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APPLICATION NUMBER:

125293

MEDICAL REVIEW(S)

Clinical Review of Complete Response

Date	08-20-10
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Subject	Clinical Review
NDA/BLA #	BLA 125293 Complete Response
Supplement#	37
Applicant	Savient, Inc.
Date of Submission	March 15, 2010
PDUFA Goal Date	September 14, 2010
Proprietary Name / Established (USAN) names	Krystexxa Pegloticase
Dosage forms / Strength	Intravenous, 8 mg every 2 weeks
Proposed Indication(s)	Treatment of chronic gout in patients refractory to conventional therapy
Recommended:	<i>Approval, with revisions to proposed labeling</i>

1. Introduction

Pegloticase is a PEGylated recombinant mammalian uricase (urate oxidase) enzyme that metabolizes uric acid into soluble allantoin. Pegloticase is being developed for the treatment of patients with chronic gout and hyperuricemia who have failed, or who are intolerant to, conventional uric acid-lowering therapies, e.g., allopurinol.

The original biologic licensing application for pegloticase was submitted October 31, 2008 and received a complete response on July 31, 2009 due to deficiencies in the chemistry, manufacturing, and control program and on inspection of the manufacturing facilities. The clinical data submitted with the original BLA was derived from two replicate, placebo controlled, randomized, double-blind, trials in 212 subjects with gout and hyperuricemia who were refractory, or intolerant, to allopurinol. Studies 405 and 406 randomized eligible subjects in a 2:2:1 ratio to one of three treatment arms: pegloticase 8 mg intravenously (IV) every 2 weeks, pegloticase 8 mg IV every 4 weeks, or placebo IV, respectively. Both studies used the proportion of subjects achieving a plasma uric acid (PUA) level <6 mg/dL at least 80% of the time at Months 3 and 6 of the 6-month studies for the primary efficacy endpoint. These data provided substantial evidence of the efficacy of pegloticase for the treatment of hyperuricemia in patients refractory, or intolerant, to conventional uric acid-lowering therapies. Subjects who completed the double-blind study were eligible to enroll in Study 407, a 24-month open-label extension study designed to continue treating subjects using open-label pegloticase 8 mg every 2 weeks or every 4 weeks.

Review of the original submission's safety database, which consisted of 273 subjects, identified several major safety signals associated with pegloticase treatment: 1) a higher rate of serious cardiovascular events, 2) a high incidence of infusion reactions, and 3) infusion

reactions meeting clinical criteria for anaphylaxis. Based on her analysis of the data and the conclusions of a consult from Dr. Stephen Grant of the Division of Cardiovascular and Renal Products, the primary reviewer, Dr. Rosemarie Neuner, concluded that the cardiovascular events did not fit a particular pattern and were not obviously unusual in view of the unequal randomization and multiple underlying risk factors of the patients involved. Additionally, Dr. Neuner noted that limitations associated with the pegloticase safety database precluded determination of the product's true cardiovascular risk. Pegloticase was highly immunogenic with 88% of patients in the pegloticase every 2 week group and 89% of patients in the pegloticase every 4 weeks group seroconverting to antibody positive status over the course of the studies. Higher titers of antibody to pegloticase were associated with higher rates of infusion reactions and decreases in urate-lowering effects of therapy. A review of all infusion reactions contained in the safety database by an internal pulmonary and allergy consultant from the Division of Pulmonary and Allergy Products revealed that approximately 5% of these patients met clinical criteria for anaphylaxis despite the mandated administration of antihistamines, acetaminophen, and corticosteroids prior to study drug infusions to attenuate infusion reactions. None of these cases of anaphylaxis resulted in a death of a subject. After weighing all the data, Dr. Neuner concluded that the overall risk/benefit relationship of pegloticase every 2 weeks is favorable in the intended target patient population.

An Arthritis Advisory Committee meeting was convened on June 16, 2009 to discuss the risks and benefits associated with pegloticase treatment in patients with gout and hyperuricemia refractory to conventional therapy. The committee could not reach agreement as to whether there was a true cardiovascular safety signal given the small number of cases and the multiple comorbidities of the subjects and recommended collecting additional postmarketing information. While the committee voted 14 to 1 in favor of approval, several members stated that it would be important to limit the use of pegloticase to patients who were truly refractory to conventional therapy.

The clinical review of this complete response submission will focus on the updated safety information collected since the 120-Day Safety Update with special focus on the safety signals identified in Dr. Neuner's original review, namely cardiovascular adverse events, infusion reactions, and anaphylaxis. No additional efficacy data were required or submitted for the complete response application. The reader is referred to Dr. Neuner's original clinical review of BLA 125293 for details of the efficacy and safety results submitted in the original BLA.

2. Background

Gout is typically characterized by recurrent attacks of acute inflammatory arthritis; however, a proportion of patients will develop chronic manifestations including arthritis, bone erosions, and tophi. The underlying pathophysiology of gout results from deposition of uric acid crystals into articular spaces and soft tissues and is more likely to happen in patients with hyperuricemia. Although many individuals with hyperuricemia never develop gout, the likelihood of developing the disease increases with increasing circulating levels of uric acid above 6 mg/dL. Acute gout flares are typically managed with non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, corticosteroids, or ACTH. Patients with three or more acute gout flares within a year and who have hyperuricemia are treated with uric acid lowering drugs, including the uricosuric drug probenecid and the anti-xanthine oxidase antagonists, allopurinol and febuxostat. A significant minority of these patients are refractory to, or intolerant of, these uric acid lowering drugs and are subject to prolonged episodes of recurrent arthritis and large tophi deposition.

Dr. Neuner's original clinical review of BLA 125293 found no issues concerning efficacy; however, in the clinical trials a higher proportion of patients in the pegloticase treatment arms developed cardiovascular serious adverse events than in the control arms and was associated with serious infusion reactions and adverse events meeting clinical criteria for anaphylaxis. The higher rate of serious cardiovascular events was seen in both pegloticase treatment arms without a clear dose relationship. Dr. Neuner, Dr. Grant, and the members of the Arthritis Committee concluded that the distribution of cardiovascular deaths and serious cardiovascular adverse events was not easily attributable to pegloticase given the subjects underlying comorbidities and the unequal randomization in the clinical trials; however, all parties agreed that there remains a degree of uncertainty about the cardiac safety of pegloticase due to the small sample size and limited duration of follow-up. (b) (4)

While a large cardiovascular outcome study may offer more conclusive results, it is not practical in this patient population since this is an orphan population.

Since pegloticase is a non-human protein, it is not surprising that more than 90% of all pegloticase-treated subjects developed anti-pegloticase antibodies to the product raising a concern for allergic reactions and infusion reactions. In fact, higher titers of antibody to pegloticase were associated with higher rates of infusion reactions and decreases in urate-lowering effects of therapy. To limit the frequency and severity of infusion reactions in the Phase 3 clinical trials, all patients were mandated to receive a standard pre-treatment prophylaxis regimen consisting of an antihistamine, acetaminophen, and corticosteroid prior to each infusion. Management of infusion reactions also included the slowing or stopping of the infusion with or without the administration of fluids or additional drugs as necessary. Despite these measures, a high proportion of subjects experienced moderate-to-severe infusion reactions within the pegloticase every 4 weeks group (36%) and the pegloticase every 2 weeks group (18%).

A consultant review of the infusion reactions by Dr. Susan Limb of the Division of Pulmonary and Allergy Products revealed that approximately 5% of these subjects met clinical criteria for anaphylaxis, which was higher than the Applicant's original estimate of anaphylaxis based on investigators' assessment of cases. This observed rate is likely lower than it would have been had the trial not mandated the use of the standard pre-treatment prophylaxis regimen described above. None of these cases of anaphylaxis resulted in a death of a subject. However, in many of the cases the reactions were of sufficient concern to discontinue pegloticase therapy. Conversely, several subjects received multiple additional infusions without recurrence.

This review will concentrate on the interim safety data regarding cardiovascular adverse events, infusion reactions, and cases of anaphylaxis occurring in the open-label extension trial since the last 120-day safety update. The reader is referred to Dr. Neuner's original clinical review of BLA 125293 for details of the efficacy and safety results submitted in the original BLA.

3. Brief Summary of Efficacy

As discussed above, the efficacy data submitted with the original BLA were derived from two replicate, placebo-controlled, randomized, double-blind, trials in 212 subjects with gout and hyperuricemia who were refractory, or intolerant, to allopurinol. Studies 405 and 406 randomized eligible subjects in a 2:2:1 ratio to one of three treatment arms: pegloticase 8 mg intravenously (IV) every 2 weeks, pegloticase 8 mg IV every 4 weeks, or placebo IV, respectively. Both studies used the proportion of subjects achieving a plasma uric acid level <6 mg/dL at least 80% of the time at Months 3 and 6 of the 6-month studies for the primary efficacy endpoint. The prespecified primary analysis used the intent-to-treat population and was analyzed using Fisher's exact test. A non-responder imputation was used for missing data.

As shown in Table 1, a greater proportion of subjects achieved the primary endpoint in both the pegloticase every 2 weeks (47% and 38% in studies 405 and 406, respectively) and pegloticase every 4 weeks (20% and 49% in Studies 405 and 406, respectively) treatment arms compared to placebo-treated subjects (0% in each study). The differences between each of the treatment groups and the placebo groups were statistically significant in both Studies 405 and 406. These data provide substantial evidence of the efficacy of pegloticase for the treatment of hyperuricemia in patients refractory, or intolerant, to conventional uric acid-lowering therapies.

Table 1. Primary Efficacy Endpoint For Studies 405 and 406: Proportion of Subjects Achieving a PUA < 6mg/dL for at Least 80% of the Time in Months 3 and 6 Combined (ITT Population)

Treatment Group	Number (%) of Subjects Who Met Response Criteria	95% Confidence Interval ¹	p-Value ²
Study 405			
Pegloticase q 2 Wks (N= 43)	20 (47%)	[32%, 61%]	<0.001
Pegloticase q 4 Wks (N=41)	8 (20%)	[7%, 32%]	0.044
Placebo (N=20)	0 (0%)		
Study 406			
Pegloticase q 2 Wks (N=42)	16 (38%)	[23%, 53%]	<0.001
Pegloticase q 4 Wks (N=43)	21 (49%)	[34%, 64%]	<0.001
Placebo (N=23)	0 (0%)		

¹95% confidence interval for differences in responder rate between corresponding pegloticase groups vs. placebo
²P-value using Fisher's exact test to compare corresponding pegloticase group vs. placebo.
 Source: Dr. Rosemarie Neuner's clinical review, Table 32

In both studies, the every 2-week dosing regimen reduced mean plasma uric acid levels to <6 mg/dL throughout the double-blind period of the trial, while the every 4-week dosing regimen reduced mean uric acid levels to <6 mg/dL for the entire 6-months only in Study 406. Additionally, the every 4-week dosing regimen was less effective at resolving tophi, a major secondary endpoint. These results suggest that the every 2-week regimen is more efficacious than the every 4-week regimen and given that the 2-week regimen demonstrated a better safety profile than the every 4-week regimen, the every 2-week regimen is preferable and recommended for marketing. For additional details of the study designs and efficacy results, the reader is referred to Dr. Rosemarie Neuner's clinical review for the original BLA 125293.

Tophi resolution was evaluated as a major secondary endpoint in Studies 405 and 406. Tophi were assessed using digital photographs and defined as “measurable” and “unmeasured” by a central blinded reader who prospectively identified sites of tophi to be evaluated in the studies. A complete response was defined as complete resolution (100%) of at least one of the subjects’ identified “measurable” or “unmeasured” tophi, with lesser degrees of response termed: marked response, partial response, or stable disease. While only 8% of subjects in the placebo arm had complete tophus response, a total of 45% of subjects treated with pegloticase every 2-week arm and 26% in the every 4 week arm had a complete tophus response. This response was statistically significant for the pegloticase every 2 week group and trended positive in the every 4 week arm but failed to reach statistical significance. These results are clinically meaningful given that tophi resolution is rarely seen in the chronic gout population using standard uric acid lowering drugs.

4. Safety

Sources of data for the safety update in this complete response submission include the updated cumulative safety data from subjects who were enrolled in the completed randomized, double-blinded, placebo-controlled Studies 405 and 406 and from those subjects who then participated in the ongoing open-label extension trial, Study 407. The new safety data encompasses the time from the clinical database soft-lock of the 120-Day Safety Update on November 3, 2008 to the current safety database soft-lock of September 16, 2009. This new data adds an additional 105 person-years since the 120-Day Safety Update while also adding to the total number of subjects treated longer than 12 months with 110, 102, and 71 total patients being treated for ≥ 12 , ≥ 18 , ≥ 24 months, respectively. Table 2 shows the disposition of subjects enrolled in Study 407. Approximately 70% of subjects who were enrolled in the double-blind studies and randomized to the pegloticase treatment arms continued in the open-label extension study (Table 2).

Table 2. Subject Disposition for Open-Label Extension Study 407

	Combined treatment assignments during double-blind periods ¹		
	Pegloticase Q 2 wks	Pegloticase Q 4 wks	Placebo
Subjects Treated in Double-Blind Studies (ITT)	85	84	43
Completed Double-Blind Study, n (%)	59 (69)	59 (70)	39 (91)
Continued on OLE Study, n (%)	57 (97)	56 (95)	38 (97)
OLE Study Treatment Arm Selection, n (%)²			
Q 2 wks	34 (60)	25 (45)	23 (61)
Q 4 wks	23 (40)	28 (50)	16 (39)
Observational Arm	0	2 (5)	.0
Withdrew from OLE Study, n (%)^{2,3}	12 (17)	18 (33)	18 (46)
Adverse Events	2 (4)	6 (10)	8 (21)
Withdrawal of Consent	3 (5)	3 (5)	5 (13)
Lost to Follow-up	1 (2)	3 (5)	1 (3)
Administrative	2 (4)	2 (4)	1 (3)
Treatment Failure	1 (2)	2 (4)	2 (5)
Non-Compliance	2 (4)	1 (2)	1 (3)
Death	1 (2)	1 (2)	0
Protocol Violation	0	0	0
¹ Treatment arms combined from Studies 405 and 406			
² expressed as percentage of corresponding subjects who continued on to OLE Study			
³ numbers represent placebo-treated subjects who entered the OLE Study and were treated with open-label Pegloticase Q 2wks or Q 4 wks			

The ICH E1A guidance document recommends that under normal circumstances products intended for chronic use should have a total of 1500 patients treated with the study drug including 300-600 treated for 6 months and 100 treated for at least one year. However, the

same guidance also recommends adjusting the recommended size of the safety database depending on the size of the patient population. Given that the population in question for this application is an orphan population with an estimated prevalence of 100,000 the size of the safety database for pegloticase is not unreasonable.

Where appropriate, the safety tables that follow attempt to compare safety data between the double-blind periods of Studies 405 and 406 to the safety data collected during the open-label extension period of Study 407. Direct comparisons between the two study periods were limited to some degree by the Applicant's combining subject data from the double-blind and open-label extension studies. Further complicating the comparison, were features incorporated in the design of Study 407 that allowed subjects entering the study to determine their treatment frequency of pegloticase, either every 2 weeks or every 4 weeks, or to an observational arm of the study. Subjects were also allowed to switch treatment arms up to two times over the 24-month period. Subjects who completed treatment in C0405 or C0406 but who did not wish to receive further treatment with pegloticase. As shown in Table 3, 82 subjects initially enrolled to receive pegloticase every 2 weeks, 67 subjects received pegloticase every 4 weeks, and 2 subjects entered the observational arm. Despite the ability to switch treatment arms, the majority of patients remained in their original chosen treatment group. Overall, the minor limitations of the data did not interfere with the ability to adequately assess the current safety data within the context of the original clinical review.

Table 3. Changes in Treatment Arms During Open-Label Extension Study 407

	Initial treatment arm assignment in OLE Study n	First Switch in OLE Study 407			Second Switch in OLE Study 407		
		Pegloticase 8 mg		Observation Arm n (%)	Pegloticase 8 mg		Observation Arm n (%)
		Q 2 wks n (%)	Q 4 wks n (%)		Q 2 wks n (%)	Q 4 wks n (%)	
Pegloticase Q 2 wks ¹	82	57 (70)	9 (11)	16 (20)	2 (2)	0	0
Pegloticase Q 4 wks ¹	67	10 (15)	50 (75)	7 (10)	0	0	3 (5)
Observation Arm	2	0	0	2 (100)	0	0	0

¹Treatment arms combined from Studies 405 and 406
 Source: Sponsor Table 48 from the ISS

- **Discussion of deaths, serious adverse events, adverse events leading to discontinuation, general adverse events and results of laboratory tests**

Deaths

There were a total of 9 deaths reported in the pegloticase clinical development program up to the time of the 120-Day Safety Update and are discussed in detail in Dr. Neuner's review. Since the database lock of the 120-Day Safety Update there has been one death reported. Subject C0406-301-002 was a 54-year-old male with late stage AIDS (HIV-2), chronic renal disease, and non-insulin dependent diabetes who was initially randomized to the pegloticase every 2-weeks treatment arm during the double-blind period and then to the pegloticase every 4-weeks in the open label extension trial. Three months after his last pegloticase infusion, the subject was hospitalized for pneumonia and required artificial ventilation. The subject was extubated after 7 days and requested a "do not resuscitate" status. Over the next 24 hours he developed multiple organ failure and died on hospital Day 15. This does not appear to be related to pegloticase treatment given the subject's underlying comorbidities and the time since the last infusion.

Serious Adverse Events

A total of 53 new serious adverse events were reported since the 120-Day Safety Update bringing the total to 205 serious adverse events reported to date over the course of Studies 405, 406, and 407. Five new serious adverse events preferred terms were reported for the first time in the clinical development program including respiratory failure, worsening lumbar stenosis, ankle fracture, femoral artery occlusion, and arterial thrombosis of limb. None of the serious adverse events appeared to be related to pegloticase.

The rate of serious adverse events since the 120-Day Safety Update is 0.51 events/person-years, which is comparable to the 0.58 events/person-years rate during the time leading up to the locking of the 120-Day Safety database. Table 5 shows the number of new serious adverse events that have occurred beyond the 120-Day Safety Update by Body System and Preferred Term. Of note, there was only a single case of a serious adverse event related to an infusion reaction. Overall, the rate and type of serious adverse events reported since the 120-Day Safety Update is consistent with those seen in the initial clinical review by Dr. Neuner.

Table 5. New Serious Adverse Events Beyond the 120-Day Safety Update by Body System & Preferred Term Including Infusion Reactions and Gout Flares

	Pegloticase-Treated Subjects During Double-Blind and OLE Periods		Previous Placebo Subjects	
	Pegloticase Q 2wk ¹	Pegloticase Q 4 wk ¹	Pegloticase Q 2wk n=23	Pegloticase Q 4 wk n=16
Number of SAEs, n	19	27	6	1
Subjects with SAEs, n	10	12	5	1
System Organ Class Preferred Term	n	n	n	n
Infections & Infestations	3	2	1	0
Pneumonia	1	1	0	0
Arthritis Bacterial	1	0	0	0
Bronchitis	0	1	0	0
Osteomyelitis	0	0	1	0
Urinary Tract Infection	1	0	0	0
Cardiac Disorders	1	2	2	0
CHF	1	1	1	0
Atrial Fibrillation	0	0	1	0
Myocardial Infarction	0	1	0	0
General Disorders & Administration Site Conditions	2	3	0	0
Asthenia	0	1	0	0
Chest Pain	1	0	0	0
Infusion Related Reaction	0	1	0	0
Non-Cardiac Chest Pain	0	1	0	0
Peripheral Edema	1	0	0	0
Musculoskeletal & Connective Tissue Disorders	2	2	0	0
Gouty Tophus	1	0	0	0
Lumbar Spinal Stenosis	0	1	0	0
Musculoskeletal Pain	1	0	0	0
Shoulder Pain	0	1	0	0
Renal & Urinary Disorders	1	3	1	0
Renal Failure	0	1	1	0
Renal Failure Acute	1	1	0	0
Renal Cyst	0	1	0	0
Renal Failure Chronic	0	0	1	0

¹ Absolute number of cumulative events for the double-blind and OLE study periods are listed. Number of subjects differed between study periods due to subject discontinuation and changing of treatment arms during the OLE study. Refer to Table for subject disposition.
 Source: Sponsor's Table 68 from ISS.

Table 5. New Serious Adverse Events Beyond the 120-Day Safety Update by Body System & Preferred Term Including Infusion Reactions and Gout Flares (continued)

	Pegloticase-Treated Subjects During Double-Blind and OLE Periods		Previous Placebo Subjects	
	Pegloticase Q 2wk	Pegloticase Q 4 wk	Pegloticase Q 2wk n=23	Pegloticase Q 4 wk n=16
Gastrointestinal Disorders	2	1	0	0
Constipation	1	0	0	0
Diarrhea	0	1	0	
Diverticular Perforation	1	0	0	0
Injury, Poisoning & Procedural Complications	0	3	0	0
Ankle Fracture	0	1	0	0
Humerus Fracture	0	1	0	0
Multiple Fractures	0	1	0	0
Metabolism & Nutrition Disorders	2	1	0	0
Fluid Overload	1	1	0	0
Hypoglycemia	1	0	0	0
Respiratory, Thoracic & Mediastinal Disorders	2	1	0	0
Nasal Septum Deviation	1	0	0	0
Pulmonary Embolism	1	0	0	0
Respiratory Failure	0	1	0	0
Vascular Disorders	0	2	1	0
Hypotension	0	1	1	
Arterial Thrombosis Limb	0	1	0	0
Femoral Artery Occlusion	0	1	0	0
Surgical & Medical Disorders	1	0	0	1
Impl Defibrillator Replacement	1	0	0	0
Inguinal Hernia Repair	1	0	0	0
Wound Treatment	0	0	0	1
Immune System Disorders	0	1	0	0
Anaphylactoid Reaction	0	1	0	0
Investigations	0	1	0	0
Creatinine Clearance Decreased	0	1	0	0
Nervous System Disorders	1	0	0	0
Hepatic Encephalopathy	1	0	0	0
Psychiatric Disorders	0	1	0	0
Depression	0	1	0	0
Suicidal Ideation	0	1	0	0
Skin and Subcutaneous Tissue d/o	0	1	0	0
Skin Necrosis	0	1	0	0

¹ Absolute number of cumulative events for the double-blind and OLE study periods are listed. Number of subjects differed between study periods due to subject discontinuation and changing of treatment arms during the OLE study. Refer to Table for subject disposition.
 Source: Sponsor's Table 68 from ISS. 2 of 2

Discontinuations Due to Adverse Events

As shown in Table 6, nine new adverse events leading to discontinuation from the study were reported since the 120-Day Safety Update. The rate of adverse events that have lead to discontinuation since the 120-Day Safety Update is 0.05 events/person-years, which is less than the 0.17 events/person-years rate during the time leading to the locking of the 120-Day Safety database. Overall, the pattern of adverse events causing discontinuation remains consistent with previously submitted data in the original BLA and no single adverse event occurred in more than one subject.

Table 6. New Adverse Events Beyond the 120-Day Safety Update that Led to Study Discontinuation by Body System & Preferred Term

	Pegloticase-Treated Subjects During Double-Blind and OLE Periods		Placebo-Treated Subjects During Double-Blind Study	
	Pegloticase Q 2wk ¹	Pegloticase Q 4 wk ¹	Pegloticase Q 2wk n=23	Pegloticase Q 4 wk n=16
Number of Adverse Events Leading to Discontinuation	2	5	0	2
Number of Subjects with Adverse Event Leading to Discontinuation	2	5	0	2
System Organ Class Preferred Term	n	n	n	n
Cardiac Disorders	0	2	0	0
CHF	0	1	0	0
Myocardial Infarction	0	1	0	0
Infections & Infestations	2	0	0	0
Arthritis Bacterial	1	0	0	0
Upper Respiratory Tract Infection	1	0	0	0
General Disorders & Administration Site Conditions	0	1	0	0
Infusion Related Reaction	0	1	0	0
Immune System Disorders	0	1	0	0
Anaphylactoid Reaction	0	1	0	0
Musculoskeletal & Connective Tissue Disorders	0	0	0	1
Gout	0	0	0	1
Renal & Urinary Disorders	0	1	0	0
Renal Failure Acute	0	1	0	0
Surgical & Medical Disorders	0	0	0	1
Wound Treatment	0	0	0	1

¹ Absolute number of cumulative events for the double-blind and OLE study periods are listed. Number of subjects differed between study periods due to subject discontinuation and changing of treatment arms during the OLE study. Refer to Table for subject disposition.
 Source: Sponsor's Table 73 from ISS.

Common Adverse Events and Laboratory Tests

A total of 741 new adverse events were reported since the 120-Day Safety Update including infusion reactions and gout flares (Table 7). A total of 313 new adverse events were reported in the pegloticase every 2-week arm and 272 new adverse events reported in the pegloticase every 4-week arm. One hundred fifty six (156) new adverse events occurred in subjects who previously received placebo during the double-blind periods and enrolled into one of the two pegloticase treatment groups (data not shown). The reader is referred to Table 56 of the Applicants current submission for a full listing of treatment-emergent adverse events reported during Studies 405, 406, and 407. Overall, the rate of adverse events since the 120-Day Safety Update is 7.1 events/person-years, which is approximately half of the rate during the time up to the locking of the 120-Day Safety database (14.4 events/person-years). There were 93 new adverse event preferred terms reported since the 120-Day Safety Update that were not previously reported in the previous review of safety data. All of the cases of new adverse event preferred terms were reported only once except for coccydynia, periodontal disease, limb injury, and pulmonary edema, each of which were reported in two subjects. Analysis of hematology and chemistry laboratory assessments did not demonstrate a change from those found in Dr. Neuner's review. This may suggest that chronic treatment with pegloticase for longer than one year may not affect subject's laboratory tests.

Table 7. Summary of Treatment-Emergent Adverse Events Including Infusion Reactions and Gout Flares of Pegloticase-Treated Subjects by Treatment Group for the Double-Blind and Open-Label Extension Periods

	Pegloticase 8 mg			
	Q 2 wks n=85		Q 4 wks n=84	
	120-Day Safety Update	Current Safety Update	120-Day Safety Update	Current Safety Update
Number of AEs	1233	1546	1658	1930
	n (%)	n (%)	n (%)	n (%)
Subjects with AEs	84 (99)	84 (99)	84 (100)	84 (100)
Subjects with SAEs	29 (34)	33 (39)	30 (36)	36 (43)
Subjects with Treatment Discontinued Due to AE	20 (24)	20 (24)	22 (26)	27 (32)

AE: adverse event; SAE: serious adverse event; Source: Sponsor's Table 53 from ISS.

In general, the rate and types of adverse events were similar to that reported in the review of the original submission by Dr. Neuner and no new safety signals are identified in this review of the safety data submitted since the 120-Day Safety Update.

Special safety concerns

Cardiovascular Adverse Events

A total of 15 subjects experienced a cardiovascular-related adverse event since the 120-Day Safety Update. The rate of cardiovascular adverse events occurring since the 120-Day Safety Update is 8.6 events per 100 person-years and is comparable to the 8.4 events per 100 person-years observed in the Phase 3 clinical studies prior to the locking of the 120-Day Safety database. The Applicant's cardiovascular adjudication committee identified 9 new serious cardiovascular-related adverse events since the 120-Day Safety Update, of which one met criteria as an Anti-platelet Trialists Collaborative (APTC) event. Table 8 shows the Applicant's adjudication committee's assessment of serious cardiovascular events for the 6-month controlled period and the open-label extension period using APTC criteria. The rate of APTC events during the 6-month controlled period was 4 events/100 patient-years compared to 1.4 events/100 patient-years during the open-labeled period. Similarly, the rate of non-APTC events during the 6-month controlled period was 12 events/100 patient-years compared to 6.6 events/100 patient-years during the open-labeled period. The Agency's analysis of adjudicated events during the 6-month double-blind period by categorizing cardiovascular events as ischemic or non-ischemic in nature, categories showed results that are similar to that of the Applicant's analysis (Table 8). Overall, these data show that a similar number of APTC and non-APTC events occurred in both the controlled and open-labeled periods of the trial and that chronic exposure to pegloticase did not appear to increase the overall risk for cardiovascular adverse events.

Table 8. Major Cardiovascular Adverse Events Occurring in the Pegloticase Double-Blind and Open-Label Extension Studies

	6-Month Controlled Period			Open-Label Extension Period		
	Placebo n=43	Pegloticase Q 2 wk n=85	Pegloticase Q 4 wk n=84	Previous Placebo n=39 ¹	Pegloticase Q 2 wk n=59 ² (total inc pbo=82)	Pegloticase Q 4 wk n=51 ² (total inc pbo=67)
FDA DCRP-Adjudicated Analysis						
Subjects with Major CV AE, n(%)	1 (2)	5 (6)	3 (4)	3 (8)	6 (10)	1 (2)
Ischemic CVD						
Sudden death	0	2	0	0	0	0
Nonfatal MI	0	0	1	0	2	1
“Troponin leak”	1	0	0	0	0	0
TIA	0	0	1	0	0	0
Heart Failure						
CHF	0	2	0	2	4	0
Cardiac Arrhythmias						
SVT	0	0	1	1	0	0
VT	0	1	0	0	0	0
Applicant Adjudicated Analysis						
Subjects with Major CV AE, n(%)	0	4 (5) ³	6 (8)	5 (13)	8 (14) ³	1 (2)
APTC Events						
CV death	0	2	0	0	0	0
Nonfatal MI	0	0	1	0	2	1
Nonfatal Stroke	0	0	0	0	0	0
Non-APTC CV Events						
Angina	0	0	1	0	0	0
CHF	0	2	1	2	4	0
Arrhythmia	0	1	1	1	0	0
DVT/PE	0	0	1	2	3	0
TIA	0	0	1	0	0	0

¹ 23 placebo pts went to q2wk, 16 to q4wk, 2 to observation only; 4/5 subjects in this column were on pbo q2wk; the other on obs.
² Patients were allowed to select their dose regimen in OLE and switch up to 2 times. See Table 47 of ISS for transition numbers.
³ One subject experienced more than one event
 Source: Dr. Sarah Okada's CDTL review, Dr Neuner's Tables 53 and 54, Sponsor Table 65 from the ISS

Congestive heart failure (CHF) was the most commonly occurring cardiovascular adverse event in both the 6-month controlled period and the open-label extension study. A potential mechanism to account for the increased incidence of CHF would be the increased fluid and protein load from the biweekly pegloticase infusions, as well as the corticosteroid bolus prior to each infusion, in a patient population with underlying cardiac disease. Given that the targeted patient population for pegloticase is likely to have underlying cardiovascular disease, language should be added into the product label to warn physicians of an increased risk of CHF in patients treated with pegloticase.

Overall, the rate and types of adverse events observed during the current safety update were similar to those reported in the review of the original submission by Dr. Neuner. No new cardiovascular safety signals are identified in this review of the safety data submitted since the 120-Day Safety Update.

Anaphylaxis

For her review of the original submission, Dr. Neuner obtained an internal consultation from Dr. Susan Limb of the Division of Pulmonary and Allergy Products for help in assessing cases of anaphylaxis among the range of infusion reactions observed in the pegloticase safety database which included the Phase 1 Study 402, Phase 2 Study 403, and Phase 3 Studies 405, 406, and 407. Dr. Limb used the diagnostic criteria proposed by the NIAID/FAAN Joint Symposium¹ on Anaphylaxis to characterize adverse events as anaphylaxis based on their presenting signs and symptoms regardless of the presence or absence of IgE antibody to the suspected allergen. Based on her review of the data, Dr. Limb concluded there were 14 cases meeting the NIAID/FAAN proposed diagnostic criteria for anaphylaxis in the pegloticase safety database resulting in an overall estimated frequency of anaphylaxis associated with pegloticase of 5% (14 out of 273 subjects who received IV pegloticase). A formal review for cases meeting the NIAID/FAAN diagnostic criteria for anaphylaxis in the current safety update was not performed as only one subject was reported to have had a serious adverse event related to an infusion reaction. Subject C0405-122-002 received placebo during the 6-month double-blind period and then received pegloticase 8 mg every 2 weeks in the open-label extension period when they experienced chest discomfort, headache, hypertension, and musculoskeletal discomfort during their thirty-eighth infusion. These symptoms, although severe, are not typical of those associated with an anaphylactic reaction.

Although no subjects died due to anaphylaxis in the pegloticase development program, a black box warning should be considered in the product label given the frequency of anaphylaxis in subjects treated with pegloticase and the potential for death or serious morbidity.

Infusion Reactions

Dr. Neuner's review of the 6-month controlled studies clearly demonstrated an increased incidence of infusion reactions in subjects treated with pegloticase every 2-weeks and every 4-weeks compared to placebo-treated subjects (26%, 41% vs. 5%, respectively). Infusion reactions were defined by the Applicant as an adverse event, or cluster of adverse events, that occurred during or within 2 hours after the end of the study drug infusion. The most common signs and symptoms associated with an infusion reaction included back pain, chest discomfort/pain, chills, dizziness, dyspnea, erythema/flushing, headache, hyperhidrosis, hypertension/hypotension, muscle spasms, nausea, pain, pruritis, rash, tachycardia, throat tightness, urticaria, and wheezing. The data in Table 9 shows the incidence of infusion reactions, and the occurrence of the first infusion reaction, that occurred during the 6-month controlled periods. Infusion reactions occurred with nearly equal frequency regardless of the number of pegloticase dosing infusions. Moreover, the data demonstrate that subjects are at risk for developing their first infusion reaction at any infusion of pegloticase regardless of not having had an infusion reaction during previous infusions of pegloticase.

¹ Sampson, HA et al. J Allergy Clin Immunol 2006; 117:391-7

Table 9. Incidence of Infusion Reactions in Studies 405 and 406

	Pegloticase 8mg Q 2 wks n=85, n (%)	Pegloticase 8mg Q 4 wks n=84, n (%)	Placebo n=84, n (%)
Any Infusion Reaction	22 (26)	34 (41)	2 (5)
Serious Infusion Reaction	4 (5)	7 (8)	0
Percentage¹ of Subjects with Infusion Reactions, by Dose			
Week 1 (Dose 1)	1 (1)	4 (5)	1 (2)
Week 3 (Dose 2)	4 (5)	1 (1)	1 (2)
Week 5 (Dose 3)	6 (8)	16 (20)	1 (2)
Week 7 (Dose 4)	7 (9)	0	1 (2)
Week 9 (Dose 5)	5 (7)	15 (20)	0
Week 11 (Dose 6)	3 (4)	0	0
Week 13 (Dose 7)	1 (1)	8 (11)	0
Week 15 (Dose 8)	3 (4)	2 (3)	0
Week 17 (Dose 9)	4 (6)	13 (20)	0
Week 19 (Dose 10)	3 (5)	1 (1)	0
Week 21 (Dose 11)	2 (3)	8 (13)	0
Week 23 (Dose 12)	3 (5)	1 (2)	0
Percentage¹ of Subjects with First Infusion Reactions, by Dose			
Week 1 (Dose 1)	1 (5)	4 (12)	1 (50)
Week 3 (Dose 2)	4 (18)	1 (3)	NA
Week 5 (Dose 3)	3 (14)	15 (44)	NA
Week 7 (Dose 4)	5 (23)	NA	1 (50)
Week 9 (Dose 5)	1 (5)	6 (18)	NA
Week 11 (Dose 6)	2 (9)	NA	NA
Week 13 (Dose 7)	1 (5)	2 (6)	NA
Week 15 (Dose 8)	3 (14)	1 (3)	NA
Week 17 (Dose 9)	NA	4 (12)	NA
Week 19 (Dose 10)	2 (9)	NA	NA
Week 21 (Dose 11)	NA	1 (3)	NA
Sources: Dr. Sarah Okada and Sponsor Tables 28, 29, 31, and 33 of ISS Denominators are remaining subjects in the treatment group			

Since anti-pegloticase antibodies mediate a large proportion of the adverse events associated with the infusion reactions and neutralize pegloticase's enzymatic activity, the sponsor conducted a post hoc analysis investigating whether a relationship existed between the rate of infusion reactions and the loss of pegloticase activity. Table 10 shows that the loss of pegloticase response, defined as a serum uric acid ≥ 6 mg/dL, was strongly associated with subjects experiencing an infusion reaction. As expected, those patients experiencing an infusion reaction coincident with their first pegloticase dose also had serum uric acid levels ≥ 6 mg/dL.

A total of 96 of 212 (45%) subjects treated during the double-blind and open-label extension periods reported infusion reactions. Of these 96 subjects, 2 subjects received placebo and 10 subjects experienced an infusion reaction with their first infusion of pegloticase. Of the remaining 84 pegloticase-treated subjects who experienced infusion reactions, 71 (85%) subjects had a preceding serum uric acid ≥ 6 mg/dL compared to 13 (15%) subjects who had a serum uric acid < 6 mg/dL.

Table 10. Infusion Reactions by Treatment Group and Serum Uric Acid Levels

	Pegloticase-Treated Subjects During Double-Blind and OLE Periods				Placebo-Treated Subjects During Double-Blind Study OLE Period			
	Q 2 wks n=85		Q 4 wks n=84		Q 2 wks n=23		Q 4 wks n=16	
	≤ 6 mg/dL	≥ 6 mg/dL	≤ 6 mg/dL	≥ 6 mg/dL	≤ 6 mg/dL	≥ 6 mg/dL	≤ 6 mg/dL	≥ 6 mg/dL
Subjects with Infusion Reaction n (%)	27 (32)		43 (51)		12 (52)		12 (75)	
Serum Uric Acid	≤ 6 mg/dL	≥ 6 mg/dL	≤ 6 mg/dL	≥ 6 mg/dL	≤ 6 mg/dL	≥ 6 mg/dL	≤ 6 mg/dL	≥ 6 mg/dL
n (% subjects with infusion reaction in dose group)								
Infusion Reaction @ Any Visit	3 (11)	24 (89)	8 (19)	35 (81)	0	12 (100)	2 (17)	10 (83)
Infusion Reaction @ 1st Visit	0	1 (4)	0	4 (9)	0	4 (33)	0	1 (8)
Source: Sponsor Table 77 Data for placebo subjects from Studies 405 and 406 not shown								

The Applicant contends that had pegloticase treatment been discontinued when the subjects' serum uric acid values were first found to be ≥ 6 mg/dL that the infusion reactions would have been prevented. Of note, all but 1 subject who met criteria for anaphylaxis had serum uric acid levels ≥ 6 mg/dL.

Based on these data the Applicant has proposed a Risk Evaluation and Mitigation Strategy (REMS) that recommends discontinuing pegloticase treatment if a patient's serum uric acid exceeds 6 mg/dL under the premise that a loss of ability to maintain normalized uric acid values < 6 mg/dL is predictive of the risk for infusion reactions. Dr. Ruthanna C. Davi of the Office of Biostatistics noted in her review that the Applicant's analysis does not address what effect stopping pegloticase early in certain subjects may have on the efficacy of the product in the intended patient population. Additionally, Dr. Davi notes that the Applicant's analysis is relying on the serum uric acid level *at the time* of the infusion reaction as a predictor of the event; however, in clinical practice, it is much more likely that the physician would know the serum uric acid level at the *previous* visit and not the serum uric acid level at the time of the current infusion. Consequently, use of the serum uric acid level prior to the infusion should be used as the measure for deciding whether pegloticase treatment should be discontinued. Dr. Davi used descriptive statistics to evaluate the benefit of pegloticase infusions versus the risk of developing an infusion reaction if pegloticase infusions were discontinued after subjects demonstrated one serum uric acid > 6 mg/dL compared to two consecutive serum uric acid elevations ≥ 6 mg/dL (Table 11). Additional analyses regarding different cutoff values of

serum uric acid were also explored. All analyses relied only on serum uric acid levels prior to the infusion reaction, which simulates the clinical setting.

Table 11: Benefit-Risk of Stopping Pegloticase (8 mg every 2 weeks) Early

Pegloticase Stopping Rule	Infusion Reaction Observed Before Reaching Criteria			Efficacy Responder ¹²		
	C405 (N=43) n (%)	C406 (N=42) n (%)	Pooled (N=85) n (%)	C405 (N=43) n (%)	C406 (N=42) n (%)	Pooled (N=85) n (%)
No Stopping Criteria	11 (26%)	11 (26%)	22 (26%)	20 (47%)	16 (38%)	36 (42%)
One SUA > 6 mg/dL	3 (7%)	4 (10%)	7 (8%)	15 (35%)	16 (38%)	31 (36%)
One SUA > 7 mg/dL	3 (7%)	4 (10%)	7 (8%)	16 (37%)	16 (38%)	32 (38%)
One SUA > 8 mg/dL	4 (9%)	5 (12%)	9 (11%)	17 (40%)	16 (38%)	33 (39%)
Two consecutive SUA > 6 mg/dL	6 (14%)	6 (14%)	12 (14%)	19 (44%)	16 (38%)	35 (41%)
Two consecutive SUA > 7 mg/dL	6 (14%)	6 (14%)	12 (14%)	19 (44%)	16 (38%)	35 (41%)
Two consecutive SUA > 8 mg/dL	7 (16%)	6 (14%)	13 (15%)	20 (47%)	16 (38%)	36 (42%)

¹Efficacy responder was defined in the study protocols as a subject who achieved and maintained plasma uric acid concentrations less than 6 mg/dL for at least 80% of the time during months 3 and 6 combined.
²No placebo subjects in either C405 or C406 were efficacy responders. Two subjects who received placebo experienced an infusion reaction while their serum uric acid levels were each above 10 mg/dL.
 Source: Dr. Ruth Davi's Statistical Review Table 3

As shown in Table 11, 26% of subjects from Studies 405 and 406 who were treated with pegloticase 8 mg every 2 weeks developed an infusion reaction and 42% met the Studies' primary endpoint. If pegloticase treatment was discontinued after a single elevation in serum uric acid >6mg/dL only 8% of subjects would have experienced an infusion reaction but at the expense of lowering efficacy to 36% of subjects achieving the primary endpoint. However, discontinuing pegloticase treatment after subjects had two consecutive elevations of serum uric acid would decrease the incidence of infusion reactions to 14% of subjects while maintaining efficacy at approximately 41% of subjects. Use of higher elevations of serum uric acid did not change the overall analysis. Since pegloticase is intended to target a subset of hyperuricemic patients who are refractory to conventional uric acid lowering therapies, continuing pegloticase

therapy until a patient has had two consecutive elevated serum uric acid levels before discontinuing therapy may allow for an acceptable risk-benefit as opposed to discontinuation of treatment after a single elevated serum uric acid. In fact, Dr. Davi's review includes several examples demonstrating subjects from Studies 405 and 406 who had a single serum uric acid >6 mg/dL but still responded to pegloticase after subsequent infusions (b) (4)

The reader is referred to Dr. Ruthanna Davi's review for full discussion of these analyses.

Given the high incidence of infusion reactions despite pre-infusion prophylaxis and the inability to predict when an infusion reaction is likely to occur, language should be added to the product label addressing the frequency of infusion reactions, recommend pre-infusion prophylaxis with an antihistamine, non-steroidal anti-inflammatory drug, and corticosteroid, and to alert healthcare providers that patients are at risk of an infusion reaction with any pegloticase infusion. Additional language regarding stopping guidelines for patients with serum uric acid levels ≥ 6 mg/dL should be also be added to the product label

• Safety Conclusions

The safety data from the pegloticase Phase 3 trials and open-label extension trial have identified three main areas of concern: 1) a higher rate of serious cardiovascular events, 2) a high frequency of infusion reactions and 3) cases of anaphylaxis.

Overall it is difficult to say conclusively whether the safety data indicate a clear safety signal regarding cardiovascular adverse events as the overall data are insufficient to reach firm conclusions. The higher rate of serious cardiovascular events was seen in both pegloticase treatment arms compared to placebo-treated subjects but there was no clear relationship to dose or pattern of adverse events. Furthermore, the rate of cardiovascular events was stable throughout the double-blind and open-label extension portions of the trial suggesting no additional risk to subjects with prolonged exposure to pegloticase. The Office of Surveillance and Epidemiology (OSE) Division of Epidemiology (DEPI) was consulted during this review cycle for their opinion regarding the utility of a postmarketing observational epidemiology study as suggested by the June 16, 2009 Arthritis Advisory Committee. As expressed in their June 6, 2010 consult, OSE/DEPI's opinion is that an epidemiology study will unlikely be helpful given that the causality of the cardiovascular events is so confounded by the patients underlying comorbidities, small sample size, and long duration of exposure to other gout treatments. Consequently, they concluded that the usual practice of reporting adverse events to the manufacturer and the Agency should be sufficient.

Infusion reactions and cases meeting clinical criteria for anaphylaxis are highly correlated with antibodies to pegloticase. Although no subjects died due to anaphylaxis in the pegloticase development program, a black box warning should be considered in the product label given the

frequency of anaphylaxis in subjects treated with pegloticase and the potential for death or serious morbidity. To help reduce the risk of infusion reactions and anaphylaxis the product label should include instructions to the physician recommending use of a preinfusion prophylactic regimen of antihistamines, non-steroidal anti-inflammatory drugs, and corticosteroids. Additionally, language should be added advising physicians to discontinue pegloticase treatment in patients who have had an anaphylactic reaction, serious infusion reactions, or two consecutive uric acid levels ≥ 6 mg/dL, which demonstrates a loss of efficacy of the drug due to neutralizing antibodies and an increased risk of developing an infusion reaction. Given the small number of patients enrolled in the pegloticase developmental program, an observational safety study enrolling 500 patients treated with pegloticase for one year duration should be required. Patients enrolled should have hyperuricemia and gout and be refractory to standard uric acid lowering therapies (e.g., allopurinol). The study should evaluate the frequency and severity of infusion reactions, anaphylaxis, and immune complex-related adverse events (e.g., serum sickness) and to capture serious adverse events associated with pegloticase therapy.

• Labeling

Based on review of the data submitted in support of this application, this medical officer has the following recommendations for the product's label:

1. The tradename KRYSTEXXA™ is acceptable. It has been deemed acceptable by both DMETS and the Division.
2. KRYSTEXXA should have a Medication Guide. A MedGuide has been proposed by the Applicant and is currently under review by both DRISC and the Division
3. Patients treated with pegloticase should have their serum uric acid levels monitored on a biweekly basis prior to receiving their pegloticase infusions in order to identify serum uric acid levels ≥ 6 mg/dL consistent with loss of therapeutic effectiveness due to antibody formation. Patients with two consecutive serum uric acid levels ≥ 6 mg/dL should have their treatment with the product discontinued to minimize their risk of having an adverse reaction (e.g., infusion reaction or anaphylaxis)
4. Treatment with pegloticase should also be discontinued in patients who experience anaphylaxis, severe infusion reaction, or who have 2 infusion reactions
5. Information regarding the [REDACTED] (b) (4) anaphylaxis in the safety database should be placed in a Black Box Warning in the label to alert prescribers about this safety risk
6. Information regarding the increase risk of patients to have worsening of congestive heart failure with pegloticase infusions should also be included

[REDACTED] (b) (4)

• **Recommendations/Risk Benefit Assessment**

• **Recommended Regulatory Action**

I recommend approval, pending agreement can be reached on revisions to labeling, Postmarketing Commitments/Requirements, and REMS.

• **Risk Benefit Assessment**

The July 31, 2009 Complete Response letter was issued for deficiencies in the chemistry, manufacturing, and control (CMC) program and on inspection of the manufacturing facilities. The clinical data submitted with the original BLA was reviewed by Dr. Rosemarie Neuner who recommended approval for pegloticase for the orphan designated indication of chronic gout and hyperuricemia in patients refractory to conventional therapy. Dr. Neuner's review of the data contained in the original application was sufficient to support a finding of efficacy and safety for pegloticase when administered as a dosing regimen of 8 mg every 2 weeks via intravenous infusion in gout patients who have failed to adequately respond to optimal therapy with other urate lowering agents.

The current safety update reviewed here consisted of the updated cumulative safety data from subjects who were enrolled in the completed randomized, double-blinded, placebo-controlled Studies 405 and 406 and from those subjects who then participated in the ongoing open-label extension trial, Study 407. The new safety data encompassed the time from the clinical database soft-lock of the 120-Day Safety Update on November 3, 2008 to the current safety database soft-lock of September 16, 2009. This new data added an additional 105 person-years since the 120-Day Safety Update while also adding to the total number of subjects treated longer than 12 months with 110, 102, and 71 total patients being treated for ≥ 12 , ≥ 18 , ≥ 24 months, respectively. Overall, the safety data was consistent with Dr. Neuner's review and no new safety signals were identified. No additional efficacy data was included in the current submission.

This reviewer is in agreement with Dr. Neuner regarding the recommendation of approval for pegloticase when administered as a dosing regimen of 8 mg every 2 weeks via intravenous infusion in gout patients with hyperuricemia who have failed to adequately respond to optimal therapy with other urate lowering agents. The reader is referred to Dr. Neuner's review of BLA 125293 for details of the efficacy and safety results submitted in the original BLA, and for the full Risk Benefit Assessment of pegloticase.

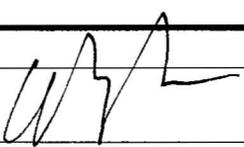
- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS)**

As agreed upon after the first review cycle, the Applicant will be required to submit a Risk Evaluation Mitigation Strategy (REMS) for pegloticase which will include a Medication Guide and Communication Plan. Exact language is currently being revised but will correspond with the language agreed upon in the product label.

- **Recommendation for Postmarketing Commitments and Postmarketing Requirements**

An observational safety study enrolling 500 patients treated with pegloticase for one year duration. Patients enrolled should have hyperuricemia and gout and be refractory to standard uric acid lowering therapies (e.g., allopurinol). The study should include the following objectives: 1) evaluate the frequency and severity of infusion reactions, anaphylaxis, and immune complex-related adverse events; and 2) identify serious adverse events associated with pegloticase therapy.

Summary Basis for Regulatory Action

Date	July 31, 2009
From	Curtis J. Rosebraugh, MD, MPH Director, Office of Drug Evaluation II  7/31/09
Subject	Summary Review
NDA/BLA #	BLA 125293
Supp #	
Applicant Name	Savient Pharmaceutical
Proprietary / Established (USAN) Names	Krystexxa pegloticase
Dosage Forms / Strength	IV infusion 8 mg/ml
Proposed Indication(s)	Treatment of refractory gout
Action:	<i>Complete Response</i>

Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding pegloticase and the reader should refer to the reviews in the action package for a more detailed discussion. Pegloticase is a recombinant PEGylated uricase (uric acid oxidase) enzyme produced by E. Coli that has been developed for the orphan population of patients with chronic gout that have failed conventional uric acid-lowering therapies. The treatment of gout focuses on reducing uric acid levels and there are several approved products including agents that increase uric acid secretion (uricosuric agents) and inhibit uric acid formation (xanthine oxidase inhibitors). Pegloticase works by a novel mechanism from other approved gout treatments by supplying an enzyme (uricase) that lowers uric acid by metabolizing it to allantoin and hydrogen peroxide. Many mammalian species, with the exception of humans and primates, have uricase and utilize this mechanism of uric acid management.

Dr. Siegel and Neuner point out in their reviews that there is an approved uricase, Rasburicase, which is used to prevent hyperuricemia in patients at risk for tumor-lysis syndrome, but that repeated use is limited by the fact that it is a foreign protein that is highly immunogenic eliciting an antibody response leading to hypersensitivity reactions upon re-exposure. To reduce the risk of similar immunogenic responses, pegloticase was developed as a PEGylated product since addition of PEG to foreign proteins reduces the risk of antibody formation, although the effectiveness of this strategy in reducing immunogenic response was not tested in this program.

There are several areas of concern with this application:

- 1) The Division of Therapeutic Proteins has determined that the product proposed for commercial use has not been demonstrated to be physicochemically equivalent to the material used in the Phase 3 trial

2) The Product Quality Microbiology team has determined that there are multiple deficiencies at the drug substance manufacturing facility related to microbial control and good manufacturing practices. Additionally the sponsor has not been able to meet the typical standard of being able to produce three lots of product meeting requirements for microbial control

3) There was an imbalance of cardiovascular serious events associated with the use of pegloticase

4) Pegloticase treatment is associated with serious infusion reactions and anaphylaxis despite prophylactic pretreatment

5) Pharmacology-Toxicology review demonstrated vacuolation of several organs

Issues 1 and 2 above will lead to a complete response for this application as will be discussed below, while issues 3, 4, and 5 can be address post-approval should this application be approved in the future.

Efficacy

The agency has accepted the surrogate endpoint of lowering uric acid as an acceptable endpoint for potential gout-treatment agents. The primary endpoint for the two Phase 3 trials was the proportion of patients achieving plasma uric acid (PUA) level of less than 6 mg/dL at least 80% of the time during months three and six for each six-month trial. Noted is that the sponsor actually analyzed plasma uric acid (PUA) when in reality clinicians in practice would monitor serum uric acid (SUA), but this difference should have no practice impact. (b) (4)

Please see Dr. Siegel's discussion regarding dose selection and details for the trial protocols, but for the Phase 3 trials a dose of 8 mg IV was given every 2 weeks or every 4 weeks and the results compared to placebo.

The following tables demonstrate the results of the study and are from Dr. Siegel's review (page 15) by way of Dr. Neuner's review.

Table 1: Treatment Response PUA < 6 mg/dL for at Least 80% of the Time in Months 3 and 6 for Study 405 (ITT Population)

	Pegloticase 8 mg every 2 weeks (N=43)	Pegloticase 8 mg every 4 weeks (N=41)	Placebo (N=20)
PUA < 6 mg/dl for at Least 80% of the Time in Month 3			
Number (%)	25 (58%)	13 (32%)	1 (5%)
95% Confidence Interval ¹	[35.6, 70.7]	[9.6, 43.9]	
P-Value ²	<0.001	0.024	
PUA <6 mg/dL for at Least 80% of the Time in Month 6			
Number (%)	20 (47%)	11 (27%)	0
95% Confidence Interval ¹	[31.6, 61.4]	[13.3, 40.4]	
P-Value ²	<0.001	0.011	
PUA <6 mg/dL for at Least 80% of the Time in Months 3 and 6 Combined			
Number (%)	20 (47%)	8 (19.5%)	0
95% Confidence Interval ¹	[31.6, 61.4]	[7.4, 31.6]	
P-Value ²	<0.001	0.044	

¹95% confidence interval for differences in responder rate between corresponding pegloticase groups vs. placebo

²P-value using Fisher's exact test to compare corresponding pegloticase group vs. placebo.

Sponsor's Table 11; p. 58

Table 2: Treatment Response PUA < 6 mg/dL for at Least 80% of the Time in Months 3 and 6 for Study 406 (ITT Population) (Primary Endpoint)

	Pegloticase 8 mg every 2 weeks (N=42)	Pegloticase 8 mg every 4 weeks (N=43)	Placebo (N=23)
PUA < 6 mg/dl for at Least 80% of the Time in Month 3			
Number (%)	19 (45%)	21 (49%)	1 (4%)
95% Confidence Interval ¹	[23.7, 58.1]	[27.4, 61.6]	
P-Value ²	<0.001	<0.001	
PUA <6 mg/dL for at Least 80% of the Time in Month 6			
Number (%)	17 (41%)	18 (42%)	0
95% Confidence Interval ¹	[25.6; 55.3]	[27.1, 56.6]	
P-Value ²	<0.001	<0.001	
PUA <6 mg/dL for at Least 80% of the Time in Months 3 and 6 Combined			
Number (%)	16 (38%)	21 (49%)	0
95% Confidence Interval ¹	[23.4, 52.8]	[33.9, 63.8]	
P-Value ²	<0.001	<0.001	

¹95% confidence interval for differences in responder rate between corresponding pegloticase groups vs. placebo

²P-value using Fisher's exact test to compare corresponding pegloticase group vs. placebo.

Sponsor's Table 11; p. 57

These results demonstrate that pegloticase 8 mg every 2 weeks is effective at maintaining PUA <6 mg/dl at the six month time interval compared to placebo. The table below (Page 16-Dr. Siegel's review) demonstrates the evaluation of resolution of tophi during the Phase 3 trials.

Table 3: Assessment of Patient's Overall Tophus Response for Pooled Studies 405 and 406 (Tophus-Evaluable ITT Population)

	Pegloticase q 2 wks (N=62)	Pegloticase q 4 wks (N=64)	Placebo (N=29)
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Week 13			
# of Subjects with Evaluable Tophi	46	48	25
Complete Response	10 (22%)	4 (8%)	0 (0%)
Partial Response	11 (24%)	9 (19%)	4 (16%)
Stable Disease	20 (44%)	28 (58%)	13 (52%)
Progressive Disease	5 (11%)	7 (15%)	8 (32%)
P-Value¹	0.002	0.068	
P-Value²	0.011	0.292	
Week 19			
# of Subjects with Evaluable Tophi	44	43	26
Complete Response	16 (36%)	12 (28%)	2 (8%)
Partial Response	11 (25%)	9 (21%)	3 (12%)
Stable Disease	12 (27%)	19 (44%)	14 (54%)
Progressive Disease	5 (11%)	3 (7%)	7 (27%)
P-Value¹	0.001	0.004	
P-value²	0.010	0.063	
Week 25			
# of Subjects with Evaluable Tophi	40	42	25
Complete Response	18 (45%)	11 (26%)	2 (8%)
Partial Response	8 (20%)	10 (24%)	6 (24%)
Stable Disease	10 (25%)	16 (38%)	11 (44%)
Progressive Disease	4 (10%)	5 (12%)	6 (24%)
P-Value¹	0.002	0.061	
P-value²	0.002	0.109	

¹An ordinal score was assigned for each response (e.g., Complete Response = 1, Partial Response = 2, Stable Disease = 3, and Progressive Disease = 4) and used to compute the P-value, which is based on two sample Wilcoxon test to compare corresponding pegloticase groups vs. placebo.

²P-value based on Fisher's exact test to compare percent of Complete Response between corresponding pegloticase groups vs. placebo.

Adapted Sponsor's Table 31; p. 74 from ISE

I find the tophi response table and the photographs presented at the advisory committee meeting demonstrating tophi resolution very compelling in demonstrating the efficacy of pegloticase. This is especially impressive considering the rapidity with which the tophi resolved, and reinforces that this treatment would offer an advance in treating the consequence of refractory gout as to my knowledge no approved treatments have demonstrate tophi resolution to this degree, especially in the limited time frame as those of the clinical trials. Also noted in Dr. Neuner's review was that pegloticase had similar impressive results in reducing tender and swollen joints and reducing gout flares. So combining the primary endpoint demonstration of uric acid decrease along with this secondary endpoint clearly demonstrates the efficacy of pegloticase in refractory gout.

Safety

As Dr. Siegel points out, the safety database for pegloticase is limited with only 273 subjects receiving at least one dose and 101 subjects receiving the drug for at least a year. Although small, considering the limited the size of the intended population, this is an adequate size safety database for this orphan indication and should reveal common events. As mentioned earlier, the main safety concerns are higher rate of cardiac events and immunogenicity with resultant anaphylaxis/infusion reactions of pegloticase. It is also important to recognize that

the potential of antibody formation to pegloticase could also result in decrease/lack of efficacy as well the safety issues above.

The cardiovascular findings are summarized in the two tables below from Dr. Siegel's review (page 20).

Table 4: Analyses of Subjects with Major Cardiac Adverse Events Experienced by Patients for the Pooled Safety Database for the Controlled Studies 405 and 406 as Attributed by FDA

Major Cardiac Adverse Events	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Total Pegloticase (N=169)	Placebo (N=43)
Number of Subjects with Major Cardiac AEs:	5 (6%)	3 (4%)	8 (5%)	1 (2%)
Ischemic Cardiovascular Disease:				
Sudden Death	2	0	2	0
Inferiolateral Myocardial Infarction	0	1	1	0
"Troponin Leak"	0	0	0	1
Transient Ischemic Attack	0	1	1	0
Heart Failure:				
Heart Failure	2	0	2	0
Cardiac Arrhythmias:				
Supraventricular Tachycardia	0	1	1	0
Ventricular Tachycardia	1	0	1	0

Table 5: Analyses of Subjects with Major Cardiac Adverse Events by Sponsor's Cardiac Event Adjudication Committee for the Pooled Safety Database from the Controlled Studies 405 and 406

Major Cardiac Adverse Events	Pegloticase q 2 wks (N=85) n (%)	Pegloticase q 4 wks (N=84) n (%)	Total Pegloticase (N=169) n (%)	Placebo (N=43) n (%)
Number (%) of Subjects with Major CV Events	4 (5%)	6 (8%)	10 (6%)	0 (0%)
All APTC* Events:	2 (2%)	1 (1%)	3 (2%)	0 (0%)
Cardiovascular Deaths	2	0	2	0
Non-Fatal Myocardial Infarction	0	1	1	0
Non-Fatal Stroke	0	0	0	0
Non-APTC CV Events:	2 (2%)**	5 (6%)	8 (5%)	0 (0%)
Angina	0	1	1	0
Congestive Heart Failure	2	1	3	0
Arrhythmia	1	1	2	0
Deep Venous Thrombosis	0	1	1	0
Transient Ischemic Attack	0	1	1	0

* Anti-Platelet Trialist Collaborative

** Two subjects had multiple events: Subject 406-311-005 had 2 events (CHF and arrhythmia); Subject 405-122-003 had both an APTC event (MI) and a non-APTC event (DVT)

There is a slight numeric imbalance, and I believe that while there is a degree of uncertainty given this imbalance, that the limited numbers of events make any conclusions speculative. Considering the limited numbers of subjects that should be exposed to pegloticase for this

indication, any type of randomized outcome study to further evaluate this would probably be impossible. Dr. Siegel and our OSE colleagues feel that an observational epidemiologic registry may be a way to collect additional information. I'm not sure this will ever resolve the issue, but given that other methods are not practical, this may be the best, and only, way to sort out this issue or at least give us an indication if we have a problem that has a large imbalance. In approaching how to handle this issue, I am very cognizant that the population at risk should be limited to those that have failed other therapies, and this drug did demonstrate substantial efficacy for a population that otherwise would be suffering. As such, I believe it would be proper to not let this issue, given the fragility of conclusions, by itself disallow patient access. Labeling should reflect this finding and our uncertainty should approval occur at a future date.

Infusion reactions were very common occurring in 26% (n=22 of 85) of subjects in the every 2 week group compared to 5% (2 of 43) in the placebo group with 18% of subjects experiencing moderately severe to severe reactions. Dr. Susan Limb reviewed these cases and noted that several of these cases met criteria for anaphylaxis. Her analysis demonstrated that the overall frequency for all dosages and regimens was 5.1% (14 of 273) and for the dose given every two weeks the frequency of anaphylaxis was 7.3% (9 out of 123). This is a considerable rate particularly when viewed that prophylactic administration of antihistamines, acetaminophen and IV corticosteroids prior to each infusion may have blunted or obscured symptoms in some subjects. To put this in perspective though, Dr. Limb notes that an estimated rate of anaphylaxis of 5% is not unusually high compared to other porcine-derived biologic products. Should this drug receive approval in the future, labeling will need to address this issue and anaphylaxis should be the subject of a REMS. Although we expect these types of reactions with porcine biologic products, and the formation of antibodies to the active agent seems a reasonable explanation, one could wonder if the safety profile might be improved somewhat if this product had less bioburden (to be discussed under CMC).

