

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125293

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

<i>BLA</i>	125293	<i>Submission Dates</i>	0000 (10/31/2008) 0008 (02/05/2009)
<i>Brand Name</i>	-		
<i>Generic Name</i>	Pegloticase		
<i>Reviewer</i>	Ping Ji, Ph.D.		
<i>Team Leader</i>	Suresh Doddapaneni, Ph.D.		
<i>PM Primary Reviewers</i>	Venkatesh Atul Bhattaram,, Ph.D., Ping Ji. Ph.D.		
<i>PM Team Leader</i>	Yaning Wang, Ph.D.		
<i>OCP Division</i>	Division of Clinical Pharmacology-II		
<i>OND Division</i>	Division of Anesthesia, Analgesia, and Rheumatology		
<i>Sponsor</i>	Savient Pharmaceuticals, Inc.		
<i>Relevant IND(s)</i>	10122		
<i>Submission Type; Code</i>	505 (b) (1)	P	
<i>Formulation; Strength(s)</i>	Solvent solution for intravenous infusion, 8 mg/vial		
<i>Indication</i>	Treatment failure gout		
<i>Proposed Dosing Regimen</i>	8 mg every 2 weeks		

Table of Contents

Table of Contents	1
1 Executive Summary	2
1.1 Recommendations	2
1.2 Phase IV Commitments	2
1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings	2
2 Question-Based Review	9
2.1 General Attributes	9
2.2 General Clinical Pharmacology	10
2.3 Intrinsic Factors	18
2.4 Extrinsic Factors	18
2.5 Immunogenicity	18
2.6 General Biopharmaceutics	18
2.7 Analytical Section	24
3 Detailed Labeling Recommendations	29
4 Appendices	33
4.1 Proposed Package Insert (Original and Annotated)	33
4.2 Individual Study Review	54
4.3 Pharmacometrics Review	68
4.4 Cover Sheet and OCP Filing/Review Form	106

1 Executive Summary

1.1 Recommendations

The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background

Pegloticase (also referred to as PEG-uricase in this review), subject of BLA 125293, was developed by Savient Pharmaceuticals, Inc. for the Treatment Failure Gout (TFG) to control hyperuricemia (i.e., excess uric acid in the blood) and to manage the signs and symptoms of gout. Pegloticase is a genetically engineered recombinant mammalian uricase (urate oxidase) covalently attached to methoxy polyethylene glycol (m-PEG).

TFG is clinically indicated as hyperuricemia in patients with severe gout in whom conventional therapy is contraindicated or has been ineffective. Current conventional treatments for gout include drugs that either block urate formation (allopurinol) or promote uric acid excretion (probenecid). Such therapy is sometimes ineffective or intolerant. A small number of patients with severe gout develop allergic reactions to the most commonly used agent (allopurinol), which can be life threatening. For these individuals, no alternative therapies are available. Pegloticase was developed as a bio-uricolytic agent for TFG to meet the unmet medical need.

The clinical development program focused on establishing safety, efficacy, and PK characteristics of the product in the gout patients and is supported by six studies: two Phase 1 studies (C0401 and C0402), one Phase 2 study (C0403), and three Phase 3 studies (C0405, C0406 and C0407). Study C0401 investigated the PK and drug effect on symptomatic gout after subcutaneous administration. This study was discontinued due to adverse events (generalized urticaria in two subjects following 12 mg pegloticase administration). Study C0407 is an ongoing trial to assess the long term safety and efficacy of pegloticase. Both C0401 and C0407 are not included in the current review. Summarized in this review are the remaining four studies: study C0402 assessing the PK, safety and tolerability of pegloticase, study C0403 assessing the PK, safety, efficacy of pegloticase, and studies C0405 and C0406 assessing the PK, efficacy, and safety of pegloticase. The proposed dosing regimen is 8 mg every 2 weeks.

