (ongoing 5 years and 9 months), and cardiac catheterization and stent insertion (x3, ongoing 6 years). The subject received his first dose of study drug on 27 Jul 2006 and his most recent study drug infusion on 10 Aug 2006 (Dose 2).

On (b) (6), the subject was hospitalized for angina. He had experienced episodes of chest pain the week preceding (b) (6), which grew progressively worse; he reported having had three episodes of increased chest pain within one 24-hour period. The subject was admitted to the hospital on (b) (6) for cardiac catheterization. Results of the procedure on (b) (6) revealed two small blocked arteries, which was unchanged from a prior visualization (date of previous procedure unspecified). The subject was treated with heparin intravenously (IV) (dose unspecified) during his evaluation.

The internal mammary artery to the mid left anterior descending (LAD) was widely patent. The left circumflex (LCX) had a 50% mid stenosis. The right coronary artery (RCA) had widely patent stents. The superficial vein graft (SVG) to the diagonal and the SVG to the obtuse marginal was widely patent with good flow. He had 60% stenosis in the posterolateral branch beyond the anastomosis of the graft to the vessel, and 90% stenosis in the small posterolateral branch, which was unchanged from prior examination. The subject had abnormal left ventricular systolic function (LVEF 50%), with inferoapical-anteroapical hypokinesis notes. His left ventricular diastolic function was also abnormal, with elevated resting left ventricular end-diastolic pressure (LVEDP). The subject recovered and was discharged in stable condition on (b) (6).

Study drug was unchanged and the subject continued in the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (prednisone), Norvasc (amlodipine), Accupril (quinapril hydrochloride), Zocor (simvastatin), Lopressor (metoprolol tartrate), glyceryl trinitrate, Oxycocet, clopidogrel, lansoprazole, modafinil, and alprazolam.

The event of angina resulted in the subject's hospitalization and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that this event was unlikely related to the study drug.

His medical history also included fatigue (ongoing 3 months), depression (ongoing 4 years and 9 months), anxiety (ongoing 4 years and 9 months), sleep apnea syndrome (unknown duration), and uvuloplasty (1 month).

Subject No.: C0406 / 311-005	
Manufacturer Report No.: 07US000158	
Double Blind Study Drug:	8 mg PEG-uricase every 2 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Arrhythmia [Arrhythmia]
Investigator Causality Assignment:	Unlikely
Outcome:	Resolved

Subject 311-005 was a 67 year-old Caucasian male with a cardiovascular history who experienced arrhythmia of severe intensity. He also had a concurrent non-serious adverse event (AE) of hypokalemia (15 Apr 2007). This subject was initially diagnosed with gout in 1996. His relevant medical history included implantable defibrillator insertion (3 years 3 months), atrial fibrillation (ongoing 5 years 10 months), cardiac arrhythmia (ongoing 5 years 9 months), chronic kidney failure (ongoing 6 years 6 months), mitral valve prolapse (ongoing 7 years 8 months), cardiomegaly (ongoing 17 years), hypertension (ongoing 17 years), and liver sclerosis (ongoing 4 years 8 months). While on the study, the subject experienced a serious adverse event of peripheral edema on (b) (6) (refer to Narrative 07US000137) and of pneumonia on (b) (6) (refer to Narrative 07US000170). The subject received his first dose of study drug on 16 Jan 2007, and 6 more scheduled doses prior to this event. The subject received his most recent study drug infusion prior to this event on 12 Apr 2007 (Dose 7).

On , the subject was admitted to the hospital for arrhythmia of severe intensity. Earlier the same day, the subject sustained an automatic implantable cardioverter defibrillator shock followed by syncope and was taken to the emergency room (ER). His potassium level was 3.4 mg/dL (normal range [NR] of the hospital laboratory not known) on admission, which was after the subject took potassium 40 mEq (prior to the defibrillator shock). Information from the defibrillator revealed that the subject had experienced one episode of ventricular tachycardia. Two attempts of tachycardia pacing were initiated, followed by shocks. The subject was treated with potassium 40 mEq twice daily (bid), hydralazine 10 mg bid for borderline hypotension, and Imdur (isosorbide) 30 mg every day (qd) (reason unspecified).

During his hospitalization, the subject had no shortness of breath at rest, chest pain, paroxysmal or nocturnal dyspnea, or orthopnea. He was in sinus rhythm with a controlled ventricular rate between 80-90 and had a ventricular paced rhythm. The subject had hypokalemia, which was considered to be due to diuretics (reported as non-serious AE of moderate intensity, unlikely related). He recovered and was discharged from the hospital on (b) (6).

Study drug was unchanged and the subject continued in the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), Pepcid AC (famotidine), potassium chloride, Centrum (vitamins), Vicodin (hydrocodone bitartrate, acetaminophen), Zaroxolyn (metolazone), Toprol XL (metoprolol succinate extended release), hydralazine, bumetanide, levothyroxine, Coumadin (warfarin sodium), dextromethorphan hydrobromide, Inspra (eplerenone), and Digitek (digoxin).

The event of arrhythmia resulted in the subject's hospitalization and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that this event was unlikely related to the study drug.

His medical history also included hypothyroidism (ongoing 7 years 6 months), umbilical hernia (ongoing 5 years 6 months), onychomycosis (ongoing 39 years) peptic ulcer (5 years 6 months), and cholecystitis (3 years 5 months).

Subject No.: C0406 / 311-005	
Manufacturer Report No.: 07US000137	
Double Blind Study Drug:	8 mg PEG-uricase every 2 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Lower Extremity Edema [Oedema Peripheral]
Investigator Causality Assignment:	Unlikely
Outcome:	Resolved

Subject 311-005 was a 67 year-old Caucasian male with a cardiovascular history who developed lower extremity edema that was mild in severity. He also had concurrent non-serious adverse events (AEs) of sinus infection (27 Feb 2007, resolved 04 Mar 2007), right elbow swelling (13 Mar 2007, resolved 21 Mar 2007), a fall (14 Mar 2007), avulsion of left fourth fingernail (14 Mar 2007), and abrasion of the left side of forehead (14 Mar 2007, resolved 21 Mar 2007). This subject was initially diagnosed with gout in 1996. His relevant medical history included liver sclerosis (ongoing 4 years 8 months), implantable defibrillator insertion (3 years 3 months), atrial fibrillation (ongoing 5 years 10 months), cardiac arrhythmia (ongoing 5 years 9 months), chronic kidney failure (ongoing 6 years 6 months), mitral valve prolapse (ongoing 7 years 8 months), cardiomegaly (ongoing 17 years), and hypertension (ongoing 17 years). While on the study, the subject experienced a serious adverse event of cardiac arrhythmia on (b) (6) (refer to Narrative 07US000158) and of pneumonia on (b) (6) (refer to Narrative 07US000170). The subject received his first dose of study drug on 16 Jan 2007, and 3 more scheduled doses prior to this event. The subject received his most recent study drug infusion on 28 Feb 2007 (Dose 4).

On , the subject arrived in the emergency room (ER) with significant increased lower extremity edema of mild intensity and was admitted to the hospital with a diagnosis of acute congestive heart failure, fluid overload, and chronic kidney disease. His symptoms began 01 Mar 2007 with increasing lower extremity edema. Vital signs upon admission were blood pressure (BP) 80/59 mmHg, heart rate (HR) 83 beats per minute (bpm), respiratory rate (RR) 18 breaths per minute (bpm) and O_2 saturation 95% (on room air). The subject's vital signs on 13 Mar 2007 (pre-Dose 5) were BP 90/62 mmHg, HR 89 bpm, RR 20 bpm, and temperature 36.9 C; and on 27 Mar 2007 (pre-Dose 6) were BP 86/53 mmHg, HR 88 bpm, RR 18 bpm, and temperature 37.1°C. Physical examination revealed no acute distress, jugular venous distention to the angle of the mandible, bilateral rales in the bases of the lungs; heart with normal S1, S2, regular heart rate and rhythm, and a 3/6 holosystolic murmur at the lower sternal border. Additionally, the subject's abdomen was soft, nontender, and nondistended; and he had no hepatosplenomegaly and had 2 to 3+ bilateral lower extremity edema to the knees. Laboratory test results revealed negative results for the first set of cardiac enzymes, digoxin level within therapeutic window, blood urea nitrogen (BUN) 59, creatinine 2.0, and sodium 135. Chest X-ray revealed bilateral pulmonary vascular congestion and cephalization. The subject's electrocardiogram (ECG) results revealed ventricular pacing at 84 bpm; his screening ECG results revealed a ventricular paced rhythm (22 Dec 2006). Treatment included Bumex (bumetanide) drip 0.25 mg/hr, changed to 2 mg intravenously (IV) q12 (25 Mar 2007), and to Bumex 2 mg by mouth twice daily (bid). The subject was also treated with Zaroxolyn (metolazone) 5 mg every day (qd) (22 Mar 2007 to 27 Mar 2007).

During his hospitalization, the subject diuresed and showed rapid improvement in his lower extremity edema. He had no significant shortness of breath and his edema improved with only minimal trace 1+ pedal edema on (b) (6). The subject recovered, and was discharged from the hospital on (b) (6).

Study drug was unchanged and the subject continued in the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), Pepcid AC, amoxicillin, potassium chloride, Centrum (vitamins), Toprol XL, hydralazine, bumetanide, levothyroxine, Coumadin, Inspra, and Digitek (digoxin).

The event of lower extremity edema resulted in the subject's hospitalization and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that this event was unlikely related to the study drug.

His medical history also included hypothyroidism (ongoing 7 years 6 months), umbilical hernia (ongoing 5 years 6 months), onychomycosis (ongoing 39 years), peptic ulcer (5 years 6 months), and cholecystitis (3 years 5 months).

Subject No.: C0406 / 315-005	
Manufacturer Report No.: 07US000147	
Double Blind Study Drug:	8 mg PEG-uricase every 2 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Sudden Death Attributed to Cardiac Arrhythmia [Arrhythmia]
Investigator Causality Assignment:	Unlikely
Outcome:	Death

Subject 315-005 was a 69 year-old Caucasian male who experienced sudden death ascribed post mortem to cardiac arrhythmia, in the context of a long history of cardiac disease. This subject was initially diagnosed with gout in 2000. His medical history relevant to the event included bradycardia (ongoing 1 month), coronary artery disease (ongoing 16 years), coronary artery bypass graft (x3; 16 years), peripheral vascular disorder (ongoing 16 years), cardiac murmur (ongoing 1 month), hypercholesterolemia (ongoing 16 years), left carotid artery occlusion (ongoing 10 years), right carotid endarterectomy (3 years), bilateral lower extremity edema (ongoing 16 years), diabetic neuropathy (ongoing 36 years), diabetes mellitus (ongoing 38 years), hypertension (ongoing 38 years), obesity (ongoing unknown duration), and hyperkalemia (ongoing unknown duration), chronic kidney failure (ongoing 8 years), and renal artery stent placement (4 years). The subject received his first dose of study drug on 29 Nov 2006 and 8 more scheduled doses prior to this event. The subject received his most recent study drug infusion on 27 Mar 2007 (Dose 9).

On 03 Apr 2007, the subject complained of weakness. The next day, (b) (6) he was taken to his primary care physician by his wife who noted that the subject had not felt well the past few days. The subject was weak, achy, and had no appetite; but no specific findings were noted by the physician. Muscle weakness due to Pravachol was considered. He denied vomiting or fever. His BP was 100/62 mmHg, and his cardiac examination was 'regular'. He presented with less edema than observed previously.

Blood drawn on (b) (6) revealed alanine aminotransferase 28 IU/L (normal range [NR] 0 – 55 IU/L), elevated aspartate aminotransferase 54 IU/L (NR 5 - 34 IU/L), blood urea nitrogen (BUN) 114 mg/dL (NR 8 – 26 mg/dL) and creatinine 4.1 mg/dL (NR 0.7 - 1.3 mg/dL). Results also revealed glomerular filtration rate estimated 15 mL/min, calcium 11.7 mg/dL (NR 8.8 - 10.0 mg/dL), total creatinine kinase 194 IU/L (NR 30 - 200 IU/L), bicarbonate 22 mEq/L (NR 23 - 31 mEq/L), glucose 231 mg/dL (NR 80 - 115 mg/dL), potassium 4.8 mmol/L (NR 3.5 - 5.1 mmol/L), sodium 138 mEq/L (NR 136 - 145 mEq/L), white blood cells 7.5 $x10^3/\mu L$ (NR 3.1 - 8.5 $x10^3/\mu L$), POLY 79% (NR 25 - 62%), lymphocytes 10% (NR 22 - 39%), monocytes 11 (NR 2 - 10), hemoglobin (Hb) 12.0 g/dL (NR 14.0 - 18.0 g/dL), hematocrit (Hct) 34% (NR 40 - 54%), platelets 166 $x10^3/\mu L$ (NR 140 - 440 $x10^3/\mu L$), and erythrocyte sedimentation rate 59 mm/hr (NR 0 - 20 mm/hr).

Laboratory results at screening (07 Nov 2006) revealed creatinine 3.0 mg/dL (NR 0.6 - 1.4 mg/dL), BUN 78 mg/mL (NR 9 – 24 mg/mL), potassium 5.4 mEq/L (NR 3.6 - 5.2 mEq/L), creatinine clearance 43 mL/min, Hb 11.9 g/dL (NR 13.2 – 17 g/dL), and Hct 35.1% (NR 40 - 54%). Laboratory results at Dose 7 (27 Feb 2007), revealed creatinine 3.2 mg/dL, BUN 70 mg/mL, potassium 5.3 mEq/L, creatinine clearance 40 mL/min, Hb 11.2 g/dL, and Hct 33.3%. There is no documentation from the patient's local physician as to whether or not the elevated potassium was noted or considered to be a risk.

The subject felt worse on (b) (6) and was driven to the hospital by his wife. The subject died on (b) (6) while on the way to the hospital. The cause of death was reported as cardiac arrhythmia (without electrocardiographic evidence).

Study drug was discontinued permanently on (b) (6). The subject died on (b) (6).

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), omeprazole, PhosLo, Nephro Caps (folic acid, vitamins), clonidine hydrochloride, Pravachol (pravastatin sodium) , Cardizem (diltiazem extended release) , furosemide, Micardis (telmisartan, magnesium oxide), metolazone, prednisone, citalopram, iron, aspirin, stool softener, Kayexalate (sodium polystyrene sulfonate), Humulin N (insulin injection, isophane), Humalog (insulin lispro), and Hectorol (doxercalciferol).

The event of cardiac arrhythmia resulted in the subject's death. The Investigator and Clinical Research Physician at Savient felt that this event was unlikely related to the study drug.

His medical history also included skin ulcer right foot (ongoing 2 months), depression (ongoing 2 years), bilateral cataract removal with lens implants (5 years), left foot second toe deformity and amputation (5 years), osteoarthritis (ongoing 6 years), gastroesophageal reflux disease (ongoing 6 years), blisters (ongoing 6 years), and constipation (ongoing 2 years).

