

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**125293**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

**BLA Number:** STN 125293-0037

**Drug Name:** Krystexxa™ (Pegloticase, PEG-uricase and PURICASE®)

**Indication(s):** “To control the clinical consequences of hyperuricemia in patients with severe gout in whom conventional therapy is contraindicated or has been ineffective” (per Orphan Drug Designation granted February 21, 2001)

**Applicant:** Savient Pharmaceuticals, Inc.

**Date(s):** Letter date: March 15, 2010  
PDUFA date: September 15, 2010

**Review Priority:** Priority

**Biometrics Division:** Division of Biometrics II

**Statistical Reviewer:** Ruthanna C. Davi *Ruthanna C. Davi 8/4/10*

**Concurring Reviewer:** Joan Buenconsejo, Statistical Team Leader *Joan Buenconsejo, 8/4/10*

**Medical Division:** Division of Pulmonary, Allergy, and Rheumatology Products

**Clinical Team:** Medical Reviewer: Keith Hull  
Medical Team Leader: Sarah Okada

**Project Manager:** Ramani Sista

**Keywords:**  
BLA, benefit-risk

# Table of Contents

<b>1.</b>	<b>EXECUTIVE SUMMARY.....</b>	<b>3</b>
1.1	CONCLUSIONS AND RECOMMENDATIONS .....	3
1.2	BRIEF OVERVIEW OF CLINICAL STUDIES.....	3
1.3	STATISTICAL ISSUES AND FINDINGS .....	3
<b>2.</b>	<b>INTRODUCTION .....</b>	<b>4</b>
2.1	OVERVIEW .....	4
2.2	DATA SOURCES .....	4
<b>3.</b>	<b>STATISTICAL EVALUATION.....</b>	<b>5</b>
3.1	STUDY DESIGN (C0405 AND C0406).....	5
3.2	BENEFIT-RISK OF PEGLOTICASE WHEN STOPPING DOSING EARLY.....	6
<b>4.</b>	<b>SUMMARY AND CONCLUSIONS.....</b>	<b>9</b>
4.1	STATISTICAL ISSUES AND COLLECTIVE EVIDENCE .....	9
4.2	CONCLUSIONS AND RECOMMENDATIONS .....	10
<b>5.</b>	<b>APPENDIX 1.....</b>	<b>11</b>

# 1. EXECUTIVE SUMMARY

## 1.1 Conclusions and Recommendations

Choosing the most appropriate rule for stopping pegloticase dosing is a subjective clinical decision and may vary from clinician to clinician and/or patient to patient and is beyond the scope of this statistical review. The conclusion of this review is that clear communication (in labeling or by other means) of the efficacy and safety that can be expected under applicable stopping rules is needed so that the clinician may make an informed decision regarding stopping pegloticase early for a particular patient.

## 1.2 Brief Overview of Clinical Studies

As part of this submission, the sponsor has proposed a Risk Evaluation and Mitigation Strategy (REMS) which includes criteria for stopping pegloticase early (i.e., earlier than was prescribed in the phase 3 studies) in an effort to minimize the frequency with which infusion reactions occur. Data used to support this proposal stem from the results of two identically designed phase 3 pivotal studies referred to as C0405 and C0406 and each titled, "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". These studies were previously submitted (October 31, 2008), reviewed (statistical review dated July 9, 2009), and discussed by the FDA Arthritis Advisory Committee (June 16, 2009). A Complete Response (CR) letter was issued by the Office of Drug Evaluation II on July 31, 2009. Among other things, the CR letter stated that, "we have determined that a REMS is necessary for Krystexxa (pegloticase) to ensure that the benefits of the drug outweigh the risks of severe infusion reactions and anaphylaxis...". The sponsor's currently proposed REMS recommends stopping pegloticase if a patient's serum uric acid exceeds 6 mg/dL claiming that, "loss of ability to maintain normalized uric acid values (less than 6 mg/dL) is predictive of risk of infusion reactions". The current submission does not address the effect such a rule may have on the efficacy of pegloticase. The focus of this review will be to evaluate the benefit-risk of various criteria for stopping pegloticase including the effect such rules may have on the previously reviewed primary efficacy results and the occurrence of infusion reaction. The ideal set of criteria for stopping pegloticase is one that allows continued administration of pegloticase when there is potential for efficacy to be realized but still discontinues pegloticase prior to the occurrence of infusion reactions.

## 1.3 Statistical Issues and Findings

The following statistical issues and their impact have been described in the context of the review. Please refer to the specified section for details.

- The sponsor does not address what effect stopping pegloticase early in certain subjects may have on the efficacy of the product in the population. The focus of this review is to evaluate the benefit-risk of various criteria for stopping pegloticase including the effect such rules have on the previously reviewed primary efficacy results and the occurrence of infusion reaction. If an alternate dosing recommendation is made in labeling, the

efficacy of the product described in the clinical studies section should also be reflective of this change. (Section 3.2)

- Some of the sponsor's justification of a cut off of 6 mg/dL in serum uric acid (SUA) relies on the SUA level **at the time of the infusion reaction** as a predictor of the event. In clinical practice however, this value would likely not be available to the physician. The SUA acid at the **previous** visit would need to be used as the measure for deciding whether pegloticase treatment should be stopped or continued. (Section 3.2)

## 2. INTRODUCTION

### 2.1 Overview

As part of this submission, the sponsor has proposed a Risk Evaluation and Mitigation Strategy (REMS) which includes criteria for stopping pegloticase early (i.e., earlier than was prescribed in the phase 3 studies) in an effort to minimize the frequency with which infusion reactions occur. Data used to support this proposal stem from the results of two identically designed phase 3 pivotal studies referred to as C0405 and C0406 and each titled, "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". These studies were previously submitted (October 31, 2008), reviewed (statistical review dated July 9, 2009), and discussed by the FDA Arthritis Advisory Committee (June 16, 2009). A Complete Response (CR) letter was issued by the Office of Drug Evaluation II on July 31, 2009. Among other things, the CR letter stated that, "we have determined that a REMS is necessary for Krystexxa (pegloticase) to ensure that the benefits of the drug outweigh the risks of severe infusion reactions and anaphylaxis...". The sponsor's currently proposed REMS recommends stopping pegloticase if a patient's serum uric acid exceeds 6 mg/dL claiming that, "loss of ability to maintain normalized uric acid values (less than 6 mg/dL) is predictive of risk of infusion reactions". The current submission does not address the effect such a rule may have on the efficacy of pegloticase. The focus of this review will be to evaluate the benefit-risk of various criteria for stopping peloticase including the effect such rules may have on the previously reviewed primary efficacy results and the occurrence of infusion reaction. The ideal set of criteria for stopping pegloticase is one that allows continued administration of pegloticase in subjects where there is potential for efficacy to be realized but discontinues pegloticase in subjects who would experience infusion reaction(s) if treatment continued.

### 2.2 Data Sources

The following data sets were submitted electronically in the current submission and utilized in this review.

\\STN125293\0037\m5\datasets\iss\analysis\ADAE.xpt  
\\STN125293\0037\m5\datasets\iss\analysis\ADLAB.xpt

In addition, the following data set was submitted electronically in the October 31, 2009 submission and utilized in this review.

All submitted data sets were found to be adequately documented and organized.

### 3. STATISTICAL EVALUATION

#### 3.1 Study Design (C0405 and C0406)

Study C0405 and C0406 were multi-center studies with a primary objective of demonstrating the superiority of pegloticase over placebo in reducing plasma uric acid (PUA) as determined by the primary efficacy endpoint. The target population for these studies was comprised of hyperuricemic (serum uric acid (SUA)  $\geq 8$  mg/dL) adults ( $\geq 18$  years of age) diagnosed with symptomatic gout, in whom conventional therapy had been contraindicated or was ineffective. Symptomatic gout was defined as occurring in subjects having at least one of the following at the time of study enrollment: (i) at least three gout flares in the previous 18 months, (ii) at least one gout tophus, or (iii) gouty arthritis. Subjects in whom conventional therapy had been ineffective were subjects who had failed to reach SUA normalization following treatment with a medically appropriate maximum dose of allopurinol over at least three months. In total, the protocol specified six inclusion and 15 exclusion criteria for enrollment in these studies.

Eligible subjects washed out of any uric-acid-lowering agents at least one week before randomization and were required to refrain from using these agents throughout the study. At the screening visit, subjects not already on a prophylactic regimen of colchicine or non-steroidal anti-inflammatory drug (NSAID) to prevent gout flares were placed on one of these agents (with the dose regimen individualized for each subject by the investigators), unless medically contraindicated. In addition to gout flare prophylaxis, subjects were given injection site reaction prophylaxis consisting of fexofenadine 60 mg the night before and morning of each infusion, acetaminophen 1000 mg the morning of each infusion, and hydrocortisone 200 mg i.v. immediately prior to each infusion. A nationwide shortage of hydrocortisone and other short-acting corticosteroids developed during the course of the study; therefore, if 200 mg hydrocortisone was not available, a substitution with 40 mg methylprednisolone was allowed as long as the nationwide shortage persisted. If neither drug was available, the investigator could choose between 20 mg prednisone the night before the infusion or, with prior approval by the sponsor, substitution with another corticosteroid at an equivalent dosage and administered at an appropriate time before the infusion.

After the washout/screening period, patients were randomly assigned (in a 2:2:1 ratio stratified by presence/absence of tophi) to the following treatments to be received throughout the 24-week treatment period

- (1.) 8 mg pegloticase every 2 weeks (subsequently referred to as 8 mg/2 weeks)
- (2.) 8 mg pegloticase every 4 weeks alternating with placebo every two weeks to maintain the treatment blind (subsequently referred to as 8 mg/ 4 weeks)
- (3.) placebo every 2 weeks

The primary efficacy endpoint for these studies was the percentage of subjects achieving and maintaining PUA concentrations less than 6 mg/dL for at least 80% of the time during months 3 and 6 combined.

### 3.2 Benefit-Risk of Pegloticase when Stopping Dosing Early

As background, the primary efficacy results (as described in the October 31, 2008 submission) for the pegloticase 8 mg / 2 weeks and placebo groups for studies C405 and C406 are given in Table 1. On their face, the primary efficacy analyses presented in Table 1 support the efficacy of 8 mg / 2 weeks of pegloticase over placebo.

<b>Table 1: Primary Efficacy Analysis – Proportion of Subjects with PUA Concentrations &lt;6 mg/dL for at least 80% of the Time During Months 3 and 6 Combined (ITT)</b>				
	<b>Study C405</b>		<b>Study C406</b>	
	<b>Peg 8 mg/2 wks (N=43)</b>	<b>Placebo (N=20)</b>	<b>Peg 8 mg/2 wks (N=42)</b>	<b>Placebo (N=23)</b>
<b>Number Responders (%)</b>	20 (47%)	0 (0%)	16 (38%)	0 (0%)
<b>95% CI for diff. relative to placebo<sup>1</sup></b>	(32%, 61%)		(23%, 53%)	
<b>p-value for comparison to placebo<sup>2</sup></b>	<0.001		<0.001	

1. Binomial confidence interval for difference in proportions

2. Fisher’s exact test

Source: Sponsor analyses (C405 and C406 clinical study reports, table 11 of October 31, 2008 submission)

Also as background, as part of the review of the October 31, 2008 submission, the FDA medical team highlighted the frequency of infusion reactions as an important factor in characterizing the safety of pegloticase. The proportions of subjects experiencing at least one infusion reaction and a comparison of the pegloticase groups to placebo groups are given in Table 2. These data suggest an increased risk of infusion reaction with pegloticase over placebo.