Mechanism of Action

In humans, uric acid (UA) is the terminal metabolite of purine degradation. In most animals, UA is further catalyzed to allantoin by the enzyme urate oxidase or uricase. Allantoin is 5–10 times more soluble than UA, and is more readily eliminated by the kidneys. Thus, in most lower mammals, serum urate levels are quite low ($< 120 \mu\text{mol/l}$ or $< 2.0 \text{ mg/dl}$, usually $30\text{--}60 \mu\text{mol/l}$ or $0.5\text{--}1.0 \text{ mg/dl}$). In humans, however, this metabolic route of elimination is inoperative owing to mutation of the urate oxidase gene during evolution. Thus, when blood levels of uric acid are in the hyperuricemic range due to reduced renal proximal tubular UA excretion, deposition of monosodium urate crystals (MSU) can occur in tissues throughout the body and lead to gout. The individual patient's immune response to MSU crystals determines the range of gout signs and symptoms, with primarily rheumatologic and renal manifestations. The crystals are pathogenic in gout. Pegloticase catalyzes the oxidation of uric acid to allantoin and therefore reduces the blood concentrations of uric acid sufficiently below the solubility limit to bring existing crystal accumulations into solution to alleviate the signs and symptoms of gout.

Clinical Pharmacology

Pharmacokinetic Findings Following single 1-hour i.v. infusions of 0.5 to 12.0 mg of pegloticase in 23 patients with symptomatic gout (study C0402), pegloticase exposure increased approximately proportionally to the dose administered. Mean terminal half-life ranged from 152 to 332 hours.

Figure 1. Mean plasma concentrations of pegloticase after IV administration of pegloticase 0.5 to 12 mg (study C0402).

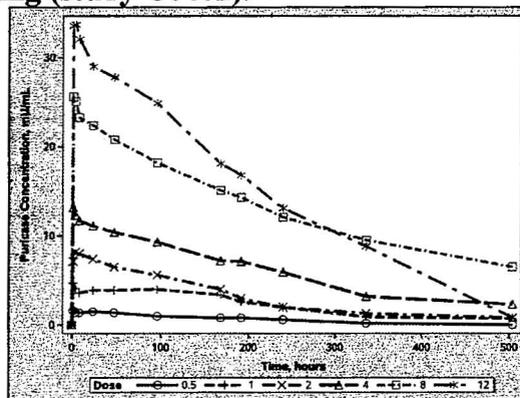


Table 1. Summary statistics (mean and coefficient of variation) of pharmacokinetic parameters for pegloticase after IV administration of pegloticase 0.5 to 12 mg (study C0402).

Parameter	Dose (mg)					
	0.5	1	2	4	8	12
AUC(0-inf) (mU.h/mL)	479.26 (55.27%)	2350.19 (33.13%)	1996.25 (90.32%)	3970.83 (76.64%)	9166.54 (11.39%)	8543.45 (38.74%)
AUC(0-t) (mU.h/mL)	243.12 (55.57%)	997.29 (69.73%)	1510.63 (80.89%)	2839.06 (70.33%)	6325.68 (10.05%)	6271.61 (38.81%)
Cmax (mU/mL)	1.7 (18.18%)	4.8 (32.07%)	8.6 (29.94%)	14.2 (19.44%)	26.0 (10.80%)	36.0 (15.71%)
T1/2 (h)	203.37 (57.50%)	331.88 (15.33%)	152.67 (63.89%)	166.71 (75.63%)	300.45 (7.05%)	162.92 (40.14%)

Note: N=4 per group with the exception of the 1 mg where N=3.

After multiple dose administrations, the accumulation index was 1.42 for AUC and 1.86 for Cmax at the dose of 8 mg every 2 weeks, and the accumulation was minimal for the dose of 8 mg every 4 weeks (study C0403).

Figure 2. Mean pegloticase serum concentrations-time profiles after multiple i.v. infusions (study C0403).