While approximately 90% of subjects have antibodies to pegloticase, most of that seems to be directed to PEG itself and not to uricase (the protein portion). This conclusion is somewhat tenuous as our immunogenicity reviewers felt that the anti-PEG antibody assay is probably inadequate. It should be expected however, that patients receiving other drugs containing PEG after receiving pegloticase, could have allergic reactions. Also, since most of the antibody formation was not directed at uricase, most patients should not experience a decrease in efficacy. In any regard, efficacy can be easily monitored by routine checking of SUA levels.

The sponsor presented data at the advisory committee meeting that indicated that infusion/anaphylactic reactions may be limited mainly to those that have high titers of antibody formation and that these high titers are also associated with lack of efficacy as noted by increases in PUA levels. They retrospectively noted that most of these reactions occurred in subjects with uric acid levels around 6 mg/dL, which led them to conclude that an effective risk mitigation strategy would be to routinely monitor SUA and stop infusions if levels exceed 6 mg/dL. This will need some more evaluation by us, but if this drug does obtain approval in future, this type of strategy may decrease those that are at risk, particularly since they may have little to no benefit.

As mentioned above, the pharmacology/toxicology nonclinical studies demonstrated treatment-duration and dose-related vacuoles in multiple tissues in chronic dose studies that

was not reversible. Immunohistochemical studies showed the vacuoles to contain pegloticase and PEG and were in multiple organs located in macrophages probably as a result of phagocytosis although vacuoles in the adrenal gland and heart were not located in macrophages. Of note, vacuoles are seen in nonclinical studies with other PEGylated products, including approved products. The pathologic studies did not reveal any gross functional changes or adverse pathology to the animals that were associated with the vacuoles (though rat splenic macrophages had decreased functional responses to lipopolysaccharide induced activation). The PT reviews conclude that while no adverse effects of vacuoles were observed in the animal studies, the long-term effects associated with accumulation of vacuoles is unknown and recommend that the sponsor conduct, as a postmarketing requirement, in vitro and/or ex vivo assessments of aortic endothelial cell and adrenal function following co-culture with pegloticase. I agree with Dr. Siegel's assessment that while no adverse effects of vacuolation in animal studies were observed that the vacuoles are nonetheless of concern and that additional studies of the functional consequences of vacuolation should be conducted.

CMC/Microbiology/facilities review

Dr. Siegel has an excellent summary of these issues in his review. In summary, the effectiveness, bioavailability and reduced immunogenicity of this product is theoretically dependent upon the PEGylated/protein ratio. The Division of Therapeutic Proteins can not assure physicochemical comparability between the product used in the Phase 3 trials and the proposed commercial material as the Phase 3 material has (b) (4). (b) (4)

(b) (4)
This uncertainty will contribute to this application not being approved on this cycle. I note that while that the Phase 3 and commercial products also have a different (b) (4)

The Product Quality/Microbiology team does not recommend approval because of multiple problems with the facilities inspection concerning microbial control and good manufacturing practices. They have also concluded that the sponsor will need to be able to produce at least three lots of pegloticase that meet reasonable standards for microbial control. The Office of Compliance issued a 13-item Form FDA 483 with selected observations (among many) being; release of multiple lots of drug substance with unacceptably high levels of bioburden (indicating microbial contamination) during the (b) (4) with no established limits for each step; inadequate (b) (4); inadequate maintenance, repair and cleanliness of buildings. These issues also contribute to this application not being approved at this time.

Advisory Committee Meeting

The committee voted 14:1 in favor of approval when the consideration was limited to the efficacy and safety of pegloticase. The CMC and inspection issues were not presented. Please see the comments by Dr. Siegel for further details regarding panel discussion.

Conclusions and Recommendations

Pegloticase is very effective at reducing PUA levels and, for some subjects, causes total resolution of tophi in a short time frame. This drug has the potential to be a very important agent in the treatment of refractory gout. However, this application has a myriad of serious CMC and manufacturing deficiencies that prohibit approval, including not being able to demonstrate that the Phase 3 material is representative of the commercial product. This is very disappointing as there are patients that are in serious need of this agent, but it is also disappointing because the sponsor has employed very poor quality standards for development and production making it such that we cannot approve this application.

Of course, counterbalancing the efficacy of pegloticase, it is recognized that it has some serious adverse effects, and should only be used in refractory gout in those truly suffering. As such, at such time that CMC and manufacturing issues are resolved which would allow marketing, pegloticase use should be informed by an effective REMS.

Regarding the REMS, I agree that should approval occur in the future, pegloticase will need a Medication Guide and Communication Plan and an assessment of effectiveness of the REMS. If the initial REMS should not succeed in mitigating risks (patients with serum uric acid > 6 mg/dL receiving pegloticase and having anaphylaxis), then we will have to revisit whether Elements to Assure Safe Use are needed.

At present, due to (for want of a better word) shoddy CMC and manufacturing, I recommend a complete response for this application. I think the sponsor should be encouraged to set up an IND process for those in need of this agent until they gain marketing approval. The product that the sponsor should use for this purpose should be that produced by proper technique (b) (4) that has limited microbial bioburden and not the product they made by inferior technique that contains high bioburden. While I'm not sure of our legal authority to require that the higher quality product (product with less bioburden) is given to patients in need, we should explore our legal options should the sponsor not agree.



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

Summary Review for Regulatory Action

Date	July 30, 2009
From	Bob A. Rappaport, M.D.  Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
BLA #	125293
Applicant Name	Savient Pharmaceuticals
Date of Submission	October 31, 2008
PDUFA Goal Date	August 1, 2009
Proprietary Name / Established (USAN) Name	Krystexxa Pegloticase
Dosage Forms / Strength	Sterile parenteral solution, 8 mg/mL for intravenous infusion
Proposed Indication	For the treatment of patients with refractory gout
Recommended Action:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Rosemarie Neuner, M.D., M.P.H.
Statistical Review	Ruthanna C. Davi, Ph.D.; Dionne Price, Ph.D.; Tom Permutt, Ph.D.
Pharmacology Toxicology Review	BeLinda Hayes, Ph.D.; R. Daniel Mellon, Ph.D.; Paul Brown, Ph.D.
CMC Review/OBP Review	Howard Anderson, Ph.D.; Richard Ledwidge, Ph.D.; Emanuela Lacana, Ph.D., Joao Pedras-Vasconcelos, Ph.D.; Susan Kirshner, Ph.D., Ph.D.; Amy Rosenberg, M.D.
Microbiology Review	Mary E. Farbman, Ph.D.; Kalavati Suvarna, Ph.D.; Patricia F. Hughes, Ph.D.; Concepcion Cruz, Acting Branch Chief
Clinical Pharmacology Review	Ping Ji, Ph.D.; Venkatesh Atul Bhattaram, Ph.D.; Yaning Wang, Ph.D.; Suresh Doddapaneni, Ph.D.
DCRP	Steven Grant, M.D.
DPAP	Susan Limb, M.D.
DDMAC	Samuel M. Skariah, Pharm.D.; Michael Sauers; Sangeeta Vaswani, Pharm.D.; Robert Dean, M.B.A.
DSI	Susan Leibenhaut, M.D.; Constance Lewin, M.D., M.P.H.
CDTL Review	Jeffrey Siegel, M.D.
OSE/DMEPA	Cathy A. Miller, M.P.H.; Kellie Taylor, Pharm.D., M.P.H.; Denise Toyer, Pharm.D.; Carol Hoquist, R. Ph.
OSE/DAEA	N/A
OSE/DRISK	Kathryn O'Connell, M.D. Ph.D.; Suzanne Berkman Robottom, Pharm.D.; Mary Demsey; Christopher Wheeler, Pharm.D.; Claudia Karwoski, Pharm.D.
OSE/DEPI	N/A

OND=Office of New Drugs
 DDMAC=Division of Drug Marketing, Advertising and Communication
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DSI=Division of Scientific Investigations
 DRISK= Division of Risk Management
 DAEA=Division of Adverse Event Analysis
 CDTL=Cross-Discipline Team Leader
 DEPI= Division of Epidmiology
 DCRP=Division of Cardio-Renal Products
 DPAP=Division of Pulmonary and Allergy Products

BLA 125293

2

Krystexxa

Division Director's Review and Summary Basis for Recommendation for Complete Response
Action

July 30, 2009

1. Introduction

Krystexxa (pegloticase) is an aqueous solution of a recombinant, PEGylated uricase (uric acid oxidase) enzyme produced in *E. Coli*, intended to treat gout in patients who have been refractory to treatment with the available approved drug products. Pegloticase is primarily derived from the porcine uricase gene with an (b) (4) derived from the baboon uricase gene, (b) (4). The uricase molecule is a homotetramer that is then PEGylated to produce a 9 PEG molecules per monomer ratio.

2. Background

Savient Pharmaceuticals submitted this BLA in October of 2008 after completing two adequate and well-controlled clinical trials of Krystexxa in gout patients who had failed or who were intolerant of allopurinol and/or other approved uric acid lowering drug products. Krystexxa lowers uric acid by a different mechanism than previously approved products for chronic gout. Acting as the uricase enzyme, it metabolizes uric acid to allantoin, excreted in the urine, and hydrogen peroxide, converted to water and oxygen by catalase. Lowering serum uric acid levels to below 6 mg/dL chronically is known to result in a long-term reduction in the frequency of gout attacks, and is thought to be, therefore, associated with the resorption of tophi. Treatment with drugs that reduce uric acid levels chronically results in an increased frequency of gout flares early on, and prophylactic treatments are generally administered to prevent these episodes. In the early studies of pegloticase, there was a high incidence of infusion reactions, in spite of the degree of pegylation. Therefore, the sponsor was asked to develop a prophylactic regimen to reduce the incidence of these reactions.

3. CMC

The OBP, Division of Therapeutic Proteins review team is recommending that this application not be approved as the product used in the Phase 3 clinical studies was determined to be physicochemically different from the product intended for commercial use. The Phase 3 product has (b) (4)

In addition, the Product Quality Microbiology review team is recommending that the application not be approved based on findings during facilities inspection relating to microbial control and good manufacturing practices. Finally, inadequate data exists to show that three lots of pegloticase drug substance intended for Krystexxa manufacture have met the requirements for microbial control.

I concur with the product reviewers and Dr. Siegel that these deficiencies must be addressed before Krystexxa can be approved for marketing.

4. Nonclinical Pharmacology/Toxicology

While Drs. Hayes and Mellon have concluded that the application is approvable from a pharmacology/toxicology perspective, they have recommended that certain post-marketing studies be required. Their major concern noted upon review of the toxicology studies was the finding of treatment-duration and dose-related vacuoles seen in the spleen, adrenal cortex, duodenum, jejunum, liver and the intimal endothelial cells of the aortic outflow tract of the heart. These vacuoles were not reversible and immunohistochemical studies demonstrated that they contained pegloticase and PEG. The vacuoles in the spleen, liver, duodenum and jejunum were located in macrophages, but the vacuoles in the adrenal gland and heart were not. Vacuoles have been seen in nonclinical studies of other PEGylated products, some of which have been approved. However, the long-term effects of the vacuoles, particularly in the adrenals and heart, are unknown. Therefore, Drs. Hayes and Mellon have recommended the requirement of post-marketing in vitro and/or ex vivo studies of aortic endothelial cell and adrenal function following co-culture with pegloticase. I agree that these studies should be required.

The sponsor performed a Segment 2 reproductive toxicology study in the rat and no maternal toxicity, embryofetal developmental adverse effects or teratogenic effects were seen. Based on a prior agreement with the former division responsible for this application, no studies were conducted to assess fertility and early embryonic development or prenatal and postnatal development. However, the Office of New Drugs has reevaluated these requirements for biological products since that time and they are now generally required in all cases. Therefore, Drs. Hayes and Mellon are recommending post-marketing requirement of Segment 1 and Segment 3 studies in rats, and a second Segment 2 study in rabbits. I concur with their recommendations. While the prevalence of gout in pre-menopausal women is extremely low and, therefore, it is likely that the population of women of child-bearing potential with refractory gout could be minimal, I recommend that the Segment 3 study be required and that the onus be on the sponsor to provide adequate data to demonstrate that this study is not warranted, should they choose to do so.

5. Clinical Pharmacology/Biopharmaceutics

The following summary is reproduced from page 8 of Dr. Siegel's review:

The Clinical Pharmacology review team determined that the submission was acceptable.

General clinical pharmacology/biopharmaceutics considerations

In single-dose studies the pegloticase exposure increased in a dose-proportional manner. The terminal half-life ranged from approximately 150 to 300 hours. Uric acid concentrations decreased with increasing dose. Doses of 1 mg reduced plasma uric acid

BLA 125293

4

Krystexxa

Division Director's Review and Summary Basis for Recommendation for Complete Response
Action

July 30, 2009

levels to below 6 mg/dL. A popPK analysis identified anti-pegloticase antibodies and body surface area as significant covariates associated with increased clearance of pegloticase.

Demographic interactions/special populations

PopPK studies did not identify weight, gender, age or serum creatinine to have a significant effect on the pharmacokinetics of pegloticase. The effect of hepatic function on the PK of pegloticase was not studied.

Thorough QT study or other QT assessment

Thorough QT studies are not usually required for biologics since biologic proteins do not have a propensity to interact with cardiac ion channels. QT studies were not conducted for pegloticase.

I concur with the review team and Dr. Siegel that there are no outstanding clinical pharmacology or biopharmaceutics issues.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

The choice of a final dosing regimen for inclusion in the product labeling was based on a Phase 2 study which evaluated single IV doses of pegloticase and on the results of the two Phase 3 studies. Study C0402 demonstrated a dose-dependent decrease in plasma uric acid levels as the dose was increased from 0.5 to 12 mg. The duration of uric acid suppression was also dose dependent. At doses of 8 and 12 mg the mean plasma uric acid levels remained below 6 mg/dL for greater than 300 hours. In the Phase 3 studies, C0405 and C0406, 8 mg IV administered every 2 weeks reduced the mean plasma uric acid levels to below 6 mg/dL consistently, but this was only demonstrated in Study C0406 for a dosing regimen of every 4 weeks. This finding was supported by a better resolution of tophi with the every 2 week regimen. Thus, the sponsor recommends that the every 2 week regimen be the labeled dosing regimen and the clinical review team and I concur with this recommendation.

The sponsor conducted two replicate adequate and well-controlled Phase 3 trials of Krystexxa the design of which was agreed upon by the division in a Special Protocol Agreement submitted for one of the trials. The studies were randomized, 6-month trials that compared the 8 mg IV dose of Krystexxa administered on an every 2 week interval and an every 4 week interval to placebo. The subjects had established gout and a screening uric acid of at least 8 mg/dL. They were to have documented intolerance to allopurinol or failure to respond to the maximal recommend dose. These studies were performed prior to the approval of Febuxostat, a new product with the same mechanism of action as allopurinol, xanthine oxidase inhibition. In order to reduce the incidence of the expected gout flares that occur during uric acid

BLA 125293

5

Krystexxa

Division Director's Review and Summary Basis for Recommendation for Complete Response
Action

July 30, 2009

lowering therapy, the subjects were treated with either colchicine or an NSAID. To reduce the risk of infusion reactions, subjects were treated with fexofenadine, acetaminophen and hydrocortisone prophylactically.

Randomization was stratified in both studies based on the presence or absence of tophi as resolution of tophi was a key secondary outcome measure. The primary outcome measure was the proportion of patients who achieved a plasma uric acid level below 6 mg/dL at least 80% of the time during months 3 and 6. The following tables reproduced from page 15 of Dr. Siegel's review summarize the results of the primary endpoint analyses:

Table 1: Treatment Response PUA < 6 mg/dL for at Least 80% of the Time in Months 3 and 6 for Study 405 (ITT Population)

	Pegloticase 8 mg every 2 weeks (N=43)	Pegloticase 8 mg every 4 weeks (N=41)	Placebo (N=20)
PUA < 6 mg/dl for at Least 80% of the Time in Month 3			
Number (%)	25 (458%)	13 (32%)	1 (5%)
95% Confidence Interval ¹	[35.6, 70.7]	[9.6, 43.9]	
P-Value ²	<0.001	0.024	
PUA <6 mg/dL for at Least 80% of the Time in Month 6			
Number (%)	20 (47%)	11 (27%)	0
95% Confidence Interval ¹	[31.6, 61.4]	[13.3, 40.4]	
P-Value ²	<0.001	0.011	
PUA <6 mg/dL for at Least 80% of the Time in Months 3 and 6 Combined			
Number (%)	20 (47%)	8 (19.5%)	0
95% Confidence Interval ¹	[31.6, 61.4]	[7.4, 31.6]	
P-Value ²	<0.001	0.044	

¹95% confidence interval for differences in responder rate between corresponding pegloticase groups vs. placebo

²P-value using Fisher's exact test to compare corresponding pegloticase group vs. placebo.

Sponsor's Table 11; p. 58

Table 2: Treatment Response PUA < 6 mg/dL for at Least 80% of the Time in Months 3 and 6 for Study 406 (ITT Population) (Primary Endpoint)

	Pegloticase 8 mg every 2 weeks (N=42)	Pegloticase 8 mg every 4 weeks (N=43)	Placebo (N=23)
PUA < 6 mg/dl for at Least 80% of the Time in Month 3			
Number (%)	19 (45%)	21 (49%)	1 (4%)
95% Confidence Interval¹	[23.7, 58.1]	[27.4, 61.6]	
P-Value²	<0.001	<0.001	
PUA <6 mg/dL for at Least 80% of the Time in Month 6			
Number (%)	17 (41%)	18 (42%)	0
95% Confidence Interval¹	[25.6; 55.3]	[27.1, 56.6]	
P-Value²	<0.001	<0.001	
PUA <6 mg/dL for at Least 80% of the Time in Months 3 and 6 Combined			
Number (%)	16 (38%)	21 (49%)	0
95% Confidence Interval¹	[23.4, 52.8]	[33.9, 63.8]	
P-Value²	<0.001	<0.001	

¹95% confidence interval for differences in responder rate between corresponding pegloticase groups vs. placebo

²P-value using Fisher's exact test to compare corresponding pegloticase group vs. placebo.

Sponsor's Table 11; p. 57

There were a number of secondary endpoints studied and analyzed in the two Phase 3 trials. The sponsor did not address the issue of multiplicity in the statistical analyses of these endpoints and, therefore, while they were generally supportive of the primary outcome analyses, [REDACTED] (b) (4) and I will not discuss them in this review, with one exception. The reader is referred to Drs. Neuner, Davi and Siegel's reviews for a thorough discussion of these endpoints.

The one secondary outcome measure that merits further discussion is the sponsor's analysis of reduction in tophi size. Tophi size was assessed according to a standardized paradigm that employed digital photographs evaluated by a central, blinded reader. To be considered for inclusion in this analysis, tophi had to be at least 5 mm in at least one diameter and had to have distinguishable borders or be at least 10 mm in at least one diameter, if the borders were not distinguishable to the reader. A complete response was defined as complete resolution of at least one of these tophi. Lesser responses were denoted partial response or stable disease. The following table, reproduced from page 16 of Dr. Siegel's review, summarizes the results of this analysis:

Table 3: Assessment of Patient’s Overall Tophus Response for Pooled Studies 405 and 406 (Tophus-Evaluable ITT Population)

	Pegloticase q 2 wks (N=62)	Pegloticase q 4 wks (N=64)	Placebo (N=29)
Week 13			
# of Subjects with Evaluable Tophi	46	48	25
Complete Response	10 (22%)	4 (8%)	0 (0%)
Partial Response	11 (24%)	9 (19%)	4 (16%)
Stable Disease	20 (44%)	28 (58%)	13 (52%)
Progressive Disease	5 (11%)	7 (15%)	8 (32%)
P-Value ¹	0.002	0.068	
P-Value ²	0.011	0.292	
Week 19			
# of Subjects with Evaluable Tophi	44	43	26
Complete Response	16 (36%)	12 (28%)	2 (8%)
Partial Response	11 (25%)	9 (21%)	3 (12%)
Stable Disease	12 (27%)	19 (44%)	14 (54%)
Progressive Disease	5 (11%)	3 (7%)	7 (27%)
P-Value ¹	0.001	0.004	
P-value ²	0.010	0.063	
Week 25			
# of Subjects with Evaluable Tophi	40	42	25
Complete Response	18 (45%)	11 (26%)	2 (8%)
Partial Response	8 (20%)	10 (24%)	6 (24%)
Stable Disease	10 (25%)	16 (38%)	11 (44%)
Progressive Disease	4 (10%)	5 (12%)	6 (24%)
P-Value ¹	0.002	0.061	
P-value ²	0.002	0.109	

¹An ordinal score was assigned for each response (e.g., Complete Response = 1, Partial Response =2, Stable Disease = 3, and Progressive Disease = 4) and used to compute the P-value, which is based on two sample Wilcoxon test to compare corresponding pegloticase groups vs. placebo.

²P-value based on Fisher’s exact test to compare percent of Complete Response between corresponding pegloticase groups vs. placebo.

Adapted Sponsor’s Table 31; p. 74 from ISE

Table 6 represents the sponsor’s analyses of the reduction in tophi and includes only subjects with evaluable tophi at the appropriate time point, not the entire “tophus-evaluable population” making these results subject to bias. A sensitivity analysis, for Week 25, considering the “unable to evaluate” cases as failures leads to the same qualitative conclusions as that of the sponsor; however, the descriptive proportions from the sensitivity analysis are notably lower for the Krystexxa groups than those from the sponsor’s analyses. Using the sensitivity analysis the proportions of subjects with complete response at week 25 were 29% (18 of 62), 17% (11 of 64) and 7% (2 of 29) for the Krystexxa every 2 weeks groups, every 4 weeks groups, and placebo groups, respectively.

The following is reproduced from Dr. Siegel’s addendum to his CDTL review:

With respect to the multiple secondary endpoints, Dr. Davi noted that no multiplicity correction was planned for in the protocol. Therefore the tests for statistical significance should be interpreted with caution since the probability of a type I error would increase beyond the usual

BLA 125293

Krystexxa

Division Director’s Review and Summary Basis for Recommendation for Complete Response Action

July 30, 2009

0.05 level. This argument suggests that for the secondary endpoints generally (b) (4). However, an exception should be made for the clinically important secondary endpoint of resolution of tophi for the following reasons. In her review, Dr. Davi notes that secondary endpoints that have a direct scientific link with the primary efficacy endpoint would be less subject to increases in type I error. This consideration applies to the secondary endpoint of tophi specifically in that they have a direct scientific link with plasma uric acid levels. Tophi represent deposits of uric acid in tissues. As plasma uric acid levels are maintained below the saturation level for uric acid (approximately 6.0 mg/dL) total body urate stores fall, leading to resorption of tissue deposits of uric acid. (b) (4)

Rather, they included only patients for whom data were available suggesting that they are prone to bias. When Dr. Davi applied a sensitivity analysis (imputing non-response for missing data) to those secondaries they lost statistical significance. A total of 45% of patients experienced tophus resolution in the Applicant's analysis and 29% using a conservative sensitivity analysis using non-responder imputation for missing data. For the tophi analysis, the p value was less than 0.05 and retained statistical significance in sensitivity analysis. A further consideration that provides evidence for resolution of tophi with pegloticase is that the natural history of tophi is not to resolve, as shown by the almost zero incidence of tophi resolution in the placebo group. Based on these considerations I recommend that the tophi outcomes be reported in the label (b) (4).

I concur with Dr. Siegel's assessment, conclusions and recommendations regarding the secondary outcome measures.

8. Safety

The overall safety data base for this application consisted of 273 subjects who received at least one dose of Krystexxa. Of those 273 subjects, 127 were treated for at least 6 months and 101 were treated for one year or longer. I concur with the clinical review team that this is a reasonably sized data base considering the limited number of patients with gout who are unresponsive to the available approved medications. There were three deaths in the Krystexxa every two weeks group and one in the every four weeks group. Two of the deaths in the every two weeks arm were due to cardiac events in subjects with prior cardiovascular histories. The third death in that arm was due to MRSA sepsis which developed from a decubitus ulcer. The death in the every four week arm was due to renal and cardiac failure in a patient with end-stage cardiomyopathy. While I agree with Drs. Neuner and Siegel that the sepsis death was probably unrelated to exposure to Krystexxa, I do not agree that we can rule out that the drug played some role in exacerbating the underlying cardiovascular conditions in the other three subjects, considering the signal of possible cardiotoxicity associated with Krystexxa discussed below. Dr. Neuner also reports on the death a subject in the open-label extension study. This patient died of sepsis related to a necrotizing skin lesion greater than 30 days after his last dose of study medication. He was being treated with numerous medications, one of which was prednisone. This death is not likely to have been related to Krystexxa exposure.

Serious events and discontinuations due to adverse events occurred with greater frequency in the Krystexxa-treated subjects compared to the placebo-treated subjects. In particular, higher rates of cardiovascular events, infusion reactions and gout flares occurred in the subjects exposed to Krystexxa. There were higher incidences of diarrhea, acute renal failure and muscle spasms in the Krystexxa subjects. There were also higher rates of severe diarrhea, asthenia, cellulitis, dyspnea, vomiting and various pain complaints in the Krystexxa subjects. The most common adverse events seen in subjects treated with Krystexxa at higher rates than in subjects treated with placebo were: headache, nausea, back pain, contusion, nasopharyngitis, increased blood pressure, vomiting, pruritis, pyrexia, and chest pain. There were no clinically concerning changes in laboratory values or vital signs.

Cardiovascular Toxicity

As noted above, there was a higher rate of cardiovascular adverse event in the Krystexxa arms of the controlled trials compared to the placebo arms. The following tables are reproduced from pages 19 and 20 of Dr. Siegel's review and summary the sponsor's initial count of the cardiac serious adverse events via MedDRA Preferred Terms, the cardiac serious events adjudicated by the FDA's cardiology consultant, Dr. Grant, and the adjudicated events from the sponsor's blinded adjudication committee:

Table 4: Cardiac Serious Adverse Events (SAEs) via MedDRA Preferred Terms for the Pooled Safety Database from Controlled Studies 405 and 406 by Sponsor

MedDRA Preferred Term	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Total Pegloticase (N=169)	Placebo (N=43)
Number (%) of Subjects with Cardiac SAEs	4 (5%)*	3 (4%)	7 (4%)*	0 (0%)
Ischemic Cardiovascular Disease:				
Cardiac Arrest	1	0	1	0
Myocardial Infarction	0	1	1	0
Angina Pectoris	0	1	1	0
Heart Failure:				
Congestive Cardiac Failure	1	0	1	0
Cardiac Arrhythmias:				
Arrhythmia	2	0	2	0
Tachycardia	0	1	1	0

*One patient had both CHF and arrhythmia.
Adapted from Sponsor's Table 34; p. 72-3 of ISS

Table 5: Analyses of Subjects with Major Cardiac Adverse Events Experienced by Patients for the Pooled Safety Database for the Controlled Studies 405 and 406 as Attributed by FDA

Major Cardiac Adverse Events	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Total Pegloticase (N=169)	Placebo (N=43)
Number of Subjects with Major Cardiac AEs:	5 (6%)	3 (4%)	8 (5%)	1 (2%)
Ischemic Cardiovascular Disease:				
Sudden Death	2	0	2	0
Inferolateral Myocardial Infarction	0	1	1	0
“Troponin Leak”	0	0	0	1
Transient Ischemic Attack	0	1	1	0
Heart Failure:				
Heart Failure	2	0	2	0
Cardiac Arrhythmias:				
Supraventricular Tachycardia	0	1	1	0
Ventricular Tachycardia	1	0	1	0

Table 6: Analyses of Subjects with Major Cardiac Adverse Events by Sponsor’s Cardiac Event Adjudication Committee for the Pooled Safety Database from the Controlled Studies 405 and 406

Major Cardiac Adverse Events	Pegloticase q 2 wks (N=85) n (%)	Pegloticase q 4 wks (N=84) n (%)	Total Pegloticase (N=169) n (%)	Placebo (N=43) n (%)
Number (%) of Subjects with Major CV Events	4 (5%)	6 (8%)	10 (6%)	0 (0%)
All APTC* Events:	2 (2%)	1 (1%)	3 (2%)	0 (0%)
Cardiovascular Deaths	2	0	2	0
Non-Fatal Myocardial Infarction	0	1	1	0
Non-Fatal Stroke	0	0	0	0
Non-APTC CV Events:	2 (2%)**	5 (6%)	8 (5%)	0 (0%)
Angina	0	1	1	0
Congestive Heart Failure	2	1	3	0
Arrhythmia	1	1	2	0
Deep Venous Thrombosis	0	1	1	0
Transient Ischemic Attack	0	1	1	0

* Anti-Platelet Trialist Collaborative

** Two subjects had multiple events: Subject 406-311-005 had 2 events (CHF and arrhythmia); Subject 405-122-003 had both an APTC event (MI) and a non-APTC event (DVT)

Both Dr. Grant and the division clinical review team concluded that, while the numbers of events were too low to reach a definitive conclusion regarding the cardiotoxicity of Krystexxa, this signal does raise a concern that will require further evaluation.

Anaphylaxis/Infusion Reactions

Infusion reactions were common in the Krystexxa-treated subjects. Twenty-six percent of subjects in the every two week arms and 41% in the every four week arms experienced infusion reactions. Of the infusion reactions in the every two week arm, 13% were moderate and 5% were severe. A consult was obtained from the Division of Pulmonary and Allergy Products (DPAP) to allow for further evaluation of these events. Dr. Limb of DPAP applied the diagnostic criteria for anaphylaxis developed by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium, published in the Journal of Allergy and Clinical Immunology in 2006. These criteria take a primarily clinical perspective in the definition and diagnosis of anaphylaxis and do not require a specific immunologic mechanism (i.e., presence of absence of IgE antibodies).

The following is reproduced from page 8 of Dr. Limb's review:

Based on the 14 cases suggestive of anaphylaxis identified in the single-dose and multiple dose pegloticase IV studies, the estimated frequency of anaphylaxis is 5.1% (14 of 273 patients). For the Q2wk regimen, the frequency is 7.3% (9 out of 123); for the Q4wk regimen, the frequency is 3.9% (4 out of 126), which is a reverse of the trend observed for infusion reactions as a whole. Given the small numbers, the difference in frequency between the two dosing regimens is difficult to interpret and may be due to chance and variability in safety reporting. As the use of routine prophylaxis may have blunted or obscured certain signs and symptoms, the true rate of anaphylaxis and other hypersensitivity reactions may be underestimated. Since complete study information for Study C0409 was not included in the BLA, the rate calculation does not include patients or infusions from Study C0409.

(b) (4)

Immunogenicity

Approximately 90% of subjects treated with Krystexxa developed anti-pegloticase antibodies. One third of the subjects developed high-titer antibodies which were highly correlated with lack of efficacy and infusion reactions. The anti-pegloticase antibodies appear to be directed at PEG rather than uricase based on the finding that only a small subset of subjects with anti-uricase antibodies. While the sponsor's anti-PEG assay demonstrated positive results in only 40% of subjects, Dr. Pedras-Vasconcelos notes that the data likely indicate an inadequately sensitive assay.

While the high incidence of anti-pegloticase antibodies resulting in lack of efficacy and possible anaphylactic reactions is of concern, the sponsor has outlined a mechanism for monitoring serum uric acid levels that should serve to mitigate this risk to a reasonable degree.

BLA 125293

12

Krystexxa

Division Director's Review and Summary Basis for Recommendation for Complete Response

Action

July 30, 2009

9. Advisory Committee Meeting

From page 22 of Dr. Siegel's review:

A meeting of the Arthritis Advisory Committee was held on June 16, 2009 to discuss pegloticase for chronic gout refractory to conventional therapy. The committee was supplemented by members from the Cardiovascular and Renal Drug Products Advisory Committee and the Drug Safety Advisory Committee. There was no consensus on the committee as to whether there was a true cardiovascular safety signal, especially given the small number of cases, the lack of a biologically plausible mechanism and the multiple comorbidities. Nonetheless, committee members favored collecting additional information postmarketing possible by means of an observational epidemiology study.

The committee voted overwhelmingly in favor of approval: 14 to 1. However, a number of committee members stated that it would be important to limit use of the product to patients who were truly refractory to conventional therapy. There was support for monitoring of uric acid with each dose to avoid infusion reactions.

I think it is important to note that during the Open Public Hearing portion of the meeting a number of patients provided moving testimony regarding the need for drugs to treat gout sufferers who are refractory to or intolerant of other approved therapies. These patients who suffered from refractory gout, and who had had severely disfiguring and painful tophi, presented testimony and (for some) photographic documentation of complete or near complete resolution of those tophi after having been treated with Krystexxa. Their concerns are not considered lightly, but product quality and safety concerns must also be considered critical for these patients. One option for the sponsor would be to provide product under a treatment IND while they are addressing the CMC and microbiology concerns.

10. Pediatrics

Gout is extremely rare in the pediatric population and, as such, it would not be possible to conduct studies in children. The particular indication in this application, refractory gout, has been designated an orphan indication and, therefore, the application is exempt from PREA.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

The review team proposed a number of labeling changes to the package insert. However, as we are unable to approve the drug at this time, we will need to reassess the label language on the next review cycle.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

I recommend a Complete Response action.

- Risk Benefit Assessment

I concur with the review team that the sponsor has provided evidence to support the efficacy and safety of Krystexxa for the treatment of refractory gout. While the risk of anaphylaxis/infusion reactions is of concern with this product, it should be adequately managed in the infusion centers where Krystexxa will be administered. The sponsor has proposed that monitoring uric acid levels for an increase back to a level of 6 mg/dL while on treatment with Krystexxa will allow prescribers to be alerted to the possible development of high antibody levels, the resultant loss of efficacy, and an increased risk of immunogenic reactivity. The clinical review team agrees with this conclusion and I concur. The cardiovascular signal will require further evaluation, however. I also concur that the product quality deficiencies are of significant concern and must be addressed and resolved prior to approval. Finally, I agree with the review teams in regard to their recommended PMRs and PMCs. However, as I am recommending that the application not be approved at this time, the sponsor should be asked to undertake all of these studies and development plans as soon as possible and provide as many final study reports, as well as documentation of manufacturing and control improvements, when they resubmit their response to the Complete Response letter.

The clinical review team concurs with the Advisory Committee's recommendation for a post-marketing observational study to evaluate cardiovascular adverse events. I agree that this study is appropriate and necessary. While a prospective outcome study would be more likely to provide useful information, the population available for study is limited and this observational study is probably the best quality study that would actually be feasible to perform.

I concur with the pharmacology/toxicology review team that the sponsor should perform the following studies:

- 1) An 18-month repeat-dose toxicology study in dog to evaluate the impact of cytoplasmic vacuoles in the adrenal gland and the aortic outflow tract of the heart
- 2) A fertility and early embryonic development study in the rat (Segment 1)
- 3) An embryofetal development study in a second species (Segment 2)

- 4) A prenatal/postnatal development study in a second species (Segment 3)
See my comments above (Section 4) regarding this study.

The Product Quality review team has recommended a number of studies. These studies fall into two major categories:

- 1) The product used in the Phase 3 clinical studies was determined to be physicochemically different from the product intended for commercial use (see Section 3 above). From page 2 of Dr. Rosenberg's review, "Additional clinical studies are necessary to support the use of pegloticase manufactured with the commercial process or alternatively, [the sponsor] may validate the Phase III process for commercialization."
- 2) There are numerous good manufacturing deficiencies that have been clearly delineated in the Product Quality reviews. These deficiencies must be addressed with appropriate studies or the development of appropriate manufacturing processes.

The Product Quality Microbiology review team is recommending that the application not be approved based on findings during facilities inspection relating to microbial control and good manufacturing practices. These deficiencies must be addressed with appropriate studies or the development of appropriate microbial controls and manufacturing processes.

Inadequate data exists to show that three lots of pegloticase drug substance intended for Krystexxa manufacture have met the requirements for microbial control. These three lots were initially found to be contaminated with microbial growth and, although "cleaned" and no longer containing bacteria, it will be necessary for the sponsor to provide adequate data to show that additional contaminants resulting from the earlier presence of bacteria do not currently remain in this product.

I concur with the recommendations from the Product Quality and Microbiology review teams.

- Recommendation for Postmarketing Risk Management Activities

The sponsor submitted a REMs proposal. The DRISK review team reviewed that REMS but recommended a modified version of the sponsor's proposal. The sponsor, the DRISK review team and the clinical review team have agreed upon a REMS that would consist of a Medication Guide, a Communication Plan and an assessment of the effectiveness of the REMS. The Communication Plan would consist of, at a minimum, Dear Healthcare Provider letters for prescribers and infusion center medical personnel,

non-promotional print service announcements in rheumatology journals, and non-promotional information at major internal medicine and rheumatology meetings.

Although the DRISK team left the decision to the clinical team regarding whether to include [REDACTED] (b) (4), they strongly recommend that the plan entail the least burden possible. The clinical review team has recommended that ETASU are not necessary as infusion centers are knowledgeable about, experienced with and well-equipped to handle infusion reactions. [REDACTED] (b) (4)

[REDACTED] The DRISK team also recommended that the sponsor be required to submit post-marketing cardiovascular events and serious infusion reactions as expedited reports. I agree concur with these recommendations.



FDA Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II
Division of Anesthesia, Analgesia and Rheumatology Products

Addendum to Cross-Discipline Team Leader Memorandum

Date: July 27, 2009

To: File, BLA 125293

From: Jeffrey Siegel, M.D. *Jeffrey n. siegel 7/27/09*
Clinical Team Leader
ODE II - Division of Anesthesia, Analgesia and Rheumatology
Products (DAARP)

Re: Inclusion of Secondary Endpoints in Krystexxa product labeling
BLA 125319
Savient Pharmaceutical
Proposed indication: Treatment of refractory gout

With respect to the multiple secondary endpoints, Dr. Davi noted that no multiplicity correction was planned for in the protocol. Therefore the tests for statistical significance should be interpreted with caution since the probability of a type I error would increase beyond the usual 0.05 level. This argument suggests that for the secondary endpoints generally [REDACTED] (b) (4). However, an exception should be made for the clinically important secondary endpoint of resolution of tophi for the following reasons. In her review, Dr. Davi notes that secondary endpoints that have a direct scientific link with the primary efficacy endpoint would be less subject to increases in type I error. This consideration applies to the secondary endpoint of tophi specifically in that they have a direct scientific link with plasma uric acid levels. Tophi represent deposits of uric acid in tissues. As plasma uric acid levels are maintained below the saturation level for uric acid (approximately 6.0 mg/dL) total body urate stores fall, leading to resorption of tissue deposits of uric acid. [REDACTED] (b) (4)

[REDACTED] Rather, they included only patients for whom data were available suggesting that they are prone to bias. When Dr. Davi applied a sensitivity analysis (imputing non-response for missing data) to those secondaries they lost statistical significance. A total of 45% of patients experienced tophus resolution in the Applicant's analysis and 29% using a conservative sensitivity analysis using non-responder imputation for missing data. For the tophi analysis, the p value was less than 0.05 and retained statistical significance in sensitivity analysis. A further consideration that provides evidence for resolution of tophi with pegloticase is that the natural history of tophi is not to resolve, as shown by the almost zero incidence of tophi resolution in the placebo group. Based on these considerations I recommend that the tophi outcomes be reported in the label [REDACTED] (b) (4)



FDA Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II
Division of Anesthesia, Analgesia and Rheumatology Products

Cross-Discipline Team Leader Memorandum

Date	July 10, 2009
From	Jeffrey Siegel, M.D. <i>Jeffrey N. Siegel 7/10/09</i>
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	BLA 125293
Supplement#	
Applicant	Savient Pharmaceutical
Date of Submission	October 31, 2008
PDUFA Goal Date	August 1, 2009
Proprietary Name / Established (USAN) names	Krystexxa/pegloticase
Dosage forms / Strength	8 mg/mL for IV infusion
Proposed Indication(s)	Treatment of refractory gout
Recommended:	<i>Complete Response</i>

TABLE OF CONTENTS

1. Introduction to Review	4
2. Background	5
3. CMC/Microbiology/Device	6
3.1. General product quality considerations	6
3.2. Facilities review/inspection	6
4. Nonclinical Pharmacology/Toxicology	7
4.1. General nonclinical pharmacology/toxicology considerations	7
4.2. Carcinogenicity	7
4.3. Reproductive toxicology	8
5. Clinical Pharmacology/Biopharmaceutics	8
5.1. General clinical pharmacology/biopharmaceutics considerations	8
5.2. Demographic interactions/special populations	8
5.3. Thorough QT study or other QT assessment	8
5.4. Notable issues	8
6. Clinical/Statistical	9
6.1. General Discussion	9
6.2. Efficacy	9
6.2.1. Dose identification/selection and limitations	9
6.2.2. Phase 3/ clinical studies essential to regulatory decision	11
6.2.3. Other efficacy studies	17
6.2.4. Discussion of primary and secondary reviewers' comments and conclusions	17
6.2.5. Pediatric use/PREA waivers/deferrals	17
6.2.6. Discussion of notable efficacy issues	17
6.3. Safety	17
6.3.1. General safety considerations	17
6.3.2. Safety findings from submitted clinical trials	18
6.3.3. Safety update	21
6.3.4. Immunogenicity	21
6.3.5. Discussion of primary reviewer's comments and conclusions	22
6.3.6. Discussion of notable safety issues	22
7. Advisory Committee Meeting	22
8. Financial Disclosure	23
9. Labeling	23
9.1. Proprietary name	23
9.2. Physician labeling	23
10. DSI audits	23

11. Recommendations/Risk Benefit Assessment.....	23
11.1. Recommended Regulatory Action.....	23
11.2. Risk Benefit Assessment.....	23
11.3. Recommendation for Postmarketing Risk Evaluation and Management (REMS) Strategies	24
11.4. Safety concerns to be followed postmarketing	24
11.5. Postmarketing studies	24
11.5.1. Required studies (PMRs).....	24
11.5.2. Commitments (PMCs)	25
11.5.3. Other agreements with Sponsor	25

1. Introduction to Review

Savient Pharmaceuticals submitted this biologic licensing application for pegloticase (KRYSTEXXA) for the treatment of gout in patients refractory to conventional therapies. Pegloticase is a recombinant, PEGylated uricase (uric acid oxidase) enzyme produced in *E. coli*. The Applicant designed their clinical development program to address the use of pegloticase in the orphan population of patients with chronic gout who had failed or who were intolerant to conventional uric acid-lowering therapies, such as allopurinol. They approached the Agency in an End-of-Phase 2 meeting in which they proposed to conduct two replicate randomized trials assessing safety and efficacy. The Agency agreed that it was acceptable to use as the primary endpoint the validated surrogate endpoint of lowering serum uric acid to less than 6 mg/dL. However, since the primary endpoint was a surrogate endpoint the Agency encouraged the sponsor to collect as much data as possible to determine whether treatment also offered a benefit to patients as assessed by clinical outcomes.

The Applicant conducted two replicate, randomized, Phase 3 trials in patients who had failed or who were intolerant to allopurinol. The trials compared pegloticase 8 mg by intravenous infusion given every 2 weeks to the same dose given every 4 weeks to placebo. An important additional feature of the trials is that they mandated a prophylactic regimen to prevent gout flares and also mandated prophylactic treatment prior to each infusion to prevent infusion reactions. The safety database for pegloticase consists of a total of 273 patients who received any IV dose of pegloticase. For the 8 mg IV every 2 week regimen, 66 patients were treated for at least 6 months, and 53 for at least one year. In addition, for the pegloticase 8 mg IV every 4 week dose regimen there are safety data on 61 patients treated for at least 6 months and 48 treated for at least one year. The Applicant proposes a recommended dose of pegloticase 8 mg every 2 weeks by intravenous infusion.

Review of this application revealed important issues in several areas: 1) Clinical: there are no issues concerning efficacy; however, in the clinical trials a higher proportion of patients in the pegloticase treatment arms developed cardiovascular serious adverse events than in the control arms. In addition, pegloticase treatment was associated with serious infusion reactions and adverse events meeting clinical criteria for anaphylaxis; 2) Product: there were concerns about whether the product proposed for commercial use was demonstrated to be equivalent to the material used in the Phase 3 trials. For Microbiology, the reviewer could not recommend approval until summary data for the microbial challenge test (container closure integrity test) validation was provided and reviewed. The Product Quality/Microbiology review team does not recommend approval because of multiple issues concerning microbial control of the drug substance manufacturing process. In addition, inspectors of the drug substance manufacturing facility recommend a non-concur approval because of multiple deficiencies; 3) Pharmacology-Toxicology: Although there were no issues that would preclude approval, animal toxicology studies showed vacuolation in several organs that will require additional study postmarketing.

2. Background

Gout is a condition characterized by acute flares and chronic manifestations. The underlying predisposing factor for gout is elevated levels of uric acid. While many individuals with hyperuricemia never develop gout the likelihood of developing gout increases with increasing circulating levels of uric acid above 6 mg/dL. The first manifestation of gout is generally an acute, painful attack of monoarthritis, typically involving the great toe (termed podagra). Although some patients have a single episode of acute gout, many go on to develop chronic gout, which is manifest as recurrent episodes of acute gout as well as deposition of uric acid crystals in tissues, termed tophi. Acute attacks of gout are treated with anti-inflammatories, including non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, corticosteroids and ACTH. The goal of treatment of chronic gout is to reduce uric acid levels to below 6 mg/dL with urate-lowering drugs to reduce the risk of gout flares and to resolve tophi.

While there are several products (both uricosuric agents and xanthine oxidase inhibitors) that are approved as urate-lowering therapies, the most common treatment is the xanthine oxidase inhibitor allopurinol. However, use of allopurinol is limited by the occurrence of hypersensitivity reactions, including rare life-threatening events, the need for dose reduction in patients with chronic renal insufficiency and the fact that it is not effective at lowering uric acid below the target level of 6 mg/dL in a large number of patients.

Pegloticase reduces uric acid levels by a fundamentally different mechanism than previously approved treatments for gout. It is a recombinant, porcine-derived, PEGylated uric acid oxidase (uricase) that lowering serum uric acid by metabolizing uric acid to allantoin and hydrogen peroxide. Because total body uric acid stores are large in patients with gout, lowering uric acid with products like pegloticase is not expected to be effective acutely for gouty arthritis or tophi. However, reducing uric acid levels to below 6 mg/dL chronically is associated with the long-term reduction in the frequency of gout attacks and with resorption of tophi. In fact, acute treatment with urate-lowering therapies is associated with an increased frequency of gout attacks. Thus, prophylactic treatment to prevent flares of gout is recommended when patients initiate treatment with urate-lowering therapies.

If it is approved, pegloticase would not be the first uricase to be marketed. Rasburicase is an approved uricase to prevent hyperuricemia in patients with tumor lysis syndrome. Repeated use of Rasburicase is limited by the fact that it is a foreign protein that elicits an antibody response in treated patients, leading to hypersensitivity reactions on re-exposure. To reduce the risk of similar immunogenic responses, pegloticase was developed as a PEGylated product since addition of PEG to foreign proteins reduces the risk of antibody formation.

In early development of pegloticase given subcutaneously, some patients developed hypersensitivity reactions, including a case of generalized urticaria. Consequently, the Applicant stopped the development of subcutaneous administration in favor of the intravenous route. The Applicant met with the Agency in an end-of-Phase 2 meeting in August, 2005. At that meeting it was agreed that the Applicant would conduct two

replicate Phase 3 trials using two dose regimens of pegloticase: 8 mg IV given either every 2 weeks or every 4 weeks. The primary endpoint was to be the proportion of patients achieving a uric acid less than 6 mg/dL at least 80% of the time during months 3 and 6. The primary endpoint was to be analyzed separately for each trial, but the clinical secondary endpoints were to be pooled between the two trials to increase the likelihood of achieving statistical significance. Noting the high rate of infusion reactions in the Phase 2 trials the Agency told the Applicant they should devise a prophylactic regimen to reduce the frequency of, and severity of, infusion reactions.

3. CMC/Microbiology/Device

3.1. General product quality considerations

Pegloticase is a PEGylated recombinant uricase produced in *E coli*. The gene is derived chiefly from the porcine uricase gene with a (b) (4) sequence derived from the baboon uricase gene. (b) (4)

The uricase molecule is a homotetramer that is PEGylated in a controlled manner to produce a 9 PEG molecule per monomer ratio. The 9 PEG/monomer ratio was decided balancing two considerations: increasing amounts of PEG reduce uricase activity, while increasing amounts of PEG reduce immunogenicity.

The Division of Therapeutic Proteins, OBP, does not recommend approval because of issues concerning the comparability of the product used in Phase 3 trials and the product intended for commercial use (b) (4)

The Drug Product/Microbiology review team is withholding a recommendation of approval until the Applicant provides validation summary data on the microbial challenge test (container closure integrity test) and that data can be reviewed. In addition, they recommend as a post-marketing requirement the development and validation of a shipper suitable for transporting the finished product vials within the US.

The Product quality/microbiology review team is not recommending approval because of issues raised on the facilities inspection and because of multiple problems concerning microbial control, including the fact that the firm has not provided data from at least three lots of pegloticase showing that the manufacturing process is able to meet reasonable standards for microbial control.

3.2. Facilities review/inspection

The Office of Compliance issued a 13-item Form FDA 483. Objectionable conditions were observed within “the quality system, production system, facilities and equipment system, materials management system, and laboratory system.” The observations included: the release of multiple lots of drugs substance with unacceptably high levels of bioburden during the (b) (6) steps with no established bioburden limits for each step in the process; the finding of inadequate (b) (6) technique in the conduct of the bulk (b) (6) process; inadequate maintenance, repair and cleanliness of the buildings and facilities, including two leaking pipes in the fermentation suite and brown faucet

water in the area used to wash hands before entering the clean production areas. The review team recommends a non-concur approval until the deficiencies are resolved. At the time of writing of this memo, the inspector's non-concur approval recommendation has not been finalized by DMPQ/ICB.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review team states that the BLA may be approved pending revisions to the proposed label and agreement on recommended postmarketing studies.

4.1. General nonclinical pharmacology/toxicology considerations

The major concern regarding the pharmacology/toxicology nonclinical studies was the finding of vacuoles in multiple tissues in chronic dose studies. The pharmacology/toxicology reviewer, Dr. Belinda Hayes, states that "repeat-dose toxicity studies of 12 weeks or 39-weeks duration in the dogs revealed vacuolation as the toxicity finding associated with pegloticase administration. The incidence of vacuolation was treatment-duration and dose-related. After dosing up to 5 mg/kg for 12 weeks, vacuolation was only observed in the spleen. The major target organ of toxicity was identified as adrenal cortex, duodenum, heart, jejunum, liver and spleen." The vacuolation in the heart was observed in intimal endothelial cells of the aortic outflow tract. It was not reversible. Immunohistochemical studies showed the vacuoles to contain pegloticase and PEG. The vacuoles in the spleen, liver, duodenum and jejunum were located in macrophages and probably result from physiologic phagocytosis of pegloticase. In contrast, the vacuoles in the adrenal gland and heart were not located in macrophages. Of note, vacuoles are seen in nonclinical studies with other PEGylated products, including approved products. The pathologic studies did not reveal any functional changes or adverse pathology associated with the vacuoles. However, in vitro functional responses were diminished in macrophages from pegloticase-treated rats. Dr. Hayes concludes that while no adverse effects of vacuoles were observed in the animal studies, the long-term effects associated with accumulation of vacuoles is unknown.

The pharmacology/toxicology review team recommends the Applicant conduct as a postmarketing requirement "in vitro and/or ex vivo assessments of aortic endothelial cell and adrenal function following co-culture with pegloticase." I agree that while no adverse effects of vacuolation in animal studies were observed that the vacuoles are nonetheless of concern and that additional studies of the functional consequences of vacuolation should be conducted.

4.2. Carcinogenicity

Carcinogenicity studies are not generally conducted with biologics unless there is reason for concern about carcinogenic effects of a particular product. The Applicant did not conduct carcinogenicity studies with pegloticase. The pharmacology/toxicology reviewer agreed that carcinogenicity studies were not needed.

4.3. *Reproductive toxicology*

The Applicant assessed the effects of pegloticase on embryofetal development (Segment 2) in the rat. No maternal toxicity was observed and there were no teratogenic effects seen and there were no adverse effects on embryofetal development noted.

No studies were conducted to assess fertility and early embryonic development (Segment 1) or perinatal and postnatal development per prior agreement with the Agency based on expectations current at the time. Since that time the Agency has revised expectations to require Segment 1-3 studies when feasible.

The pharmacology/toxicology review team recommends the following studies be conducted as postmarketing requirements:

1. Conduct a fertility study in the rat model (Segment 1)
2. Conduct a embryo-fetal development study in the rabbit model (Segment 2)
3. Conduct a peri-natal and post-natal development study in the rat model (Segment 3)

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review team determined that the submission was acceptable.

5.1. *General clinical pharmacology/biopharmaceutics considerations*

In single-dose studies the pegloticase exposure increased in a dose-proportional manner. The terminal half-life ranged from approximately 150 to 300 hours. Uric acid concentrations decreased with increasing dose. Doses of 1 mg reduced plasma uric acid levels to below 6 mg/dL. A popPK analysis identified anti-pegloticase antibodies and body surface area as significant covariates associated with increased clearance of pegloticase.

5.2. *Demographic interactions/special populations*

PopPK studies did not identify weight, gender, age or serum creatinine to have a significant effect on the pharmacokinetics of pegloticase. The effect of hepatic function on the PK of pegloticase was not studied.

5.3. *Thorough QT study or other QT assessment*

Thorough QT studies are not usually required for biologics since biologic proteins do not have a propensity to interact with cardiac ion channels. QT studies were not conducted for pegloticase.

5.4. *Notable issues*

None.

6. Clinical/Statistical

6.1. General Discussion

The Applicant conducted a clinical development program for pegloticase in the treatment of patients with chronic gout refractory or intolerant to conventional urate-lowering therapies. At an End-of-Phase 2 meeting it was agreed that they would conduct two randomized, placebo-controlled Phase 3 trials. It was agreed that a primary endpoint was acceptable consisting of the proportion of patients who achieved the target uric acid level of less than 6 mg/dL at least 80% of the time at months 3 and 6 of the 6-month trials. Although uric acid is a validated surrogate for clinical benefit in patients with gout the Agency recommended the Applicant collect as much information as possible on potential clinical benefits of pegloticase to better determine the risk/benefit relationship for the product. To that end, the Phase 3 trials assessed tophus resorption, gout flares, tender and swollen joints as secondary endpoints. The Agency recommended the protocol incorporate multiplicity adjustments and ranking for secondary endpoints. However, the Applicant did not incorporate such multiplicity adjustments.

At the End-of-Phase 2 meeting the Agency noted the high frequency of infusion reactions and recommended the Applicant incorporate a mandatory prophylactic regimen to reduce the frequency and severity of infusion reactions. The Agency also recommended the protocols include a prophylactic regimen to prevent gout flares.

The Applicant submitted one of the two replicate Phase three studies as a special protocol assessment (SPA). The Agency agreed to the SPA. It was agreed that while the primary endpoints for the trials would be analyzed separately, it was acceptable to pool data from the two Phase 3 trials for assessing the secondary endpoints.

The Phase 3 trials both demonstrate positive results on the primary endpoint of uric acid reduction with the pegloticase 8 mg IV every 2 week regimen. The pooled trials demonstrated an effect on resolution of tophi. There were no major issues with respect to the primary efficacy results. The safety database consisted of a total of 273 patients who received any IV dose of pegloticase. For the 8 mg IV every 2 week regimen, 66 patients were treated for at least 6 months, and 53 for at least one year. In addition, for the pegloticase 8 mg IV every 4 week dose regimen there are safety data on 61 patients treated for at least 6 months and 48 treated for at least one year. Major issues were a higher proportion of patients experiencing serious cardiac adverse events in the pegloticase treatment arms, infusion reactions, adverse events meeting clinical criteria for anaphylaxis and a high rate of immunogenicity.

6.2. Efficacy

6.2.1. Dose identification/selection and limitations

Study C0402 evaluated single IV doses of pegloticase (Figure 1; this figure and Figure 2 copied from the Clinical Pharmacology review of Drs. Ping Ji and Venkatesh Atul Bhattaram). Plasma uric acid decreased in a dose-dependent manner with doses from 0.5 to 12 mg. The duration of suppression of uric acid also increased with increasing dose.

At doses of 8 and 12 mg mean plasma uric acid levels remained below 6 mg/dL for more than 300 hours.

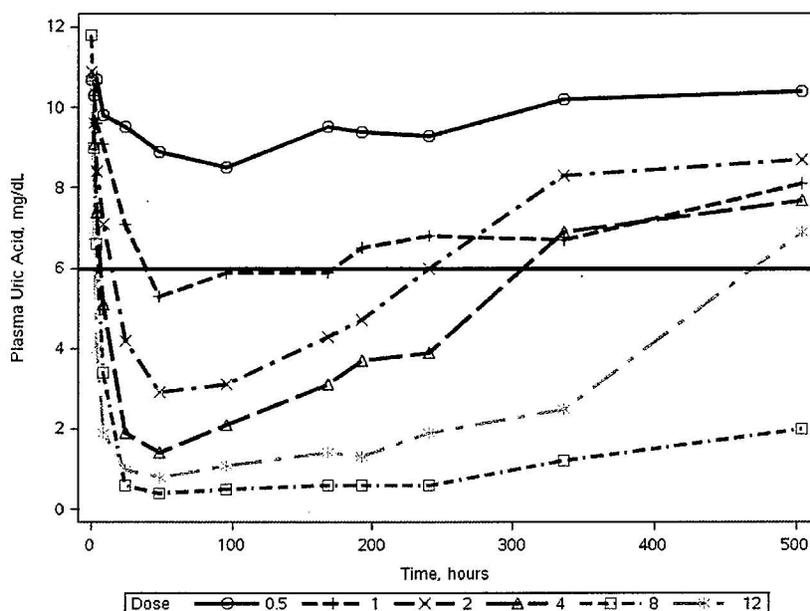


Figure 1: Mean plasma uric acid concentrations after single intravenous dose administration of 0.5, 1, 2, 4, 8, or 12 mg of pegloticase (study C0402).

The 8 mg IV dose was studied further in the Phase 3 trials. Those studies compared placebo to pegloticase 8 mg IV given every 2 or every 4 weeks. In both studies (Figure 2) the every 2 week regimen reduced mean plasma uric acid levels to below 6 throughout the trial. In contrast, the every 4 week regimen reduced mean urate levels consistently to below 6 mg/dL in Study C0406 but not C0405. In addition, the every 4 week regimen was less effective at resolving tophi (see below). These results suggest that the every 2 week regimen is more efficacious than the every 4 week regimen. Given that the 2 week regimen did not show worse safety than the every 4 week regimen the data indicate that the every 2 week regimen is preferable.

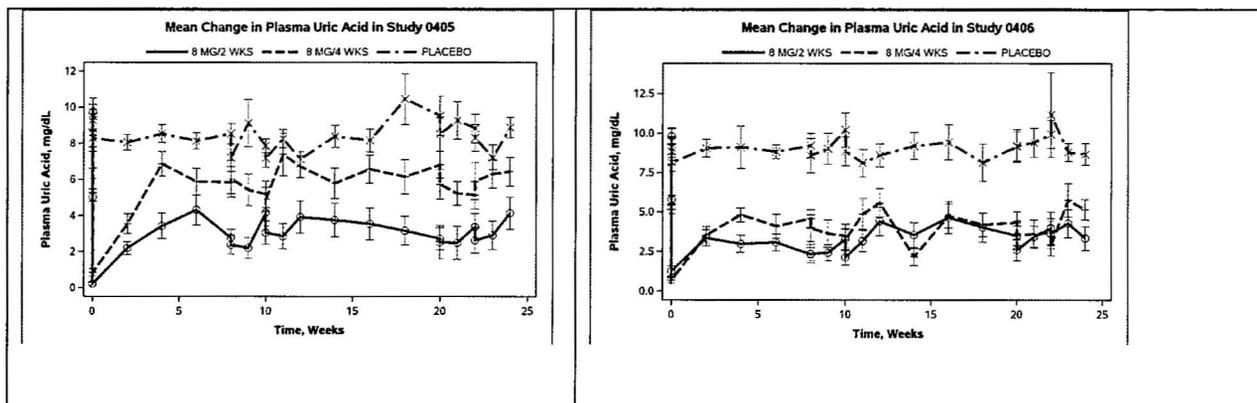


Figure 2: Mean (\pm SE) changes in plasma uric acid in studies C0405 (left) and C0406 (right) (based on actual week data)

6.2.2. Phase 3/ clinical studies essential to regulatory decision

The Applicant conducted two replicate Phase 3 trials, Studies C0405 and C0406 (hereafter called Studies 405 and 406). The studies were randomized, controlled, 6-month studies comparing pegloticase 8 mg IV given either every 2 weeks or every 4 weeks or placebo. The protocols specified enrollment of adult patients 18 years of age or older with symptomatic gout defined as either 3 or more gout attacks in the prior 18 months, a documented tophus or gouty arthritis. Screening uric acid was to be 8 mg/dL or higher. Enrolled patients were to have documented intolerance to allopurinol or failure to normalize uric acid despite maximal recommended doses. The study excluded patients with uncontrolled cardiac disease or end-stage renal disease. Patients were washed out of any concomitant urate-lowering therapies for 1 week before enrollment. Patients completing the study had the option to enroll in a long-term extension trial (Study 407).

Gout flares and infusion reactions were expected events during treatment with pegloticase. To reduce the risk of gout flares patients were required to take either colchicine 0.6 or 1.2 mg daily or the recommended dose of a non-steroidal anti-inflammatory drug. To reduce the risk of infusion reactions patients were instructed to take 60 mg fexofenadine orally at bedtime the night before the infusion, 60 mg of fexofenadine and 1000 mg of acetaminophen orally the morning of the infusion, and were then given 200 mg of hydrocortisone intravenously immediately prior to the trial infusion.

A total of 100 subjects was planned for each of the Phase 3 trials. Randomization was carried out in a 2:2:1 ratio for the every 2 week, every 4 week and placebo study arms, respectively. Randomization was stratified for the presence/absence of tophi. The primary endpoint was the proportion of patients with a plasma uric acid below 6 mg/dL at least 80% of the time during months 3 and 6. The prespecified primary analysis was the intent-to-treat (ITT) population analyzed based on Fisher's exact test. A non-responder

imputation was specified for missing data. No multiplicity adjustment was specified for the two treatment arms.

Study disposition for Studies 405 and 406 are shown in Table 1 and Table 2 (these and all other tables and figures in this section copied from the clinical review of Dr. Rosemarie Neuner). As shown in the tables, approximately 90% of patients in the placebo arms completed the 24-week studies. In contrast, fewer subjects (approximately 70%) completed the studies in the pegloticase treatment arms. The main reason for premature withdrawal in the pegloticase treatment arms was adverse event or withdrawal of consent.