<b>Table 2: Proportion of Subjects with Infusion Reaction (ITT)</b>				
	<b>Study C405</b>		<b>Study C406</b>	
	<b>Peg 8 mg/2 wks (N=43)</b>	<b>Placebo (N=20)</b>	<b>Peg 8 mg/2 wks (N=42)</b>	<b>Placebo (N=23)</b>
<b>Number subjects with infusion reaction at any visit (%)</b>	11 (26%)	1 (5%)	11 (26%)	1 (4%)
<b>p-value for comparison to placebo<sup>1</sup></b>	0.08		0.04	

1. Fisher’s exact test

Source: Sponsor analyses (C405 and C406 clinical study reports, section 14.3 table 33 of October 31, 2008 submission)

At the Arthritis Advisory Committee meeting held on June 16, 2009, the sponsor suggested that the occurrence of infusion reactions could be mitigated by stopping administration of pegloticase when subjects' serum uric acid (SUA) levels rise above 6 mg/dL. The committee expressed interest in this type of approach but questioned whether a cutoff of 6 mg/dL was supported by the data. Analyses to determine an appropriate cutoff (if one exists) that could help to minimize the number of infusion reactions by stopping pegloticase in subjects who are not likely to realize benefit from the treatment but still allow continuation of the drug in the subjects who may eventually benefit from the product were requested by the committee.

In the current submission, the sponsor has proposed a Risk Evaluation and Mitigation Strategy (REMS) including criteria for stopping pegloticase early (i.e., earlier than was prescribed in the phase 3 studies) in an effort to minimize the frequency with which infusion reactions occur. The currently proposed REMS recommends stopping pegloticase if a patient's serum uric acid exceeds 6 mg/dL claiming that, "loss of ability to maintain normalized uric acid values (less than 6 mg/dL) is predictive of risk of infusion reactions". The sponsor's justification for a cut-off of 6 mg/dL stems from the infusion reactions data resulting from studies C0405 and C0406. An excerpt from the proposed REMS including the sponsor's justification for this cut-off is provided below.



As can be seen from the excerpt, the current submission does not address what effect stopping pegloticase early in certain subjects may have on the efficacy of the product in the population.

\_\_\_\_\_ (b) (4);  
\_\_\_\_\_

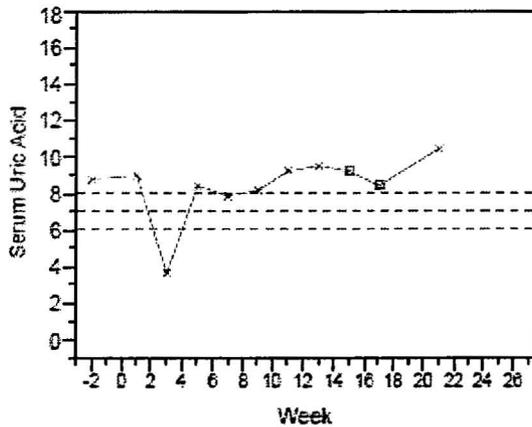
\_\_\_\_\_ In clinical practice however, this value would likely not be available to the physician.

Rather the serum uric acid at the previous visit would need to be used as the measure for deciding whether pegloticase treatment should be stopped or continued.

The focus of this review is to use descriptive statistics to evaluate the benefit-risk of various criteria for stopping pegloticase including the effect such rules may have on overall efficacy and the occurrence of infusion reaction. All descriptive statistics provided in this review rely only on serum uric acid levels **prior** to the infusion reaction, not serum uric acid levels **at** the time of the infusion reaction.

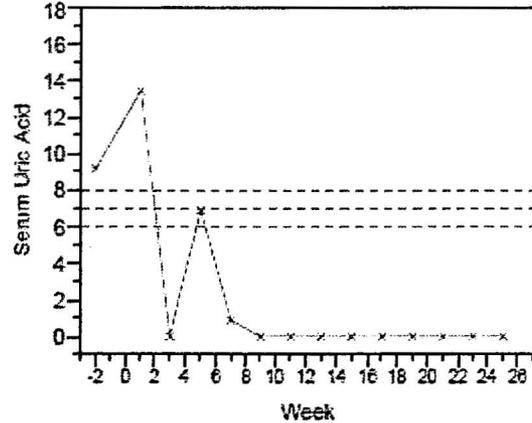
To illustrate the need for a carefully constructed set of criteria for stopping pegloticase, consider, as an example, the serum uric acid levels of subjects C0405-108-003 and C0405-101-001 provided in Figures 1 and 2 (and also provided as part of appendix 1). The need to stop dosing for subject C0405-108-003 prior to the occurrence of the infusion reactions at weeks 15 and 17 (marked by blue squares in the graphic) clearly would have been identified using the proposed cut-off of serum uric acid above 6 mg/dL; however, this criteria would also stipulate that dosing for subject C0405-101-001 be stopped after week 5 resulting in a loss of efficacy that became apparent after week 9. Graphical displays of the serum uric acid levels and the occurrence of infusion reactions (if they occurred) for each subject are provided in appendix 1. These plots are grouped according to treatment group (pegloticase 8 mg every 2 weeks and placebo), whether or not the subject was considered a responder for the primary efficacy analysis, and whether or not the subject reported an infusion reaction.

Figure 1



Plot for Subject=C0405-108-003

Figure 2



Plot for Subject=C0405-101-001

As previously described, the ideal set of criteria for stopping pegloticase is one that allows continued administration of pegloticase in subjects where there is potential for efficacy to be realized but discontinues pegloticase in subjects who would experience infusion reaction(s) if treatment continued. This ideal criteria likely does not exist but criteria that approach this ideal, balancing the benefit and risk of continued pegloticase treatment, is needed. Table 3 summarizes the benefit-risk of several different criteria for stopping pegloticase early. The sets of criteria provided in Table 3 are not exhaustive; rather they represent options that were developed by the sponsor and FDA medical and statistical teams in considering the serum uric acid plots in appendix 1.

Pegloticase Stopping Rule	Infusion Reaction Observed Before Reaching Criteria			Efficacy Responder <sup>12</sup>		
	C405 (N=43)	C406 (N=42)	Pooled (N=85)	C405 (N=43)	C406 (N=42)	Pooled (N=85)
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%)

1. Efficacy 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.

2. No 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.

Choosing the most appropriate rule for stopping pegloticase dosing is a subjective clinical decision and may vary from clinician to clinician and/or patient to patient and is beyond the scope of this statistical review. The conclusion of this review is that clear communication (in labeling or by other means) of the efficacy and safety that can be expected under applicable stopping rules is needed so that the clinician may make an informed decision regarding stopping pegloticase early for a particular patient.

## 4. SUMMARY AND CONCLUSIONS

### 4.1 Statistical Issues and Collective Evidence

The following statistical issues and their impact have been described in the context of the review. Please refer to the specified section for details.

- The sponsor does not address what effect stopping pegloticase early in certain subjects may have on the efficacy of the product in the population. The focus of this review is to evaluate the benefit-risk of various criteria for stopping pegloticase including the effect such rules have on the previously reviewed primary efficacy results and the occurrence of infusion reaction. If an alternate dosing recommendation is made in labeling, the efficacy of the product described in the clinical studies section should also be reflective of this change. (Section 3.2)
- Some of the sponsor's justification of a cut off of 6 mg/dL in serum uric acid (SUA) relies on the SUA level at the time of the infusion reaction as a predictor of the event. In clinical practice however, this value would likely not be available to the physician. The SUA acid at the **previous** visit would need to be used as the measure for deciding whether pegloticase treatment should be stopped or continued. (Section 3.2)

## **4.2 Conclusions and Recommendations**

Choosing the most appropriate rule for stopping pegloticase dosing is a subjective clinical decision and may vary from clinician to clinician and/or patient to patient and is beyond the scope of this statistical review. The conclusion of this review is that clear communication (in labeling or by other means) of the efficacy and safety that can be expected under applicable stopping rules is needed so that the clinician may make an informed decision regarding stopping pegloticase early for a particular patient.

**5. APPENDIX 1**

**APPEARS THIS WAY ON ORIGINAL**





U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**BLA Number:** STN 125293-0000

**Drug Name:** Pegloticase (also known as PEG-uricase and PURICASE®)

**Indication(s):** "To control the clinical consequences of hyperuricemia in patients with severe gout in whom conventional therapy is contraindicated or has been ineffective" (per Orphan Drug Designation granted February 21, 2001)

**Applicant:** Savient Pharmaceuticals, Inc.

**Date(s):** Stamp date: October 31, 2008

PDUFA date: August 1, 2009

**Review Priority:** Priority

**Biometrics Division:** Division of Biometrics II

**Statistical Reviewer:** Ruthanna C. Davi *Ruthanna C. Davi*

**Concurring Reviewers:** Dionne Price, Statistical Team Leader *Dionne Price*

Tom Permutt, Division of Biometrics II Director *Thomas Permutt*

**Medical Division:** Division of Analgesics, Anesthetics, and Rheumatology Products

**Clinical Team:** Rosemarie Neuner, Medical Reviewer

Jeff Siegel, Medical Team Leader

**Project Manager:** Diana Walker

**Keywords:**

NDA, clinical studies, multiplicity, pooling studies

## Table of Contents

<b>1. EXECUTIVE SUMMARY.....</b>	<b>3</b>
1.1 CONCLUSIONS AND RECOMMENDATIONS.....	3
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES .....	3
1.3 STATISTICAL ISSUES AND FINDINGS.....	4
<b>2. INTRODUCTION.....</b>	<b>6</b>
2.1 OVERVIEW .....	6
2.2 DATA SOURCES.....	8
<b>3. STATISTICAL EVALUATION.....</b>	<b>9</b>
3.1 EVALUATION OF EFFICACY .....	9
3.2 EVALUATION OF SAFETY.....	21
<b>4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS.....</b>	<b>22</b>
4.1 GENDER, RACE AND AGE.....	22
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS.....	24
<b>5. SUMMARY AND CONCLUSIONS.....</b>	<b>24</b>
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE.....	24
5.2 CONCLUSIONS AND RECOMMENDATIONS.....	26

# 1. EXECUTIVE SUMMARY

## 1.1 Conclusions and Recommendations

Studies C405 and C406 adequately demonstrate that the proportion of subjects with plasma uric acid (PUA) concentrations <6 mg/dL for at least 80% of the time during months 3 and 6 combined is higher with 8 mg Pegloticase every 2 weeks than placebo. Due to the high statistical significance associated with this comparison, this conclusion is considered robust despite the lack of a pre-specified multiplicity correction for the two dose groups studied. This conclusion is also robust to the choice of statistical methods and does not appear to differ within any of the subgroups examined. Comparison of the proportion of subjects with PUA concentrations <6 mg/dL for at least 80% of the time during months 3 and 6 combined for the 8 mg Pegloticase every 4 weeks group to placebo is significant for study C406 but only marginally so for study C405 and is complicated by the lack of a pre-specified multiplicity correction. However, in considering both studies C405 and C406 in concert, it is unlikely that the result in study C405 is a spurious finding and thus it is appropriate to conclude that the 8 mg Pegloticase every 4 weeks group was associated with a higher proportion of subjects with PUA concentrations <6 mg/dL for at least 80% of the time during months 3 and 6 combined than was placebo. This result does not appear to differ within any of the subgroups examined.

Analyses of secondary efficacy endpoints were generally supportive of the primary efficacy results; however, no multiplicity correction was planned for in the protocol for the numerous secondary endpoints examined. Therefore the hypothesis tests associated with the secondary endpoints should be interpreted with caution as the probability of at least one type I error occurring is increased beyond the usual 0.05. This is especially important in the context of this product since analyses of the secondary endpoints were, as per-protocol, conducted pooling studies C405 and C406 and thus there is no replication of these results. In addition, sponsor analyses for the secondary endpoints often excluded subjects with unavailable data at week 25. While sensitivity analyses designed to address this issue often lead to qualitative conclusions regarding the treatment effect that were similar to the sponsor's analyses, the descriptive statistics associated with the results were, in some cases, notably different.