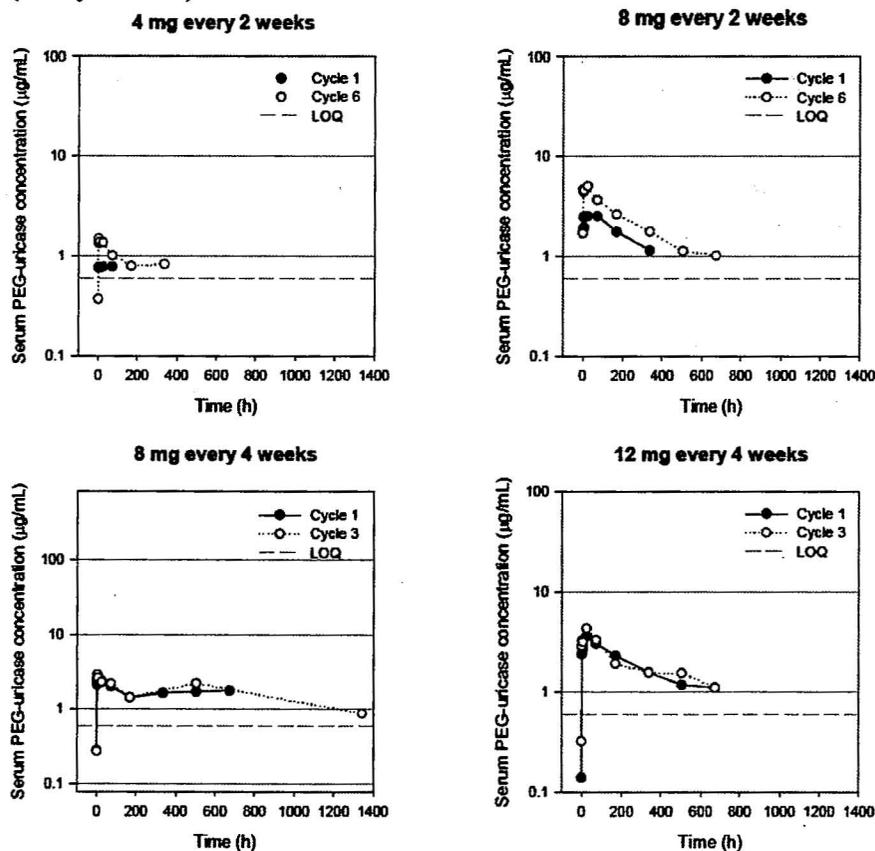


Table 2. Summary of PK parameters of serum pegloticase following multiple i.v. infusions (study C0403).