APPENDIX 5: NARRATIVES FOR SUBJECTS WHO HAD SERIOUS OR SIGNIFICANT INFUSION REACTIONS

Appendix 5
Narratives for Subjects who had Serious or Significant Infusion Reactions

Study Subject No.	Date of Event	Event Description	Treatment Group	Outcome
Study C0405: Subject 101-004	(b) (6)	infusion-related reaction	Pegloticase 8 mg q 4 weeks RCT	Resolved; study drug discontinued
Study C0405: Subject 102-003	(b) (6)	infusion-related reaction	Pegloticase 8 mg q 2 weeks RCT	Resolved; study drug discontinued
Study C0405: Subject 103-004	(b) (6)	infusion-related reaction	Pegloticase 8mg q 4 weeks RCT	Resolved; study drug discontinued
Study C0405: Subject 105-001	(b) (6)	infusion-related reaction	Pegloticase 8 mg q 2 weeks RCT	Resolved; study drug discontinued
Study C0405: Subject 107-006	(b) (6)	infusion-related reaction	Pegloticase 8 mg q 4 weeks RCT	Resolved; study drug discontinued
Study C0405: Subject 113-001	(b) (6)	infusion-related reaction	Pegloticase 8 mg q 4 weeks RCT	Resolved
Study C0405: Subject 117-001	(b) (6)	infusion-related reaction	Pegloticase 8 mg q 4 weeks RCT	Resolved
Study C0405: Subject 117-002	(b) (6)	infusion-related reaction	Pegloticase 8 mg q 2 weeks RCT	Resolved; study drug discontinued
Study C0405: Subject 122-010		infusion-related reaction	Pegloticase 8 mg q 4 weeks RCT	Resolved; study drug discontinued
Study C0405: Subject 129-005	(b) (6)	infusion-related reaction	Pegloticase 8 mg q 4 weeks RCT	Resolved
Study C0405: Subject 129-001	(b) (6)	infusion-related reaction	Pegloticase 8 mg q 2 weeks RCT; Pegloticase 8 mg q 2 weeks OLE	Resolved
Study C0405: Subject 130-001	(b) (6)	infusion-related reaction	Pegloticase 8 mg q 4 weeks RCT	Resolved; study drug discontinued
Study C0405: Subject 133-005	(b) (6)	infusion-related reaction	Pegloticase 8 mg q 4 weeks RCT	Resolved; study drug discontinued
Study C0406: Subject 308-003	(b) (6)	infusion-related reaction	Pegloticase 8 mg q 2 weeks RCT	Resolved
Study C0406: Subject 311-001	(b) (6)	infusion-related reaction	Pegloticase 8 mg q 4 weeks RCT; Pegloticase 8 mg q 2 weeks OLE	Resolved; study drug discontinued
Study C0406: Subject 313-007	(b) (6)	infusion-related reaction	Pegloticase 8 mg q 2 weeks RCT	Resolved; study drug discontinued
Study C0406: Subject 319-004	(b) (6)	infusion-related reaction	Pegloticase 8 mg q 4 weeks RCT	Resolved; study drug discontinued
Study C0406: Subject 330-007	(b) (6)	infusion-related reaction	Pegloticase 8 mg q 4weeks RCT	Recovered; study drug discontinued

Appendix 5
Narratives for Subjects who had Serious or Significant Infusion Reactions

Study C0406: Subject 401-006	(b) (6)	infusion-related reaction	Pegloticase 8 mg q 4 weeks RCT	Resolved

Subject No.: C0405 / 101-004	
Manufacturer Report No.: 06US000044	
Double Blind Study Drug:	8 mg PEG-uricase every 4 weeks, intravenously
Classification of the Event:	Withdrawal Due to Adverse Event
Date of Event:	(b) (6)
Event:	Infusion-Related Reaction [Infusion-Related Reaction]
Investigator Causality Assignment:	Probable
Outcome:	Resolved; Study Drug Discontinued

Subject 101-004 was a 50 year-old Caucasian male who experienced an infusion-related reaction at the time of his fifth study drug infusion characterized by facial flushing and swelling of moderate intensity, resulting in the subject's withdrawal from the study. The subject also experienced concurrent adverse events of elevated blood pressure (BP) (24 Oct 2006, resolved 21 Nov 2006) and polyuria (14 Nov 2006, resolved 21 Nov 2006). This subject was initially diagnosed with gout in 1999. He had no known relevant medical history. The subject received his first dose of study drug on 26 Sep 2006 and 3 additional dose administrations prior to this event. He received his most recent study drug infusion on 21 Nov 2006 (Dose 5), the same day as the event.

On 21 Nov 2006, the subject experienced an infusion reaction characterized by facial flushing and swelling of moderate intensity. His vital signs at baseline were BP 140/96 mmHg, heart rate (HR) 97 bpm, respiratory rate (RR) 16 bpm, and temperature 37.4°C (11:50). The study drug infusion was started at 12:00, and at 12:50, the subject experienced facial erythema in the form of moderate facial flushing and diffuse facial redness, together with moderate swelling of his lip and tongue. His infusion was stopped at 12:55 and his vital signs at that time were BP 143/100 mmHg, HR 106 bpm, RR 16 bpm, and temperature 37.3°C. Physical examination revealed angioedema in his lips and tongue, and no cardiac/pulmonary signs or symptoms. Electrocardiogram (ECG) results the same day revealed sinus tachycardia; his screening ECG results were normal. The subject's tryptase level was 15.0 μg/L (normal range 1.9-13.5μg/L). He was treated with Benadryl (diphenhydramine hydrochloride) 50 mg and Decadron (dexamethasone) 2 mg intravenously (IV) at 12:55, followed by a second dose of Decadron 2 mg IV at 13:15. His vital signs at 13:30 were BP 130/87 mmHg, HR 88 bpm, RR 16 bpm, and temperature 37.2°C. Vital signs at 14:00 were BP 121/80 mmHg, HR 88 bpm, RR 16 bpm, and temperature 37.2°C. The subject recovered at 14:00 the same day, and prednisone taper was started the next day, 22 Nov 2006.

Study drug was permanently discontinued the same day and the subject was discontinued from the study on 09 Jan 2007.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), Vicodin ES (hydrocodone bitartrate, acetaminophen), and Procardia XL (nifedipine).

The event of infusion-related reaction characterized by facial flushing and swelling led to the subject's withdrawal from the study. The Investigator and the Clinical Research Physician at Savient felt that the event was probably related to the study drug.

His medical history also included hypertension (ongoing 7 years), diarrhea with daily colchicine (ongoing unknown duration), nausea with allopurinol > 300 mg once daily (ongoing unknown duration), decreased hearing (ongoing 3 years), pneumonia (x2; 1 year), hypercholesterolemia (1 year 6 months), renal colic (3 years), kidney infection (5 years), and vasectomy (unknown duration).

Subject No.: C0405 / 102-003	
Manufacturer Report No.: 06US000026	
Double Blind Study Drug:	8 mg PEG-uricase every 2 weeks, intravenously
Classification of the Events:	Serious Adverse Event
Date of Events:	(b) (6)
Events:	Infusion-Related Reaction [Infusion-Related Reaction]
Investigator Causality Assignment:	Probable
Outcome:	Resolved; Study Drug Discontinued

Subject 102-003 was a 23 year-old Caucasian male who experienced an infusion reaction at the time of his fourth study drug infusion, characterized by moderate tongue edema and dyspnea; resulting in the subject's withdrawal from the study. This subject was initially diagnosed with gout in 2001. He had no known relevant medical history. The subject received his first dose of study drug on 17 Aug 2006 and 3 additional dose administrations without adverse consequences. The subject received his most recent study drug infusion on 12 Oct 2006 (Dose 5), the same day as the event.

On (b) (6), the subject experienced an infusion reaction characterized by moderate lingual swelling and mild dyspnea. His vital signs at baseline were blood pressure (BP) 130/60 mmHg, heart rate (HR) 66 beats per minute (bpm), respiratory rate (RR) 14 breaths per minute (bpm), and temperature 97.0°F (13:57). The study drug infusion was started at 13:59, and at 14:12, the subject complained of mild nausea, which lasted 10 minutes. Vital signs at 14:15 were BP 132/62 mmHg, HR 76 bpm, RR 16 bpm, and temperature 97.1°F. At 14:25, the subject had moderate lingual swelling and mild dyspnea. No other directed physical examination findings were reported. An electrocardiogram was performed at this time, revealing sinus rhythm and abnormal precordial QRS contour, considered not clinically significant. Vital signs revealed BP 136/68 mmHg, HR 80 bpm, and RR 16 bpm. At 14:30, the study drug infusion was stopped and the subject was placed under observation. At 14:38, Benadryl 25 mg was administered intravenously. Vital signs were recorded every 15 minutes until the subject was discharged. A tryptase level revealed 6.0 µg/L (normal range: 1.9-13.5 µg/L). His dyspnea resolved at 14:50 and his lingual swelling resolved at 15:05. His vital signs at 15:00 were BP 134/70 mmHg, HR 68 bpm, RR 16 bpm, and temperature 98.0°F. The subject was discharged at 17:15 and was considered to be fully recovered.

Study drug was permanently discontinued the same day and the subject was discontinued from the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), and protocol-prescribed gout flare prophylaxis (colchicine).

The infusion reaction characterized by moderate tongue edema and dyspnea was reported as serious and resulted in the subject's withdrawal from the study. The Investigator and Clinical Research Physician at Savient felt that this event was probably related to the study drug.

His medical history also included joint crepitations (ongoing unknown duration), adenoidectomy (15 years), and tonsillectomy (16 years).

Subject No.: C0405 / 103-004	
Manufacturer Report No.: 06US000032	
Double Blind Study Drug:	8 mg PEG-uricase every 4 weeks, intravenously
Classification of the Event:	Withdrawal Due to Adverse Event
Date of Event:	(b) (6)
Event:	Infusion-Related Reaction [Infusion-Related Reaction]
Investigator Causality Assignment:	Probable
Outcome:	Resolved; Study Drug Discontinued

Subject 103-004 was a 39 year-old Caucasian male who experienced an infusion-related reaction following his first study drug infusion, characterized by moderate chest discomfort, wheezing, and muscle spasm; resulting in the subject's withdrawal from the study. This subject was initially diagnosed with gout in 1995. He had no known relevant medical history. The subject received his first dose of study drug on 26 Oct 2006 (Dose 1), the same day as the event.

On (b) (6), the subject experienced an infusion reaction characterized by moderate chest tightness, wheezing, and muscle spasm in his thoracic and lumbar spine region. His vital signs at baseline were blood pressure 130/88 mmHg, heart rate 54 beats per minute (bpm), respiratory rate 18 breaths per minute (bpm), and temperature 97.1°F (10:45). Study drug infusion was started at 10:50. Approximately 5 minutes after the study drug infusion began, the subject experienced lower back pain which quickly progressed to moderate-severe muscle spasm in his thoracic and lumbar spine region (10:55). He complained of chest pain, when deep breathing due to the back pain. The study infusion was stopped immediately (10:55) and his muscle spasms resolved. His tryptase level was 6.7 μg/L (normal range 1.9-13.5 μg/L) and an electrocardiogram (ECG) revealed T-wave inversion in Lead III, which the Investigator considered not significant. The subject's baseline ECG had revealed sinus bradycardia (rate unknown). Physical examination revealed wheezes on forced expiration and normal heart examination results. The infusion was restarted 35 minutes later (11:30) at a slowed rate of 62.5 mL/hr. At approximately 12:50, the subject complained of chest tightness and wheezing. On physical examination, the Investigator noted wheezing in the subject's right upper and left upper lobes. The infusion was stopped. A second ECG revealed a T-wave inversion in Lead III, which the Investigator considered questionably insignificant. A second tryptase level revealed 6.1 μg/L. The Investigator advised the subject to go to the hospital for evaluation; however, the subject did not present himself to the hospital. Upon discharge from the site, the subject experienced wheezing only with forced expiration. The subject recovered from the infusion reaction the following day, (b) (6).

Study drug was discontinued the same day and the subject was discontinued from the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (Indocin [indomethacin], Prilosec), Vicodin (acetaminophen/hydrocodone), and Legatrin (quinine sulfate).

The infusion-related reaction characterized by chest discomfort, wheezing, and muscle spasms resulted in the subject's withdrawal from the study. The Investigator and Clinical Research Physician at Savient felt that this infusion-related adverse event was probably related to study drug.

The subject's medical history also included colitis (ongoing 5 years), nephrolithiasis (ongoing 3 years), and hypoglycemia (ongoing 10 years).

Subject No.: C0405 / 105-001	
Manufacturer Report No.: 06US000041	
Double Blind Study Drug:	8 mg PEG-uricase every 2 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Infusion-Related Reaction [Infusion-Related Reaction]
Investigator Causality Assignment:	Probable
Outcome:	Resolved; Study Drug Discontinued

Subject 105-001 was a 66 year-old Caucasian male who experienced a serious infusion reaction at the time of his third dose of study drug, characterized by blood pressure (BP) decreased, hyperhidrosis, incontinence, and tremor; resulting in the subject's withdrawal from the study. His relevant medical history included hypertension (HTN; ongoing unknown duration). This subject was initially diagnosed with gout in 1986. His relevant medical history included a previous non-serious infusion reaction on 06 Nov 2006 (Dose 2) characterized by chills, HTN, and tachycardia of moderate intensity, that resolved the same day. The subject received his first dose of study drug on 24 Oct 2006 and 1 additional dose administration prior to this event. The subject received his most recent study drug infusion on (b) (6) (Dose 3), the same day as the event.

On (b) (6), the subject experienced an infusion reaction characterized by diaphoresis and hypotension. He was administered 20 mg prednisone orally as pre-infusion prophylaxis on 19 Nov 2006, the day preceding his third dose because of the earlier infusion reaction (Dose 2). The subject's third study drug infusion was started at 12:15 and was completed at 15:15. He experienced an infusion reaction 30 minutes after completion of the infusion (15:45). He was diaphoretic, hypotensive, and ashen-colored. He also reported feeling hot and confused. The subject denied shortness of breath and chest pain.

20 Nov 2006	**Vital Signs**			
	BP (mmHg)	**Heart Rate (beats/minute)**	**Respiratory Rate (breaths/minute)**	**Temperature (°F)**
Baseline	138/79	83	20	96.1
15:45	88/60	85	22	*
16:15	95/52	73	24	*
16:55	113/71	81	22	99.6

*Not reported
BP = blood pressure

The subject was placed in reverse Trendelenburg positioning and was administered Normal Saline 500 mL intravenously. He subsequently developed rigors. Electrocardiogram results revealed 100% paced rhythm (rate between 73 to 81). His tryptase level was 6.0 µg/L. His laboratory results (complete blood count, electrolytes, liver function tests, troponin, and creatine phosphokinase [CPK] MB fraction) were all within normal limits. His symptoms resolved and he recovered the same day (b) (6); however, the subject was hospitalized overnight for observation.

Laboratory results on (b) (6) revealed hemoglobin 13.1 g/dL (normal range [NR] 13.9- 18 g/dL), hematocrit 38.9 g/dL (NR 41-52 g/dL), red blood cell 4.35 M/cmm (NR 4.44-6.1 M/cmm, white blood cell 10.82 k/cmm (NR 4.6–10.8 k/cmm), blood urea nitrogen 23 mg/dL (NR 9-20 mg/dL), creatinine 1.3 mg/dL (NR 0.5–1.2 mg/dL),

potassium 3.8 mmol/L (NR 3.5-5.0 mmol/L), troponin 0.03 ng/dL (NR 0–10 ng/mL), and CPK 125 U/L (NR 5–180 U/L). The subject was considered to have recovered on (b) (6).

Study drug was discontinued the same day and the subject was discontinued from the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), enalapril, metoprolol, warfarin, levothyroxine, digoxin, lovastatin, and hydrochlorothiazide.

The infusion reaction characterized by BP decreased, hyperhidrosis, incontinence, and tremor was reported as serious. The Investigator and Clinical Research Physician at Savient felt that this event was probably related to the study drug.

His medical history also included cardiovascular disease (ongoing 7 years); cardiac murmur (ongoing 7 years); drug hypersensitivity allergy to allopurinol, diazepam, and diphenhydramine (ongoing unknown duration); hypothyroidism (ongoing 10 years); HTN (ongoing 1 year); coronary artery surgery (7 years ago); aortic valve replacement (7 years ago); dual chamber pacemaker user (ongoing 7 years); and hyperlipidemia (ongoing 7 years).

Subject No.: C0405 / 107-006	
Manufacturer Report No.: 07US000150	
Double Blind Study Drug:	8 mg PEG-uricase every 4 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Infusion-Related Reaction [Infusion-Related Reaction]
Investigator Causality Assignment:	Possible
Outcome:	Resolved; Study Drug Discontinued

Subject 107-006 was a 31 year-old Caucasian male who experienced a serious infusion-related reaction at the time of his seventh study drug infusion, characterized by bronchospasm and pallor; resulting in the subject's withdrawal from the study. The subject also experienced a concurrent adverse event of insomnia (March 2007; ongoing). This subject was initially diagnosed with gout in 1989. He had no known relevant medical history. The subject received his first dose of study drug on 17 Jan 2007 and 6 additional dose administrations prior to this event. The subject received his most recent study drug infusion on (b) (6) (Dose 7), the same day as the event.