## 1.2 Brief Overview of Clinical Studies

The sponsor has submitted the results of two identically designed phase 3 pivotal studies to support the regulatory approval of Pegloticase with the following indication: "to control the clinical consequences of hyperuricemia in patients with severe gout in whom conventional therapy is contraindicated or has been ineffective". (Indication is quoted per Orphan Drug Designation granted February 21, 2001.)

The pivotal studies referred to as C0405 and C0406 are each titled, "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". As part of these studies, subjects were randomly assigned to the following treatment groups in a 2:2:1 ratio: 8 mg pegloticase every 2 weeks, 8 mg pegloticase every 4 weeks, and placebo every 2 weeks throughout the 24

week treatment period. The primary objective of the studies was to demonstrate the superiority of pegloticase over placebo in reducing plasma uric acid (PUA) as determined by the primary efficacy endpoint (i.e., the percentage of subjects achieving and maintaining PUA concentrations less than 6 mg/kL for at least 80% of the time during months 3 and 6 combined). Numerous secondary efficacy endpoints were also examined as part of these studies. Among these, tophus burden, number of swollen and tender joints, and frequency of gout flares were selected by the medical team as being of particular interest and thus are examined, along with the primary efficacy endpoint, in this review. The medical team also highlighted the frequency of infusion reactions as an important factor in characterizing the safety of this product and thus that endpoint is examined in this review.

The Division of Analgesics, Anesthetics, and Rheumatology Products (DARRP) Advisory Committee was convened on June 16, 2009 primarily for discussion of possible safety concerns associated with pegloticase including cardiovascular events and infusion reactions.

### 1.3 Statistical Issues and Findings

The following statistical issues and their impact have been described in the context of the review. Please refer to the specified section for details.

- Exclusions from the per-protocol (PP) group were fairly frequent and perhaps more importantly were imbalanced across the treatment groups. The PP groups included approximately 60% to 70% of the subjects randomized to the pegloticase groups and approximately 80% of subjects randomized to the placebo groups. This pattern was similar in both studies. These post-randomization differences in exclusion rates are likely to have been related to treatment assignment and thus significantly bias the by-treatment group comparisons within the PP group. Note: This bias does not adversely impact the analysis of the primary efficacy endpoint in the ITT group. Please see the next comment. (Section 3.1.2)
- Subjects who withdrew from the study before month 6 were, by protocol definition, considered nonresponders for the primary efficacy analysis in the intent-to-treat group. This may be considered a fair representation of the efficacy in these subjects in that the subjects' reasons for withdrawal from the study (i.e., commonly adverse event or withdrew consent) indicate the study treatment could not be tolerated in exchange for whatever efficacy may have been being achieved and thus for all intents and purposes, the study treatment failed for those subjects. Therefore, the primary efficacy results in the ITT group likely remain reliable despite the more frequent early withdrawal from the studies for the Pegloticase groups relative to that of placebo. (Section 3.1.2)
- As would be expected due to the random treatment assignment associated with the 24-week treatment period, balance among the treatment groups in demographic and baseline characteristics appears adequate to allow by-treatment group differences in post-randomization outcomes for this period to be attributed to treatment effects and not an artifact of an imbalance in pre-randomization characteristics in both studies C405 and C406. (Section 3.1.2)
- The optional 24 month open label extensions associated with studies C405 and C406 does not provide reliable by-treatment group comparisons as there could be inappropriate imbalances in covariates. For the extension, subjects and investigators chose between every 2-week or every 4-week dosing of 8 mg pegloticase or an

- observational arm (no pegloticase treatment). This period was intended to evaluate the long-term safety and durability of efficacy of pegloticase; however, these data are limited due to the lack of randomly assigned treatment groups. (Section 3.1.1)
- The primary efficacy analyses seem to support the efficacy of both dosing regimens of pegloticase over placebo in that the relevant p-values are all less than the prespecified alpha level of 0.05; however, interpretation of this data is made more difficult since no multiplicity correction for the two dose groups was specified in the protocol. The marginally statistically significant comparison of pegloticase 8 mg/4 wks to placebo in study C405 could be interpreted as a spurious finding. However, in light of the highly statistically significant result for this comparison in the replicate study, study C406, it is unlikely that there truly is no difference between pegloticase 8 mg/4 wks and placebo. Therefore, in considering all of the primary efficacy results for both studies in concert it is reasonable to conclude that the efficacy of both dosing regimens of pegloticase have been adequately demonstrated to be different from placebo for the primary efficacy endpoint. (Section 3.1.2)
  - Despite recommendations from the medical division during the planning of studies 405 and 406, no multiplicity correction was planned for in the protocol for the numerous secondary endpoints examined. Therefore the hypothesis tests associated with the secondary endpoints should be interpreted with caution as the probability of at least one type I error occurring is increased beyond the usual 0.05. Endpoints that are highly correlated with the primary efficacy endpoint and have a fairly direct scientific link with the primary efficacy endpoint (e.g., reduction in tophi) are less subject to increases in type I error as opposed to endpoints that are not as highly correlated with the primary efficacy endpoint (e.g. patient reported outcomes). Additional efficacy claims for the product based on the secondary endpoints should be considered on a case-by-case basis taking into account the clinical importance of the result as well as the connection of the endpoint with the primary endpoint. This is especially important in the context of this product since analyses of the secondary endpoints were, as per-protocol, conducted pooling studies C405 and C406 and thus there is no replication of these results. (Section 3.1.2)
  - Analyses provided by the sponsor in the integrated summary of efficacy of the reduction in tophi include only subjects with evaluable tophi at week 25, not the entire “tophus-evaluable population”. The by-treatment group comparisons in the subset of subjects in the “tophus-evaluable population” who also were evaluable at week 25 may be biased. A sensitivity analysis addressing this issue and considering the “unable to evaluate” cases as failures leads to the same qualitative conclusions as the sponsor’s analyses in that the pegloticase 8 mg/2 weeks group comparison to placebo is associated with a p-value smaller than the nominal significance level of 0.05 and the pegloticase 8 mg/ 4weeks comparison to placebo is not; however, the descriptive proportions are notably lower for the pegloticase groups in the sensitivity analysis than in the sponsor’s analyses. (Section 3.1.2)
  - The sponsor’s analysis of the change from baseline to week 25 in the number of swollen or tender joints excludes subjects who did not attend a week 25 visit. This type of analysis is not appropriate in that it excludes subjects based on a post-randomization characteristic that is likely affected by treatment assignment. This analysis also is not consistent with the protocol which specified that missing data should be imputed using the last-observation-carried-forward (LOCF) approach for most secondary efficacy

endpoints. The sensitivity analysis imputing subjects with missing data using LOCF methods is provided. The sensitivity analysis yields the same qualitative conclusions for the pegloticase 8 mg/2 weeks comparison to placebo as the sponsor's analysis. Although the sensitivity analysis yields similar numerical trends to the sponsor's analysis for the pegloticase 8 mg/ 4 weeks comparison to placebo, the qualitative conclusions from the sponsor's analysis and the sensitivity analysis are not the same in that the change from baseline to week 25 in the mean number of swollen or tender joints was associated with a p-value less than the nominal significance level of 0.05 in the sponsor's analysis but not in the sensitivity analysis. (Section 3.1.2)

- The sponsor's analysis of the proportion of subjects experiencing gout flares excludes subjects who did not attend at least one month 4-6 visit. This type of analysis is not appropriate in that it excludes subjects based on a post-randomization characteristic that is likely affected by treatment assignment. A sensitivity analysis imputing subjects with missing data as having had at least one flare yields similar numerical trends to the sponsor's analysis; however, the sponsor's analysis of the proportions of subjects experiencing at least one flare in months 4-6 reveals a p-value less than the nominal significance level 0.05 for comparison to placebo of the pegloticase 8 mg/2 wks group but not the pegloticase 8 mg/4 wks group while neither the pegloticase 8 mg/2 wks or pegloticase 8 mg/4 wks comparisons to placebo are associated with p-values less than the nominal significance level of 0.05 in the sensitivity analysis. (Section 3.1.2)
- Studies C405 and C406 suggest that the proportions of subjects experiencing at least one infusion reaction were higher in each of the pegloticase groups compared to placebo. The sponsor suggested that the occurrence of infusion reactions could be mitigated by stopping administration of pegloticase when subjects' uric acid levels rise above 6 mg/dL. The DAARP Advisory Committee expressed interest this type of approach for mitigation of infusion reactions but questioned whether a cutoff of 6 mg/dL was supported by the data. Analyses to determine an appropriate cutoff (if one exists) are being undertaken and will be discussed in an addendum to this statistical review. (Section 3.1.2)
- Descriptive summaries of the primary efficacy variable by gender, age, and race for both studies C405 and C406 did not reveal any differing treatment effects among these subgroups.

## 2. INTRODUCTION

### 2.1 Overview

The sponsor has submitted the results of two identically designed phase 3 pivotal studies to support the regulatory approval of Pegloticase with the following indication: "to control the clinical consequences of hyperuricemia in patients with severe gout in whom conventional therapy is contraindicated or has been ineffective". (Indication is quoted per Orphan Drug Designation granted February 21, 2001.)

The pivotal studies referred to as C0405 and C0406 are each titled, "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". As part of these studies, subjects

were randomly assigned to the following treatment groups in a 2:2:1 ratio: 8 mg pegloticase every 2 weeks, 8 mg pegloticase every 4 weeks, and placebo every 2 weeks throughout the 24 week treatment period. The primary objective of the studies was to demonstrate the superiority of pegloticase over placebo in reducing plasma uric acid (PUA) as determined by the primary efficacy endpoint (i.e., the percentage of subjects achieving and maintaining PUA concentrations less than 6 mg/kL for at least 80% of the time during months 3 and 6 combined). Numerous secondary efficacy endpoints were also examined as part of these studies. Among these, tophus burden, number of swollen and tender joints, and frequency of gout flares were selected by the medical team as being of particular interest and thus are examined, along with the primary efficacy endpoint, in this review. The medical team also highlighted the frequency of infusion reactions as an important factor in characterizing the safety of this product and thus that endpoint is also examined in this review.

The Division of Analgesics, Anesthetics, and Rheumatology Products (DARRP) Advisory Committee was convened on June 16, 2009 primarily for discussion of possible safety concerns associated with pegloticase including cardiovascular events and infusion reactions.

Communication with the sponsor regarding these studies is documented under IND 10122. Pertinent parts of the statistical portion of those communications are summarized herein. Discussions among the Division and sponsor with respect to the sponsor's request for a special protocol assessment (for study C0405) occurred between August 2005 and May 3, 2006. In the course of these discussions, the following notable statistical concerns were communicated to the sponsor.

- In early discussions, the Division agreed with the sponsor's proposal for the primary efficacy analysis comparing the proportion of pegloticase-treated patients achieving a plasma uric acid concentration <6 mg/dL for at least 80% of the time compared to placebo-treated patients during months 3 and 6. The Division indicated that patients with missing data for the primary efficacy analysis (i.e., those who withdrew from the study prior to month six) should be considered treatment failures. Ultimately, this analysis plan was formally documented in the protocol, agreed to as part of the special protocol assessment agreement, and implemented (by the sponsor) in creation of the study report.
- Regarding pooling of studies C0405 and C0406 for analysis of the secondary efficacy endpoints, the Division stated the following.



(b) (4)

The acceptability of pooling studies C0405 and C0406 for the analyses [redacted] (b) (4) was not addressed in discussions among the sponsor and Division [redacted] (b) (4)

[redacted] In addition, the sponsor was cautioned that a statistical analysis plan addressing the multiplicity problem associated with numerous secondary endpoints was recommended. Pooling of the studies for the secondary efficacy endpoints was described in the protocol and agreed to by the Division as part of a special protocol assessment agreement. No multiple comparison correction for the secondary endpoints was provided in the protocol.