Table 1: Subject Disposition for Study 405

	Pegloticase 8 mg every 2 weeks (N=44)	Pegloticase 8 mg every 4 weeks (N=43)	Placebo (N=22)	Total (N=128)
Number of Patients Randomized	44	43	22	109
Number of Patients Treated (ITT)	43	41	20	104
Number of Patients with Evaluable Tophus	29	31	14	74
Number of Patients that Completed the Week 24 Study Visit:				
Enrolled in OLE	30 (70%)	27 (66%)	19 (95%)	76 (73%)
Did not Enroll in OLE	29 (97%)	26 (96%)	18 (95%)	
Did not Enroll in OLE	1 (3%)	1 (4%)	1 (5%)	
Number of Patients Withdrawn Prematurely Before Week 24:				
Non-compliance	13 (30%)	14 (34%)	1 (5%)	28 (27%)
Adverse Event	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Withdrew Consent	8 (19%)	9 (22%)	0 (0%)	17 (16%)
Lost to Follow-Up	3 (7%)	3 (7%)	0 (0%)	6 (6%)
Protocol Violation	0 (0%)	0 (0%)	1 (5%)	1 (1%)
Death	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Death	1 (2%)	1 (2%)	0 (0%)	2 (2%)

Table 2: Subject Disposition for Study 406

	Pegloticase 8 mg every 2 weeks (N=46)	Pegloticase 8 mg every 4 weeks (N=46)	Placebo (N=24)	Total (N=134)
Number of Patients Randomized	46	46	24	116
Number of Patients Randomized But Not Dosed:	4	3	1	8
Number of Patients Treated (ITT)	42	43	23	108
Number of Patients with Evaluable Tophus	33	33	15	81
Number of Patients that Completed the Week 24 Study Visit:				
Enrolled in OLE	29 (69%)	32 (74%)	20 (87%)	81 (75%)
Did not enroll in OLE	28 (97%)	32 (94%)	20 (100%)	78 (96%)
	1 (3%)	2 (6%)	0 (0%)	3 (4%)
Number of Patients Withdrawn Prematurely Before Week 24:				
Non-compliance	13 (31%)	11 (26%)	3 (13%)	27 (25%)
Adverse Event	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Withdrew Consent	7 (17%)	7 (16%)	1 (4%)	15 (56%)
Lost to Follow-Up	5 (12%)	3 (7%)	1 (4%)	9 (33%)
Protocol Violation	0 (0%)	1 (2%)	1 (4%)	2 (7%)
Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	2 (5%)	0 (0%)	0 (0%)	2 (7%)

The mean age of enrolled subjects was 55 and with approximately 80% were male. The mean weight was 100 kg and the mean BMI was 33 kg/m². Demographics were well balanced between study arms. The enrolled patients had moderate to severe gout with a mean duration of disease of 15 years, a mean of 10 acute flares in the preceding 18 months. A total of 63% reported their acute flares as severe or crippling. The allopurinol treatment history for enrollment was reported as allopurinol ineffective in 18%, allergy or hypersensitivity in 40% and renal insufficiency or GI toxicity in the remaining patients. A total of 73% had tophi. Consistent with the known association between gout and cardiovascular disease there was a high prevalence of baseline cardiovascular disease among enrolled patients (Table 3). Overall, the baseline disease characteristics were well balanced between study arms.

Table 3: Number (%) of Patient Reported Cardiovascular-Related Conditions in Subjects Who Participated in Studies 405 and 406

Medical Condition	Pegloticase 8 mg q 2 wks (N=85)	Pegloticase 8 mg q 4 wks (N=84)	Placebo (N=43)	Total (N=212)
At least one of the following cardiovascular conditions:	73 (86%)	71 (85%)	35 (81%)	179 (84%)
Cardiac Arrhythmias	19 (22%)	8 (10%)	7 (16%)	34 (16%)
Cardiac Failure/LV Dysfunction	12 (14%)	8 (10%)	6 (14%)	26 (12%)
Cerebrovascular Disease	4 (5%)	3 (4%)	1 (2%)	8 (4%)
Coronary Disease	14 (17%)	16 (19%)	9 (21%)	39 (18%)
Diabetes	24 (28%)	18 (21%)	8 (19%)	50 (24%)
Dyslipidemia	42 (49%)	41 (49%)	20 (47%)	103 (49%)
Hypertension	62 (73%)	60 (71%)	31 (72%)	153 (72%)
Vascular Disease, Peripheral	7 (8%)	6 (7%)	3 (7%)	16 (8%)
Venous Thromboembolic Disease	3 (4%)	2 (2%)	2 (5%)	7 (4%)
Obesity (BMI \geq 30)	50 (59%)	55 (66%)	24 (56%)	129 (61%)
Chronic Kidney Disease	26 (31%)	25 (30%)	9 (21%)	60 (28%)
Sleep Apnea	8 (9%)	9 (11%)	6 (14%)	23 (11%)

The primary endpoint for both Phase 3 trials was the proportion of patients with plasma uric acid less than 6 mg/dL at least 80% of the time in months 3 and 6. As shown in Table 4 and Table 5, although no patient achieved this level of urate lowering in the placebo group, a statistically significantly greater proportion of patients in each of the pegloticase treatment arms met the primary endpoint. In Study 406 a similar proportion of patients in the every 2 week and every 4 week groups (38% and 49%, respectively) met the primary endpoint. In contrast, in Study 405 a smaller proportion of patients met the primary endpoint in the every 4 week group (20%) than in the every 2 week group (47%).

Table 4: Treatment Response PUA < 6 mg/dL for at Least 80% of the Time in Months 3 and 6 for Study 405 (ITT Population)

	Pegloticase 8 mg every 2 weeks (N=43)	Pegloticase 8 mg every 4 weeks (N=41)	Placebo (N=20)
PUA < 6 mg/dl for at Least 80% of the Time in Month 3			
Number (%)	25 (458%)	13 (32%)	1 (5%)
95% Confidence Interval ¹	[35.6, 70.7]	[9.6, 43.9]	
P-Value ²	<0.001	0.024	
PUA <6 mg/dL for at Least 80% of the Time in Month 6			
Number (%)	20 (47%)	11 (27%)	0
95% Confidence Interval ¹	[31.6, 61.4]	[13.3, 40.4]	
P-Value ²	<0.001	0.011	
PUA <6 mg/dL for at Least 80% of the Time in Months 3 and 6 Combined			
Number (%)	20 (47%)	8 (19.5%)	0
95% Confidence Interval ¹	[31.6, 61.4]	[7.4, 31.6]	
P-Value ²	<0.001	0.044	

¹95% confidence interval for differences in responder rate between corresponding pegloticase groups vs. placebo

²P-value using Fisher's exact test to compare corresponding pegloticase group vs. placebo.

Sponsor's Table 11; p. 58

Table 5: Treatment Response PUA < 6 mg/dL for at Least 80% of the Time in Months 3 and 6 for Study 406 (ITT Population) (Primary Endpoint)

	Pegloticase 8 mg every 2 weeks (N=42)	Pegloticase 8 mg every 4 weeks (N=43)	Placebo (N=23)
PUA < 6 mg/dl for at Least 80% of the Time in Month 3			
Number (%)	19 (45%)	21 (49%)	1 (4%)
95% Confidence Interval ¹	[23.7, 58.1]	[27.4, 61.6]	
P-Value ²	<0.001	<0.001	
PUA <6 mg/dL for at Least 80% of the Time in Month 6			
Number (%)	17 (41%)	18 (42%)	0
95% Confidence Interval ¹	[25.6; 55.3]	[27.1, 56.6]	
P-Value ²	<0.001	<0.001	
PUA <6 mg/dL for at Least 80% of the Time in Months 3 and 6 Combined			
Number (%)	16 (38%)	21 (49%)	0
95% Confidence Interval ¹	[23.4, 52.8]	[33.9, 63.8]	
P-Value ²	<0.001	<0.001	

¹95% confidence interval for differences in responder rate between corresponding pegloticase groups vs. placebo

²P-value using Fisher's exact test to compare corresponding pegloticase group vs. placebo.

Sponsor's Table 11; p. 57

Resolution of tophi was evaluated in Studies 405 and 406 as a secondary endpoint. Tophi were assessed using digital photographs in a standard manner. Photographs were assessed by a central blinded reader who prospectively identified sites of tophi to be evaluated in the studies. Two types of tophi were distinguished, so called "measurable" and "unmeasured" tophi. To be considered "measurable," tophi had to be at least 5 mm in diameter and to have borders distinguishable by the central reader. "Unmeasured" tophi had less easily distinguishable borders; they had to be at least 10 mm at baseline in

order for there to be confidence that the reader could reliably assess changes in size. A complete response was defined as complete resolution (100%) of at least one of the patients' identified "measurable" or "unmeasured" tophi, with less degrees of response termed marked response, partial response or stable disease. As shown in Table 6, approximately 10% of patients in the placebo arm had complete tophus response. In contrast a total of 45% of patients in the every 2 week arm and 26% in the every 4 week arm had a complete tophus response. This response was statistically significant for the every 2 week group and trended positive in the every 4 week arm but failed to reach statistical significance. Dr. Davi, the statistical reviewer, notes that the analysis in Table 6 excludes some patients in the tophus evaluable population because some patients had unevaluable tophi at Week 25 (e.g., due to poor image quality in the photograph). She conducted a conservative sensitivity analysis imputing unevaluable subjects as failures and concluded that the qualitative conclusions for the two analyses remain the same. The nominal p value for the pegloticase every 2 week group remains below 0.05

Table 6: Assessment of Patient's Overall Tophus Response for Pooled Studies 405 and 406 (Tophus-Evaluable ITT Population)

	Pegloticase q 2 wks (N=62)	Pegloticase q 4 wks (N=64)	Placebo (N=29)
Week 13			
# of Subjects with Evaluable Tophi	46	48	25
Complete Response	10 (22%)	4 (8%)	0 (0%)
Partial Response	11 (24%)	9 (19%)	4 (16%)
Stable Disease	20 (44%)	28 (58%)	13 (52%)
Progressive Disease	5 (11%)	7 (15%)	8 (32%)
P-Value¹	0.002	0.068	
P-Value²	0.011	0.292	
Week 19			
# of Subjects with Evaluable Tophi	44	43	26
Complete Response	16 (36%)	12 (28%)	2 (8%)
Partial Response	11 (25%)	9 (21%)	3 (12%)
Stable Disease	12 (27%)	19 (44%)	14 (54%)
Progressive Disease	5 (11%)	3 (7%)	7 (27%)
P-Value¹	0.001	0.004	
P-value²	0.010	0.063	
Week 25			
# of Subjects with Evaluable Tophi	40	42	25
Complete Response	18 (45%)	11 (26%)	2 (8%)
Partial Response	8 (20%)	10 (24%)	6 (24%)
Stable Disease	10 (25%)	16 (38%)	11 (44%)
Progressive Disease	4 (10%)	5 (12%)	6 (24%)
P-Value¹	0.002	0.061	
P-value²	0.002	0.109	

¹An ordinal score was assigned for each response (e.g., Complete Response = 1, Partial Response = 2, Stable Disease = 3, and Progressive Disease = 4) and used to compute the P-value, which is based on two sample Wilcoxon test to compare corresponding pegloticase groups vs. placebo.

²P-value based on Fisher's exact test to compare percent of Complete Response between corresponding pegloticase groups vs. placebo.

Adapted Sponsor's Table 31; p. 74 from ISE

6.2.3. *Other efficacy studies*

None.

6.2.4. *Discussion of primary and secondary reviewers' comments and conclusions*

The primary clinical reviewer, Dr. Rosemarie Neuner, concluded that in both Studies 405 and 406 that a significantly greater proportion of patients met the primary endpoint of uric acid less than 6 mg/dL at least 80% of the time in months 3 and 6 in the two pegloticase treatment arms than in control. She also concluded that more patients had a complete tophus response in the every 2 week group than in controls. The statistical reviewer, Dr. Ruthanna Davi, concluded that the studies adequately demonstrated that a higher proportion of patients treated with pegloticase 8 mg IV every 2 weeks achieved the primary endpoint than patients receiving placebo. Dr. Davi was concerned about the lack of prespecified multiplicity adjustment but the conclusion of efficacy was robust for the every 2 week group because of the high statistical significance. She notes that for the every 4 week group that the comparison to placebo was significant for Study 406 but only marginally so for Study 405. Nonetheless, she concludes that considering both studies together that it is unlikely that the result for the every 4 week group is spurious. Thus it is appropriate to also conclude efficacy for the every 4 week group. I concur with the conclusions of Drs. Neuner and Davi.

6.2.5. *Pediatric use/PREA waivers/deferrals*

Gout is quite rare in children and it would not be possible to conduct studies in children due to the small number of patients available. Therefore, the Applicant would qualify for a waiver to conduct studies in children under PREA. However, since gout refractory to conventional treatments is an orphan indication this application is exempt from PREA.

6.2.6. *Discussion of notable efficacy issues*

There are no notable efficacy issues.

6.3. *Safety*

6.3.1. *General safety considerations*

The safety database for pegloticase consists of 273 patients who received at least one dose. As shown in Table 7, for the every 2 week and every 4 week groups, respectively, a total of 66 and 61 patients were treated for at least 6 months and a total of 53 and 48 patients were treated for a year or longer. Although the ICH E1A guidance document recommends a total of 1500 patients treated overall and 300-600 treated for 6 months and 100 treated for at least one year for products intended for chronic use, that guidance document also recommends adjusting the recommended size of the safety database depending on the size of the patient population. Given that the population in question for this application is an orphan population with an estimated prevalence of 100,000 the size of the safety database for pegloticase is not unreasonable.

Table 7: Number of Pegloticase Infusions and Study Duration for Subjects Who Received Multiple Doses of Pegloticase in the Phase 2 and 3 Trials (Studies 403, 405, 406 and 407)

	Pegloticase 8 mg q 2 wks (N=116)	Pegloticase 8 mg q 4 wks (N=113)
Number of Pegloticase Infusions per Subject		
Mean (SD)	17 (11)	11 (9)
Median (Min, Max)	19 (1, 38)	8 (1, 32)
Study Duration (Days)¹		
Mean (SD)	316 (172.2)	306 (182.2)
Median (Min, Max)	327 (29, 658)	286 (1, 623)
Study Duration (Weeks)		
0-16 weeks	17 (15%)	17 (15%)
>16 weeks	99 (85%)	96 (85%)
>28 weeks	66 (57%)	61 (54%)
>52 weeks	53 (46%)	48 (42%)
>77 weeks	13 (11%)	14 (12%)

Note: Number of infusions excludes placebo infusions.

¹For subjects enrolled in Studies 405 or 406 with initial pegloticase treatment, the study duration is defined as the sum of study durations in the double-blind studies (405 or 406) and open label study (407). However, for subjects with placebo treatment in Studies 405 or 406, only the study duration in 407 is included in the summary.

Adapted Sponsor's Tables 11 and 12; p. 42-43 of ISS

There were several deaths in the clinical trials of causes that are expected in this patient population, primarily due to cardiac events and infections. The main safety concerns are: a higher rate of cardiac serious adverse events in the pegloticase treatment arms; infusion reactions; events meeting clinical criteria for anaphylaxis; and immunogenicity.

6.3.2. Safety findings from submitted clinical trials

During the controlled portions of the clinical trials there were 3 deaths in the pegloticase every 2 week group (3/85, 3%), 1 in the every 4 week group (1/85, 1%) and 1 in the placebo group (1/43, 2%). Overall, the rates do not appear substantially different in the different study arms. Two of the deaths in the every 2 week arm were due to cardiac events in patients with extensive prior cardiovascular history. The third death occurred in a patient with MRSA sepsis related to a decubitus ulcer. The death in the every 4 week arm was secondary to renal failure in a patient with end-stage cardiomyopathy who developed heart failure and renal failure. None of these seem likely related to study medication and all have ample predisposing risk factors.

A higher rate of serious adverse events was observed in patients in the pegloticase every 2 week group (24%) and every 4 week group (23%) as compared to placebo (12%). This higher rate reflects a higher rate of infusion-related reactions and cardiac disorders, both of which will be discussed in more detail below. More patients in the pegloticase treatment arms withdrew early due to toxicity (19% and 20% in the every 2 week and every 4 week arms, respectively) than in the placebo arm (2%). The major causes of early withdrawal in the pegloticase groups were infusion reactions and gout flares.

The higher rate of cardiac serious adverse events in the pegloticase groups reflects a variety of different types of events with no clear pattern (Table 8). The higher rate reflects individual events of cardiac arrest, MI, angina, heart failure, tachyarrhythmia and 2 cases of arrhythmia.

Table 8: Cardiac Serious Adverse Events (SAEs) via MedDRA Preferred Terms for the Pooled Safety Database from Controlled Studies 405 and 406 by Sponsor

MedDRA Preferred Term	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Total Pegloticase (N=169)	Placebo (N=43)
Number (%) of Subjects with Cardiac SAEs	4 (5%)*	3 (4%)	7 (4%)*	0 (0%)
Ischemic Cardiovascular Disease:				
Cardiac Arrest	1	0	1	0
Myocardial Infarction	0	1	1	0
Angina Pectoris	0	1	1	0
Heart Failure:				
Congestive Cardiac Failure	1	0	1	0
Cardiac Arrhythmias:				
Arrhythmia	2	0	2	0
Tachycardia	0	1	1	0

*One patient had both CHF and arrhythmia.
Adapted from Sponsor’s Table 34; p. 72-3 of ISS

An internal cardiology consultant, Dr. Stephen Grant, from the Division of Cardiovascular and Renal Drug Products reviewed the individual cases and categorized them as shown in Table 9. This analysis again showed events in several different categories with no clear pattern to suggest a particular mechanism. Overall, the events fit into categories of ischemic cardiovascular disease, heart failure and cardiac arrhythmias. The Applicant conducted their own analysis of the cardiovascular serious adverse events, using a blinded adjudication committee to categorize the events as meeting APTC criteria or not. Their results (Table 10) are similar to those of Dr. Grant. Based on his review of the data, Dr. Grant concluded (as summarized in Dr. Neuner’s review) “that the distribution of cardiovascular deaths and of cardiac SAEs due to ischemic vascular disease and/or heart failure was not obviously unusual even considering the decreased duration of exposure in the pegloticase treatment arms due to more pegloticase-treated subjects withdrawing prior to study conclusion. However, there remains a degree of uncertainty about the cardiac safety of pegloticase because so few events were observed due to the limited number of subjects enrolled and limited duration of follow-up.”

Table 9: Analyses of Subjects with Major Cardiac Adverse Events Experienced by Patients for the Pooled Safety Database for the Controlled Studies 405 and 406 as Attributed by FDA

Major Cardiac Adverse Events	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Total Pegloticase (N=169)	Placebo (N=43)
Number of Subjects with Major Cardiac AEs:	5 (6%)	3 (4%)	8 (5%)	1 (2%)
Ischemic Cardiovascular Disease:				
Sudden Death	2	0	2	0
Inferolateral Myocardial Infarction	0	1	1	0
“Troponin Leak”	0	0	0	1
Transient Ischemic Attack	0	1	1	0
Heart Failure:				
Heart Failure	2	0	2	0
Cardiac Arrhythmias:				
Supraventricular Tachycardia	0	1	1	0
Ventricular Tachycardia	1	0	1	0

Table 10: Analyses of Subjects with Major Cardiac Adverse Events by Sponsor’s Cardiac Event Adjudication Committee for the Pooled Safety Database from the Controlled Studies 405 and 406

Major Cardiac Adverse Events	Pegloticase q 2 wks (N=85) n (%)	Pegloticase q 4 wks (N=84) n (%)	Total Pegloticase (N=169) n (%)	Placebo (N=43) n (%)
Number (%) of Subjects with Major CV Events	4 (5%)	6 (8%)	10 (6%)	0 (0%)
All APTC* Events:	2 (2%)	1 (1%)	3 (2%)	0 (0%)
Cardiovascular Deaths	2	0	2	0
Non-Fatal Myocardial Infarction	0	1	1	0
Non-Fatal Stroke	0	0	0	0
Non-APTC CV Events:	2 (2%)**	5 (6%)	8 (5%)	0 (0%)
Angina	0	1	1	0
Congestive Heart Failure	2	1	3	0
Arrhythmia	1	1	2	0
Deep Venous Thrombosis	0	1	1	0
Transient Ischemic Attack	0	1	1	0

* Anti-Platelet Trialist Collaborative

** Two subjects had multiple events: Subject 406-311-005 had 2 events (CHF and arrhythmia); Subject 405-122-003 had both an APTC event (MI) and a non-APTC event (DVT)

Infusion reactions were common in pegloticase-treated patients. A total of 26% and 41% of patients in the every 2 week and every 4 week arms, respectively, experienced infusion reactions as compared to 5% in the placebo arm. For the infusion reactions in the every 2 week arm proposed for marketing, 13% of patients experienced moderately severe

reactions and 5% had severe reactions. The specific symptoms characterizing these reactions include urticaria, dyspnea, chills, hyperhydrosis, pruritus, some of which are potentially allergic in nature. To further characterize these reactions an internal allergy consult was obtained from the Division of Pulmonary and Allergy Products. Dr. Susan Limb reviewed the data on allergic reactions particularly focusing on reactions that could be classified as anaphylaxis. Dr. Limb applied criteria recently developed by NIAID/FAAN¹ that allow classification of anaphylaxis without regard to potential mechanism, i.e., presence/absence of IgE antibodies. She found that, of the events categorized as infusion reactions with a hypersensitivity component, that 7 met criteria for anaphylaxis. In addition, she found 7 additional adverse events that met criteria for anaphylaxis. Overall, approximately 5% of pegloticase-treated patients had adverse events meeting clinical criteria for anaphylaxis. Most of the cases meeting criteria for anaphylaxis were considered severe enough by the investigator that no further infusions were given. However, in several cases additional infusions were given with no further reactions. In other cases, reactions were observed later on re-exposure to pegloticase. None of the cases meeting clinical criteria for anaphylaxis were fatal.

No clinical significant laboratory abnormalities were observed.

6.3.3. *Safety update*

The 120-day safety update showed no new safety signals.

6.3.4. *Immunogenicity*

Immunogenicity of pegloticase was common. Overall, approximately 90% of pegloticase-treated patients developed anti-pegloticase antibodies. In many cases the antibodies were of low titer. However, approximately one-third of treated patients developed high-titer antibodies. High titer antibodies were highly correlated with lack of efficacy and with infusion reactions. No patients (none of 25) in the every 2 week group who developed high-titer antibodies had a clinical response. Similarly, infusion reactions were common in patients with high-titer antibodies (16/30 or 53%) in the every 2 week group but uncommon in patients with low-titer antibodies (1/25 or 4%).

It is important to determine whether the anti-pegloticase antibodies are directed against the foreign protein (i.e., uricase) or to the PEG. While approximately 90% of subjects have antibodies to pegloticase, only a small subset have low-titer anti-uricase antibodies. This indicates that most of the anti-pegloticase antibodies are directed against PEG. However, using the Applicant's anti-PEG assay only 40% of patients test positive. The Immunogenicity reviewer, Dr. Joao Pedras-Vasconcelos, interprets the data to indicate that the anti-PEG antibody assay is inadequately sensitive and likely underestimates the proportion of patients with antibodies to PEG. The development of anti-PEG antibodies is potentially clinically important in that there are other therapeutic products that contain

¹ Sampson HA, et al. Second symposium on the definition and management of anaphylaxis: Summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006; 117:391-7

PEG. Treatment of patients with pre-existing anti-PEG antibodies with PEG-containing products could have adverse effects on safety and efficacy.

6.3.5. Discussion of primary reviewer's comments and conclusions

The primary clinical reviewer, Dr. Rosemarie Neuner, concluded that the most concerning adverse events with pegloticase were the higher rate of serious cardiovascular adverse events, infusion reactions and events meeting clinical criteria for anaphylaxis. She noted the conclusions of the internal cardiology consultant that the events did not fit a particular pattern and were not obviously unusual in view of the unequal randomization and multiple underlying risk factors of the patients involved. She also noted that the small size of the safety database precluded reaching definite conclusions. She concluded that given the demonstrated benefits of pegloticase that the benefit:risk ratio is favorable. I agree that the evidence for a clear cardiovascular safety signal is not strong given the small numbers of cases, the lack of a clear pattern and the unequal randomization. I also agree that infusion reactions and cases meeting clinical criteria for anaphylaxis are the major safety concerns for this product.

6.3.6. Discussion of notable safety issues

Concerning the cardiovascular serious adverse events, it is not clear that the data indicate a clear safety signal. However, the data are insufficient to reach firm conclusions. A cardiovascular outcome study is not practical in this patient population since large numbers of patients are required and this is an orphan population. However, an observational epidemiologic registry would be a reasonable way to collect additional information. In an internal meeting, representatives of OSE agreed that an observational epidemiology study was a reasonable way to collect additional information. Given the difficulties devising an adequate control group in the absence of randomization such a study is unlikely to give definitive results but the information could nonetheless be helpful. Regarding the infusion reactions and cases meeting clinical criteria for anaphylaxis the risk of these events is highly correlated with antibodies to pegloticase. There are strategies that could substantially reduce the risk of infusion reactions. For example, if patients are followed for achieving a uric acid level of less than 6 mg/dL and treatment is discontinued in patients who lose a response then this could represent an effective strategy for risk mitigation.

7. Advisory Committee Meeting

A meeting of the Arthritis Advisory Committee was held on June 16, 2009 to discuss pegloticase for chronic gout refractory to conventional therapy. The committee was supplemented by members from the Cardiovascular and Renal Drug Products Advisory Committee and the Drug Safety Advisory Committee. There was no consensus on the committee as to whether there was a true cardiovascular safety signal, especially given the small number of cases, the lack of a biologically plausible mechanism and the multiple comorbidities. Nonetheless, committee members favored collecting additional information postmarketing possible by means of an observational epidemiology study.

The committee voted overwhelmingly in favor of approval: 14 to 1. However, a number of committee members stated that it would be important to limit use of the product to patients who were truly refractory to conventional therapy. There was support for monitoring of uric acid with each dose to avoid infusion reactions.

8. Financial Disclosure

Based on the information submitted by the Applicant there were no financial conflicts of interest that would have the potential to bias the data.

9. Labeling

9.1. Proprietary name

DMEPA determined that the proposed proprietary name, Krystexxa, was acceptable.

9.2. Physician labeling

At this time, the review of the Applicant's proposed product labeling is still in progress. Based on review of the data the pegloticase 8 mg every 2 week regimen should be approved as the benefit:risk profile is more favorable than the every 4 week regimen. The label should recommend monitoring uric acid before each dose. If the uric acid has returned to a level of greater than 6 mg/dL then therapy should be stopped.

10. DSI audits

DSI inspected 3 clinical sites and found no regulatory violations. In addition, audit of the Applicant's clinical laboratory service found no violations.

11. Recommendations/Risk Benefit Assessment

11.1. Recommended Regulatory Action

Before this BLA can be approved the issues raised concerning microbiology, concerning the manufacturing facility and concerning the comparability of commercial product to the product studied in the Phase 3 trials all need to be addressed. Therefore, the action for this BLA should be a Complete Response.

11.2. Risk Benefit Assessment

Review of the data from the two Phase 3 trials of pegloticase 8 mg intravenously every 2 weeks in patients with chronic gout refractory to conventional therapies demonstrated that there is substantial evidence of efficacy both for lowering uric acid to below the target level of 6 mg/dL and for resolving tophi. In the two Phase 3 trials, a statistically significantly greater proportion of patients receiving pegloticase 8 mg IV every 2 weeks achieved target urate levels than patients receiving placebo: 47% of patients in Study 405 and 38% in Study 406, compared to 0% of placebo-treated patients. In addition, in studies 405 and 406 pooled a significantly greater proportion of patients achieved

complete resolution of tophi, a clinical benefit that has never been achieved in the timeframe of a randomized trial previously.

Review of the safety data demonstrate a clear risk of immunogenicity, infusion reactions and events meeting clinical criteria for anaphylaxis. While a higher proportion of patients in the pegloticase arms experienced cardiac serious adverse events the numbers were small and the patients involved had clear predisposing comorbidities. The cardiovascular adverse events warrant further study but they do not preclude approval. Overall, the risk:benefit profile of pegloticase for chronic gout refractory to conventional therapies is favorable and the BLA should be approved from the clinical standpoint.

11.3. Recommendation for Postmarketing Risk Evaluation and Management (REMS) Strategies

The DRISK review team recommends a REMS consisting of a Medication Guide, a Communication Plan and an assessment of the effectiveness of the REMS. They state that “ETASU [Elements to Assure Safe Use] *may* be justified for pegloticase if there is reason to believe that the risk of life threatening infusion reactions cannot be adequately addressed by labeling and medical supervision/routine emergent management as per standard of care in the infusion center setting.” Since the infusion reactions and hypersensitivity reactions seen with pegloticase are similar in type and in frequency to those seen with other products commonly given in infusion centers for rheumatologic disorders, e.g., Remicade, ETASU would not be justified at this time. Therefore, I concur with DRISK that a REMS is warranted and that the elements of the REMS should be a Medication Guide, a Communication Plan and an assessment of the effectiveness of the REMS. The primary clinical reviewer, Dr. Neuner, also agrees with this recommendation.

11.4. Safety concerns to be followed postmarketing

Cases of anaphylaxis, severe infusion reactions and cardiovascular adverse events should be followed postmarketing.

11.5. Postmarketing studies

11.5.1. Required studies (PMRs)

Drug product/microbiology:

1. The development and validation of a shipper suitable for transporting the finished product vials within the US.

Drug substance/microbiology:

1. Conduct a hold time validation study of crude uricase using three production-scale runs that are tested for bioburden and endotoxin before and after the claimed hold time.

2. Conduct a hold time validation study of uricase intermediate using three production-scale runs that are tested for bioburden and endotoxin before and after the claimed hold time.
3. Conduct a hold time validation study of the [REDACTED] (b) (4) column eluates using three production scale runs that are tested for bioburden and endotoxin before and after the claimed hold time.
4. Conduct a growth promotion study for the final formulation buffer.
5. Conduct buffer hold time studies. These studies should use a bracketing approach for buffer selection and should include measurement of endotoxin as well as other microbial and biochemical parameters.
6. Conduct a study to validate the shipping practices for bulk drug substance from BTG to Enzon. This study should study the temperature of at least three packed shipping boxes of material for both the summer and winter conditions.

Pharmacology/Toxicology:

1. Conduct a fertility study in the rat model (Segment 1)
2. Conduct a embryo-fetal development study in the rabbit model (Segment 2)
3. Conduct a peri-natal and post-natal development study in the rat model (Segment 3)
4. in vitro and/or ex vivo assessments of aortic endothelial cell and adrenal function following co-culture with pegloticase.

Clinical:

1. Conduct an observational epidemiology study to assess [REDACTED] (b) (4), serious infusion reactions and adverse events meeting clinical criteria for anaphylaxis.

11.5.2. Commitments (PMCs)

None.

11.5.3. Other agreements with Sponsor

None.

CLINICAL REVIEW

Application Type	BLA
Application Number	125293
Priority or Standard	Priority
Submit Date	October 31, 2008
PDUFA Goal Date	August 1, 2009
Division / Office	Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)/ODEII
Reviewer Name	Rosemarie Neuner, MD, MPH <i>R. Neuner, MD</i>
Through	Jeffrey Siegel, MD <i>Jeffrey N. Siegel</i>
Review Completion Date	July 1, 2009 <i>7/2/09</i>
Established Name	Pegloticase
Trade Name	Krystexxa™
Therapeutic Class	Uricase enzyme
Applicant	Savient, Inc.
Formulation	8 mg/mL for IV use
Dosing Regimen	8 mg via Intravenous Infusion every 2 weeks
Indication	Treatment of chronic gout in patients refractory to conventional therapy
Intended Population	Adults

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	5
1.1	Recommendation on Regulatory Action.....	5
1.2	Risk Benefit Assessment	5
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies....	6
1.4	Recommendations for Postmarket Requirements and Commitments	7
2	INTRODUCTION AND REGULATORY BACKGROUND.....	7
2.1	Product Information	7
2.2	Tables of Currently Available Treatments for Proposed Indications	8
2.3	Availability of Proposed Active Ingredient in the United States.....	8
2.4	Important Safety Issues With Consideration to Related Drugs	8
2.5	Summary of Presubmission Regulatory Activity Related to Submission.....	9
2.6	Other Relevant Background Information.....	10
3	ETHICS AND GOOD CLINICAL PRACTICES.....	10
3.1	Submission Quality and Integrity	10
3.2	Compliance with Good Clinical Practices.....	11
3.3	Financial Disclosures.....	11
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES.....	11
4.1	Chemistry Manufacturing and Controls.....	11
4.2	Clinical Microbiology	12
4.3	Preclinical Pharmacology/Toxicology.....	13
4.4	Clinical Pharmacology	13
4.4.1	Mechanism of Action	13
4.4.2	Pharmacodynamics.....	13
4.4.3	Pharmacokinetics.....	14
5	SOURCES OF CLINICAL DATA.....	15
5.1	Tables of Studies/Clinical Trials.....	15
5.2	Review Strategy.....	17
5.3	Discussion of Individual Studies/Clinical Trials	18
6	REVIEW OF EFFICACY	64
	Efficacy Summary	65
6.1	Indication	66
6.1.1	Methods.....	66
6.1.2	Demographics	67
6.1.3	Subject Disposition.....	72
6.1.4	Analysis of Primary Endpoint(s)	74
6.1.5	Analysis of Secondary Endpoints(s).....	77

6.1.6	Other Endpoints	90
6.1.7	Subpopulations.....	90
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations.....	91
	(b) (4)	
6.1.10	Additional Efficacy Issues/Analyses	92
7	REVIEW OF SAFETY	93
	Safety Summary	93
7.1	Methods.....	94
7.1.1	Studies/Clinical Trials Used to Evaluate Safety.....	94
7.1.2	Categorization of Adverse Events	95
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence	95
7.2	Adequacy of Safety Assessments	96
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	96
7.2.2	Explorations for Dose Response	97
7.2.3	Special Animal and/or In Vitro Testing	98
7.2.4	Routine Clinical Testing.....	98
7.2.5	Metabolic, Clearance, and Interaction Workup.....	98
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	99
7.3	Major Safety Results.....	99
7.3.1	Deaths.....	101
7.3.2	Nonfatal Serious Adverse Events.....	106
7.3.3	Dropouts and/or Discontinuations	108
7.3.4	Significant Adverse Events.....	110
7.3.5	Submission Specific Primary Safety Concerns.....	111
7.4	Supportive Safety Results.....	123
7.4.1	Common Adverse Events.....	123
7.4.2	Laboratory Findings.....	124
7.4.3	Vital Signs	129
7.4.4	Electrocardiograms (ECGs).....	132
7.4.5	Special Safety Studies/Clinical Trials	133
7.4.6	Immunogenicity	133
7.5	Other Safety Explorations.....	135
7.5.1	Dose Dependency for Adverse Events.....	135
7.5.2	Time Dependency for Adverse Events	135
7.5.3	Drug-Demographic Interactions.....	135
7.5.4	Drug-Disease Interactions	136
7.5.5	Drug-Drug Interactions	136
7.6	Additional Safety Evaluations	137
7.6.1	Human Carcinogenicity	137
7.6.2	Human Reproduction and Pregnancy Data	137
7.6.3	Pediatrics and Assessment of Effects on Growth.....	138

7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound	138
7.7	Additional Submissions / Safety Issues	138
8	POSTMARKET EXPERIENCE	138
9	APPENDICES	139
9.1	Literature Review/References.....	139
9.2	Labeling Recommendations	139
9.3	Advisory Committee Meeting	140

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This clinical reviewer recommends approval for this biological licensing application for pegloticase for the orphan designated indication of chronic gout in patients refractory to conventional therapy. The data contained in this application is sufficient to support a finding of efficacy and safety for pegloticase when administered as a dosing regimen of 8 mg every 2 weeks via intravenous infusion in gout patients who have failed to adequately respond to optimal therapy with other urate lowering agents.

1.2 Risk Benefit Assessment

The efficacy of pegloticase as a treatment for refractory gout was assessed in two replicate, adequate and well-controlled dose comparison trials, Studies 405 and 406, that evaluated the efficacy and safety of pegloticase 8 mg every 2 weeks and pegloticase 8 mg every 4 weeks when administered via intravenous infusion in 212 patients with gout refractory to conventional therapy. In both trials a greater proportion of patients receiving pegloticase 8 mg every 2 weeks achieved normalization of plasma uric acid (PUA) to less than 6 mg/dL during Months 3 and 6 combined compared to placebo. Additionally, significant clinical benefit was seen in patients treated with this regimen as manifest by a reduction in tophi, a reduction in the number of swollen and tender joints, and a decrease in the frequency of gout flares as compared to placebo. However, the product's highly immunogenic profile adversely impacts on both its safety and efficacy. A decrease in product efficacy was observed in patients with high levels of anti-pegloticase antibodies. Patients with high-titer anti-pegloticase antibodies also had an increased risk of infusion reactions despite mandatory pre-treatment with a prophylactic regimen. Additionally, 5% of the patients who were reported in the safety database as having infusion reactions met clinical criteria for anaphylaxis. More patients would likely have experienced events meeting clinical criteria for anaphylaxis were it not for the mandatory pre-treatment prophylactic regimen that patients received in the Phase 3 trials. Specific safety concerns were also raised during the review of safety regarding a potential cardiovascular risk associated with the use of this product in view of the numerically higher number of cardiovascular events and deaths due to cardiac events in the pegloticase treatment arms. The relatively small safety database submitted in support of pegloticase precluded determination of the cardiovascular risk of pegloticase with greater precision. If approved, pegloticase would be the only urate lowering therapy that demonstrated tophi resorption, reduction in tender and swollen joints and reduced gout flares in the timeframe of a randomized trial. In view of the clinical benefit, the risk-benefit assessment is favorable for pegloticase every 2 weeks for patients with chronic gout who have failed to respond to conventional therapy.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Applicant submitted a Risk Evaluation Minimization Strategy (REMS) for pegloticase contained in their original submission and a revised amendment dated February 4, 2009. Their revised REMS included the following features:

(b) (4)

The Applicant's proposed plan identifies the following goals:

(b) (4)

The Applicant's proposals were reviewed by Dr. Kathryn O'Connell of the Division of Risk Management (DRISK) who recommends a REMS be instituted with the following provisions:

- Convert the PPI to a Medication Guide to improve patient compliance with important instructions to mitigate severe infusion reactions and gout flares
- Applicant needs to submit a detailed Communication Plan consisting of a "Dear HealthCare Provider letters for prescribers and infusion center medical personnel, non-promotional print service announcements in rheumatology journals, and non-promotional information at major internal medicine and rheumatology meetings"

In addition, Dr. O'Connell states that elements to assure safe use (ETASU) may be justified "if there is reason to believe that the risk of life threatening infusion reactions cannot be adequately addressed by labeling and medical supervision/routine emergent management as per standard of care in the infusion center setting." If ETASU are included in the REMS they may

include: a. prescriber enrollment with attestation; b. infusion center enrollment; c. patient enrollment and documentation of safe use conditions

I agree with DRISK that pegloticase should have a REMS. The REMS should include a MedGuide and a detailed communications plan as recommended by DRISK. In terms of ETASU, there is no evidence that the risk of life-threatening infusion reactions cannot be adequately addressed by labeling and medical supervision per standard of care in the infusion center setting. For example, the risk of infusion reactions with pegloticase seems similar to that of Remicade, which is routinely managed by rheumatologists and infusion centers as part of standard of care. Therefore, I do not recommend ETASU at this point in time. If future evidence indicates that the risks of life-threatening infusion reactions require additional measures implementing ETASU can be reconsidered.

1.4 Recommendations for Postmarket Requirements and Commitments

Since pegloticase was granted orphan drug status on February 21, 2001, it is exempted from conducting a pediatric assessment as per the provisions of the Pediatric Research Equity Act (PREA) and 21CFR314.55(d). Since gout is very rare in children, the Applicant would not be asked to conduct a study in the pediatric population.

The Applicant should be required to conduct a postmarketing observational epidemiologic study including internal controls in order to collect additional safety data regarding the occurrence of (b) (4) infusion reactions, anaphylaxis and other uncommon events (e.g., deaths). Additionally, this study should include a provision to evaluate the effectiveness of the proposed treatment guidance on avoiding infusion reactions as well as the other REMS tools.

2 Introduction and Regulatory Background

2.1 Product Information

Pegloticase, a new molecular entity, is a genetically engineered PEGylated recombinant mammalian uricase (urate oxidase). This enzyme is classified as a urate lowering therapy since it metabolizes uric acid into soluble allantoin for excretion by the kidney with hydrogen peroxide and carbon dioxide as oxidative byproducts. If approved for licensing, pegloticase will be marketed under the tradename Krystexxa™ by the Applicant, Savient Pharmaceuticals, for the indication of chronic gout in patients refractory to conventional therapy to be administered at a dose of 8 mg every 2 weeks via intravenous infusion.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 lists the treatments that are currently approved for the management of hyperuricemia:

Table 1 – Currently Available Treatments for the Management of Hyperuricemia

Product	Year of Approval	Indication
Xanthine Oxidase Inhibitors		
Allopurinol	1966	Management of patients with signs and symptoms or primary or secondary gout (i.e., acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy)
Febuxostat	2009	Chronic management of hyperuricemia in patients with gout
Uricosuric Agents		
Probenecid	1951	Treatment of the hyperuricemia associated with gout and gouty arthritis
Uricase		
Rasburicase	2002	Initial management of plasma uric acid levels in pediatric patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anti-cancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid

2.3 Availability of Proposed Active Ingredient in the United States

This product is an unapproved new molecular entity under development for licensing by the Applicant and is currently not marketed in this country.

2.4 Important Safety Issues With Consideration to Related Drugs

The gout subpopulation intended for pegloticase administration are those patients whose gout is refractory to conventional therapy. Refractory gout occurs when serum uric acid levels fail to normalize in addition to having inadequately controlled disease signs and symptoms in response to treatment with standard anti-hyperuricemic therapy at the maximum medically appropriate dose or for whom these drugs are contraindicated due to hypersensitivity reactions or tolerability issues. Due to its immunogenic potential, patients treated with pegloticase are at risk for developing

infusion reactions and anaphylaxis, as well as loss of efficacy due to antibody production.

Allopurinol is the most commonly used urate-lowering drug. However, its effectiveness is limited by a number of issues including the need to use lower doses in patients with renal insufficiency, and an adverse event profile that includes gastrointestinal, hepatic, renal, hematological and skin toxicities that occur in approximately 20% of patients who take this drug. In addition, hypersensitivity reactions occur in 2-4% of patients that in some instances have been fatal. It is estimated that approximately 5% of patients are forced to discontinue allopurinol therapy due to the development of an adverse event. Febuxostat, which was recently approved and does not require renal adjustment in dosing, may provide a therapeutic alternative for patients unable to tolerate allopurinol. Probenecid is a uricosuric agent that can be used in patients who are underexcretors of urate, however, its use is limited by the risk for developing urate renal stones and crytalluria in patients with decreased renal function or in patients who overexcrete urate.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Applicant developed pegloticase as a treatment for patients who were refractory to, or unable to tolerate, standard anti-hyperuricemic therapy. At that time, the mainstay of anti-hyperuricemic therapy for gout was allopurinol. Based on an estimated prevalence of approximately 100,000 patients with severe gout who have not responded, are allergic, or have some other contraindication to the use of standard antihyperuricemic therapy, and could benefit from treatment with pegloticase in view of its then projected risk-benefit ratio (e.g., risk of oxidative damage and immunogenicity) the sponsor was granted orphan drug status on February 21, 2001 by the Agency's Office of Orphan Products Development. Subsequently, the Applicant conducted a Phase 1 study to evaluate the safety, tolerability and efficacy of pegloticase in lowering serum uric acid in patients with gout when administered via subcutaneous injections. This study was terminated early after a number of study participants developed urticarial reactions following study injections. After the results from a second preclinical repeat dose intravenous study in dogs failed to identify any potential immunological safety signals with intravenous administration, Phase 1 testing in humans resumed. A Phase 2 study of IV pegloticase was not limited by urticaria. However, there was a 44% incidence of infusion reactions. In addition, some patients developed gout flares upon treatment with pegloticase.

At an end-of-Phase 2 (EOP2) meeting on August 16, 2005 the Applicant was advised they would need data generated from 2 adequate and well controlled trials that were adequately powered for their primary endpoint in order to support product registration. They were also told that it would be important for them to develop a standard regimen to minimize the frequency and severity of gout flares and a standard regimen of prophylaxis for gout flares. The Applicant was also informed at this meeting that no

additional toxicology studies were required unless safety concerns were identified during review of the chronic dog study or data being obtained in ongoing clinical trials that might need to be addressed through additional toxicology studies.

A special protocol assessment (SPA) agreement was reached with the Applicant on May 3, 2006 regarding their protocol and statistical analysis plan for Study C0405. Study C0405 was a Phase 3, randomized, placebo-controlled trial to evaluate the effectiveness and safety of two doses of pegloticase. As per this agreement analysis of the primary endpoint from this study and a replicate study (Study C0406) would be conducted separately while analyses of all secondary endpoints would be conducted on pooled results generated from the two pivotal trials (Studies C0405 and C0406).

A pre-BLA meeting with the sponsor was held on April 17, 2008 during which agreement was reached regarding clinical data necessary to support a biological licensing application and how these data were to be formatted for agency review. This included safety and efficacy data from approximately 80-90 patients treated continuously for at least 12 months with pegloticase via the Phase 3 double-blind and open label studies, and the potential need for an Advisory Committee meeting.

On October 31, 2008, Savient submitted this BLA for pegloticase under Section 351 of the United States Public Health Service Act and Title 21 of the Code of Federal Regulations Part 601. The application was subsequently granted priority review and an advisory committee meeting was scheduled. On January 31, 2008 the Applicant submitted a major amendment consisting of additional analyses to address cardiovascular adverse events among pegloticase-treated patients. Consequently, the Agency extended the review clock by 3 months and delayed the advisory committee meeting until June 16, 2009 to permit review of the new information.

2.6 Other Relevant Background Information

While this application was under review, the Agency approved a new uric acid-lowering drug, febuxostat. Thus, the unmet medical need for a urate lower therapy would be for patients who are unable to tolerate or fail to respond to allopurinol or febuxostat.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Savient's submission was appropriately organized to allow information to be reviewed in an acceptable manner. The Applicant's responses to all of FDA's requests were timely and well organized.

3.2 Compliance with Good Clinical Practices

According to statements included in the reports for the pivotal trials, C0405 and C0406, the Applicant certified that these studies were conducted in compliance with the following: good clinical practice standards as outlined in the Declaration of Helsinki or the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, with the institutional review board regulations as per 21 CFR (56), and the informed consent regulation as per 21 CFR (50).

The Division of Scientific Investigation (DSI) inspected 3 clinical sites that participated in the pivotal Phase 3 trials and did not find any regulatory violations over the course of their audits of these sites. Audits of the Applicant and its clinical laboratory services, Charles River Laboratories Preclinical Services, revealed no discrepancies or regulatory violations in terms of oversight and monitoring of the pivotal Phase 3 studies, test article accountability, financial disclosures, qualifications of investigators and site monitors, transfer of obligations, adverse event reports, and handling of uric acid data.

3.3 Financial Disclosures

The financial disclosure form signed by the Applicant certified that no financial arrangements had been made with any of the principal investigators or subinvestigators involved with the clinical studies where outcomes affected compensation as defined in 21 CFR 54.2(a). Additionally, none of the principal investigators or subinvestigators reportedly had a proprietary interest in this product or a significant equity in Savient, Inc., which is commercially developing pegloticase for licensing in this country as described in 21 CFR 54.2(b).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Dr. Richard Ledwidge of CDER's Division of Therapeutic Proteins, Office of Biotechnology Products/OPS, reviewed the chemistry manufacturing controls (CMC) for this application. Based on his examination of the CMC data submitted in support of pegloticase, Dr. Ledwidge's team is recommending non-approval pending resolution of product comparability issues related to the pegloticase used in the Phase 3 pivotal

studies and the commercial formulation that the Applicant wishes to market. According to Dr. Ledwidge's presentation at the wrap-up meeting, the product used in the Phase 3 studies contains (b) (4) resulting in it not being physicochemically comparable to the pegloticase formulation that the Applicant plans to market if approved. If this issue is resolved prior to the application's action date, he is recommending that the Applicant needs to conduct leachable studies for drug substance and drug product as a postmarketing commitment.

Dr. Susan Kirshner of CDER's DTP/OBP reviewed the data contained in the application regarding pegloticase's immunogenicity. Although the screening assays for anti-Pegloticase and anti-Uricase IgM and IgG antibodies have been validated, the Applicant needs to develop validated IgE and anti-PEG antibody assays. Additionally, patients who participate in future studies of the product should have their anti-Puricase and anti-PEG antibody status tracked till they revert to seronegative status. Dr. Kirshner also recommends that the Applicant consider immune tolerance induction regimens for appropriate patients in view of the negative impact that anti-Uricase antibodies have on the product's efficacy.

4.2 Clinical Microbiology

Dr. Bo Chi of CDER's Office of Compliance/DMPQ/MAPCB/BMT reviewed the portion of this application related to product closure and sterility. Based on her review of these data, specifically the microbiological attributes of the container-closure and package integrity tests, additional information regarding the validation of the microbial challenge test (e.g., container closure integrity test) needs to be submitted by the Applicant before she can recommend an approval action. In the event that this application is approved, Dr. Chi is recommending that the Applicant develop and validate a new shipper for their product that is suitable for transporting the finished drug product vials within this country as a postmarketing requirement. In order to fulfill this requirement, the Applicant will need to submit validation data in support of worst-case duration and temperature for this new shipper.

Drug substance microbiology was reviewed by Dr. Mary Farbman of CDER's Office of Compliance/DMPQ/MAPCB/BMT. Based on the Biotechnology Manufacturing Team's assessment of the microbial control over the drug substance manufacturing process, Dr. Farbman is also recommending that a non-approval action be taken on this application for the following reasons listed in her review:

- Only one batch of pegloticase has been produced with reasonable bioburden levels in the (b) (4)
- The hold times for crude uricase and uricase intermediate have not been adequately validated
- Hold times for (b) column eluates have not been validated
- The Applicant has not set bioburden and endotoxin limits for its in-process steps

- No growth promotion study has been conducted for the final formulation buffer
- The shipping validation for shipments of drug substance to the drug product manufacturing facility in Indiana was not adequately performed

4.3 Preclinical Pharmacology/Toxicology

In support of pegloticase's safety profile, the Applicant submitted the results from 22 preclinical pharmacology/toxicology studies conducted in rats, rabbits, pigs and dogs. These studies included 6 pharmacokinetic studies, 2 single- and 3 repeat-dose studies, 1 reproductive Segment-II study, and 2 macrophage functionality studies. Since this product is a biologic therapeutic product that is not expected to have an effect on human cancer, no carcinogenicity or genotoxicity studies were performed. These data were reviewed by Dr. BeLinda A. Hayes who noted vacuolization of the adrenal gland, the spleen, the liver, the duodenum and jejunum, and the outflow tract of the heart in dogs treated weekly for 39-weeks in the repeat-dose toxicity study. These vacuoles did not appear to be reversible 12 weeks after treatment termination. The etiology and the clinical relevance of these vacuoles are unclear. Based on her review of these data, Dr. Hayes recommended approval of this application provided that an agreement can be reached with the Applicant regarding conducting the following post-marketing requirements:

1. Conduct a fertility study in the rat model (Segment 1)
2. Conduct a embryo-fetal development study in the rabbit model (Segment 2)
3. Conduct a peri-natal and post-development study in the rat model (Segment 3)
4. Conduct in vitro and/or ex vivo assessments of aortic endothelial cell and adrenal function following co-culture with pegloticase

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Pegloticase catalyzes the oxidation of uric acid to allantoin, which is excreted by the kidney. Hydrogen peroxide and carbon dioxide are produced as oxidative byproducts. Oxidation of uric acid reduces the serum concentrations of uric acid below the solubility limit to bring existing crystal accumulations into solution to alleviate the signs and symptoms of gout.

4.4.2 Pharmacodynamics

The pharmacodynamic (PD) data contained in this submission was generated from the Phase 1 and 2 studies, 402 and 403, as well as the pivotal Phase 3 studies, 405 and

406. The following is a summary of key PD findings identified by Dr. Atul Bhattaram in his review of these data:

- A clear dose/concentration response relationship for reduction of serum uric acid was demonstrated in Study 402. PD data collected from this trial showed that doses of pegloticase > 1 mg resulted in mean minimal plasma uric acid (PUA) levels of < 6 mg/dL.
- Anti-pegloticase antibody was associated with lowering of the plasma pegloticase concentrations and the loss of effect on plasma uric acid
- A benefit-risk analysis for identifying the optimal dosing regimen for pegloticase based on data generated from Studies 405 and 406 (e.g., achieving a PUA < 6mg/dL for at least 80% of the time during Months 3 and 6 [benefit] versus the risk of having an infusion reaction) identified the pegloticase 8 mg every 2 weeks regimen as the optimal dosing regimen for the product

Based on his review of these data, Dr. Bhattaram recommends approval of this application without the need for any postmarketing commitments.

4.4.3 Pharmacokinetics

The pharmacokinetic (PK) data contained in this submission was generated from the Phase 1 and 2 studies, 402 and 403, as well as the pivotal Phase 3 studies, 405 and 406. The following is a summary of key PK findings identified by Dr. Ping Ji:

- An approximately dose proportional increase in pegloticase exposure based on mean pegloticase concentrations time profiles was seen in Study 402
- Mean terminal half-life for pegloticase ranged from 152 to 332 hours
- Following multiple dose administrations in Study 403, the accumulation index (AI) was 1.42 for the area under the curve (AUC) and 1.86 for the C_{max} for the dose 8 mg every 2 weeks. The accumulation of the product was minimal for the dose of 8 mg every 4 weeks.
- Anti-pegloticase antibody appeared to affect pegloticase exposure with a 32% increase in clearance (CL) and a 25% increase in volume of distribution (V). Body surface area was shown to be positively related to CL and V.
- No pharmacokinetic studies with regards to interactions with drugs, herbal products, diet or smoking were conducted in support of this application

Based on her review of these data, Dr. Ji recommends approval of this application without the need for any postmarketing commitments.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

As part of their clinical development program for pegloticase for the control of hyperuricemia in patients with severe gout in whom conventional therapy is contraindicated or has been ineffective, the sponsor conducted a total of six clinical studies: two Phase 1 trials (401 and 402), one Phase 2 trial (403), and three Phase 3 trials (405, 406 and 407). An additional Phase 3 trial (409) was initiated just prior to submission of this application. These studies are summarized in the following Table 2:

Table 2- Key Design Features of Pegloticase Trials

Study/ Objectives	Study Design; Duration; Number of Study Sites	Dosage Regimen; Route of Administration	Number of Subjects	Diagnosis and Entry Criteria	Primary Endpoint (EP)
Phase 1					
Protocol C0401 Objectives: 1. Determine the single dose PK profile and safety of 5 ascending dose levels of pegloticase via SC injection 2. Determine the antibody response to the product 3. Evaluate the dose effect on plasma uric acid levels	Single-center, open-label, dose-escalating tolerance, safety and PK	Single dose of pegloticase 4 mg, 8 mg, 12 mg, and 24 mg via subcutaneous injection	N=13 4 Subjects per first 3 dose cohorts; 1 Subject in 24 mg cohort	Adults age ≥ 18 years with hyperuricemia defined as a PUA ≥ 7mg/dL; a diagnosis of symptomatic gout defined as: ≥ 1 tophus, and/or having experienced a gout flare within the previous 6 months and/or having chronic gouty arthritis despite conventional urate-lowering therapy	N/A
Protocol C0402 Objectives: 1. Determine single dose PK profile and safety of 6 ascending doses of IV pegloticase 2. Assess the dose effect on plasma uric acid levels 3. Determine the product's safety and immune response profiles	Single-center, open-label, dose-escalating tolerance, safety and PK	Single dose of pegloticase 0.5 mg, 1 mg, 2 mg, 4 mg, 8 mg and 12 mg via intravenous infusion	N=24 4 Subjects per dose cohort	Adults age ≥ 18 years with hyperuricemia defined as a PUA ≥ 7 mg/dL; a diagnosis of symptomatic gout defined as: ≥ 1 tophus, and/or having experienced a gout flare within the previous 6 months and/or having chronic gouty arthritis despite conventional urate-lowering therapy	N/A
Phase 2					
Protocol C0403 Objectives: 1. Assess the effect of multiple doses of pegloticase on SUA 2. Determine the multiple dose PK profile of pegloticase 3. Assess the safety and tolerability of multiple doses of pegloticase	Multicenter, randomized, open-label, parallel-group, dose-ranging, efficacy, safety, and PK	Pegloticase 4 mg q 2 wks, 8 mg q 2 wks, 8 mg q 4 weeks, 12 mg q 4 weeks for 3 months via intravenous infusion	N=41 4mg q 2 wks: 4/7 completed; 8mg q 2 wks: 8/8 completed; 8mg q 4 wks: 8/13 completed; 12 mg q 4 wks: 6/13 completed	Adults age ≥ 18 years with hyperuricemia defined as a PUA ≥ 8 mg/dL; a diagnosis of symptomatic gout defined as: ≥ 1 tophus, and/or having experienced a gout flare within the previous 6 months and/or having chronic gouty arthritis for whom conventional urate-lowering therapy is contraindicated or has been ineffective	Proportion of subjects maintaining a PUA concentration < 6 mg/dL for at least 80% of the time during the treatment period
Phase 3					
Protocol C0405 Objectives: 1. Demonstrate superiority in response rate vs. placebo in percentage achieving plasma uric acid concentrations < 6mg/dL for at least 80% of the time during months 3 and 6 2. Reduction in tophus burden, frequency of gout flares, number of swollen and tender joints and improvement in patient reported outcomes	Multicenter, randomized, double-blind, placebo-controlled, 26-week, comparative parallel group study. Study utilized randomization ratio of 2:2:1 stratified by the presence or absence of tophi. 26 sites in U.S. and Mexico	Pegloticase 8 mg q 2 weeks and 8 mg q 4 weeks via intravenous infusion Placebo via intravenous infusion	N= 104 Pegloticase Groups: q 2 weeks: 44 randomized; 30 completed q 4 weeks: 43 randomized; 27 completed Placebo Group: 22 randomized; 19 completed	Adults age ≥ 18 years with hyperuricemia defined as a PUA ≥ 8 mg/dL; a diagnosis of symptomatic gout defined as: 3 disease flares within 18 months, or ≥ gouty tophus, or gout arthritis; and history of hypersensitivity or failure to normalize PUA following ≥ 3 months treatment with allopurinol at maximum labeled dose (800 mg daily) or at a medically appropriate lower dose based on dose-limiting toxicity or dose-limiting comorbidity (e.g., renal impairment)	Proportion of subjects maintaining a PUA concentration < 6 mg/dL for at least 80% of the time during Months 3 and 6.

* Study C0401: Terminated.

Adapted from Sponsor's 5.2 Tabular Listing of All Clinical Studies located in Module 5

Table 2- Key Design Features of Pegloticase Trials (cont.)

Study/ Objectives	Study Design; Duration; Number of Study Sites	Dosage Regimen; Route of Administration	Number of Subjects	Diagnosis and Entry Criteria	Primary Endpoint (EP)
Phase 3 (cont.)					
Protocol C0406 Objectives: 1. Demonstrate superiority in response rate vs. placebo in percentage achieving plasma uric acid concentrations < 6mg/dL for at least 80% of the time during months 3 and 6 2. Reduction in tophus burden, frequency of gout flares, number of swollen and tender joints and improvement in patient reported outcomes	Multicenter, randomized, double-blind, placebo-controlled, 26-week, comparative parallel group study. Study utilized randomization ratio of 2:2:1 stratified by the presence or absence of tophi. Sites in United States and Mexico	Pegloticase 8 mg every 2 weeks and 8 mg every 4 weeks via intravenous infusion Placebo via intravenous infusion	N=108 Pegloticase Groups: q 2 weeks: 46 randomized; 29 completed q 4 weeks: 46 randomized; 32 completed Placebo Group: 24 randomized; 20 completed	Adults age ≥ 18 years with hyperuricemia defined as a PUA ≥ 8 mg/dL; a diagnosis of symptomatic gout defined as: 3 disease flares within 18 months, or ≥ gouty tophus, or gout arthritis; and history of hypersensitivity or failure to normalize PUA following ≥ 3 months treatment with allopurinol at maximum labeled dose (800 mg OD) or at a medically appropriate lower dose based on dose-limiting toxicity or dose-limiting co-morbidity (e.g., renal impairment)	Proportion of subjects maintaining a PUA concentration < 6 mg/dL for at least 80% of the time during Months 3 and 6.
Open-Label Extension Studies					
Protocol C0407** Objective: Evaluate the long-term safety, treatment effect and durability of response	Multicenter, uncontrolled, open-label, 24-month continuation study in subjects who completed Protocol C0405 or C0406	Pegloticase 8 mg every 2 weeks and 8 mg every 4 weeks via intravenous infusion Observational group (no treatment)	N=151 149 subjects continuing Pegloticase 2 subjects in observational group	Subjects with gout who had completed Protocol 405 or 406	N/A
Protocol C0409** Objective: Evaluate the safety and clinical effect of re-exposure to a 24-week course of treatment in subjects whose last exposure to pegloticase has been > 1 year to study entry	Multicenter, uncontrolled, open-label, 24 week re-exposure study	Pegloticase 8 mg every 2 weeks via intravenous infusion	Target: 18 subjects Enrolled: 7	Subjects previously treated with intravenous pegloticase during Phase 1 and 2 studies (C0402, C0403, C0405, C0406, and C0407) whose last exposure to the product was > 1 year prior to study entry	N/A

**Studies C0407 and C0409: Ongoing.

Adapted from Sponsor's 5.2 Tabular Listing of All Clinical Studies located in Module 5

5.2 Review Strategy

The applicant conducted two replicate adequate and well-controlled trials, Studies 405 and 406, in support of this application. Additionally, the applicant submitted the interim results of an ongoing open-label extension (OLE) study, 407, in support of durability of the product's effectiveness with prolonged exposure, the results from the uncontrolled Phase 1 (401 and 402) and Phase 2 proof-of-concept studies, and preliminary data from the re-exposure study 409. This medical officer reviewed the results from the

Applicant's pivotal trials (405 and 406) for efficacy. The other studies (401, 401, 403, 407 and 409) were not reviewed in support of pegloticase's efficacy as a treatment for the control of hyperuricemia in patients with severe gout in whom conventional therapy is contraindicated or has been ineffective for the following reasons: they were all uncontrolled open-label trials; one study evaluated a different route of administration (subcutaneous injection) that is not being developed for marketing due to safety issues related to route of administration; they evaluated doses of pegloticase that were not studied in the pivotal Phase 3 trials; or they were not designed to evaluate the efficacy (i.e., primary objective was safety) of the product.

The safety database included all subjects who participated in the pivotal Phase 3 trials, in the OLE study as well as the safety data collected from the Phase 1 and 2 studies. These data will be discussed in Section 7.

5.3 Discussion of Individual Studies/Clinical Trials

Pegloticase's efficacy as an antihyperuricemic agent was evaluated by the Applicant in two Phase 3 clinical efficacy trials, Studies 405 and 406, which utilized identical study protocols. The design of the shared protocol will be presented first followed by a discussion of the individual study reports for these trials and the interim report for the ongoing open-label extension trial 407.

Review of the common protocol utilized in Studies 405 and 406:

Title: Randomized, multicenter, double-blind, placebo-controlled efficacy and safety study of 8 mg PEG-uricase in two dose regimens in hyperuricemic subjects with symptomatic gout.