On (b) (6), the subject experienced a serious infusion reaction characterized by an episode of flash pulmonary edema (bronchospasm and pallor) of moderate intensity. His vital signs at baseline were blood pressure (BP) 133/63 mmHg, heart rate (HR) 87 beats per minute (bpm), respiratory rate (RR) 18 breaths per minute (bpm), and temperature 98.2°F (09:50). His screening physical examination revealed normal heart and lung function; however, the subject was morbidly obese. The study drug infusion began at 10:00. At 10:20, the subject experienced shortness of breath of moderate intensity, was pale, had difficulty hearing, and became light-headed. The study drug was stopped immediately (10:20) and the subject was treated with 100 mg Solu-Medrol (methylprednisolone) intravenous (IV) push and Benadryl (diphenhydramine) 25 mg IV push. His oxygen saturation fell to 82% and he was placed on O_2 (5L). His electrocardiogram (ECG) results revealed sinus tachycardia (107 bpm), poor R wave progression, probable electrode misplacement or clockwise rotation, and a vertical electrical axis consistent with pulmonary disease, compared to his normal ECG results at his baseline visit. The subject's tryptase level was 6.3 µg/L (normal range 1.9-13.5 µg/L). His vital signs were BP 203/68 mmHg, HR 118 bpm, RR 22 bpm, and temperature 98.3°F (10:30). The subject was seen in the emergency room (ER) approximately 1 hour later (11:46). His vital signs upon admission to the ER were BP 138/75 mmHg, HR 116 bpm, RR 16 bpm, temperature 98°F, and O_2 saturation 98% (on room air). His breathing was non-labored. The subject was treated with Pepcid (famotidine) 20 mg orally, and prednisone. A posterior-anterior and left lateral chest x-ray revealed possible bilateral pleural effusions (12:45) and physical examination revealed normal heart sounds and breath sounds, non-tender abdomen, and no respiratory distress (13:38). The ER physician listed the final diagnosis as allergic reaction. According to the Investigator, the infusion reaction could have also been caused by saline and steroid administration. The subject recovered and was discharged the same day, (b) (6).

Study drug was discontinued the same day as the onset of the event and the subject was discontinued from the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (Naprosyn), lisinopril/hydrochlorothiazide, Nexium, Pepcid, Crestor, Prilosec, Prinzide, and salbutamol.

The serious infusion-related reaction characterized by flash pulmonary edema resulted in the subject's withdrawal from the study. The Investigator and Clinical Research Physician at Savient felt that the event was possibly related to the study drug. The Investigator felt the event could have also possibly been due to saline and steroids.

The subject's medical history also included chronic obstructive pulmonary disease (ongoing 5 months), depression (ongoing 6 months), obesity (ongoing 20 years), asthma (ongoing 31 years), hyperlipidemia (ongoing 3 years), hypertension (ongoing 5 years), and psoriasis (ongoing 5 years). The subject reported that he has smoked for 1 year.

Subject No.: C0405 / 113-001	
Manufacturer Report No.: 06US000054	
Double Blind Study Drug:	8 mg PEG-uricase every 4 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Infusion-Related Reaction [Infusion-Related Reaction]
Investigator Causality Assignment:	Possible
Outcome:	Resolved

Subject 113-001 was a 61 year-old American Indian or Alaskan Native male who experienced an infusion reaction at the time of his third study drug infusion, characterized by chest pain, nausea, and vomiting of moderate intensity, for which the infusion was stopped permanently. This subject also experienced an adverse event of insomnia (06 Dec 2006, resolved 07 Dec 2006). This subject was initially diagnosed with gout in 2005. His relevant medical history included atrial fibrillation (ongoing 1 year 7 months). The subject received his first dose of study drug on 07 Nov 2006 and 2 additional dose administrations prior to this event. The subject received his most recent study drug infusion on (b) (6) (Dose 3), the same day as the event.

On (b) (6), the subject experienced an infusion reaction characterized by diaphoresis and shortness of breath. At 10:15, approximately 30 minutes after the start of the study drug infusion, the subject complained of moderate to severe discomfort that progressed to nausea, vomiting, and chest pain/tightness. He also became diaphoretic and temporarily had shortness of breath. The subject's study drug infusion was stopped and he continued to have symptoms of chest tightness. His electrocardiogram results indicated atrial fibrillation, with rapid ventricular response and ventricular rate of 133. Consequently, he was moved to the emergency room where he received metoprolol, which lowered his heart rate to his stated baseline rate of 100-110 beats per minute. The subject recovered approximately 3 hours later at 13:15 the same day (b) (6) and was discharged without hospital admission.

Study drug was unchanged and the subject continued in the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), spironolactone, furosemide, atenolol, diltiazem ER, and warfarin.

The infusion reaction was assessed as medically significant by the Investigator. The Investigator and Clinical Research Physician at Savient felt that this event was possibly related to the study drug.

His medical history also included chronic kidney disease (ongoing 4 years), hypertension (ongoing 2 years 7 months), and lymphoedema (ongoing 1 year 7 months).

Subject No.: C0405 / 117-001	
Manufacturer Report No.: 06US000009	
Double Blind Study Drug:	8 mg PEG-uricase every 4 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Infusion-Related Reaction [Infusion-Related Reaction]
Investigator Causality Assignment:	Possible
Outcome:	Resolved

Subject 117-001 was a 60 year-old Latino male who experienced an infusion reaction at the time of his fifth study drug infusion, characterized by chest tightness, throat tightness, shortness of breath and electrocardiogram (ECG) changes resulting in discontinuation of the infusion and hospitalization. The subject also experienced concurrent adverse events of increased transaminases (28 Jun 2006, ongoing) and eye pruritus (30 Aug 2006, resolved 09 Oct 2006). This subject was initially diagnosed with gout in 1990. His relevant medical history included coronary artery disease with stent placement (ongoing 1 month), hypertension (ongoing 20 years), and hypercholesterolemia (ongoing unknown duration). The subject received his first dose of study drug on 05 Jul 2006 and 3 additional dose administrations prior to this event. The subject received his most recent study drug infusion on (b) (6) (Dose 5), the same day as the event.

On , the subject developed mild chest tightness approximately 1 hour and 15 minutes after the start of his fifth study drug infusion. His vital signs at baseline were blood pressure (BP) 148/92 mmHg, heart rate (HR) 62 beats per minute (bpm), respiratory rate (RR) 17 breaths per minute (bpm), and temperature 97.3°F. The subject's infusion was started at 9:40. Vital signs at 10:30 were BP 148/82 mmHg, HR 58 bpm, RR 18 breaths/minute, and temperature 96.9°F. The infusion was stopped at 10:55, at which time his vital signs were BP 178/110 mmHg, HR 64 bpm, RR 20 breaths/minute, and temperature 94.9°F. No other directed physical examination findings were reported. He was administered Benadryl (diphenhydramine hydrochloride) 50 mg intravenously and Normal Saline 115 mL. The subject reported having some mild yet slight throat tightness and shortness of breath. At 11:30, his BP was 162/98 mmHg, HR 64 bpm, RR 20 breaths/minute, temperature 96.8°F. At 12:00, BP was 144/86 mmHg, HR 64 bpm, RR 18 breaths/minute, and temperature 96.8°F.

The subject’s symptoms resolved at 11:00, 5 minutes after he was administered Benadryl.

An ECG was obtained, which revealed HR 68 bpm, normal sinus rhythm with anterolateral ST-T abnormalities consistent with acute ischemia, and T-wave inversion in leads I, aVL, V2, and V4-V6, which was considered significant when compared to his baseline results.

His baseline/screening ECG on 22 Jun 06 indicated that subject was in normal sinus rhythm (rate 82) with multiple premature complexes, ventricular and sub-ventricular. The ECG also showed right atrial enlargement, (consider?) left atrial enlargement and nonspecific lateral T wave abnormalities. A cardiologist was consulted, blood was drawn for tryptase, and the subject was given ASA 325 mg before he was transferred to the emergency room (ER) at 12:30.

Laboratory results were unrevealing.

While hospitalized, the subject was found to have an 80-85% right coronary artery lesion on angiography and underwent an emergency coronary stent placement. The subject was monitored in the intensive care unit for 24 hours. On (b) (6), the subject was considered stable and was cleared for discharge.

Study drug was discontinued at this visit (on (b) (6) and the subject continued in the study. The subject received his next dose of study drug on 12 Sep 2006.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), Voltaren (diclofenac), verapamil, Flexeril (cyclobenzaprine hydrochloride), unspecified thyroid preparations, Lipitor (atorvastatin calcium), and Protonix (pantoprazole).

The infusion reaction resulted in the subject's hospitalization and was reported as serious. The Investigator and Medical Monitor at Savient felt that the event was possibly related to the study drug.

The subject's medical history also included hypothyroidism (ongoing 12 months) and elevated liver enzymes/hepatitis (both ongoing 2 years).

Subject No.: C0405 / 117-002	
Manufacturer Report No.: 06US000005	
Double Blind Study Drug:	8 mg PEG-uricase every 2 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Infusion-Related Reaction [Infusion-Related Reaction]
Investigator Causality Assignment:	Probable
Outcome:	Resolved; Study Drug Discontinued

Subject 117-002 was a 39 year-old Latino male who experienced an infusion-related reaction at the time of his third study drug infusion, characterized by respiratory and gastrointestinal symptoms resulting in discontinuation of the infusion and study withdrawal. The subject also experienced concurrent adverse events of erectile dysfunction (2006, ongoing) and fatigue (08 Aug 2006, ongoing). This subject was initially diagnosed with gout in 1980 and had a 10-year history of gastritis. He had no other known relevant medical history. The subject received his first dose of study drug on 12 Jul 2006 and 2 additional dose administrations prior to this event. The subject received his most recent study drug infusion on (b) (6) (Dose 3), the same day as the event.

On (b) (6), the subject experienced an infusion-related reaction (severe) characterized by respiratory and gastrointestinal symptoms. At 11:30, approximately 12 minutes after his study drug infusion began, the subject developed mild to moderate throat tightness; mild chest tightness; mild to moderate shortness of breath; moderate labored breathing; and mild shaking, chills, dizziness, fatigue, diaphoresis, pallor, and gastrointestinal upset. No other directed physical examination findings were reported. The infusion was discontinued and the subject was administered Benadryl (diphenhydramine hydrochloride) 50 mg intravenously, Normal Saline, and oxygen. No urticaria, rash, or angioedema was observed. His electrocardiogram results were normal and his tryptase was 13.9 μg/L (normal range 1.9 μg/L–13.5 μg/L). The subject's vital signs on (b) (6) were within normal limits.

His oxygen treatment was removed at 12:30. The subject's infusion reaction stopped at 12:45, he recovered and was discharged 45 minutes later with oral prednisone 40 mg and Benadryl 50 mg.

Study drug was discontinued permanently on and the subject was discontinued from the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine, indomethacin, Nexium [esomeprazole magnesium]), and Oxycocet.

The event of infusion-related reaction was reported as medically significant by the Investigator. The Investigator and Clinical Research Physician at Savient felt that the event was probably related to the study drug.

The subject's medical history also included chronic kidney disease (ongoing unknown duration), renal colic (ongoing unknown duration), anemia (ongoing 4 months), gastritis (ongoing 10 years) and osteoporosis (ongoing unknown duration).

Subject No.: C0405 / 122-010	
Manufacturer Report No.: 06US000040	
Double Blind Study Drug:	8 mg PEG-uricase every 4 weeks, intravenously
Classification of the Event:	Withdrawal Due to Adverse Event
Date of Event:	(b) (6)
Event:	Infusion-Related Reaction [Infusion-Related Reaction]
Investigator Causality Assignment:	Probable
Outcome:	Resolved; Study Drug Discontinued

Subject 122-010 was a 74 year-old African American male who experienced a non-serious infusion-related reaction during his fifth dose of study drug, consisting of blood pressure increased, dyspnea, hypoxia, tachycardia, and urticaria, which resulted in a permanent stop to infusion. This subject was initially diagnosed with gout in 1974. He had no known relevant medical history. The subject received his first dose of study drug on 21 Sep 2006 and 4 more doses prior to this event. The subject received his fifth dose of study drug on (b) (6) (Dose 5), the same day as the event.

On (b) (6) the subject experienced a non-serious infusion reaction of moderate intensity. His vital signs at baseline were blood pressure (BP) 129/65 mmHg, heart rate (HR) 78 beats per minute (bpm), respiratory rate (RR) 24 breaths per minute (bpm), and temperature 36.6°C (08:30). His study drug infusion had begun at 09:00 and approximately 30 minutes later, the subject began experiencing shortness of breath. The infusion was stopped at 09:33. The subject was sitting up, appeared anxious and in moderate respiratory discomfort. He was diaphoretic and had an urticarial eruption around his face, neck, and trunk. A directed physical examination also revealed mild BP increased, moderate dyspnea, mild hypoxia, mild tachycardia, and mild urticaria around his face, chest, back, axilla, and abdomen. Upon examination, vital signs revealed elevated BP (144/60 mmHg) and HR (101 bpm) (09:33). Repeat vital signs were: BP 184/72 mmHg, HR 109 bpm (09:40); BP 113/63 mmHg, HR 89 bpm (09:50); and BP 123/62 mmHg, HR 94 bpm, RR 24 bpm, and temperature 36.2ºC (10:05).

At the time of the infusion reaction, lung examination revealed no wheezing or crackles and heart examination revealed tachycardia. The subject had no angioedema, urticaria, or edema. An echocardiogram (ECG) revealed no acute changes from baseline; baseline ECG results on (b) (6) showed ST changes compatible with ischemia and a T-wave abnormality. His tryptase level was 36.8 µg/L (normal range 1.9-13.5 µg/L). The subject was treated with diphenhydramine 50 mg intravenously and nebulized albuterol. His oxygen saturation was 87% on room air and O_2 2L/min was started. His pulse oximetry while receiving nebulized albuterol on oxygen was 96%-99%, and he was titrated off upon recovery in order to maintain O_2 saturation greater than 90%. The subject's shortness of breath, tachycardia, and elevated BP resolved over a period of 10-15 minutes and his other symptoms resolved within 2 hours from the time they had begun. His vital signs at the time revealed BP 133/75 mmHg, HR 74 bpm, RR 22 bpm, temperature 36.1ºC (11:40); BP 165/76 mmHg, HR 92 bpm, RR 20 bpm, and temperature 35.9ºC (13:50). The subject recovered the same day. His study drug infusion was permanently discontinued.

Study drug was permanently discontinued the same day and the subject was withdrawn from the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), Cardura (doxazosin), Lasix (furosemide), lisinopril, clonidine, hydralazine, potassium, Proscar (finasteride).

The infusion-related reaction consisting of shortness of breath resulted in the subject’s withdrawal from the study. The Investigator and Clinical Research Physician at Savient felt that the event was probably related to the study drug.

The subject's medical history also included benign prostatic hyperplasia (ongoing 1 year), hypokalemia (ongoing 8 years), sleep apnea syndrome (ongoing 8 months), chronic kidney failure (ongoing 10 years), hypertension (ongoing 40 years), dry eye (ongoing unknown duration), psoriasis (ongoing unknown duration), and herpes simplex (ongoing unknown duration).

Subject No.: C0405 / 129-005	
Manufacturer Report No.: 07US000119	
Double Blind Study Drug:	8 mg PEG-uricase every 4 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Infusion-Related Reaction [Infusion-Related Reaction]
Investigator Causality Assignment:	Possible
Outcome:	Resolved

Subject 129-005 was a 38 year-old Caucasian male with a history of hypertension (ongoing 2 years) who developed infusion-related elevated blood pressure (BP). He had no other relevant medical history. This subject was initially diagnosed with gout in 1985. He received his first dose of study drug on (b) (6), the same day as the event.

On (b) (6), the subject developed an infusion-related elevation in his BP. The subject presented to the site for his first infusion of study drug on (b) (6). His baseline vital signs were BP 193/122 mmHg, heart rate (HR) 63 beats per minute (bpm), respiratory rate (RR) 16 breaths per minute (bpm), and temperature 97.7°F (9:00). The subject reported that he had not taken his antihypertensive medications. He was sent home to take his medication, and returned to the site with BP 171/110 mmHg (9:30) and BP 166/100 mmHg (10:00). The subject reported that "great fluctuations" in his blood pressure were not uncommon. The Investigator examined the subject. The subject received pre-infusion medication, hydrocortisone 200 mg (10:20), and study drug infusion was started (10:25).