- Regarding the analysis of tophi, the Division indicated that individual tophi within a single patient are not expected to be independent thus analyses considering tophi as the unit of observation will be considered exploratory. And that whether tophi information is included in the label is a review issue. (per letter dated March 16, 2006) The key analysis for tophus burden described in the protocol and agreed to as part of the special protocol assessment agreement is, appropriately, one considering the patients as the unit of observation.

On May 3, 2006, the Division documented their concurrence that the protocol design and planned statistical analyses were adequate to address the objectives necessary to support a marketing application for PEG-uricase for the control of hyperuricemia in patients with symptomatic gout in whom conventional therapy is contraindicated or has been ineffective. Special protocol assessment status for study C0406 was not addressed.

## 2.2 Data Sources

The following data sets were submitted electronically and utilized in the review of this study.

crt\dataset\405\analysis\ADAE.xpt  
crt\dataset\405\analysis\ADEFF.xpt  
crt\dataset\405\analysis\ADLAB.xpt  
crt\dataset\406\analysis\ADAE.xpt  
crt\dataset\406\analysis\ADEFF.xpt  
crt\dataset\406\analysis\ADLAB.xpt  
datasets\ise\group-a\analysis\ADEFF.xpt

All submitted data sets were found to be adequately documented and organized.

### 3. STATISTICAL EVALUATION

#### 3.1 Evaluation of Efficacy

##### 3.1.1 Study Design (Studies C0405 and C0406)

Study C0405 and C0406 were multi-center studies with a primary objective of demonstrating the superiority of pegloticase over placebo in reducing plasma uric acid (PUA) as determined by the primary efficacy endpoint. The target population for these studies was comprised of hyperuricemic (serum uric acid (SUA)  $\geq$  8 mg/dL) adults ( $\geq$  18 years of age) diagnosed with symptomatic gout, in whom conventional therapy had been contraindicated or was ineffective. Symptomatic gout was defined as occurring in subjects having at least one of the following at the time of study enrollment: (i) at least three gout flares in the previous 18 months, (ii) at least one gout tophus, or (iii) gouty arthritis. Subjects in whom conventional therapy had been ineffective were subjects who had failed to reach SUA normalization following treatment with a medically appropriate maximum dose of allopurinol over at least three months. In total, the protocol specified six inclusion and 15 exclusion criteria for enrollment in these studies.

Eligible subjects washed out of any uric-acid-lowering agents at least one week before randomization and were required to refrain from using these agents throughout the study. At the screening visit, subjects not already on a prophylactic regimen of colchicine or non-steroidal anti-inflammatory drug (NSAID) to prevent gout flares were placed on one of these agents (with the dose regimen individualized for each subject by the investigators), unless medically contraindicated. In addition to gout flare prophylaxis, subjects were given injection site reaction prophylaxis consisting of fexofenadine 60 mg the night before and morning of each infusion, acetaminophen 1000 mg the morning of each infusion, and hydrocortisone 200 mg i.v. immediately prior to each infusion. A nationwide shortage of hydrocortisone and other short-acting corticosteroids developed during the course of the study; therefore, if 200 mg hydrocortisone was not available, a substitution with 40 mg methylprednisolone was allowed as long as the nationwide shortage persisted. If neither drug was available, the investigator could choose between 20 mg prednisone the night before the infusion or, with prior approval by the sponsor, substitution with another corticosteroid at an equivalent dosage and administered at an appropriate time before the infusion.

After the washout/screening period, patients were randomly assigned (in a 2:2:1 ratio stratified by presence/absence of tophi) to the following treatments to be received throughout the 24-week treatment period

- (1.) 8 mg pegloticase every 2 weeks (subsequently referred to as 8 mg/2 weeks)
- (2.) 8 mg pegloticase every 4 weeks alternating with placebo every two weeks to maintain the treatment blind (subsequently referred to as 8 mg/ 4 weeks)
- (3.) placebo every 2 weeks

There was an optional 24 month open label extension for these studies during which subjects and investigators chose between every 2-week or every 4-week dosing of 8 mg pegloticase or an observational arm (no pegloticase treatment). This period was intended to evaluate the long-term safety and durability of efficacy of pegloticase; however, these data are

limited due to the lack of randomly assigned treatment groups. Randomly assigning treatment is a fundamental component of a clinical trial necessary to reliably attribute differences between treatment groups to a treatment effect rather than a by-treatment group imbalance in covariates. The absence of randomization in the follow-up period makes substantiating any efficacy or safety conclusions with this data impossible. Therefore, the data resulting from the follow-up period are not evaluated in this review.

The primary efficacy endpoint for these studies was the percentage of subjects achieving and maintaining PUA concentrations less than 6 mg/dL for at least 80% of the time during months 3 and 6 combined. Collection of blood samples for the analysis of PUA that contributed to the calculation of the primary efficacy endpoint were to occur at the following time points

#### Month 3

- (1.) three times during week 9 (i.e., twice at visit 6, both pre-dose 5 and 2 hours post-dose 5 and at visit 7, 24 hours post-dose 5)
- (2.) once during week 10 (i.e., at visit 8, 7 days post-dose 5)
- (3.) twice during week 11 (i.e., twice at visit 9, both pre-dose 6 and 2 hours post-dose 6)
- (4.) once during week 12 (i.e., at visit 10, 7 days post-dose 6)
- (5.) once during week 13 (i.e., at visit 11, pre-dose 7)

#### Month 6

- (1.) three times during week 21 (i.e., twice at visit 15, both pre-dose 11 and 2 hours post-dose 11 and at visit 16, 24 hours post-dose 11)
- (2.) once during week 22 (i.e., at visit 17, 7 days post-dose 11)
- (3.) twice during week 23 (i.e., twice at visit 18, both pre-dose 12 and 2 hours post-dose 12)
- (4.) once during week 24 (i.e., at visit 19, 7 days post-dose 12)
- (5.) once during week 25 (i.e., at visit 20, 14 days post-dose 12)

From these measurements, for each subject, a PUA time curve could be drawn by connecting neighboring PUA values with a straight line. That is it was assumed that PUA changed linearly from one measurement point to the next. Linear interpolation was used to determine the time point (in hours) at which the PUA time curve crossed 6 mg/dL. Finally, the primary efficacy endpoint was calculated by dividing the number of hours the curve was below 6 mg/dL during months 3 and 6 by the total number of hours in months 3 and 6 for each subject. A subject was considered a responder if this measure was greater than 80%. If PUA levels were missing at visits 6 (pre-dose), 11, 15 (pre-dose), or 20, the baseline PUA level for that subject was imputed. Other missing PUA values were ignored by drawing the straight line to the PUA value at the next available time point. Subjects who withdrew from the study before month six were to be considered nonresponders for the primary efficacy analysis.

The primary efficacy analysis was to be conducted in the intent to treat group (ITT), using Fisher's exact test to compare the PUA responder rate between each treatment group and placebo. No multiplicity correction for the comparison of two doses to placebo was

planned for in the protocol. The ITT group was defined as all randomized subjects who received at least one dose of study medication. In addition to Fisher's exact test, 95% confidence intervals for the differences in the primary endpoint between each pegloticase treatment group and placebo were to be provided.

Numerous secondary efficacy endpoints were also examined as part of these studies. No multiplicity correction was planned for in the protocol for the secondary endpoints. Analyses of the secondary endpoints was, as per-protocol, conducted pooling studies C405 and C406. Among the secondary endpoints measured, tophus burden, number of swollen and tender joints, and frequency of gout flares were selected by the medical team as being of particular interest for evaluation of the efficacy of pegloticase.

Assessment of individual tophi was made through digital photographs of the hands and feet (obtained in a standardized manner) along with photographs of up to two other representative sites of tophaceous disease. Baseline photographs were sent to a central reader to prospectively identify sites of disease present at the start of treatment. Up to five measurable tophi were chosen by the central reader for measurement over the course of the study. To be considered "measurable", tophi were required to be  $\geq 5$  mm at baseline in the longest dimension, and must have had borders distinguishable to the trained central reader. Up to two tophi that were representative of the subject's tophus burden but which could not be accurately measured due to location, shape, or other factors, were also followed during the study. The "unmeasured" tophi had to have been approximately 10 mm or greater at baseline in order for there to be confidence that the reader could reliably assess changes in size. Follow-up photographs of the identified measured and unmeasured tophi were obtained at weeks 13, 19, and 25. At each of these time points, tophi that were deemed measured at baseline were measured again and classified according to the following scale.

- complete response – 100% decrease in the area of the tophus,
- marked response – at least a 75% decrease in the area of the tophus,
- partial response – at least a 50% decrease in the area of the tophus,
- stable disease – neither a 50% decrease nor a 25% increase in the area of the tophus can be demonstrated,
- progressive disease – a 25% or more increase in the area of the tophus,
- unable to evaluate – the tophus cannot be accurately measured for any reason at any given post-baseline time point (e.g., image missing or of poor quality, obvious infection of the tophus)

Unmeasured tophi were semi-quantitatively assessed by the central reader in comparison to baseline and classified according to the following scale.

- complete response – the disappearance of the tophus,
- improved – an approximate 50% or more reduction from baseline in the size of the tophus,
- stable disease – neither improvement nor progression from baseline can be determined
- progressive disease – an approximate 50% or more increase from baseline in the area of the tophus
- unable to evaluate – the tophus cannot be assessed for any reason at any given post-baseline timepoint (e.g., image missing or of poor quality, obvious infection of the tophus)

Any newly appearing tophus in the photographic field which wasn't present at baseline was to be noted by the central reader.

For analysis, these results were to be summarized into an assessment of "overall tophi response" for a subject based upon the best response among all tophi (including measured and unmeasured) for that subject and were to be categorized as follows.

- complete response
- partial response (including individual tophi graded as marked response or partial response for measurable tophi and as improved for unmeasured tophi)
- stable disease
- progressive disease

If any single tophus shows progression, or if a new tophus appears during the study, the overall response for that subject was to be categorized as progressive disease, regardless of the response of any other tophi. New tophi arising outside the region of photographed at baseline were to be captured by the investigator on the case report form and were to also result in an overall response assessment of progressive disease.

The number of swollen or tender joints was measured at baseline and weeks 13, 19, and 25. For each subject and visit, the investigator indicated whether pain was absent or present and whether swelling was absent or present for each joint or bursae by responding to a check-list of 60 pre-specified joints and bursae.

Gout flares were assessed at baseline and all post-randomization visits. Patients were to self-report gout flares which were then to be confirmed by the investigator through questioning and/or direct observation. The occurrence, severity, and duration of each confirmed flare were to be recorded by the investigators.

The medical team also highlighted the frequency of infusion reactions as an important factor in characterizing the safety of pegloticase. Therefore statistical analysis of infusions reactions are also undertaken in this review.