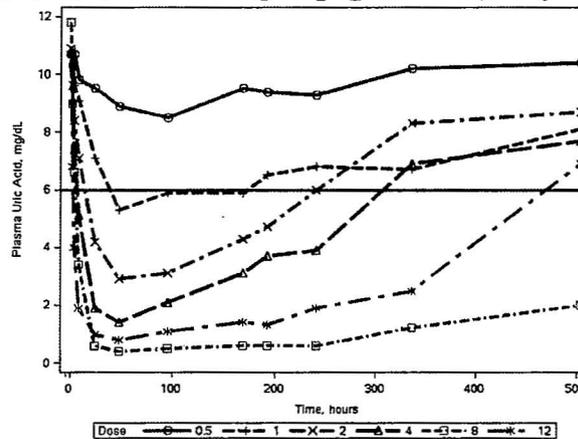
Treatment	Cycle	Median (Range)								
		AUC ₀₋₂₄ (mcg·h/mL)	AUC ₀₋₁₆₈ (mcg·h/mL)	AUC _{0-t} (mcg·h/mL)	AUC _{inf} (mcg·h/mL)	C _{max} (mcg/mL)	T _{max} (h)	Half-life (h)	CL (L/h)	V _{area} (L)
4 mg every 2 weeks	1	17.0 (15.0-18.9)	NC	18.1 (15.0-17.0)	NC	0.800 (0.768-1.14)	6.5 (1.58-168)	NC	NC	NC
	6	34.2 (22.7-51.9)	251 (132-369)	132 (97.1-657)	1230 (322-2138)	1.62 (1.51-2.94)	1.60 (1.50-23.5)	414 (210-617)	0.00609 (0.00609-0.00609)	NC
8 mg every 2 weeks	1	50.3 (20.5-71.7)	355 (245-489)	608 (264-838)	1090 (568-1494)	2.95 (1.98-4.81)	22.9 (1.50-168)	274 (198-308)	0.00734 (0.00536-0.0141)	2.67 (2.31-3.95)
	6	122 (61.1-186)	710 (326-1034)	1361 (326-2734)	1546 (456-3815)	5.96 (2.87-8.89)	6.00 (1.50-21.9)	160 (95.8-371)	0.00681 (0.00447-0.0114)	NC
8 mg every 4 weeks	1	41.4 (15.7-92.9)	269 (151-759)	304 (151-1751)	1337 (579-2549)	2.50 (1.34-5.14)	23.4 (1.67-71.5)	280 (239-296)	0.00673 (0.00314-0.0138)	2.43 (1.36-5.96)
	3	46.5 (25.4-72.8)	403 (231-577)	231 (81.2-3936)	1935 (146-6337)	2.81 (1.92-4.56)	23.2 (1.50-70.9)	399 (61.6-940)	0.00349 (0.00349-0.00349)	NC
12 mg every 4 weeks	1	59.6 (30.7-114)	478 (252-765)	1047 (97.6-2574)	1566 (991-3052)	3.52 (1.53-5.79)	23.2 (1.50-71.5)	329 (181-403)	0.00767 (0.00393-0.0121)	3.30 (1.82-4.05)
	3	84.0 (63.5-139)	519 (398-567)	670 (398-1821)	925 (628-2216)	4.64 (3.28-6.18)	14.6 (1.52-23.4)	119 (92.8-282)	0.00671 (0.00659-0.00683)	NC

NC – not calculated.

A population PK analysis was conducted based on data from the two phase 3 studies (studies C0405 and C0406). A one-compartment model with linear elimination was found to best fit the plasma pegloticase concentration time profiles. Body surface area and overall anti-pegloticase antibody response were identified as significant covariates for PK parameters clearance (CL) and volume of distribution (V). An increase in anti-pegloticase antibody response led to 32% increase in CL and 25% increase in V. Body surface area was found to be positively related with CL and V.