Objectives:

Primary Objective:

- To assess the efficacy of pegloticase versus placebo in reducing plasma uric acid (PUA) levels to < 6 mg/dL for at least 80% of the time during months 3 and 6 in subjects with hyperuricemia and symptomatic gout in whom conventional uric acid lowering therapy was contraindicated or ineffective

Secondary Objectives:

- To evaluate pegloticase's ability to lower plasma uric acid as compared to placebo via the following:
 - Reduction in tophus burden
 - Incidence and frequency of gout flares
 - Reduction in the number of swollen and tender joints
 - Improvement in patient reported health related quality of life assessments

Safety Objectives:

- To determine the safety and tolerability of pegloticase in gout patients

- To assess the incidence of infusion reactions and gout flares
- To determine the incidence of clinically manifested allergic reactions to PEG-uricase
- To characterize the immunogenicity profile of pegloticase

Study Design:

Studies 405 and 406 were to have been 6-month, multicenter, randomized, double-blind, placebo-controlled, three-arm, parallel group, Phase 3 replicate trials in symptomatic hyperuricemic gout patients with documented unresponsiveness and/or hypersensitivity to conventional urate lowering therapy. A total enrollment of 100 subjects in each study was planned. The overall duration of these studies was to have been 26 weeks which included an initial 2-week screening period followed by 24 weeks of study treatment. As part of the screening process for these trials, eligible study candidates were to have undergone a 1-week drug washout of all antihyperuricemic therapy that they had been taking. The common protocol also stipulated that all potential study subjects were to have also initiated prophylactic gout therapy unless medically contraindicated for the duration of their study participation.

Patients who successfully completed the screening process were to have been randomized via a 2:2:1 ratio stratified for the presence or absence of tophi to one of 3 treatment groups: 8 mg pegloticase every 2 weeks, 8 mg pegloticase every 4 weeks or placebo. To maintain study blind, all subjects were to have received a biweekly intravenous infusion of study medication over the course of the double-blind portion of the trial. The protocol stipulated that all patients were to have been premedicated with a prophylactic infusion reaction regimen before receiving each study infusion.

Patients who completed these studies were to have the option of continuing to receive active treatment with pegloticase by enrolling in a 12-month, open-label extension trial (Study 407).

Major Inclusion Criteria:

Subjects were to have been men and women ≥ 18 years of age who met all of the following criteria:

1. Had a screening serum uric acid (SUA) ≥ 8 mg/dL
2. Had symptomatic gout which was defined as at least 3 gout flares experienced in the 18 months prior to entry, or at least 1 gout tophus, or gouty arthritis
3. The use of conventional therapy was to have been contraindicated or ineffective. A history of hypersensitivity and/or failure to have normalized SUA after treatment with the maximum labeled dose of allopurinol (800 mg/day) or at a medically appropriate dose that was based on dose-limiting toxicity and/or comorbidity was to have been documented from the subject's medical record or have been elicited during the study screening interview.

4. Female subjects of childbearing potential were to have practiced an acceptable method of contraception in addition to having a negative serum pregnancy test.

Exclusion Criteria:

Potential trial candidates were to have been prohibited from participating in this trial if any of the following criteria applied:

1. Had unstable angina
2. Had uncontrolled arrhythmia
3. Had non-compensated congestive heart failure
4. Had uncontrolled hypertension (\geq than 150/90 mg/Hg)
5. Had history of end-stage renal disease necessitating dialysis
6. Had a hemoglobin < 8 g/dL (males) or < 7 g/dl (females)
7. Had been an organ transplant recipient
8. Had been previously treated with pegloticase, or other recombinant uricase, or any concomitant therapy with a PEG-conjugated drug
9. Had a gout flare at the screening visit that was resolved for less than 1 week prior to first treatment with study drug (exclusive of chronic synovitis/arthritis).
10. Had a history of glucose-6-phosphate dehydrogenase (G6PD) deficiency
11. Had a history of anaphylactic reaction to a recombinant protein or porcine product, or hypersensitivity to PEG
12. Had been either pregnancy or breast feeding at screening
13. Had taken an investigational drug within 4 weeks prior to study drug administration or planned to take an investigational agent during the study
14. Had a known allergy to urate oxidase or PEGylated products
15. Had any or other medical or psychological condition which, in the opinion of the investigator, could create undue risk to the subject or interfere with the subject's ability to comply with the protocol requirements, or to complete the study.

Treatment:

Patients were to have been treated with pegloticase 8 mg every 2 weeks, pegloticase 8 mg every 4 weeks or placebo administered via intravenous infusion over 120 minutes followed by a 10 ml normal saline flush. Subjects were to have remained at the study site for at least 2 hours of observation after receiving their study medication infusion in order to monitor for infusion reactions.

Removal of Patients from Treatment or Assessment:

Patients were to have been discontinued from these trials if they withdrew consent, experienced an adverse event that would have precluded further exposure, were noncompliant, incurred a protocol violation, failed to respond to study treatment or due to an administrative reason. The common protocol stipulated that subjects were free to discontinue study participation for any of the preceding reasons at any time over the course of the trial.

Concomitant Medication:

All subjects were to have been administered the following prespecified prophylactic infusion reaction regimen prior to receiving each study infusion: 60 mg fexofenadine orally at bedtime the night before the infusion, 60 mg of fexofenadine and 1000 mg of acetaminophen orally the morning of the infusion, and 200 mg of hydrocortisone intravenously immediately prior to the trial infusion. The protocol stipulated that either 0.6 to 1.2 mg/day of colchicine or the labeled analgesic dose of a NSAID taken with a proton pump inhibitor for gastric protection could be used for prophylactic therapy of gout flares on an individualized basis. Those patients who had been taking higher doses of a NSAID at study entry for prophylactic purposes were to have been allowed to continue their prescribed dose. Patients could continue to use medications prescribed for concurrent medical conditions but could not take any uric acid lowering agents (e.g., probenecid or allopurinol) for the duration of the study. All concomitant medications including analgesics were to have been recorded at each visit in each subject's case report form.

Gout Flare Treatment:

Patients who experienced an acute gout flare during the study were to have been treated with an individualized anti-inflammatory regimen that included a NSAID with a PPI, colchicine or corticosteroids as outlined below in Table 3. Use of any of these medications was to have been captured in the subjects' case report forms.

Table 3 – Protocol Approved Regimens for the Management of Acute Gout Flares During Study 405

Drugs for Treatment of Acute Gout Flares	Treatment Regimen
Non-steroidal anti-inflammatory drugs (NSAIDs) (Required co-administration of a proton pump inhibitor)	At the first sign of gout flare subject was to be started on a 5-day course of the maximal recommended daily dose of any NSAID. If the patient failed to respond after 5 days of NSAID therapy, the study investigator could initiate a course of oral corticosteroids at a dose of 0.5 -1 mg/day of prednisone or equivalent for 4 days followed by gradual tapering over 2 weeks. Higher doses of corticosteroids required prior approval of Medical Monitor.
Colchicine	Initiation of 0.6 mg of colchicine every 2 hours until the flare resolved, the onset of diarrhea, or until a total of 4 doses was administered in 24 hours (total dose of 2.4 mg in 24 hrs) followed by dosing of 0.6 mg twice a day until flare resolved. Patients taking colchicine as prophylaxis therapy could have their dose increased until the flare resolved followed by resuming their prophylactic dose regimen. In the event of colchicine intolerance, the patient could be treated at the investigator's discretion. Concomitant NSAID therapy could be used for anti-inflammatory effect or analgesia.
Corticosteroids	At the first sign of a flare an anti-inflammatory oral dose of 0.5 to 1 mg/kg daily of prednisone or equivalent could be used until 1 week after the flare had resolved followed by taper to cessation over 2 weeks. Higher doses of corticosteroids or parenteral administration required prior approval of Medical Monitor.

Efficacy and Safety Assessments:

Subject eligibility was to have been confirmed during the 14-day screening period during which an informed consent, gout history, physical exam, and clinical laboratory tests were to have been obtained. Following the screening visit, patients were to have visited their respective clinic sites weekly for the first 3 weeks of the study and then biweekly until the end of the trial to receive their study infusions and undergo both efficacy and safety assessments. Additional clinic visits for immunological assessments were to have been completed at 1 and 7 days post administration of the fifth, sixth, eleventh and twelfth doses of study infusions. Efficacy evaluations comprised of tophus assessment (photographs), swollen/tender joint counts, HAQ and SF-36, were to have been conducted at Weeks 1, 13, 19, and 25 while the assessment for acute gout flares and serum uric acid sampling were to have been performed at every scheduled trial visit. Safety was to have been assessed by monitoring for adverse events, infusion reactions (IRs) and gout flares, clinical laboratory evaluations, vital sign measurements, and physical exams at each scheduled clinic visit as well as electrocardiograms at screening and Week 25 visit.

Study Visit Schedule:

The following Tables 4a and 4b are tabular flow charts of the scheduled study visits and protocol specified procedures and evaluations:

Table 4a - Schedule of Procedures and Evaluations for Studies 405 and 406

Visit	Screening	1	2	3	4	5	6	7	8	9	10
Week	(-2 to -1)	1	24 hrs post-dose 1	3	5	7	9	24 hrs post-dose 5	7 days post-dose 5	11	12
Dose		1	2	3	4	5	6	7	8	9	10
Procedures											
Informed consent form	X										
History & physical examination	X										
Gout history & symptom severity	X										
Visit/pre-medication reminders BEFORE visit		X		X	X	X	X			X	
Tophus assessment/photography		X									
Acute gout flare assessment		X	X	X	X	X	X	X	X	X	X
Swollen/tender joint count	X										
Vital signs (X); dermatological & chest examination (Y)	X	X, Y		X, Y	X, Y	X, Y	X, Y			X, Y	
Clinical chemistries and CBC with differential	X					X					
Urinalysis	X					X					
G6PD, tryptase	X										
hCG (women of childbearing potential)	X										
12-lead ECG	X										
Administer SF-36 and HAQ		X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Assign flare prophylaxis and treatment; begin washout and flare prophylaxis	X										
Urine for uric acid : creatinine ratio		X			X		X				
Pre-dose* urine sample for future analysis		X	X	X		X				X	
Blood samples for PUA and uricase activity (X) and SUA (Y)		X ¹ , Y	X	X, Y	X, Y	X, Y	X ¹ , Y	X	X	X ¹ , Y	X
Blood samples for antibody and CH50 testing		X		X	X		X				
Administer pegloticase after pre-medicating, monitor infusions		X		X	X	X	X			X	
Assess for adverse events		X	X	X	X	X	X	X	X	X	X

Sponsor's Table 1; p. 17

Table 4b (cont.) - Schedule of Procedures and Evaluations for Studies 405 and 406

Visit	11	12	13	14	15	16	17	18	19	20	21
Week	13	15	17	19	21		22	23	24	25	27**
						24 hrs post dose 11	7 days post dose 11	12	7 days post dose 12	14 days post dose 12	
Dose	7	8	9	10	11						
Procedures											
Visit/pre-medication reminders BEFORE visit	X	X	X	X	X			X			
Physical examination	X									X	X
Acute gout flare assessment	X	X	X	X	X	X	X	X	X	X	X
Tophus assessment/photography	X			X						X	
Swollen/tender joint count	X			X						X	
Vital signs (X); dermatological & chest examination (Y)	X	X, Y	X, Y	X, Y	X, Y			X, Y		X	X
Clinical chemistries and CBC with differential	X			X						X	X
Urinalysis	X			X						X	X
hCG (women of childbearing potential)	X									X	
12-lead ECG										X	
Administer SF-36 and HAQ	X			X						X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Urine for uric acid:creatinine ratio			X		X						
Pre-dose* urine sample for future analysis		X		X				X		X	
Blood samples for PUA & uricase activity (X) and SUA (Y)	X, Y	X, Y	X, Y	X, Y	X ¹ , Y	X	X	X ¹ , Y	X	X, Y	
Blood samples for antibody and CH50 testing	X		X		X					X	
Administer pegloticase after pre-medicating, monitor infusions	X	X	X	X	X			X			
Assess for adverse events	X	X	X	X	X	X	X	X	X	X	X

¹ Pre and post-dose samples.

* Pre-dose means samples were collected prior to dosing on days that drug was administered.

** Subjects continuing to receive pegloticase followed OLE Study Schedule and did NOT have this visit.

Sponsor's Table 1 (cont.); p. 18

Outcome Measures:

Primary efficacy endpoint:

The primary efficacy variable for these trials was the proportion of patients whose PUA concentrations remained < 6 mg/dL for at least 80% of the time during Months 3 and 6. Subjects' PUA levels were to have been measured via a validated bioanalytical assay at a central laboratory on blood samples collected at every study visit from each patient. To prevent unblinding, these measurements were not to have been disclosed to study investigators.

Secondary efficacy endpoints:

These studies had a number of secondary efficacy endpoints defined as follows:

- Plasma Uric Acid (PUA) – the following endpoints were to have been calculated based on serial PUA levels collected from patients at prespecified time points (e.g., Visits 6, 7, 8, 9, 10 and 11 for Month 3 and Visits 15, 16, 17, 18, 19 and 20 for Month 6) that were measured as described above:
 - Percentage of non-hyperuricemic time: This endpoint was to have been computed by taking the ratio between the time during which the PUA level remains below 6 mg/dL and the entire time interval within Months 3 and 6. It was to be calculated via the following equation where T1 and T2 represent the total time intervals for Months 3 and 6, respectively, and W1

and W2 hours are the time intervals during which the PUA level remains below 6 mg/dL for Months 3 and 6, respectively:

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

- Mean PUA – This was to have represented the area under the PUA time curve divided by the corresponding time interval. Area under the PUA curve was to have been calculated using the linear trapezoidal rule during Months 3 and 6.
- Reduction in mean PUA – This was to have been calculated by subtracting the baseline PUA level from the mean PUA during Months 3 and 6.
- Percent reduction in mean PUA from baseline – This endpoint was to have been computed via the following equation:

$$\text{Percent reduction in mean PUA} = \frac{(\text{Mean PUA during Months 3 and 6} - \text{Baseline PUA})}{\text{Baseline PUA}} \times 100$$

- Clinical Outcomes:
 - Reduction of tophus burden: At the baseline visit, all subjects were to have had standardized photographs taken of their hands, feet, and up to 2 other areas where tophaceous deposits were present. These baseline photographs were to have been reviewed by a central blinded reader via the MedStudio® image analysis software package whose role was to identify and measure up to 5 tophi that were to be targeted for treatment response. The protocol specified that measurable tophi had to be ≥ 5 mm in the longest dimension at baseline and have borders that were distinguishable to the central reader. The protocol also specified that up to 2 tophi which measured ≥ 10 mm in the longest dimension at baseline but could not be accurately measured due to location, shape or other factors could also be evaluated at the reader's discretion as representative of the subject's tophus burden. Follow-up photographs of the same anatomical regions were to have been taken at Weeks 13, 19 and 25. Patients who did not have tophi present at baseline were to have been examined for the emergence of new deposits over the course of the study. These photographs were to be read via a locked sequential program that prevented the reader from re-reading prior photographs and changing their previous assessment. Measurable tophi were to have been measured as follows: along the longest diameter and the longest perpendicular to that diameter. The response of each tophus to treatment was to have been graded via the following 7 categories: complete response (CR: 100% decrease in tophus area), marked response (MR: at least a 75% decrease in area), improved (I: approximately $\geq 50\%$ reduction from baseline in size of unmeasured tophi), partial response (PR: at least 50% decrease in area), stable disease (SD: neither a 50% decrease nor a 25% increase in area can be demonstrated and/or neither

improvement nor progression from baseline in area of unmeasurable tophi), progressive disease (PR: $\geq 25\%$ increase in the area or $\geq 50\%$ increase from baseline in area of unmeasurable tophi), or unable to evaluate (UE: tophus cannot be accurately measured or assessed for any reason at any given post baseline time point). The best categorical response reported among all tophi (measurable and unmeasurable) was to have been used to determine an overall tophus response of complete response (CR: no partial response for either measurable or unmeasured tophus), partial response (PR: if marked response or partial response but no complete response or progressive disease for measurable or improved for unmeasured tophus); stable disease (SD: no complete response, partial response, or progressive disease for either measurable or unmeasured tophus), progressive disease (PD: progressive disease for any measurable or unmeasured tophi or if any new tophus appears), or unable to evaluate (unable to evaluate for all measurable or unmeasured tophi).

- Number of swollen and tender joints: This was to have been determined by the results from standardized joint examinations conducted by study investigators that evaluated 54 joints including the olecranon, prepatellar and anserine bursae, and bilateral hands and feet for tenosynovitis. Study investigators were to have also evaluated each subject's disease activity via a Clinician's Global Assessment (CGA). The latter assessment was to be comprised of a 100 mm visual analogue scale (VAS) where a score of 0 = very good and score of 100 = very bad.
- Incidence of gout flares: The occurrence, severity and duration of each gout flare were to have been self-reported by study subjects and confirmed by the principal investigators via direct observation or questioning.
- Patient Reported Outcomes (PRO): Two patient reported health-related quality of life assessment tools were to have been evaluated:
 - Short Form (SF-36) Health Status Survey: This is a 36-item self-reported questionnaire that was to be used to evaluate the 8 subdomains needed to calculate the 3 summary scores: physical component summary (PCS), mental component summary (MCS), and the arthritis-specific health index (ASHI). Average scores in healthy normal population age 55-64 for males and females combined are 47 for PCS and 52 for MCS. Higher scores represent better mental and physical quality of life. The ASHI is weighted to measure bodily pain, other areas of physical and role functioning and well being that are associated with arthritic conditions.
 - Health Assessment Questionnaire Disability Index (HAQ-DI) – This is a self-reported functional status instrument that was to be used to measure disability over a 1-week period as assessed by 8 domains of functionality. The highest scores from the 8 domains (range: 0-24) are summed and divided by 8 to yield a Functional Disability Index (range: 0-3 with higher

scores indicative of increased functional disability). Subject's global well being and pain severity were to have also been evaluated via a 100 mm visual VAS.

Statistical Design, Definitions of Analyzed Populations and Analyses Plan:

The sample size calculation for these studies was based on the efficacy and safety data generated from the Applicant's Phase 1 and 2 pegloticase studies, a natural history study of treatment failure gout, and infusion reaction data from a tumor necrosis factor inhibitor. With a projected enrollment of 100 patients in each trial randomized via 2:2:1 ratio (pegloticase 8 mg/2 weeks: n= 40 subjects; pegloticase 8 mg/4 weeks: n=40 subjects; placebo: n=20 subjects) these studies were to have greater than 80% power to show a 30% difference in responder rates between each pegloticase treatment group versus the placebo group at a significance level of p=0.05 for each comparison. The assumptions that were used in these statistical power calculations included a 35% response rate for the active treatment groups and a 5% response rate for placebo patients. No interim analyses were to have been conducted. The common protocol stipulated that the trials' enrollment goal could be adjusted if there was a greater than 20% drop-out rate of subjects. Since the drop out rate was estimated to be less than 20% after the first 60 patients were randomized in each trial, an adjustment in the enrollment goal was not required.

Three populations were to have been used for analysis. They were defined as follows: Intent-to-Treat (ITT) Population: was to have consisted of all randomized subjects who had received at least 1 dose of study medication.

Per-Protocol (PP) Population: was to have consisted of a subset of the ITT population and included all subjects who had no major deviations from the study protocol, and had completed 6 months of the study.

Tophus-Evaluable Population (TEP): was to have consisted of all subjects with a tophus at baseline and any subjects who developed new tophi over the course of the study.

The statistical analysis plan (SAP) stipulated that the primary endpoints for each of the Phase 3 trials were to have been analyzed separately using the intent-to-treat population and non-responder methodology to account for missing data. Intermittent missing pre-dose PUA values were to have been imputed with the baseline PUA level for that subject. Other intermittent missing PUA values were to have been replaced by the average of the scores at the immediately previous and the next available time points for that subject. Analyses of the primary endpoint were to have been conducted via the Fisher's exact test with computation of 95% confidence intervals for treatment differences between the pegloticase treatment groups and the placebo group, however, no multiplicity correction for the comparison of two doses to placebo was planned for in the SAP. For purposes of this analysis, a responder to therapy was to have been defined as a subject for whom the proportion of time that the PUA time curve was < 6 mg/dL was at least 80% of the time during both treatment Months 3 and 6.

The SAP also stipulated that the secondary endpoints were to have been analyzed based on pooled data from the two Phase 3 trials but no multiplicity correction was prespecified for these calculations. The four secondary PUA endpoints were to have been calculated via pair-wise comparisons between the pegloticase treatment groups versus the placebo group using a two-sample t-test for normally distributed data. Analogous non-parametric techniques were to have been used in the event that the data was not normally distributed. Missing PUA data from Visits 6, 11, 15 and 20 was to have been imputed by using subjects' baseline PUA concentration carried forward.

Reduction of tophus burden was to have been analyzed by comparing the number of patients with an overall tophus response of "complete response" in each pegloticase treatment group versus placebo group via the Fisher's exact test. Additionally, a two-sample Wilcoxon test was to have been performed via a 4-point ordinal conversion of the overall categorical tophi responses (e.g., complete response, partial response, stable disease, or progressive disease) for each pegloticase treatment group versus placebo. Time to tophus resolution defined as the earliest time at which one of the target tophi shows $\geq 50\%$ decrease in size was to have been calculated also via Kaplan-Meier plots for each treatment group. The number of patients with partial or complete tophus resolution at each examination was to have also been summarized by treatment. These analyses were to have been conducted on the TEP.

The common protocol specified pairwise comparisons between the pegloticase treatment groups and the placebo group for the number of tender and swollen joints and the physician's global assessment using the two sample t-test. If these data were not normally distributed, nonparametric tests were to have been used instead. Analyses of the change from baseline at Weeks 13, 19 and 25 were to have been conducted via a linear model where treatment was a fixed factor and the baseline value was a covariate. The one sample paired t-test was to have been used to perform within group comparisons for each treatment group.

The frequency of gout flares in the pegloticase treatment groups was to have been compared to that of the placebo group via the Fisher's exact test. Since it was anticipated that patients who received pegloticase during the trials would have more gout flares during the first 3 months of treatment despite mandatory gout prophylaxis therapy and that the rate should decrease during the second 3 months of the study, the common protocol specified that the frequency of gout flares during these two periods were to be analyzed separately for differences in treatment between each pegloticase dose group compared to placebo via a two-sample t-test. A weekly flare burden Index (WFB) was to have been calculated based on a 4-point scoring system (i.e., none = 0, mild =1, moderate =2, and severe = 3) of the severity of gout flares reported that was to be presented graphically by treatment group.

The two-sample t-test was to have been used to conduct pairwise comparisons of the summary analyses scores calculated for the SF-36's PCS, MCS and ASHI as well as the 8 subdomain scores generated for the pegloticase treatment groups versus the placebo treatment group. If these data were not normally distributed, nonparametric tests were to have been used instead. Analysis of change from baseline was to have been conducted via a linear model where treatment was a fixed factor and the baseline value was a covariate for each summary analysis score. The one sample paired t-test was to have been used to perform within group comparisons at different visits for each treatment group.

The common protocol specified that the comparative analyses for the HAQ-DI score, VAS pain scale scores and patient's well being were to have been conducted in the same manner as described above for the SF-36. Additionally, a Fisher's exact test utilizing a non-responder analysis for missing data was to have been performed to compare treatment differences in responder rates of the HAQ-DI for the pegloticase groups versus placebo. Subjects who demonstrated a 0.22 improvement in their HAQ-DI score were to have been considered responders for the physical function analysis.

Safety Evaluation:

The analysis of safety assessment was to have been conducted on the intent-to-treat population. Safety assessment was to have included adverse events (AEs), serious adverse events (SAEs), infusion reactions, clinical lab data, vital signs, ECG and incidence of anti-pegloticase antibody development. All AEs were to have been coded using the Medical Dictionary for Regulatory Affairs (MedDRA) coding dictionary (Version 9.0). The incidences of treatment-emergent AEs were to have been summarized by system organ class (SOC) and Medical Dictionary for Regulatory Affairs (MedDRA) preferred term by overall and treatment group. The common protocol specified that treatment-emergent adverse events were any event with a start date occurring on or after the first dose, or if an already existing AE worsened on or after the first dose. If a subject reported the same AE more than once that event was to be counted only once using the most severe intensity.

Clinical lab data results for hematology, serum chemistry and urinalysis testing as well as changes in vital signs and physical exam were to have been reviewed and summarized for within treatment changes and for changes from baseline for each treatment group. Additionally, shift tables based on changes from the normal ranges were to have been created.

Electrocardiogram results were to have been reported as the frequency and percentage of normal/abnormal tests at screening and Week 25 for each treatment group.

Immunogenicity Assessments:

Concentrations of non-neutralizing and neutralizing anti-pegloticase antibodies and anti-PEG antibodies were to have been assessed in subjects' serum via ELISA assays. The common protocol stipulated that the following relationships between anti-pegloticase or anti-PEG antibody titers were to have been evaluated: PUA responder status, the incidence and severity of infusion reactions, and the percentage of non-hyperuricemic time during Months 3 and 6. Additionally, IgE antibodies to pegloticase and CH50 levels were to have been also measured and summarized via descriptive statistics. The relationship between decreases below normal values of CH50 and infusion reactions was to have been also evaluated.

Pharmacokinetic (PK)/Pharmacodynamic (PD) Assessments:

Based on serial assays that measured the serum concentration of pegloticase over the course of the trial, following PK parameters for pegloticase were to have been calculated: CL, V_c, AUC_{0-T}, C_{max}, T_{max}, K_{el}, and t_{1/2}.

Study Conduct

Protocol Amendments:

Listed below are the 3 protocol amendments that were made to Studies 405 and 406. Each amendment was approved by the Agency's reviewing division prior to being implemented as per the Special Protocol Assessment (SPA) process.

1. Amendment 1 (implemented on March 17, 2006)

Minor changes to the statistical analysis sections were made. These revisions included:

- A change in the imputation technique from last observation carried forward to a nonresponder analysis for missing data was to be used in conducting the HAQ-DI analyses
- The Fisher's exact test instead of the Chi square test was to be used when performing the pairwise comparative analysis for infusion reaction rates
- Omitting an analysis based on response of each individual tophus to treatment

2. Amendment 2 (implemented on November 13, 2006)

The following 3 changes were made to the common protocol:

- Permitted the enrollment of subjects who had an inter-flare interval of < 1 week
- Removal from the common protocol of the previously specified pegloticase dose regimen to be used in the open-label extension study
- Addition of 10 ml urine collections at 9 prespecified study visits that were to be used for future analyses of urate pool biomarkers

3. Amendment 3 (implemented on June 1, 2007)

The following 4 changes were made to the common protocol:

- Removal from the common protocol of the necessity to record vital signs prior to performing phlebotomy

- Removal from the common protocol of the necessity to record vital signs in the position in which subjects will be infused (e.g., sitting or supine)
- Clarification of the 120 minute infusion time-window of +/- 15 minutes
- Due to a nationwide shortage of hydrocortisone, permitted the substitution of 40 mg methylprednisolone for the 200 mg of hydrocortisone administered intravenously immediately prior to the study drug infusion as part of the mandatory infusion reaction prophylactic therapy. If neither of these corticosteroid formulations were available, the study investigator had a choice between 20 mg of prednisone administered orally on the night before the study infusion, or substitution with another corticosteroid at an equivalent dosage that was to be administered at an appropriate time before the study infusion with the prior approval of the study's medical monitor.

Results from Study 405:

Disposition:

This study was conducted at 29 centers located in the United States and Canada. Of the 128 potential patients screened for this study, 19 were considered to have been screening failures as follows: 13 due to an exclusionary lab test result, 3 subjects due to withdrawal of consent, and 3 subjects for other reasons. A tabular summary of subjects' disposition for Study 405 is shown in Table 5. Overall, the rate of study completion was higher in the placebo treatment group (95%) as compared to the pegloticase every 2 weeks (70%) and pegloticase every 4 weeks (66%) treatment groups. The major reasons for study discontinuation were similar for the two pegloticase treatment arms but differed from the placebo group. The most common reason for early study withdrawal in the pegloticase groups was adverse events (19% for the pegloticase every 2 weeks group and 22% for the pegloticase every 4 weeks group), followed by withdrawal of consent (7% and 7%, respectively), deaths (2% and 2%, respectively), protocol violation (2% and 0% respectively) and noncompliance (0% and 2%). In the placebo group, only 1 subject (5%) withdrew from the study prematurely due to lost to follow up.

Table 5 – Subject Disposition for Study 405

	Pegloticase 8 mg every 2 weeks (N=44)	Pegloticase 8 mg every 4 weeks (N=43)	Placebo (N=22)	Total (N=128)
Number of Patients Randomized	44	43	22	109
Number of Patients Treated (ITT)	43	41	20	104
Number of Patients with Evaluable Tophus	29	31	14	74
Number of Patients that Completed the Week 24 Study Visit:				
Enrolled in OLE	30 (70%)	27 (66%)	19 (95%)	76 (73%)
Did not Enroll in OLE	29 (97%)	26 (96%)	18 (95%)	
	1 (3%)	1 (4%)	1 (5%)	
Number of Patients Withdrawn Prematurely Before Week 24:				
Non-compliance	13 (30%)	14 (34%)	1 (5%)	28 (27%)
Adverse Event	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Withdrew Consent	8 (19%)	9 (22%)	0 (0%)	17 (16%)
Lost to Follow-Up	3 (7%)	3 (7%)	0 (0%)	6 (6%)
Protocol Violation	0 (0%)	0 (0%)	1 (5%)	1 (1%)
Death	1 (2%)	0 (0%)	0 (0%)	1 (1%)
	1 (2%)	1 (2%)	0 (0%)	2 (2%)

Adapted Sponsor's Table 4; p. 45

Protocol Deviations and Violations:

A total of 35 randomized patients incurred one or more protocol deviations/violations over the course of this trial. The following table (Table 6) shows that the rate of protocol deviations/violations was comparable for the two pegloticase treatment groups (40% for the every 4 weeks group and 38% for the every 2 weeks group) but was higher as compared to the placebo group (18%). Overall, the most common protocol deviation/violation was due to missed Month 3 and Month 6 study visits (22%), followed by did not receive study medication (4%) and failure to meet study entry criteria (2%). All 35 subjects who incurred protocol deviations/violations were excluded from the per protocol analysis. The 5 randomized patients who did not receive study medication were excluded from the ITT population which was used in calculating the primary and secondary endpoints. Further review of these protocol deviations (i.e., missed visits) reveals that they did not impact on the outcome of the primary efficacy endpoint due to the prespecified imputation techniques for missing data in the statistical analysis plan.

Table 6 – Tabular Summary of Subjects with Protocol Deviations/Violations

	Pegloticase 8 mg every 2 weeks (N=44)	Pegloticase 8 mg every 4 weeks (N=43)	Placebo (N=22)	Total (N=128)
Number of Subjects with Protocol Deviations/Violations	14 (38%)	17 (40%)	4 (18%)	35 (27%)
Failure to Meet Inclusion/Exclusion Criteria	1 (2%)	1 (2%)	0 (0%)	2 (2%)
Did Not Receive Any Study Medications	1 (2%)	2 (5%)	2 (9%)	5 (4%)
Missed Month 3 and Month 6 Visits	12 (27%)	14 (33%)	2 (9%)	28 (22%)

Sponsor's Table 1.2; Appendix 16.2

Demographics:

A summary of the baseline demographics of patients who participated in this trial is shown in Table 7. Subjects treated with pegloticase were demographically similar to those who received placebo during this study. The patients who participated in these studies had a mean age of 57 years and were overwhelmingly male (77%) and Caucasian (75%). There was a good representation of other ethnic groups (13% Black, 6% Hispanic and 4% American Indian/ Alaskan Native). More females were randomized to the pegloticase every 2 weeks treatment group (30%) as compared to the pegloticase every 4 weeks group (15%) and placebo group (25%). The majority of subjects were overweight as evidenced by mean BMI of 34 which is consistent with the increasing number of metabolic syndrome patients who develop gout. Additionally, the majority of patients reported that they did not drink alcohol which increases the risk for gout attacks. However, more subjects randomized to the pegloticase every 2 weeks (42%) and every 4 weeks (34%) treatment groups reported alcohol ingestion as compared to the placebo group (20%).

Table 7 – Tabular Summary of Baseline Demographic Characteristics of Subjects Enrolled in Study 405 (Intent-to-Treat [ITT] Population)

	Pegloticase 8 mg every 2 weeks (N=43)	Pegloticase 8 mg every 4 weeks (N=41)	Placebo (N=20)	Total (N=104)
Age (years):				
Mean (SD)	58 (15)	55 (13)	57 (13)	57 (14)
Gender:				
Male	30 (70%)	35 (85%)	15 (75%)	80 (77%)
Female	13 (30%)	6 (15%)	5 (25%)	24 (23%)
Race:				
American Indian/Alaskan Native	2 (5%)	2 (5%)	0 (0%)	4 (4%)
Asian	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Hispanic/Latino	2 (5%)	3 (7%)	1 (5%)	6 (6%)
Black	4 (9%)	4 (10%)	5 (25%)	13 (13%)
Pacific Islander/Native Hawaiian	0 (0%)	0 (0%)	0 (0%)	0 (0%)
White	32 (74%)	32 (78%)	14 (70%)	78 (75%)
Other	2 (5%)	0 (0%)	0 (0%)	2 (2%)
Weight (kg):				
Mean (SD)	102 (22)	105 (27)	102 (22)	103 (24)
Height (cm)				
Mean (SD)	171 (11)	176 (11)	175 (10)	174 (11)
BMI (kg/m²)				
Mean (SD)	35 (8)	34 (8)	33 (6)	34 (8)
Alcohol Consumption:				
Yes	18 (42%)	14 (34%)	4 (20%)	36 (35%)
No	25 (58%)	27 (66%)	16 (80%)	68 (65%)

Sponsor's Table 5; p. 47 and Table 3.3; p. 184.

Table 8 is a tabular summary of subjects' gout history and disease status. More patients randomized to placebo (75%) had crystal proven gout than those randomized to the pegloticase every 2 weeks (61%) and every 4 weeks (54%) treatment groups. The overall mean duration since the first gout attack was 16 years and the overall mean duration since the first diagnosis of gout was 15 years for the study population. The mean number of gout flares per year reported by the three treatment groups was similar (11 attacks per year for the pegloticase treatment groups versus 13 attacks per year for the placebo group), the majority of which were described to be oligoarticular (2-3 joints) or polyarticular (>3 joints) (74%) and moderate to severe (98%) in nature. Overall, 61% of the total study population had chronic synovitis and/or arthropathy due to gout. A similar percentage of patients randomized to the pegloticase every 4 weeks group (76%) had tophaceous deposits as patients randomized to pegloticase every 2 weeks (67%) and placebo patients (70%). A higher incidence of surgery for gout (excluding arthrocentesis) was reported by placebo patients (30%) as compared to the pegloticase every 2 weeks (16%) and every 4 weeks (22%) patients. More patients in the placebo group (30%) also had a history of gout-related kidney disease as compared to the pegloticase every 2 weeks (16%) and every 4 weeks (22%) treatment group, but the mean number of renal colic episodes in the past year was similar between the 3

treatment groups (0.79 episodes for pegloticase every 2 weeks, 0.71 episodes for pegloticase every 4 weeks, and 0.80 episodes for placebo). A minority of the patient population (5%) in this study reported having another arthritic condition that could potentially confound their gout assessments. Based on these data, the study population that participated in this trial had moderate to severe gout and was reasonably balanced across study arms.

Table 8 – Tabular Summary of Subjects’ Gout History and Disease Status (ITT Population) Who Participated in Study 405

	Pegloticase 8 mg every 2 weeks (N=43)	Pegloticase 8 mg every 4 weeks (N=41)	Placebo (N=20)	Total (N=104)
Confirmed Presence of Uric Acid Crystals				
Yes	26 (61%)	22 (54%)	15 (75%)	63 (61%)
No	17 (40%)	19 (46%)	5 (25%)	41 (40%)
Number of Years Since First Gout Attack Mean (SD)	17 (13)	16 (11)	12 (9)	16 (12)
Number of Years Since First Diagnosis of Gout Mean (SD)	16 (14)	16 (11)	12 (9)	15 (12)
Number of Acute Flares in the Past 18 Months Mean (SD)	11 (12)	11 (15)	13 (11)	11 (15)
Pattern of Acute Flares				
Monoarticular (One Joint)	12 (28%)	10 (25%)	4 (21%)	26 (26%)
Oligoarticular (2-3 Joints)	12 (28%)	12 (30%)	9 (47%)	33 (32%)
Polyarticular (> 3 Joints)	19 (44%)	18 (45%)	6 (32%)	43 (42%)
Severity of Acute Flares				
Mild (Uncomfortable)	2 (5%)	0 (0%)	1 (5%)	3 (3%)
Moderate (Limiting)	10 (23%)	12 (30%)	6 (31%)	28 (28%)
Severe (Crippling)	31 (72%)	28 (70%)	12 (63%)	71 (70%)
Chronic Synovitis/Arthropathy				
Yes	27 (63%)	23 (56%)	13 (65%)	63 (61%)
No	16 (37%)	18 (44%)	7 (35%)	41 (39%)
History of Gout-Related Kidney Disease				
Yes	8 (19%)	6 (15%)	6 (30%)	20 (19%)
No	35 (81%)	35 (85%)	14 (70%)	84 (81%)
Tophi				
Yes	29 (67%)	31 (76%)	14 (70%)	74 (71%)
No	14 (33%)	10 (24%)	6 (30%)	30 (28%)
Surgery for Gout (Excluding Arthrocentesis)				
Yes	7 (16%)	9 (22%)	6 (30%)	22 (21%)
No	36 (84%)	32 (78%)	14 (70%)	82 (79%)
Another Arthritis Condition Potentially Confounding Diagnosis of Gout				
Yes	1 (2%)	3 (7%)	1 (5%)	5 (5%)
No	42 (98%)	38 (93%)	19 (95%)	99 (95%)
Number of Episodes of Renal Colic in the Past Year Mean (SD)	0.79 (2.5)	0.71 (3.8)	0.80(2.3)	0.76(3.0)

Sponsor’s Table 6; p.49

Since this study's protocol specifically targeted hyperuricemic gout patients with documented unresponsiveness and/or hypersensitivity to allopurinol, a summary of patient eligibility based on prior allopurinol exposure is shown in Table 9:

Table 9 – Patient Eligibility as Per Allopurinol Treatment History for Enrollment in Study 405 (ITT Population)

	Pegloticase 8 mg every 2 weeks (N=43)	Pegloticase 8 mg every 4 weeks (N=41)	Placebo (N=20)	Total (N=104)
Allopurinol ineffective	3 (7%)	7 (17%)	2 (10%)	12 (12%)
History of Allergy/Hypersensitivity	23 (54%)	13 (32%)	9 (45%)	45 (43%)
Renal insufficiency	8 (19%)	6 (15%)	4 (20%)	18 (17%)
GI intolerance	8 (19%)	11 (27%)	4 (20%)	23 (22%)
Other	1 (2%)	4 (10%)	1 (5%)	6 (6%)

Sponsor's Table 7; p. 50

Treatment with allopurinol was reported to be ineffective by 12% of all patients who participated in this study, while it was contraindicated in another 43% due to history of allergy or hypersensitivity reaction. The remaining 45% of subjects were unable to use allopurinol due to tolerability issues related to comorbid conditions such as renal insufficiency (17%) or gastrointestinal intolerance (22%). These data demonstrate that the subjects who participated in this study were the population intended to use this product.

As summarized in Table 10, many of the subjects who participated in Study 405 suffered from serious co-morbid medical conditions including vascular system disorders (73%), metabolic and nutritional disorders (72%), renal and urinary disorders (54%), and cardiac disorders (41%). There was also a high prevalence of conditions that increased the risk for hyperuricemia (e.g., hypertension [72%], renal failure [19%], and obesity [19%]).

Table 10 – Tabular Summary of Comorbid Medical Conditions Reported by > 10% of Subjects Who Participated in Study 405 (ITT Population)

MedDRA Body System Preferred Term	Pegloticase 8 mg every 2 weeks (N=43)	Pegloticase 8 mg every 4 weeks (N=41)	Placebo (N=20)	Total (N=104)
Vascular Disorders:	30 (70%)	30 (73%)	16 (80%)	76 (73%)
Hypertension	30 (70%)	30 (73%)	15 (75%)	75 (72%)
Metabolism and Nutrition Disorders:	31 (72%)	29 (71%)	15 (75%)	75 (72%)
Hypercholesterolemia	14 (33%)	7 (17%)	5 (25%)	26 (25%)
Hyperlipidemia	8 (19%)	11 (27%)	6 (30%)	25 (20%)
Obesity	10 (23%)	5 (12%)	5 (25%)	20 (19%)
Diabetes Mellitus	6 (14%)	2 (5%)	5 (25%)	13 (13%)
Musculoskeletal and Connective Tissue Disorders:	30 (70%)	28 (68%)	12 (60%)	70 (67%)
Immune System Disorders:	30 (70%)	20 (49%)	12 (60%)	62 (60%)
Drug Hypersensitivity	27 (63%)	17 (42%)	11 (55%)	55 (53%)
Renal and Urinary Disorders:	22 (51%)	22 (54%)	12 (60%)	56 (54%)
Renal Failure	11 (26%)	6 (15%)	3 (15%)	20 (19%)
Renal Failure Chronic	4 (9%)	10 (24%)	5 (25%)	19 (18%)
Nephrolithiasis	6 (14%)	4 (10%)	3 (15%)	13 (13%)
Glomerulonephritis	0 (0%)	1 (2%)	1 (5%)	2 (2%)
Gastrointestinal Disorders:	24 (56%)	21 (51%)	9 (45%)	54 (52%)
Cardiac Disorders:	18 (42%)	13 (32%)	12 (60%)	43 (41%)
Coronary Artery Disease	4 (9%)	6 (15%)	5 (25%)	15 (14%)
Atrial Fibrillation	4 (9%)	3 (7%)	3 (15%)	10 (10%)
Cardiac Failure Congestive	3 (7%)	4 (10%)	3 (10%)	10 (10%)
Bundle Branch Block Right	3 (7%)	0 (0%)	2 (10%)	5 (5%)
Cardiomyopathy	2 (5%)	2 (5%)	1 (5%)	5 (5%)
Angina Pectoris	1 (2%)	2 (5%)	0 (0%)	3 (3%)
Arrhythmia	1 (2%)	1 (2%)	0 (0%)	2 (2%)
Arteriosclerosis Coronary Artery	1 (2%)	1 (2%)	0 (0%)	2 (2%)
Dilatation Atrial	2 (5%)	0 (0%)	0 (0%)	2 (2%)
Ischemic Cardiomyopathy	0 (0%)	1 (2%)	1 (5%)	2 (2%)
Nervous System Disorders:	18 (42%)	15 (37%)	7 (35%)	40 (39%)
Respiratory, Thoracic and Mediastinal Disorders:	14 (33%)	15 (37%)	9 (45%)	38 (37%)
Psychiatric Disorders:	10 (23%)	14 (34%)	8 (40%)	32 (31%)
General Disorders and Administration Site Conditions:	19 (44%)	6 (15%)	6 (30%)	31 (30%)
Investigations:	13 (30%)	7 (17%)	6 (30%)	26 (25%)
Endocrine Disorders:	11 (26%)	8 (20%)	3 (15%)	22 (21%)
Skin and Subcutaneous Tissue Disorders:	10 (23%)	4 (10%)	6 (30%)	20 (19%)
Infections and Infestations:	11 (26%)	6 (15%)	1 (5%)	18 (17%)
Eye Disorders:	6 (14%)	7 (17%)	3 (15%)	16 (15%)
Blood and Lymphatic System Disorders:	8 (19%)	3 (7%)	4 (20%)	15 (14%)
Social Circumstances:	5 (12%)	6 (15%)	0 (0%)	11 (11%)
Postmenopause	2 (5%)	3 (7%)	0 (0%)	5 (5%)
Cardiac Assistance Device User	3 (7%)	0 (0%)	0 (0%)	3 (3%)
Smoker	0 (0%)	2 (5%)	0 (0%)	2 (2%)

Adapted Sponsor's Table 6.2; p. 201-16.

Study participants in each treatment group additionally reported taking concomitant medications (e.g., beta-blockers, salicylate, insulin, diuretics, warfarin, vitamin B12, amlodipine, and losartan) that are known to interfere with uric acid metabolism as listed in Table 11. Higher percentage of patients randomized to the pegloticase every 4 weeks (54%) and placebo group (55%) as compared to the pegloticase every 2 weeks group (37%) were taking beta-blockers. More patients in the placebo arm (25%) were also taking concomitant warfarin as compared to the pegloticase every 2 weeks (7%) and every 4 weeks (2%) treatment groups. Both of these drugs can increase serum uric acid levels by interfering with its urinary excretion. However, the usage of the other drugs that could potentially interfere with uric acid metabolism was similar across the 3 treatment groups and should not impact on the study's outcome.

Table 11 – Tabular Summary of Concomitant Medications Taken by ≥ 10% of Patients in Study 405 by Treatment Group (ITT Population)

WHO Drug Preferred Term of Medication	Pegloticase 8 mg every 2 weeks (N=43)	Pegloticase 8 mg every 4 weeks (N=41)	Placebo (N=20)
Subjects With at Least 1 Concomitant Medication	42	40	20
Anti-Gout Drugs:	27 (63%)	24 (59%)	14 (70%)
Colchicine	26 (61%)	24 (59%)	13 (65%)
Acid Related Disorder Drugs:	22 (51%)	17 (42%)	9 (45%)
Omeprazole	5 (12%)	6 (15%)	6 (30%)
Esomeprazole	10 (23%)	5 (12%)	0
Lansoprazole	3 (7%)	5 (12%)	3 (15%)
Pantoprazole	5 (12%)	3 (7%)	0
Rabeprazole	1 (2%)	1 (2%)	2 (10%)
Analgesics:	28 (65%)	24 (59%)	15 (75%)
Vicodin	11 (26%)	13 (32%)	4 (20%)
Paracetamol	8 (19%)	7 (17%)	5 (25%)
Oxycocet	7 (16%)	3 (7%)	3 (15%)
Oxycodone	2 (5%)	3 (7%)	3 (15%)
Tramadol	5 (12%)	1 (2%)	1 (5%)
Pethidine Hydrochloride	2 (5%)	1 (2%)	2 (10%)
Propacet	1 (2%)	1 (2%)	3 (15%)
Acetylsalicylic Acid	1 (2%)	1 (2%)	2 (10%)
Tramadol Hdydrochloride	1 (2%)	1 (2%)	2 (10%)
Morphine	1 (2%)	0	2 (10%)
Anti-Inflammatory Drugs:	12 (28%)	12 (29%)	7 (35%)
Celecoxib	5 (12%)	2 (5%)	1 (5%)
Indomethacin	2 (5%)	3 (7%)	3 (15%)
Ibuprofen	2 (5%)	3 (7%)	2 (10%)
Drugs Acting on the Renin-Angiotensin System	27 (63%)	22 (54%)	11 (55%)
Lisinopril	8 (19%)	6 (15%)	3 (15%)
Losartan Potassium	4 (9%)	6 (15%)	2 (10%)
Lotrel	3 (7%)	1 (2%)	2 (10%)
Enalapril	2 (5%)	1 (2%)	2 (20%)
Beta-Blocking Drugs:	16 (37%)	22 (54%)	11 (55%)
Atenolol	2 (5%)	10 (24%)	3 (15%)
Metoprolol	5 (12%)	8 (20%)	2 (10%)
Metoprolol Succinate	5 (12%)	3 (7%)	1 (5%)
Carvedilol	1 (2%)	2 (5%)	2 (10%)
Corticosteroids Systemic:	19 (44%)	19 (46%)	8 (40%)
Prednisone	15 (35%)	19 (46%)	8 (40%)
Serum Lipid Reducing Drugs:	26 (61%)	15 (37%)	9 (45%)
Simvastatin	6 (14%)	4 (10%)	4 (20%)
Atorvastatin	8 (17%)	5 (12%)	0
Fish Oil	5 (12%)	1 (2%)	1 (5%)
Diuretics:	24 (56%)	19 (46%)	11 (55%)
Furosemide	14 (33%)	13 (32%)	10 (50%)
Spironolactone	6 (14%)	1 (2%)	3 (15%)

Sponsor's Table 8; p. 52-4.

Table 11 – Tabular Summary of Concomitant Medications Taken by ≥ 10% of Patients in Study 405 by Treatment Group (ITT Population) (cont.)

WHO Drug Preferred Term of Medication	Pegloticase 8 mg every 2 weeks (N=43)	Pegloticase 8 mg every 4 weeks (N=41)	Placebo (N=20)
Systemic Antibacterials:	15 (35%)	21 (51%)	8 (40%)
Levofloxacin	3 (7%)	7 (17%)	3 (15%)
Cefalexin	4 (9%)	7 (17%)	1 (5%)
Ciprofloxacin	3 (7%)	4 (10%)	3 (15%)
Azithromycin	5 (12%)	2 (5%)	2 (10%)
Vancomycin	1 (2%)	1 (2%)	2 (10%)
Antithrombotic Agents:	18 (42%)	13 (32%)	11 (55%)
Acetylsalicylic Acid	13 (30%)	11 (27%)	6 (30%)
Clopidogrel	3 (7%)	5 (12%)	4 (20%)
Warfarin	3 (7%)	1 (2%)	5 (25%)
Heparin	3 (7%)	1 (2%)	2 (10%)
Calcium Channel Blockers:	7 (16%)	15 (37%)	6 (30%)
Amlodipine	2 (5%)	7 (17%)	2 (10%)
Nifedipine	1 (2%)	3 (7%)	2 (10%)
Systemic Antihistamines:	8 (19%)	17 (42%)	2 (10%)
Diphenhydramine Hydrochloride	5 (12%)	7 (17%)	0
Diphehydramine	0	5 (12%)	0
Mineral Supplements:	11 (26%)	8 (20%)	7 (35%)
Potassium Chloride	5 (12%)	2 (5%)	1 (5%)
Calcium Carbonate	2 (5%)	0	2 (10%)
Psychoanaleptics:	10 (23%)	10 (24%)	6 (30%)
Sertaline	3 (7%)	3 (7%)	3 (15%)
Duloxetine Hydrochloride	3 (7%)	1 (2%)	2 (10%)
Psycholeptics:	8 (1%)	10 (24%)	4 (20%)
Alprazolam	0	5 (12%)	1 (5%)
Midazolam Hydrochloride	2 (5%)	1 (2%)	2 (10%)
Anti-Diabetic Agents:	9 (21%)	7 (17%)	5 (25%)
Glipizide	1 (2%)	3 (7%)	2 (10%)
Insulin Aspart	2 (5%)	0	2 (10%)
Cardiac Therapy:	5 (12%)	8 (20%)	7 (35%)
Glyceryl Trinitrate	3 (7%)	6 (15%)	1 (5%)
Digoxin	1 (2%)	2 (5%)	3 (15%)
Antianemic Preparations:	5 (12%)	8 (20%)	6 (30%)
Ferrous Sulfate	4 (9%)	1 (2%)	2 (10%)
Vitamin B12	1 (2%)	2 (5%)	3 (15%)
Thyroid Therapy:	6 (14%)	5 (12%)	2 (10%)
Levothyroxine Sodium	4 (9%)	3 (7%)	2 (10%)
Cough and Cold Preparations:	4 (9%)	3 (7%)	4 (20%)
Hydrocodone	0	2 (5%)	2 (10%)
Laxatives:	7 (16%)	1 (2%)	3 (15%)
Docusate Sodium	4 (9%)	0	3 (15%)
Other Respiratory System Products:	5 (12%)	2 (5%)	1 (5%)
Oxygen	5 (12%)	2 (5%)	1 (5%)
Blood Substitutes and Perfusion Solutions:	3 (7%)	1 (2%)	2 (10%)
Sodium Chloride	1 (2%)	0	2 (10%)
Other Nervous System Drugs:	0	1 (2%)	2 (10%)
Methadone	0	1 (2%)	2 (10%)

The protocol permitted patients to take medications to treat gout flares they experienced over the course of the study. This information is summarized in Table 12. More patients randomized to the placebo treatment group (90%) reported taking at least 1 gout flare medication over the course of the study as compared to subjects in the pegloticase every 2 weeks (77%) and pegloticase every 4 weeks (68%) treatment groups. The most commonly used gout flare medications in this trial were: systemic corticosteroids (62%), antigout preparations (33%), anti-inflammatory drugs (16%), and analgesics (13%).

Table 12 – Tabular Summary of Gout Flare Medications Taken by ≥ 5% of Patients by Treatment Group During Study 405

WHO Drug Preferred Term of Medication	Pegloticase 8 mg every 2 weeks (N=43)	Pegloticase 8 mg every 4 weeks (N=41)	Placebo (N=20)
Subjects Taking at Least 1 Gout-Flare Medication	33 (77%)	28 (68%)	18 (90%)
Corticosteroids for Systemic Use:	27 (63%)	23 (56%)	14 (70%)
Prednisone	19 (44%)	20 (49%)	12 (60%)
Methylprednisolone	9 (21%)	2 (5%)	1 (5%)
Triamcinolone Acetonide	2 (5%)	1 (2%)	2 (10%)
Dexamethasone	1 (2%)	0	1 (5%)
Triamcinolone	0	0	1 (5%)
Anti-Inflammatory Drugs:	6 (14%)	8 (20%)	3 (15%)
Indomethacin	3 (7%)	2 (5%)	2 (10%)
Ibuprofen	0	1 (2%)	1 (5%)
Anti-Gout Drugs:	17 (40%)	10 (24%)	7 (35%)
Colchicine	17 (40%)	10 (24%)	7 (35%)
Probenecid	0	0	1 (5%)
Analgesics:	7 (16%)	4 (10%)	2 (10%)
Paracetamol	1 (2%)	4 (10%)	1 (5%)
Vicodin	4 (9%)	0	1 (5%)
Anesthetics:	2 (5%)	1 (2%)	2 (10%)
Lidocaine	0	1 (2%)	2 (10%)

Note: Medications taken during the study, i.e., after first dose of study medication.
 Sponsor's Table 9; p. 55

Treatment Compliance:

The number of study infusions and the amount of each study dose administered to each patient was to have been captured and recorded by the study investigators in both the subjects' medical records and CFR. These data were to have been used to calculate overall compliance listed in Table 13. Overall, study compliance was good with a total mean number of 10 study infusions per subject having been administered over the course of the study that was similar between the 3 treatment arms.

Table 13 – Number of Infusions Administered During Study 405

	Pegloticase 8 mg every 2 weeks (N=43)	Pegloticase 8 mg every 4 weeks (N=41)	Placebo (N=20)	Total (N=104)
Mean (S. D.)	10 (2.8)	10 (3.4)	12 (1.3)	10 (2.9)
Median (Min, Max)	12 (3,12)	12 (1,12)	12 (6,12)	12 (1,12)
Number of Infusions (%)				
1	0 (0%)	1 (2%)	0 (0%)	1 (1%)
2	0 (0%)	1 (2%)	0 (0%)	1 (1%)
3	2 (5%)	1 (2%)	0 (0%)	3 (3%)
4	1 (2%)	2 (5%)	0 (0%)	3 (3%)
5	1 (2%)	3 (7%)	0 (0%)	4 (4%)
6	3 (7%)	0 (0%)	1 (5%)	4 (4%)
7	1 (2%)	2 (5%)	0 (0%)	3 (3%)
8	1 (2%)	1 (2%)	0 (0%)	2 (2%)
9	2 (5%)	0 (0%)	0 (0%)	2 (2%)
10	1 (2%)	2 (5%)	0 (0%)	3 (3%)
11	2 (5%)	1 (2%)	0 (0%)	3 (3%)
12	29 (67%)	27 (66%)	19 (95%)	75 (72%)

Adapted Sponsor's Table 48, p. 126.

Efficacy:

The primary efficacy parameter for Study 405 was the proportion of patients whose PUA was normalized to less than 6 mg/dL for at least 80% of the time during Months 3 and 6 combined. Subjects who maintained a PUA concentration below 6 mg/dL for at least 80% of time during Months 3 and 6 combined were considered "PUA responders." The results generated from the primary analysis are shown in Table 14. Higher portions of patients in both the pegloticase every 2 weeks (47%) and pegloticase every 4 weeks (20%) treatment groups showed a response to therapy as compared to the placebo group (0%) ($p \leq 0.044$ for each pegloticase treatment group versus placebo).

Table 14 – Treatment Response PUA < 6 mg/dL for at Least 80% of the Time in Months 3 and 6 for Study 405 (ITT Population)

	Pegloticase 8 mg every 2 weeks (N=43)	Pegloticase 8 mg every 4 weeks (N=41)	Placebo (N=20)
PUA < 6 mg/dl for at Least 80% of the Time in Month 3			
Number (%)	25 (458%)	13 (32%)	1 (5%)
95% Confidence Interval ¹	[35.6, 70.7]	[9.6, 43.9]	
P-Value ²	<0.001	0.024	
PUA <6 mg/dL for at Least 80% of the Time in Month 6			
Number (%)	20 (47%)	11 (27%)	0
95% Confidence Interval ¹	[31.6, 61.4]	[13.3, 40.4]	
P-Value ²	<0.001	0.011	
PUA <6 mg/dL for at Least 80% of the Time in Months 3 and 6 Combined			
Number (%)	20 (47%)	8 (19.5%)	0
95% Confidence Interval ¹	[31.6, 61.4]	[7.4, 31.6]	
P-Value ²	<0.001	0.004	

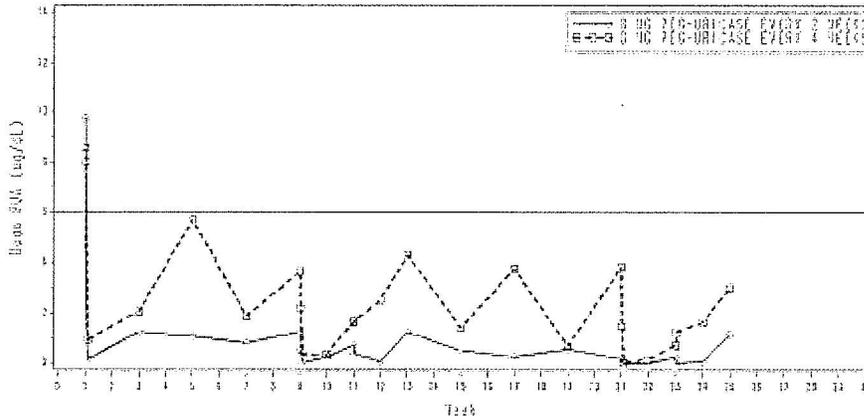
¹95% confidence interval for differences in responder rate between corresponding pegloticase groups vs. placebo

²P-value using Fisher's exact test to compare corresponding pegloticase group vs. placebo.

Sponsor's Table 11; p. 58

Figures 1 and 2 below graphically depict the mean PUA concentration profile for responders and nonresponders to study therapy over the 26 weeks of the trial. These figures graphically illustrate a rapid decrease in serum PUA following the administration of the first infusion of pegloticase in both the every 2 week and every 4 week groups. This response is maintained throughout the remainder of the study by patients who meet the prespecified response criteria as shown in Figure 1. Note that the placebo group does not appear in Fig.1 as there were no responders in the placebo group. In contrast, patients who were classified as non-responders had an initial drop in plasma uric acid that was subsequently lost (Figure 2).

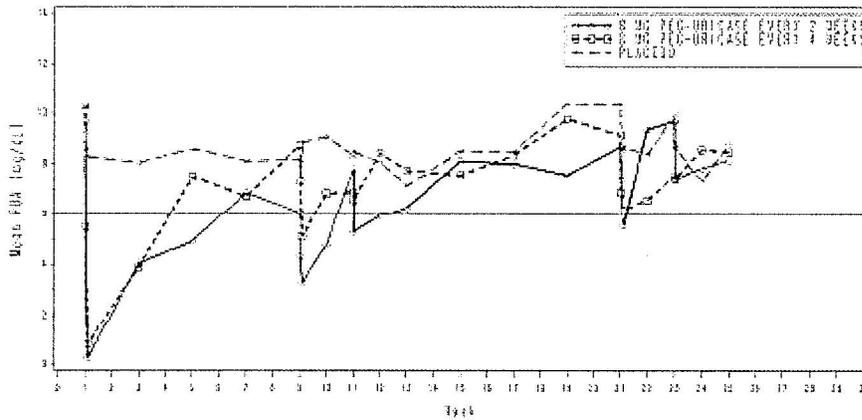
Figure 1 – Mean PUA Concentrations for PUA Responders by Pegloticase Treatment Group for Study 405 (ITT Population)



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Sponsor's Fig. 4; p. 62.

Figure 2 – Mean PUA Concentration for PUA Non-Responder by Treatment Group for Study 405 ITT Population)



Sponsor's Figure 5; p. 62

The statistics reviewer, Dr. Ruthanna Davi, notes that no multiplicity correction was specified for the primary endpoint. For the pegloticase every 2 weeks group the conclusion of efficacy is considered robust because of the high statistical significance associated with the comparison to placebo. For the pegloticase every 4 weeks group the statistical significance is only marginal. Dr. Davies concludes, however, that it is unlikely that the finding of efficacy for the every 4 weeks group is spurious in light of the overall results of Studies 405 and 406 taken in concert. Thus, Study 405 demonstrated

the efficacy of pegloticase for the primary endpoint for both the every 2 weeks and the every 4 weeks dose regimens.

No sensitivity analyses were performed on the primary endpoint. Since the SAP stipulated that the analyses of the secondary endpoints were to be conducted on pooled data generated from this trial and its sister trial, Study 406, these results will be presented and discussed in Section 6.

Efficacy Conclusion:

Significantly greater proportions of patients in both the pegloticase every 2 weeks and pegloticase every 4 weeks treatment groups had normalization of PUA to < 6 mg/dL during Months 3 and 6 as compared to placebo.

Results from Study 406:

Disposition:

This study was conducted at 27 centers located in the United States and Mexico. Of the 134 potential patients screened for this study, 18 were considered to have been screening failures as follows: 15 due to an exclusionary lab test result, 2 subjects due to withdrawal of consent, and 1 subject for other reasons. A tabular summary of subjects' disposition for Study 406 is shown in Table 15. Overall, the rate of study completion was higher in the placebo treatment group (87%) as compared to the pegloticase every 2 weeks (69%) and pegloticase every 4 weeks (74%) treatment groups. The major reasons for study discontinuation were similar for the two pegloticase treatment arms but differed from the placebo group. The most common reason for early study withdrawal in the pegloticase groups was adverse events (17% for the pegloticase every 2 weeks group and 16% for the pegloticase every 4 weeks group), followed by withdrawal of consent (12% and 7%, respectively), deaths (2% and 0%, respectively) and lost to follow-up (0% and 2%, respectively). A total of 3 patients withdrew prematurely from the placebo group as follows: 1 subject (2%) due to an adverse event, 1 subject (4%) due to withdrew consent, and 1 subject (2%) due to lost to follow up .

Table 15 – Subject Disposition for Study 406

	Pegloticase 8 mg every 2 weeks (N=46)	Pegloticase 8 mg every 4 weeks (N=46)	Placebo (N=24)	Total (N=134)
Number of Patients Randomized	46	46	24	116
Number of Patients Randomized But Not Dosed:	4	3	1	8
Number of Patients Treated (ITT)	42	43	23	108
Number of Patients with Evaluable Tophus	33	33	15	81
Number of Patients that Completed the Week 24 Study Visit:				
Enrolled in OLE	29 (69%)	32 (74%)	20 (87%)	81 (75%)
Did not enroll in OLE	28 (97%)	32 (94%)	20 (100%)	78 (96%)
	1 (3%)	2 (6%)	0 (0%)	3 (4%)
Number of Patients Withdrawn				
Prematurely Before Week 24:				
Non-compliance	13 (31%)	11 (26%)	3 (13%)	27 (25%)
Adverse Event	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Withdrew Consent	7 (17%)	7 (16%)	1 (4%)	15 (56%)
Lost to Follow-Up	5 (12%)	3 (7%)	1 (4%)	9 (33%)
Protocol Violation	0 (0%)	1 (2%)	1 (4%)	2 (7%)
Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	2 (5%)	0 (0%)	0 (0%)	2 (7%)

Adapted Sponsor's Table 4; p. 45

Protocol Deviations:

A total of 35 randomized patients incurred one or more protocol deviations/violations over the course of this trial. The following table (Table 16) shows that the rate of protocol deviations/violations was higher for the pegloticase every 2 weeks treatment group (37%) as compared to pegloticase every 4 weeks group (30%) and the placebo group (17%). Overall, the most common protocol deviation/violation was due to missed Month 3 and Month 6 study visits (19%), followed by did not receive study medication (6%) and used allopurinol (prohibited drug) (1%). All 35 subjects who incurred protocol deviations/violations were excluded from the per protocol analysis. The 8 randomized patients who did not receive study medication were excluded from the ITT population which was used in calculating the primary and secondary endpoints. Further review of these protocol deviations (i.e., missed or late visits) reveals that they did not impact on the trial's primary efficacy outcome due to the prespecified imputation techniques for missing data in the statistical analysis plan.