Ongoing measurements showed BP 171/110 mmHg (10:55), BP 165/122 mmHg (11:25), and BP 220/140 mmHg (11:55), when a decision was made to slow the infusion rate (rate unknown). The subject's BP increased to 228/120 mmHg (12:10). The study drug infusion was stopped. Blood was drawn, revealing tryptase level 4.4 μg/L (normal range [NR] 1.9 - 13.5 μg/L). An electrocardiogram revealed a strain pattern in the precordial leads, possibly due to the subject's hypertension. The subject's BP increased to 240/130 mmHg (12:25) and he took a second blood pressure pill. The subject complained of a slight headache. No additional physical examination findings were reported. His BP was 230/140 mmHg (12:50). Subsequent BP measurements were 242/130 mmHg (13:45) and 238/130 mmHg (14:40). He went to the emergency room that same evening (b) (6) and was admitted to the hospital. The subject reported that while in the hospital, his BP would come down to normal and then spike back up. The subject recovered and was discharged from the hospital on (b) (6).

Study drug was unchanged and the subject continued in the study. The subject received his next dose of study drug on 12 Mar 2007.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), MS Contin (morphine sulfate), Lortab (hydrocodone bitartrate, paracetamol), Tylenol (paracetamol), Tylenol Arthritis (paracetamol), clonidine, and Detrol (tolterodine).

The event of elevated BP resulted in the subject's hospitalization and was reported as serious. The Investigator and Clinical Research Physician at Savient felt that the event was possibly related to the study drug.

The subject's medical history also included hypertonic bladder (ongoing 2 years), insomnia (ongoing 2 years), numerous surgeries for gouty tophus and gouty tophus under the skin (4 years and ongoing unknown duration, respectively), bipolar disorder (ongoing unknown duration), and smoker (ongoing 3 years).

Subject No.: C0405 / 129-001	
Manufacturer Report No.: 07US000262	
Open Label Study Drug:	8 mg pegloticase every 2 weeks, intravenously
Double Blind Study Drug:	8 mg pegloticase every 2 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Infusion-Related Reaction [Infusion Related Reaction], Attributed to Solu-Medrol
Investigator Causality Assignment:	Unlikely
Outcome:	Resolved

Subject 129-001 was a 52 year-old Hispanic male who experienced a severe infusion reaction to Solu-Medrol characterized by flushing, facial redness, and profuse sweating. This subject was initially diagnosed with gout in 1985. He had no relevant medical history, nor did he experience any previous infusion reactions. He received his first dose of open-label study drug on 28 Mar 2007 and 8 additional dose administrations prior to this event. He received his most recent study drug infusion (8 mg pegloticase every 2 weeks) on 16 Jul 2007 (Dose 9).

On (b) (6), the subject experienced a severe infusion reaction thought to be due to the Solu-Medrol infusion and not a reaction to the study drug. His prescribed pretreatment medications included 60 mg fexofenadine (21:00 on 15 Jul 2007), 1000 mg acetaminophen (06:15 on 16 Jul 2007), and 40 mg IV Solu-Medrol (08:55 on 16 Jul 2007) (the reason for the use of Solu-Medrol was being queried at the time of this writing). His vital signs at baseline were blood pressure (BP) 126/72 mmHg, heart rate (HR) 74 beats per minute (bpm), respiratory rate (RR) 16 breaths per minute (bpm), and temperature 98.2°(F) (08:30). At 08:57, 2 minutes after the Solu-Medrol infusion was started, the subject experienced a reaction to Solu-Medrol; he experienced flushing, facial redness and profuse sweating. No rash or swelling was found during physical examination. Treatment included 20 mg prednisone (time unknown). The reaction to Solu-Medrol lasted 13 minutes and resolved at 10:00, without any recurrence. His repeat vital signs were BP 128/75 mmHg, HR 65 bpm, RR 16 bpm, and temperature 97.3°F (11:05). The study infusion was started at 10:05 at a rate of 20 ml/hr and was completed at 12:05.

The study drug regimen was unchanged and the subject continued in the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (naproxen, Prevacid [lansoprazole]), Inegy, and Vytorin (ezetimibe/simvastatin).

The event of infusion-related reaction was reported as serious. The Investigator and Clinical Research Physician at Savient felt that the event was unlikely related to the study drug.

His medical history also included hyperlipidemia (ongoing 10 years).

Subject No.: C0405 / 130-001	
Manufacturer Report No.: 07US000102	
Double Blind Study Drug:	8 mg PEG-uricase every 4 weeks, intravenously
Classification of the Event:	Severe Non-serious Infusion Reaction
Date of Event:	(b) (6)
Event:	Infusion-Related Reaction [Infusion-Related Reaction]
Investigator Causality Assignment:	Probable
Outcome:	Resolved; Study Drug Discontinued

Subject 130-001 was a 52 year-old Caucasian female who experienced a non-serious infusion-related reaction during her 5th dose of study drug, characterized by back pain and throat tightness, resulting in the discontinuation of the infusion and study withdrawal. The subject had no additional concurrent adverse events reported. This subject was initially diagnosed with gout in 1996. She had no known relevant medical history including no known drug allergies. The subject experienced a previous non-serious non-severe infusion reaction characterized by moderate dyspnea, nausea, and pain during Dose 3 (11 Jan 2007), which was treated with diphenhydramine and resolved the same day. The subject received her first dose of study drug on 14 Dec 2006 and 4 more doses prior to this event. The subject received her most recent study drug infusion on (b) (6) (Dose 5), the same day as the event.

On (b) (6), the subject experienced a non-serious infusion reaction. The subject had received prednisone 20 mg on (b) (6) (at 20:00) as pre-infusion prophylaxis because of a prior infusion reaction. Her baseline vital signs were blood pressure (BP) 118/82 mmHg, heart rate (HR) 72 beats per minute (bpm), respiratory rate (RR) 18 breaths per minute (bpm), and temperature 98.5ºF. The study drug infusion was started at 10:18, at a rate of 60 mL/hr. At 10:24, the subject developed back pain and throat tightness after receiving 5 mL of study drug. No additional physical examination findings were reported. The infusion was discontinued immediately and the subject was administered Benadryl (diphenhydramine) 50 mg. Her vital signs at 10:26 were BP 150/92 mmHg, HR 106 bpm, and RR 16 bpm, and her electrocardiogram showed non-specific intraventricular conduction delay. Her tryptase level was 18.5 µg/L (normal range [NR] 1.9-13.5 µg/L). The subject recovered 29 minutes after her symptoms had begun and she continued to be monitored for 1 hour post-infusion. Her vital signs at 11:05 were BP 108/80 mmHg, HR 76 bpm, RR 14 bpm, and temperature 99.1ºF, and she was discharged to home.

Study drug was discontinued the same day and the subject was discontinued from the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), Norvasc (amlodipine), Prometrium (progesterone), Premarin (estrogens conjugated), prednisone, furosemide, Protonix (pantoprazole), Cozaar (losartan potassium), metoprolol, levothyroxine, and Aleve (naproxen sodium).

The non-serious infusion-related reaction, consisting of back pain and throat tightness, resulted in the subject's withdrawal from the study. The Investigator and Clinical Research Physician at Savient felt that the event was probably related to the study drug.

The subject's medical history also included arteriosclerosis coronary artery (ongoing 2 years), hypothyroidism (ongoing 2 years), gastroesophageal reflux disease (ongoing 2 years), hypertension (ongoing 33 years), chronic kidney failure (ongoing 33 years), systemic lupus erythematosus (ongoing 39 years), Stevens-Johnson syndrome (unknown duration), myocardial infarction (unknown duration), coronary artery surgery (unknown duration), pericardial excision (unknown duration), myalgia (ongoing unknown duration), postmenopause (ongoing unknown duration), and myositis (ongoing unknown duration).

Subject No.: C0405 / 133-005	
Manufacturer Report No.: 07US000171	
Double Blind Study Drug:	8 mg PEG-uricase every 4 weeks, intravenously
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Infusion-Related Reaction [Infusion-Related Reaction]
Investigator Causality Assignment:	Probable
Outcome:	Resolved; Study Drug Discontinued

Subject 133-005 was a 34 year-old Caucasian male who experienced an infusion-related reaction at the time of his seventh study drug infusion, characterized by severe chest pain. The subject experienced no concurrent adverse events. This subject was initially diagnosed with gout in 2004. His relevant medical history included cardiomyopathy (ongoing 1 month), cardiac failure congestive (ongoing 1 month), and hypertension (ongoing 1 year 1 month). This subject had previously experienced serious adverse events of severe gout on 24 Feb 2007 (refer to Narrative 07US000117) and necrotizing fasciitis on 03 Apr 2007 (refer to Narrative 07US000149). The subject also experienced a non-serious non-severe infusion reaction characterized by mild erythema on 05 April 2007, following Dose 5 of study drug; the infusion was stopped and the event resolved the same day. The subject received his first dose of study drug on 08 Feb 2007 and 5 more scheduled doses prior to this event. The subject received Dose 7 of study drug on (b) ((b) the same day as the event.

On , the subject experienced chest pain, which was severe in intensity. His vital signs at baseline were blood pressure (BP) 146/78 mmHg, heart rate (HR) 80 beats per minute (bpm), respiratory rate (RR) 16 breaths per minute (bpm), and temperature 98.3°F (13:00). Approximately 30 minutes after the start of the infusion at 14:30, the subject had complaints of nausea and abdominal pain, describing his pain as “like someone pushing on my stomach.” He also had sudden chest pain with minimal shortness of breath, and an altered level of consciousness (he was unable to describe where he was or what day it was). His vital signs were BP 159/93 mmHg, HR 86 bpm, RR 16 bpm, and temperature 98.3°F (15:00). His study drug infusion rate was slowed to 75 mL/hr and his NS was increased. His vital signs were re-checked, revealing BP 179/105 mmHg and HR 91 bpm (15:09). His study drug infusion was stopped immediately. He was treated with nitroglycerin 0.4 mg sublingually for the chest pain. An electrocardiogram (ECG) was performed, revealing normal sinus rhythm (rate 88); screening ECG results revealed a T wave abnormality (25 Jan 2007). His chest pain and nausea continued and the subject was transferred to the emergency room where he remained oriented and answered questions appropriately. He described his chest pain as tightness and reported having abdominal pain. He was also found to be diaphoretic on physical examination. He was in no respiratory distress, had normal breath sounds without wheezing, rales or rhonchi, HR and rhythm were regular, heart sounds normal, strong peripheral pulses, and no peripheral edema or jugular vein distention. A neurological examination revealed orientation x 3, mood and affect were normal; neuro check was normal as tested, and no motor or sensory deficits. Electrocardiogram results revealed no ST depression, no inverted T waves, no PR depression, normal axis, and no ectopy. Repeat ECG findings revealed the same findings (2x). The subject’s vital signs were BP 136/78 mmHg, HR 90 bpm, RR 18 bpm, temperature 97.5°F, and oxygen saturation 98 (on a non-rebreather mask) (15:44). A head computed tomography scan revealed no acute disease and multiple ECGs confirmed the absence of any ST segment elevation, depression, or symmetrically inverted T-waves. His cardiac enzymes (serial troponin), complete blood count, and D-dimer were normal. His repeat vital signs were BP 127/66 mmHg, HR 80 bpm, RR 18 bpm, and oxygen saturation 96% (19:55). The subject's symptoms resolved and he was released the same day 07 May 2007. The subject recovered on 08 May 2007. Blood was drawn for tryptase level on 09 May 2007, revealing 2.1 μg/L (normal range 1.9-13.5 μg/L).}

Study drug was discontinued and the subject withdrew from the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (prednisone), Coreg (carvedilol), enalapril, glipizide, Lexapro (escitalopram oxalate), Prevacid (lansoprazole), torsemide, trazodone, oxycodone, OxyContin (oxycodone hydrochloride), and ferrous sulfate.

The event of chest pain was considered by the Investigator to be medically significant and was considered serious. The Investigator and Clinical Research Physician at Savient felt that this event was probably related to the study drug.

His medical history also included diabetes mellitus non-insulin-dependent (ongoing 1 year), osteoarthritis (ongoing 1 year), gastroesophageal reflux disease (ongoing 3 months), tension headache (ongoing 1 month), depression (ongoing 1 year), insomnia (ongoing 1 year), sleep apnea syndrome (ongoing 1 year 4 months), arthralgia (ongoing 1 year 1 month), abdominal hernia (ongoing 1 year 6 months), and drug hypersensitivity to hydrocodone (ongoing 2 years).

Subject No.: C0406 / 308-003	
Manufacturer Report No.: 07US000127	
Double Blind Study Drug:	8 mg PEG-uricase every 2 weeks, intravenously
Classification of the Event:	Withdrawal Due to Adverse Event
Date of Event:	(b) (6)
Event:	Infusion-Related Reaction [Infusion-Related Reaction]
Investigator Causality Assignment:	Probable
Outcome:	Resolved

Subject 308-003 was a 36 year-old Caucasian male who developed an infusion-related reaction at the time of his second dose administration, characterized by muscle spasms, resulting in the subject's withdrawal from the study. This subject was initially diagnosed with gout in 1997. His relevant medical history included drug hypersensitivity to Remicade (infliximab; anaphylactic reaction to Remicade [infliximab]) (ongoing 2 years). The subject received his first dose of study drug on 02 Mar 2007. The subject received his most recent study drug infusion on (b) (6) (Dose 2), at the time of the event.

On (b) (6), the subject experienced an infusion-related reaction characterized by muscle spasms. His baseline vital signs were blood pressure (BP) 137/93 mmHg, heart rate (HR) 84 beats per minute (bpm), respiratory rate (RR) 20 bpm, and temperature 37.1°C (11:59). The study drug infusion was started at 12:00, and at 12:12, the subject began rubbing his head. His face was flushed and clammy, and he complained of severe back and leg cramps. The study drug infusion was interrupted and restarted at a new rate. His vital signs were BP 163/67 mmHg, HR 72 bpm, RR 20 bpm, and temperature 37.1°C (12:15). He was treated with Solu-Cortef (hydrocortisone) 100 mg IVP and Lactated Ringer's solution 250 mL infusion (12:18). His ECG results and tryptase level (4.8 µg/L [normal range 1.9-13.5 µg/L]) were normal (12:45). The subject's symptoms resolved at 13:12, and the study drug infusion was restarted at 62 mL/hr at that time. The infusion rate was increased to 90 mL/hr at 13:45 and to 125 mL/hr at 14:05. His vital signs were BP 145/97 mmHg, HR 89 bpm, RR 16 bpm, and temperature 37.2°C (14:12).

At 14:22, the subject reported that his symptoms had returned. His infusion rate was decreased to 62 mL/hr, and he reported having no further muscle spasms. The infusion rate was increased to 90 mL/hr 8 minutes later (14:30). His cramping started again 5 minutes later (14:35), followed by nausea (14:50). His vital signs were BP 150/84 mmHg, HR 89 bpm, RR 20 bpm, and temperature 35.7°C (14:42). The study drug infusion was permanently discontinued and the subject recovered (15:00). His vital signs at 15:02 were BP 142/92 mmHg, HR 92 bpm, RR 20 bpm, and temperature 36.0°C, and he was discharged at 17:00.

Study drug was discontinued the same day and the subject was withdrawn from the study at his request.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), and phentermine.

The event of muscle spasms, an infusion-related reaction, was considered medically significant by the Investigator. The Investigator and Clinical Research Physician at Savient felt that this event was probably related to the study drug.

His medical history also included drug hypersensitivity to allopurinol (ongoing 1 year) and decreased joint range of motion (ongoing 1 month).