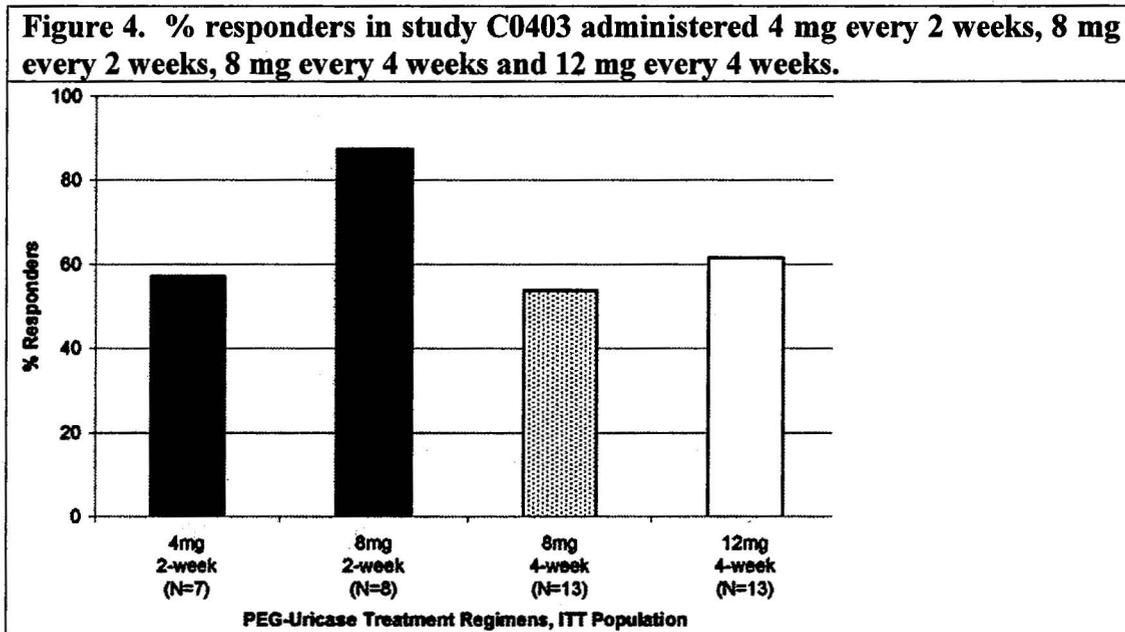
Pharmacodynamic Findings After single i.v. infusions (study C0402), uric acid levels decreased with increasing pegloticase dose or concentrations. At dose levels above 1 mg, the uric acid levels were reduced below the solubility concentration of 6 mg/dL. The duration of suppression of uric acid appeared to be positively associated with pegloticase dose.

Figure 3. Mean plasma uric acid concentrations after single intravenous dose administration of 0.5, 1, 2, 4, 8, or 12 mg of pegloticase (study C0402).

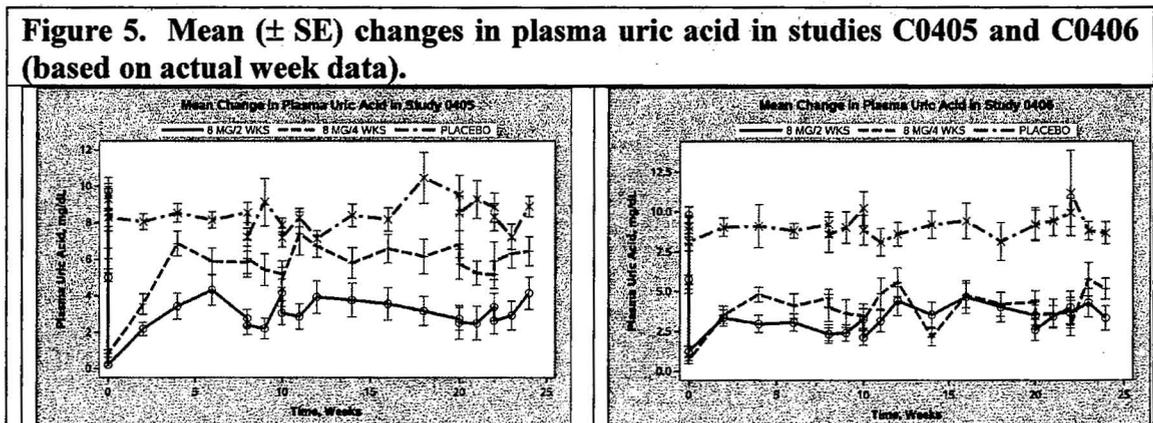


The uric acid lowering potential of pegloticase administered as 4 mg every 2 weeks, 8 mg every 2 weeks, 8 mg every 4 weeks and 12 mg every 4 weeks were evaluated in the Phase 2 study C0403. The percentage of patients classified as Responders (subjects whose PUA remained ≤ 6 mg/dL for at least 80% of the treatment period) are shown in

Figure 4. The highest percentage of responders were observed in the group administered 8 mg every 2 weeks.