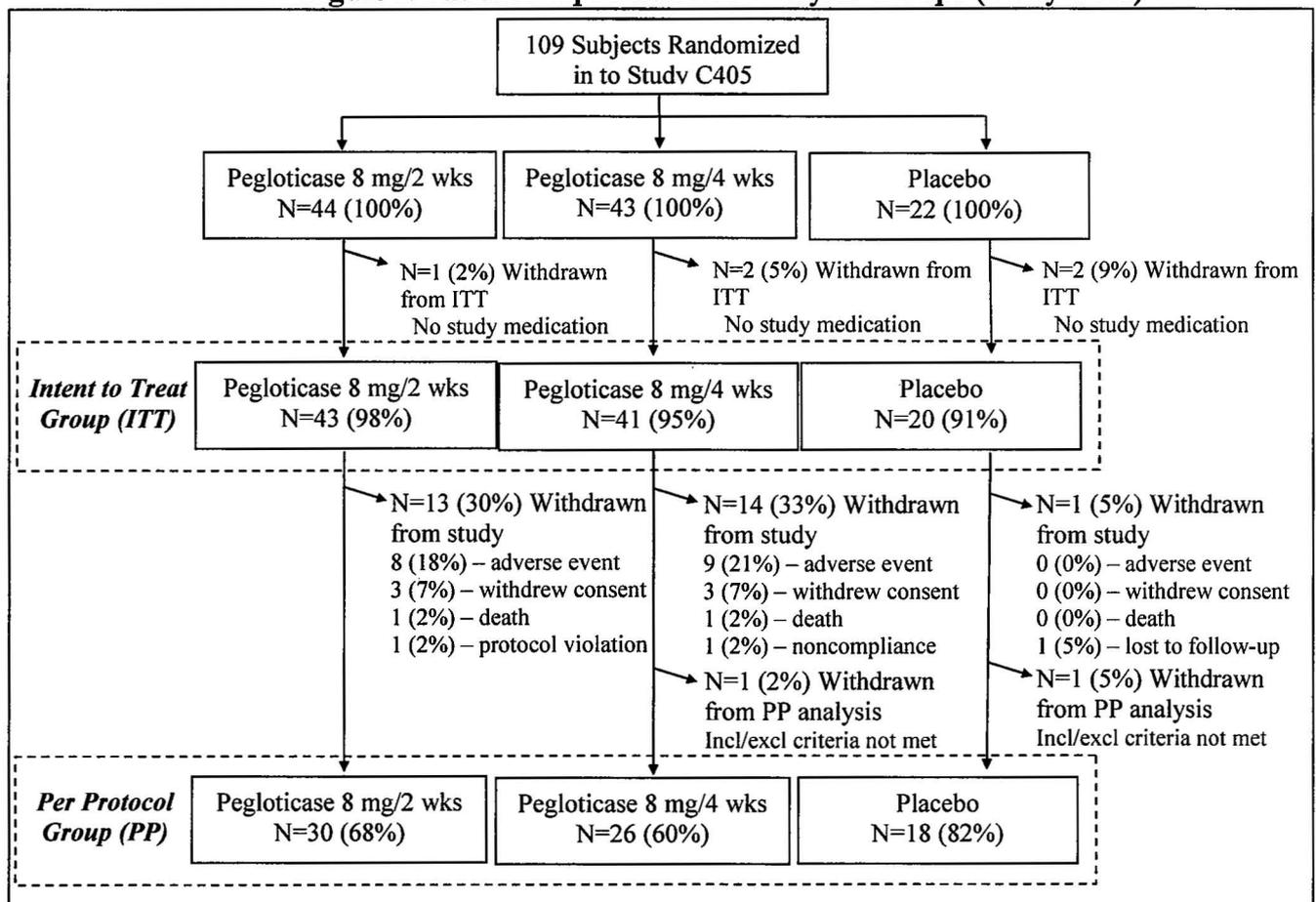
### **3.1.2 Results (Studies C0405 and C0406)**

One hundred nine subjects were randomized (2:2:1 and stratified by the presence or absence of tophi) into study C405 as follows: 44 to receive pegloticase 8 mg/2 weeks, 43 to receive pegloticase 8 mg/4 weeks and 22 to receive placebo. For study C406, 116 subjects were randomized (2:2:1 and stratified by the presence or absence of tophi) as follows: 46 to receive pegloticase 8 mg/2 weeks, 46 to receive pegloticase 8 mg/4 weeks and 24 to receive placebo. Five subjects in study C405 and 8 subjects in study C406 did not receive study medication thus per protocol definition, there were 104 subjects in study C405 and 108 subjects in study C406 who were included in the ITT groups. Figures 1 and 2 describe the randomizations and the inclusion or exclusion of subjects from the ITT and per protocol (PP) analysis groups for studies C405 and C406, respectively.

In both studies C405 and C406, exclusions from the PP group were fairly frequent and perhaps more importantly were imbalanced across the treatment groups. The PP group ultimately included approximately 60% to 70% of the subjects randomized to the pegloticase groups and approximately 80% of subjects randomized to the placebo groups. This pattern

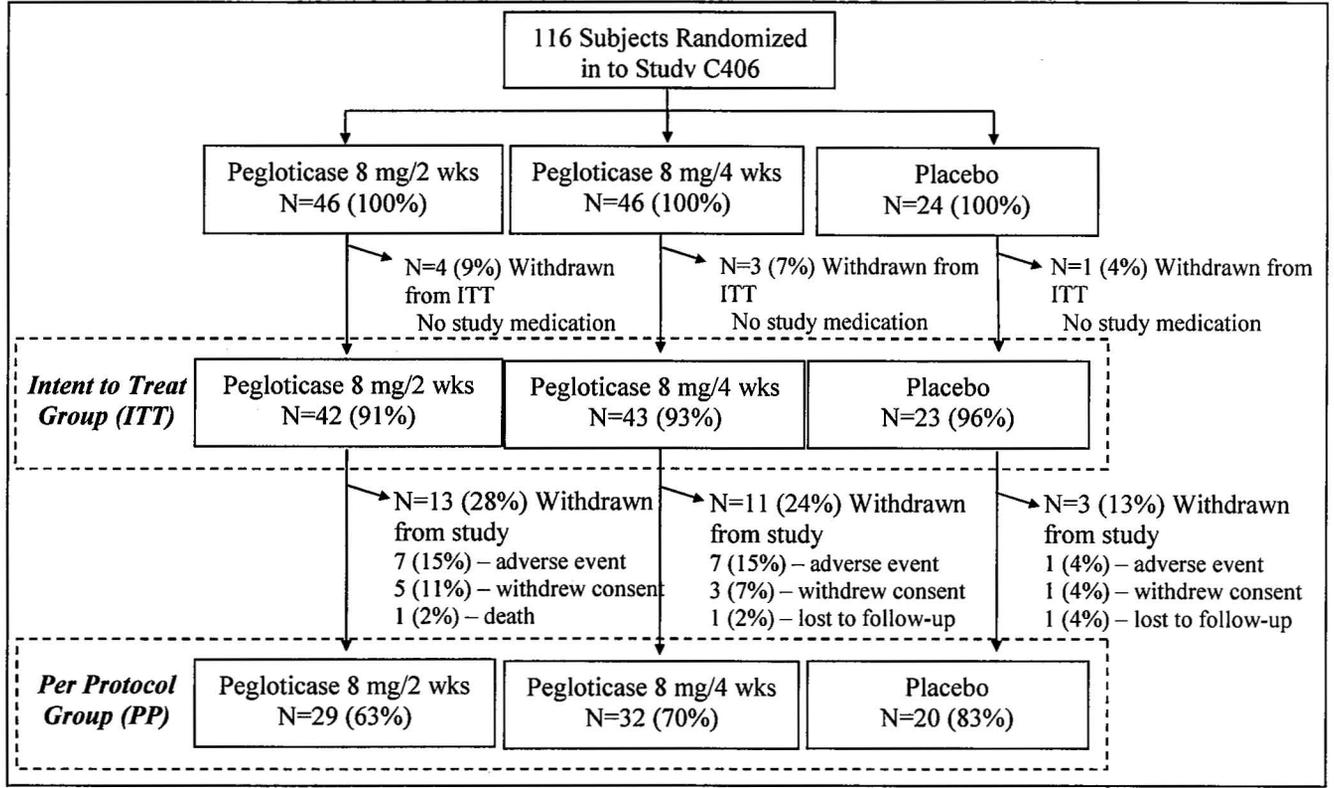
was similar in both studies. These post-randomization differences in exclusion rates are likely to have been related to treatment assignment and thus significantly bias the by-treatment group comparisons within the PP group. Therefore, the results of the PP group are not considered further in this review. 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. This may be considered a fair representation of the efficacy in these subjects in that the subjects' reasons for withdrawal from the study (i.e., commonly adverse event or withdrew consent) indicate the study treatment could not be tolerated in exchange for whatever efficacy may have been being achieved and thus for all intents and purposes, the study treatment failed for those subjects. Therefore, the primary efficacy results in the ITT group likely remain reliable despite the more frequent early withdrawal from the studies for the Pegloticase groups relative to that of placebo.

**Figure 1: Patient Disposition and Analysis Groups (Study C405)**



Source: Sponsor analyses (C405 clinical study report, table 4) and reviewer analyses

**Figure 2: Patient Disposition and Analysis Groups (Study C406)**



Source: Sponsor analyses (C406 clinical study report, table 4) and reviewer analyses

Demographic and baseline characteristics for the ITT groups provided by the sponsor in the clinical study reports for studies C405 and C406 and augmented by FDA reviewer analyses are summarized in Table 1.

Reviewer analyses indicate that the difference in the proportions of subjects with a history of gout-related kidney disease in the Pegloticase 8 mg/4 wks treatment group and the placebo group in study C406 is associated with a nominal p-value less than 0.05 ( $p=0.0495$ ); however from a statistical perspective, this is very likely to be a spurious finding and is not considered a detriment to the study or an indication that the random treatment assignment was inadequate. No other differences between the Pegloticase treatment groups and placebo with associated p-values less than 0.05 were noted in demographic and baseline characteristics in the ITT groups for studies C405 or C406. As would be expected due to the random treatment assignment, balance among the treatment groups in demographic and baseline characteristics appears adequate to allow by-treatment group differences in post-randomization outcomes to be attributed to treatment effects and not an artifact of an imbalance in pre-randomization characteristics.