Table 16 – Tabular Summary of Subjects with Protocol Deviations/Violations for Study 406

	Pegloticase 8 mg every 2 weeks (N=46)	Pegloticase 8 mg every 4 weeks (N=46)	Placebo (N=24)	Total (N=134)
Number of Subjects with Protocol Deviations/Violations	17 (37%)	14 (30%)	4 (17%)	35 (26%)
Used Allopurinol	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Did Not Receive Any Study Medications	4 (9%)	3 (7%)	1 (4%)	8 (6%)
Missed Month 3 and Month 6 Visits	13 (28%)	10 (22%)	3 (13%)	26 (19%)

Sponsor's Table 1.2; Appendix 16.2

Demographics:

A summary of the baseline demographics of patients who participated in this trial is shown in Table 17. Subjects treated with pegloticase were demographically similar to those who received placebo during this study. The patients who participated in these studies had a mean age of 54 years and were overwhelmingly male (86%) and Caucasian (60%). There was a good representation of other ethnic groups (13% Black, 17% Hispanic, 5% Pacific Islander/Native Hawaiian and 2% American Indian/ Alaskan Native). More females were randomized to the pegloticase every 4 weeks treatment group (21%) as compared to the pegloticase every 2 weeks group (10%) and placebo group (9%). The majority of subjects were overweight as evidenced by mean BMI of 32 which is consistent with the increasing number of metabolic syndrome patients who develop gout. Additionally, the majority of patients reported that they did not drink alcohol which increases the risk for gout attacks. However, more subjects randomized to the placebo group (48%) reported alcohol ingestion as compared to the pegloticase every 2 weeks (46%) and every 4 weeks (42%) treatment groups.

Table 17 – Tabular Summary of Baseline Demographic Characteristics of Subjects Enrolled in Study 406 (Intent-to-Treat [ITT] Population)

	Pegloticase 8 mg every 2 weeks (N=46)	Pegloticase 8 mg every 4 weeks (N=46)	Placebo (N=24)	Total (N=134)
Age				
Mean (SD)	54 (16)	54 (14)	54 (11)	54 (14)
Gender				
Male	38 (91%)	34 (79%)	21 (91%)	93 (86%)
Female	4 (10%)	9 (21%)	2 (9%)	15 (14%)
Race:				
American Indian/Alaskan Native	1 (2%)	0 (0%)	1 (4%)	2 (2%)
Asian	1 (2%)	1 (2%)	0 (0%)	2 (2%)
Hispanic/Latino	11 (26%)	5 (12%)	2 (9%)	18 (17%)
Black	4 (10%)	8 (19%)	2 (9%)	14 (13%)
Pacific Islander/Native Hawaiian	3 (7%)	1 (2%)	1 (4%)	5 (5%)
White	22 (52%)	27 (63%)	16 (70%)	65 (60%)
Other	0 (0%)	1 (2%)	1 (4%)	2 (2%)
Weight (kg)				
Mean (SD)	95 (22)	97 (29)	98 (32)	97 (27)
Height (cm)				
Mean (SD)	174 (9)	174 (12)	177 (11)	175 (10)
BMI (kg/m²)				
Mean (SD)	31 (6)	32 (8)	31 (8)	32 (7)
Alcohol Consumption:				
Yes	15 (36%)	18 (42%)	11 (48%)	44 (33%)
No	27 (64%)	25 (58%)	12 (52%)	64 (48%)

Sponsor's Table 5; p. 48 and Table 3.3; p.182

Table 18 is a tabular summary of subjects' gout history and disease status. There were no differences in gout history or disease status between the three treatment groups. Overall, 53% of the subjects who participated in the study had crystal proven gout. The overall mean duration since the first gout attack was 17 years and the overall mean duration since the first diagnosis of gout was 15 years for the study population. The mean number of gout flares per year reported by the three treatment groups was similar (8-9 attacks), the majority of which were described to be polyarticular (>3 joints) or oligoarticular(2-3 joints) (64%%) and moderate to severe (92%) in nature. Overall, 56% of the total study population had chronic synovitis and/or arthropathy due to gout. The percentage of patients randomized to the pegloticase treatment group with tophaceous deposits was similar for these two groups (79% and 77%, respectively) but higher as compared to 65% of placebo patients with tophaceous disease. A higher incidence of surgery for gout (excluding arthrocentesis) was reported by placebo patients (30%) as compared to the pegloticase every 2 weeks (14%) and every 4 weeks (26%) patients. More patients in the pegloticase every 4 week group (23%) also had a history of gout-related kidney disease as compared to the pegloticase every 2 weeks (10%) and the placebo group (4%), but the mean number of renal colic episodes in the past year was similar between the 3 treatment groups (0.03 episodes for pegloticase

every 2 weeks, 0.00 episodes for pegloticase every 4 weeks, and 0.09 episodes for placebo). A minority of the patient population (6%) in this study reported having another arthritic condition that could potentially confound their gout assessments. Based on these data, the study population that participated in this trial had moderate to severe gout and could potentially show a response to study therapy.

Table 18– Tabular Summary of Subjects’ Gout History and Disease Status (ITT Population) Who Participated in Study 406

	Pegloticase 8 mg every 2 weeks (N=42)	Pegloticase 8 mg every 4 weeks (N=43)	Placebo (N=23)	Total (N=108)
Number of Years Since First Gout Attack Mean (SD)	17 (10)	18 (10)	17 (11)	17 (10)
Number of Years Since First Diagnosis of Gout Mean (SD)	15 (11)	16 (9)	15 (10)	15 (10)
Confirmed Presence of Uric Acid Crystals				
Yes	22 (52%)	23 (54%)	12 (52%)	57 (53%)
No	20 (48%)	20 (47%)	11 (48%)	51 (47%)
Number of Acute Flares in the Past 18 Months Mean (SD)	9 (9)	8 (6)	8 (11)	8 (8)
Pattern of Acute Flares				
Monoarticular (One Joint)	16 (39%)	14 (33%)	8 (36%)	38 (36%)
Oligoarticular (2-3 Joints)	9 (22%)	12 (29%)	10 (46%)	31 (30%)
Polyarticular (> 3 Joints)	16 (39%)	16 (38%)	4 (18%)	36 (34%)
Severity of Acute Flares				
Mild (Uncomfortable)	5 (12%)	1 (2%)	2 (9%)	8 (8%)
Moderate (Limiting)	14 (34%)	15 (36%)	9 (41%)	38 (36%)
Severe (Crippling)	22 (54%)	26 (62%)	11 (50%)	59 (56%)
Chronic Synovitis/Arthropathy				
Yes	23 (55%)	24 (56%)	13 (57%)	60 (56%)
No	19 (45%)	19 (44%)	10 (44%)	48 (44%)
History of Gout-Related Kidney Disease				
Yes	4 (10%)	10 (23%)	1 (4%)	15 (14%)
No	38 (91%)	33 (77%)	22 (96%)	93 (86%)
Tophi				
Yes	33 (79%)	33 (77%)	15 (65%)	81 (75%)
No	9 (21%)	10 (23%)	8 (35%)	27 (25%)
Surgery for Gout (Excluding Arthrocentesis)				
Yes	6 (14%)	11 (26%)	7 (30%)	24 (22%)
No	36 (86%)	32 (74%)	16 (70%)	84 (78%)
Another Arthritis Condition Potentially Confounding Diagnosis of Gout				
Yes	4 (10%)	1 (2%)	1 (4%)	6 (6%)
No	38 (91%)	42 (98%)	22 (96%)	102(94%)
Number of Episodes of Renal Colic in the Past Year Mean (SD)	0.03 (0.16)	0.00 (0.00)	0.09(0.42)	0.03(0.22)

Sponsor's Table 6; p.50

Since this study’s protocol specifically targeted hyperuricemic gout patients with documented unresponsiveness and/or hypersensitivity to allopurinol, a summary of patient eligibility based on prior allopurinol exposure is shown in Table 19:

Table 19 – Patient Eligibility as Per Allopurinol Treatment History for Enrollment in Study 406 (ITT Population)

	Pegloticase 8 mg every 2 weeks (N=42)	Pegloticase 8 mg every 4 weeks (N=43)	Placebo (N=23)	Total (N=108)
Allopurinol ineffective	13 (31%)	10 (23%)	3 (13%)	26 (24%)
History of Allergy/Hypersensitivity	17 (41%)	15 (35%)	8 (35%)	40 (37%)
Renal insufficiency	4 (9.5%)	5 (12%)	6 (26%)	15 (14%)
GI intolerance	4 (9.5%)	8 (19%)	2 (8.7%)	14 (13%)
Other	4 (9.5%)	5 (12%)	4 (17%)	13 (12%)

Sponsor’s Table 7; p. 51

Treatment with allopurinol was reported to be ineffective by 24% of all patients who participated in this study, while it was contraindicated in another 37% due to history of allergy or hypersensitivity reaction. The remaining 39% of subjects were unable to use allopurinol due to tolerability issues related to comorbid conditions such as renal insufficiency (14%), gastrointestinal intolerance (13%) or for other reasons (12%). These data demonstrate that the subjects who participated in this study were the population intended to use this product.

As summarized in Table 20, many of the subjects who participated in Study 406 suffered from serious co-morbid medical conditions including vascular system disorders (74%), metabolic and nutritional disorders (53%), renal and urinary disorders (32%), and cardiac disorders (20%). There was also a high prevalence of conditions that increased the risk for hyperuricemia (e.g., hypertension [70%], renal failure [14%], and obesity [14%]).

Table 20 – Tabular Summary of Comorbid Medical Conditions Reported by > 10% of Subjects Who Participated in Study 406 (ITT Population)

MedDRA Body System Preferred Term	Pegloticase 8 mg every 2 weeks (N=43)	Pegloticase 8 mg every 4 weeks (N=43)	Placebo (N=23)	Total (N=108)
Vascular Disorders:	31 (74%)	30 (70%)	16 (70%)	77 (71%)
Hypertension	31 (74%)	30 (70%)	15 (65%)	76 (70%)
Metabolism and Nutrition Disorders:	22 (52%)	26 (61%)	9 (39%)	57 (53%)
Hypercholesterolemia	7 (17%)	9 (21%)	2 (9%)	18 (17%)
Hyperlipidemia	7 (19%)	6 (14%)	3 (13%)	16 (15%)
Obesity	4 (10%)	9 (21%)	2 (9%)	15 (14%)
Diabetes Mellitus	6 (14%)	7 (16%)	2 (9%)	14 (13%)
Musculoskeletal and Connective Tissue Disorders:	21 (50%)	17 (40%)	13 (57%)	51 (47%)
Immune System Disorders:	15 (36%)	21 (49%)	11 (48%)	47 (44%)
Drug Hypersensitivity	14 (33%)	15 (35%)	7 (30%)	36 (33%)
Gastrointestinal Disorders:	18 (43%)	18 (42%)	9 (39%)	45 (42%)
Renal and Urinary Disorders:	14 (33%)	15 (35%)	6 (26%)	35 (32%)
Renal Failure	8 (19%)	5 (12%)	2 (9%)	15 (14%)
Renal Failure Chronic	3 (7%)	4 (9%)	2 (9%)	9 (8%)
Nephrolithiasis	2 (5%)	2 (5%)	1 (4%)	5 (5%)
Glomerulonephritis	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Respiratory, Thoracic and Mediastinal Disorders:	7 (17%)	12 (28%)	6 (26%)	25 (23%)
Psychiatric Disorders:	9 (21%)	10 (23%)	6 (26%)	25 (23%)
Investigations:	9 (21%)	12 (28%)	4 (17%)	25 (23%)
Nervous System Disorders:	6 (14%)	11 (26%)	6 (26%)	23 (21%)
Skin and Subcutaneous Tissue Disorders:	9 (21%)	11 (26%)	3 (13%)	23 (21%)
Cardiac Disorders:	10 (23%)	10 (23%)	2 (9%)	22 (20%)
Coronary Artery Disease	4 (10%)	3 (7%)	1 (4%)	8 (7%)
Atrial Fibrillation	5 (12%)	0 (0%)	1 (4%)	6 (6%)
Cardiac Failure Congestive	2 (5%)	1 (2%)	0 (0%)	3 (3%)
Bundle Branch Block Right	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Congestive Cardiomyopathy	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Angina Pectoris	0 (0%)	2 (5%)	0 (0%)	2 (2%)
Arrhythmia	3 (7%)	0 (0%)	0 (0%)	3 (3%)
Cardiac Failure	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Dilatation Atrial	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Cardiomegaly	1 (2%)	0 (0%)	0 (0%)	1 (1%)
General Disorders and Administration Site Conditions:	6 (14%)	6 (14%)	4 (17%)	16 (15%)
Blood and Lymphatic System Disorders:	5 (12%)	5 (12%)	3 (13%)	13 (12%)
Infections and Infestations:	6 (14%)	6 (14%)	1 (4%)	13 (12%)
Eye Disorders:	5 (12%)	6 (14%)	0 (0%)	11 (10%)
Endocrine Disorders:	4 (10%)	4 (9%)	1 (4%)	9 (8%)
Social Circumstances:	2 (5%)	2 (5%)	0 (0%)	4 (4%)
Postmenopause	1 (2%)	0 (0%)	0 (0%)	1 (1%)

Adapted Sponsor's Table 6.2; p. 199-214.

Study participants in each treatment group additionally reported taking concomitant medications (e.g., beta-blockers, salicylate, insulin, diuretics, warfarin, vitamin B12, amlodipine, and losartan) that are known to interfere with uric acid metabolism as listed in Table 21. A higher percentage of patients randomized to the pegloticase every 4 weeks (52%) and the pegloticase every 2 weeks group (47%) were taking beta-blockers as compared to the placebo group (39%). More patients in the pegloticase every 2 weeks group (12%) were also taking concomitant warfarin as compared to the placebo arm (4%) and the pegloticase every 4 weeks (2%) treatment groups. A higher percentage of patients in the pegloticase every 4 weeks group (28%) was taking concomitant aspirin therapy as compared to the pegloticase every 2 weeks group (19%) and placebo group (13%). Use of these 3 drugs (particularly low dose aspirin therapy) can increase serum uric acid levels by interfering with its urinary excretion. The usage of the other drugs that could potentially interfere with uric acid metabolism was similar across the 3 treatment groups.

Table 21 – Tabular Summary of Concomitant Medications Taken by ≥ 10% of Patients in Study 406 by Treatment Group (ITT Population)

WHO Drug Preferred Term of Medication	Pegloticase 8 mg every 2 weeks (N=42)	Pegloticase 8 mg every 4 weeks (N=43)	Placebo (N=23)
Subjects With at Least 1 Concomitant Medication	42	43	23
Anti-Gout Drugs:	28 (67%)	25 (58%)	13 (57%)
Colchicine	27 (64%)	25 (56%)	13 (57%)
Acid Related Disorder Drugs:	25 (60%)	24 (56%)	14 (61%)
Omeprazole	15 (36%)	12 (28%)	11 (48%)
Lansoprazole	5 (12%)	2 (5%)	0
Pantoprazole	1 (2%)	2 (5%)	3 (13%)
Analgesics:	21 (50%)	28 (65%)	10 (44%)
Paracetamol	9 (21%)	15 (35%)	3 (13%)
Vicodin	3 (7%)	5 (12%)	5 (22%)
Anti-Inflammatory Drugs:	20 (48%)	21 (49%)	14 (61%)
Indomethacin	7 (17%)	6 (14%)	3 (13%)
Ibuprofen	3 (7%)	5 (12%)	4 (17%)
Naproxen	1 (2%)	7 (16%)	2 (9%)
Celecoxib	2 (5%)	5 (12%)	1 (4%)
Drugs Acting on the Renin-Angiotensin System	22 (52%)	22 (51%)	10 (44%)
Lisinopril	6 (14%)	7 (16%)	5 (22%)
Enalapril	5 (12%)	2 (5%)	1 (4%)
Beta-Blocking Drugs:	22 (52%)	20 (47%)	9 (39%)
Atenolol	7 (17%)	7 (16%)	4 (17%)
Metoprolol Succinate	5 (12%)	6 (14%)	1 (4%)
Metoprolol	5 (12%)	4 (9%)	0
Carvedilol	5 (12%)	2 (5%)	1 (4%)
Systemic Corticosteroids:	18 (43%)	19 (44%)	5 (22%)
Prednisone	14 (33%)	17 (40%)	3 (13%)
Serum Lipid Reducing Drugs:	20 (48%)	16 (37%)	6 (26%)
Atorvastatin	8 (19%)	4 (9%)	0
Fish Oil	6 (14%)	0	2 (9%)
Diuretics:	14 (33%)	12 (28%)	7 (30%)
Furosemide	7 (17%)	9 (21%)	5 (22%)
Systemic Antibacterials:	13 (31%)	11 (26%)	8 (35%)
Ciprofloxacin	7 (17%)	3 (7%)	0
Azithromycin	2 (5%)	3 (7%)	3 (13%)
Levofloxacin	0	1 (2%)	3 (13%)
Antithrombotic Agents:	14 (33%)	14 (33%)	4 (17%)
Acetylsalicylic Acid	8 (19%)	12 (28%)	3 (13%)
Warfarin	5 (12%)	1 (2%)	1 (4%)

Sponsor's Table 8; p. 54

Table 21 – Tabular Summary of Concomitant Medications Taken by ≥ 10% of Patients in Study 406 by Treatment Group (ITT Population) (cont.)

WHO Drug Preferred Term of Medication	Pegloticase 8 mg every 2 weeks (N=42)	Pegloticase 8 mg every 4 weeks (N=43)	Placebo (N=23)
Calcium Channel Blockers:	12 (29%)	13 (30%)	5 (22%)
Amlodipine	5 (12%)	5 (12%)	2 (9%)
Felodipine	1 (2%)	1 (2%)	3 (13%)
Vitamins:	9 (21%)	9 (21%)	7 (30%)
Multivitamins	4 (10%)	6 (14%)	1 (4%)
Systemic Antihistamines:	4 (10%)	14 (33%)	5 (22%)
Diphenhydramine Hydrochloride	0	9 (21%)	1 (4%)
Fexofenadine	0	2 (5%)	3 (13%)
Drugs for Treatment of Bone Disease:	6 (14%)	4 (9%)	0
Alendronate Sodium	5 (12%)	2 (5%)	0

Sponsor's Table 8; p. 54

The protocol permitted patients to take medications to treat gout flares they experienced over the course of the study. This information is tabularly summarized in Table 22. More patients randomized to the pegloticase every 2 weeks (81%) and pegloticase every 4 weeks (86%) treatment groups reported taking at least 1 gout flare medication over the course of the study as compared to subjects in placebo treatment group (70%). The most commonly used gout flare medications in this trial were: systemic corticosteroids (49%), anti-inflammatory drugs (41%), antigout preparations (25%), and analgesics (10%).

Table 22 – Tabular Summary of Gout Flare Medications Taken by ≥ 5% of Patients by Treatment Group During Study 406

WHO Drug Preferred Term of Medication	Pegloticase 8 mg every 2 weeks (N=42)	Pegloticase 8 mg every 4 weeks (N=43)	Placebo (N=23)
Subjects Taking at Least 1 Gout-Flare Medication	34 (81%)	37 (86%)	16 (70%)
Systemic Corticosteroids:	22 (52%)	22 (51%)	9 (39%)
Prednisone	20 (48%)	21 (49%)	8 (35%)
Methylprednisolone	4 (10%)	4 (9%)	1 (4%)
Anti-Inflammatory Drugs:	16 (38%)	19 (44%)	9 (39%)
Indomethacin	6 (14%)	10 (23%)	5 (22%)
Naproxen	6 (14%)	6 (14%)	1 (4%)
Diclofenac	3 (7%)	1 (2%)	1 (4%)
Anti-Gout Drugs:	13 (31%)	10 (23%)	4 (17%)
Colchicine	12 (29%)	10 (23%)	4 (17%)
Analgesics:	3 (7%)	7 (16%)	1 (4%)
Paracetamol	2 (5%)	3 (7%)	0 (0%)

Sponsor's Table 9; p. 54

Treatment Compliance:

The number of study infusions and the amount of each study dose administered to each patient was to have been captured and recorded by the study investigators in both the subjects' medical records and CFR. These data were to have been used to calculate overall compliance listed in Table 23. Overall, study compliance was good with a total mean number of 10 study infusions per subject having been administered over the course of the study that was similar between the 3 treatment arms.

Table 23 – Number of Infusions Administered During Study 406

	Pegloticase 8 mg every 2 weeks (N=42)	Pegloticase 8 mg every 4 weeks (N=43)	Placebo (N=23)	Total (N=108)
Mean (S. D.)	9 (4.0)	10 (3.4)	12 (1.1)	10 (3.4)
Median (Min, Max)	12 (1,12)	12 (1,12)	12 (7,12)	12 (1,12)
Number of Infusions (%)				
1	3 (7%)	1 (2%)	0 (0%)	4 (4%)
2	2 (5%)	2 (5%)	0 (0%)	4 (4%)
3	1 (2%)	2 (5%)	0 (0%)	3 (3%)
4	2 (5%)	0 (0%)	0 (0%)	2 (2%)
5	2 (5%)	1 (2%)	0 (0%)	3 (2%)
6	0 (0%)	1 (2%)	0 (0%)	1 (1%)
7	0 (0%)	2 (5%)	1 (5%)	3 (3%)
8	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9	2 (5%)	0 (0%)	0 (0%)	2 (2%)
10	0 (0%)	2 (5%)	1 (4%)	3 (3%)
11	0 (0%)	0 (0%)	1 (4%)	1 (1%)
12	30 (71%)	32 (74%)	20 (87%)	82 (76%)

Adapted Sponsor's Table 48, p. 123.

Efficacy:

The primary efficacy parameter for Study 406 was the proportion of patients whose PUA was normalized to less than 6 mg/dL for at least 80% of the time during Months 3 and 6 combined. Subjects who maintained a PUA concentration below 6 mg/dL for at least 80% of time during Months 3 and 6 combined were considered "PUA responders." The results generated from the primary analysis are shown in Table 24. Higher portions of patients in both the pegloticase every 2 weeks (38%) and pegloticase every 4 weeks (49%) treatment groups showed a response to therapy as compared to the placebo group (0%) ($p \leq 0.001$ for each pegloticase treatment group versus placebo). The statistical reviewer, Dr. Ruthanna Davi, notes, that no multiplicity correction was specified for the primary endpoint. However, she considers the conclusion of efficacy robust because of the high statistical significance associated with the comparisons to placebo.

Table 24 – Treatment Response PUA < 6 mg/dL for at Least 80% of the Time in Months 3 and 6 for Study 406 (ITT Population) (Primary Endpoint)

	Pegloticase 8 mg every 2 weeks (N=42)	Pegloticase 8 mg every 4 weeks (N=43)	Placebo (N=23)
PUA < 6 mg/dl for at Least 80% of the Time in Month 3			
Number (%)	19 (45%)	21 (49%)	1 (4%)
95% Confidence Interval ¹	[23.7, 58.1]	[27.4, 61.6]	
P-Value ²	<0.001	<0.001	
PUA <6 mg/dL for at Least 80% of the Time in Month 6			
Number (%)	17 (41%)	18 (42%)	0
95% Confidence Interval ¹	[25.6; 55.3]	[27.1, 56.6]	
P-Value ²	<0.001	<0.001	
PUA <6 mg/dL for at Least 80% of the Time in Months 3 and 6 Combined			
Number (%)	16 (38%)	21 (49%)	0
95% Confidence Interval ¹	[23.4, 52.8]	[33.9, 63.8]	
P-Value ²	<0.001	<0.001	

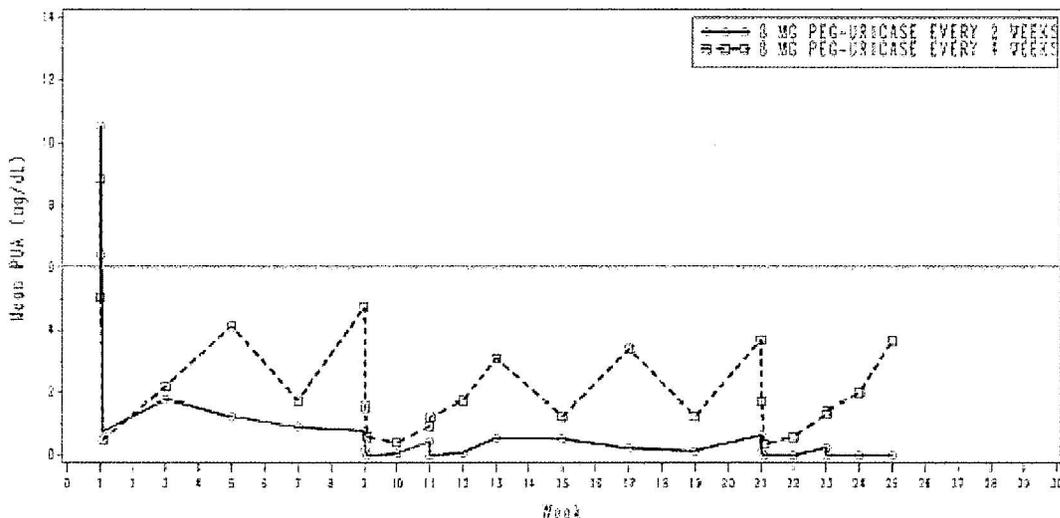
¹95% confidence interval for differences in responder rate between corresponding pegloticase groups vs. placebo

²P-value using Fisher's exact test to compare corresponding pegloticase group vs. placebo.

Sponsor's Table 11; p. 57

Figures 3 and 4 below graphically depict the mean PUA concentration profile for responders and nonresponders to study therapy over the 26 weeks of the trial. These figures graphically illustrate a rapid decrease in serum PUA following the administration of the first infusion of pegloticase in both the every 2 week and every 4 week groups. This response is maintained throughout the remainder of the study by patients who meet the prespecified response criteria as shown in Figure 3. Note that the placebo group does not appear in Fig.1 as there were no responders in the placebo group. In contrast, patients who were classified as non-responders had an initial drop in plasma uric acid that was subsequently lost (Figure 4).

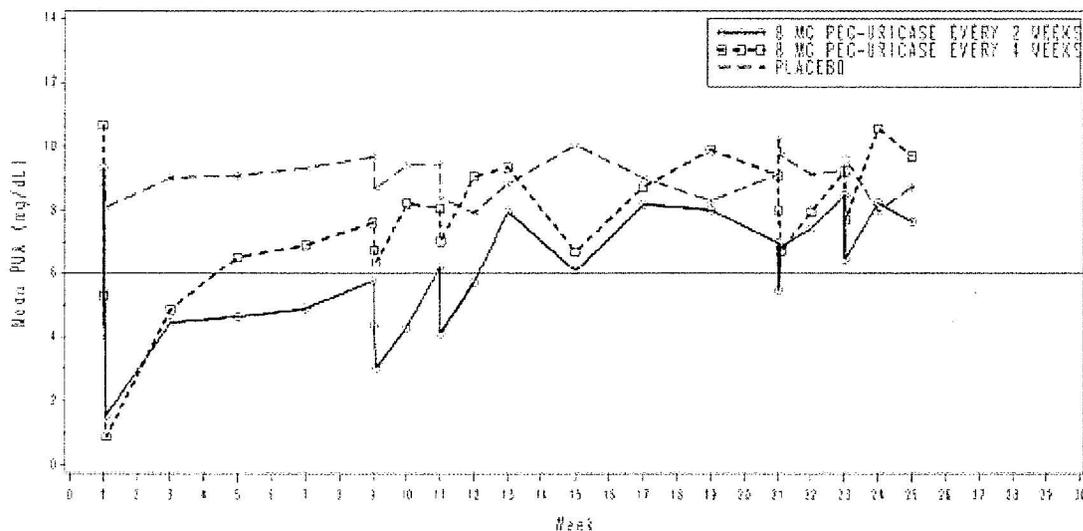
Figure 3 – Mean PUA Concentrations for PUA Responders by Pegloticase Treatment Group for Study 406 (ITT Population)



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Sponsor's Fig. 4; p. 61.

Figure 4 – Mean PUA Concentration for PUA Non-Responder by Treatment Group for Study 406 ITT Population)



Sponsor's Figure 5; p. 61

No sensitivity analyses were performed on the primary endpoint. Since the SAP stipulated that the analyses of the secondary endpoints were to be conducted on pooled data generated from this trial and its sister trial, Study 405, these results will be presented and discussed in Section 6.

Efficacy Conclusion:

Significantly greater proportions of patients in both the pegloticase every 2 weeks and pegloticase every 4 weeks treatment groups had normalization of PUA to < 6 mg/dL during Months 3 and 6 as compared to placebo.

Study 407

(Note: This is an interim 12-month preliminary review of safety and efficacy data gathered up to a visit cutoff date of March 31, 2008 as of the softlock date of May 31, 2008 for this 24-month ongoing trial.)

Title: Multicenter, open-label extension study of 8 mg PEG-uricase in subjects who completed Protocols C0405 Or C0406 for symptomatic gout.

Objectives:

Primary Objective:

- To evaluate the long-term safety of subjects treated with pegloticase for more than 6 months
 - Describe the safety profile of pegloticase with respect to adverse events, lab measurements, physical exam and ECG
 - Determine the incidence of infusion reactions
 - Determine the incidence of clinically manifested allergic reactions to pegloticase
 - Characterize the potential for immunogenicity of pegloticase by lab evaluations

Secondary Objectives:

- To determine the treatment effect, duration of response, and the clinical outcomes in subjects treated with pegloticase for symptomatic gout with respect to the following parameters:
 - Plasma uric acid (PUA)
 - Patient-reported outcomes (PROs)
 - Tophus response as assessed by image analysis
 - The number of swollen and tender joints
 - Clinician's Global Assessment (CGA)
 - Incidence, frequency and severity of gout flares

Exploratory Objectives:

- To evaluate changes in biochemical markers of bone and cartilage metabolism in response to pegloticase treatment

Study Design:

Studies 407 was to have been a 12-month, multicenter, open-label extension Phase 3b study to evaluate the long-term safety and efficacy of pegloticase in the treatment of

patients with refractory symptomatic gout who had completed the randomized controlled trials C0405 and C0406. The trial was to consist of two active treatment arms (pegloticase every 2 weeks and pegloticase every 4 weeks) and an observational arm. At the last study visit of these preceding trials, treatment group assignment for each patient was to be determined by the study investigator. Subjects who opted not to receive additional treatment with pegloticase were to have been enrolled in the observation arm. Patients who were unable to tolerate the chosen treatment regimen could stop treatment and were to have been followed-up in the observational arm. The protocol stipulated that medications that were administered in the previous protocols to control gout flares were to have been continued for the first three months of treatment in this trial. After 3 months the gout flare prophylaxis medications were to have been discontinued at the discretion of the study investigator. Subjects in the observational arm of the study were to have been permitted to receive other urate lowering therapy at the discretion of the study investigator. Additionally, all patients were to have been premedicated with a prophylactic infusion reaction regimen before receiving each study infusion.

Major Inclusion Criteria:

In order to be eligible for this trial, potential study subjects were to have been previously treated and completed either of the randomized, controlled trials (C0405 and C0406).

Exclusion Criteria:

Potential trial candidates were to have been prohibited from participating in this trial if any of the following criteria applied:

1. Had unstable angina
2. Had uncontrolled arrhythmia
3. Had non-compensated congestive heart failure
4. Had uncontrolled hypertension (\geq than 150/90 mm/Hg)
5. Had history of end-stage renal disease necessitating in the need for dialysis
6. Had a hemoglobin < 8 g/dL (males) or < 7 g/dl (females)
7. Had been either pregnancy or breast feeding at entry
8. Had a known allergy to urate oxidase or PEGylated products
9. Had any or other medical or psychological condition which, in the opinion of the investigator, could create undue risk to the subject or interfere with the subject's ability to comply with the protocol requirements, or to complete the study.

Treatment:

Patients who elected to continue pegloticase therapy were to have been treated with pegloticase 8 mg every 2 weeks or pegloticase 8 mg every 4 weeks administered via intravenous infusion over 120 minutes followed by a 10 ml normal saline flush. Subjects were to have remained at the study site for at least 2 hours of observation after receiving their study medication infusion in order to monitor for infusion reactions.

Removal of Patients from Treatment or Assessment:

Subjects were to have been discontinued from these trials if they withdrew consent, experienced an adverse event that would have precluded further exposure, were noncompliant, or incurred a protocol violation. The common protocol stipulated that subjects were free to discontinue study participation for any of the preceding reasons at any time over the course of the trial. Patients who discontinued study medication had the option of continuing in the observation arm of the trial.

Concomitant Medication:

All subjects who elected to continue pegloticase therapy were to have been administered the following prespecified prophylactic infusion reaction regimen prior to receiving each study infusion: 60 mg fexofenadine orally at bedtime the night before the infusion, 60 mg of fexofenadine and 1000 mg of acetaminophen orally the morning of the infusion, and 200 mg of hydrocortisone intravenously immediately prior to the trial infusion. The protocol stipulated that patients were to continue their gout prophylaxis regimen (e.g., either 0.6 to 1.2 mg/day of colchicine or the labeled analgesic dose of a NSAID taken with a proton pump inhibitor for gastric protection) that they had started during the randomized controlled trials but these medications could be discontinued at the discretion of the study investigator after completing the first 3 months of this study. Patients could continue to use medications prescribed for concurrent medical conditions but could not take any uric acid lowering agents (e.g., probenecid or allopurinol) for the duration of the study, however, subjects being followed in the observational arm of this trial were to have been permitted to use other urate-lowering drugs at the discretion of the study investigator. All concomitant medications including analgesics were to have been recorded at each visit in each subject's case report forms.

Gout Flare Treatment:

Patients who experienced an acute gout flare during the study were to have been treated with an individualized anti-inflammatory regimen that included a NSAID with a PPI, colchicine or corticosteroids as outlined in the common protocol for Studies 405 and 406. Use of any of these medications was to have been captured in the subjects' case report forms.

Efficacy and Safety Assessments:

Following the first study visit, subjects' clinic visits for treatment, safety and efficacy assessments were to have been dependent on which treatment group they were assigned: patients in the pegloticase every 2 weeks group were seen every 2 weeks patients in the pegloticase every 4 weeks group were seen every 4 weeks and patients in the observational arm were seen every 4 weeks until study completion. Efficacy evaluations comprised of tophus assessment (photographs), swollen/tender joint counts, HAQ and SF-36, were to have been conducted at Weeks 1, 13, 25, 37, 49 and end of study visit while the assessment for acute gout flares were to have been

performed at every scheduled trial visit. Blood samples for measurement of PUA, uricase, CRP, serum allantoin were to have been collected at Weeks 9, 11, 13, 21, 23, 25, and 37 and end of study visit. Urine samples were to have been collected at Weeks 1, 25 and end of study visit for measurement of urinary caboxyterminal cross-linking telopeptide of collagen (U-CTX) and allantoin. Safety was to have been assessed by monitoring for adverse events, infusion reactions (IRs) and gout flares, clinical laboratory evaluations, vital sign measurements, and physical exams at each scheduled clinic visit as well as electrocardiograms end of study visit visit.

Study Visit Schedule:

The following Tables 25a, b and c are tabular flow charts of the scheduled study visits and protocol specified procedures and evaluations for each study arm:

Table 25a – Schedule of Procedures and Evaluations for Pegloticase every 2 Weeks Treatment Group in Study 407

Visit	1*	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	
Week	1	3	5	7	9	11	13	15	17	19	21	23	25	27	29	31	33	35	37	39	41	43	45	47	49	51	EO S ⁶	
Dose	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26		
Informed Consent	x																											
Physical Exam													x															x
Acute Gout Flare Assessment		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Tophus Assessment/Photography							x						x															x
Swollen/Tender Joint Count							x						x															x
Vital Signs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dermatological & Chest exam ⁵	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistries							x						x															x
Hematology							x						x															x
Urinalysis							x						x															x
hCG (women of childbearing potential)																												x
Urine CTx ¹ /Urine allantoin ¹	x ²												x															x
Urine for uric acid:creatinine ratio								x					x								x							x
12-lead ECG ²													x															x
SF-36/HAQ-DI									x				x															x
Tryptase ⁷																												x
Blood samples for PUA & uricase					x ³	x	x				x ³	x	x							x								x
Uric Acid meter (if available) reading by study staff					x ³	x	x				x ³	x	x							x								x
Blood for Antibody																												x
Blood CH50																												x
C-reactive protein	x ⁴		x		x		x						x								x							x
Serum allantoin ⁵	x ⁴												x															x
Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Assess adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Administer PEG-uricase after pre-medicating, monitor infusion	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

¹Procedures from Week 25 C0405/C0406 will be used for this visit ²Samples not in Ph-3 studies and added to this study ³Second morning voided specimen ⁴Obtain for any severe infusion reaction and / or cardiopulmonary event ⁵Pre and 2-hours post dose samples ⁶performed at early termination and one month after the last dose ⁷Analysis to be performed in the future ⁸Performed prior to each dose ⁹Obtain at the time of any infusion reaction

Table 25b – Schedule of Procedures and Evaluations for Pegloticase every 2 Weeks Treatment Group in Study 407

Visit	1*	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Week	1	5	9	11	13	17	21	23	25	29	33	37	41	45	49	EOS ⁴
Dose	1	2	3		4	5	6		7	8	9	10	11	12	13	
Informed Consent	x															
Physical Exam									x							x
Acute Gout Flare Assessment		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Tophus Assessment/Photography					x				x							x
Swollen/Tender Joint Count					x				x			x			x	x
Vital Signs		x	x		x	x	x		x	x	x	x	x	x	x	x
Dermatological & Chest exam ⁵		x	x		x	x	x		x	x	x	x	x	x	x	x
Chemistries					x				x			x				x
Hematology					x				x			x				x
Urinalysis					x				x			x				x
hCG (women of childbearing potential)																x
Urine CTx ¹ ; Urine allantoin ¹									x							x
Urine for uric acid:creatinine ratio					x				x			x				x
12-lead ECG ²																x
SF-36; HAQ-DI					x				x							x
Tryptase ⁷																
Blood samples for PUA & uricase			x ³	x	x			x ³	x	x		x				x
Uric Acid meter (if available) reading by study staff			x ³	x	x			x ³	x	x		x				x
Blood for Antibody					x				x			x				x
Blood CH50					x				x			x				x
C-Reactive Protein			x	x	x				x			x				x
Serum allantoin ⁸									x							x
Concomitant Medications		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Assess adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Administer PEG-uricase after pre-medicating, monitor infusion	x	x	x		x	x	x		x	x	x	x	x	x	x	

¹Procedures from Week 25 C0405/C0406 will be used for this visit ²Samples not in Ph 3 studies and added to this study ³Second morning voided specimen ⁴Obtain for any severe infusion reaction and / or cardiopulmonary event ⁵Pre and 2 hours post dose samples ⁶performed at early termination and one month after the last dose ⁷Analysis to be performed in the future ⁸Performed prior to each dose ⁹Obtain at the time of any infusion reaction

Table 25c – Schedule of Procedures and Evaluations for Observational Group in Study 407

Visit	1*	2	3	4	5	6	7	8	9	10	11	12	13
Week	1	5	9	13	17	21	25	29	33	37	41	45	49/EOS
Informed Consent	x												
Physical Exam							x						x
Acute Gout Flare Assessment		x	x	x	x	x	x	x	x	x	x	x	x
Tophus Assessment/Photography				x			x						x
Swollen/Tender Joint Count				x			x			x			x
Vital Signs				x			x			x			x
Chemistries				x			x			x			x
Hematology				x			x			x			x
Urinalysis				x			x			x			x
Urine CTx ¹ ; Urine for Allantoin ¹							x						x
Urine for uric acid:creatinine ratio				x			x						x
12-lead ECG													x
SF-36; HAQ-DI				x			x			x			x
Serum UA		x	x										
Blood for Antibody				x			x						x
Blood CH50				x									
C-reactive protein		x	x	x			x			x			x
Serum allantoin ²							x						x
Concomitant Medications		x	x	x	x	x	x	x	x	x	x	x	x
Assess adverse events		x	x	x	x	x	x	x	x	x	x	x	x

¹Procedures from Week 25 C0405/C0406 will be used for this visit ²Samples not in Ph 3 studies and added to this study ³Second morning voided specimen ⁴Analysis to be performed in the future

The efficacy results from Study 407 will not be presented since it is an open-label study and they are non-controlled. The safety results will be discussed in Section 7.

6 Review of Efficacy

Efficacy Summary

The clinical data submitted in support of pegloticase as a treatment of chronic symptomatic gout in patients refractory to conventional therapy was generated from two identically designed Phase 3 trials, 405 and 406. These trials were multicenter, randomized, double-blind, placebo-controlled parallel group dose comparison studies in 212 patients with treatment failure gout that evaluated the efficacy of two dosing regimens of pegloticase when administered via intravenous infusion as either 8 mg every 2 weeks or 8 mg every 4 weeks compared to placebo. The primary objective of these trials was to demonstrate the superiority of pegloticase over placebo in reducing PUA as assessed by the primary efficacy endpoint (e.g., the percentage of subjects who achieved and maintained PUA levels <6 mg/dL for at least 80% of the time during Months 3 and 6 combined.) In both of these studies a greater proportion of patients achieved the primary endpoint for the pegloticase every 2 weeks regimen (Study 405: 47%; Study 406: 38%) and for the pegloticase every 4 weeks regimen (Study 405: 20%; Study 406: 49%) as compared to placebo (Study 405: 0%; Study 406: 0%). The difference between each of the pegloticase treatment groups and the placebo group were statistically significant for both trials (Study 405 - pegloticase every 2 weeks versus placebo: $p < 0.001$; pegloticase every 4 weeks versus placebo: $p = 0.044$) (Study 406 – pegloticase every 2 weeks versus placebo: $p < 0.001$; pegloticase every 4 weeks versus placebo: $p < 0.001$). The statistical reviewer concluded that due to the high statistical significance of the comparisons that the every 2 week regimen demonstrated efficacy for the primary endpoint despite the lack of a pre-specified multiplicity adjustment. She also notes that the primary endpoint result is statistically significant for Study 406 for the every 4 weeks dose but only marginally so for Study 405. However, she notes that considering the results for 405 and 406 together the results in 405 are unlikely to be a spurious finding. Thus, she concludes that the pegloticase every 4 week group also shows efficacy for increasing the proportion of patients of patients with a PUA <6 mg/dL during months 3 and 6. The results from subgroup analyses for gender, age and sex of the primary endpoint were not shown to be significantly different, however, the small number of patients involved in these analyses raises questions concerning the validity of these findings.

Since the primary endpoint for the pivotal studies was based on a validated surrogate endpoint (e.g., PUA <6 mg/dL) additional support for a clinical benefit for treatment with pegloticase was derived from a number of clinical secondary endpoints based on pooled data generated from Studies 405 and 406. The magnitude of the decrease in mean PUA levels during Months 3 and 6 combined was greater in both pegloticase treatment groups as compared to placebo ($p < 0.001$ for both treatment group comparisons versus placebo). Significantly higher proportions of patients treated with pegloticase every 2 weeks achieved a complete tophus response compared to placebo-

treated patients (p -value ≤ 0.002). In addition, a significantly greater proportion of patients receiving pegloticase every 2 weeks had a tophus response based on the ordinal (ranked) scores of complete response, partial response, stable disease, and progression of disease compared to placebo-treated patients. Analyses of data for the same outcomes for the pegloticase every 4 week group were not as robust with only a significantly higher proportion of subjects achieving a categorical response at Week 19 as compared to placebo ($p=0.004$), while the other comparative analyses at the remaining time points showed only positive trends. At the Week 25 timepoint, patients treated with pegloticase every 2 weeks also had a significant reduction in the number of swollen or tender joints as compared to placebo ($p<0.001$). However, the results for the pegloticase every 4 week group versus placebo for the swollen and tender joint counts trended toward improvement ($p=0.025$). The incidence of gout disease flares in the pegloticase every 2 week group was lower than placebo during the last 3 months of the trial ($p=0.007$) while the incidence of gout flares in the pegloticase every 4 weeks dose group was comparable to that of placebo treated patients ($p=0.321$) and was also observed to be higher than placebo during the last 2 months of the study. Additionally, patients receiving pegloticase every 2 or 4 weeks achieved significant improvements in function and pain relative to subjects receiving placebo as assessed by the SF-36 PCS ($p<0.001$ for both treatment group comparisons), HAQ-DI ($p=0.001$ for both treatment group comparisons), pain assessment ($p<0.001$ for the pegloticase every 2 weeks comparison and $p=0.029$ for the pegloticase every 4 weeks comparison), PGA ($p<0.001$ for the pegloticase every 2 weeks comparison and $p=0.001$ for the pegloticase every 4 weeks comparison), and CGA ($p<0.001$ for the pegloticase every 2 weeks comparison and $p=0.003$ for the pegloticase every 4 weeks comparison). However, since a correction for multiplicity was not performed in calculating these secondary endpoints, declaring statistical significance for them using unadjusted p -values may be inappropriate particularly since they were based on pooled data without replication of their results.

6.1 Indication

Treatment of chronic symptomatic gout in patients refractory to conventional therapy

6.1.1 Methods

Efficacy data contained in the submission generated from the two replicate 6-month, multicenter, double-blind, placebo-controlled, parallel group trials in 212 patients with refractory symptomatic gout were reviewed to assess Savient's product application. Analyses of pertinent subgroups were also conducted. All primary and secondary analyses were confirmed by the FDA's statistical reviewer. The design of the common protocol utilized in these trials was discussed in Section 5.3.

6.1.2 Demographics

As summarized in the following tables (Tables 26 and 27), the three treatment groups in the Phase 3 trials were generally well balanced with respect to baseline demographics and gout disease characteristics and history. The subjects who participated in these studies were overwhelmingly Caucasian males and had a mean age of 55 years. These patients were also overweight as evidenced by body mass index (BMI) of 33 which is consistent with the fact that obesity is a risk factor for gout. The majority (62%) of subjects reported that they did not drink alcohol, another risk factor for gout.

Table 26 – Demographic Characteristics of Subjects Enrolled in Combined Phase 3 Studies 405 and 406

	Pegloticase 8 mg q 2 weeks (N=85)	Pegloticase 8 mg q 4 weeks (N=84)	Placebo (N=43)	Total (N=212)
Age				
Mean (SD)	56 (16)	55 (13)	55 (12)	55 (14)
Gender				
Male	68 (80%)	69 (82%)	36 (84%)	173 (82%)
Female	17 (20%)	15 (18%)	7 (16%)	39 (18%)
Race:				
American Indian/Alaskan Native	3 (4%)	2 (2%)	1 (2%)	6 (3%)
Asian	2 (2%)	1 (1%)	0 (0%)	3 (1%)
Hispanic/Latino	13 (15%)	8 (10%)	3 (7%)	24 (11%)
Black	8 (9%)	12 (14%)	7 (16%)	27 (13%)
Pacific Islander/Native Hawaiian	3 (4%)	1 (1%)	1 (2%)	5 (2%)
White	54 (64%)	59 (70%)	30 (70%)	143 (68%)
Other	2 (2%)	1 (1%)	1 (2%)	4 (2%)
Weight (kg)				
Mean (SD)	98 (22)	101 (28)	100 (27)	100 (26)
Height (cm)				
Mean (SD)	173 (10)	175 (11)	176 (11)	174 (11)
BMI (kg/m²)				
Mean (SD)	33 (7)	33 (8)	32 (7)	33 (8)
Alcohol Consumption:				
Yes	33 (39%)	32 (38%)	15 (35%)	80 (38%)
No	52 (61%)	52 (62%)	28 (65%)	132 (62%)

Sponsor's Table 12; p. 49 of ISE

The overall mean duration of disease since the first gout attack was 17 years and the overall mean duration since the first diagnosis of gout was 15 years for the study population. A total of 57% of the subjects had crystal-proven disease. The mean number of gout flares over the last 18 months reported by the three treatment groups was similar (10 attacks per year). The majority of subjects (69%) described their gout flares as multiarticular (e.g., \geq 2-3 joints) and moderate to severe (95%) in nature. Overall, 58% of the total study population had chronic synovitis and/or arthropathy due

to gout and 73% had tophaceous deposits at baseline. A minority of patients (17%) reported a history of gout-related kidney disease with a mean number of renal colic episodes of 0.4 per year. Ninety-five percent of the subjects did not have another arthritis condition that could potentially interfere with study evaluations. Based on these data, the study population that participated in this trial had moderate to severe gout.

Table 27 – Summary of Subjects’ Gout History and Disease Status (Intent-to-Treat [ITT] Population) Who Participated in Combined Phase 3 Studies 405 and 406

	Pegloticase 8 mg q 2 wks (N=85)	Pegloticase 8 mg q 4 wks (N=84)	Placebo (N=43)	Total (N=212)
Number of Years Since First Gout Attack: Mean (SD)	17 (12)	17 (10)	15 (10)	17 (11)
Number of Years Since First Diagnosis of Gout: Mean (SD)	15 (12)	16 (10)	13 (10)	15 (11)
Confirmed Presence of Uric Acid Crystals:				
Yes	48 (57%)	45 (54%)	27 (63%)	120 (57%)
No	37 (44%)	39 (46%)	16 (37%)	92 (43%)
Number of Acute Flares in the Past 18 Months: Mean (SD)	10 (11)	10 (11)	10 (16)	10 (12)
Pattern of Acute Flares:				
Monoarticular (One Joint)	28 (33%)	24 (29%)	12 (29%)	64 (31%)
Oligoarticular (2-3 Joints)	21 (25%)	24 (29%)	19 (46%)	64 (31%)
Polyarticular (> 3 Joints)	35 (42%)	34 (42%)	10 (24%)	79 (38%)
Severity of Acute Flares:				
Mild (Uncomfortable)	7 (8%)	1 (2%)	3 (7%)	11 (5%)
Moderate (Limiting)	24 (29%)	27 (33%)	15 (37%)	66 (32%)
Severe (Crippling)	53 (63%)	54 (66%)	23 (56%)	130 (63%)
Chronic Synovitis/Arthropathy:				
Yes	50 (59%)	47 (56%)	26 (61%)	123 (58%)
No	35 (41%)	37 (44%)	17 (40%)	89 (42%)
History of Gout-Related Kidney Disease:				
Yes	12 (14%)	16 (19%)	7 (16%)	35 (17%)
No	73 (86%)	68 (81%)	36 (84%)	177 (84%)
Tophi:				
Yes	62 (73%)	64 (76%)	29 (67%)	155 (73%)
No	23 (27%)	20 (24%)	14 (33%)	57 (27%)
Surgery for Gout (Excluding Arthrocentesis)				
Yes	13 (15%)	20 (24%)	13 (30%)	46 (22%)
No	72 (85%)	64 (76%)	30 (70%)	166 (78%)
Another Arthritis Condition Potentially Confounding Diagnosis of Gout:				
Yes	5 (6%)	4 (5%)	2 (5%)	11 (5%)
No	80 (94%)	80 (95%)	41 (95%)	201 (95%)
Number of Episodes of Renal Colic in the Past Year: Mean (SD)	0.4 (1.9)	0.4 (2.7)	0.4 (1.6)	0.4 (2.2)

Adapted Sponsor’s Table 14; p.52 of ISE

Since these studies’ protocols specifically targeted hyperuricemic gout patients with documented unresponsiveness and/or hypersensitivity to allopurinol, it is important to

assess how patients qualify for enrollment. A summary of patient eligibility based on prior allopurinol exposure is shown in Table 28 below. Overall 58% of patients reported that they could not use allopurinol either due to a history of allergy or hypersensitivity or unresponsiveness to drug therapy.

Table 28 – Patient Eligibility as Per Allopurinol Treatment History for Enrollment in Phase 3 Studies 405 and 406 (ITT Population)

	Pegloticase 8 mg q 2 weeks (N=85)	Pegloticase 8 mg q 4 weeks (N=84)	Placebo (N=43)	Total (N=212)
Allopurinol Ineffective	16 (19%)	17 (20%)	5 (12%)	38 (18%)
History of Allergy/Hypersensitivity	40 (47%)	28 (33%)	17 (40%)	85 (40%)
Renal Insufficiency	12 (14%)	11 (13%)	10 (23%)	33 (16%)
GI Intolerance	12 (14%)	19 (23%)	6 (14%)	37 (17%)
Other	5 (6%)	9 (11%)	5 (12%)	19 (9%)

Adapted Sponsor's Table 7; p. 50 Clinical Study 405 Report and Table 7; p. 51 Clinical Study 406 Report

The following table (Table 29) summarizes the co-morbid medical conditions reported by 10% or more of the subjects who participated in the Phase 3 trials. Overall, large percentages of the subjects in these studies suffered from a variety of diseases commonly associated with gout such as hypertension (71%), renal failure (30% for the combined terms renal failure and chronic renal failure), diabetes mellitus (22% for the combined terms insulin or non-insulin dependent) and obesity (17%).

Table 39 – Tabular Summary of Comorbid Medical Conditions Reported by > 10% of Subjects Who Participated in Studies 405 and 406 via MedDRA Body System (ITT Population)

MedDRA Body System Preferred Term	Pegloticase 8 mg q 2 wks (N=85)	Pegloticase 8 mg q 4 wks (N=84)	Placebo (N=43)	Total (N=212)
Vascular Disorders:	61 (72%)	60 (71%)	32 (74%)	153 (73%)
Hypertension	61 (72%)	60 (71%)	30 (70%)	151 (71%)
Metabolism and Nutrition Disorders:	53 (62%)	55 (65%)	24 (56%)	132 (62%)
Hypercholesterolemia	21 (25%)	16 (19%)	7 (16%)	44 (21%)
Hyperlipidemia	15 (18%)	17 (20%)	9 (21%)	41 (19%)
Obesity	14 (16%)	14 (17%)	7 (16%)	35 (17%)
Diabetes Mellitus	11 (13%)	9 (11%)	7 (16%)	27 (13%)
Diabetes Mellitus Non-Insulin Dependent	12 (14%)	7 (8%)	1 (2%)	20 (9%)
Musculoskel. and Connective Tissue Dis.:	51 (60%)	45 (54%)	25 (58%)	121 (57%)
Immune System Disorders:	45 (53%)	41 (49%)	23 (53%)	109 (51%)
Drug Hypersensitivity	41 (48%)	32 (38%)	18 (42%)	91 (43%)
Gastrointestinal Disorders:	42 (49%)	39 (46%)	18 (42%)	99 (47%)
Renal and Urinary Disorders:	36 (42%)	37 (44%)	18 (42%)	91 (43%)
Renal Failure	19 (22%)	11 (13%)	5 (12%)	35 (17%)
Renal Failure Chronic	7 (8%)	14 (17%)	7 (16%)	28 (13%)
Nephrolithiasis	8 (9%)	6 (7%)	4 (9%)	18 (8%)
Glomerulonephritis	0 (0%)	2 (2%)	1 (2%)	3 (1%)
Cardiac Disorders:	28 (33%)	23 (27%)	14 (33%)	65 (31%)
Coronary Artery Disease	8 (9%)	9 (11%)	6 (14%)	23 (11%)
Atrial Fibrillation	9 (11%)	3 (4%)	4 (9%)	16 (8%)
Cardiac Failure Congestive	5 (6%)	5 (6%)	3 (7%)	13 (6%)
Cardiomyopathy	3 (4%)	4 (5%)	2 (5%)	9 (4%)
Bundle Branch Block Right	4 (5%)	0 (0%)	2 (5%)	6 (3%)
Angina Pectoris	1 (2%)	4 (5%)	0 (0%)	5 (2%)
Arrhythmia	4 (5%)	1 (1%)	0 (0%)	5 (2%)
Arteriosclerosis Coronary Artery	1 (2%)	1 (2%)	0 (0%)	2 (2%)
Nervous System Disorders:	24 (28%)	26 (31%)	13 (30%)	63 (30%)
Respirat., Thoracic and Mediastinal Dis.:	21 (25%)	27 (32%)	15 (35%)	63 (30%)
Psychiatric Disorders:	19 (22%)	24 (29%)	14 (33%)	57 (27%)
Investigations:	22 (26%)	19 (23%)	10 (23%)	51 (24%)
Gen. Disorders and Administ. Site Cond.:	25 (29%)	12 (14%)	10(23%)	47 (22%)
Skin and Subcutaneous Tissue Disorders:	19 (22%)	15 (18%)	9 (21%)	43 (20%)
Endocrine Disorders:	15 (18%)	12 (14%)	4 (9%)	31 (15%)
Infections and Infestations:	17 (20%)	12 (14%)	2 (5%)	31 (15%)
Blood and Lymphatic System Disorders:	13 (15%)	8 (10%)	7 (16%)	28 (13%)
Eye Disorders:	11 (13%)	13 (15%)	3 (7%)	27 (13%)

Adapted Sponsor's Table A6.1; p. 275-296 of IES.

Table 30 summarizes all of the cardiovascular-related conditions reported by subjects in Studies 405 and 406. The majority of patients (84%) who participated in these studies also had pre-existing cardiovascular disease including coronary artery disease (18%), cardiac arrhythmias (16%), and cardiac failure/left ventricular dysfunction (12%).

Table 30 – Tabular Summary of Number (%) of Patient Reported Cardiovascular-Related Conditions in Subjects Who Participated in Studies 405 and 406

Medical Condition	Pegloticase 8 mg q 2 wks (N=85)	Pegloticase 8 mg q 4 wks (N=84)	Placebo (N=43)	Total (N=212)
At least one of the following cardiovascular conditions:	73 (86%)	71 (85%)	35 (81%)	179 (84%)
Cardiac Arrhythmias	19 (22%)	8 (10%)	7 (16%)	34 (16%)
Cardiac Failure/LV Dysfunction	12 (14%)	8 (10%)	6 (14%)	26 (12%)
Cerebrovascular Disease	4 (5%)	3 (4%)	1 (2%)	8 (4%)
Coronary Disease	14 (17%)	16 (19%)	9 (21%)	39 (18%)
Diabetes	24 (28%)	18 (21%)	8 (19%)	50 (24%)
Dyslipidemia	42 (49%)	41 (49%)	20 (47%)	103 (49%)
Hypertension	62 (73%)	60 (71%)	31 (72%)	153 (72%)
Vascular Disease, Peripheral	7 (8%)	6 (7%)	3 (7%)	16 (8%)
Venous Thromboembolic Disease	3 (4%)	2 (2%)	2 (5%)	7 (4%)
Obesity (BMI ≥ 30)	50 (59%)	55 (66%)	24 (56%)	129 (61%)
Chronic Kidney Disease	26 (31%)	25 (30%)	9 (21%)	60 (28%)
Sleep Apnea	8 (9%)	9 (11%)	6 (14%)	23 (11%)

LV = Left ventricular; BMI = body mass index
 Adapted Sponsor's Table 20; p. 58 of updated ISS

6.1.3 Subject Disposition

A tabular summary of subjects' disposition from the pooled pivotal studies is shown in Table 31:

Table 31 – Subject Disposition for Combined Studies 405 and 406

	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Placebo (N=43)	Total (N=212)
Number of Patients Randomized	90	89	46	225
Number of Patients Treated (ITT)	85	84	43	212
Number of Patients with Evaluable Tophi	62	64	29	155
Number of Patients that Completed Study 405 or 406:	59 (69%)	59 (70%)	39 (91%)	157 (74%)
Continued on OLE	57 (97%)	56 (95%)	38 (97%)	151 (96%)
Did Not Continue on OLE	2 (3%)	3 (5%)	1 (3%)	6 (4%)
Number of Patients Withdrawn Prematurely Before Week 24 from Study 405 or 406:	26 (31%)	25 (30%)	4 (9%)	55 (26%)
Non-compliance	0 (0%)	1 (1%)	0 (0%)	1 (0.5%)
Adverse Event ¹	16 (19%)	17 (20%)	1 (2%)	34 (16%)
Withdrew Consent	7 (8%)	6 (7%)	1 (2%)	14 (7%)
Lost to Follow-Up	0 (0%)	0 (0%)	2 (5%)	2 (1%)
Protocol Violation	1 (1%)	0 (0%)	0 (0%)	1 (0.5%)
Death	2 (2%)	1 (1%)	0 (0%)	3 (1%)

OLE = Open Label Extension; ITT = Intent to Treat Population

¹Note: Based on review of patient narratives this includes the final disposition of Subject 308-003 pegloticase q 2 weeks and Subject 319-004 pegloticase q 4 weeks who discontinued treatment due to infusion reaction adverse events instead of withdrawal of consent and lost to follow up.

Adapted Sponsor's Table 11; p. 48 from ISE

A total of 225 patients were randomized in the combined studies, out of which 212 (94%) were considered the intent to treat (ITT) population on which all the primary and secondary efficacy analyses were conducted. A total of 155 (73%) patients had evaluable tophi. The overall rate of study completion was 74% with more placebo-treated patients (91%) completing the study as compared to patients randomized to the pegloticase every 2 weeks (69%) and every 4 weeks (70%) treatment groups. A majority (96%) of the patients who completed the studies went on to participate in the open label extension (Study 407). The major reasons for discontinuation were similar for the two pegloticase treatment groups, but differed from that of the placebo group. The most common reason for early study withdrawal was adverse events in both the pegloticase every 2 weeks (19%) and pegloticase every 4 weeks (20%) treatment groups which was nearly nine times the rate seen in the placebo group (2%). More patients also withdrew earlier from the study due to withdrawal of consent in the pegloticase every 2 weeks group (8%) and pegloticase every 4 weeks group (7%) as compared to the placebo group (2%). The major reason for early withdrawal for placebo treated patients was lost to follow-up (5%) as compared to no patients withdrawing for this reason from the pegloticase treatment groups. Note that the subjects who withdrew from the study before month 6 were, by protocol definition, considered nonresponders for the primary efficacy analysis in the ITT group. Among patients who received at least one dose of study medication there were no deaths in the placebo population, but a total of 3 deaths

occurred in patients treated with pegloticase (2 subjects in the every 2 weeks group and 1 subject in the every 4 weeks group). One death occurred in a patient randomized to placebo; however, this patient died before receiving study medication. Receiving at least one dose of study medication was required, by protocol definition, for inclusion in the ITT group thus this placebo patient was not included in the ITT analyses.