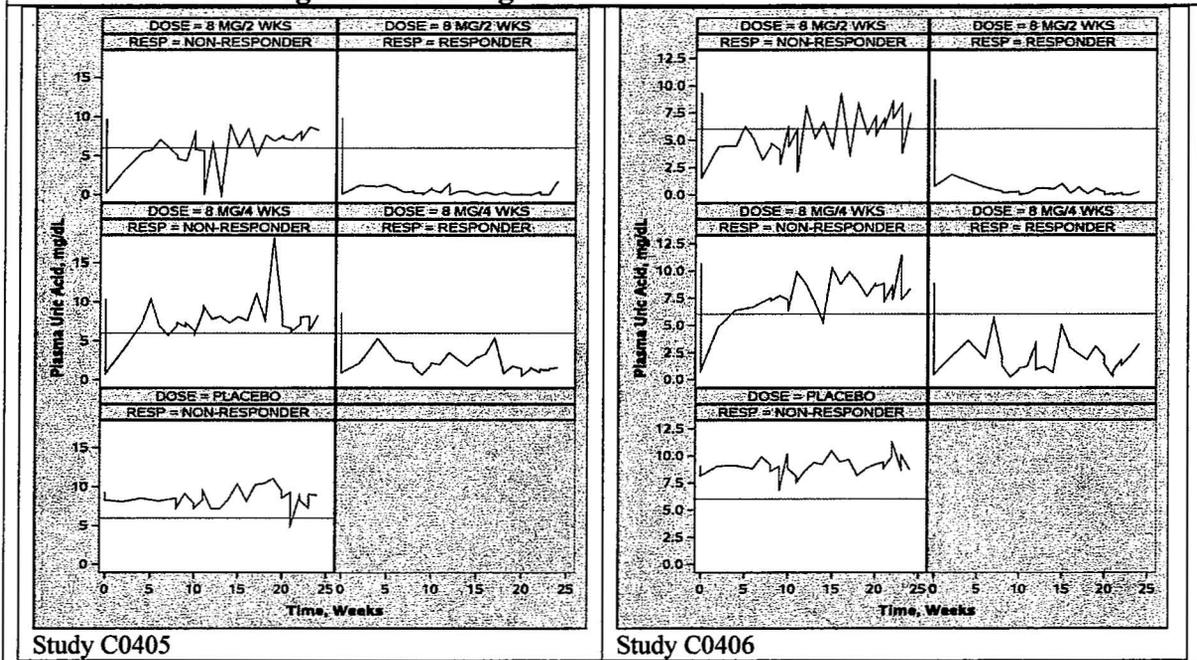


In the two phase 3 studies (studies C0405 and C0406), 8 mg dose was administered every 2 or 4 weeks along with placebo. Both studies showed that the two dosing regimens had better response compared to placebo based on the primary endpoint (% of subjects achieving and maintaining PUA concentrations < 6 mg/dL for at least 80% of the time during Months 3 and 6 combined. These patients are classified as responders.)



In studies C0405 and C0406, subjects who failed to achieve or maintain PUA concentrations < 6 mg/dL for at least 80% of the time during Months 3 and 6 combined discontinued early in the study due to tolerability issues were characterized as non-responders. Figure 6 shows the mean time course of plasma uric acid in responders vs non-responders after administration of placebo, 8 mg every 4 weeks and 8 mg every 2 weeks. Patients classified as non-responders did not show sustained reduction in plasma uric acid levels.