Subject No.: C0406 / 311-001	
Manufacturer Report No.: 07US000189	
Open Label Study Drug:	8 mg pegloticase every 2 weeks, intravenously
Double Blind Study Drug:	8 mg pegloticase every 4 weeks
Classification of the Event:	Serious Adverse Event
Date of Event:	(b) (6)
Event:	Infusion-Related Reaction [Infusion-Related Reaction]
Investigator Causality Assignment:	Probable
Outcome:	Resolved; Study Drug Discontinued

Subject 311-001 was a 51 year-old Caucasian male who experienced a serious infusion reaction characterized by severe crushing chest pain; resulting in the permanent discontinuation of the study drug. This subject was initially diagnosed with gout in 1975. His medical history included sleep apnea syndrome (unknown duration), coronary artery disease (ongoing 5 years), multiple catheterizations with stents to the right coronary artery, left circumflex artery, and posterior descending artery (ongoing 6 years), hypertension (ongoing 5 years), hypercholesterolemia (ongoing 5 years 9 months), depression (ongoing 4 years 9 months), anxiety (ongoing 4 years 9 months), fatigue (ongoing 3 months), and uvuloplasty (1 month). This subject experienced a severe non-serious infusion reaction on 23 Aug 2006 (Dose 3; refer to Narrative 06US000007) characterized by severe pain in his left fifth metacarpophalangeal (MCP) joint, and a moderate non-serious infusion reaction on 20 Sep 2006 (Dose 5) consisting of chest pain, dizziness, and rash; both events occurred while participating in double-blind study C0406. He also experienced a serious adverse event of angina on 15 Aug 2006 (refer to Narrative 06US000006). This subject had also experienced a severe non-serious infusion-related reaction at Dose 3 (23 Aug 2006), and a non-severe non-serious infusion-related reaction at Dose 5 (20 Sep 2006), while participating in double-blind study C0406. He received his first dose of open-label study drug (8 mg pegloticase every 2 weeks) on 08 May 2007 (Dose 1) and received his most recent dose on (b) (6) the same day as the event.

On (b) (6), the subject experienced a serious infusion reaction characterized by severe crushing chest pain. The subject had taken his prescribed pre-infusion medication except for fexofenadine the day before the infusion. Information documenting his vital signs at baseline and pre-infusion physical examination was unavailable. His study drug infusion was started at 125 mL/hr (09:18). At 9:45, the subject had complaints of severe crushing chest pain and the infusion was stopped permanently. Physical examination revealed no angioedema, and no facial or tongue swelling. His heart and lung examination was normal. The subject was treated with nitroglycerin (glyceryl trinitrate; 2 doses). The subject's electrocardiogram (ECG) results were normal; his screening ECG results had revealed left atrial hypertrophy (23 Jul 2006). His tryptase level was 5.5 μg/L (NR 1.9 - 13.5 μg/L). The subject recovered at 09:55 the same day.

The study drug regimen was discontinued and the subject was transitioned to the observational arm of the study the same day.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), Viagra (sildenafil), Provigil (modafinil), naproxen, Prevacid (lansoprazole), Xanax (alprazolam), Norvasc (amlodipine), Accupril (quinapril hydrochloride), Zocor (simvastatin), Percocet (oxycodone hydrochloride, acetaminophen), oxycodone, and OxyContin (oxycodone hydrochloride).

The infusion reaction was reported as serious. The Investigator and Clinical Research Physician at Savient felt that this event was probably related to the study drug.

He had no other known medical history.

Subject No.: C0406 / 313-007	
Manufacturer Report No.: 07US000148	
Double Blind Study Drug:	8 mg PEG-uricase every 2 weeks, intravenously
Classification of the Event:	Withdrawal Due to Adverse Event
Date of Event:	(b) (6)
Event:	Infusion-Related Reaction [Infusion-Related Reaction]
Investigator Causality Assignment:	Probable
Outcome:	Resolved; Study Drug Discontinued

Subject 313-007 was a 62 year-old Pacific Islander male who experienced an infusion reaction characterized by facial flushing, hypotension, tachycardia, and urticaria during his first study drug infusion. The subject experienced no concurrent adverse events (AEs). This subject was initially diagnosed with gout in 1972. He had no known relevant medical history. The subject received his first dose of study drug on (b) (6) event.

On (b) (6), the subject experienced a non-serious infusion reaction of mild intensity. His pre-medication included hydrocortisone 200 mg IV at 11:05; however, he did not take his fexofenadine and acetaminophen pre-infusion medications. The subject's vital signs were blood pressure (BP) 142/87 mmHg, heart rate (HR) 86 beats per minute (bpm), respiratory rate (RR) 20 breaths per minute (bpm), and temperature 36.9°C (10:35) and the study infusion was started at 11:37. At 11:55, the subject developed facial flushing, followed by diffuse pruritus. Physical examination at the time of the event revealed urticaria on the subject's face, chest, back, palms, hands, feet, and legs. No other directed physical examination findings were reported. The infusion was stopped at 11:55; his vital signs were BP 81/21 mmHg, HR 115 bpm, and temperature 36.9°C. The subject had complaints of lightheadedness. His treatment included NS IV 250 mL/hr, hydrocortisone 100 mg IV, Benadryl (diphenhydramine) 50 mg IV, and Demerol 25 mg IV given twice for rigors. Electrocardiogram (ECG) results revealed tachycardia; screening ECG results revealed premature ventricular contractions (06 Mar 2007). His tryptase level was 7.1 µg/L (normal range [NR] 1.9 - 13.5 µg/L). Repeat vital signs were BP 137/88 mmHg and HR 98 bpm (RR not reported) (12:45). The subject's symptoms resolved at 13:35. His vital signs at 13:55 were BP 139/74 mmHg and HR 110 bpm.

Study drug was permanently discontinued on the same day, (b) (6), and the subject was withdrawn from the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), methotrexate, Zocor (simvastatin), Aspirin (ASA), folic acid, glipizide, Norvasc (amlodipine), and Prevacid (lansoprazole).

The infusion reaction resulted in the permanent discontinuation of the study drug. The Investigator and Clinical Research Physician at Savient felt that this event was probably related to the study drug.

His medical history included hyperlipidemia (ongoing 1 year), cardiac murmur (ongoing 1 year), hypertension (ongoing 2 years), and diabetes mellitus non-insulin-dependent (ongoing 2 years).

Subject No.: C0406 / 319-004	
Manufacturer Report No.: 06US000031	
Double Blind Study Drug:	8 mg PEG-uricase every 4 weeks, intravenously
Classification of the Event:	Serious Infusion Reaction
Date of Event:	(b) (6)
Event:	Infusion-Related Reaction [Infusion-Related Reaction]
Investigator Causality Assignment:	Possible
Outcome:	Resolved; Study Drug Discontinued

Subject 319-004 was a 53 year-old Caucasian male who experienced a serious infusion reaction characterized by stomach bloating and shortness of breath, which was severe in intensity. This subject was initially diagnosed with gout in 1974. He had no known relevant medical history. The subject received his first dose of study drug on 25 Sep 2006 and received two more schedule doses prior to this event. The subject received his most recent study drug infusion on (b) (6) at the time of the event.

On (b) (6), the subject experienced a severe infusion reaction. His vital signs at baseline were blood pressure (BP) 110/85 mmHg, heart rate (HR) 80 beats per minute (bpm), respiratory rate (RR) 18 breaths per minute (bpm), and temperature 36.4°C. The study drug infusion began at 12:15. The subject's vital signs during the infusion were BP 105/84 mmHg, HR 79 bpm, RR 18 bpm, temperature 36.6°C (12:45); and BP 110/68 mmHg, HR 78 bpm, RR 18 bpm, temperature 36.6°C (13:15). At 13:40, during the infusion, the subject got up to void. He returned to his chair at 13:50 with complaints of stomach bloating and shortness of breath. The study drug infusion was stopped 5 minutes later (13:55), and he was given oxygen through a nasal canula. He began complaining of abdominal cramping; he also developed paleness and headache, and began sweating and wheezing. His vital signs at 14:00 were BP 162/99 mmHg, HR 57 bpm, and RR 25 bpm (temperature not reported). Hydrocortisone 100 mg was administered intravenously (IV), followed by epinephrine 0.5 mg IV and a call was made to 911. He was administered two puffs of a Combivent inhaler with resolution of wheezing. Electrocardiogram (ECG) results were normal. The subject then became stable and had no further difficulty breathing. His vital signs at 14:10 were BP 146/90 mmHg, HR 70 bpm, RR 22 bpm (temperature not reported). The emergency medical team arrived and took the subject to the hospital, where he was evaluated and released the same day. The subject was not admitted to the hospital. No other physical examination findings were reported during or after the infusion reaction.

The subject returned to the site on (b) (6) and blood drawn for tryptase at 09:25 was within normal range (4.0 µg/L [normal range 1.9 - 13.5 µg/L]). Results of an electrocardiogram performed at the same time were normal. The subject recovered at 10:00 on (b) (6).

Study drug was discontinued permanently on (b) (6), and the subject withdrew from the study (lost to follow-up on 27 Oct 2006).

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (Indocin [indomethacin] and Nexium [esomeprazole magnesium]).

The infusion reaction was reported as serious. The Investigator and Clinical Research Physician at Savient felt that this event was possibly related to the study drug.

The subject had no other reported medical history.

Subject No.: C0406 / 330-007	
Manufacturer Report No.: 07US000075	
Double Blind Study Drug:	8 mg PEG-uricase every 4 weeks, intravenously
Classification of the Event:	Withdrawal Due to Adverse Event
Date of Event:	(b) (6)
Event:	Infusion-Related Reaction [Infusion-Related Reaction]
Investigator Causality Assignment:	Probable
Outcome:	Recovered; Study Drug Discontinued

Subject 330-007 was a 55 year-old Caucasian male who experienced a medically significant infusion reaction of moderate intensity, termed “anaphylactic” by the Investigator. The subject experienced no concurrent adverse events (AEs). This subject was initially diagnosed with gout in 1984. His known medical history relevant to the event included drug hypersensitivity to penicillin (ongoing unknown duration). The subject received his first dose of study drug on 30 Oct 2006 and 4 more scheduled doses prior to this event. The subject received his most recent study drug infusion on (b) (6) the same day as the event.

On (b) (6), the subject experienced an infusion reaction (IR) that was medically significant and moderate in intensity. Baseline vital signs included blood pressure (BP) 138/89mmHg, heart rate (HR) 76 beats per minute (bpm), respiratory rate (RR) 20 breaths per minute (bpm), and temperature 98.3°F. The study drug infusion began at 15:10 (site time). At 15:15, the subject became flushed, diaphoretic, short of breath, and complained of being light headed. The physical examination revealed clear lungs, HR regular, skin warm and moist and flushed with good capillary refill. At 15:45, a fine scattered, non-pruritic rash appeared, his skin was flushed, and he had sweat on his arms. The infusion was stopped at 15:15 and was the IV line was flushed with 10 ml normal saline. Treatment included Benadryl (diphenhydramine) 25 mg intravenously (IV). Normal saline was infused at 25 mL/hr IV. At 15:20, the subject's BP was 143/80 mmHg, HR 83 bpm, and RR 20 bpm. At 15:25, the subject's BP was 148/96 mmHg and HR 81 bpm. An electrocardiogram (ECG) was performed at 15:27, and revealed non-specific ST-T changes and left ventricular hypertrophy voltage; unchanged from his baseline ECG results (23 Oct 2006). A tryptase level on (b) (6) was 10.3 µg/L (normal range [NR] 1.9 - 13.5 µg/L). The subjects' symptoms resolved at 15:30. At 15:40, the subject's BP was 145/92 mmHg and HR 71 bpm. As noted above (physical examination), a fine, scattered, non-pruritic rash appeared at 15:45 on the subject's arms bilaterally. At 16:00, the subject's BP was 139/90 mmHg, HR 70 bpm, RR 16 bpm, and temperature 98.0 ºF. At 17:00, the subjects’ vital signs were BP 140/86 mmHg, HR 71 bpm, and RR 12 bpm. The subject was given prednisone 40 mg po at 18:00 and discharged home. The rash remained on his arms, therefore he was given an additional 30 mg dose of prednisone to take in the morning if needed, and he was instructed to follow up at the office the following morning.

Study drug was permanently discontinued the same day, (b) (6), and the subject was withdrawn from the study.

Concomitant medications at the onset of the event included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone), protocol-prescribed gout flare prophylaxis (colchicine), esomeprazole magnesium, and naproxen.

The event of infusion-related reaction was termed “anaphylaxis” by the Investigator, was considered medically significant by the Investigator. The Investigator and Clinical Research Physician at Savient felt that this event was probably related to the study drug.

His medical history also included C6-C7 cervical disc herniation (1 month) and hypercholesterolemia (ongoing 23 years).

Subject No.: C0406 / 401-006	
Manufacturer Report No.: 07MX000104 / 07MX000160	
Double Blind Study Drug:	8 mg PEG-uricase every 4 weeks, intravenously
Classification of the Event:	Non-serious Infusion Reaction
Date of Event:	(b) (6)
Event:	Infusion-Related Reaction [Infusion-Related Reaction]
Investigator Causality Assignment:	Possibly
Outcome:	Resolved

Subject 401-006 was a 31 year-old Hispanic male who experienced two non-serious infusion reactions of moderate intensity. The subject experienced no additional concurrent adverse events (AEs). This subject was initially diagnosed with gout in 2004. His relevant medical history includes hypertension (ongoing 1 year). The subject received his first dose of study drug on 19 Dec 2006 and 4 more scheduled doses prior to this event. The subject was receiving his fifth study drug infusion on (b) (6) the time of this event.

On (b) (6), the subject experienced a non-serious, non-severe infusion reaction characterized by facial hyperaemia, facial oedema, tachycardia, dyspnoea and back pain. Study drug infusion started at 10:10. Five minutes after the start of the infusion, the subject developed facial hyperaemia, facial oedema, tachycardia, and dyspnoea, followed by back pain, all of moderate intensity. The study drug infusion was stopped. Physical examination revealed blood pressure (BP) 120/70 mmHg, heart rate (HR), 96 beats per minute (bpm), respiratory rate (RR) 28 breaths per minute (bpm), and temperature 36.3°C. No other physical findings were noted. His vital signs at baseline were BP 118/86 mmHg, HR 80 bpm, RR 16 bpm and T 35.5°C. An electrocardiogram (ECG) was performed showing sinus tachycardia. The subject was treated with hydrocortisone 100 mg IV, metamizole 500 mg IV and chloropyramine 20 mg IV and oxygen was administered. A blood sample for tryptase was drawn and the result was 47.7 µg/L (normal range [NR] 1.9 - 13.5 µg/L). Signs and symptoms resolved and the infusion was restarted at 10:45. Study drug was dissolved in 500 mL normal saline solution and administered at a rate of 200 mL/hour. The infusion was completed at 13:10. The subject did not report any further symptoms. Final vital signs were BP 120/86 mmHg, HR 80 bpm, RR 16 bpm and T 36°C.

Study drug was unchanged and the subject continued in the study.

The subject had a subsequent infusion reaction on (b) (6) (Dose 9) which was moderate in intensity and characterized by dyspnoea, facial erythema and hypotension. In addition to his pre-infusion prophylactic regimen, he also received prednisone, 20 mg the night before the infusion. Study drug infusion began at 10:00 at a rate of 250 mL/hour (500 mL volume). At 11:40, the subject developed facial rubor, hypotension and dyspnoea of moderate intensity. The infusion was stopped. At 11:45, the subject was treated with hydrocortisone 100 mg IV, and at 12:50 with 500 mL of intravenous saline. Vital signs at 12:00 were BP of 80/60 mmHg, HR 80 bpm, RR 20 bpm and T 36.2°C. Baseline VS were BP 130/80 mmHg, HR 84 bpm, RR 22 bpm and T 36°C. No other physical findings were noted. An ECG was performed with normal results, and blood was drawn for tryptase, resulting in a level of 7.0 µg/L. Vital signs obtained at 13:00 were BP of 114/80, P of 84, and RR of 20 and T of 36°C. All signs and symptoms resolved at 13:00 and the infusion was restarted at that time. The infusion completed at 13:30. The subject did not report any further symptoms. VS at the end of the infusion were BP 134/90 mmHg 84 bpm RR 20 bpm and T 36.0°C.

Study drug was unchanged and the subject continued in the study. The subject completed all doses of study drug.