**Table 1: Demographic and Baseline Characteristics (ITT)**

Demographic/Baseline Characteristic		Study C405					Study C406				
		Peg 2 wks N=43	Peg 4 wks N=41	Placebo N=20	p-value <sup>1</sup> Peg q2 vs. plc	p-value <sup>1</sup> Peg q4 vs. plc	Peg 8 mg/2 wks	Peg 8 mg/4 wks	Placebo	p-value <sup>1</sup> Peg q 2 vs. plc	p-value <sup>1</sup> Peg q4 vs. plc
Age (years)	Mean (SD)	58.2 (15.3)	55.1 (13.3)	57.2 (13.1)	0.8	0.6	54.3 (15.7)	53.9 (13.5)	53.8 (11.4)	0.9	1.0
Ethnic Origin	White N(%)	32 (74%)	32 (78%)	14 (70%)	0.7	0.5	22 (52%)	27 (63%)	16 (70%)	0.2	0.6
	Non-White N(%)	11 (26%)	9 (22%)	6 (30%)			20 (48%)	16 (37%)	7 (30%)		
Gender	Female N(%)	13 (30%)	6 (15%)	5 (25%)	0.7	0.3	4 (10%)	9 (21%)	2 (9%)	0.9	0.2
	Male N(%)	30 (70%)	35 (85%)	15 (75%)			38 (90%)	34 (79%)	21 (91%)		
Weight (kg)	Mean (SD)	101.6 (22.2)	104.8 (27.8)	101.8 (21.9)	0.98	0.7	94.7 (22.3)	97.4 (29.0)	98.1 (31.7)	0.6	0.9
Height (cm)	Mean (SD)	171.1 (10.8)	175.9 (10.9)	20 (174.6)	0.2	0.6	174.3 (9.4)	173.7 (11.9)	176.8 (11.5)	0.3	0.3
BMI (kg/m <sup>2</sup> )	Mean (SD)	34.9 (8.0)	33.7 (7.7)	33.3 (6.4)	0.4	0.8	31.0 (6.1)	32.1 (8.3)	31.3 (8.3)	0.9	0.7
Years since 1 <sup>st</sup> gout attack <sup>2</sup>	Mean (SD)	17.6 (13.3)	16.1 (11.3)	12.3 (9.0)	0.1	0.2	17.2 (9.5)	18.0 (9.7)	16.7 (10.8)	0.8	0.6
Years since 1 <sup>st</sup> gout diagnosis	Mean (SD)	16.1 (13.5)	15.5 (10.7)	11.8 (8.9)	0.2	0.2	14.7 (10.5)	15.6 (9.1)	14.7 (10.3)	1.0	0.7
Presence of uric acid crystals confirmed	Yes	26 (60%)	22 (54%)	15 (75%)	0.3	0.1	22 (52%)	23 (54%)	12 (52%)	1.0	0.9
	No	17 (40%)	19 (46%)	5 (25%)			20 (48%)	20 (47%)	11 (48%)		
# Acute flares in the past 18 months <sup>2</sup>	Mean (SD)	10.8 (11.6)	11.0 (15.0)	13.2 (21.1)	0.6	0.6	8.8 (9.3)	8.3 (5.9)	7.6 (10.6)	0.6	0.7
Pattern of acute flares <sup>2</sup>	One joint	12 (28%)	10 (25%)	4 (21%)	0.8	0.7	16 (39%)	14 (33%)	8 (36%)	0.6	0.7
	2-3 joints	12 (28%)	12 (30%)	9 (47%)			9 (22%)	12 (29%)	10 (46%)		
	>3 joints	19 (44%)	18 (45%)	6 (32%)			16 (39%)	16 (38%)	4 (18%)		
Severity of acute flares <sup>2</sup>	Mild	2 (5%)	0 (0%)	1 (5%)	.5	.4	5 (12%)	1 (2%)	2 (9%)	1.0	0.2
	Moderate	10 (23%)	12 (30%)	6 (32%)			14 (34%)	15 (36%)	9 (41%)		
	Severe	31 (72%)	28 (70%)	12 (63%)			22 (54%)	26 (62%)	11 (50%)		
Chronic synovitis/ Arthropathy	Yes	27 (63%)	23 (56%)	13 (65%)	0.9	0.5	23 (55%)	24 (56%)	13 (57%)	0.9	1.0
	No	16 (37%)	18 (44%)	7 (35%)			19 (45%)	19 (44%)	10 (44%)		
History of gout-related kidney disease	Yes	8 (19%)	6 (15%)	6 (30%)	0.3	0.2	4 (10%)	10 (23%)	1 (4%)	0.5	0.0495
	No	35 (81%)	35 (85%)	14 (70%)			38 (90%)	33 (77%)	22 (96%)		
Tophi	Yes	29 (67%)	31 (76%)	14 (70%)	0.8	0.6	33 (79%)	33 (77%)	15 (65%)	0.2	0.3
	No	14 (33%)	10 (24%)	6 (30%)			9 (21%)	10 (23%)	8 (35%)		
Surgery for gout, excluding arthrocentesis	Yes	7 (16%)	9 (22%)	6 (30%)	0.2	0.5	6 (14%)	11 (26%)	7 (30%)	0.1	0.7
	No	36 (84%)	32 (78%)	14 (70%)			36 (86%)	32 (74%)	16 (70%)		
Another arthritis condition	Yes	1 (2%)	3 (7%)	1 (5%)	0.6	0.7	4 (10%)	1 (2%)	1 (4%)	0.5	0.6
	No	42 (98%)	38 (93%)	19 (95%)			38 (90%)	42 (98%)	22 (96%)		

1. Test of difference between each Pelagticase group and placebo: t-test for continuous and chi-square test for nominal/ordinal variables.

2. Small amount (<3%) of missing data ignored.

Source: Combination of Sponsor analyses (C405 and C406 clinical study reports, tables 5 and 6) and reviewer analyses

All primary efficacy analyses were conducted using the statistical procedures specified in the protocol and described in section 3.1.1 of this document. The primary efficacy results for studies C405 and C406 are given in Table 2.

	Study C405			Study C406		
	Peg 8 mg/2 wks (N=43)	Peg 8 mg/4 wks (N=41)	Placebo (N=20)	Peg 8 mg/2 wks (N=42)	Peg 8 mg/4 wks (N=43)	Placebo (N=23)
<b>Number Responders (%)</b>	20 (47%)	8 (20%)	0 (0%)	16 (38%)	21 (49%)	0 (0%)
<b>95% CI for diff. relative to placebo<sup>1</sup></b>	(32%, 61%)	(7%, 32%)		(23%, 53%)	(34%, 64%)	
<b>p-value for comparison to placebo<sup>2</sup></b>	<0.001	0.044		<0.001	<0.001	

1. Binomial confidence interval for difference in proportions

2. Fisher's exact test

Source: Sponsor analyses (C405 and C406 clinical study reports, table 11)

On their face, the primary efficacy analyses presented in Table 2 support the efficacy of both dosing regimens of pegloticase over placebo in that the relevant p-values are all less than the prespecified alpha level of 0.05; however, interpretation of this data is made more difficult since no multiplicity correction for the two dose groups was specified in the protocol. In the absence of a prespecified multiplicity plan, a very conservative approach, such as the Bonferonni approach, could be and often is implemented with the logic that if such a standard can be satisfied, then the significance of the hypothesis tests would stand up to any reasonable multiplicity approach and thus the statistical significance is valid despite the lack of a prespecified plan for handling multiplicity. In this case, if the Bonferonni approach is applied, the pegloticase 8 mg/2 wks comparison to placebo would be considered statistically significant in both studies ( $p < 0.001$  in each study). Similarly the pegloticase 8 mg/4 wks comparison to placebo in study C406 would also be considered statistically significant ( $p < 0.001$ ). The comparison of pegloticaes 8 mg/2 wks to placebo in study C405 may be questioned however, as  $p = 0.044$  is greater than the alpha level of 0.025 required by the Bonferoni approach in this setting. As previously stated though, the Bonferonni method is a highly conservative approach and there are many multiplicity plans that if prespecified would have deemed this comparison statistically significant. Also, in light of the highly statistically significant result for this comparison in the replicate study, study C406, it is unlikely that there truly is no difference between pegloticase 8 mg/4 wks and placebo. Thus it is unlikely that the marginally statistically significant comparison of pegloticase 8 mg/4 wks to placebo in study C405 is a type I error. Therefore, in considering all of the primary efficacy results for both studies in concert and applying a common sense approach to multiplicity, it is reasonable to conclude that the efficacy of both dosing regimens of pegloticase have been adequately demonstrated to be different from placebo.

Analyses of three of the numerous secondary efficacy endpoints examined in these studies (i.e., tophus burden, number of swollen and tender joints, and frequency of gout flares) are provided in Tables 3a through 5b. These three endpoints were selected by the FDA medical team as being of particular interest for evaluation of the efficacy of pegloticase. In considering these analyses, the reader should be cautioned that no multiplicity correction was

planned for in the protocol for the secondary endpoints or applied here and therefore these hypothesis tests should be interpreted with caution as the probability of at least one type I error occurring is increased beyond the usual 0.05 due to the examination of such a large number of secondary endpoints. Endpoints that are highly correlated with the primary efficacy endpoint and have a fairly direct scientific link with the primary efficacy endpoint (e.g., reduction in tophi) are less subject to increases in type I error as opposed to endpoints that are not as highly correlated with the primary efficacy endpoint (e.g. patient reported outcomes). These secondary analyses are being presented as supportive to the primary efficacy analyses and additional efficacy claims for the product based on the secondary endpoints should be considered on a case-by-case basis taking into account the clinical importance of the result as well as the connection of the endpoint with the primary endpoint. This is especially important in the context of this product since analyses of the secondary endpoints were, as per-protocol, conducted pooling studies C405 and C406 and thus there is no replication of these results.

At baseline, 155 subjects in studies C405 and C406 combined had at least one tophus: 62 subjects in the pegloticase 8 mg/ 2 wks groups, 64 in the pegloticase 8 mg/4 wks groups, and 29 in the placebo groups. This subset of subjects, the “tophus-evaluable population” was to be used for the analysis of tophus response while those without tophus at baseline were to be excluded. Overall tophus response was measured as specified in the protocol and described in section 3.1.1 of this document. The proportions of subjects in each treatment group with complete response (meaning there was complete resolution for at least one of the subject’s measured or unmeasured tophi) are given in Tables 3a and 3b. Table 3a includes analyses provided by the sponsor in the integrated summary of efficacy. Note though that this analysis includes only subjects with evaluable tophi at week 25, not the entire “tophus-evaluable population”. While treatment assignment within the “tophus-evaluable population” is appropriately random since the presence or absence of tophi at baseline was measured prior to random treatment assignment, the by-treatment group comparisons in the subset of subjects in the “tophus-evaluable population” who also were evaluable at week 25 may be biased as additional subjects are being excluded based on a post-randomization characteristic that may have been influenced by treatment assignment. The mechanism for subjects to be considered unevaluable at week 25 was through categorization by the central reader. That is, tophi were to be categorized by the central reader as “unable to evaluate” if an individual tophi could not be assessed for any reason at any given post-baseline timepoint (e.g., image missing or of poor quality, obvious infection of the tophus). A sensitivity analysis addressing this issue and considering the “unable to evaluate” cases as failures is provided in Table 3b. Although this analysis is conservative (in that more failures are imputed in the pegloticase treatment groups than the placebo group due to higher “unable to evaluate” rates in the pegloticase groups), this analysis has the important advantage of incorporating all subjects in the “tophus-evaluable population”. The qualitative conclusions from these two analyses are the same in that the pegloticase 8 mg/2wks group comparison to placebo is associated with a p-value smaller than the nominal significance level of 0.05 and the pegloticase 8 mg/4wks comparison to placebo is not.

<b>Table 3a: Selected Secondary Efficacy Analysis: Complete Response for Overall Tophus Response at Week 25 (“Tophus-Evaluable Population”)</b>			
	<b>Studies C405 and C406 Pooled</b>		
	<b>Peg 8 mg/2 wks (N=62)</b>	<b>Peg 8 mg/4 wks (N=64)</b>	<b>Placebo (N=29)</b>
<b>Number Subject with Evaluable Tophi at Week 25<sup>1</sup></b>	40	42	25
<b>Number Subjects with Complete Response (%)</b>	18/40 = 45%	11/42 = 26%	2/25 = 8%
<b>p-value for comparison to placebo<sup>2</sup></b>	0.002	0.109	

1. Tophi were to be categorized by the central reader as “unable to evaluate” if an individual tophi could not be assessed for any reason at any given post-baseline timepoint (e.g., image missing or of poor quality, obvious infection of the tophus).

2. Fisher’s exact test comparing proportions of subjects with of complete response.

Source: Sponsor analyses (Integrated Summary of Efficacy, table 31)

<b>Table 3b: Sensitivity Analysis: Complete Response for Overall Tophus Response at Week 25 with Un-Evaluable Subjects as Failures (“Tophus-Evaluable Population”)</b>			
	<b>Studies C405 and C406 Pooled</b>		
	<b>Peg 8 mg/2 wks (N=62)</b>	<b>Peg 8 mg/4 wks (N=64)</b>	<b>Placebo (N=29)</b>
<b>Number Subject with Evaluable Tophi at Week 25<sup>1</sup></b>	40	42	25
<b>Number Subjects with Complete Response (%)</b>	18/62 = 29%	11/64 = 17%	2/29 = 7%
<b>p-value for comparison to placebo<sup>2</sup></b>	0.03	0.3	

1. Tophi were to be categorized by the central reader as “unable to evaluate” if an individual tophi could not be assessed for any reason at any given post-baseline timepoint (e.g., image missing or of poor quality, obvious infection of the tophus). In this sensitivity analysis, these subjects are assumed to have an overall tophus response less than a complete response.