6.1.4 Analysis of Primary Endpoint(s)

Studies 405 and 406 were adequate and well controlled trials by virtue of their double-blind, randomized, controlled design. These two trials shared a common protocol, which was intended to evaluate the safety and efficacy of pegloticase as a treatment of chronic symptomatic gout in patients refractory to conventional therapy. Although gout is a fairly common disease affecting approximately 5 million people in this country, refractory gout occurs in a very small subgroup of these patients (e.g., target population of less than 100,000) which limits the clinical use of pegloticase. The use of plasma uric acid (PUA) with a limit of < 6 mg/dL as a surrogate endpoint in these studies is acceptable since uric acid concentrations higher than this are associated with the clinical signs and symptoms of gout while PUA below this level are thought to be clinically associated with resorption of gouty tophi and the prevention of gout flares. The latter is a validated surrogate endpoint that has been used to demonstrate the efficacy of other urate lowering agents. It was appropriate for the Applicant to employ a placebo-controlled study design for the Phase 3 trials to assess pegloticase's efficacy in order to demonstrate a clinical benefit associated with its use as well as to determine the product's risk/benefit ratio.

The primary endpoint for both of the Phase 3 trials was the proportion of subjects who maintained a plasma uric acid (PUA) concentration < 6 mg/dL for at least 80% of the time during Months 3 and 6 versus placebo. For statistical purposes, patients who were able to normalize their PUA to < 6 mg/dL and maintained it for at least 80% of the time during Months 3 and 6 were classified as "responders." For the primary analyses, patients who withdrew from the study before Month 6 were imputed as non-responders. Intermittent missing pre-dose PUA values were imputed with the baseline PUA level for that subject. Other intermittent missing PUA values were replaced by the average of the scores at the immediately previous and the next available time points for that subject.

Table 32 – Primary Efficacy Endpoint: PUA < 6mg/dL for at Least 80% of the Time in Months 3 and 6 Combined For Studies 405 and 406 (ITT Population)

Treatment Group	Number (%) of Subjects Who Met Response Criteria	95% Confidence Interval ¹	P-Value ²
Study 405			
Pegloticase q 2 Wks (N= 43)	20 (47%)	[32%, 61%]	p<0.001
Pegloticase q 4 Wks (N=41)	8 (20%)	[7%, 32%]	p=0.044
Placebo (N=20)	0 (0%)		
Study 406			
Pegloticase q 2 Wks (N=42)	16 (38%)	[23%, 53%]	p<0.001
Pegloticase q 4 Wks (N=43)	21 (49%)	[34%, 64%]	p<0.001
Placebo (N=23)	0 (0%)		

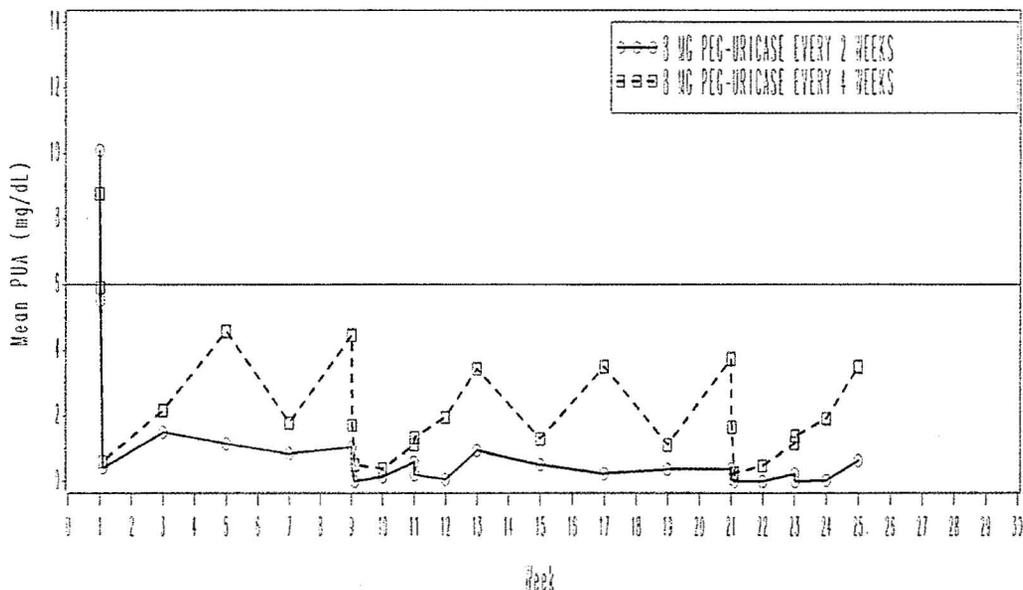
¹95% confidence interval for differences in responder rate between corresponding pegloticase groups vs. placebo

²P-value using Fisher's exact test to compare corresponding pegloticase group vs. placebo.

Adapted Sponsor's Table 11; p. 58 and Table 11; p. 57 from the clinical reports for Studies 405 and 406, respectively.

As shown in Table 32, for both studies, a greater proportion of patients achieved the primary endpoint in both the pegloticase every 2 weeks (47% and 38% in studies 405 and 406, respectively) and every 4 weeks (20% and 49% in Studies 405 and 406, respectively) treatment groups as compared to placebo (0% and 0% in each study). The differences between each of the treatment groups and the placebo groups were statistically significant in both Study 405 (p < 0.001 for pegloticase every 2 weeks versus placebo and p = 0.044 for pegloticase every 4 weeks versus placebo) and Study 406 (p < 0.001 for each pegloticase treatment group versus placebo). As noted above (see efficacy summary), the statistical reviewer concluded that even though there was no prespecified multiplicity adjustment, considering the results of 405 and 406 together, that efficacy was demonstrated for both pegloticase treatment arms. Additional support for the validity of these findings may be seen in the following Figures 1 and 2, which graphically depict the mean PUA concentration profile for responders and nonresponders over time for the pooled studies by treatment group. These figures graphically illustrate a rapid initial decrease in mean PUA concentration following the administration of the first dose of pegloticase. This response is maintained throughout the remainder of the study by patients in both groups who meet the prespecified response criteria as shown in Fig. 1. Note that the placebo group does not appear in Figure 5 as there were no responders in the placebo groups in either study. In contrast, patients who were classified as non-responders had an initial drop in plasma uric acid that was subsequently lost (Figure 6).

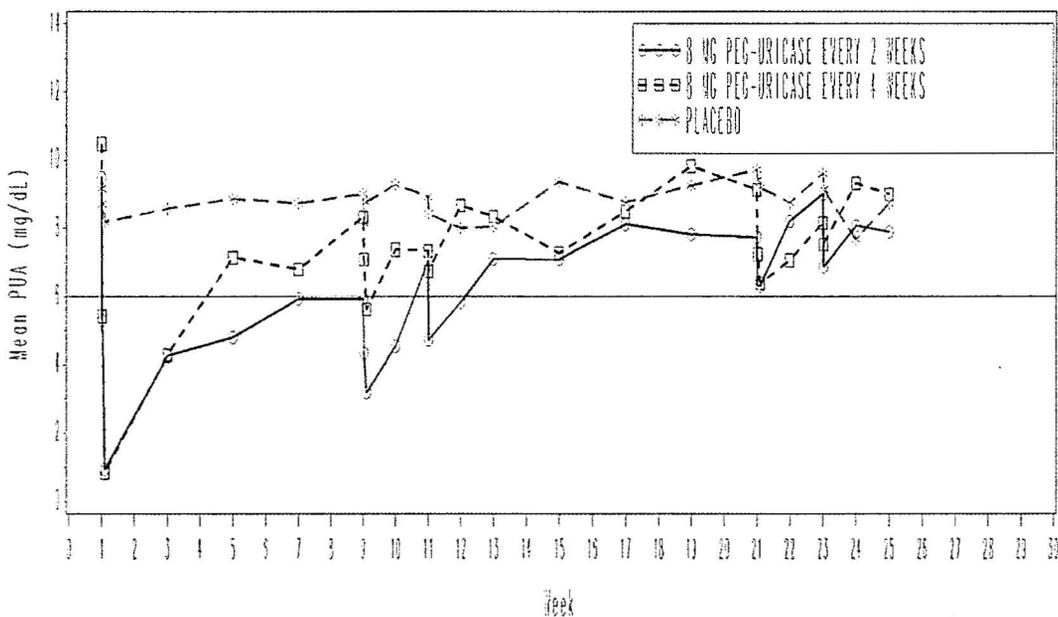
Figure 5 – Mean PUA Concentration for PUA Responders for Pooled Studies 405 and 406 (ITT Population)



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Note: PUA levels which were less than the lower limit of quantitation were interpreted as 0 mg/dL. Sponsor's Figure 3; p. 62 of ISE

Figure 6 – Mean PUA Concentration for PUA Non-Responders for Pooled Studies 405 and 406 (ITT Population)



Note: PUA levels which were less than the lower limit of quantitation were interpreted as 0 mg/dL. Sponsor's Figure 3; p. 62 of ISE

6.1.5 Analysis of Secondary Endpoints(s)

A number of secondary variables were evaluated, as specified in the protocol, based on pooled efficacy data generated from the pivotal Studies 405 and 406. Many of these secondary endpoints were assessed in order to determine if a clinical benefit (e.g., resolution of tophi, swollen/tender joint counts, and frequency of gout flares) was associated with the administration of pegloticase. Trends within each study in the secondary endpoints were generally similar to the overall results. No multiplicity correction was planned for in the protocol or implemented here for the secondary endpoints. Due to multiplicity concerns, declaring statistical significance of these secondary endpoints using unadjusted p-values may be inappropriate. The remaining discussion will highlight secondary endpoints of interest.

Mean PUA

As listed in the following table (Table 33), the mean baseline PUA levels for the pooled patients treated with pegloticase every 2 weeks, pegloticase every 4 weeks and placebo were between 9 and 10 mg/dL. Both the pegloticase every 2 weeks and every 4 weeks treatment groups had lower mean PUA levels during Month 3, Month 6, and combined Months 3 and 6 as compared to placebo-treated patients during these time intervals ($p < 0.001$ for all comparisons). The mean PUAs for the pegloticase every 2 weeks treatment group were numerically lower than those of the pegloticase every 4 weeks treatment group at each of these prespecified time intervals.

Table 33 – Mean PUA¹ at Month 3, Month 6, and Combined Months 3 and 6 by Treatment Group for Pooled Studies 405 and 406 (ITT Population)

	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Placebo (n=43)
Baseline PUA:			
Number of Subjects	84	83	42
Mean (mg/dL) (SD)	9.8 (3.0)	9.9 (3.1)	9.2 (2.8)
Month 3:			
Number of Subjects	73	74	43
Mean (mg/dL) (SD)	3.0 (3.3)	5.1 (4.0)	8.5 (2.3)
P-Value²	<0.001	<0.001	
Month 6:			
Number of Subjects	61	60	40
Mean (mg/dL) (SD)	3.2 (4.1)	4.9 (3.8)	8.8 (2.3)
P-Value²	<0.001	<0.001	
Months 3 and 6 Combined:			
Number of Subjects	61	60	40
Mean (mg/dL) (SD)	2.9 (3.6)	4.8 (3.7)	8.6 (2.0)
P-Value²	<0.001	<0.001	

¹Mean PUA: Individual subject mean PUA was defined and calculated as the area under the PUA time curve for each subject divided by the corresponding time interval.

²P-value based on two sample t-test to compare corresponding pegloticase group vs. placebo.

Adapted Sponsor's Table 24; p. 67 of ISE.

Tophus Assessments

Patients with tophaceous deposits at baseline had standardized digital photographs of their bilateral hands and feet and up to 2 other sites taken at Weeks 13, 19 and 25. These serial photographs were read by a blinded central reader who assessed them for the size of each target tophus utilizing a validated image analysis software system (MedStudio®). Change from baseline for each measurable tophus (defined as ≥ 5 mm at baseline in longest dimension with distinguishable borders) was to be scored via a pre-specified 6-point categorical system (e.g., complete response, marked response, partial response, stable disease, progressive disease, and unable to evaluate). Up to 2 unmeasured tophi (e.g., due to location, shape or other factors) were to have been also followed over the course of the study and semi-quantitatively assessed utilizing another 5-point categorical system (e.g., complete response, improved, stable disease, progressive disease, and unable to evaluate). An overall tophus response for each subject based on the best response among all tophi for that subject at a given visit was also determined.

At baseline, 155 subjects in Studies 405 and 406 combined had at least one tophus: 62 subjects in the pegloticase every 2 weeks groups, 64 in the pegloticase every 4 weeks groups, and 29 in the placebo groups. This subset of subjects, the "tophus-evaluable population" is used for the analysis of tophus response while those without tophi at baseline are excluded. Treatment assignment within this subgroup is appropriately

random (and thus differences between treatment groups in outcome can be reliably attributed to a treatment effect and not an imbalance in covariates) since the randomizations for each study were stratified by the presence or absence of tophi at baseline. For the pooled data from Studies 405 and 406 at Weeks 13, 19 and 25, significantly higher proportions of patients treated with pegloticase every 2 weeks achieved a complete tophus response compared to placebo-treated patients (p-value \leq 0.002; refer to Table 34). In addition, a significantly greater proportion of patients receiving pegloticase every 2 weeks had a tophus response based on the ordinal (ranked) scores of complete response, partial response, stable disease, and progression of disease compared to placebo-treated patients. Analyses of data for the same outcomes for the pegloticase every 4 week group were not as robust with only a significantly higher proportion of subjects achieving a categorical response at Week 19 as compared to placebo (p=0.004), while the other comparative analyses at the remaining time points showed only positive trends. The overall tophus response analyses from each of the studies independently were similar to each other and to the pooled results.

Table 34 – Assessment of Patient's Overall Tophus Response for Pooled Studies 405 and 406 (Tophus-Evaluable ITT Population)

	Pegloticase q 2 wks (N=62)	Pegloticase q 4 wks (N=64)	Placebo (N=29)
Week 13			
# of Subjects with Evaluable Tophi	46	48	25
Complete Response	10 (22%)	4 (8%)	0 (0%)
Partial Response	11 (24%)	9 (19%)	4 (16%)
Stable Disease	20 (44%)	28 (58%)	13 (52%)
Progressive Disease	5 (11%)	7 (15%)	8 (32%)
P-Value¹	0.002	0.068	
P-Value²	0.011	0.292	
Week 19			
# of Subjects with Evaluable Tophi	44	43	26
Complete Response	16 (36%)	12 (28%)	2 (8%)
Partial Response	11 (25%)	9 (21%)	3 (12%)
Stable Disease	12 (27%)	19 (44%)	14 (54%)
Progressive Disease	5 (11%)	3 (7%)	7 (27%)
P-Value¹	0.001	0.004	
P-value²	0.010	0.063	
Week 25			
# of Subjects with Evaluable Tophi	40	42	25
Complete Response	18 (45%)	11 (26%)	2 (8%)
Partial Response	8 (20%)	10 (24%)	6 (24%)
Stable Disease	10 (25%)	16 (38%)	11 (44%)
Progressive Disease	4 (10%)	5 (12%)	6 (24%)
P-Value¹	0.002	0.061	
P-value²	0.002	0.109	

¹An ordinal score was assigned for each response (e.g., Complete Response = 1, Partial Response = 2, Stable Disease = 3, and Progressive Disease = 4) and used to compute the P-value, which is based on two sample Wilcoxon test to compare corresponding pegloticase groups vs. placebo.

²P-value based on Fisher's exact test to compare percent of Complete Response between corresponding pegloticase groups vs. placebo.

Adapted Sponsor's Table 31; p. 74 from ISE

For purposes of analyses for Studies 405 and 406, the time to tophus resolution was specified as the earliest assessment time at which one of the target tophi showed a complete resolution and was based on the tophus-evaluable population. The following table (Table 35) shows a total of 21 subjects from the pegloticase every 2 weeks group, 12 subjects from the pegloticase every 4 weeks group, and 2 subjects from the placebo group who demonstrated resolution of a tophus. The median time to tophus resolution was similar for all three treatment groups: 124 days for the pegloticase every 2 weeks group, 128 days for the pegloticase every 4 weeks group and 137 days for the placebo group.

Table 35 – Time to Tophus Resolution for Subjects in Pooled Studies 405 and 406 (Tophus-Evaluable ITT Population)

	Pegloticase q 2 wks (N=62)	Pegloticase q 4 wks (N=64)	Placebo (n=29)
Time to Tophus Resolution¹ (Days)			
Number of Subjects with Resolution of 1 Tophi:	21	12	2
Median	124 days	128 days	137 days
Range (min, max)	(75, 192)	(85, 147)	(127, 146)

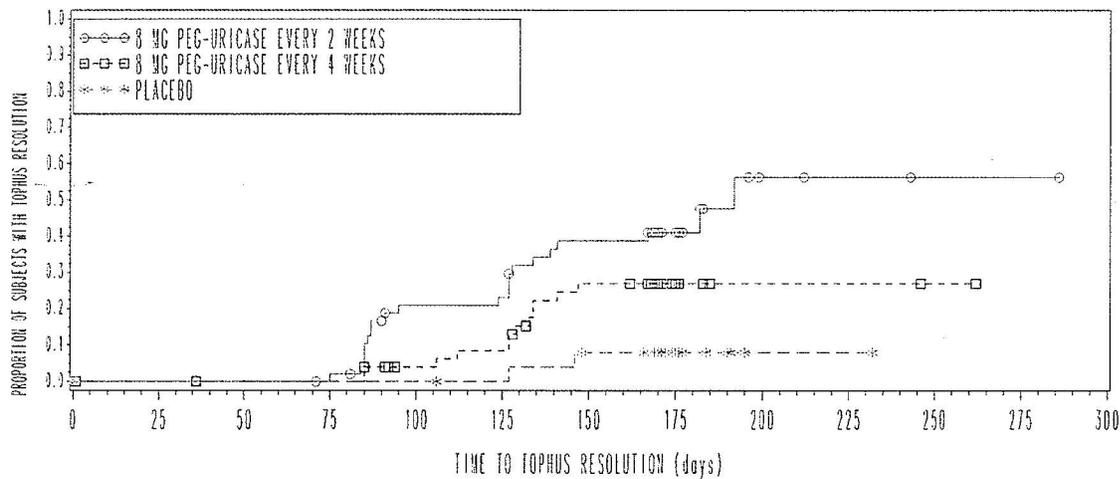
Note: Subjects without complete response (CR) at any visit were excluded from the analysis.

¹Time is calculated as [Visit date of CR – first dose date +1]

Adapted Sponsor’s Table 36; p. 83 of ISE.

Figure 7 below shows a Kaplan-Meier plot of the time to complete resolution of tophus in the three treatment groups.

Figure 7 – Kaplan-Meier Plot of Time to Tophus Resolution for Patients Participating in Pooled Studies 405 and 406 (Tophus Evaluable ITT Population)



Note: Censored subjects are represented with symbols.
 Sponsor’s Fig. 5; p. 84 of the ISE.

Patient Reported Outcomes

The Short Form Health Status Survey (SF-36) and the Health Assessment Questionnaire – Disability Index (HAQ-DI) were the two patient reported outcome measures used to evaluate the clinical consequences of pegloticase therapy. Although 8 domains of the SF-36 were assessed in Studies 405 and 406, only the results from the physical component, mental component and arthritis-specific health index (ASHI)

summaries will be presented below. Average scores in an age-corrected, healthy normal population for males and females combined for the Physical Component Summary (PCS) and the Mental Component Summary (MCS) were estimated to be 47 and 52, respectively. Table 36 below summarizes the analysis of the results of the responder analyses of the mean PCS scores for the pooled Studies 405 and 406. The baseline PCS scores for all treatment groups were numerically lower than those expected in the general U.S. population. However, there was a baseline imbalance in the PCS scores between treatment arms with higher scores in the pegloticase every 2 week group (35.2) than in the placebo group (31.0). At the Week 25 time point, both pegloticase treatment groups showed significantly greater change over baseline than the placebo group (p<0.001).

Table 36 – Tabular Summary of the SF-36 Physical Component Summary (PCS) Score for Pooled Studies 405 and 406 (ITT Population)

	Pegloticase 8 mg every 2 weeks (N=85)	Pegloticase 8 mg every 4 weeks (N=84)	Placebo (N=43)
Baseline Visit:			
Number of Subjects	83	84	43
Mean (SD)	35.2 (10.9)	33.3 (9.8)	31.0 (11.1)
Week 25 :			
Number of Subjects	61	63	38
Mean (SD)	40.4 (11.3)	39.4 (10.6)	30.2 (11.9)
Change From Baseline to Week 25:			
Number of Subjects	59	63	38
Mean (SD)	6.4 (8.6)	5.6 (8.7)	-0.87 (8.3)
P-value¹	<0.001	<0.001	--

¹P-value from the two sample t-test that is used to compare means of the corresponding treatment group vs. placebo. Adapted Sponsor's Table 37; p. 91 of the ISE.

The baseline MCS scores for all three treatment groups were similar to each other (range: 47.9 to 49.4) but numerically lower than that expected in the age-matched U.S. population (52) as shown in Table 37. No differences between study arms were seen in the change from baseline to Week 25 in the MCS scores.

Table 37 - Tabular Summary of SF-36 Mental Component Summary (MCS) Score for Pooled Studies 405 and 406 (ITT Population)

	Pegloticase q 2 weeks (N=85)	Pegloticase q 4 weeks (N=84)	Placebo (N=43)
Baseline Visit			
Number	83	84	43
Mean (SD)	49.4 (12.7)	45.4 (11.8)	47.9 (12.0)
P-value ¹	0.523	0.259	
Week 25			
Number	61	63	38
Mean (SD)	52.7 (10.1)	46.8 (12.5)	51.3 (10.4)
P-value ¹	0.529	0.062	
Change From Baseline to Week 25			
Number	59	63	38
Mean (SD)	4.2 (10.5)	0.67 (10.2)	2.4 (8.8)
P-value ¹	0.385	0.383	--

¹P-value from the two sample t-test that is used to compare means of the corresponding treatment group vs. placebo. Adapted Sponsor's Table 40; p. 95 of the ISE.

The HAQ-DI assesses disease-related physical function. Scores for this instrument range from 0 to 3 with higher scores indicative of worse physical function. The mean baseline HAQ-DI scores for all three treatment groups were similar and ranged from 1.1 to 1.24 indicating moderate levels of physical impairment (Table 38). At the week 25 time point both pegloticase treatment groups showed significantly greater improvement over baseline in HAQ-DI than the placebo group (p = 0.001).

Table 38 – Health Assessment Questionnaire – Disability Index (HAQ-DI): Physical Function Component Analyses for Pooled Studies 405 and 406 (ITT Population)

	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Placebo (N=43)
Baseline Visit:			
Number	83	84	43
Mean (SD)	1.1 (0.86)	1.21 (0.86)	1.24 (0.95)
P-value ¹	0.418	0.858	
Week 25:			
Number	62	63	38
Mean (SD)	0.84 (0.82)	0.85 (0.81)	1.31 (0.91)
P-value ¹	0.010	0.010	
Change From Baseline to Week 25:			
Number	60	63	38
Mean (SD)	-0.33 (0.65)	-0.25 (0.54)	0.08 (0.35)
P-value ¹	0.001	0.001	--

Note: Scores range from 0 (best) to 3 (worst) and were calculated according to statistical analysis plan (SAP).

¹P-value from the two sample t-test that is used to compare means of the corresponding treatment group vs. placebo. Adapted Sponsor's Table 46; p. 106 of the ISE.

Pain assessment is a component of the HAQ. Pain was evaluated by patient assessment using a 100 mm visual analogue scale (VAS) where no pain equals a zero score and severe pain equals a 100. Table 39 below summarizes the results of the HAQ assessment of pain for the pooled phase 3 studies. Mean baseline HAQ pain scores were within a comparable range (i.e., 44.2 to 53.9) for all 3 treatment groups. At the Week 25 time point, mean pain scores showed a significant decrease for both pegloticase treatment groups but had increased in the placebo group.

Table 39 – HAQ Assessment of Pain for Subjects Who Participated in Pooled Studies 405 and 406 (ITT Population)

	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Placebo (N=43)
Baseline Visit:			
Number of Subjects	84	84	43
Mean (SD)	44.2 (28.7)	45.1 (27.0)	53.9 (28.0)
P-value ¹	0.066	0.087	
Week 25:			
Number of Subjects	62	63	37
Mean (SD)	28.4 (25.8)	33.1 (27.9)	57.2 (27.6)
P-value ¹	<0.001	<0.001	
Change From Baseline to Week 25:			
Number of Subjects	61	63	37
Mean (SD)	-19.4 (29.5)	-9.33 (25.8)	2.95 (28.3)
P-value ¹	<0.001	0.029	--

Note: Values range from 0 to 100, where 0 = no pain, and 100 = severe pain.

¹P-value unadjusted for multiple comparisons from the two sample t-test that is used to compare means of the corresponding treatment group vs. placebo.

Adapted from Sponsor's Table 53; p. 113 of ISE.

The Patient Global Assessment (PGA) of the HAQ is also scored by subjects using a 100-mm VAS scale scored where increasing scores are indicative of poorer function. (Note: Spanish speaking patients who participated in this study were not included in the HAQ-PGA assessment since this scale is not included in the validated Spanish HAQ questionnaire.) The following table (Table 40) shows that the baseline HAQ-PGA scores ranged from a low of 42.4 for the pegloticase every 2 weeks group to a high of 51.6 for the placebo group. At the Week 25 time point, mean PGA scores showed a significant decrease for both pegloticase treatment groups consistent with an improvement in PGA but had increased (worsened PGA) in the placebo group.

Table 40– HAQ Patient Global Assessment (PGA) for Subjects Who Participated in Pooled Studies 405 and 406 (ITT Population)

	Pegloticase q 2 weeks (N=85)	Pegloticase q 4 weeks (N=84)	Placebo (N=43)
Baseline Visit			
Number	73	78	40
Mean (SD)	42.4 (24.8)	49.8 (24.9)	51.6 (24.9)
P-value ¹	0.064	0.714	
Week 25			
Number	52	58	35
Mean (SD)	27.1 (22.6)	34.9 (24.7)	53.4 (25.5)
P-value ¹	<0.001	0.001	
Change From Baseline to Week 25			
Number	51	58	35
Mean (SD)	-17.5 (24.9)	-13.6 (25.5)	4.23 (20.2)
P-value ¹	<0.001	0.001	--

Note: Values range from 0 to 100, where 0 = very well, and 100 = very poor.

¹P-value from the two sample t-test that is used to compare means of the corresponding treatment group vs. placebo.

Adapted Sponsor's Table 56; p. 117 of the ISE.

Number of Swollen and Tender Joints

The arthritic manifestations of gout disease activity were evaluated by conducting swollen and tender joint counts at baseline, Weeks 13, 19 and 25. Table 41 shows that patients had multiple tender and swollen joints at baseline. At Week 25, patients in the pegloticase every 2 week and every 4 week treatment groups showed a greater decrease than placebo in tender joints, in swollen joints and in the number of joints that were either tender or swollen.

Table 41 – Tabular Summary of Analyses of Number of Swollen or Tender Joints of Subjects Who Participated in Pooled Studies 405 and 406 (ITT Population)

	Pegloticase q 2 weeks (N=85)	Pegloticase q 4 weeks (N=84)	Placebo (N=43)
Baseline Visit:			
Number of Subjects	84	83	43
Mean (SD)	20.5 (22.1)	21.1 (21.3)	27.3 (26.5)
P-value[†]	0.130	0.159	
Week 25:			
Number of Subjects	61	63	38
Mean (SD)	7.1 (12.1)	7.8 (11.3)	23.3 (26.8)
P-value[†]	<0.001	<0.001	
Change From Baseline to Week 25:			
Number of Subjects	60	62	38
Mean (SD)	-14.9 (20.1)	-12.3 (17.2)	-2.9 (23.8)
P-value[†]	0.009	0.025	

[†]P-value from the two sample t-test that is used to compare means of the corresponding treatment group vs. placebo. Adapted Sponsor's Table 59; p. 121 from ISE.

A clinician's global assessment (CGA) of gout disease activity was included as part of the joint evaluations. The CGA was assessed via a 100 mm VAS with higher scores indicating a bad state. The following table (Table 42) shows that the baseline mean CGA scores were similar between the 3 treatment groups and indicated moderately severe disease. At the Week 25 time point, the pegloticase every 2 weeks group and the pegloticase every 4 weeks treatment group showed a significantly greater decrease in PGA scores than the placebo group ($p < 0.001$ and $p=0.003$, respectively).

Table 42 – Tabular Summary of Analyses of Clinician’s Global Assessment (CGA) of Subjects Who Participated in Pooled Studies 405 and 406 (ITT Population)

	Pegloticase 8 mg every 2 weeks (N=85)	Pegloticase 8 mg every 4 weeks (N=84)	Placebo (N=43)
Baseline Visit:			
Number	84	83	43
Mean (SD)	47.6 (28.3)	49.7 (28.0)	52.6 (28.8)
P-value ¹	0.353	0.589	
Week 25:			
Number	61	63	38
Mean (SD)	16.5 (19.5)	21.3 (22.2)	43.8 (32.1)
P-value ¹	<0.001	<0.001	
Change From Baseline to Week 25:			
Number	60	62	38
Mean (SD)	-33.9 (25.7)	-26.2 (31.2)	-8.9 (20.3)
P-value ¹	<0.001	0.003	--

Note: VAS score ranging from 0 to 100, where 0 = very good to 100 = very bad. This is part of the clinical tender/swollen joint count assessment.

¹P-value from the two sample t-test that is used to compare means of the corresponding treatment group vs. placebo. Adapted Sponsor’s Table 63; p. 127 from ISE.

Gout Flares

Treatment of gout patients with urate-lowering therapies is associated with an increased risk of gout flare. Despite prophylactic therapy it was expected that some patients may experience gout flares due to the expected fluctuations in PUA levels over the course of Studies 405 and 406 as a result of pegloticase’s biological activity. Data regarding these events was analyzed as a secondary endpoint. The incidence and frequency of gout flares reported by the pooled subjects from Studies 405 and 406 during the Months 1 to 3 and Months 4 to 6 were compared by treatment group. Table 43 summarizes the flare incidence for these time intervals. A significantly higher proportion of patients in the pegloticase every 2 weeks (75%) and every 4 weeks (81%) treatment groups experienced flares during Months 1 to 3 as compared to placebo treated patients (54%) (p = 0.016 and p = 0.002, respectively). Over the second half of these studies during Months 4 to 6, the opposite was observed with a higher proportion of placebo patients (67%) experiencing gout flares as compared to patients treated with pegloticase every 2 weeks (41%) and pegloticase every 4 weeks (57%). The incidence of flares during Months 4 to 6 for the pegloticase every 2 week group was significantly lower as compared to placebo (p=0.007) but was comparable to that of the pegloticase every 4 weeks group and placebo (p=0.321).

Table 43 – Tabular Summary of Flare Incidence over the Course of Pooled Studies 405 and 406

	Pegloticase 8 mg every 2 weeks (N=85)	Pegloticase 8 mg every 4 weeks (N=84)	Placebo (N=43)
Month 1 to Month 3:			
n/N (%)	64/85 (75%)	68/84 (81%)	23/43 (54%)
P-value¹	0.016	0.002	
Month 4 to Month 6:			
n/N (%)	28/69 (41%)	39/69 (57%)	29/43 (67%)
P-value¹	0.007	0.321	

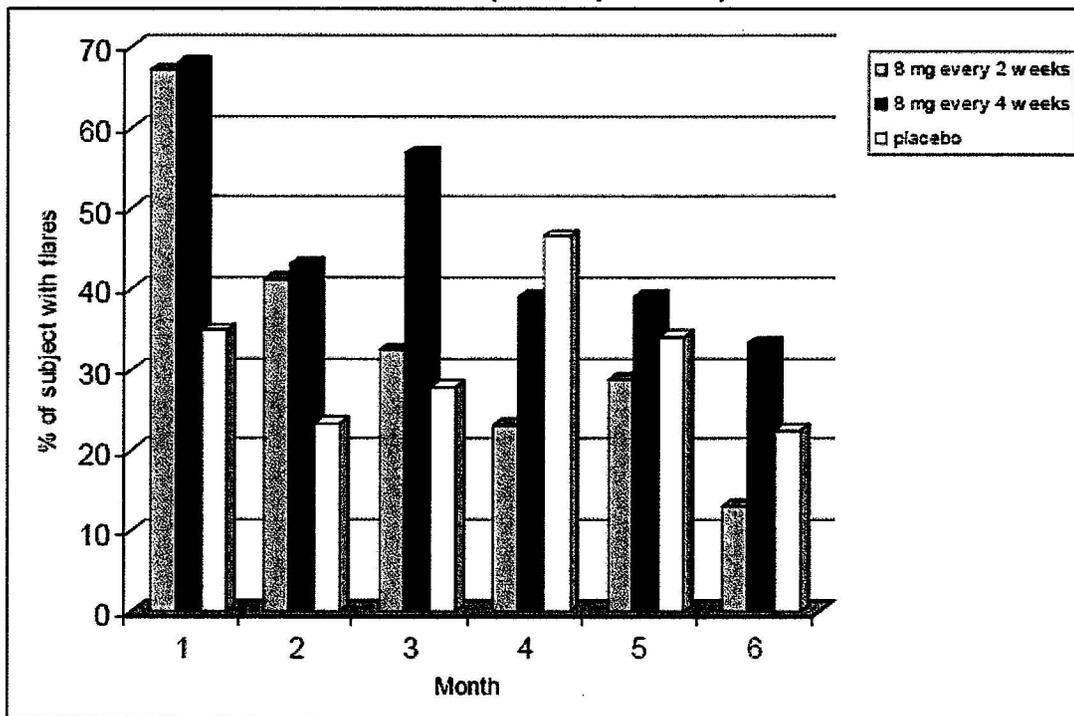
Note: “n” represents number of subjects who experienced flares during the periods of interest, Months 1-3 and Months 4-6. “N” represents total number of subjects with at least one visit during the periods of interest.

¹P-value using Fisher’s exact test used to compare number of responders reporting flares.

Adapted Sponsor’s Table 66; p. 133 of the ISE.

The following figure (Figure 8) graphically depicts the incidence of gout flares on a monthly basis over the course of the pooled Phase 3 studies by treatment group. As described above, a higher percentage of patients in both pegloticase treatment groups experienced gout flares during the first 3 months of the trials. Starting at Month 4, the incidence of gout flares for the pegloticase every 2 week treatment group fell to below that of the placebo group, and continued to remain lower during Months 5 and 6. In contrast, the incidence of flares for the pegloticase every 4 week group fell during Months 5 and 6 as compared to earlier time points, but remained higher than that of the placebo group during these time points.

Fig. 8 – Incidence of Flares at Each Month by Treatment Group for Pooled Studies 405 and 406 (ITT Population)



Sponsor's Fig. 14; p. 131 of the ISE

Severity of gout flares was also examined (Table 44 below). Over the course of these pooled pivotal studies, 60% of the placebo group reported their gout attacks as moderate-to-severe in nature as compared to 68% of the patients in the pegloticase every 2 weeks group and 70% of patients in the pegloticase every 4 weeks group. During the first half of these studies (Months 1-3), 30% of the placebo subjects reported having moderate-to-severe flares of gout as compared to 65% of subjects in the pegloticase every 2 weeks and 64% of subjects in the pegloticase every 4 weeks treatment groups. With prolonged exposure to pegloticase, the number of patients who reported moderate-to-severe attacks during Months 4-6 decreased to 25% for the pegloticase every 2 weeks group and 39% for the pegloticase every 4 weeks group as compared to 49% of placebo treated patients.

Table 44 – Tabular Summary of Patients with Gout Flares by Severity for the Pooled Studies 405 and 406 (ITT Population)

	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Placebo (N=43)
During Study Period¹			
Number of Patients²	85	84	43
None	20 (24%)	14 (17%)	8 (19%)
Mild	7 (8%)	11 (13%)	9 (21%)
Moderate	37 (44%)	38 (45%)	20 (47%)
Severe	21 (25%)	21 (25%)	6 (14%)
Months 1-3			
Number of Patients²	85	84	43
None	22 (26%)	16 (19%)	21 (49%)
Mild	7 (8%)	14 (17%)	9 (21%)
Moderate	37 (44%)	35 (42%)	11 (26%)
Severe	19 (22%)	19 (23%)	2 (5%)
Months 4-6			
Number of Patients²	69	69	43
None	41 (59%)	30 (44%)	14 (33%)
Mild	11 (16%)	12 (17%)	8 (19%)
Moderate	12 (17%)	21 (30%)	15 (35%)
Severe	5 (7%)	6 (9%)	6 (14%)

Note: Missing severity response for gout flare was imputed as severe unless the subject experienced another occurrence within the same period for which severity was recorded.

Note: If the same subject in a given treatment had more than one occurrence, only the most severe occurrence was taken.

¹During the study period = first dose to 4 weeks after last dose

²N represents the number of subjects who had a visit within each time period.

Sponsor's Table 69; p. 135.

6.1.6 Other Endpoints

No other exploratory endpoints were evaluated in the Phase 3 pivotal trials.

6.1.7 Subpopulations

Table 45 lists subgroup analyses by gender, age and race of the primary endpoint for each of the pivotal Phase 3 trials. (Note: These analyses were conducted by statistical reviewer for this application.) Review of the data presented in this table did not reveal any subgroup that did not exhibit a treatment effect of pegloticase. However, ability to detect small differences in effects is limited by the small number of subjects involved in each analysis.

Table 45 – Subgroup Analyses: Proportion of Subjects with PUA Concentrations < 6mg/dL for at Least 80% of the Time During Months 3 and 6 Combined by Gender, Age and Race (ITT Population)

	Study 405			Study 406		
	Pegloticase every 2 wks	Pegloticase every 4 wks	Placebo	Pegloticase every 2 wks	Pegloticase every 4 wks	Placebo
Females						
Number of Responders (%)	8/13 (62%)	1/6 (17%)	0/5 (0%)	2/4 (50%)	6/9 (67%)	0/2 (0%)
P-value for Comparison to Placebo	0.04	1.0		0.5	0.2	
Males						
Number of Responders (%)	12/30 (40%)	7/35 (20%)	0/15 (0%)	14/38 (37%)	15/34 (44%)	0/21 (0%)
P-value for Comparison to Placebo	0.004	0.09		0.001	<0.001	
Age < 55 years						
Number of Responders (%)	4/18 (22%)	1/18 (6%)	0/10 (0%)	9/24 (38%)	10/25 (40%)	0/13 (0%)
P-value for Comparison to Placebo	0.3	1.0		0.02	0.008	
Age >55 years						
Number of Responders (%)	16/25 (64%)	7/23 (30%)	0/10 (0%)	7/18 (39%)	11/18 (61%)	0/10 (0%)
P-value for Comparison to Placebo	0.001	0.07		0.03	0.002	
White						
Number of Responders (%)	14/32 (44%)	8/32 (25%)	0/14 (0%)	8/22 (36%)	9/27 (33%)	0/16 (0%)
P-value for Comparison to Placebo	0.004	0.09		0.012	0.016	
Non-White						
Number of Responders (%)	6/11 (55%)	0/9 (0%)	0/6 (0%)	8/20 (40%)	12/16 (75%)	0/7 (0%)
P-value for Comparison to Placebo	0.04	NA		0.07	0.001	

Analyses courtesy of Dr. Ruthanna Davi, Staff Statistician

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

As part of their clinical development program for pegloticase, the Applicant conducted Phase 1 and 2 dose-ranging studies to identify a safe and efficacious dose for evaluation in their Phase 3 trials. Based on 3-month efficacy data generated from the proof-of-concept Phase 2 study, C0403, the 8-mg and 12-mg doses of pegloticase were shown to have the greatest effect on PUA levels. However, the 8-mg dose group had a better safety and tolerability profile than the 12-mg dose of the product. The 8-mg and 12-mg dosing groups were also associated with lower uric acid levels (lower C_{min} and $C_{average}$) and a more rapid decrease in these levels (smaller t_{min}) than the 4-mg dose. Additionally, the terminal elimination half-life of pegloticase was shown to be approximately 10 days in most subjects. Pegloticase's long half life supported by the finding that very low concentrations of the product were sufficient to achieve marked lowering of uric acid for up to 4 weeks provided the rationale for administering the product every 2 or 4 weeks in the replicate Phase 3 studies. The results from the 2

replicate Phase 3 studies showed that treatment with pegloticase 8 mg every 2 weeks dosing regimen resulted in a significantly higher proportion of subjects with PUA < 6mg/dL for at least 80% of the time during Months 3 and 6 combined as compared to placebo in each study. However, the results from the pegloticase 8 mg every 4 weeks group were not as robust in Study 405 as they were in Study 406, and were complicated by the lack of a prespecified correction for multiplicity. Additionally, the supporting data generated from the clinically relevant secondary endpoints for tophus reduction, swollen and tender joints and gout flares were more robust for the pegloticase 8 mg every 2 weeks regimen than they were for the 8 mg every 4 weeks regimen. Besides being clinically less efficacious, the pegloticase 8 mg every 4 weeks regimen was also associated with a higher rate of infusion reactions than were seen in the pegloticase 8 mg every 2 weeks dosing regimen. Overall, these results favor the pegloticase 8 mg every 2 weeks as the optimal regimen.

(b) (4)



6.1.10 Additional Efficacy Issues/Analyses

No correction for multiplicity issues was prespecified by the SAP for either Study 405 or 406 to be used in conducting the analyses of these trials' primary and secondary endpoints. The results for the primary endpoints in both studies for the pegloticase every 2 weeks dosing regimen were robust due to the high statistical significance associated with these comparisons to placebo. However, the magnitude of the statistical significance for the results of the primary endpoint findings associated with the pegloticase every 4 weeks group comparisons to placebo was lower than for the every 2 week group. Additionally, the clinical benefit associated with the pegloticase every 4 week dose appears less as demonstrated by lesser effects on resolution of tophi and decreasing gout flares. Overall, when weighed against the higher rate of infusion reactions that were seen in the pegloticase 8 mg every 4 weeks dosing regimen as discussed in Section 7, the lesser clinical benefits with every 4 weeks dosing favors the pegloticase every 2 weeks dosing regimen.

7 Review of Safety

Safety Summary

The review of pegloticase's safety database identified concerns in three main areas: 1) a higher rate of serious cardiovascular events, 2) the occurrence of infusion reactions and allergic reactions and 3) immunogenicity of pegloticase with an adverse impact on efficacy and safety. Deaths were seen in all study arms, including the placebo arm. However, the rate of mortality was higher in the controlled trials in the pegloticase every 2 weeks arm (3 cases or 4%) than in the pegloticase every 4 weeks arm (1%) or the placebo arm (1%). The deaths were related to infections and cardiovascular events and occurred in patients with multiple underlying risk factors for these adverse events. The higher rate of serious cardiovascular events was seen in both pegloticase treatment arms and demonstrated no relation to dose. The cardiovascular events showed no particular pattern and included arrhythmias, ischemic events and congestive heart failure. A consultation from the FDA Division of Cardiovascular and Renal Drug Products concluded that the distribution of cardiovascular deaths and cardiac SAEs was not obviously unusual in view of the fact that they occurred in patients predisposed to such events and taking into account the unequal randomization in the clinical trials.

A higher proportion of patients experienced serious adverse events in the pegloticase every 4 weeks (23%) and pegloticase every 2 weeks (24%) treatment groups as compared to placebo treated patients (12%) due to the high rate of infusion reactions seen in the pegloticase every 4 weeks (41%) and pegloticase every 2 week (26%) groups. A higher proportion of patients experienced moderate-to severe infusion reactions in the pegloticase every 4 weeks group (36%) as compared to the pegloticase every 2 weeks group (18%). The occurrence of infusion reactions peaked with the administration of Dose 3 or 4 of pegloticase and declined thereafter. Pegloticase was highly immunogenic with 88% of patients in the pegloticase every 2 week group and 89% of patients in the pegloticase every 4 weeks group seroconverting to antibody positive status over the course of these studies. Higher titers of antibody to pegloticase were associated with higher rates of infusion reactions and decreases in urate-lowering effects of therapy. A review of all infusion reactions contained in the safety database by an internal pulmonary and allergy consultant from the Division of Pulmonary and Allergy Products (DPAP) revealed that approximately 5% of these patients met clinical criteria for anaphylaxis, which was higher than the Applicant's original estimate of anaphylaxis based on investigator assessment of cases of anaphylaxis. This observed rate is likely lower than it would have been if the trial hadn't mandated use of a regimen comprised of antihistamines, acetaminophen and corticosteroids that was administered prior to each study infusion in order to prevent the occurrence of these events. None of these cases of anaphylaxis resulted in a death of a subject. However, in many of the cases the reactions were of sufficient concern to discontinue pegloticase therapy. Nonetheless, a few patients received multiple additional infusions without recurrence.

Pegloticase-treated patients were more likely to withdraw early due to AEs (19-20%). The main causes of withdrawal due to AEs were infusion reactions (9% and 13% of patients in the every 2 weeks and every 4 weeks groups, respectively) and gout flares (6% and 4% of patients in the every 2 weeks and every 4 weeks groups, respectively) as compared to placebo group (0% infusion reactions, and 1% gout flares). These are expected findings in view of its immunogenic potential and mechanism of action that results in fluctuations of serum uric acid producing gout flares.

Review of the clinical data found no evidence of an adverse effect of pegloticase on clinical lab test parameters or vital signs. The additive risk from concomitant use of systemic corticosteroids did not result in an increased risk for serious infections nor were cases of hemolytic events found during the examination of the safety database. Review of the long-term safety data generated from the ongoing 24-month open-label extension (OLE) trial, Study 407, did not reveal any new safety signals. The pattern of AEs in Study 407 was consistent with that observed in the randomized controlled studies.

Limitations associated with the pegloticase safety database include the small size of the randomized trials that precludes determination of the product's true cardiovascular risk, and the small numbers of patients available for subgroup analyses of gender, age, and race.

Another safety issue besides the cardiovascular risk, and risk for infusion reactions and anaphylaxis that have not been adequately explored is the issue of re-exposure risk to the product due to its immunogenicity. A small Phase 3b study to assess this risk is currently underway.

Taking into account the demonstrated clinical benefits of the pegloticase every 2 weeks regimen (e.g., tophi resolution, improvement in tender and swollen joints and reduced gout flares) the risk/benefit relationship is favorable.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In support of this BLA, the Applicant submitted safety data from a total of 6 studies: two Phase 1 trials (401 and 402), one Phase 2 trial (403), and three Phase 3 trials (405, 406 and 407). A tabular summary of these trials can be found in the Table 2 in Section 5. Study 401 evaluated pegloticase administered via subcutaneous injection. This study was terminated early by the Applicant due to the unexpected finding of urticarial reactions following study injections in 2 subjects participating in this trial. The safety data from this trial is therefore not included in the product's safety database. Another

24-week, open label Phase 3 trial (409) to evaluate the risk of re-exposure to pegloticase every 2 weeks in symptomatic gout patients who had participated in previous studies of the product was initiated just prior to submission of this application. The safety information collected from this small ongoing trial was also not included in the BLA safety database. Additionally, the original safety database contained only 12-month preliminary data reported from a clinical cut-off data of March 31, 2008 (soft-lock date of May 31, 2008) from the 24-month OLE study 407 which is currently ongoing. The 120-day safety update included additional safety information collected from Study 407 through a clinical cut-off date of August 29, 2008 (soft-lock date of November 3, 2008). Data from these studies were summarized in the individual study reports, the Integrated Summary of Safety and the electronic datasets for adverse events, lab data and vital signs.

All safety analyses were performed on the data generated from the double-blind safety population (Studies 405 and 406) and the preliminary data collected from the on-going open-label extension study (Study 407).

7.1.2 Categorization of Adverse Events

Verbatim terms of AEs recorded in the case report forms (CRF) by investigators was coded by the Applicant using MedDRA dictionary Preferred Term and System Organ Class (SOC) (version 9.0). A listing of all AEs coded in this manner including the corresponding verbatim terms was included in the CRF for review. The MedDRA coding of the information generated from clinical trials conducted by the applicant was generally acceptable. Additionally, the clinical lab and vital sign ranges for clinically significant abnormal results was reviewed and appeared to be appropriate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The pegloticase safety population, which was defined as all patients who received at least 1 dose of study medication, was summarized by the Applicant in four pooled population groups based on study design and phase:

- Population Group A: double-blind placebo-controlled Phase 3 studies of IV pegloticase (Studies 405 and 406)
- Population Group B: All Phase 3 studies including long-term safety OLE study (405, 406 and 407)
- Population Group C: All subjects who received multiple doses of IV pegloticase in Phase 2 and 3 studies (403, 405, 406 and 407)
- Population Group D: All subjects treated with IV pegloticase in Phase 1, 2, and 3 studies (402, 403, 405, 406, and 407)

Population Groups C and D contained inappropriately pooled data generated from both uncontrolled and controlled single- and multiple-dose studies that evaluated a variety of doses not under consideration for licensing or were evaluated for varying durations of exposure (e.g., 1 day to 24-months of cumulative exposure) which could result in a potential underestimation of the safety risk associated with pegloticase. The safety data contained in Population Group A was appropriately pooled since these data were generated from adequate and well-controlled trials (405 and 406) suitable for use in determining the product's safety profile based on the reported AE, clinical lab results, vital signs and ECG that were presented separately for each of the two dose pegloticase dose regimens that were evaluated. Additionally, the Population Group B dataset contained appropriately pooled safety data since it was comprised of cumulative AE data generated from subjects who continued to receive long-term treatment with pegloticase in the OLE following completion of the randomized controlled studies necessary for the determination of safety risks associated with prolonged product exposure.

7.2 Adequacy of Safety Assessment

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

At the time of the initial submission, the extent of exposure to either the 8 mg every 2 week or 8 mg every 4 week pegloticase dosing regimens for the multiple dosing Studies 403, 405, 406 and 407 was as shown in Table 46 below. The median number of infusions for the every 2 week dose regimen proposed for marketing was 19 with a total of 1972 infusions administered overall. The median study duration for subjects who received 8 mg every 2 weeks of pegloticase was 327 days and 286 days for those subjects who received 8 mg every 4 weeks. A combined total of 101 patients from both pegloticase dose groups had exposure for at least 12 months, out of which 27 patients had exposure for at least 18 months. With the 120-day safety update, these numbers increased to 121 patients from both pegloticase dose groups with exposure for at least 12 months and 95 patients with exposure for at least 18 months.

Ordinarily for a product intended for chronic use, the ICH E1A guideline would apply with respect to the size of the safety database. The ICH E1A guidance document specifies a safety database of 1500 patients treated overall, 300-600 treated for at least 6 months and 100 treated for at least 1 year. However, ICH E1A guidelines specify that the size of the target population should be taken into account when determining the appropriate size of the safety database. Given that the target population for pegloticase is patients with gout refractory to conventional treatment, an orphan indication, the size of the safety database is appropriate.

Table 46 – Summary of Number of Pegloticase Infusions and Study Duration for Subjects Who Received Multiple Doses of Pegloticase in the Phase 2 and 3 Trials (Studies 403, 405, 406 and 407)

	Pegloticase 8 mg q 2 wks (N=116)	Pegloticase 8 mg q 4 wks (N=113)
Number of Pegloticase Infusions per Subject		
Mean (SD)	17 (11)	11 (9)
Median (Min, Max)	19 (1, 38)	8 (1, 32)
Study Duration (Days)¹		
Mean (SD)	316 (172.2)	306 (182.2)
Median (Min, Max)	327 (29, 658)	286 (1, 623)
Study Duration (Weeks)		
0-16 weeks	17 (15%)	17 (15%)
>16 weeks	99 (85%)	96 (85%)
>28 weeks	66 (57%)	61 (54%)
>52 weeks	53 (46%)	48 (42%)
>77 weeks	13 (11%)	14 (12%)

Note: Number of infusions excludes placebo infusions.

¹For subjects enrolled in Studies 405 or 406 with initial pegloticase treatment, the study duration is defined as the sum of study durations in the double-blind studies (405 or 406) and open label study (407). However, for subjects with placebo treatment in Studies 405 or 406, only the study duration in 407 is included in the summary.

Adapted Sponsor's Tables 11 and 12; p. 42-43 of ISS

7.2.2 Explorations for Dose Response

As part of their product development program for pegloticase, the Applicant conducted a Phase 1 single-dose, dose-escalation study (402) and a Phase 2 multiple repeat-dose ranging study (403) in order to identify an efficacious and safe dose of pegloticase for evaluation in the pivotal Phase 3 studies. Pharmacodynamic (PD) data generated from Study 402 indicated that pegloticase doses ≥ 2 mg provided clinically relevant decreases in PUA. Analyses of data generated from Study 403 showed that the 8-mg and 12-mg doses of pegloticase were similar in terms of efficacy; however, the 8-mg dose was associated with a better safety profile. Additionally, non-compartmental pharmacokinetic analyses revealed that 8-mg and 12-mg doses of pegloticase were associated with lower uric acid levels (as manifested by a lower C_{max} and $C_{average}$) as well as a more rapid decrease in these levels (as measured by a smaller t_{max}) as compared to the 4-mg dose. Pegloticase's long half-life in conjunction with the finding of very low concentrations of the product were sufficient to achieve marked suppression of uric acid for up to 4 weeks, and thus supported the use of pegloticase every 2 or 4 weeks in the pivotal Phase 3 trials.

7.2.3 Special Animal and/or In Vitro Testing

Because of vacuolization seen in the repeat-dose animal studies, the Applicant performed an in vivo/in vitro study that evaluated the functionality of splenic macrophages in rats exposed to pegloticase for 4 weeks. The results of this bioassay showed decrease functionality of macrophages that contained vacuoles which was reversible after 2 weeks of treatment cessation. The material in these vacuoles appears to be derived from pegloticase.

7.2.4 Routine Clinical Testing

Subjects who participated in the pivotal trials, 405 and 406, were to have the following lab tests serially performed at screening and at Weeks 7, 13, 19, and 25:

- Complete cell count (CBC) with differential and platelet count, hemoglobin and hematocrit
- Serum chemistries: albumin, alkaline phosphatase, ALT, AST, BUN, calcium, carbon dioxide, chloride, creatinine, glucose, lactic dehydrogenase, phosphorus, potassium, sodium, direct bilirubin, total bilirubin and total protein
- Urinalysis: including pH, specific gravity, protein, glucose, ketones, nitrite, occult blood, bilirubin, and urobilinogen

Additionally, subjects were to have pre-infusion blood samples collected at Weeks 1, 3, 5, 9, 13, 17, 21, and 25 for antibody testing and CH50.

ECGs were to have been performed at screening and Week 25. Complete physical exams of all subjects were to have been conducted by study investigators at screening and at Weeks 13 and 25. Vital signs including oral temperature, sitting pulse rate, respiratory rate, and blood pressure were to have been measured at all study visits.

During the first 12 months of the OLE study, 407, the same clinical lab tests, physical exams and ECG assessments were scheduled to occur at Weeks, 13, 25, 37 and at the end of study visit. Serum samples were for the measurement of allantoin, a byproduct of pegloticase's oxidative metabolism of urate, were scheduled for collection at Weeks 1, 13, and the end of study visit for the OLE population who continued receiving pegloticase.

Overall, the types of clinical lab testing and physical assessments as well as the timing of these assessments were appropriate for the population studied in these trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable for this application since it is a therapeutic biologic protein.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Rasburicase is the only recombinant urate oxidase that is available in this country. It is used for the initial management of tumor lysis syndrome in children undergoing anti-cancer therapy for leukemia, lymphoma, or solid tumor malignancies. Use of rasburicase has resulted in hypersensitivity reactions including anaphylaxis, methemoglobinemia and antibody production. In view of this, subjects with G6PD deficiency were prohibited from participating in any of the clinical studies conducted with pegloticase, however, subjects were routinely serially monitored for the possibility of hemolytic events during the clinical trials. Additionally, the Phase 3 common protocol mandated that all patients were to receive prophylactic therapy for infusion reactions. Subjects who had an infusion reaction despite these measures were to have serum tryptase levels measured in order to determine the etiology of these events. Serum immunoglobulin and CH50 levels were also monitored in these studies. The Applicant examined infusion reaction case reports to see if the signs and symptoms reported with these events were consistent with anaphylaxis. Based on the safety data and corresponding analyses contained in this submission, the Applicant made a diligent effort to monitor and identify similar adverse events associated with pegloticase. The results of these efforts are discussed in the following sections of this review.

7.3 Major Safety Results

All safety analyses were performed on the population that received at least 1 infusion of study medication. Table 47 summarizes adverse events (AEs) that were reported in the pegloticase safety database presented as pooled safety data from the 2 controlled trials (Studies 405 and 4060) by treatment group as well as cumulative adverse event data collected from patients who completed these studies and continued to receive pegloticase through their participation in the ongoing open-label extension (OLE) Study 407. Safety data collected from patients who had previously received placebo during the controlled studies and initiated pegloticase therapy in the OLE was also reviewed and will be discussed as pertinent. The majority of subjects (over 90% in each of the study arms) in the pivotal pegloticase studies experienced at least 1 AE during their participation in these studies.

Table 47 – Tabular Summary of Treatment-Emergent Adverse Events Including Infusion Reactions and Gout Flares Reported by Subjects by Treatment Group for the Pooled Controlled Studies 405 and 406 and Open-Label Extension Study 407

	6-Month Controlled Studies 405 and 406			24 Month Open Label Extension Study 407	
	Placebo (N=43)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)
Number Of Adverse Events (AE)	370	693	870	1044	1411
Number of Subjects with AEs	41 (95%)	80 (94%)	84 (100%)	83 (98%)	84 (100%)
Number of Subjects with Serious AEs (SAE)	5 (12%)	20 (24%)	19 (23%)	24 (28%)	27 (32%)
Number of Subjects with Infections	22 (51%)	30 (35%)	40 (48%)	41 (48%)	54 (64%)
Number of Subjects with Serious Infections	4 (9%)	3 (4%)	5 (6%)	3 (4%)	7 (8%)
Number of Subjects with Malignancy	1 (2%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Number of Subjects with Infusion Reactions (IR)	2 (5%)	22 (26%)	34 (41%)	26 (31%)	38 (45%)
Number of Subjects Who Discontinued Due to AEs	1 (2%)	16 (19%)	17 (20%)	18 (21%)	21 (25%)
Deaths	1 (2%)	3 (4%)	1 (1%)	0 (0%)	2 (2%)

Note: Except for the "Number of AEs", subjects are counted only once in each row.
 Adapted Sponsor's Tables 24, 37, 40 and 69; p.56, 79, 81 and 127, respectively of the ISS.

Controlled data from the 6-month studies show that treatment with pegloticase was associated with a higher rate of serious adverse events (SAEs). The proportions of patients in the pegloticase every 2 week (24%) and every 4 week (23%) groups who developed an SAE were comparable but were higher than in the placebo group (12%). With prolonged exposure, the incidence of SAEs increased slightly for both dose groups of pegloticase-treated patients. The proportion of patients who experienced an infection or a serious infection during the controlled studies was not increased in the pegloticase groups compared to the placebo group. Overall, the number of cases of malignancies in this safety database was low and did not increase with prolonged exposure. Since pegloticase is a non-human protein there is the potential for developing an antibody response to the product, which could manifest as an infusion reaction. In fact the proportion of patients experiencing an infusion reaction was increased in the pegloticase-treated patients compared to controls in spite of the standardized pre-treatment prophylaxis regimen (26% and 41% in the two pegloticase study arms versus 5% in the placebo group). Notably the rate of infusion reactions was lower in the group receiving more frequent infusions (every 2 weeks, 26%) than in patients receiving less frequent infusions (every 4 weeks, 41%). Most of the patients who had an infusion reaction had it in the first 6 months of treatment. However, some additional cases were observed after 6 months.

During the controlled studies, the proportions of patients who experienced an AE leading to withdrawal were similar for both pegloticase treatment groups (19-20%) but were much higher as compared to placebo (1%). These proportions slightly increased with increasing duration of exposure. More deaths occurred during the controlled studies with a higher proportion occurring in the pegloticase every 2 weeks treatment group (3/85, 3%) as compared to the pegloticase every 4 week (1/85, 1%) and placebo group (1/43, 1%). These deaths and the 2 deaths that occurred during the OLE study will be further discussed below.

Deaths

There were a total of 9 deaths reported in the pegloticase clinical development program as follows: 3 deaths in the pegloticase every 2 weeks group, 3 deaths in the pegloticase every 4 weeks group, and 3 deaths in the placebo group. (Note: Two deaths occurred more than 30 days after the last dose of study drug was administered; a tabular summary of all 9 deaths can be found in Table 48.) Two of the 3 deaths that occurred in patients receiving pegloticase every 2 weeks (Subjects 405-203-001 and 406-315-005) were due to sudden death in patients with histories of extensive cardiovascular disease including end-stage cardiomyopathy (ejection fraction of 17%), congestive heart failure (CHF), coronary atherosclerotic heart disease and coronary artery bypass. Additionally, both of these patients had multiple other comorbid conditions that increased their risk for developing a fatal cardiovascular event. The third subject who died in the pegloticase every 2 weeks group (Subject 406-301-003) was an 89-year-old male resident of a nursing home who developed an infected perianal decubitus ulcer from sleeping in a chair. Subsequently, he died of sepsis secondary to methicillin resistant staphylococcus aureus (MRSA) after refusing additional invasive medical treatment for his infection after failing extensive antibiotic therapy.

Two of the 3 deaths in the pegloticase every 4 weeks group occurring in patients during the open-label extension were also due to sepsis. Both of these patients (Subjects 407-122-004 and 406-325-001) had originally received pegloticase every 4 weeks while in the controlled studies, but opted to switch to the every 2 week dose regimen prior to entering the open-label extension trial. Subject 407-122-004, a 53-year-old female, had developed oxacillin-resistant staphylococcus aureus osteomyelitis of her right first metatarsophalanx (MTP) that resulted in the amputation of her toe. She subsequently became septic despite antibiotic therapy and died following removal of life support after failing to respond to aggressive medical management. The other patient who died due to sepsis in the pegloticase every 4 weeks group was a 63-year-old male (Subject 406-325-001) who developed necrotizing skin lesions on his face and hands approximately 4 weeks after receiving his last dose of study medication. Since these lesions were not considered to be of infectious origin, he was treated with a course of 60 mg a day of prednisone pending the results of a skin biopsy and cultures of these lesions. He was

hospitalized 1 week later for treatment of septic shock and renal failure after developing cellulitis of his left arm and died following the removal of life support after failing to respond to aggressive medical treatment. Cultures of the skin lesions grew out both streptococcus and staphylococcus and were supported by the histopathology results from the skin biopsy which were consistent with an ongoing infectious process. The third patient who died in the pegloticase every 4 week group was a 64-year-old male with end-stage cardiomyopathy (ejection fraction of 10-15%), CHF, coronary artery disease, atrial fibrillation, and status post pacemaker insertion who did not disclose his full medical history at the time of study enrollment (protocol violation). He was hospitalized a day after receiving his second study infusion for the treatment of acute dyspnea secondary to CHF. He developed acute renal failure during his hospitalization that required dialysis. This patient's death was the result of renal failure after he refused additional dialysis treatments.

Of the three patients who died in the placebo group, one patient (Subject 406-301-014) died post randomization prior to receiving a dose of study medications. The remaining 2 patients (Subjects 405-101-005 and 406-311-002) died 4 months after receiving their scheduled study infusions. These two patients withdrew from the study after being lost to follow up post-hospitalization for treatment of urosepsis and a severe gout flare and a recurrence of CLL, respectively. Both of these deaths were attributed to the patients underlying medical conditions (i.e., cardiac disease and CLL).

In considering the deaths occurring in the pegloticase clinical development program it is important to consider which events may be related to the drug and which to concomitant conditions. In that regard it is clear that the patient population enrolled in the studies is at increased risk of mortality as shown by the occurrence of one death in a randomized patient in the short time before the first dose of study medication and by the occurrence of 2 additional deaths in the placebo group 4 months after their last placebo infusion. In addition, it is also clear that many of the deaths occurred in patients with comorbidities that predispose to serious cardiovascular events and infections including advanced congestive heart failure, diabetes mellitus, hypertension and renal failure.