Concomitant medications at the onset of the event of 13 Feb 2007 included protocol-prescribed infusion-reaction prophylaxis (fexofenadine, acetaminophen, and hydrocortisone) and protocol-prescribed gout flare prophylaxis (colchicine), and enalapril. Prednisone 20 mg the night before infusions was added as pre-infusion medication after the first infusion reaction at Dose 5, and was continued for all subsequent infusions.

The infusion reaction on (b) (6) was moderate in intensity. The Investigator and Clinical Research Physician at Savient felt that this event was possibly related to the study drug.

The infusion reaction on (b) (6) was also moderate in intensity. The Investigator and Clinical Research Physician at Savient felt that this event was possibly related to the study drug.

APPENDIX 6: POST-HOC CARDIOVASCULAR ADJUDICATION REPORT

METHODS OF EVALUATING CLINICAL CASES BY THE CARDIOVASCULAR ADJUDICATION COMMITTEE

WILLIAM B. WHITE, M.D. , PROFESSOR OF MEDICINE, UNIVERSITY OF CONNECTICUT SCHOOL OF MEDICINE, FARMINGTON, CONNECTICUT AND CHAIR, PEGLOTICASE CARDIOVASCULAR ADJUDICATION COMMITTEE

General rules of process

Study investigators and the sponsor identified subjects who developed potential cardiovascular (CV) events during the clinical trials with pegloticase. The relevant blinded clinical evidence for each event was compiled by the Sponsor (with the assistance of the study site), and sent to the members of the Committee for review and independent adjudication. Final adjudication of each death or CV event were reached by consensus of the reviewing members. Members of the committee had no previous knowledge of results of pegloticase studies and were not involved in such studies. A detailed Charter was developed and agreed upon by all Committee members and the sponsor prior to the initiation of the adjudication process blinded to treatment group.

If an event could not be classified due to a lack of clinical documentation, the CV Events Adjudication Committee Chair could send, via the Sponsor, additional queries to the study site, if necessary, to obtain additional information If after these efforts, the available information was still not sufficient to adjudicate the event, the event would have been classified as "Insufficient Data".

Each committee member completed and signed an Individual Adjudication Form for each event; the original was forwarded to the Chair. The Chair reviewed the Individual Adjudication Forms to determine if the committee agreed on the classification of the event. For those events that were not agreed upon, the Committee reviewed those cases together and come to a conclusion by simple majority vote. Once agreement was reached, the Chair prepared a Final Adjudication form.

Documents Provided to the Committee for Adjudication

For each death or potential CV event, the Sponsor compiled all relevant supporting documentation including but not limited to those listed below. Document packets were sent to the CV Event Adjudication Committee members with as complete a dossier of the information as possible. In addition, if multiple related or evolving events occurred in a single subject, the set of the events were processed together and sent to the Committee members.

Documents provided for adjudication of a case included:

A. CIOMS Reports including a narrative summary of the event.

B. Case Report pages describing the event by investigator/coordinator.

C. Accompanying blinded/redacted source documentation (whenever available).

   a. Copies of pertinent laboratory, imaging and cardiac testing reports

   b. Copies of hospital admission notes and all pertinent hospital record progress notes related to the event (Physician notes and Nursing notes).

   c. Copies of surgical, consultant and pathology reports.

   d. Hospital discharge summary.

   e. Certified death/autopsy summary (if applicable)

Cardiovascular Events –Definitions

The CV Events Adjudication Committee reviewed all deaths and all serious adverse events in a blinded fashion. To arrive at an adjudicated diagnosis of a CV event, the following definitions were used:

A. Anti-Platelet Trialist Collaborative (APTC) Events

i. **Non-Fatal Myocardial Infarction**: the presence of 2 of the 3 following criteria: a) chest pain, b) abnormal values of cardiac enzymes (MB fraction of creatinine phosphokinase and/or troponin), c) myocardial

injury current or the development of new Q waves in 2 contiguous leads of the electrocardiogram.

ii. **Non-Fatal Stroke**: ischemic or hemorrhagic stroke defined as an acute, focal neurologic event that persisted for > 24 hours. Confirmation by imaging studies (magnetic resonance imaging or computerized tomography of the brain) will be sought in all cases, but will not be an absolute requirement for adjudication of the event.

iii. **Cardiovascular deaths**: Including sudden/unexplained death, or other cardiac death.

B. **Non-APTC Major Adverse Cardiovascular Events**

i. **Unstable Angina (includes Acute Coronary Syndrome)** documented by a hospitalization or emergency department visit, not meeting the acute MI definition above, and characterized by ischemic discomfort at rest for at least 10 minutes.

ii. **Coronary revascularization** defined as percutaneous transluminal angioplasty or coronary artery bypass graft surgery.

iii. **Transient ischemic attacks** documented by a hospitalization or emergency department visit, not meeting the definition of stroke above, and characterized by focal, transient (< 24 hours) neurological signs and symptoms.

iv. **Venous and peripheral arterial vascular thrombotic events** defined as evidence of venous thrombosis of the lower extremities or pelvis, pulmonary embolism, peripheral arterial embolism and/or occlusion (peripheral gangrene or ischemia).

v. **Congestive heart failure** defined as hospitalization or emergency department visit due to dyspnea, shortness of breath, and/or edema accompanied by auscultatory findings of pulmonary vascular congestion. Institution of therapy for heart failure is required. Radiographic and/or echocardiographic documentation is desirable but not required.

vi. **Arrhythmia, no evidence of ischemia** – atrial (atrial fibrillation, supraventricular tachycardia, sick sinus syndrome) or ventricular

arrhythmias (ventricular tachycardia, ventricular fibrillation), or high-grade heart block (Mobitz 2, complete heart block) that has developed without evidence of myocardial ischemia or infarction as the underlying etiology.

vii. **Cerebral revascularization** – defined as percutaneous transluminal angioplasty or surgical revascularization of carotid and cerebral arteries.

CARDIOVASCULAR EVENT
ADJUDICATION for SAVIENT CLINICAL TRIALS – Final Analysis

William B. White, MD, Professor of Medicine
Chief, Hypertension and Vascular Diseases at the
Calhoun Cardiology Center, University of Connecticut School of Medicine, Farmington

		DOUBLE-BLIND CLINICAL TRIALS (0405 AND 0406)
Subject ID	**SAE Term**	**Adjudication Diagnosis with Commentary and Rationale for Diagnosis**
101-005	Syncope	**Syncope** – patient had syncopal episode in association with dehydration. **Adjudcation – non-cardiovascular event** (note: this patient died months after study discontinuation ; there are insufficient data to evaluate the cause of death
102-006	1. Dyspnea 28 Oct 2006 2. Renal failure 30 Oct 2006	**1. Congestive heart failure** – exacerbation of existing heart failure with symptoms of severe dyspnea, radiographic evidence of heart failure, and improvement in symptoms with parenteral diuretic therapy. **Adjudication: non-APTC CV event** **2. Acute renal failure** – Patient developed acute renal failure following diuresis mentioned above; refused long-term dialysis and died 1 week later. **Adjudication: non-cardiovascular death**
109-005	Dyspnea	**Dyspnea (non specific)** patient had negative evaluation for cardiac ischemia and /or infarction, heart failure, and pulmonary embolism **Adjudication: non-cardiac event**
122-003	1. Cardiac disorders and myocardial infarction 30 Aug 2006 2. Vascular disorders/deep vein thrombosis 4 Oct 2006	**1. Nonfatal inferior wall myocardial infarction** – patient presented with angina, increased cardiac enzymes (troponin and CPK-MB), and injury current in inferior wall leads of the ECG. Improved with circumflex a. angioplasty. **Adjudication – APTC CV event** **2. Deep venous thrombosis –** lower extremity edema , positive duplex ultrasound, improvement with heparin/warfarin. **Adjudication – non-APTC CV event**
124-001	Cardiac disorders/cardiac failure	**Congestive Heart Failure –** patient had symptom complex of dyspnea, with signs of pulmonary vascular congestion and improvement following aggressive parenteral diuresis. **Adjudication – non APTC CV event**

203-001	Cardiac disorders/ cardiac arrest	**Cardiovascular death** – sudden death after physical exertion (history of heart disease) **Adjudication: APTC CV event**
301-002	Chest pain	**Non-cardiac chest pain** – history is not suggestive of cardiac etiology; normal cardiac enzymes and normal exercise tolerance test **Adjudication: non-cardiovascular event.**
301-003	MRSA sepsis	**Non-cardiovascular death** – patient developed MRSA sepsis following development of infected decubitus ulcer. **Adjudication: Non-CV event**
301-006	Cardiac disorders/re-entry tachycardia	**Cardiac arrhythmia** – patient developed supra-ventricular tachycardia with minimal ST-T changes; no evidence of cardiac ischemia ; converted to sinus rhythm following beta-blocker and adenosine administration. **Adjudication: Non-APTC CV event**
301-012	Transient ischemic attack	**Transient ischemic attack** – patient developed dysarthria followed by transient expressive aphasia; no permanent symptoms/signs. CT imaging negative for infarct. **Adjudication: non-APTC CV event**
301-014	Multi-organ failure	**Non-cardiovascular death** – in this case, the death occurred prior to administration of any study drug because the patient was admitted to the hospital and died of multiple organ failure (sparse documentation). **Adjudication non-CV event**
311-001	Cardiac disorders/angina pectoris	**Unstable angina** – patient developed angina at rest; complete evaluation did not show evidence for myocardial infarction. Underwent coronary intervention (PTCA/stent). **Adjudication: non-APTC CV event**
311-002	Congestive heart failure and aortic stenosis	**Non-cardiovascular death** – patient with chronic lymphocytic leukemia developed renal failure/fluid overload. Refused dialysis and subsequently died within days of end-stage renal failure. **Adjudication: non-CV event**
311-005	1. Peripheral edema (01 Mar 2007) 2. Arrhythmia (15 Apr 2007)	**1. Congestive heart failure** – patient had signs and symptoms of heart failure but no evidence for myocardial infarction or ischemia. Had significant improvement with parenteral diuresis. **Adjudication: non-APTC CV event** **2. Cardiac arrhythmia** – patient with implanted defibrillator ; had 2 shocks, interrogation of device showed 2 episodes of sustained ventricular tachycardia **Adjudication: non-APTC CV event**

315-006	Cardiac arrhythmia	**Cardiovascular death** – patient died suddenly while en route to a hospital with spouse. No ECG was supplied ; there is a history of renal failure and dehydration. **Adjudication: CV death**
Open-Label Extension Studies (043 and 047)		
Subject ID	**SAE Term**	**Adjudication Diagnosis with Commentary and Rationale for Diagnosis**
002-001	Renal Failure	**Renal failure** – patient hospitalized for progressive renal insufficiency and anemia. No evidence of cardiovascular event. **Adjudication: non-cardiovascular event**
002-003	Lacunar infarct	**Non-fatal stroke** – persistent left-sided hemiparesis in a 77 y/o woman with vascular disease. MRI showed small vessel disease but clinical signs and symptoms are consistent with an ischemic stroke. **Adjudication: APTC event (stroke)**
009-002	1. Chest pain, angina (7 Oct 2004) 2. Chest pain, angina (18 Oct 2004)	**1. Non-cardiac chest pain** – 4 days in hospital with persistent chest pain, no ECG or cardiac enzyme changes; patient had normal exercise tolerance test the previous year. **Adjudication: non-cardiovascular event** **2. Non-cardiac chest pain** – this was the 5th admission for chest pain; led to cardiac catheterization which showed no evidence for coronary disease. **Adjudication: non-cardiovascular event**
118-001	Chest pain	**Non-cardiac chest pain.** Atypical chest pain ; had cardiology consult , normal ECG, negative cardiac enzymes; normal cardiac catheterization in 2005. . **Adjudication: non-cardiovascular event**
122-004	1. Worsening chronic kidney disease (24 Apr 2007) 2. Myocardial infarction (24 Apr 2008) 3. Bilateral lower extremity DVT (11 Aug 2007) 4. Sepsis	**1. Admission to switch from hemodialysis to peritoneal dialysis** – could not tolerate hemodialysis due to hypotension . . **Adjudication: non-cardiovascular event** **2. Nonfatal myocardial infarction.** significant angina accompanied by inferior wall ST segment injury pattern and markedly increased CPK-MB and troponins. Treated successfully with coronary intervention/bare metal stents. **Adjudication: APTC event.** **3. Venous thrombosis** – patient had cellulitis and necrotic foot that led to toe amputation and debridement. Developed DVT which results in placement of an inferior vena cava filter. **Adjudication: non-APTC CV event.**

		4. Non-cardiovascular death – developed widespread ORSA and enterococcal infections (peritonitis) ; hypotension followed by probable stroke and coma – taken off life support. **Adjudication: non-cardiovascular event**
129-002	Acute renal failure	**Non-cardiovascular event** – admission to hospital for hallucinations, moderate renal insufficiency, hypoxemia and possible pyelonephritis. . **Adjudication: non-cardiovascular event**
130-002	Bilateral DVT	**Venous thrombosis** – Large bilateral iliofemoral venous thrombosis diagnosed by duplex ultrasonography. **Adjudication: non-APTC CV event**
130-004	Syncope	**Non-cardiovascular event** – ill-defined event – patient complained of 'near syncope' for a 20 minute period; had normal blood pressures; CT scan showed remote/old right frontal infarct; had implantable defibrillator which was interrogated and showed no evidence for a cardiac arrhythmia. . **Adjudication: non-cardiovascular event**
130-006	Right carotid stenosis	**Cerebrovascular revascularization** – right carotid endarterectomy after duplex ultrasound demonstrated high grade stenosis ; no neurologic symptoms reported. **Adjudication: non-APTC CV event**
133-001	Hypotension/renal disorder	**Non-cardiovascular event** – acute renal failure after development of an obstructive uropathy and post-obstructive diuresis. . **Adjudication: non-cardiovascular event**
204-001	Left leg deep venous thrombosis	**Venous thrombosis** – patient had evidence for left superficial femoral and popliteal venous thrombosis by clinical and duplex ultrasound exam.
301-002	Syncope	**Non-cardiovascular event** – patient with severe hypoglycemia and syncope – induced by patient taking an 'over-dose' of glyburide. . **Adjudication: non-cardiovascular event**
301-017	1. Pain in arm and breast 2. Hypertension (17 Jan 2008) 3.Chest pain (02 Apr 2008) 4. Chest pain (24 Apr 2008)	**1. Non-cardiovascular event** – non-cardiac pain ; ECG showed a paced rhythm with LBBB pattern; patient also had a negative workup for pulmonary and cardiac processes with CT of chest, chest x-ray, echocardiogram and biochemical data. . **Adjudication: non-cardiovascular event** **2. Non-cardiovasular event** – had non-cardiac chest pain ; a BP at home was 188/60 mHg but fell to 134/60 mmHg in the emergency department. ECG showed paced

		rhythm ; negative exercise tolerance test. . **Adjudication: non-cardiovascular event** **3. Non-cardiovascular event** – chest pain radiating to the jaw ; all testing negative for ischemia/infarction . . **Adjudication: non-cardiovascular event** **4. Non-cardiovascular event** – recurrent chest pain similar to hospitalization 3 weeks earlier; underwent cardiac cath – did not show hemodynamically significant lestion. Treated medically. . **Adjudication: non-cardiovascular event**
307-006	1. Acute renal failure (13 May 2008) 2. Congestive heart failure (9 June 2008)	**1. Non-fatal myocardial infarction** – patient admitted for knee surgery – 3 days post-operatively had several increased troponins and CPK-MB levels. Note clearance of enzymes was probably impacted upon by poor cardiac and renal function> **Adjudication: APTC event** **2. Congestive heart failure** – 1 month after knee surgery, patient developed shortness of breath, edema, hypertension, signs of pulmonary vascular congestion; treated with parenteral diuresis and improved. **Adjudication: non-APTC CV event**
311-005	1. Replacement of ICD/abdominal pan and distension (21 July 2008) 2. Congestive heart failure (19 Sept 2008)	**1. Non-cardiovascular event** – elective replacement of ICD battery. **Adjudication: non-cardiovascular event** **2. Congestive heart failure** – patient admitted with ascites, edema and pulmonary vascular congestion. Treated with aggressive diuresis. **Adjudication: non-APTC CV event.**
325-002	Pulmonary embolism	**Venous thromboembolism** – had both DVT and pulmonary embolism in a patient with Factor V Leiden deficiency; treated with inferior vena cava filter. **Adjudication: non-APTC CV event.**
327-002	Chest pain	**Non-cardiovascular event** – non-cardiac chest pain accompanied by normal ECG, normal cardiac enzymes, and negative/normal exercise tolerance test. **Adjudication: non-cardiovascular event**

W. B. Wheton
24 January 2009

APPENDIX 7: POST-HOC EVALUATION OF PHASE 3 RCT EKGs

QT STUDY REPORT

Savient Pegloticase Trials

(Trial C 0405 and C0406)

PURPOSE

The purpose of this study was to evaluate EKG's from two clinical Trials (Trial C 0405 and C0406) on uricase as to changes in QT and QTc intervals.