2. Fisher’s exact test comparing proportions of subjects with complete response.

Source: Reviewer analyses

The number of swollen or tender joints was measured as specified in the protocol and described in section 3.1.1 of this document. The change from baseline to week 25 in the mean number of swollen or tender joints for each treatment group is given in Tables 4a and 4b. Table 4a contains the analysis of this endpoint presented by the sponsor in the Integrated Summary of Efficacy, excluding subjects who did not attend a week 25 visit. This type of analysis is not appropriate in that it excludes subjects based on a post-randomization characteristic that is likely affected by treatment assignment. This analysis also is not consistent with the protocol which specified that missing data should be imputed using the last-observation-carried-forward approach for most secondary efficacy endpoints. Table 4b provides the protocol-specified analysis (i.e., using LOCF to impute missing data).

Qualitative conclusions from the sponsor’s analysis and the sensitivity analysis for the comparison of pegloticase 8 mg/ 2 weeks to placebo are the same in that the change from baseline to week 25 in the mean number of swollen or tender joints were associated with p-values less than the nominal significance level of 0.05. The qualitative conclusions from the sponsor’s analysis and the sensitivity analysis for comparison of pegloticase 8 mg/4 weeks to placebo are not the same. The change from baseline to week 25 in the mean number of swollen or tender joints was associated with a p-value less than the nominal significance level of 0.05 in the sponsor’s analysis but not in the sensitivity analysis.

<b>Table 4a: Selected Secondary Efficacy Analysis: Number of Swollen or Tender Joints at Week 25 (ITT)</b>			
	<b>Studies C405 and C406 Pooled</b>		
	<b>Peg 8 mg/2 wks (N=85)</b>	<b>Peg 8 mg/4 wks (N=83)</b>	<b>Placebo (N=43)</b>
<b>Mean at baseline</b>	20.5 (22.1)	21.1 (21.3)	27.3 (26.5)
<b>Number of subjects with a week 25 visit <sup>1</sup></b>	60	62	38
<b>Mean change from baseline to week 25 (SD)</b>	-14.9 (20.1)	-12.3 (17.2)	-2.9 (23.8)
<b>p-value for comparison to placebo<sup>2</sup></b>	0.009	0.025	

1. Analysis excludes subjects who did not attend a week 25 visit.

2. Two sample t-test

Source: Sponsor analyses (Integrated Summary of Efficacy, table 59)

<b>Table 4b: Sensitivity Analysis: Number of Swollen and Tender Joints at Week 25 (ITT)</b>			
	<b>Studies C405 and C406 Pooled</b>		
	<b>Peg 8 mg/2 wks (N=85)</b>	<b>Peg 8 mg/4 wks (N=84)</b>	<b>Placebo (N=43)</b>
<b>Mean at baseline</b>	20.5 (22.1)	21.1 (21.3)	27.3 (26.5)
<b>Number of subjects with a week 25 visit <sup>1</sup></b>	60	62	38
<b>Mean change from baseline to week 25 (SD)</b>	-11.3	-9.7	-3.7
<b>p-value for comparison to placebo<sup>2</sup></b>	0.04	0.08	

1. Missing data is imputed with LOCF approach.

2. Two sample t-test

Source: Reviewer analyses

The incidence of gout flares was measured as specified in the protocol and described in section 3.1.1 of this document. The proportion of subjects experiencing gout flares in each treatment group during months 1-3 and months 4-6 are presented in Tables 5a and 5b. Table 5a contains the analysis of this endpoint presented by the sponsor in the Integrated Summary of Efficacy, excluding subjects who did not attend at least one month 4-6 visit. This type of analysis is not appropriate in that it excludes subjects based on a post-randomization characteristic that is likely affected by treatment assignment. Table 5b provides the same analysis but imputes subjects with missing data as having had at least one

flare. This approach is likely conservative in that the proportions of subjects with missing data are higher in the pegloticase groups than the placebo group and therefore more flares are being imputed for the pegloticase groups than the placebo group. For months 1-3, the comparisons of the proportion of subjects with at least one flare in the pegloticase groups to that of the placebo group were associated with a p-values less than the nominal 0.05. The sponsor's analysis of the proportions of subjects experiencing at least one flare in months 4-6 reveals a p-value less than the nominal significance level 0.05 for comparison to placebo of the pegloticase 8 mg/2 wks group but not the pegloticase 8 mg/4 wks group. The numerical trends in the months 4-6 data are consistent for the sponsor's analysis and the analysis imputing subjects with missing data as having had at least one flare but the p-values are not. Neither the pegloticase 8 mg/2 wks or pegloticase 8 mg/4 wks comparisons to placebo are associated with p-values less than the nominal significance level of 0.05 in the analysis imputing subjects with missing data as having had at least one flare.

<b>Table 5a: Selected Secondary Efficacy Analysis: Frequency of Gout Flares (ITT)</b>			
	<b>Studies C405 and C406 Pooled</b>		
	<b>Peg 8 mg/2 wks (N=85)</b>	<b>Peg 8 mg/4 wks (N=84)</b>	<b>Placebo (N=43)</b>
<b>Months 1-3</b>			
<b>Number of subjects with at least one flare in months 1-3</b>	64/85 = 75%	68/84 = 81%	23/43 = 54%
<b>p-value for comparison to placebo</b>	0.02	0.002	
<b>Months 4-6</b>			
<b>Number of subjects with at least one flare in months 4-6</b>	28/69 = 41%	39/69 = 57%	29/43 = 67%
<b>p-value for comparison to placebo</b>	0.007	0.321	

1. Analysis excludes subjects who did not attend at least one month 4-6 visit.

2. Fisher's exact test

Source: Sponsor analyses (Integrated Summary of Efficacy, table 66)

<b>Studies C405 and C406 Pooled</b>			
	<b>Peg 8 mg/2 wks (N=85)</b>	<b>Peg 8 mg/4 wks (N=84)</b>	<b>Placebo (N=43)</b>
<b>Months 1-3</b>			
<b>Number of subjects with at least one flare in months 1-3</b>	64/85 = 75%	68/84 = 81%	23/43 = 54%
<b>p-value for comparison to placebo</b>	0.02	0.002	
<b>Months 4-6</b>			
<b>Number of subjects with at least one flare in months 4-6</b>	44/85 = 52%	54/84 = 64%	29/43 = 67%
<b>p-value for comparison to placebo</b>	0.1	0.8	

1. Analyses impute occurrence of at least one flare for subjects who did not attend at least one month 4-6 visit.

2. Fisher's exact test

Source: Reviewer analyses

### 3.2 Evaluation of Safety

The medical team highlighted the frequency of infusion reactions as an important factor in characterizing the safety of pegloticase. Therefore statistical analyses of infusions reactions are included in this section. Adverse events that occurred during or within two hours following the end of study drug infusion were evaluated for possible characterization as infusion reactions. The proportions of subjects experiencing at least one infusion reaction and comparison of each of the pegloticase groups to placebo are given in Table 6. These data suggest an increased risk of infusion reaction with either dose of pegloticase over placebo.

	<b>Study C405</b>			<b>Study C406</b>		
	<b>Peg 8 mg/2 wks (N=43)</b>	<b>Peg 8 mg/4 wks (N=41)</b>	<b>Placebo (N=20)</b>	<b>Peg 8 mg/2 wks (N=42)</b>	<b>Peg 8 mg/4 wks (N=43)</b>	<b>Placebo (N=23)</b>
<b>Number subjects with infusion reaction at any visit (%)</b>	11 (26%)	16 (39%)	1 (5%)	11 (26%)	18 (42%)	1 (4%)
<b>p-value for comparison to placebo<sup>1</sup></b>	0.08	0.006		0.04	0.001	

1. Fisher's exact test

Source: Sponsor analyses (C405 and C406 clinical study reports, section 14.3 table 33)

At the DAARP Advisory Committee meeting held on 6/16/09, the sponsor suggested that the occurrence of infusion reactions could be mitigated by stopping administration of pegloticase when subjects' uric acid levels rise above 6 mg/dL. The committee expressed interest this type of approach but questioned whether a cutoff of 6 mg/dL was supported by the data. Analyses to determine an appropriate cutoff (if one exists) that could help to

minimize the number of infusion reactions (by stopping pegloticase in subjects who are not realizing benefit from the treatment) but still allow continuation of the drug in the subjects who may eventually benefit from the product are being undertaken and will be discussed in an addendum to this statistical review.

## **4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS**

### **4.1 Gender, Race and Age**

Descriptive summaries of the primary efficacy variable by gender, age, and race for both studies C405 and C406 are given in Table 7. No differing treatment effects among the subgroups examined were noted.

**Table 7: Subgroup Analyses – Proportion of Subjects with PUA Concentrations <6 mg/dL for at least 80% of the Time During Months 3 and 6 Combined by Gender, Age and Race (ITT)**

Females						
	Study C405			Study C406		
	Peg 8 mg/2 wks (N=43)	Peg 8 mg/4 wks (N=41)	Placebo (N=20)	Peg 8 mg/2 wks (N=42)	Peg 8 mg/4 wks (N=43)	Placebo (N=23)
# 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 <sup>1</sup>	0.04	1.0		0.5	0.2	
Males						
	Study C405			Study C406		
	Peg 8 mg/2 wks (N=43)	Peg 8 mg/4 wks (N=41)	Placebo (N=20)	Peg 8 mg/2 wks (N=42)	Peg 8 mg/4 wks (N=43)	Placebo (N=23)
# 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 <sup>1</sup>	0.004	0.09		0.001	<0.001	
Age ≤ 55 years						
	Study C405			Study C406		
	Peg 8 mg/2 wks (N=43)	Peg 8 mg/4 wks (N=41)	Placebo (N=20)	Peg 8 mg/2 wks (N=42)	Peg 8 mg/4 wks (N=43)	Placebo (N=23)
# 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 <sup>1</sup>	0.3	1.0		0.02	0.008	
Age > 55 years						
	Study C405			Study C406		
	Peg 8 mg/2 wks (N=43)	Peg 8 mg/4 wks (N=41)	Placebo (N=20)	Peg 8 mg/2 wks (N=42)	Peg 8 mg/4 wks (N=43)	Placebo (N=23)
# 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 <sup>1</sup>	0.001	0.07		0.03	0.002	
White						
	Study C405			Study C406		
	Peg 8 mg/2 wks (N=43)	Peg 8 mg/4 wks (N=41)	Placebo (N=20)	Peg 8 mg/2 wks (N=42)	Peg 8 mg/4 wks (N=43)	Placebo (N=23)
# 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 <sup>1</sup>	0.004	0.09		0.012	0.016	
Non-White						
	Study C405			Study C406		
	Peg 8 mg/2 wks (N=43)	Peg 8 mg/4 wks (N=41)	Placebo (N=20)	Peg 8 mg/2 wks (N=42)	Peg 8 mg/4 wks (N=43)	Placebo (N=23)
# 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 <sup>1</sup>	0.04	NA		0.07	0.001	

1. Fisher's exact test

Source: Sponsor analyses (C405 and C406 clinical study reports, table 11)

## 4.2 Other Special/Subgroup Populations

No other special subgroups were identified for analysis in the course of this review.

# 5. SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues and Collective Evidence

The following statistical issues and their impact have been described in the context of the review. Please refer to the specified section for details.