Table 48 – Tabular Summary of Subjects Who Died While Participating in Pegloticase Studies

Subject Number	Age/Sex	Cause of Death	Onset	Died >30 Days After Last Dose	Pertinent History
Pegloticase 8 mg every 2 weeks					
405-203-001	61yo/M	Cardiac Arrest	Double Blind	No	Died despite medical resuscitation efforts following period of strenuous physical activity. H/O CHF, HTN, NIDDM, asthma, angina pectoris, end-stage cardiomyopathy (ejection fraction 17%) and insomnia. Concomitant meds: colchicine, furosemide, spironolactone, metoprolol, lisinopril, simvastatin, nitroglycerin, isosorbide, terbutaline, budesonide, celecoxib, glibenclamide, trazodone, rosiglitazone, and Tylenol #3.
406-315-005	69yo/M	Cardiac Arrhythmia	Double Blind	No	C/O weakness, aches, pains, and anorexia x 7 days S/P Study Dose 9. Evaluated by PMD on day prior to death without diagnosis and normal cardiac exam. Died in-route to hospital. H/O CAD, S/P CAGB, DM with neuropathy, PVD, bilateral edema, HTN, obesity, chronic renal failure, S/P renal artery stent, left carotid artery occlusion, and S/P right carotid endarterectomy. Concomitant meds: colchicine, omeprazole, clonidine, pravastatin, diltiazem, furosemide, metolazone, prednisone, citalopram, ASA, insulin, Kayexalate, and doxercalciferol.
406-301-003	89yo/M	MRSA Sepsis	Double Blind	Yes	Completed all 12 study infusions during double-blind study. Developed MRSA sepsis during course of antibiotics for a perianal decubitus ulcer he developed while sleeping in chair due to back pain in a nursing home. Pt. died after refusing additional antibiotics or invasive surgical procedures. H/O CAHD, S/P metal prosthetic aortic valve, cardiac arrhythmia, S/P pacemaker, PVD, HTN, hypothyroidism, dyslipidemia, and wheezing. Concomitant meds: furosemide, quinapril, coreg, dopamine, Zocor, warfarin, esomepraole, heparin, insulin, levothyroxine, metoprolol, simvastatin, tamsulosin, Zosyn, Mucinex and potassium.

H/O = History of; C/O = complained of; CHF = congestive heart failure; HTN = hypertension; NIDDM = non-insulin dependent diabetes mellitus; S/P = status post; CAD = coronary artery disease; CAGB = coronary artery grafted bypass; DM = diabetes mellitus; PVD = peripheral vascular disease; CA = cancer; GERD = gastroesophageal reflux disease

Table 48 – Tabular Summary of Subjects Who Died While Participating in Pegloticase Studies (conti.)

Subject Number	Age/Sex	Cause of Death	Onset	Died >30 Days After Last Dose	Pertinent History
Pegloticase 8 mg every 4 weeks					
407-122-004	54yo/F	ORSA Sepsis	OLE	No	Developed DVT and osteomyelitis of right first MTP culture positive for ORSA s/p amputation of digit. She became septic despite antibiotics and was transferred to MICU where she became progressively unresponsive and died S/P withdrawal of life support at family's request. H/O HTN, focal segmental glomerulonephritis, pancreatitis, chronic renal failure, hypercholesterolemia, peritonitis, S/P peritoneal dialysis, S/P hip fracture, and bilateral DVT. Concomitant meds: colchicine, metronidazole, vancomycin, metoprolol, amiodarone, sevelamer and aztreonam.
405-102-006	64yo/M	Kidney Failure S/P Dialysis Withdrawal Secondary to Congestive Heart Failure; End-Stage Cardio- myopathy	Double Blind	No	Hospitalized for acute dyspnea and pedal edema secondary to CHF one day S/P Study Dose 2 (blinded placebo infusion). During hospitalization the patient developed acute renal failure and was started on dialysis. Pt. requested that dialysis be withdrawn after 2 treatments. He was transferred to a hospice unit and subsequently died. H/O HTN, atrial fibrillation, CAD, S/P coronary stents, S/P pacemaker, chronic renal failure, and cardiomyopathy x 10 years (ejection fraction 10-15%) that was not reported to the study investigator. Concomitant meds: colchicine, clopidogel, ASA, digoxin, lansoprazole, furosemide, carvedilol, ramipril, amiodarone, potassium, metoprolol, glyceryl trinitrate, temazepam, alprazolam, propacet, oxycocet, and sildenafil.

H/O = History of; C/O = complained of; CHF = congestive heart failure; HTN = hypertension; NIDDM = non-insulin dependent diabetes mellitus; S/P = status post; CAD = coronary artery disease; CAGB = coronary artery grafted bypass; DM = diabetes mellitus; PVD = peripheral vascular disease; CA = cancer; GERD = gastroesophageal reflux disease

Table 48 – Tabular Summary of Subjects Who Died While Participating in Pegloticase Studies (conti.)

Subject Number	Age/Sex	Cause of Death	Onset	Died >30 Days After Last Dose	Pertinent History
Pegloticase 8 mg every 4 weeks					
406-325-001	63 yo/M	Cellulitis/sepsis secondary to necrotizing skin lesion	OLE	Yes	Pt. became septic following a course of systemic corticosteroids for necrotizing skin lesions. Biopsy of skin lesions and cultures were positive for streptococcus and staphylococcus. While hospitalized he arrested and died 3 days later S/P withdrawal of life support and pressor therapy at family's request. H/O CHF, dilated cardiomyopathy, and S/P implanted cardiac defibrillator. Meds: captopril, ASA, furosemide, digoxin, metolazone, spironolactone and metoprolol. simvastatin, omeprazole, prednisone, and naproxen.
Placebo					
406-301-014	85yo/F	Multi-organ Failure	S/P randomization	N/A	Pt. hospitalized for unknown reasons prior to receiving first study dose during which she developed multiorgan failure and died. H/O HTN, Azotemia and Bilateral Breast CA. Concomitant meds: enalapril, metoprolol, digoxin, ASA, simvastatin, warfarin, colchine, prednisone, furosemide, valsartan, verapamil, metolazone, meclozine, and potassium.
405-101-005	67yo/M	Cardiac Disease	Double-Blind	Yes	Pt. lost to follow up S/P transfer to a rehab center post-hospitalization for a severe gout flare and urosepsis. He died 4 months after last dose of study meds. H/O CAHD, CHF, S/P cardiac stent, HTN, GERD, DM, hyperlipidemia, dsyphonia, and post-herpetic neuralgia. Concomitant meds: prednisone, pantoprazole, HCTZ, simvastatin, metoprolol, nifedpine, gabapentin, furosemide, clopidogrel, ASA, fluticasone, insulin, enalapril, Augmentin, amoxicillin, APAP, Tylenol #3.
406-311-002	80yo/M	Chronic Lymphocytic Leukemia (CLL)	Double-Blind	Yes	Pt. had stable CLL when he enrolled in study which reoccurred during Month 4 at which time he withdrew from the study and died 4 months later as a result of CLL

H/O = History of; C/O = complained of; CHF = congestive heart failure; HTN = hypertension; NIDDM = non-insulin dependent diabetes mellitus; S/P = status post; CAD = coronary artery disease; CAGB = coronary artery grafted bypass; DM = diabetes mellitus; PVD = peripheral vascular disease; CA = cancer; GERD = gastroesophageal reflux disease

7.3.2 Nonfatal Serious Adverse Events

During the controlled studies, a higher proportion of patients experienced SAEs in the pegloticase every 2 week (24%) and every 4 week group (23%) than in the placebo group (Table 49). Three system organ classes contributed to the higher overall rates of SAEs in the pegloticase groups: general disorders and administration site conditions, musculoskeletal and connective tissue disease, and cardiac disorders.

The higher rate of SAEs seen in the musculoskeletal and connective tissue disease conditions in the pegloticase every 2 week group is attributable to single cases of hemarthrosis, steroid myopathy, osteoarthritis and synovial cyst, none of which have a clear relationship to study drug. Rather they appear related to concomitant medical conditions and concomitant medications. Table 49 below highlights the SAE profiles for the other two remaining system organ classes. Review of these data shows that the higher rates of SAEs observed in the general disorders and administration site conditions for the pegloticase treatments are primarily due to infusion reactions, which are an expected adverse event associated with the product due to its immunogenicity.

The higher rates of cardiac disorders reported in the pegloticase every 2 week (5%) and every 4 week (4%) treatment groups as compared to placebo (0%) were unexpected and will be discussed further with other safety areas of interest. Review of the 24 SAEs (14 SAEs in the pegloticase every 2 weeks group and 10 SAEs in the pegloticase every 4 weeks group) contained in the 120-day safety update that occurred in patients participating in the ongoing OLE study showed that they were similar to what had been observed during the controlled studies, and did not indicate any additional safety signals.

Table 49 – Number (%) of Subjects with Serious Adverse Events (SAEs) Including Infusion Reactions and Gout Flares in the Safety Database for the Controlled Studies 405 and 406 and Open-Label Extension Study 407

Adverse Event Via MedDRA System Organ Class (SOC) and Preferred Term	6-Month Controlled Studies 405 and 406			24-Month Open Label Extension Study 407	
	Placebo (N=43)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)
Number of SAE	14	34	30	45	50
Number (%) of Subjects with SAE	5 (12%)	20 (24%)	19 (23%)	24 (28%)	27 (32%)
Gen. Disorders and Adm. Site Condit.:	0 (0%)	7 (8%)	7 (8%)	10 (12%)	10 (12%)
Infusion Related Reaction	0 (0%)	4 (5%)	7 (8%)	5 (6%)	8 (10%)
Chest Pain	0 (0%)	1 (1%)	0 (0%)	2 (2%)	1 (1%)
Peripheral Edema	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Pyrexia	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Adverse Drug Reaction	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Asthenia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Infections and Infestations:	4 (9%)	3 (4%)	5 (6%)	3 (4%)	7 (8%)
Pneumonia	1 (2%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Cellulitis	0 (0%)	1 (1%)	1 (1%)	1 (1%)	2 (2%)
Bacterial Arthritis	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Staphylococcal Cellulitis	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Herpes Zoster	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Localised Infection	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Necrotising Fasciitis	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Perianal Abscess	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pyelonephritis	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Sepsis	0 (0%)	1 (1%)	0 (0%)	1 (1%)	1 (1%)
Staphylococcal Sepsis	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Infection	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Osteomyelitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Musculoskel. and Connective Tissue Disease:	2 (5%)	7 (8%)	2 (2%)	9 (11%)	3 (4%)
Gout	2 (5%)	4 (5%)	1 (1%)	5 (6%)	1 (1%)
Fistula	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Hemarthrosis	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Steroid Myopathy	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Osteoarthritis	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Synovial Cyst	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Pain in Extremity	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Rotator Cuff	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Cardiac Disorders:	0 (0%)	4 (5%)	3 (4%)	4 (5%)	3 (4%)
Arrhythmia	0 (0%)	2 (2%)	0 (0%)	2 (2%)	0 (0%)
Angina Pectoris	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Cardiac Arrest	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Congestive Cardiac Failure	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Myocardial Infarction	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Tachycardia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)

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.

Adapted Sponsor's Tables 34; p. 72-3 and Table B8.3 in Appendix of ISS.

7.3.3 Dropouts and/or Discontinuations

Patients treated with pegloticase were more likely to withdraw early due to adverse events. Table 50 below is a tabular summary of the AEs experienced by the patients who discontinued study treatment during the controlled Studies 405 and 406 and open-label extension Study 407. The overall proportions of patients who discontinued due to treatment-emergent adverse events were similar for the pegloticase every 2 weeks (19%) and pegloticase every 4 weeks (20%) treatment groups but were higher as compared to the placebo group (2%). Review of these data indicated that the differences in rates of premature study withdrawals were primarily due to higher drop-out rates associated with infusion reactions (9% and 13%) and gout flares (6% and 4%) in the pegloticase every 2 weeks and every 4 weeks treatment groups as compared to the placebo group (0% infusion reactions, and 1% gout flares). The rates of early subject withdrawal increased with prolonged exposure to pegloticase particularly in the every 4 week group (25%) as compared to the every 2 week group (21%). Rates of premature study withdrawal were similar in the 120-day safety update except that one patient (Subject 406-308-002) who continued to receive pegloticase every 2 weeks dropped out of the ongoing open-label extension study due to bronchitis and cardiac failure.

Table 50 – Number (%) of Subject with Who Prematurely Withdrew Due to Treatment-Emergent Adverse Events Including Infusion Reactions and Gout Flares for the Pooled Controlled Studies 405 and 406 and OLE Study 407

MedDRA System Organ Class Preferred Term	6-Month Pooled Controlled Studies 405 and 406			24 Month Open Label Extension Study 407	
	Placebo (N=43)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)
Number of AEs Leading to Withdrawal	3	16	33	20	39
Number (%) of Subjects with AEs Leading to Withdrawal	1 (2%)	16 (19%)	17 (20%)	18 (21%)	21 (25%)
Gen. Disord. and Adm. Site Cond.:					
Infusion Reactions	0 (0%)	8 (9%)	11 (13%)	7 (8%)	13 (16%)
Fatigue	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Musculoskel. and Connect. Tiss. Dis.:					
Gout	1 (2%)	5 (6%)	3 (4%)	5 (6%)	3 (4%)
Fistula	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Gouty Arthritis	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Pain in Extremity	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Shoulder Pain	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Cardiac Disorders:					
Cardiac Arrest	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Extrasystoles	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Infections and Infestations:					
Localized Infection	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Staphylococcal Sepsis	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Investigations:					
Blood Creatinine Increased	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Blood Glucose Increased	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Blood Urea Increased	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Renal Creat. Clearance Dec.	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Ear and Labyrinth Disorders:					
Vertigo	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Gastrointestinal Disorders:					
Erosive Gastritis	0 (0%)	1 (1%)	0 (0%)	1 (1%)	1 (1%)
Nervous System Disorders:					
Migraine	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Psychiatric Disorders:					
Depression	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1 (1%)
Suicidal Behaviour	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)

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. Table amended to include the 2 subjects who discontinued from the study due to infusion reactions (C406-308-003 and C406-319-004) after the database soft lock.

Adapted Sponsor's Table 34; p. 72-3 and Table B8.4 from Appendix of ISS

Table 50 – Number (%) of Subject with Who Prematurely Withdrew Due to Treatment-Emergent Adverse Events Including Infusion Reactions and Gout Flares for the Pooled Controlled Studies 405 and 406 and OLE Study 407 (cont.)

MedDRA System Organ Class Preferred Term	6-Month Pooled Controlled Studies 405 and 406			24 Month Open Label Extension Study 407	
	Placebo (N=43)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)
Respiratory System Disorders:	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1 (1%)
Dyspnea Exacerbated	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1 (1%)
Lung Infiltrate	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Skin and Subcut. Tiss. Disorders:	0 (0%)	0 (0%)	1 (1%)	0 (0%)	2 (2%)
Angioneurotic Edema	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Urticaria	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Erythema	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Hyperhidrosis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Surgical and Medical Procedures:	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Abdominal Operation	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)

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. Table amended to include the 2 subjects who discontinued from the study due to infusion reactions (C406-308-003 and C406-319-004) after the database soft lock.

Adapted Sponsor's Table 34; p. 72-3 and Table B8.4 from Appendix of ISS

7.3.4 Significant Adverse Events

Table 51 is a tabular listing of AEs observed during controlled Studies 405 and 406 by treatment arm that were rated as severe in nature by study investigators. The most common severe AEs reported during the controlled trials as compared to placebo were: diarrhea (5% for total pegloticase versus 2% for placebo), acute renal failure (2% for total pegloticase versus 0% for placebo), and muscle spasms (2% for total pegloticase versus 0% for placebo). Review of the cumulative data for the OLE study shows similar patterns of severe AEs with a small increase in frequency with prolonged exposure.

Table 51 – Tabular Summary of Number (%) of Subjects with Severe Adverse Events Reported by ≥ 2 Pegloticase-Treated Patients in the Pooled Controlled Studies 405 and 406 and Open-Label Extension 407

MedDRA System Organ Class Preferred Term	Placebo (N=43)	Pegloticase 8 mg every 2 weeks (N=85)	Pegloticase 8 mg every 4 weeks (N=84)	Total Pegloticase (N= 169)	Cumulative 24-Month Open Label Extension All Pegloticase (N=169)
Diarrhea	1 (2%)	2 (2%)	3 (4%)	5 (3%)	8 (5%)
Acute Renal Fail.	0 (0%)	2 (2%)	1 (1%)	3 (2%)	4 (2%)
Arthralgia	1 (2%)	2 (2%)	1 (1%)	3 (2%)	5 (3%)
Fatigue	1 (2%)	2 (2%)	1 (1%)	3 (2%)	4 (2%)
Muscle Spasms	0 (0%)	1 (1%)	2 (2%)	3 (2%)	3 (2%)
Arrhythmia	0 (0%)	2 (2%)	0 (0%)	2 (1%)	2 (1%)
Asthenia	0 (0%)	1 (1%)	1 (1%)	2 (1%)	3 (2%)
Cellulitis	0 (0%)	1 (1%)	1 (1%)	2(1%)	2 (1%)
Dyspnea	0 (0%)	1 (1%)	1 (1%)	2 (1%)	2 (1%)
Hypertension	0 (0%)	1 (1%)	1 (1%)	2 (1%)	2 (1%)
Pain	0 (0%)	1 (1%)	1 (1%)	2 (1%)	2 (1%)
Vomiting	0 (0%)	1 (1%)	1 (1%)	2 (1%)	4 (2%)

Adapted from Sponsor's Table B9.3, Append.23.4

7.3.5 Submission Specific Primary Safety Concerns

a. Cardiac

Due to an imbalance in the number of serious cardiac adverse events between study arms (Table 49), further examinations of the safety database were undertaken by both the Applicant and the Agency. As shown in Table 52 the imbalance reflects various different types of events, including 2 cases of arrhythmia and single cases of tachycardia, congestive heart failure, cardiac arrest, MI and angina pectoris.

Table 52 - Cardiac Serious Adverse Events (SAEs) via MedDRA Preferred Terms for the Pooled Safety Database from Controlled Studies 405 and 406 by Sponsor

MedDRA Preferred Term	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Total Pegloticase (N=169)	Placebo (N=43)
Number (%) of Subjects with Cardiac SAEs	4 (5%)*	3 (4%)	7 (4%)*	0 (0%)
Ischemic Cardiovascular Disease:				
Cardiac Arrest	1	0	1	0
Myocardial Infarction	0	1	1	0
Angina Pectoris	0	1	1	0
Heart Failure:				
Congestive Cardiac Failure	1	0	1	0
Cardiac Arrhythmias:				
Arrhythmia	2	0	2	0
Tachycardia	0	1	1	0

*One patient had both CHF and arrhythmia.
 Adapted from Sponsor's Table 34; p. 72-3 of ISS.

During the FDA's review of the pegloticase application, the Applicant submitted an amendment with the findings of an independent blinded cardiovascular adjudication committee that conducted a post hoc review of all possible cardiovascular events from the pegloticase Phase 2 (Study 403), Phase 3 (Studies 405 and 406) and the ongoing open label extension (Study 407) trials. The committee used the following definitions in their analysis of these data:

1. Anti-Platelet Trialist Collaborative (APTC) Events
 - a. Non-fatal myocardial infarction
 - b. Non-fatal stroke
 - c. Cardiovascular deaths
2. Non-APTC Major Adverse Cardiovascular Events (MACE)
 - a. Unstable angina (includes acute coronary syndrome)
 - b. Coronary revascularization
 - c. Transient ischemic attacks

Table 53 summarizes the results of this analysis as it pertains to data from the double-blind portion of Studies 405 and 406.

Table 53 – Analyses of Subjects with Major Cardiac Adverse Events by Sponsor’s Cardiac Event Adjudication Committee for the Pooled Safety Database from the Controlled Studies 405 and 406

Major Cardiac Adverse Events	Pegloticase q 2 wks (N=85) n (%)	Pegloticase q 4 wks (N=84) n (%)	Total Pegloticase (N=169) n (%)	Placebo (N=43) n (%)
Number (%) of Subjects with Major CV Events	4 (5%)	6 (8%)	10 (6%)	0 (0%)
All APTC* Events:	2 (2%)	1 (1%)	3 (2%)	0 (0%)
Cardiovascular Deaths	2	0	2	0
Non-Fatal Myocardial Infarction	0	1	1	0
Non-Fatal Stroke	0	0	0	0
Non-APTC CV Events:	2 (2%)**	5 (6%)	8 (5%)	0 (0%)
Angina	0	1	1	0
Congestive Heart Failure	2	1	3	0
Arrhythmia	1	1	2	0
Deep Venous Thrombosis	0	1	1	0
Transient Ischemic Attack	0	1	1	0

* Anti-Platelet Trialist Collaborative

** Two subjects had multiple events: Subject 406-311-005 had 2 events (CHF and arrhythmia); Subject 405-122-003 had both an APTC event (MI) and a non-APTC event (DVT).

The overall rates of both APTC events and non-APTC events are comparable for both pegloticase treatment groups but higher as compared to the placebo treatment group. In terms of non-APTC events, there were 3 subjects (2%) in the pegloticase every 2 weeks group, 5 subjects (6%) in the pegloticase every 4 weeks group and none in the placebo group. Based on the above data, no meaningful conclusions were drawn by this committee due to the small sample size and skewed randomization (i.e., 2:2:1).

An internal consultant, Dr. Stephen Grant, from the Agency’s Division of Cardiovascular and Renal Drug Products also reviewed these data. Table 54 summarizes the findings of this review. Based on the Dr. Grant’s analysis of these data, there were a total of 5 major cardiac AEs that occurred in the pegloticase every 2 weeks group (6%), 3 events in the every 4 week group (4%), and 1 event in the placebo group (2%). All of these events occurred in patients who had pre-existing comorbid risk factors for the development of major cardiac adverse events. The occurrence of these events is not unexpected given the high prevalence of underlying cardiovascular disease in the patient population who participated in these trials. Dr. Grant concluded that the distribution of cardiovascular deaths and of cardiac SAEs due to ischemic vascular disease and/or heart failure was not obviously unusual even considering the decreased duration of exposure in the pegloticase treatment arms due to more pegloticase-treated subjects withdrawing prior to study conclusion. However, there remains a degree of uncertainty about the cardiac safety of pegloticase because so few events were

observed due to the limited number of subjects enrolled and limited duration of follow-up.

Table 54 –Analyses of Subjects with Major Cardiac Adverse Events Experienced by Patients for the Pooled Safety Database for the Controlled Studies 405 and 406 as Attributed by FDA

Major Cardiac Adverse Events	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Total Pegloticase (N=169)	Placebo (N=43)
Number of Subjects with Major Cardiac AEs:	5 (6%)	3 (4%)	8 (5%)	1 (2%)
Ischemic Cardiovascular Disease:				
Sudden Death	2	0	2	0
Inferiolateral Myocardial Infarction	0	1	1	0
“Troponin Leak”	0	0	0	1
Transient Ischemic Attack	0	1	1	0
Heart Failure:				
Heart Failure	2	0	2	0
Cardiac Arrhythmias:				
Supraventricular Tachycardia	0	1	1	0
Ventricular Tachycardia	1	0	1	0

In order to better assess the cardiovascular safety of pegloticase, outlier and quartile analyses were undertaken for changes in both blood pressure (> 20 mm Hg) and pulse rate (\geq 100 bpm), as well as examination of electrocardiographic abnormalities identified on the final electrocardiograms of subjects enrolled in Studies 405 and 406 consistent with myocardial infarction or prolongation of the QT interval. These analyses did not identify any additional safety signals. However, these retrospective analyses are limited and should not be considered exculpatory because only very large differences among subjects in the treatment groups could have been detected. The measurement of blood pressure and QT interval in studies 405 and 406 was performed neither frequently nor carefully enough to have detected smaller but clinically important changes.

Review of the 120-day safety data update identified an additional 2 case reports of SAEs of cardiac origin. One of these events occurred in a 52-year-old male patient (Subject 405-120-001) who had a myocardial infarction one day after receiving his pegloticase every 4 weeks study infusion. This patient had a history of hyperlipidemia but no other risk factors for coronary atherosclerosis. The second case occurred in a patient (Subject 406-307-006) with known ischemic heart disease with an implanted cardioverter-defibrillator and pacemaker who was receiving pegloticase infusions every 2 weeks who was hospitalized for treatment of congestive heart failure. One other SAE of cardiac origin was identified on search of the safety database for the Phase 1 and 2 studies. The patient was a 77-year-old female (Subject 403-002-003) with a history of coronary artery disease, hypertension, hyperlipidemia, diabetes mellitus, pulmonary

embolus and deep venous thrombosis who had a transient ischemic attack (TIA) 4 weeks following the administration of her second dose of pegloticase 12 mg every 4 weeks in the Phase 2 dose ranging study (Study 403). This patient recovered from her TIA and continued in the study.

b. Hematological

Since one of the byproducts of pegloticase’s enzymatic breakdown of uric acid is hydrogen peroxide, a safety concern regarding the development of hemolytic anemias and other hematological adverse events was raised. The Applicant excluded G6PD-deficient patients from the trials and proposes that these patients should not use the product if pegloticase is marketed. Table 55 summarizes the MedDRA preferred AE term for hematological AEs that occurred during the controlled Studies 405 and 406 as well as during the open-label extension, Study 407. Overall, these proportions were similar for the 3 treatment groups and with prolonged exposure to the product. Further review of these data does not identify any pattern of hematologic AEs that were either dose-associated or associated with prolonged exposure to pegloticase.

Table 55 - Number (%) of Subjects with Hematological Adverse Events via MedDRA Preferred Term by Treatment Group in the Safety Database for the Controlled Studies 405 and 406 and Open-Label Extension Study 407

MedDRA System Organ Class Collapsed Preferred AE Term	6-Month Pooled Controlled Studies 405 and 406			24 Month Open Label Extension Study 407	
	Placebo (N=43)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)
Hematological	5 (12%)	12 (14%)	7 (8%)	12 (14%)	9 (11%)
Anemia	4 (9%)	7 (8%)	4 (5%)	7 (8%)	5 (6%)
Neutropenia	0 (0%)	2 (2%)	1 (1%)	1 (1%)	0 (0%)
Febrile Neutropenia	1 (2%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Increased Hematocrit	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Leukocytosis	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1 (1%)
Leukopenia	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Thrombocythemia	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)
Thrombocytopenia	0 (0%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)
Red Cell Count Decreased	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (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.

Adapted Sponsor’s Table A8.2, Appendix 23.2 from Hematologic section and Table B8.2 Appendix from Hematologic section of the ISS.

c. Allergic Manifestations

Due to concerns raised by the occurrence of urticaria seen with subcutaneous injection in Study 401 and the immunogenicity profile of pegloticase, the safety database was searched for hypersensitivity-type allergic AEs (Table 56). Overall, there were more allergic AEs in the pegloticase treatment arms (28% and 51%) than in the placebo arm (16%). Most of the cases were characterized as infusion-related reactions. In addition, there were 2 cases of urticaria reported in both the pegloticase every 2 weeks and every 4 weeks treatment groups as compared to none in the placebo group. There was 1 case of angioedema in a patient who received pegloticase every 4 weeks as compared to none in the pegloticase every 2 weeks and placebo groups. With prolonged exposure no new cases of angioedema or urticaria were observed in the open-label extension or in the 120-day safety update.

Table 56 – Number (%) of Subjects with Allergic Adverse Events via MedDRA Preferred Term by Treatment Group in the Safety Database for the Controlled Studies 405 and 406 and Open-Label Extension Study 407

MedDRA System Organ Class Collapsed Preferred AE Term	6-Month Pooled Controlled Studies 405 and 406			24 Month Open Label Extension Study 407	
	Placebo (N=43)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)
Allergic	7 (16%)	24 (28%)	43 (51%)	30 (35%)	49 (58%)
Infusion-Related Reaction	2 (5%)	22 (26%)	35 (42%)	26 (31%)	39 (46%)
Rash	3 (7%)	2 (2%)	3 (4%)	5 (6%)	5 (6%)
Urticaria	0 (0%)	2 (2%)	2 (2%)	2 (2%)	2 (2%)
Rash Macular	1 (2%)	2 (2%)	0 (0%)	2 (2%)	1 (1%)
Seasonal Allergy	0 (0%)	0 (0%)	3 (4%)	0 (0%)	3 (4%)
Wheezing	0 (0%)	0 (0%)	3 (4%)	0 (0%)	3 (4%)
Drug Hypersensitivity	1 (2%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Rash Papular	0 (0%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Angioneurotic Edema	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Face Edema	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Rash Generalized	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rash Maculo-Papular	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rhinitis Allergic	0 (0%)	0 (0%)	1 (1%)	1 (1%)	3 (4%)
Throat Tightness	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)

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.

Adapted Sponsor's Table A8.2, Appendix 23.2 from Allergic section and Table B8.2 Appendix 23.4 from Allergic section of the ISS.

The allergic adverse events shown in Table 56 exclude similar types of events that occurred as a component of an infusion-related reaction. Since the majority of allergic AEs were attributed to infusion-related reactions, defined by the Applicant as a cluster

of AEs that occurred during or within 2 hours after the end of the study medication infusion, additional examination of these component events was undertaken and is presented in Table 59. Although some of the component events associated with infusion-related reactions should be classified as hypersensitivity type reactions (i.e., urticaria, rash, throat tightness, and wheezing) they were attributed as components of infusion reactions due to the timing of their appearance.

d. Infusion Reactions

The majority of patients who receive pegloticase develop at least some level of antibodies to the product raising a concern for allergic reactions and infusion reactions. To limit the occurrence of hypersensitivity and infusion reactions observed during the Phase 1 and Phase 2 studies, all patients received a standard pre-treatment prophylaxis regimen consisting of 60 mg fexofenadine the night before followed in the morning by another dose of 60 mg of fexofenadine with 1000 mg acetaminophen, and 200 mg of hydrocortisone IV immediately prior to each infusion. In addition to supportive medical care and monitoring, the management of infusion reactions included the slowing or stopping of the infusion followed by either restarting the study infusion more slowly or discontinuing it, with or without the administration of fluids, diphenhydramine, or corticosteroids depending on the severity of the reaction. However, one patient (Subject 406-319-004) did require treatment with 1 dose of epinephrine for a moderate infusion reaction characterized by flushing, diaphoresis, shortness of breath, light headedness and rash but recovered without sequelae. Five other patients were sent to the emergency room for additional monitoring after experiencing moderate-to-severe infusion reactions but they also recovered without sequelae. Table 57 summarizes the number and severity of infusion reactions observed during the controlled Studies 405 and 406 and the open-label extension Study 407. The proportion of infusion reactions was highest in patients treated with pegloticase every 4 weeks (41%) as compared to every 2 weeks (26%) versus placebo (5%). With prolonged exposure these rates increased to 45% for the pegloticase every 4 weeks group and 31% for the pegloticase every 2 weeks group. Review of the data contained in the 120-day safety update revealed that these rates remained comparable with increasing duration of product exposure (49% and 29%). In terms of severity of these AEs, 36% of patients reported having moderate-to-severe infusion reactions in the pegloticase every 4 weeks treatment group as compared to 18% of patients in the pegloticase every 2 weeks group and 5% in the placebo. Review of the data in the 120-day safety update regarding the proportion of patients with moderate to severe infusions reactions with increasing duration of exposure were comparable to earlier data (40% and 23% for the every 4 week group and every 2 weeks group, respectively).

Table 57 – Number (%) of Patients Experiencing Infusions Reactions by Severity for Pooled Controlled Studies 405 and 406 and OLE Study 407

Infusion Reaction Severity	6-Month Pooled Controlled Studies 405 and 406			24 Month Open Label Extension Study 407	
	Placebo (N=43)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)
Number (%) of Infusion Reactions	2 (5%)	22 (26%)	34 (41%)	26 (31%)	38 (45%)
Mild	0	7 (8%)	4 (5%)	7 (8%)	56%
Moderate	2 (5%)	11 (13%)	22 (26%)	14 (17%)	24 (29%)
Severe	0	4 (5%)	8 (10%)	5 (6%)	9 (11%)

Note: An infusion reaction is an event or cluster of events that occurred during or within two hours after an infusion. Missing severity response for infusion reaction was imputed as "Severe" if there was no infusion reaction reported on a prior dose visit. Otherwise, prior severity was carried forward.
 Adapted Sponsor's Table 91; p. 178 and Table B11.3 Appendix of ISS

Table 58 summarizes the occurrence of infusion reactions by dose and pooled treatment group during the controlled studies. The rate of occurrence of infusion reactions peaked at Dose 3 (44%) for the pegloticase every 4 week group and at Dose 4 (23%) for the pegloticase every 2 week and decreased thereafter.

Table 58 – Number (%) of Patients Who Experienced an Infusion Reaction¹ by Treatment Group and Dose Number for Pooled Controlled Studies 405 and 406

Infusion Reaction Reported at:	Placebo (N=43)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	All Pegloticase (N=169)
Number (%) of Subjects with First Infusion Reaction at:				
Dose 1	1 (50%)	1 (5%)	4 (12%)	5 (9%)
Dose 2	NA	4 (18%)	1 (3%)	5 (9%)
Dose 3	NA	3 (14%)	15 (44%)	18 (32%)
Dose 4	1 (50%)	5 (23%)	NA	5 (9%)
Dose 5	NA	1 (5%)	6 (18%)	7 (13%)
Dose 6	NA	2 (9%)	NA	2 (4%)
Dose 7	NA	1 (5%)	2 (6%)	3 (5%)
Dose 8	NA	3 (14%)	1 (3%)	4 (7%)
Dose 9	NA	NA	4 (12%)	4 (7%)
Dose 10	NA	2 (9%)	NA	2 (4%)
Dose 11	NA	NA	1 (3%)	1 (2%)

NA = not applicable

¹Note: Sponsor defined an infusion AE as an event or cluster of events that occurred during or within 2 hours after an infusion.

*Subjects randomized to the pegloticase 8 mg every 4 weeks were administered placebo infusions at Doses 2, 4, 6, 8, and 10 in order to maintain study blind.

Adapted Sponsor's Tables 37 and 40; p. 79 and 81 of ISS.

Further characterization of the most common component signs and symptoms (i.e., AEs that occurred during or within 2 hours after the end of the study medication infusion) of

infusion reactions are shown in Table 59. During the controlled studies, the most commonly reported signs and symptoms associated with study infusions by patients in the every 2 week group were urticaria (11%), dyspnea (7%), erythema (6%), and flushing (6%), whereas in the every 4 week group patients reported symptoms of chest discomfort (10%), chest pain (10%), erythema (10%) and pruritus (10%). In the placebo group infusion reactions were characterized by dyspnea (2%) and flushing (2%). These rates of events for both pegloticase treatment groups remain comparable with prolonged exposure in the OLE Study 407 and on review of the data in the 120-day safety update. Overall, a higher proportion of patients in the every 2 week group (11%) reported having urticaria associated with their infusions as compared to the every 4 week group (7%) but the proportions of the other component events that could also be classified as hypersensitivity type reactions (i.e., rash, throat tightness, and wheezing) were similar for the 2 pegloticase treatment groups. The rates of these events also did not increase with increasing exposure in the OLE study or on review of the data in the 120-day safety update.

Table 59 – Tabular Summary of the Most Common Signs and Symptoms Associated with Infusion Reactions Reported by 4 or More Subjects in the Pooled Controlled Studies 405 and 406 and the OLE Study 407

MedDRA Preferred Term for Component AEs of Infusion-Related Reaction	6-Month Pooled Controlled Studies 405 and 406			24-Month Open Label Extension Study 407	
	Placebo (N=43)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)
Back Pain	0 (0%)	1 (1%)	6 (7%)	3 (4%)	6 (7%)
Chest Discomfort	0 (0%)	3 (4%)	8 (10%)	5 (6%)	11 (13%)
Chest Pain	0 (0%)	1 (1%)	8 (10%)	2 (2%)	9 (11%)
Chills	0 (0%)	4 (5%)	0 (0%)	5 (6%)	0 (0%)
Dizziness	0 (0%)	3 (4%)	1 (1%)	4 (5%)	1 (1%)
Dyspnea	1 (2%)	6 (7%)	6 (7%)	7 (8%)	8 (10%)
Erythema	0 (0%)	5 (6%)	8 (10%)	5 (6%)	10 (12%)
Flushing	1 (2%)	5 (6%)	7 (8%)	8 (9%)	8 (10%)
Headache	0 (0%)	1 (1%)	4 (5%)	1 (1%)	5 (6%)
Hyperhidrosis	0 (0%)	4 (5%)	2 (2%)	6 (7%)	5 (6%)
Hypertension	0 (0%)	4 (5%)	1 (1%)	4 (5%)	2 (2%)
Hypotension	0 (0%)	3 (4%)	1 (1%)	3 (4%)	1 (1%)
Muscle Spasms	0 (0%)	2 (2%)	2 (2%)	4 (5%)	3 (4%)
Nausea	0 (0%)	2 (2%)	6 (7%)	0 (0%)	6 (7%)
Pain	0 (0%)	1 (1%)	6 (7%)	0 (0%)	6 (7%)
Pruritus	0 (0%)	3 (4%)	8 (10%)	3 (4%)	8 (10%)
Rash	0 (0%)	3 (4%)	6 (7%)	3 (4%)	6 (7%)
Tachycardia	0 (0%)	3 (4%)	3 (4%)	3 (4%)	3 (4%)
Throat Tightness	0 (0%)	1 (1%)	2 (2%)	1 (1%)	4 (2%)
Urticaria	0 (0%)	9 (11%)	6 (7%)	9 (11%)	7 (8%)
Vomiting	0 (0%)	1 (1%)	3 (4%)	2 (2%)	5 (6%)
Wheezing	0 (0%)	2 (2%)	2 (2%)	2 (2%)	2 (2%)

Adapted Sponsor's Tables 44 and 93; p. 86 and 181 of ISS

Categorizing adverse events as allergic reactions versus infusion reactions versus hypersensitivity reactions versus anaphylaxis is complicated by the fact that the clinical signs and symptoms of these phenomena are broadly overlapping. Consequently, one type of reaction (e.g., anaphylaxis versus infusion reaction) is not always differentiated from another in a consistent manner. In view of this, the review division requested an internal consultation from the Division of Pulmonary and Allergy Products (DPAP) for help in assessing the spectrum of infusion reactions observed in the pegloticase safety database. In classifying the pegloticase associated infusion reactions, Dr. Susan Limb, the DPAP consultant used the diagnostic criteria proposed by the NIAID/FAAN Joint Symposium on Anaphylaxis¹ for unknown allergen for anaphylaxis. These diagnostic criteria characterize adverse events as anaphylaxis based on their presenting signs and symptoms regardless of the presence or absence of IgE antibody to the suspected allergen. Based on the above criteria for anaphylaxis, the pulmonary consultant identified seven cases (Table 60) of anaphylaxis that had been coded by the applicant as "infusion reactions with a hypersensitivity constellation of symptoms." None were fatal. Of note, in all but one case no subsequent infusions were given suggesting that these cases meeting the case definition for anaphylaxis were of sufficient severity that the treating clinician and patient decided not to continue with pegloticase infusions.

Table 60 – Tabular Summary of Seven Cases of Anaphylaxis Reported During Studies 405 and 406

Age/Sex	Event	Symptoms/Treatment	Immune Parameters	Outcome
Pegloticase every 2 weeks				
23yo/M	IR 26 minutes into 4 th infusion	Lingual swelling, dsypnea, and nausea. Treated with diphenhydramine 25 mg IV.	Serum tryptase: 6.0 mcg/L Anti-pegloticase Ab titer: 21,870	Stopped study infusions
74yo/M	IR 30 minutes into 5 th infusion	Dyspnea, urticaria on face, neck, and trunk with hypoxia (O2 saturation: 87%) elevated BP (184/72), tachycardia (101bpm). Treated with IV diphenhydramine and albuterol	Serum tryptase: 36.8 mcg/L Anti-pegloticase Ab titer: 90 Prior IgE titer 60; negative titer on day of IR	Stopped study infusions
62yo/M	IR 18 minutes into 1 st infusion. Did not take prophylactic APAP or fexofenadine	Facial flushing, diffuse pruritus, generalized urticaria, tachycardia (115 bpm), hypotension (81/21 mm Hg), rigors and lightheadedness. Treated with IV diphenhydramine and Demerol.	Serum tryptase: 7.1 mcg/L	Stopped study infusions
40yo/M	IR during 2 nd OL dose	Eye pruritus, periorbital edema, chest discomfort, throat irritation, arthralgia, and back pain. Treated with diphenhydramine and epinephrine. Prior H/O IR with back pain, chest discomfort and dsypnea during RCT	N/A	Stopped study infusions
Pegloticase every 4 weeks				
31yo/M	IRs at 5 minutes into 5 th and 100 minutes into 9 th infusions	First IR: facial edema, facial hyperemia, dsypnea, tachycardia (96 bpm) and back pain. Treated with IV hydrocortisone, metamizole, chlorophyramine and oxygen/ Second IR: facial erythema, hypotension (80/60 mm Hg) and dsypnea. Infusion D/C temporarily and treated with hydrocortisone and saline. Completed infusion 2hrs. later	First serum tryptase: 47.7 mcg/L Second serum tryptase: 7 mcg/L	Completed study
68yo/M	N/A	Flushing, hypotension dizziness, and vomiting.	N/A	Subsequent infusions with repeat IRs
51yo/M	N/A	Flushing, conjunctival hyperemia, chest discomfort and hypotension	N/A	Stopped study infusions

IR = infusion reaction; IV = intravenous; BP = blood pressure; Ab = antibody; bpm = beats per minute; APAP = acetaminophen; H/O = history of; RCT = randomized clinical trial, D/C = discontinued; N/A = not applicable or available

Reference range for serum tryptase: 1.9-13.5 mcg/L

Additionally, the pulmonary consultant identified 7 other potential cases of anaphylaxis that met the NIAID/FAAN diagnostic criteria that occurred in patients participating in the Phase 1 and 2 studies (402 and 403) and the Phase 3 studies and open-label extension (405, 406 and 407). These cases are summarized in Table 61. None of the cases resulted in fatality. Of these 7 cases, 3 were given no further infusions, 3 received 3-8 additional infusions without experiencing a subsequent infusion reaction. And 1 received 4 additional infusions before experiencing another infusion reaction and stopping treatment.

Table 61 – Tabular Summary of Seven Potential Cases of Anaphylaxis Reported During Studies 402, 403, 405, 406 and 407

Age/Sex	Event	Symptoms/Treatment	Immune Parameters	Outcome
Pegloticase every 2 weeks				
60yo/M	IR at 3 rd infusion	Severe allergic reaction described as thick lip feeling, rash, burning, itching, diaphoresis, nausea, and hypotension	N/A	Stopped study infusions
39yo/M	IR at 3 rd infusion	Throat tightness, pallor, dyspnea, chest discomfort, dizziness, abdominal discomfort, hyperhidrosis, chills, tremor.	Anti-pegloticase Ab titer: 270 IgE titer: 60	Stopped study infusions
45yo/M	IR 60 minutes into 4 th infusion	Chest pain, dyspnea, wheezing, and rash.	Serum tryptase: 8.8 mcg/L	Continued in study to receive 8 more infusions without IR
61yo/M	IR 135 minutes into 3 rd infusion	Urticaria and wheezing.	Serum tryptase: 10.5 mcg/L Anti-pegloticase Ab titer: 810 Anti-PEG Ab titer: 84	Received 3 more infusions without IR
66yo/M	IR 2 minutes into 6 th infusion	Erythema, flushing and hypotension.	Serum tryptase: 11.2 mcg/L	Received 6 more infusions without IR
Pegloticase every 4 weeks				
34yo/M	IR during first infusion	Urticaria and chest tightness	N/A	Stopped study infusions
70yo/m	IR 5 minutes into 3 rd infusion; IR during 7 th infusion	First IR: dyspnea, erythema, and pruritus. Second IR: shortness of breath, dyspnea and erythema.	Serum tryptase: 5.5 mcg/L	Continued to receive 4 more study infusions until second IR and then stopped study infusions.

IR = infusion reaction; IV = intravenous; Ab = antibody; N/A = not applicable or available
 Reference range for serum tryptase: 1.9-13.5 mcg/L

Based on her review of the infusion reaction adverse event data, the Dr. Limb concluded there were at least 14 cases meeting the NIAID/FAAN proposed diagnostic criteria for anaphylaxis in the safety database submitted in support of pegloticase. The estimated frequency of anaphylaxis associated with pegloticase was 5.1% (14 out of 273 patients who received IV pegloticase). By dose regimen, the frequency of anaphylaxis was 7.3% (9 out of 126 patients) for the every 2-week regimen, and 3.9% for the every 4-week regimen. This is a reverse of the trend observed for infusion reactions as a whole since a higher rate of infusion reactions, 41%, occurred in the every 4 week treatment group as compared to 26% in the every 2 week pegloticase treatment group. However, in view of the small numbers, the difference in frequency between the two dosing regimens is difficult to interpret and may be due to chance and variability in safety reporting. Since the Phase 3 studies were conducted with mandatory prophylactic administration of antihistamines, acetaminophen, and IV corticosteroids prior to pegloticase infusion, the rate of reactions meeting the clinical criteria for anaphylaxis would likely have been higher without the mandatory prophylaxis regimen. Based on the cases identified, the presence of IgE, IgG or IgM antibodies against the product did not appear to have a predictive effect.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

As was shown in the preceding Table 47, most patients (> 90%) experienced an adverse event during the controlled studies. Table 62 summarizes the most commonly reported adverse events reported by 5% or more patients at a frequency higher than 1% in the pegloticase treated population excluding gout flares and infusion reactions during the controlled Studies 405 and 406. The adverse events by preferred MedDRA term most commonly reported by pegloticase-treated patients were: headache (10%), nausea (9%), back pain (6%), nasopharyngitis (6%), and increased blood pressure (4%). With the exception of headache, these rates were comparable to those seen in placebo treated patients during these studies. No other patterns of adverse events were noted on further review of the data not shown. Review of the data contained in the 120-day safety update that occurred in patients participating in the ongoing OLE study showed that the AEs were similar in pattern to what had been observed during the controlled studies, and did not indicate any additional potential safety signals.

Table 62 – Adverse Events Occurring in ≥ 5% of Subjects at Greater than 1% Frequency in Pegloticase-Treated Subjects Compared to Placebo (Excluding Gout Flares and Infusion Reactions) During the Controlled Studies 405 and 406

Adverse Event via MedDRA Preferred Term	Placebo (N=43) n (%)	Pegloticase q 2 wks (N=85) n (%)	Pegloticase q 4 wks (N=84) n (%)	Total Pegloticase (N=169) n (%)
Nausea	1 (2%)	10 (12%)	6 (7%)	16 (9%)
Headache	4 (9%)	8 (9%)	9 (11%)	17 (10%)
Back Pain	2 (5%)	3 (4%)	7 (8%)	10 (6%)
Contusion	1 (2%)	7 (8%)	0 (0%)	7 (4%)
Nasopharyngitis	1 (2%)	6 (7%)	4 (5%)	10 (6%)
Blood Pressure Increased	0 (0%)	0 (0%)	6 (7%)	6 (4%)
Dyspnea	2 (5%)	4 (5%)	5 (6%)	9 (5%)
Vomiting	1 (2%)	4 (5%)	5 (6%)	9 (5%)
Pruritis	0 (0%)	3 (4%)	5 (6%)	8 (5%)
Pyrexia	1 (2%)	2 (2%)	5 (6%)	7 (4%)
Chest Pain	1 (2%)	5 (6%)	4 (5%)	9 (5%)
Constipation	2 (5%)	5 (6%)	2 (2%)	7 (4%)

Adapted Sponsor's Table A8.1, Appendix ISS.

7.4.2 Laboratory Findings

Laboratory data from the randomized controlled trials, 405 and 406, were presented as follows: serial changes from baseline and serial shifts from baseline at Weeks 7, 13, 19, and 25. The Applicant provided normal ranges of values for each lab parameter assessed. These were reviewed and the clinically acceptable range for normal appeared appropriate. The findings from these analyses for the Week 25 timepoint (end of study visit) are as follows:

a. Hematology-

Due to concerns regarding the potential for hemolytic anemias to occur in patients treated with pegloticase secondary to hydrogen peroxide produced by the enzyme's metabolic activity, hematological lab data results were examined for signs of this phenomena. At Week 25, more patients in the pegloticase every 2 weeks and 4 weeks groups experienced shifts in baseline from normal to low in hemoglobin (14% and 9%, respectively), hematocrit (9% and 9%, respectively) and erythrocyte count (15% and 11%, respectively) as compared to the placebo group (5% for each indice) (Table 63). Further examination revealed that these shifts for each parameter were of similar magnitude with those seen at earlier timepoints over the courses of these studies. However, mean decreases in both hematocrit and hemoglobin were also seen at Week 25 for both pegloticase treatment groups and the placebo group which were

similar in magnitude for all three treatment groups. Additionally, more patients in the pegloticase every 2 weeks and 4 weeks groups had shifts in baseline from normal to low in platelet counts (3% and 2%, respectively) as well as shifts from normal to high (3% and 6%, respective) as compared to placebo (0%). Overall, these findings do not appear to be clinically meaningful.

Table 63 – Number (%) of Subjects with Shift in Hematological Indices for Combined Studies 405 and 406

Week 25	Pegloticase 8 mg every 2 weeks (N=85)			Pegloticase 8 mg every 4 weeks (N=84)			Placebo (N=43)		
	Baseline								
	Low	Normal	High	Low	Normal	High	Low	Normal	High
Hemoglobin:									
Low	8 (14%)	8 (14%)	0 (0%)	8 (13%)	6 (9%)	0 (0%)	7 (18%)	2 (5%)	0 (0%)
Normal	4 (7%)	37 (63%)	0 (0%)	2 (3%)	42 (66%)	5 (8%)	1 (3%)	24(63%)	1 (3%)
High	0 (0%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	3 (8%)
Hematocrit:									
Low	9(15%)	5 (9%)	0 (0%)	8 (13%)	6 (9%)	0 (0%)	7 (18%)	2 (5%)	0 (0%)
Normal	3 (5%)	42(71%)	0 (0%)	6(9%)	43 (67%)	1 (2%)	5 (13%)	21(55%)	0 (0%)
High	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	2 (5%)
Erythrocytes:									
Low	5 (9%)	9 (15%)	0 (0%)	6(9%)	7 (11%)	0 (0%)	4 (11%)	2 (5%)	0 (0%)
Normal	4 (7%)	41 (70%)	0 (0%)	1 (2%)	48 (75%)	2 3%)	2 (5%)	28(74%)	1 (3%)
High	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Platelets:									
Low	1 (2%)	2 (3%)	0 (0%)	3 (5%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal	1 (2%)	47 (81%)	3 (5%)	0 (0%)	48 (76%)	7 (11%)	0 (0%)	33(89%)	2 (5%)
High	0 (0%)	2 (3%)	2 (3%)	0 (0%)	4 (6%)	0 (0%)	0 (0%)	0 (0%)	2 (5%)

Sponsor's Table A17.1; Appendix 23.2

Table 64 shows shifts in white blood cell counts at the Week 25 timepoint. More subjects in the placebo group had shifts from normal to high in their leukocyte counts (13%) as compared to the pegloticase every 2 weeks (2%) and every 4 weeks group (8%). The differences between study arms were small and did not appear clinically significant. However, more patients treated with pegloticase every 2 weeks and every 4 weeks had shifts from normal to low in their lymphocyte counts (20% and 9%, respectively) as well as to shifts from normal to high (5% and 2%, respectively) as compared to placebo (11% and 0%, respectively). Further exploration of these data showed that the shifts from normal to low in the absolute lymphocyte count which is a more sensitivity measurement of these cells were comparable for all three treatment groups (pegloticase every 2 weeks: 12%; pegloticase every 4 weeks: 9%; and placebo 8%). No shifts from normal to high were observed in the absolute lymphocyte counts for all 3 treatment groups. Shifts in neutrophil counts were also examined. Although more subjects had shifts from normal to high in the pegloticase every 2 weeks and every 4 weeks group (20% and 19%, respectively) for this cell type as compared to placebo (11%), the placebo group had a higher percentage of patients (18%) who

experienced shifts from normal to high in the absolute neutrophil count which is a more sensitive measurement for this cell type as compared to the pegloticase every 2 weeks and every 4 weeks groups (10% and 6%, respectively). Similarly, more patients in the pegloticase every 2 weeks and every 4 weeks groups had shifts from normal to low in neutrophil counts (3% and 2%, respectively) as compared to placebo (0%). However, for the absolute neutrophil count more placebo patients (5%) had shifts from normal to low for this measure as compared to the pegloticase groups which had comparable rates of shifts (0-2%). The rates of shifts from normal to low for monocyte counts were comparable for all 3 treatment groups (range: 8-11%), however, more patients in the pegloticase every 4 weeks group had shifts from normal to high (6%) for this cell count as compared to the pegloticase every 2 weeks and placebo groups (0%). The findings observed on review of the mean change from baseline for the WBC indices were similar in nature. None of these changes appeared clinically meaningful.

Due to pegloticase's immunogenicity and risk for causing hypersensitivity reactions, changes in peripheral eosinophil and basophil counts were also examined. As shown in Table 64, more subjects had shifts from normal to high in their eosinophil counts in the pegloticase every 2 weeks group (7%) as compared to the pegloticase every 4 weeks and placebo group who had similar rates of shift elevations for this cell type (2% and 3%, respectively). Review of the rates of shift elevations in absolute eosinophil count revealed that these were similar for the pegloticase every 2 weeks and placebo groups (5% and 3%, respectively) as compared to the pegloticase every 4 weeks group (0%). Comparable findings on review of the mean change over baseline data for these cell lines were noted. Again, none of these findings appeared clinically meaningful.

Table 64 – Number (%) of Subjects with Shift in White Blood Cell Counts (WBC) for Combined Studies 405 and 406

Week 25	Pegloticase 8 mg every 2 weeks (N=85)			Pegloticase 8 mg every 4 weeks (N=84)			Placebo (N=43)		
	Baseline								
	Low	Normal	High	Low	Normal	High	Low	Normal	High
Leukocytes:									
Low	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)
Normal	1 (2%)	44 (75%)	10(17%)	0 (0%)	47 (73%)	8 (13%)	0 (0%)	29(76%)	1 (3%)
High	0 (0%)	1 (2%)	3 (5%)	0 (0%)	5 (8%)	4 (6%)	0 (0%)	5(13%)	2 (5%)
Lymphocytes:									
Low	7 (12%)	12 (20%)	0 (0%)	15(23%)	6 (9%)	0 (0%)	4 (11%)	4 (11%)	0 (0%)
Normal	9 (15%)	28 (48%)	0 (0%)	4 (6%)	38 (59%)	0 (0%)	6 (16%)	24(63%)	0 (0%)
High	0 (0%)	3 (5%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Absol.Lymphocytes:									
Low	6 (10%)	7 (12%)	0 (0%)	11(17%)	6 (9%)	0 (0%)	3 (8%)	3 (8%)	0 (0%)
Normal	3 (5%)	42 (71%)	0 (0%)	0 (0%)	46 (72%)	1 (2%)	2 (5%)	29(75%)	0 (0%)
High	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Neutrophils:									
Low	0 (0%)	2 (3%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal	0 (0%)	33 (56%)	7 (12%)	1 (2%)	39 (61%)	2 (3%)	0 (0%)	28(74%)	3 (8%)
High	0 (0%)	12 (20%)	5 (9%)	0 (0%)	12 (19%)	9 (14%)	0 (0%)	4 (11%)	3 (8%)
Absol. Neutrophils:									
Low	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	2 (5%)	0 (0%)
Normal	1 (2%)	37 (63%)	11(19%)	0 (0%)	38 (59%)	11(17%)	0 (0%)	21(55%)	5 (13%)
High	0 (0%)	6 (10%)	4 (7%)	0 (0%)	4 (6%)	10(16%)	0 (0%)	7 (18%)	3 (8%)
Monocytes:									
Low	1 (2%)	6 (10%)	0 (0%)	3 (5%)	7 (11%)	0 (0%)	0 (0%)	3 (8%)	0 (0%)
Normal	3 (5%)	43 (73%)	2 (3%)	1 (2%)	47(73%)	1 (2%)	0 (0%)	35(92%)	0 (0%)
High	0 (0%)	2 (3%)	2 (3%)	0 (0%)	4 (6%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Eosinophils:									
Low	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal	0 (0%)	55 (93%)	0 (0%)	0 (0%)	60 (94%)	2 (3%)	0 (0%)	36(95%)	0 (0%)
High	0 (0%)	4 (7%)	0 (0%)	0 (0%)	1 (2%)	1 (2%)	0 (0%)	1 (3%)	1 (3%)
Absol. Eosinophils:									
Low	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal	0 (0%)	53 (90%)	3 (5%)	0 (0%)	61 (95%)	2 (3%)	0 (0%)	35(92%)	1 (3%)
High	0 (0%)	3 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1(3%)	1 (3%)
Basophils:									
Low	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal	0 (0%)	46 (78%)	8 (14%)	0 (0%)	47(73%)	9 (14%)	0 (0%)	30(79%)	4 (11%)
High	0 (0%)	1 (2%)	4 (7%)	0 (0%)	6 (9%)	2 (3%)	0 (0%)	2 (5%)	2 (5%)
Absol. Basophils:									
Low	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal	0 (0%)	55 (93%)	4 (7%)	0 (0%)	59(92%)	5 (8%)	0 (0%)	36(95%)	0 (0%)
High	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (5%)

Sponsor's Table A17.1; Appendix 23.2

b. Liver Function Tests (LFTs)-

Table 65 summarizes the shift changes in liver function tests for all 3 treatment groups during the randomized controlled studies. Review of these data reveals that more patients in the placebo group had shift elevations in their ALT (15%), AST (10%), and alkaline phosphatase (3%) levels at Week 25 as compared to the pegloticase every 2

weeks (5%, 5% and 2%) and every 4 weeks groups (0%, 3% and 3%, respectively). No shift changes were observed in any of the 3 treatment groups for total bilirubin (0%). The rates for shift elevation in LDH levels were comparable but higher for both the pegloticase every 2 weeks (10%) and placebo groups (8%) as compared to the pegloticase every 4 weeks group (3%). Similar findings were observed on review of the results for the mean change from baseline for LFTs. Overall, none of these findings were considered to be clinically meaningful.

Table 65 – Number (%) of Subjects with Shift in Hepatic Liver Function (LFTs) for Combined Studies 405 and 406

Week 25	Pegloticase 8 mg every 2 weeks (N=85)			Pegloticase 8 mg every 4 weeks (N=84)			Placebo (N=43)		
	Baseline								
	Low	Normal	High	Low	Normal	High	Low	Normal	High
ALT:									
Low	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal	0 (0%)	36 (78%)	6 (10%)	0 (0%)	51 (81%)	3 (5%)	0 (0%)	26 (67%)	2 (5%)
High	0 (0%)	3 (5%)	4 (7%)	0 (0%)	0 (0%)	9 (14%)	0 (0%)	6 (15%)	2 (13%)
AST:									
Low	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal	0 (0%)	50 (85%)	4 (7%)	0 (0%)	54 (86%)	3 (5%)	0 (0%)	30 (77%)	2 (5%)
High	0 (0%)	3 (5%)	2 (3%)	0 (0%)	2 (3%)	4 (6%)	0 (0%)	4 (10%)	3 (8%)
Alkal. Phosphatase									
Low	0 (0%)	1 (2%)	0 (0%)	1 (2%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal	0 (0%)	50 (85%)	3 (5%)	0 (0%)	54 (86%)	2 (3%)	0 (0%)	34 (87%)	1 (3%)
High	0 (0%)	1 (2%)	4 (7%)	0 (0%)	2 (3%)	3 (5%)	0 (0%)	1 (3%)	3 (8%)
LDH:									
Low	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal	0 (0%)	48 (81%)	2 (3%)	0 (0%)	51 (85%)	3 (5%)	0 (0%)	30 (79%)	1 (3%)
High	0 (0%)	6 (10%)	3 (5%)	0 (0%)	2 (3%)	4 (7%)	0 (0%)	3 (8%)	4 (11%)
Tot. Bilirubin:									
Low	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal	0 (0%)	57 (97%)	1 (2%)	0 (0%)	63 (98%)	1 (2%)	0 (0%)	36 (92%)	0 (0%)
High	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	2 (5%)

Sponsor's Table A17.1; Appendix 23.2

c. Serum Chemistries and Electrolytes-

Since gout can also affect the kidney by the formation of urate stones or causing gouty nephropathy (i.e., parenchymal disease) test results of renal function were also examined (Table 66). The rates of shift elevations for BUN were comparable for both the pegloticase every 4 weeks (6%) and placebo group (5%) but lower than that for the pegloticase every 2 weeks group (10%). Further examination revealed more placebo patients had shift elevations in their serum creatinine levels (18%) as compared to the 2 pegloticase groups whose shift elevations for serum creatinine were similar (7% and 6%, respectively). Additionally, more patients in the placebo group had a shift from normal to low creatinine clearance (13%) as compared to the pegloticase every 2 weeks and every 4 weeks groups (2% and 3%, respectively) suggestive of a positive effect on

kidney function for pegloticase. Review of the results for mean change over baseline for these tests failed to identify any clinically significant trends.

Table 66 – Number (%) of Subjects with Shift in Renal Parameters, Glucose and Total Cholesterol for Combined Studies 405 and 406

Week 25	Pegloticase 8 mg every 2 weeks (N=85)			Pegloticase 8 mg every 4 weeks (N=84)			Placebo (N=43)		
	Baseline								
	Low	Normal	High	Low	Normal	High	Low	Normal	High
BUN:									
Low	0 (0%)	1 (2%)	0 (0%)	0 (0%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal	1 (2%)	25(42%)	5 (9%)	0 (0%)	34(53%)	6 (9%)	0 (0%)	24 (62%)	1 (3%)
High	0 (0%)	6 (10%)	21(36%)	0 (0%)	4 (6%)	18(28%)	0 (0%)	2 (5%)	12(31%)
Creatinine:									
Low	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal	0 (0%)	29(49%)	2 (3%)	0 (0%)	33(52%)	6(9%)	0 (0%)	17(43%)	2(5%)
High	0 (0%)	4 (7%)	24(41%)	0 (0%)	4(6%)	21(32%)	0 (0%)	7(18%)	13(33%)
Creatinine Clearance:									
Low	25(42%)	1(2%)	0 (0%)	26(41%)	2(3%)	0 (0%)	15(39%)	5(13%)	0(0%)
Normal	3(5%)	13(22%)	1(2%)	3(5%)	12(19%)	1(3%)	1(3%)	8(21%)	1(3%)
High	0 (0%)	2(3%)	14(24%)	0(0%)	5(8%)	0 (0%)	0 (0%)	1(3%)	8(21%)
Glucose:									
Low	0 (0%)	2 (3%)	0 (0%)	0 (0%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal	0 (0%)	40(68%)	4 (7%)	0 (0%)	53(83%)	2 (3%)	2(5%)	24 (62%)	3 (8%)
High	0 (0%)	7(12%)	6 (10%)	0 (0%)	3 (5%)	4 (6%)	0 (0%)	10 (26%)	0 (0%)
Total Cholesterol:									
Low	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal	0 (0%)	30(51%)	3 (5%)	0 (0%)	27 (42%)	7 (11%)	0 (0%)	19 (49%)	2 (5%)
High	0 (0%)	9 (15%)	17 (29%)	0 (0%)	5 (8%)	25(39%)	0 (0%)	2 (5%)	16(41%)

Sponsor's Table A17.1; Appendix 23.2

Due to the mandatory use of corticosteroids for infusion reaction prophylaxis, changes in serum glucose were also reviewed. The shift elevations in serum glucose were higher in the placebo group (26%) as compared to the pegloticase every 2 weeks (12%) and every 4 weeks (6%) groups. Since corticosteroids also affect serum cholesterol levels, the results for total cholesterol were examined as well. More patients in the pegloticase every 2 weeks group (15%) had shift elevations in total cholesterol as compared to the pegloticase every 4 weeks (8%) and placebo (5%) groups. Similar findings were observed on examination of the mean change over baseline analysis results for these clinical chemistry parameters. These findings were not considered to be clinically significant.