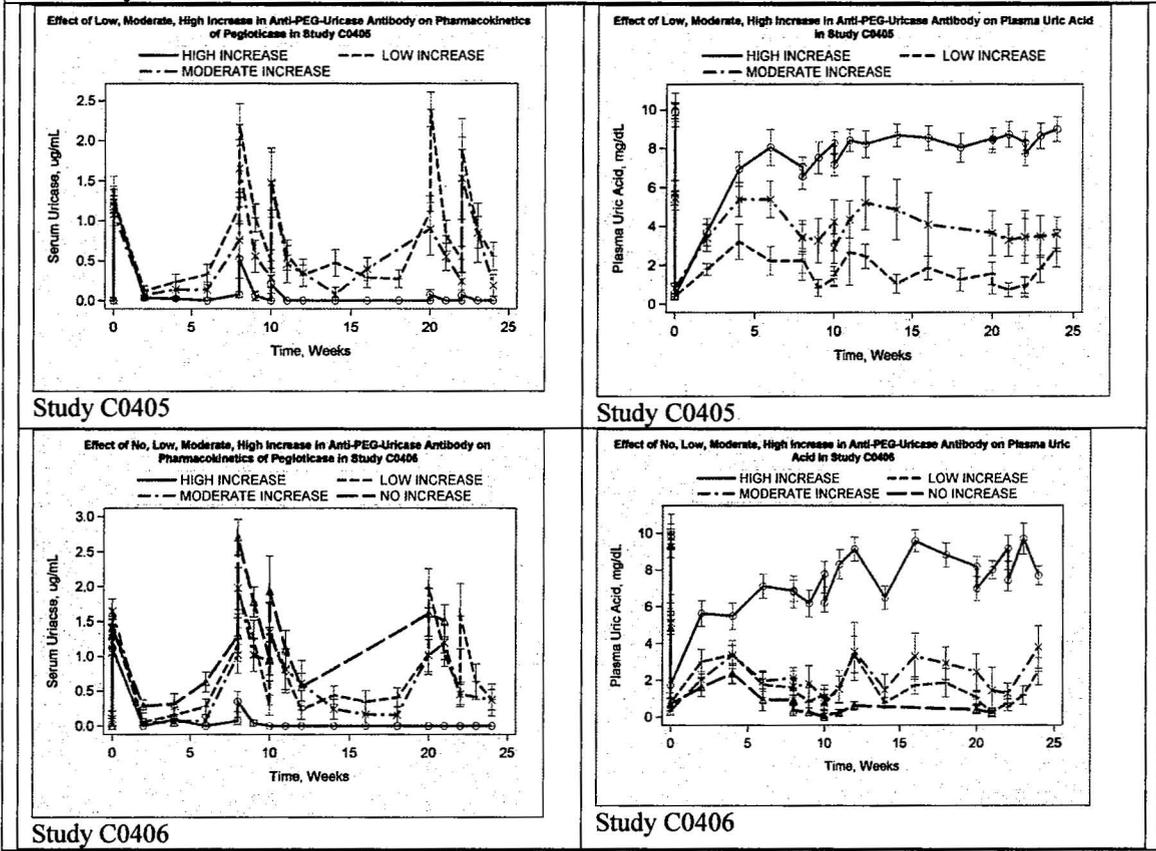
Figure 6. Mean changes in plasma uric acid after administration of placebo (PLACEBO), 8 mg every 4 weeks (8 MG/4 WKS), and 8 mg every 2 weeks (8 MG/2 WKS) in responders and non-responders in studies C0405 and C0406. The reference line indicates the target level of 6 mg/dL.



Immunogenicity

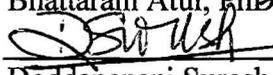
Immunogenicity was found in both single and multiple-dose administrations. The presence of anti-pegloticase antibody appears to be associated with a decrease in the exposure of pegloticase and an increase in plasma uric acid level (Figure 7). It is not known if there is a prognostic factor that would predict the likelihood of a patient developing antibodies to pegloticase. However, in responder patients, fewer subjects had high increase in antibody titer.

Figure 7. Mean (\pm SE) changes in plasma concentrations of pegloticase and uric acid in patients who have no, mild, moderate or severe increase of anti-pegloticase antibody in studies C0405 and C0406.



Note: No increase included subjects who were negative at baseline, Month 3 and Month 6 (no titer), and who were positive at baseline but with no increase from baseline in titer during Months 3 and 6 (no increase in titer).
 Low increase if titer was > 0 and ≤ 810 at Month 3 or Month 6.
 Moderate increase if titer was > 810 and ≤ 7290 at Month 3 or Month 6.
 High increase if titer > 7290 at Month 3 or Month 6.