- Exclusions from the per-protocol (PP) group were fairly frequent and perhaps more importantly were imbalanced across the treatment groups. The PP groups included approximately 60% to 70% of the subjects randomized to the pegloticase groups and approximately 80% of subjects randomized to the placebo groups. This pattern was similar in both studies. These post-randomization differences in exclusion rates are likely to have been related to treatment assignment and thus significantly bias the by-treatment group comparisons within the PP group. Note: This bias does not adversely impact the analysis of the primary efficacy endpoint in the ITT group. Please see the next comment. (Section 3.1.2)
- Subjects who withdrew from the study before month 6 were, by protocol definition, considered nonresponders for the primary efficacy analysis in the intent-to-treat group. This may be considered a fair representation of the efficacy in these subjects in that the subjects' reasons for withdrawal from the study (i.e., commonly adverse event or withdrew consent) indicate the study treatment could not be tolerated in exchange for whatever efficacy may have been being achieved and thus for all intents and purposes, the study treatment failed for those subjects. Therefore, the primary efficacy results in the ITT group likely remain reliable despite the more frequent early withdrawal from the studies for the Pegloticase groups relative to that of placebo. (Section 3.1.2)
- As would be expected due to the random treatment assignment associated with the 24-week treatment period, balance among the treatment groups in demographic and baseline characteristics appears adequate to allow by-treatment group differences in post-randomization outcomes for this period to be attributed to treatment effects and not an artifact of an imbalance in pre-randomization characteristics in both studies C405 and C406. (Section 3.1.2)
- The optional 24 month open label extensions associated with studies C405 and C406 does not provide reliable by-treatment group comparisons as there could be inappropriate imbalances in covariates. For the extension, subjects and investigators chose between every 2-week or every 4-week dosing of 8 mg pegloticase or an observational arm (no pegloticase treatment). This period was intended to evaluate the long-term safety and durability of efficacy of pegloticase; however, these data are limited due to the lack of randomly assigned treatment groups. (Section 3.1.1)
- The primary efficacy analyses seem to support the efficacy of both dosing regimens of pegloticase over placebo in that the relevant p-values are all less than the prespecified alpha level of 0.05; however, interpretation of this data is made more difficult since no multiplicity correction for the two dose groups was specified in the protocol. The marginally statistically significant comparison of pegloticase 8 mg/4 wks to placebo in

study C405 could be interpreted as a spurious finding. However, in light of the highly statistically significant result for this comparison in the replicate study, study C406, it is unlikely that there truly is no difference between pegloticase 8 mg/4 wks and placebo. Therefore, in considering all of the primary efficacy results for both studies in concert it is reasonable to conclude that the efficacy of both dosing regimens of pegloticase have been adequately demonstrated to be different from placebo for the primary efficacy endpoint. (Section 3.1.2)

- Despite recommendations from the medical division during the planning of studies 405 and 406, no multiplicity correction was planned for in the protocol for the numerous secondary endpoints examined. Therefore the hypothesis tests associated with the secondary endpoints should be interpreted with caution as the probability of at least one type I error occurring is increased beyond the usual 0.05. Endpoints that are highly correlated with the primary efficacy endpoint and have a fairly direct scientific link with the primary efficacy endpoint (e.g., reduction in tophi) are less subject to increases in type I error as opposed to endpoints that are not as highly correlated with the primary efficacy endpoint (e.g. patient reported outcomes). Additional efficacy claims for the product based on the secondary endpoints should be considered on a case-by-case basis taking into account the clinical importance of the result as well as the connection of the endpoint with the primary endpoint. This is especially important in the context of this product since analyses of the secondary endpoints were, as per-protocol, conducted pooling studies C405 and C406 and thus there is no replication of these results. (Section 3.1.2)
- Analyses provided by the sponsor in the integrated summary of efficacy of the reduction in tophi include only subjects with evaluable tophi at week 25, not the entire “tophus-evaluable population”. The by-treatment group comparisons in the subset of subjects in the “tophus-evaluable population” who also were evaluable at week 25 may be biased. A sensitivity analysis addressing this issue and considering the “unable to evaluate” cases as failures leads to the same qualitative conclusions as the sponsor’s analyses in that the pegloticase 8 mg/2 weeks group comparison to placebo is associated with a p-value smaller than the nominal significance level of 0.05 and the pegloticase 8 mg/ 4weeks comparison to placebo is not; however, the descriptive proportions are notably lower for the pegloticase groups in the sensitivity analysis than in the sponsor’s analyses. (Section 3.1.2)
- The sponsor’s analysis of the change from baseline to week 25 in the number of swollen or tender joints excludes subjects who did not attend a week 25 visit. This type of analysis is not appropriate in that it excludes subjects based on a post-randomization characteristic that is likely affected by treatment assignment. This analysis also is not consistent with the protocol which specified that missing data should be imputed using the last-observation-carried-forward (LOCF) approach for most secondary efficacy endpoints. The sensitivity analysis imputing subjects with missing data using LOCF methods is provided. The sensitivity analysis yields the same qualitative conclusions for the pegloticase 8 mg/2 weeks comparison to placebo as the sponsor’s analysis. Although the sensitivity analysis yields similar numerical trends to the sponsor’s analysis for the pegloticase 8 mg/ 4 weeks comparison to placebo, the qualitative conclusions from the sponsor’s analysis and the sensitivity analysis are not the same in that the change from baseline to week 25 in the mean number of swollen or tender joints was

- associated with a p-value less than the nominal significance level of 0.05 in the sponsor's analysis but not in the sensitivity analysis. (Section 3.1.2)
- The sponsor's analysis of the proportion of subjects experiencing gout flares excludes subjects who did not attend at least one month 4-6 visit. This type of analysis is not appropriate in that it excludes subjects based on a post-randomization characteristic that is likely affected by treatment assignment. A sensitivity analysis imputing subjects with missing data as having had at least one flare yields similar numerical trends to the sponsor's analysis; however, the sponsor's analysis of the proportions of subjects experiencing at least one flare in months 4-6 reveals a p-value less than the nominal significance level 0.05 for comparison to placebo of the pegloticase 8 mg/2 wks group but not the pegloticase 8 mg/4 wks group while neither the pegloticase 8 mg/2 wks or pegloticase 8 mg/4 wks comparisons to placebo are associated with p-values less than the nominal significance level of 0.05 in the sensitivity analysis. (Section 3.1.2)
  - Studies C405 and C406 suggest that the proportions of subjects experiencing at least one infusion reaction were higher in each of the pegloticase groups compared to placebo. The sponsor suggested that the occurrence of infusion reactions could be mitigated by stopping administration of pegloticase when subjects' uric acid levels rise above 6 mg/dL. The DAARP Advisory Committee expressed interest this type of approach for mitigation of infusion reactions but questioned whether a cutoff of 6 mg/dL was supported by the data. Analyses to determine an appropriate cutoff (if one exists) are being undertaken and will be discussed in an addendum to this statistical review. (Section 3.1.2)
  - Descriptive summaries of the primary efficacy variable by gender, age, and race for both studies C405 and C406 did not reveal any differing treatment effects among these subgroups.

## 5.2 Conclusions and Recommendations

Studies C405 and C406 adequately demonstrate that the proportion of subjects with PUA concentrations <6 mg/dL for at least 80% of the time during months 3 and 6 combined is higher with 8 mg Pegloticase every 2 weeks than placebo. Due to the high statistical significance associated with this comparison, this conclusion is considered robust despite the lack of a pre-specified multiplicity correction for the two dose groups studied. This conclusion is also robust to the choice of statistical methods and does not appear to differ within any of the subgroups examined. Comparison of the proportion of subjects with PUA concentrations <6 mg/dL for at least 80% of the time during months 3 and 6 combined for the 8 mg Pegloticase every 4 weeks group to placebo is significant for study C406 but only marginally so for study C405 and is complicated by the lack of a pre-specified multiplicity correction. However, in considering both studies C405 and C406 in concert, it is unlikely that the result in study C405 is a spurious finding and thus it is appropriate to conclude that the 8 mg Pegloticase every 4 weeks group was associated with a higher proportion of subjects with PUA concentrations <6 mg/dL for at least 80% of the time during months 3 and 6 combined than was placebo. This result does not appear to differ within any of the subgroups examined.

Analyses of secondary efficacy endpoints were generally supportive of the primary efficacy results; however, no multiplicity correction was planned for in the protocol for the numerous secondary endpoints examined. Therefore the hypothesis tests associated with the secondary

endpoints should be interpreted with caution as the probability of at least one type I error occurring is increased beyond the usual 0.05. This is especially important in the context of this product since analyses of the secondary endpoints were, as per-protocol, conducted pooling studies C405 and C406 and thus there is no replication of these results. In addition, sponsor analyses for the secondary endpoints often excluded subjects with unavailable data at week 25. While sensitivity analyses designed to address this issue often lead to qualitative conclusions regarding the treatment effect that were similar to the sponsor's analyses, the descriptive statistics associated with the results were, in some cases, notably different.

The following recommendations are being made for the Clinical Studies section of the Pegloticase labeling. Specific proposals for changes to the text to address the following issues have been conveyed to the medical division.

(b) (4)





U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmacoeconomics and Statistical Science  
Office of Biostatistics

## NDA FILING REVIEW

**BLA:** 125293

**Product Name:** Pegloticase

**Indication(s):** To control hyperuricemia and to manage the signs and symptoms of gout in patients with previous treatment failure

**Applicant:** Savient

**Stamp Date:** October 31, 2008

**Biometrics Division:** Division of Biometrics II

**Statistical Reviewer:** Ruthanna Davi *Ruthanna Davi 12/18/06*

**Concurring Reviewer:** ~~Dionne Price~~ *Thomas P. Smith 12/18/06*

**Medical Division:** Division of Anesthesia, Analgesia, and Rheumatology Products

**Medical Reviewer:** Rosemarie Neuner

**Project Manager:** Diana Walker

**Keywords:** BLA filing review

## Discussion

The sponsor has submitted the results of two nearly identically-designed key studies referred to as studies 405 and 406 in support of the efficacy of Pegloticase for controlling hyperuricemia and for managing the signs and symptoms of gout in patients with treatment failure gout.

Both studies 405 and 406 were randomized (2:2:1), double-blind, placebo-controlled, parallel group, multi-center, 24-week studies. The treatment groups were (1.) 8 mg Pegloticase every two weeks, (2.) 8 mg Pegloticase every four weeks, and (3.) placebo. According to the sponsor, the purpose of studies 405 and 406 was to demonstrate superiority of each Pegloticase group versus placebo in reducing plasma uric acid (PUA) as determined by the primary endpoint, the percentage of subjects achieving and maintaining PUA concentrations less than 6 mg/dL for at least 80% of the time during months 3 and 6 combined.

The sponsor provided statistical analyses of the primary efficacy endpoint utilizing a modified intent-to-treat group, defined as all randomized who received at least one dose of study medication, and a per-protocol group defined as a subset of the intent-to-treat group, including all subjects who had no major deviations from the study protocol and had completed at least six months of the study. The modified intent-to-treat group was protocol-specified to be used for the primary efficacy analysis.

Statistical methods used for the primary efficacy analysis include Fisher's exact test and 95% confidence intervals for the difference between each regimen of Pegloticase and placebo. No multiplicity correction for two doses of Pegloticase was specified. With further review, the lack of a multiplicity correction may not be objectionable and is not an impediment to filing.

On their face, the primary efficacy analyses provided by the sponsor seem to support the efficacy of each regimen of Pegloticase over placebo and could be sufficient to support the proposed labeling (for the primary efficacy endpoint) and therefore are adequate to allow filing. Of note however, is an apparent reversal in the dose response relationship in the two studies (i.e., Pegloticase every 2 weeks is numerically better than Pegloticase every 4 weeks in study 405 while the reverse is true in study 406). This issue will be further assessed as part of the statistical review of the application, including whether this result may be due to random variation in the data in light of the relatively small sample size for statistically assessing differences between two active regimens.

Analyses of the primary efficacy endpoint by center were conducted by FDA; however, these analyses were limited by the small sample sizes available at each center. These analyses did not reveal motivation for targeted audits of study centers by FDA's Division of Scientific Investigations.

The FDA medical team has identified cardiac events and death as important safety concerns with this product therefore, detailed statistical review of these data will also be undertaken. The application appears to include appropriate information to allow this component of the review.

The sponsor also provides subgroup analyses of the primary efficacy endpoint by gender and age. Subgroup analyses by race have been requested from the sponsor.

The electronic data sets including the efficacy data for studies 405 and 406 that are provided in the submission appear adequate for review of the studies.

## Reviewer's Conclusion

From a statistical perspective the application is sufficient for filing.