Review of the shift data and mean change over baseline values for the remaining serum chemistry and electrolytes laboratory assessments did not identify any clinically meaningful trends.

e. Urinalysis –

Review of the urinalysis shift and mean change over baseline analyses data did not reveal any clinically meaningful trends overall.

Examination of the preliminary lab data collected from the ongoing OLE, 407, contained in the original submission and in the 120-day safety update did not reveal any clinically meaningful trends or potential safety signals.

7.4.3 Vital Signs

Serial measurements of subjects' vital signs were collected at the screening visit and Weeks 13 and 25. These data were summarized by the Applicant by change from baseline (screening visit) to Week 25. Review of these data for body temperature, respiratory rate and weight were unremarkable for clinically significant changes. Table 67 presents the changes over baseline (screening visit) for heart rate, systolic and diastolic blood pressure. Review of these data does not reveal any clinically meaningful changes for any of these parameters.

Table 67 – Tabular Summary of Change from Screening Visit to Week 25 in Heart Rate and Blood Pressure from Combined Controlled Studies 405 and 406

Vital Sign	Pegloticase 8 mg every 2 weeks (N=85)	Pegloticase 8 mg every 4 weeks (N=84)	Placebo (N=43)
Heart Rate:			
Screening Visit			
Mean (SD)	74 (10)	74 (12)	72 (10)
Median (Min, Max)	72 (52, 96)	76 (46,104)	73 (51,92)
Week 25			
Mean (SD)	75 (12)	72 (11)	71 (7,9)
Median (Min, Max)	76 (52, 101)	72 (43, 99)	72 (56, 84)
Δ from Screening to Wk 25			
Mean (SD)	-0.4 (11)	-1.8 (12)	-1.7 (9.8)
Median (Min, Max)	-2 (-27, 29)	-3 (-23, 32)	-2 (-24, 17)
Systolic Blood Pressure:			
Screening Visit			
Mean (SD)	131 (14)	135 (17)	129 (13)
Median (Min, Max)	131 (100, 180)	133 (100, 196)	130 (100, 150)
Week 25			
Mean (SD)	129 (15)	130 (18)	126 (15)
Median (Min, Max)	128 (90, 173)	128 (95, 170)	125 (78, 157)
Δ from Screening to Wk 25			
Mean (SD)	-1.4 (15)	-3.2 (20)	-4.3 (16)
Median (Min, Max)	0.0 (-30, 50)	-2.0 (-52, 50)	-3.0 (-40, 36)
Diastolic Blood Pressure:			
Screening Visit			
Mean (SD)	79 (9.4)	80 (11)	79 (9.2)
Median (Min, Max)	80 (53, 98)	80 (52, 108)	80 (51, 94)
Week 25			
Mean (SD)	76 (10)	78 (12)	77 (10)
Median (Min, Max)	78 (54, 96)	78 (58, 110)	79 (55, 96)
Δ from Screening to Wk 25			
Mean (SD)	-1.1 (10)	-1.8 (11)	-2.0 (11)
Median (Min, Max)	-2.0 (-21, 24)	-1.5 (-24, 26)	-1.0 (-33, 19)

Adapted Sponsor's Table A20; Append. 23.2

As part of the cardiovascular risk assessment of the pegloticase safety database, outlier and quartile analyses for changes in both blood pressure (> 20 mm Hg) and pulse rate (\geq 100 bpm) for subjects who participated in the randomized controlled studies were conducted by the Applicant at the Agency's request. The largest increase in change over baseline blood pressure (for both systolic and diastolic) was observed in the lowest baseline quartile of subjects. These changes tended to be small and negative in the higher quartiles. A total of 12 subjects were identified in this analysis with a >20 mm Hg change in systolic blood pressure. Nine out of these 12 patients had hypertension by medical history. Another 5 subjects were identified with >20 mm Hg change in diastolic

blood pressure. Three out of these 5 patients also had hypertension. The mean changes in pulse by baseline quartile were similar across both pegloticase treatment groups and placebo. Only one patient was identified in the pulse outlier analyses. Based on these results, the outlier and quartile analyses for blood pressure and pulse did not identify any additional safety signals.

7.4.4 Electrocardiograms (ECGs)

Since pegloticase is a therapeutic biological protein that is not expected to interact with cardiac ion channels, the Applicant was not required to do QT prolongation studies as part of their pre-clinical and clinical development program. As part of the safety monitoring for the randomized controlled studies, ECGs were performed on all subjects who participated in these trials at screening and the end of study visit (Week 25). Since the common protocol for these studies did not require a central reading of ECGs, they were read on site by machine and/or by a study investigator. Table 68 shows the results of the change from screening analysis for ECGs and shows that a higher percentage of patients in the pegloticase every 2 weeks and every 4 weeks groups had normal to abnormal changes in their serial ECGs.

Table 68 – Tabular Summary of Electrocardiograms (ECGs) for Subjects Participating in Combined Controlled Studies 405 and 406

	Pegloticase 8 mg every 2 weeks (N=85)	Pegloticase 8 mg every 4 weeks (N=84)	Placebo (N=43)
Number (%) of Subjects with Screening Visit ECG:	85 (100%)	84 (100%)	43 (100%)
Normal ¹	31 (37%)	40 (48%)	24 (56%)
Abnormal ¹	54 (64%)	44 (52%)	19 (44%)
Number (%) of Subjects with Week 25 ECG:	61 (72%)	61 (73%)	38 (88%)
Normal ¹	18 (30%)	26 (43%)	21 (55%)
Abnormal ¹	43 (71%)	35 (57%)	17 (45%)
Change from Screening Visit:			
Remains Normal	13 (21%)	17 (28%)	17 (45%)
Remains Abnormal	32 (53%)	26 (43%)	13 (34%)
Normal to Abnormal	11 (18%)	9 (15%)	4 (11%)
Abnormal to Normal	5 (8%)	9 (15%)	4 (11%)

¹Percentages are computed using total number of ECGs completed as denominator.

As part of the cardiovascular risk assessment of the pegloticase safety database, all abnormal exit ECGs from these 2 studies were reviewed by the Applicant's cardiology consultants for evidence of acute myocardial infarction or QT interval prolongation at agency request. These analyses did not identify any additional safety signals. (Note: The reader is referred to Section 7.3.5.c for additional information regarding these data.)

7.4.5 Special Safety Studies/Clinical Trials

In view of the product's immunogenicity, the Applicant is currently conducting a 24-month, open-label, multicenter, re-exposure study (409) in patients who had previously received pegloticase during a Phase 1 or 2 clinical trial to determine the safety risk associated with re-exposure to the product. A short progress report about this 24-week, multicenter study was included in the original submission. In the study, a prophylaxis regimen for both gout flares and infusions reactions was mandatory for all participants. A total of 7 subjects with treatment failure gout with a product-free interval of more than 3 years have been enrolled in this trial. As of September 12, 2008, 3 out of the 7 subjects (43%) had experienced infusion reactions. None of the infusion reactions were reportedly serious or severe in nature. Two of the subjects subsequently had one or more infusion reactions resulting in the withdrawal of one subject. None of the infusions reactions were reportedly characterized by symptoms of wheezing, stridor, angioedema, rash, urticaria, or evidence of hemodynamic instability.

7.4.6 Immunogenicity

To assess the formation of antibodies to pegloticase, blood samples were tested that were drawn at Weeks 1, 2, 5, 9, 13, 17, 21, and 25 during the controlled studies. As shown in Table 69, approximately 88% of patients in the pegloticase every 2 weeks, 89% of patients in the pegloticase every 4 weeks treatment groups and 20 % of placebo patients tested positive for anti-pegloticase antibodies on at least one time point over the course of the controlled studies. A dose dependent relationship with antibody titer was not apparent.

Table 69 – Tabular Summary of Number (%) of Subjects Positive for Antipegloticase Antibody for Controlled Studies 405 and 406

Anti-Pegloticase Antibody Level	Pegloticase q 2 wks (N=83) n (%)	Pegloticase q 4 wks (N=81) n (%)	Placebo (N=43) n (%)
None	10 (12%)	9 (11%)	32 (80%)
Low	24 (29%)	24 (30%)	5 (13%)
Moderate	19 (23%)	21 (26%)	3 (8%)
High	30 (36%)	27 (33%)	0
Total Number of Subjects with Anti-Pegloticase Antibodies	73/83 (88%)	72/81 (89%)	8/40 (20%)

Adapted Sponsor's Table 10.13, Appendix 10.1 of ISS

Since the presence of antibodies could potentially reduce the biological effects of pegloticase, PUA treatment responses were examined in patients subdivided by highest

anti-pegloticase antibody titer during the combined Months 3 and 6 (Table 70) for the controlled studies. These data demonstrate that response rates decreased with increasing anti-pegloticase titer.

Table 70 – Tabular Summary of PUA Treatment Responses by Highest Anti-Pegloticase Antibody Titer During Months 3 and 6 for Combined Studies 405 and 406 (ITT Population)

	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Placebo (N=43)
Responders: PUA < 6 mg/dL for at least 80% of the time in Months 3 and 6 Combined			
Anti-Pegloticase Antibody Level	n/N (%)	n/N (%)	n/N (%)
None	7/9 (78%)	6/7 (86%)	0/34 (0%)
Low	19/25 (76%)	13/24 (54%)	0/4 (0%)
Moderate	10/16 (63%)	9/17 (53%)	0/3 (0%)
High	0/25 (0%)	1/27 (4%)	0/0 (0%)
Total Number of Subjects Anti-Pegloticase Antibody Positive	29/75 (39%)	23/75(31%)	0/41 (0%)

Note: “n” represents the number of subjects that were PUA responders in each anti-pegloticase antibody titer category. “N” within the cells represents the total number of subjects in each anti-pegloticase antibody titer category. Adapted Sponsor’s Table A10.13, Appendix 10.1, ISS.

Antibody status can also adversely affect the safety profile of pegloticase with regard to the development of infusion reactions. Table 71 summarizes the frequency of infusion reactions observed during the controlled Studies 405 and 406. These data demonstrate that the rates of infusion reactions increased directly with increasing anti-pegloticase titers.

Table 71 – Rates of Infusion Reactions by Anti-Pegloticase Antibody Titer for the Combined Controlled Studies 405 and 406

	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Placebo (N=43)
Incidence of Infusion Reactions /Number of Subjects in Antibody Category (%)			
None	1/10 (10%)	1/19 (11%)	2/32 (6%)
Low	1/25 (4%)	4/24 (17%)	0/5 (0%)
Moderate	3/19 (16%)	9/21 (43%)	0/3 (0%)
High	16/30 (53%)	18/28 (64%)	0/0 (0%)

Adapted Sponsor’s Table 11.6, Appendix 23.2, ISS.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Examination of the safety data collected from the randomized, double-blind, placebo controlled, parallel group, dose comparison Phase 3 trials (405 and 406) and from the Phase 2 multiple, repeat-dose, dose-ranging study failed to identify any trends suggestive of a possible dose-dependent relationship associated with exposure to pegloticase.

7.5.2 Time Dependency for Adverse Events

Overall, review of the cumulative long term exposure data generated from the ongoing OLE study, 407, did not reveal any new safety signals associated with prolonged exposure to pegloticase.

7.5.3 Drug-Demographic Interactions

Subgroup analyses on AEs and lab parameters were conducted on pooled data generated from the pivotal studies in order to determine if there were any drug-demographic interactions. Review of the treatment-emergent AEs by race did not identify any clinically significant trends in these studies. Table 72 summarizes the analysis of AEs by age for specific AEs where a difference in the rate of occurrence was identified for subjects' age < 65 years and \geq 65 years. Contusion (10%) and peripheral edema (29%) were observed more frequently in older patients as compared to younger patients treated with pegloticase (2% and 6%, respectively) who reported having more fatigue (8%) than those over age 65 years. Peripheral edema is probably not a drug-demographic AE since a higher rate of peripheral edema (17%) was also seen in patients \geq 65 years of age treated with placebo as compared to younger patients (13%). The higher rate of contusions is clinically insignificant and is probably related to pegloticase's route of administration (e.g., intravenous infusion). Interestingly, a higher rate of fatigue was seen in patients \geq 65 years of age (25%) treated with placebo compared to younger patients (3%) also suggesting that it is not a drug-demographic AE. Overall, there were no clinically meaningful differences in the safety profile of pegloticase in patients <65 years old compared to patients \geq 65 years old.

Table 72 – Tabular Summary of Treatment-Emergent AEs by Preferred Term and Age for Combined Controlled Studies 405 and 406

Adverse Event Preferred Term	All Pegloticase 8mg Group		Placebo	
	<65 years N=121	≥ 65 years N=48	<65 years N=31	≥ 65 years N=12
Fatigue	10 (8%)	1 (2%)	1 (3%)	3 (25%)
Contusion	2 (2%)	5 (10%)	1 (3%)	0
Peripheral Edema	7 (6%)	14 (29%)	4 (13%)	2 (17%)

Sponsor's Table 56; p. 109 ISS.

The results of an analysis of AEs by gender (Table 73) demonstrate that the rates of nausea (16%), diarrhea (28%), and contusion (16%) were higher in female patients treated with pegloticase as compared to male patients (nausea: 8%, diarrhea: 10%, and contusion: 0%). The numbers of patients involved in the analyses are too small to draw valid conclusions. Overall, there were no clinically meaningful differences in the safety profile of pegloticase in males compared to females.

Table 73 – Tabular Summary of Treatment-Emergent AEs by Preferred Term and Sex for Combined Controlled Studies 405 and 406

Adverse Event Preferred Term	All Pegloticase 8mg Group		Placebo	
	Male N=137	Female N=32	Male N=36	Female N=7
Nausea	11 (8%)	5 (16%)	1 (3%)	0
Diarrhea	14 (10%)	9 (28%)	7 (19%)	1 (14%)
Contusion	2 (2%)	5 (16%)	1 (3%)	0

Sponsor's Table 57; p. 109 ISS.

7.5.4 Drug-Disease Interactions

No drug-disease interactions were observed.

7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies were conducted by the Applicant in support of pegloticase's safety. Review of the database did not identify any AEs that appeared related to an interaction with concomitant medications.

7.6 Additional Safety Evaluations

Human Carcinogenicity

Table 74 lists the 2 malignancies observed in patients who participated in the Phase 3 pegloticase trials. One case involved an 80-year old male (Subject 406-311-002) randomized to the placebo group in Study 406 who had a recurrence of chronic lymphocytic leukemia (CLL) that had been in remission when he enrolled in the study. He was started on treatment with intravenous Campath three times a week while continuing his pegloticase study infusions. This patient ultimately withdrew from the study due to his malignancy and died from complications secondary to his CLL. The other case was a 73-year old male (Subject 405-122-003) who was found to have a skin lesion on his left ear on physical exam when he received his first study infusion. Six months later, the lesion was surgically removed after he received his final dose of study medication. The histopathology of the lesion was consistent with malignant melanoma. This case should not be attributed to pegloticase since the lesion was present prior to exposure to the product.

Table 74 – Subjects Reporting Treatment-Emergent Malignancies During Studies 405, 406 and 407

Subject Number	Age/Sex	Onset Day	Malignancy	Outcome	Causality
Placebo					
406-311-002	80 yo/M	Day 48 (Dose 4)	Chronic Lymphocytic Leukemia (Recurrent)	Ongoing	Unrelated
Pegloticase 8 mg every 4 weeks					
405-122-003	73yo/M	Day 376 (Dose 12)	Malignant Melanoma	Resolved	Unrelated

7.6.2 Human Reproduction and Pregnancy Data

All of the study protocols evaluated pegloticase as a treatment for refractory gout prohibited pregnant and breast feeding women from participating in these studies. Additionally, these studies' entry criteria required women of reproductive potential to practice effective forms of contraception for the duration of the trials. Thus, no female subjects were reported to have become pregnant during the studies.

7.6.3 Pediatrics and Assessment of Effects on Growth

This application did not contain any data generated from assessments of pegloticase's effect on growth since the Applicant has not conducted a study in children or adolescents. Since gout is very rare in children, the Applicant should not be required to conduct a study in the pediatric population. Additionally, pegloticase was granted orphan drug status on February 21, 2001. It is therefore exempted from conducting a pediatric assessment as per the provisions of the Pediatric Equity Act (PERA) and 21CFR314.55(d).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant stated in the submission that they had not received any reports of overdose associated with pegloticase. An overdose of the product would most likely result in a low or undetectable level of PUA which is currently not associated with known adverse clinical consequences. It is unlikely that pegloticase will be abused since it does not affect the central nervous system, has to be administered via intravenous infusion and its use is associated with the risk of developing infusion reactions and anaphylaxis.

7.7 Additional Submissions / Safety Issues

On January 31, 2008 the Applicant submitted a major amendment to this BLA consisting of additional post hoc analyses by a cardiovascular adjudication committee of the cardiovascular adverse events that were observed in patients exposed to pegloticase contained in the safety database. The results of these analyses and a discussion of the adjudication committee's findings can be found in the preceding Section 7.3.5.c. Additional safety information that was contained in the Applicant's 120-day safety update submitted on February 27, 2009 has been incorporated into the appropriate preceding subsections of this review.

8 Postmarket Experience

Not applicable. Pegloticase is a new molecular entity that has not been approved for marketing in any country.

9 Appendices

9.1 Literature Review/References

The Applicant conducted a review of the worldwide literature via the search engine Dialog® of the following databases: MEDLINE (1950 to present), EMBASE (1974 to present), BIOSIS (1969 to present), SCISEARCH (1974 to present), International Pharmaceutical Abstracts (1970 to present) and COCHRANE (1993 to present). A total of 53 citations were thus identified as of July 28, 2008 as follows: 4 citations describing the double-blind, placebo-controlled pivotal studies (405 and 406); 13 citations describing the results from the Phase 1 and Phase 2 studies (401, 402 and 403), 21 citations that reviewed current treatments and clinical management of patients with gout, 12 citations discussing the results of preclinical toxicology and pharmacology studies in a variety of animal modes, 7 citations that discussed the findings of open-label studies in gout patients treated with rasburicase, and 13 case reports of adverse events (methemoglobinemia and hemolysis) associated with the use of rasburicase in patients with lymphoma, post-transplant and tophaceous gout. These citations were examined for clinical content and no new safety issues related to the use of pegloticase as a treatment for gout refractory to conventional therapy were identified.

An updated literature search was conducted by this medical officer on June 29, 2008 using the search engine PubMed. A total of 14 citations were identified out of which 9 were included in the original literature review by the Applicant. Examination of the remaining 5 citations did not reveal any new potential safety signals associated with the use of the pegloticase.

References:

¹Sampson HA, et al. Second symposium on the definition and management of anaphylaxis: Summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117:391-7.

9.2 Labeling Recommendations

Based on review of the data submitted in support of this application, this medical officer has the following recommendations for the product's label:

1. The tradename KRYSTEXXA™ is acceptable. It has been deemed acceptable by both DMETS and the Division
2. KRYSTEXXA should have a Medication Guide. A MedGuide has been proposed by the Applicant and is currently under review by both DRISC and the Division
3. Patients treated with pegloticase should have their serum uric acid levels monitored (b) (4), prior to receiving their pegloticase infusions in order to identify serum uric acid levels > 6 mg/dL consistent with loss of

therapeutic effectiveness due to antibody formation. Patients with serum uric acid > 6 mg/dL should have their treatment with the product discontinued to minimize their risk of having an adverse reaction (e.g., infusion reaction or anaphylaxis)

4. Treatment with pegloticase should also be discontinued in patients who experience severe infusion reactions or who have 2 infusion reactions
5. Information regarding [REDACTED] (b) (4)
anaphylaxis in the safety database to correctly inform prescribers about this safety risk

[REDACTED] (b) (4)

9.3 Advisory Committee Meeting

On June 16, 2009 an Arthritis Advisory Committee (AAC) meeting was convened to discuss the risks and benefits associated with the use of pegloticase based on the following safety issues identified during the agency's review of the data submitted in support of this application:

- The higher rate of serious cardiovascular events that occurred in patients treated with pegloticase as compared to placebo treated patients
- The higher rate of infusion reactions and anaphylaxis observed in pegloticase-treated patients as compared to placebo-patients despite mandatory prophylactic therapy
- The high rate of seroconversion to anti-pegloticase antibody positive status in patients treated with the product that resulted in decreased efficacy and an increase in adverse reactions (infusion reactions and AEs meeting clinical criteria for anaphylaxis)

Based on the presentations by both the Applicant and the agency, and an open discussion that included the weighing of the evidence presented to them the ACC voted overwhelmingly to recommend approval of the product. The following comments and concerns were raised by the AAC over the course of their deliberations:

1. It was difficult to determine cardiovascular risk since the evidence for the latter was not overwhelming. In addition, the small sample size of the randomized controlled trials made it difficult to reach firm conclusions.
2. If approved, pegloticase would be used in patients with underlying cardiovascular risks which raised additional safety concerns due to the unknown cardiovascular risk associated with the product.
3. Safety concerns associated with the corticosteroids that are part of the premedication regimen.

4. Pegloticase should be reserved for use in patients with refractory gout who have failed to respond to optimal therapy with other urate lowering agents.
5. The severity and incidence of infusion reactions were not of major concern since most rheumatologists have encountered similar problems with other biologic therapeutic agents and know how to appropriately manage these events.
6. Prescribers would need to closely monitor patients' serum uric acid levels to minimize the risk of infusion reactions and anaphylaxis associated with the administration of pegloticase.
7. Although a postmarketing registry would not definitively capture the information necessary to precisely determine the cardiovascular risk associated with pegloticase, some form of prospective patient registry would be important in evaluating the risk for cardiovascular events, infusion reactions and anaphylaxis.
8. Data should be collected regarding the use of pegloticase in post-transplant and dialysis patients.



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: June 26, 2009

From: Stephen M. Grant, M.D.
Clinical Reviewer
Division of Cardiovascular and Renal Products /CDER

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Diana L. Walker, PhD
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products

Subject: DCRP consult to evaluate an imbalance in the occurrence of serious adverse events in the two confirmatory clinical trials submitted to support BLA 125293

This memo responds to your consult to us requesting we 1) assess the significance of a greater proportion of subjects in the active treatment arms experiencing cardiovascular deaths and other cardiovascular serious adverse events (SAEs) in the two pivotal trials of a novel biologic for the treatment of gout and 2) recommend if additional information is needed to define the cardiovascular safety of product administration. DCRP received and reviewed the following materials:

- Your consult dated 19 Dec 2008
- Portions of BLA 125293 including the proposed label, section 2.4 Nonclinical Overview, section 2.5 Clinical Overview, section 2.7.4 Summary of Clinical Safety, section 5.3.5.3 Integrated Summary of Safety, and clinical study reports for studies 402, 403, 405, 406 and 407 (including individual narratives for cardiovascular SAEs). Case report forms for subjects with cardiovascular SAEs were reviewed, if included in the BLA submission.
- As agreed upon with your division, we did not review amendment 8 dated 04 Feb 2009, which contains a *post hoc* adjudication of cardiac events, so as to avoid being biased in our review of the data contained in the original NDA submission.

Background

Savient Pharmaceuticals, Inc. has submitted a BLA to obtain authorization to market pegloticase

for treatment of "treatment failure gout" (TFG) defined as patients with gout who have been treated with allopurinol but fail to normalize serum uric acid and have inadequate control of signs and symptoms or patients with gout who can not tolerate allopurinol. Treatment failure gout is an orphan drug population.

Gout is a disease caused by a deposition of crystals of uric acid into the articular cartilage of joints, tendons and surrounding tissues, causing inflammation and pain. It is generally associated with hyperuricemia, due to inadequate renal excretion or overproduction of uric acid. In most animals, uric acid is metabolized by uricase to allantoin, which is readily excreted in the urine. Humans are one of a few mammalian species that have an inactive uricase gene and so uric acid is the terminal product of purine metabolism. As a result blood uric acid levels in humans are 10-fold higher than in most other mammals.

Pegloticase is a monomethoxyl polyethylene glycol modified recombinant uricase produced in *E. coli*. Exogenous administration of uricase results in uric acid being metabolized to hydrogen peroxide and allantoin.

Reviewer's comment: A brief pub med search did not reveal any known adverse cardiovascular effects of allantoin. A brief pub med search also did not reveal any known cardiovascular effects of pegylated proteins. The applicant claims that exposure to hydrogen peroxide is minimal because the amount produced is far less than the scavenging capacity of the blood.

Nonclinical

No safety pharmacology studies were performed and no specific nonclinical evaluation of the effect of pegloticase administration on vital signs has been performed. A single long term chronic GLP toxicology study of IV administration (b) (4) study #7533-100) was performed in dogs. Heart rates and ECGs were recorded once prior to dose initiation and during Weeks 12, 24, 39, and 51 (recovery) at approximately 5 to 15 minutes post-dose. Blood pressure was not evaluated. There was a dose related trend toward higher heart rates in male animals but not in female animals. The significance of the findings is unclear; the metabolic milieu in the dog differs from humans because dogs are not uricase deficient.

Clinical Pharmacology

The volume of distribution of pegloticase is about 5L (i.e., about blood volume) with relatively small intersubject variability after intravenous administration. Elimination is linear with a long half-life of > 200 hours. Exposure (measured by AUC) increases approximately 50% if administered every two weeks but increases minimally if administered every 4 weeks. Doses \geq 2 mg decrease plasma uric acid levels.

Clinical

The applicant conducted six clinical studies of pegloticase administration to patients with gout and hyperuricemia. No studies were conducted in healthy subjects.

Phase 1 Studies:

- **Study C0401** was an open-label single ascending dose study of SC administration of 4.0 to 24 mg to 13 subjects with gout. Local site reactions, immune reactions and large intersubject variability in exposure (presumably due to differences in absorption) led to discontinuation of the study.

- **Study C0402** was an open-label single ascending dose study of IV administration of 0.5 to 12 mg over one hour to 24 subjects with gout. No SAEs or AES assessed as severe in intensity by the investigator were observed. Vital signs were collected frequently in the first week after administration. EKGs were not acquired. No significant changes in vital signs are reported.

Phase 2 Study:

- **Study C0403** was an open label dose ranging study in which 41 subjects with “gout refractory to conventional therapy” were randomized to administration of 1) 4 mg q2 wk, 2) 8 mg q2 wk, 3) 8 mg q4 wk, or 4) 12 mg q4 wk for three months. Vital signs were collected during and between scheduled visits for administration. EKGs were acquired at screening and several weeks after the final administration. No significant changes in vital signs are reported.

Phase 3 Studies:

- **Studies C0405 and C0406** were replicate randomized, double-blind, placebo-controlled parallel group studies in which 212 subjects were randomized 2:2:1 to administration of pegloticase 8 mg IV every two weeks: pegloticase 8 mg IV every four weeks: placebo for six months. Subjects with “unstable angina,” “noncompensated congestive heart failure,” “uncontrolled arrhythmias,” and “uncontrolled hypertension” were not eligible. Vital signs were measured prior to each infusion and periodically during infusion. 12-lead EKGs were obtained at baseline and at the end of 6 months.

- Results

109 subjects were enrolled and 104 administered study drug in the USA and Canada in C0405. 116 subjects were enrolled and 108 administered study drug in the USA and Mexico in C0406. About 11% of the subjects reported a history of coronary artery disease, 36% cardiac disease, 17% renal failure, 13% diabetes, and 71% hypertension. Adverse events, (primarily infusion reactions and gouty attacks) resulted in discontinuation far more frequently in pegloticase treated subjects (~19%) than placebo subjects (~2%). About one third of subjects administered pegloticase had infusion reactions reported.

Reviewer's comment: It is likely that substantial numbers of pegloticase subjects were unblinded by the infusion reactions.

Systolic and diastolic blood pressure was measured at baseline, week 13, week 25, and end of study and is summarized in the applicant's report as means with standard deviations, medians, and ranges. No pattern is discernible. 13 subjects randomized to pegloticase had AEs of “blood pressure increased” or “hypertension” whereas 3 placebo subjects did.

Reviewer's comment: Given the scanty non-systematic measurement of blood pressure, it is not surprising that the applicant's data are not informative. An outlier analysis might be informative.

EKGs were obtained routinely only at baseline and at end of study in trials C0405 and C0406. The applicant reports that that 18.0 % of the EKGs of the subjects administered pegloticase 8 mg IV every two weeks became abnormal, 14.8 % of the EKGs of the subjects administered pegloticase 8 mg IV every four weeks became abnormal, and 10.5% of placebo subjects.

Reviewer's comment: The ECGs were read at the investigator's site and I could not find any attempt to control the quality of acquisition or interpretation. The applicant should characterize the nature of abnormalities detected.

- **Study C0407** is an ongoing open label extension study in which 149 of the 157 subjects who completed studies C0405 and C0406 are administered pegloticase 8 mg IV every two or four weeks (depending on investigator preference) for up to 24 months. The dose frequency can be changed after 6 months. 12-lead EKGs are not being acquired routinely.

No DSMB or clinical adjudication committee was used in any trial. No definition for any cardiac adverse is specified in the protocol for any study.

Cardiovascular Serious Adverse Events in all Studies

The applicant narratives of SAEs in each clinical study report were scanned for SAEs possibly cardiovascular in nature. The CRFs of subjects who appeared to have cardiac SAEs were also reviewed if contained in the BLA submission, but most were not.

The following subjects had SAEs most likely due to ischemic cardiovascular vascular disease:

1. 203-001 in trial C0405 was a 61 year-old male with ischemic cardiomyopathy and left ventricular ejection fraction of 17% taking a beta blocker, ACE inhibitor, furosemide and spironolactone. He was randomized to 8 mg pegloticase q 2 weeks and received his first dose on 28 Mar 2007. He missed doses 6 and 8. Dose 8 appears to have been held for asymptomatic hypotension; ACE inhibitor and spironolactone were discontinued. His last dose was 20 Jun at which his BP was 140/80 and bibasilar rales and pitting edema were noted. On (b) (6) he died suddenly after physical exertion.
2. Subject 122-003 in trial C0405 was 73 year-old male with a long history of cardiac disease. He was randomized to 8 mg pegloticase q 4 weeks and received his first dose and only dose of pegloticase on 03 Aug 2007. On (b) (6) he had an inferolateral MI treated by primary PCI. The subject continued in the study.
3. Subject 315-005 in trial C0406 was a 61 year old male with a long history of cardiac disease. He was randomized to 8 mg pegloticase q 2 weeks. He received his first dose of pegloticase on 29 Nov 2006 and had 8 subsequent doses with the last on 27 Mar 2007. He complained of not feeling well on 03 Apr. On (b) (6) he died while being driven to the hospital.
4. Subject 301-012 in trial C0406 was a 78 year old female randomized to 8 mg pegloticase q 4 weeks. She received her first dose and only dose of pegloticase on 26 Oct 2006. She withdrew from the study on 09 Nov. (b) (6) after withdrawing from the study she had a transient ischemic attack and recovered apparently without neurologic sequelae.
5. Subject 002003 in trial C0403 was a 77 year old female with hypertension, diabetes, and coronary artery disease administered 12 mg pegloticase q 4 weeks beginning 17 May 2006. (b) (6) after the second infusion she had a CVA. Head CT revealed evidence of small vessel disease. Her final diagnosis was lacunar stroke. She continued in the study and received her third and final dose of pegloticase.

The following subjects had myocardial injury most likely due to noncardiac SAEs:

6. Subject 110-001 in trial C0405 was 46 year-old male with a history of coronary artery

disease randomized to 8 mg pegloticase q 2 weeks. He was administered his first dose on 14 Jun 2006. On (b) (6) he was hospitalized with hematemesis complicated by hypotension requiring fluid resuscitation. His initial serum troponin was minimally elevated but subsequently declined to the normal range. The investigator withdrew the subject from the study.

7. Subject 101-005 in trial C0405 was a 67 year-old male with hypertension, diabetes mellitus, dyslipidemia and coronary artery disease (CAD). He was randomized to placebo and received his first dose on 10 Oct 2006. On (b) (6) he was hospitalized for evaluation of syncope and retrosternal chest pain. He also was febrile and hypotensive. He is reported to have had a small "troponin leak." The clinical impression was that the myocardial injury was secondary. Transthoracic echocardiography was consistent with an old inferior MI. The subject continued in the study.

The following subjects had SAEs most likely due to heart failure.

8. Subject 102-006 in trial C0406 was a 64 year old male with ischemic cardiomyopathy and left ventricular ejection fraction of 10-15%. He was randomized to 8 mg pegloticase q 4 weeks. He received his first and only dose of pegloticase on 13 Oct 2006. On (b) (6) he was hospitalized for acute heart failure. He subsequently developed acute renal failure and died in hospice a few weeks later.
9. Subject 311-005 in trial C0406 was a 67 year old male with a "cardiovascular history" s/p implantable defibrillator insertion. He was randomized to 8 mg pegloticase q 2 weeks. He received his first dose of pegloticase on 16 Jan 2007 and had 3 subsequent doses, the last on 28 Feb 2007. On (b) (6) he was hospitalized and diuresed for acute heart failure. He continued in the study.

The following subjects had SAEs most likely due to cardiac arrhythmias.

10. Subject 301-006 in trial C0406 was a 62 year old female without previous cardiac history. She was randomized to 8 mg pegloticase q 4 weeks receiving her first dose of pegloticase on 31 Aug 2006 and her last dose on 16 Oct. She developed a supraventricular tachycardia on (b) (b) which was treated with adenosine and atenolol. She continued in the study.
11. Subject 311-005 (same subject who had CHF) in trial C0406 was a 67 year old male with a "cardiovascular history" s/p implantable defibrillator insertion. He was randomized to 8 mg pegloticase q 2 weeks. On (b) (6) he had a defibrillator shock and then lost consciousness. Interrogation of the ICD revealed he had had an episode of ventricular tachycardia. He continued in the study.

The following subjects had SAEs most likely not cardiac.

1. Subject 124-001 in trial C0405. She was admitted for dyspnea and the event was reported as heart failure. Transthoracic echocardiogram revealed normal left ventricular function and diuresis resulted in prerenal azotemia. She continued in the study.
2. Subject 109-005 in trial C0405 was an 84 year-old male with hypertension and dyslipidemia. He was admitted for dyspnea. Transthoracic echocardiogram and adenosine perfusion imaging were unremarkable. He continued in the study.

3. Subject 311-001 in trial C0406. He was admitted for cardiac catheterization after episodes of chest pain and the event was reported as angina. He had a history of coronary artery disease. Cardiac angiography was unchanged from previous. He continued in the study.
4. Subject 301-002 in trial C0406. He was admitted for evaluation of chest pain and the event was reported as atypical chest pain. Serial cardiac enzymes were normal as was an exercise test. He continued in the study.
5. The same subject (301-002) was hospitalized for syncope. He had taken an extra dose of his prescribed oral hypoglycemic and was found to be hypoglycemic and responded to intravenous glucose. He continued in the study.
6. Subject 327-002 in trial C0406. He was admitted for evaluation of chest pain and the event was reported as left thoracic chest pain. Serial cardiac enzymes were normal as was an exercise echocardiogram. He continued in the study.
7. Subject 301-017 in trial C0406, who had "a significant cardiac history". She went to hospital for evaluation of self-measured high blood pressure. She was admitted for evaluation of chest discomfort. Serial troponin was normal and she was not discharged on any new cardiac medications. She continued in the study.
8. Subject 118-001 in trial C0405. He was hospitalized for evaluation of chest pain about two months after he had withdrawn from the study. He had had a normal coronary angiogram within the past three years and a history of gastroesophageal reflux. Cardiac troponin was normal and his ECG was unchanged.
9. Subject 301-012 in trial C0406 had a transient ischemic attack 35 days after withdrawing from the study.
10. Subject 130-004 in trial C0406 was a 64 year old male with ischemic cardiomyopathy and implantable cardiac defibrillator. He was hospitalized for near syncope. Troponin was normal. Interrogation of the ICD was unrevealing. He continued in the study.
11. Subject 118-001 in trial C0407, who had a normal coronary angiogram in 2005. He was hospitalized two months after withdrawing for evaluation of chest pain. He was admitted for evaluation of chest discomfort. Serial troponin was normal and his EKGs were unchanged compared to baseline and did not evolve. He was not discharged on any new cardiac medications.
12. Subject 130-004 in trial C0407, who had ischemic cardiomyopathy and implantable cardiac defibrillator. He had an episode of presyncope while a subject of trial C0406 (see above). He was hospitalized for near syncope. Creatine kinase levels were normal. He continued in the study.
13. Subject 301-017 in trial C0407, who had an episode of chest pain while a subject of trial C0406 (see above). She was hospitalized multiple times for chest pain. Serial troponin levels were normal. She continued in the study.
14. Subject 327-002 in trial C0407, who a history of cardiovascular disease. He had an episode of chest pain while a subject of trial C0406 (see above). He was admitted for evaluation of chest pain. Serial cardiac enzymes were normal as was a subsequent exercise echocardiogram. He continued in the study.

15. Subject 009002 in trial C0403 was hospitalized for chest pain twice, 1 and 2 weeks after the final infusion of study medication. EKGs and cardiac enzymes were normal. A coronary angiogram did not disclose significant coronary artery disease.

DCRP COMMENTS:

There are a number of reasons to suspect that the data used to evaluate cardiac safety may be misleading. Cardiac adverse events were not a prespecified safety endpoint in any trial so ascertainment may not be complete. Further, treatment assignment of substantial numbers of subjects in the confirmatory trials may have unblinded by infusion reactions, potentially introducing bias into investigator reporting of adverse events. Finally, it is unclear when the applicant supplied narratives were written. If written after treatment assignment was unmasked, they are likely to be biased. This reviewer found at least one adverse event of myocardial injury that did not appear to have been identified by the applicant. There may be other unidentified significant cardiac AEs.

Further, the lack of systematic evaluation of blood pressure and electrocardiograms renders any evaluation of the cardiac effects of pegloticase incomplete. Important mechanisms through which drugs may increase adverse cardiac outcomes include increasing systemic blood pressure, which predisposes to cardiac ischemic events and heart failure, and prolongation of ventricular repolarization, which predisposes to ventricular arrhythmias.

It is difficult to analyze *post hoc* the observed cardiovascular events without a postulating a mechanism through which they occur. If a mechanism can be postulated based on e.g. mechanism of action, nonclinical data, or a safety signal seen in earlier trials, then a reasonable hypothesis to be explored can be constructed. In the absence of a hypothesis, it is difficult to analyze the events since multiple ways of analyzing the data are possible. If multiple analyses are conducted, then the probability that one of them will appear meaningful by chance increases with each additional hypothesis.

How then should the cardiovascular safety data observed in the clinical studies of this novel biologic drug be analyzed? There is no guidance in this area. In this reviewer's opinion, considering all cardiac serious adverse events as a single group of occurrences for purposes of evaluating safety is not informative. For example, there is no causal mechanism common to supraventricular tachycardia and myocardial infarction so considering these SAEs as part of a single group may be misleading.

This reviewer has chosen to explore the possible association between pegloticase administration and cardiac adverse events by counting the number of events that comprise one of three common efficacy endpoints used in studies of CV drugs. Death is always the most important endpoint and counting subjects who died due to cardiovascular causes is one approach that seems valid. Ascertainment of death is likely to be complete and the only uncertainty is determining whether death is cardiovascular. Counting all the subjects who had irreversible SAEs due to ischemic vascular disease (i.e., CV death, nonfatal MI, and nonfatal stroke) should be another useful approach but may be subject to ascertainment bias; e.g., small "enzymatic" MIs without accompanying concomitant EKG changes and "silent" MIs may be less likely to be identified. Indeed, the applicant failed to identify the SAE suffered by subject 110-001 as having a cardiac component. Lastly, counting all subjects who died or were hospitalized for events that appeared due to ischemic heart disease or heart failure could be useful because they can share

some common mechanisms; hypertension for example predisposes to both. Obviously this last grouping is more likely biased than the previous two groupings since identifying the events that comprise it is more subjective.

Since there were so few events this reviewer elected to simply count events that occurred in the controlled trials. More sophisticated analyses such as time-to-event and exposure-response are unlikely to be informative. Also, only events that occurred during the placebo-controlled trials were counted. As noted above, the population enrolled in these trials had a significant prevalence of cardiovascular disease and risk factors for cardiovascular disease so the occurrence of severe cardiac AEs was to be expected.

DCRP SUMMARY:

- None of the cardiac adverse events identified appeared unusual, i.e., they all occurred in subjects predisposed to such events. With the exceptions of subjects 301-012 and 301-006, who had reversible events (TIA and SVT respectively), all subjects identified as having serious cardiovascular adverse events had significant histories of cardiovascular disease. The population enrolled in the confirmatory trials and extension study appears to have had high prevalence of cardiovascular disease so the occurrence of some cardiac serious adverse events is expected.
- All three deaths that appear to have been due to cardiovascular disease occurred in subjects randomized to pegloticase (two q2wks and one q4wks).
- This reviewer counted six SAEs (which include the three deaths discussed above) of CV death, nonfatal MI, or nonfatal stroke; five occurred in subjects randomized to pegloticase (three q2wks and two q4wks) and one to placebo.
- This reviewer counted six SAEs that resulted in CV death or hospitalization that appeared most likely due to ischemic vascular disease and/or heart failure; all six occurred in subjects randomized to pegloticase (three q2wks and three q4wks).
- 169 subjects were randomized to pegloticase and 43 to placebo in the controlled trials. The distribution of cardiovascular deaths and of cardiac SAEs due to ischemic vascular disease and/or heart failure are not obviously unusual, even considering the decreased duration of exposure to study drug in the pegloticase groups (more pegloticase subjects withdrew prior to study conclusion).
- However, there are too few cardiac SAEs to be able to allow detection of any pattern in their occurrence resulting in a degree of uncertainty about the cardiac safety of pegloticase. The total placebo exposure in the entire development program is less than 25 subject years. And only 169 subjects were exposed to pegloticase and none for more than six months in the controlled setting. Few subjects have been exposed for more than one year. Further no meaningful evaluation of the effect of pegloticase on vital signs or electrocardiograms has been performed.

DCRP RECOMMENDATIONS:

We recommend you request the applicant provide

- A summary by subject of electrocardiographic abnormalities identified on the final ECGs of subjects enrolled in studies C0405 and C0406 not identified on their entry ECGs. Any

evidence of interval myocardial infarction or prolongation of ventricular repolarization should be highlighted.

- An outlier analysis of the occurrence of hypertension. We are unaware of any precedent for specifying the cut points for such an analysis. In its absence, perhaps changes of > 20 from baseline at any timepoint would be useful. Additionally, an analysis of mean change from baseline divided into quartiles by treatment group could be informative.

Thank you for requesting our input into the review of this BLA. We welcome more discussion with you now and in the future.

DIVISION OF PULMONARY AND ALLERGY PRODUCTS
MEDICAL OFFICER CONSULTATION

Date: June 1, 2009
To: Diana Walker, RPM, Division of Anesthesia, Analgesia, and Rheumatology (DAARP)
From: Susan Limb, MD, Medical Reviewer *ASL 6/1/09*
Through: Sally Seymour, MD, Medical Team Leader *SS 6/1/09*
Through: Badrul Chowdhury, MD, PhD, Division Director *B. Chowdhury 6/1/09*
Subject: Krystexxa (pegloticase) anaphylaxis cases

General Information

NDA/IND#: BLA 125293
Sponsor: Savient Pharmaceuticals, Inc.
Drug Product: Pegloticase
Protocol: N/A
Request From: Diana Walker, RPM (DAARP)
Date of Request: February 23, 2009
Date Received: March 12, 2009
Materials Reviewed: BLA submission (October 31, 2008)

Executive Summary

This is a medical officer consultation in response to a consultation request from the Division of Anesthesia, Analgesia, and Rheumatology (DAARP) regarding hypersensitivity and potential anaphylaxis reactions associated with a new biologic product, pegloticase. Pegloticase is a monomethoxy polyethylene glycol (PEG) modified, porcine derived, recombinant uricase proposed for the treatment of hyperuricemia and to manage the signs and symptoms of gout in patients with treatment failure gout (TFG). TFG occurs in a subset of gout patients, whose hyperuricemia cannot be controlled by conventional urate lowering therapy or who are intolerant of these therapies. Pegloticase is designated as an orphan drug and is currently under Priority review.

Early in the pegloticase development program, infusion reactions were observed in a large number of patients. The infusion reactions included a range of signs and symptoms, and a substantial subset of the reactions was suggestive of immune-mediated hypersensitivity reactions, including anaphylaxis. Based on review of individual line listings, at least 14 cases meeting the NIAID/FAAN proposed diagnostic criteria for anaphylaxis were identified. The estimated frequency of anaphylaxis is 5.1% (14 of 273 patients who received IV pegloticase). For the Q2wk regimen, the frequency is 7.3% (9 out of 123); for the Q4wk regimen, the frequency is 3.9% (4 out of 126), which is a reverse of the trend observed for infusion reactions as a whole. Given the small numbers,

the difference in frequency between the two dosing regimens is difficult to interpret and may be due to chance and variability in safety reporting. Since the Phase 3 studies were conducted with mandatory prophylactic administration of antihistamines, acetaminophen and IV corticosteroids prior to pegloticase infusion, the use of routine prophylaxis may have blunted or obscured certain signs and symptoms, the true rate of anaphylaxis and other hypersensitivity reactions may be underestimated. Based on the cases identified, the presence of IgE, IgG or IgM antibodies against the drug did not appear to have a predictive effect. Other screening assessments such as skin test or graded challenge were not performed.

An estimated rate of anaphylaxis of 5% is not unusually high compared to similar porcine-derived biologic products. (b) (4)
(b) (4)
Such tests could potentially identify patients at risk for anaphylaxis and improve the risk:benefit ratio for the drug.

Overview of clinical development program and proposed labeling

The clinical development program consisted of 7 studies, including two, randomized, placebo-controlled clinical trials conducted in the US, Canada, and Mexico. A total of 273 unique patients received IV pegloticase. The two pivotal studies, Studies C0405 and C0406 had a 6-month double-blind treatment phase, followed by an open-label extension (OLE) under a separate protocol (C0407) up to 24-months in duration. Of the 157 patients enrolled in the C0405 and C0406 studies, 149 were treated with pegloticase in the OLE. Another 24-month, open-label study is ongoing under a separate protocol, Study C0409, which includes patients who participated in the Phase 2 studies and received pegloticase IV. The purpose of this study is to evaluate the safety of 8mg pegloticase Q2weeks in patients whose previous exposure to pegloticase was greater than 1 year ago. The Applicant's Integrated Summary of Safety did not include data from C0409; a separate, brief progress report was included in the BLA. The clinical development program is summarized in the table below.

Clinical development program for pegloticase				
Study	Design	Treatment	N	Duration
C0401 <i>P1 with SC formulation</i>	OL, escalating SD	Pegloticase SC		1 day
		4mg	4	
		8	4	
		12	4	
C0402 <i>P1 with IV formulation</i>	OL, escalating SD	Pegloticase IV		1 day
		0.5mg	4	
		1	4	
		2	4	
		4	4	
C0403 <i>P2 proof of concept</i>	R, OL	Pegloticase IV		12 weeks
		4mg q2wks	7	
		8mg q2wks	8	
		8mg q4wks	13	
C0405 <i>Pivotal P3 study</i>	R, DB, PC	Pegloticase IV		26 weeks
		8mg q2wks	43	
		8mg q4wks	41	
		Placebo	20	
C0406 <i>Pivotal P3 study</i>	R, DB, PC	Pegloticase IV		26 weeks
		8mg q2wks	43	
		8mg q4wks	41	
		Placebo	20	
C0407 <i>P3 OLE</i>	OLE	Pegloticase IV		24 months
		8mg q2wks	82	
		8mg q4wks	67	
C0409 <i>Not included in ISS</i>	OL	Pegloticase IV 8mg q2wks	? (ongoing)	24 months

Early in the pegloticase development program, infusion reactions were observed in a large number of patients. The infusion reactions included a range of signs and symptoms, and a substantial subset of the reactions was suggestive of immune-mediated hypersensitivity reactions, including anaphylaxis. For this reason, the Phase 3 studies were conducted with mandatory prophylactic administration of antihistamines, acetaminophen and IV corticosteroids prior to pegloticase infusion. (b) (4)

The BLA does identify a group of infusion reactions as “infusion reactions with hypersensitivity constellation of symptoms.” The Highlights section of the proposed product label mentions infusion reactions, including hypersensitivity, (b) (4)

The Warnings and Precautions section refers to a risk of infusion reactions, which may include (b) (4) Based on the Applicant’s analysis, infusion reactions are estimated to occur in 41% of patients who received 8mg pegloticase Q4 weeks and 26% in 8mg pegloticase Q2weeks compared to 5% of placebo. (b) (4)

[Redacted]

Hypersensitivity reactions associated with pegloticase

Injection site reactions with SC formulation

Local injection site reactions were noted in 8 of 13 patients upon initial single dose exposure during the early development of a SC formulation of pegloticase. Two patients in the 12 mg cohort developed delayed reactions 8 to 10 days later, starting as local site reactions and progressing to generalized urticaria. ELISA testing demonstrated anti-pegloticase IgG and IgM antibodies in 5 of the 13 patients, including the 2 patients with delayed reactions. IgE was also found in 1 of the 2 patients. Due to the high rate of hypersensitivity events, the Applicant discontinued development of the SC formulation and pursued development of the IV formulation used in Phase 2 and 3 trials.

Infusion reactions

Infusion reactions were identified early in the development of the IV formulation, occurring in approximately 44% of the patients in the Phase 2 proof of concept study (Study C0403). A range of symptoms was associated with the infusion reactions. The most common symptoms included back pain, chest discomfort, chest pain, dyspnea, erythema, flushing, headache, hyperhidrosis, muscle spasms, nausea, pain, pruritus, rash, and urticaria. As a result, DAARP recommended that routine prophylaxis be administered to patients during the phase 3 program. The prophylactic measures included fexofenadine 60 mg the night before and the morning of the infusion, acetaminophen 1000 mg the morning of the infusion, and hydrocortisone 200 mg IV immediately prior to each infusion. Infusion reactions were defined as an AE or cluster of AEs that occurred during or within 2 hours after the end of the infusion. Investigators were requested to document vital signs, physical exam findings, serum tryptase (double-blind phase only), ECG, and any additional emergent assessments performed by the treating physician. Investigators were given the option of slowing or temporarily stopping the infusion, as well as administering IV fluids, diphenhydramine, and/or corticosteroids. If the Investigator felt that the infusion reaction was consistent with anaphylaxis, the infusion was stopped.

Reviewer's comment: The routine prophylaxis for infusion reactions in the Phase 3 trials makes it difficult to calculate the true frequency of infusion reactions, of which at least a subset appear to be anaphylaxis or other drug hypersensitivity reactions. As the prophylaxis may have blunted or obscured certain signs and symptoms, the true rate of anaphylaxis and other hypersensitivity reactions may be higher than the data suggests.

The Applicant provided pooled safety analyses on 4 study populations:

- Population A: C0405 and C0406 (double-blind phase of pivotal P3 trials)
- Population B: C0405, C0406, and C0407 (P3 pivotal trials and OLE)
- Population C: C0403, C0405, C0406, and C0407 (multiple dose P2 trial and P3 pivotal trials with OLE)
- Population D: C0402, C0403, C0405, C0406, and C0407 (all patients who have participated in pegloticase IV trials except for those patients enrolled in the ongoing OL trials, C0409). For those patients who were treated with placebo in

C0406 and C0405 then switched to active treatment in C0407, only safety data from the active treatment was included.

In Population A, an infusion reaction rate of 25.9% (n=22 of 85 patients) was reported in the 8 mg pegloticase q2weeks group and 40.5% (34 of 84) in the 8 mg pegloticase q4weeks group. In comparison, the rate reported in the placebo group was 4.7% (2 of 43). For Population D, the frequency was reported by the Applicant as 38.5%.

Reviewer’s comment: The increased frequency associated with less frequent dosing suggests a possible underlying immunologic mechanism rather than a dose-related effect for at least a subset of observed IRs.

In terms of the pattern of occurrence, the IRs appear to have occurred throughout the duration of the studies, and many patients had repeat reactions. In Population A, the patients who reported an IR to pegloticase, 11.8% (n=10) in the Q2week group and 19.0% (n=16) in the Q4weeks group had a single reaction.

Incidence of infusion reactions (Population A)			
	8mg pegloticase		Placebo N=43
	Q2wks N=85	Q4wks N=84	
# infusion reactions/total pegloticase infusions	43/852	65/430	n/a
# infusion reactions/total placebo infusions	n/a	5/416	4/502
# infusion reactions			
1	10 (11.8)	16 (19.0)	1 (2.3)
2	8 (9.4)	10 (11.9)	-
3	2 (2.4)	4 (4.8)	1 (2.3)
4	1 (1.2)	-	-
5	-	3 (3.6)	-
6	-	-	-
7	1 (1.2)	1 (1.2)	-

Infusion reactions suggestive of anaphylaxis

The Applicant identified a subset of 23 patients from the Phase 3 studies as having “infusion reactions with a hypersensitivity constellation of symptoms.” None of these were identified as anaphylaxis, although one event was recoded from “anaphylaxis” to “anaphylactoid.” Upon further review of these cases, at least 7 cases meet the most conservative set of diagnostic criteria unknown allergen for anaphylaxis (due to an unknown allergen) that have been proposed by the NIAID/FAAN Joint Symposium on Anaphylaxis (Sampson HA et al. *J Allergy Clin Immunol* 2006;117:391-7). These cases are briefly described below:

- C0405-102-003 – 23yo M with IR 26 minutes into 4th infusion. Lingual swelling, dyspnea, and nausea. Treated with diphenhydramine 25 mg IV. Serum tryptase 6.0 mcg/L (1.9-13.5 mcg/L reference range). Anti PEG-uricase titer 21870 Anti-PEG titer 270. No prior history of IR and no subsequent infusions. (8mg Q2wks)
- C0405-122-010 – 74yo M with IR 30 minutes into 5th infusion. Dyspnea, urticaria on face, neck, and trunk, hypoxia (O2 sat of 87%), increased blood pressure (129/65 → 184/72 mmHg), tachycardia (78 → 101 bpm). Serum

tryptase 36.8 mcg/L. Treated with IV diphenhydramine and albuterol. Anti PEG uricase 90. Prior IgE titer 60, negative on day of IR. No prior history of IR and no subsequent infusions. (8mg Q2wks)

- C0406-313-007 – 62yo M with IR 18 minutes into 1st infusion. Did not take prophylactic fexofenadine or acetaminophen. Facial flushing, diffuse pruritus, generalized urticaria, tachycardia (86 → 115 bpm), hypotension (142/87 → 81/21 mmHg), rigors, and lightheadedness. Serum tryptase 7.1 mcg/L. Treated with IV diphenhydramine and Demerol. No prior history of IR and no subsequent infusion. (8mg Q2wks)
- C0406-401-006 – 31yo M with two separate IRs on the 5th and 9th infusions. The first IR occurred 5 minutes into the infusion. Facial edema, facial hyperemia, dyspnea, tachycardia (80 → 96 bpm) and back pain. Serum tryptase 47.7mcg/L. Treated with IV hydrocortisone, metamizole, chlorophyramine, and O2. Had a subsequent IR 1 hr 40 min into the 9th dose with facial erythema, hypotension (130/80 → 80/60 mmHg), and dyspnea. Infusion stopped temporarily and treated with hydrocortisone and saline. Was able to resume and complete infusion 2 hours later. Serum tryptase 7 mcg/L. Patient able to complete study. (8mg Q4wks)
- C0405-122-005 – 40yo M who had previously completed Study C0405 and 2 doses of OL pegloticase in study C0407. IR during 2nd OL dose. Eye pruritus, periorbital edema, chest discomfort, throat irritation, arthralgia, and back pain. Treated with diphenhydramine and epinephrine. Prior history of IR with back pain, chest discomfort, and dyspnea. No subsequent infusions. (8mg Q2wks)
- C0405-114-001 – 68 yo M. Flushing, hypotension, dizziness, vomiting. Subsequent infusions with repeat IRs. (8mg Q4wks)
- C0405-125-006 – 51yo M. Flushing, conjunctival hyperemia, chest discomfort, hypotension. No prior history of IR and no subsequent infusions. (8mg Q4wks)

In addition to the cases highlighted by the Applicant, review of individual line listings revealed 7 more potential cases of anaphylaxis from Studies C0402, C0403, C0405, C406, and C407.

- C0403-009-004 – urticaria and chest tightness. Infusion #1. No more infusions. (12 mg Q4 wks)
- C0403-006-002 – severe allergic reaction, described in SAE narrative as a thick lip feeling, rash, burning, itching, diaphoresis, nausea and hypotension. Infusion #3. No more infusions. (4mg Q2wks)
- C0405-117-002 – 39yo M. 3rd dose. Throat tightness, pallor, dyspnea, chest discomfort, dizziness, abdominal discomfort, hyperhidrosis, chills, tremor. Anti-PEG uricase 270. IgE titer 60. No more infusions. (8mg Q2wks)
- C0405-118-001 – 45yo M. 1 hr into 4th dose. Chest pain, dyspnea, wheezing, and rash. Serum tryptase 8.8 mcg/L. Patient went on to have 8 more infusions without incident. (8mg Q2wks)
- C0405-203-001 – 61yo M. 2 hrs 15 minutes into 3rd dose. Urticaria and wheezing. Serum tryptase 10.5 mcg/L. Anti PEG uricase 810, anti PEG 84. Three more infusions without reactions. (8mg Q2wks)

- C0406-321-002 – 66yo M. 2 minutes into 6th infusion. Erythema, flushing, hypotension. Serum tryptase 11.2 mcg/L. Went on to have 6 additional doses without IR. (8mg Q2wks)
- C0406-323-006 – 70yo M. 5 minutes into 3rd dose. Dyspnea, erythema, pruritus. Went on to have 4 more doses. On 7th dose, had shortness of breath, dyspnea and erythema. Serum tryptase 5.5 mcg/L. Infusion stopped and no more infusions. (8mg Q4wks)

While some of these cases may appear to be less clinically severe than the others, it is worth noting that the NIAID/FAAN diagnostic criteria do not grade the severity of anaphylaxis. By virtue of multi-organ, multi-system involvement and the unpredictable nature of anaphylaxis, all anaphylactic reactions are considered severe and potentially life-threatening.

Reviewer's comment: Based on the cases identified, the presence of IgE, IgG or IgM antibodies against the drug did not appear to have a predictive effect. There were a substantial number of seropositive patients who did not report hypersensitivity reactions. There were also several patients who had pre-existing antibodies, including IgE, against pegloticase. Other screening assessments such as skin test or graded challenge were not performed during the clinical program.

Other potential cases of hypersensitivity

In addition to these cases, the following 2 cases displayed symptoms suggestive of anaphylaxis but did not meet the NIAID/FAAN's most conservative set of diagnostic criteria:

- C0405-101-004 – 50yo M with IR 50 minutes into 5th infusion. Diffuse facial flushing and swelling, moderate swelling of lip and tongue. Serum tryptase elevated at 15.0 mcg/L. Treated with IV diphenhydramine and dexamethasone. No prior history of IR and no subsequent infusions.
- C0405-107-007 – chest discomfort with dyspnea, hypotension, loss of consciousness. History of prior IR and no subsequent infusions.

The following patients in C0403 were identified as having “hypersensitivity” resulting in study discontinuation but further details were not available:

- C0403-006-003 – hypersensitivity. Infusion #2. No more infusions.
- C0403-012-002 – hypersensitivity. Infusion #2. No more infusions.

In the interim study report submitted for Study C0409, the Applicant reports that 3 of 7 subjects have experienced IRs. Details of the reactions are not provided, but the report states that no patients experienced wheezing, stridor, angioedema, rash, urticaria, or had evidence of hemodynamic instability (as of September 12, 2008), which makes a diagnosis of anaphylaxis less likely. All 3 subjects were re-exposed and 1 of 2 subjects with subsequent reactions was withdrawn.

Two patients assigned to pegloticase treatment (C04046-203-001 and C0405-315-005) died due to cardiac arrest and cardiac arrhythmia, respectively, during the double-blind phase of the Phase 3 studies, but review of the narratives does not suggest anaphylaxis as the underlying cause. The first patient had a history of CHF with an estimated ejection fraction of 17%, hypertension, and diabetes. The patient received 7 doses of 8mg/2weeks. The patient did not receive Dose 8 and experienced cardiac arrest approximately 4 weeks after Dose 7. The second patient had a history of cardiovascular disease, peripheral vascular disease, and diabetes. The patient received 9 doses of 8mg/2weeks. Seven days after Dose 9, the patient complained of weakness. Sixteen days after Dose 9, the patient felt worse and died en route to the hospital while being driven by his wife. His death was attributed to cardiac arrhythmia by the receiving emergency room physician.

Estimated frequency of anaphylaxis

Based on the 14 cases suggestive of anaphylaxis identified in the single-dose and multiple dose pegloticase IV studies, the estimated frequency of anaphylaxis is 5.1% (14 of 273 patients). For the Q2wk regimen, the frequency is 7.3% (9 out of 123); for the Q4wk regimen, the frequency is 3.9% (4 out of 126), which is a reverse of the trend observed for infusion reactions as a whole. Given the small numbers, the difference in frequency between the two dosing regimens is difficult to interpret and may be due to chance and variability in safety reporting. As the use of routine prophylaxis may have blunted or obscured certain signs and symptoms, the true rate of anaphylaxis and other hypersensitivity reactions may be underestimated. Since complete study information for Study C0409 was not included in the BLA, the rate calculation does not include patients or infusions from Study C0409.

An estimated rate of anaphylaxis of 5% is not unusually high compared to similar porcine-derived biologic products. (b) (4)

(b) (4)
Such tests could potentially identify patients at risk for anaphylaxis and improve the risk:benefit ratio for the drug.

Thank you for the consultation. Please let us know if we can provide further assistance.

CLINICAL FILING CHECKLIST FOR BLA 125293

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	Since this is a biological product, these data deemed unnecessary.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	It's a new molecular entity that has never been marketed
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	Exempted since it has been granted Orphan Drug Product status.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	New class of agents.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested)	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR BLA 125293

	Content Parameter	Yes	No	NA	Comment
	by the Division)?				
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR BLA 125293

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. In our initial review of your application we have noted a higher proportion of patients with cardiovascular deaths and cardiovascular serious adverse events (AEs) in the pegloticase arms. Additional information regarding these adverse events may be requested.

<i>Rosemarie Keener</i>	<i>12/19/08</i>
_____ Reviewing Medical Officer	_____ Date
<i>Jeffrey N. Siegel</i>	<i>12/19/08</i>
_____ Clinical Team Leader	_____ Date