METHODS

EKG's were analyzed by two observers blinded to whether the patient received the uricase therapy or not. The QT intervals and the preceding RR intervals were measured in each lead of the 12-lead EKGs in duplicate using calipers for measurements. The QT interval was determined from the onset of the QT (initial downward deflection of "q" wave) to the end of T wave, when the T wave terminus intersects with the isoelectric line. If the T intersection was not clearly denoted, the "tangent method" was used to determine the point at which the T wave intersects with the isoelectric line. The U-wave, if present, was excluded from the analysis. The QT interval was taken as the longest QT in the 6 frontal plane leads (I, II, III, aVR, aVL, and VF). It was decided that if a QT effect will be detected, an analysis for changes in QT dispersion (QTd) will be performed. Therefore, data were recorded for potential QTd evaluation. The QTd is defined as the longest QT minus the shortest QT across the 12 leads. The QT measurements were corrected for heart rate using two different correction formulas; the Bazett and Fridericia formulas. The correction formulas are as follows:

1. Bazett formula: $QTc = QT / \sqrt{RR}$
2. Fridericia formula: $QTc = QT / \sqrt[3]{RR}$

If an EKG lead had an undeterminable QT interval that lead was omitted from the analysis. An EKG recording with 4 or more undeterminable leads were not counted in the analysis.

Each subject was anticipated to have two EKGs, one recorded at study entry (baseline) and the other at the end of study (study end). However there were a number of missing EKGs (se Results). According to FDA Guidelines, one investigator read all EKG recordings from a

given subject.

The data were recorded as hard copy and then were entered into an electronic database (MS Excel). Rate corrected QT intervals were calculated by using the worksheet's computation functions. According to the protocol, additional data were also recorded to make possible of QT dispersion calculation. Also major EKG findings were recorded if further analysis warranted.

The data on hard copies for all patients were provided to the sponsor before the blind for the readers and statistical analysis were broken. After that, the sponsor sent those EKGs that were recorded in connection to an adverse event. These EKGs were analyzed and reported in the same way as described above.

Once all of the data were provided to the sponsor, the analysis team was provided with the code assigning each patient to one of the three therapeutic groups: high dose, low dose, and placebo. To maintain integrity, QT measurements and QT corrections could not be changed in this phase and must remain the same as provided to the sponsor.

Data Analysis

The descriptive statistics includes the mean and standard deviation of measurements for each group at baseline and at the end of the study as well as for those who experienced an adverse event. Differences between groups were analyzed by employing ANOVA. Within each group, changes from baseline to study end was analyzed by paired sample t test. A two sided alpha error of less than 0.05 ($p<0.05$) was considered statistically significant. Each patient's QT was compared between each patient to determine QT prolongation; QT at study end or at infusion reaction was compared to each individual patient's baseline.

Reproducibility of QT measurement.

The inter-observer variation has been evaluated by measuring the same16 EKGs by both investigators: The mean difference in QT interval measurements between the two investigators was 11 ms with a coefficient of variance of 7.7%. The evaluation of intra-observer variation was based on measuring the same 8 EKGs twice repeatedly and compared to a reading performed by the same investigator several days prior. The mean difference between the paired QT measurements was 12.5 ms for Investigator One (CV=9.7%) and 5 ms for Investigator Two (CV=2.4%).

RESULTS

A total of 211 patients were included in this EKG analysis study from 2 Savient Pegloticase Trials, 103 from Trial C0405 and 108 from Trial C0406. Of the 211 subjects, 2 had no EKG at baseline and 27 had no EKG at study end. Furthermore 5 baseline EKGs and 7 study end EKG were excluded from the analysis due to undeterminable QT intervals, as described in the protocol. (The baseline patients excluded were: patients C0405; 103-003 and C0406: 305-001, 305-003, 305-004, 305-005. and the study end: C0406: 301-002, 305-001, 305-003, 305-004, 305-005, 308-001, and 323-001)

Of the 211 patients, 82 was randomized to receive high dose (2 weekly dosing, 42 patients in each Trial), 83 received low dose (4 weekly dosing, trial C0405: 41 patients, Trial C0406: 43 patients, and 43 received placebo, Trial C0405: 20 patients and Trial C0406 23 patients).

QT and RR measurements were performed without knowing the randomization assignment of the patients. The data were recorded as hard copy and then were entered into an electronic database (MS Excel). Rate corrected QT intervals were calculated by using the worksheet's computation functions. According to the protocol, additional data were also recorded to make possible of QT dispersion calculation. A separate tabulation is provided for each protocol as Attachment 1 and Attachment 2 of this report.

When the data entry was completed, a second set of EKGs was provided by the sponsor. These EKGs were recorded in connection to an adverse event (Infusion Adverse Event). A total 100 EKGs of 54 patients were provided. These EKGs were measured and tabulated in the same way as the baseline and study end EKGs (see above). A total of 2 EKGs were excluded due to undeterminable QT intervals (per protocol exclusions). If a patient had multiple EKGs, they were averaged to obtain representative QT data for the adverse events. A copy of this tabulation is provided as Attachment 3 and 4.

1. Evaluation of QT interval changes from baseline to study end.

The results of this analysis are summarized in Table 1. The QT effect was evaluated for each treatment arm (high dose, low dose, and placebo) Due to missing EKGs at baseline or at study end , 70 subject was eligible for this analysis in the high dose group, 64 in the low dose group and 37 in the placebo group. Paired sample t test was performed to compute the difference

and assess statistical significance (Note: this test uses within individual changes to generate mean change and derived statistical testing including p values).

As it is shown, the high dose did not result in any significant changes in the QT, QTc obtained by the Bazett formula, or in QTc obtained by the Fridericia formula. The small differences between baseline and study end QT values are clinically insignificant and due to variability. Furthermore due to the lack of a statistically significant difference, it can be considered to be a function of variation occurring naturally.

In the low dose group, only the uncorrected QT interval showed a significant increase, however QT must be corrected for heart rate, as the QT interval is partially a function of the heart rate. The rate corrected QT intervals show no clinically or statistically significant differences between the baseline and study end QT intervals.

Interestingly, the placebo group showed the greatest, but still not significant increase in the QT and rate corrected QT intervals.

Table 1. QT Interval Changes from Baseline to Study end.

High Dose (dosing 2 weekly)					
	N	Baseline	Study end	Difference	P
QT	70	392±39	395±44	3.4±38	ns (0.462)
QTc Bazett	70	423±36	428±39	5.08±35	ns (0.225)
QTc Fridericia	70	412±34	416±37	4.41±31	ns (0.236)
Low Dose (dosing 4 weekly)					
	N	Baseline	Study end	Difference	P
QT	64	385±35	395±32	10.59±31	p<0.01
QTc Bazett	64	419±30	424±38	5.41±34	ns (0.208)
QTc Fridericia	64	407±26	413±30	6.85±31	ns (0.079)
Placebo					
	N	Baseline	Study end	Difference	P
QT	37	387±38	397±39	9.46±37	ns (0.134)
QTc Bazett	37	414±33	423±33	9.57±34	ns (0.095)
QTc Fridericia	37	404±30	414±31	9.49±31	ns (0.069)

To evaluate potential differences between the 3 groups at baseline and study end, data were analyzed by using ANOVA. The advantage of this statistic is that it can compare groups at different time points using all available data without excluding those who had a missing data at either baseline or at the study end. The results of this analysis are summarized in Table 2.

Table 2. Baseline and Study End Comparisons of Study Groups Using ANOVA

QT Interval

Group	N	**Baseline** Mean±SD	Group Comparison	Difference Mean ± SE	p
High Dose	81	394±40	High vs. Low dose	2.5±6.4	ns (0.695)
Low dose	81	391±43	High vs. Placebo	5.5±7.8	ns (0.478)
Placebo	41	388±36	Low vs. Placebo	3.0±7.8	ns (0.698)
Group	N	**Study end** Mean±SD	Group Comparison	Difference Mean ± SE	p
High Dose	72	397±45	High vs. Low dose	1.1±6.7	ns (0.865)
Low dose	64	395±32	High vs. Placebo	1.28±7.9	ns (0.225)
Placebo	38	399±40	Low vs. Placebo	2.4±8.0	ns (0.765)

QTc Bazett

Group	N	**Baseline** Mean±SD	Group Comparison	Difference Mean ± SE	p
High Dose	81	424±37	High vs. Low dose	2.2±5.6	ns (0.699)
Low dose	81	423±37	High vs. Placebo	10.2±6.8	ns (0.1.44)
Placebo	41	415±31	Low vs. Placebo	7.8±6.8	ns (0.2.52)
Group	N	**Study end** Mean±SD	Group Comparison	Difference Mean ± SE	p
High Dose	72	428±39	High vs. Low dose	4.2±6.5	ns (0.512)
Low dose	64	424±38	High vs. Placebo	3.5±7.6	ns (0.643)
Placebo	38	425±34	Low vs. Placebo	0.75±7.7	ns (0.922)

QTc Fridericia

Group	N	**Baseline** Mean±SD	Group Comparison	Difference Mean ± SE	p
High Dose	81	414±34	High vs. Low dose	2.4±5.2	ns (0.649)
Low dose	81	412±35	High vs. Placebo	8.5±6.4	ns (0.187)
Placebo	41	405±29	Low vs. Placebo	6.1±6.4	ns (0.344)
Group	N	**Study end** Mean±SD	Group Comparison	Difference Mean ± SE	p
High Dose	72	417±37	High vs. Low dose	3.6±5.7	ns (0.533)
Low dose	64	413±30	High vs. Placebo	1.8±6.7	ns (0.785)
Placebo	38	415±31	Low vs. Placebo	1.75±6.8	ns (0.798)

The results indicate that there were no significant differences between the three study groups at baseline or at study end. Most importantly, the difference between the high dose and placebo group, as well as the low dose and placebo groups in the Fridericia corrected QT intervals did not exceed 2 ms at study end. The Fridericia formula is considered more reliable than the Bazett formula, which also did not detect clinically or statistically significant differences between the placebo and the low and high dose groups. The Bazett formula is known to "overcorrect" at high heart rates.

2. Evaluation of QT interval changes in patients with adverse events

This evaluation is based on paired comparisons of QT and QTc intervals measured at baseline as compared to EKG's occurring at the time of an infusion reaction, as well as the changes from adverse event to study end. Of the 55 patients with an adverse event, 54 had QT measurement at both baseline and during adverse event (22 in the high dose group, 31 in the low dose group and 1 in the placebo group.) Of the 55 patients, 45 had EKG at both adverse events and at study end (20 in the high dose group, 24 in the low dose group, and 1 in the placebo group). The result of this analysis is shown in Table 3.

Compared to baseline, the QT interval is 4.42 ms shorter during adverse event in the high dose group, which is clinically and statistically insignificant. The rate corrected QT interval with the Bazett formula indicates a significant increase from baseline to adverse event in the high dose group, while rate corrected QT interval with Fridericia formula does not indicate a significant change. Similar trends in QT and QTc interval changes were observed in the low dose group but without any statistical significance.

The Bazett formula is known to overcorrect the QT interval at higher heart rates, compared to Fridericia correction formula.

Interestingly, the single patient from the placebo group who had an adverse event showed the greatest increase in QTc exceeding 20 ms with the Fridericia formula and 35 ms with the Bazett formula, clinically significant increments.

No significant changes were observed from adverse event to study end in the QTc intervals, however a trend toward shorter QT at study end was seen in each group, possibly consistent with the phenomenon of regression to the mean.

Table 3. Evaluation of QT Interval Changes in Patients with Adverse Events

High Dose (dosing 2 weekly)

	N	Baseline	Adverse event	Difference	P
QT	22	377±37	373±36	4.42±42	ns (p=0.634)
QTc Bazett	22	418±38	437±35	19.1±40	p<0.05
QTc Fridericia	22	403±34	414±29	10.3±36	ns (p=0.183)
	N	Adverse E	Study end	Difference	P
QT	20	372±38	384±50	12.2±47	ns (p=0.260)
QTc Bazett	20	438±37	419±50	18.4±48	ns (p=0.094)
QTc Fridericia	20	414±30	407±47	7.1±44	ns (p=0.465)

Low Dose (dosing 4 weekly)

	N	Baseline	Adverse event	Difference	P
QT	31	391±50	388±43	3.1±59	ns (p=0.773)
QTc Bazett	31	428±49	445±40	16.9±62	ns (p=0.143)
QTc Fridericia	31	415±45	424±36	9.7±57	ns (p=0.352)
	N	Adverse E	Study end	Difference	P
QT	24	382+46	388±28	6.5±43	ns (p=0.471)
QTc Bazett	24	444±39	432±46	11.7±65	ns (p=0.390)
QTc Fridericia	24	421±38	415±35	6.2±53	ns (p=0.578)

Placebo (1 patient of the 37 had adverse event)

	N	Baseline	Adverse event	Study end	Difference Baseline vs. AE
QT	1	400	400	400	0
QTc Bazett	1	465	500	485	35
QTc Fridericia	1	442	464	455	22

To evaluate potential differences between the 3 groups at baseline, at adverse event, and at study end, data were also analyzed by using ANOVA. The advantage of this statistic is that it can compare groups at different time points using all available data without excluding those who

had missing data at either baseline or at the study end. The results of this analysis are summarized in Table 4. The results indicate that there were no significant differences between the three study groups at baseline, at adverse event, or at study end.

Table 4. Comparisons of Patients with Adverse event by Study Groups Using ANOVA

QT Interval				
Group	N	Baseline	Adverse Event	Study End
High Dose	22	377±37	373±36	384±50
Low dose	32	391±50	389±43	388±28
Placebo	1	400	400	400
P		ns (0.502)	ns (0.313)	ns (0.886)
QTc Bazett				
Group	N	Baseline	Adverse Event	Study End
High Dose	22	418±38	437±35	419±50
Low dose	32	429±49	444±40	432±46
Placebo	1	464	500	485
P		ns (0.482)	ns (0.258)	ns (0.340)
QTc Fridericia				
Group	N	Baseline	Adverse Event	Study End
High Dose	22	403±34	414±29	407±47
Low dose	32	415±45	424±36	415±35
Placebo	1	442	464	454
P		ns (0.451)	ns (0.229)	ns (0.466)

Furthermore, repeated measure of ANOVA were performed. This statistic includes only those patients who had EKGs at all of the 3 time points (baseline, adverse event, study end) and compare the groups based on within individual changes in QT and QTc intervals across the three time points. The results of this analysis are summarized in Table 5. Due to missing QT values at some time points, 45 patients with adverse event were included in this analysis: 20 from the high dose group, 24 from the low dose group, and 1 from the placebo group.

Table 5. Comparisons of Patients with Adverse event by Study Groups Using Repeated Measure of ANOVA

QT Interval

Group	**N**	**Baseline** Mean±SD	**Adverse Event** Mean ± SD	**Study End** Mean ± SD	**P overall** ns (0.661)
High Dose	20	377±38	372±38	384±50	
Low dose	24	380±30	383±46	388±28	
Placebo	1	400	400	400	

Group Comparisons	**P**
High dose vs. Low dose	ns (0.513)
High vs. Placebo	ns (0.469)
Low vs. Placebo	ns (0.594)

QTc Bazett

Group	**N**	**Baseline** Mean±SD	**Adverse Event** Mean ± SD	**Study End** Mean ± SD	**P overall** ns (0.131)
High Dose	20	417±39	438±37	419±50	
Low dose	24	422±36	444±39	432±46	
Placebo	1	464	500	485	

Group Comparisons	**P**
High dose vs. Low dose	ns (0.385)
High vs. Placebo	ns (0.054)
Low vs. Placebo	ns (0.090)

QTc Fridericia

Group	**N**	**Baseline** Mean±SD	**Adverse Event** Mean ± SD	**Study End** Mean ± SD	**P overall** ns (0.182)
High Dose	20	403±35	414±30	407±47	
Low dose	24	407±28	422±38	415±35	
Placebo	1	442	464	454	

Group Comparisons	**P**
High dose vs. Low dose	ns (0.479)
High vs. Placebo	ns (0.083)
Low vs. Placebo	ns (0.123)

The results indicate that there were no significant differences between the three study groups for changes in QT and QTc intervals from baseline, adverse event and study end.

Evaluation of QT dispersion. Analysis of QT dispersion was planed, if significant QT effect would have been detected in this study. However, significant QT prolongation due to drug effect has not been detected in the study, therefore analysis of QT dispersion was not analyzed further.

SUMMARY

The objective of this study was to evaluate EKG's from two clinical Trials (Trial C 0405 and Trial C0406) with uricase in terms of changes in QT and QTc intervals and assess the potential QT prolonging effect of the drug. QT measurements were made in a blinded fashion as to whether the patient received the uricase therapy or not. The QT intervals were corrected for heart rate using the Bazett and Fridericia formulas. When baseline values were compared to study end measurements, there was no indication of any QTc prolonging effect of the drug.

In a separate analysis, EKGs obtained in connection to adverse events were analyzed for changes in QT and QTc intervals from baseline to study end. There was no statistically significant increase from base line to adverse event in the QT and QTc, except for QTc Bazett , High Dose Group ($p<0.05$, Table 3). However, Bazett is known to overcorrect for high heart rate and these patients were tachycardic during the adverse event. In fact the trend observed of increasing QT to infusion reaction and decreasing to study end, that is not significant, is a natural variation within normal QT range when correction formulas for heart rate are applied. The formulas are imperfect and small increments in corrected QT can occur, though less with the Fridericia formula. Supporting this concept of the independence of this variability from drug is that the same variation is seen with the one patient with an infusion reaction on placebo.

In summary, a QT prolonging effect of uricase was not detected in this study and such an effect is highly unlikely.

John Somberg, MD, FAHA — Date 4/19/09

Janos Molnar, MD — Date 04/20/2009

APPENDIX 8: “SPYDERGRAM” SF-36 SCORES (PHASE 3 RCT)

In a “spydergram” SF-36 domain scores are presented in the following order: Physical Function (PF) at the top, 12 o’clock, followed clockwise by Role Physical (RP), Bodily Pain (BP) and General Health Perceptions (GHP), and Vitality (VT) at the 6 o’clock position, followed by Social Functioning (SF), Role Emotional (RE) and Mental Health Index (MHI) clockwise. Domain scores are plotted from 0 (worst) at the center to 100 (best) at the outside; demarcations along axes of the domains present changes of 10 points, representing 1-2 times MCID. Changes in shape and thickness of these irregular octagonal rings offer a single graphic representation to: 1. compare baseline decrements with US age and gender matched normative values, specific to each population, 2. assess treatment associated or longitudinal improvements in HRQOL, and 3. compare and contrast scores across protocols and disease states. Spydergrams allow visualization of these values simultaneously, and may be presented with Age/gender matched norms as a ‘treatment goal’

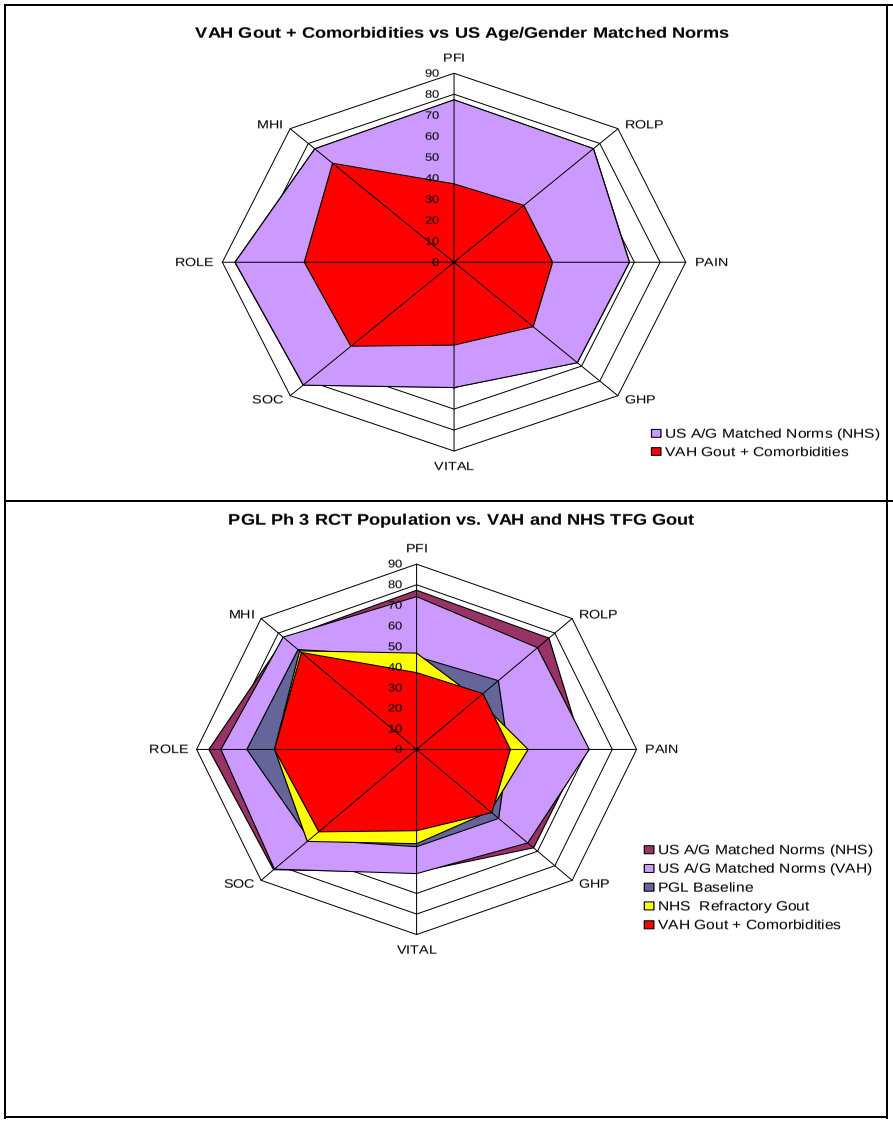


Figure 8-1. SF-36 domain scores at baseline in Pooled Phase 3 Pegloticase RCTs compared with other TFG populations and age and gender matched US norms

Spydergrams© of SF-36 domain scores illustrate decrements in reported HRQOL in (A) Veterans + Comorbidities (VAH) and (B) NHS Refractory Gout Populations vs US normative data specific to each population.

(Strand et al: A+R 2008: 56: S177)

(C) HRQOL in both TFG populations compared with Baseline scores in combined Phase 3 Pegloticase RCT population.

Inner ring = SF-36 Domain Scores; scores range from 0 – 100, higher scores better

Outer ring = Age/gender (A/g) matched US norms specific to each gout population.

Note similarities between baseline domain scores in Phase 3 Pegloticase RCT and those reported in both TFG populations. Note similarities also between Age/gender matched norms; normative data for Phase 3 Pegloticase RCT population shown below as it closely overlaps with NHS Age/gender norms.

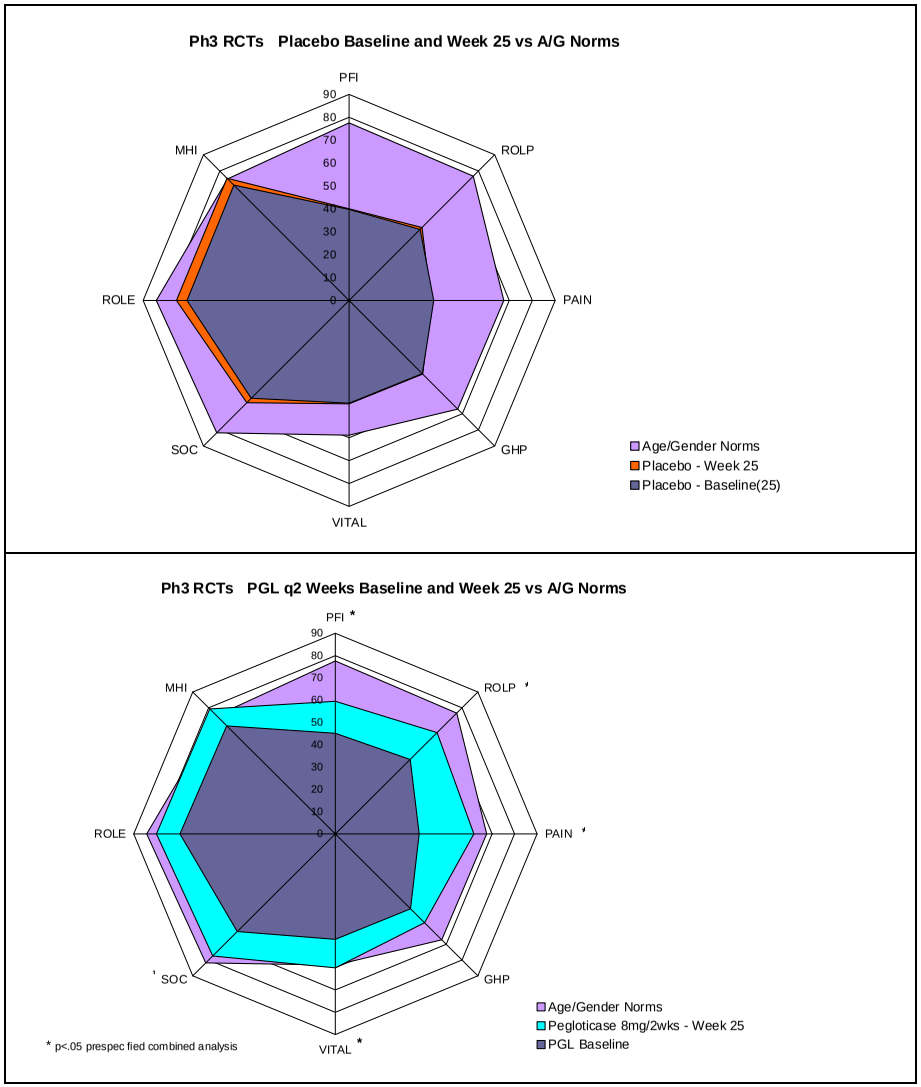


Figure 8-2. Mean Phase 3 SF-36 Domain Scores at baseline and 25 weeks in combined analysis, compared with age/gender matched US norms.

Inner ring = SF-36 domain Scores; scores range from 0 – 100, higher scores better
Outer ring = Age/gender matched US norms specific to the phase 3 population.
Middle ring = treatment associated changes at 25 weeks.
Gridlines along axes represent changes of 10 points, equivalent to 1 – 2x MCID

(A) Placebo treatment group: Note large decrements at baseline from Age/gender norms, and little to no improvement at 25 weeks..

(B) Pegloticase q 2 weeks treatment group: Note large, clinically meaningful improvements in 8 of 8 domains; changes which meet or exceed 5 – 10 points. Mean changes from baseline are statistically significant in 6 of 8 domains, which meet or exceed Age/gender norms in VIT and MHI, and approach normative values in BP, SOC, and RE.

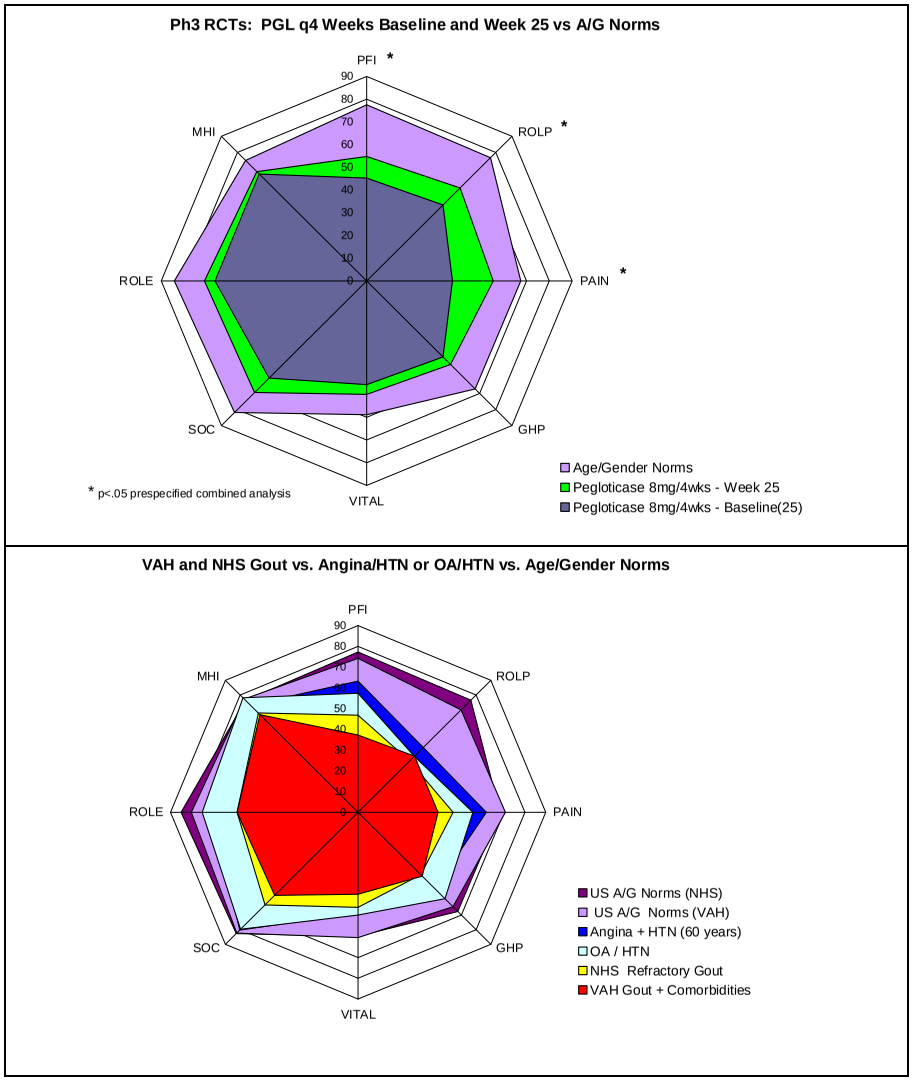


Figure 8-3. Mean Phase 3 SF-36 Domain Scores at baseline and 25 weeks in combined analysis, compared with Age/gender matched US norms.
Inner ring = SF-36 domain Scores; scores range from 0 – 100, higher scores better
Outer ring = Age/gender matched US norms specific to the phase 3 population.
Middle ring = treatment associated changes at 25 weeks.
Gridlines along axes represent changes of 10 points, equivalent to 1 – 2x MCID

Pegloticase q 4 weeks treatment group: Improvements are clinically meaningful in 4 of 8 domains; changes which meet or exceed 5 – 10 points. Mean changes from baseline are statistically significant in 3 of 8 domains

Spydergrams© of SF-36 domain scores in TFG populations compared with subjects with Osteoarthritis and Hypertension or Angina and Hypertension.
Inner ring = SF-36 Domain Scores; scores range from 0 – 100, higher scores better
Outer ring = Age/gender matched US norms specific to each gout population.

Figures illustrate decrements in reported HRQOL in Veterans + Comorbidities (VAH) in red and NHS in yellow Refractory Gout Populations vs US normative data specific to each population. HRQOL in both TFG populations compared with US population age 60 years with OA and Hypertension (light blue) or Angina and Hypertension [49].