Overall, adequate clinical pharmacology was submitted in support of BLA125293.

 6/24/09
 Ping Ji, PhD
 6/24/09
 Bhattaram Atul, PhD
 6/24/09
 Doddapaneni Suresh, PhD

2 Question-Based Review

2.1 General Attributes

2.1.1 **What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?**

Pegloticase, subject of BLA 125293, was developed by Savient Pharmaceuticals, Inc. for the Treatment Failure Gout (TFG) to control hyperuricemia (ie, excess uric acid in the blood) and to manage the signs and symptoms of gout. Pegloticase is a genetically engineered recombinant mammalian uricase (urate oxidase) covalently attached to methoxy polyethylene glycol (m-PEG).

TFG is clinically indicated as hyperuricemia in patients with severe gout in whom conventional therapy is contraindicated or has been ineffective. Current conventional treatments for gout include drugs that either block urate formation (allopurinol) or promote uric acid excretion (probenecid). Such therapy is sometimes ineffective or intolerant. A small number of patients with severe gout develop allergic reactions to the most commonly used agent (allopurinol), which can be life threatening. For these individuals, no alternative therapies are available. Pegloticase was developed as a bio-uricolytic agent for TFG to meet the unmet medical need.

The clinical development program focused on establishing safety, efficacy, and PK characteristics of the product in the gout patients and is supported by six studies: two Phase 1 studies (C0401 and C0402), one Phase 2 study (C0403), and three Phase 3 studies (C0405, C0406 and C0407). Study C0401 investigated the PK and drug effect on symptomatic gout after subcutaneous administration. This study was discontinued due to adverse events (generalized urticaria in two subjects following 12 mg pegloticase administration). Study C0407 is an ongoing trial to assess the long term safety and efficacy of pegloticase. Both C0401 and C0407 are not included in the current review. Summarized in this review are the remaining four studies: study C0402 assessing the PK, safety and tolerability of pegloticase, study C0403 assessing the PK, safety, efficacy of pegloticase, and studies C0405 and C0406 assessing the PK, efficacy, and safety of pegloticase. The proposed dosing regimen is 8 mg every 2 weeks.

2.1.2 **What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?**

Pegloticase is a bio-uricolytic enzyme. It is a modified mammalian urate oxidase (uricase) produced in *E. coli* by recombinant technology and then chemically conjugated with an average of 36 ^(b)₍₄₎ strands of 10 kDa methoxypoly (ethylene glycol) or mPEG; the total molecular weight is approximately 497 kDa. It is a tetrameric enzyme having an average of 9±1 strands of the mPEG linked to one subunit of uricase with a molecular weight of 34.2 kDa per subunit.

Pegloticase product contains (b) (4) pegloticase (delivering 8 mg of uricase protein), 2.18 mg disodium hydrogen phosphate dihydrate ($\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$), 0.43 mg. sodium dihydrogen Phosphate dihydrate ($\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$), 8.77 mg sodium chloride (NaCl) and water for injection in 1 mL volume. Pegloticase product is supplied as an 8 mg uricase protein/mL clear, colorless, sterile solution in phosphate buffered saline intended for intravenous (i.v.) infusion only. Pegloticase product is supplied in a single-use 2 mL glass vial and packaged to deliver 1 mL of drug for dilution.

2.1.3 What are the proposed mechanism of action and therapeutic indication(s)?

In humans, uric acid (UA) is the terminal metabolite of purine degradation. In most animals, UA is further catalyzed to allantoin by the enzyme urate oxidase or uricase. Allantoin is 5–10 times more soluble than UA, and is more readily eliminated by the kidneys. Thus, in most lower mammals, serum urate levels are quite low ($< 120 \mu\text{mol/l}$ or $< 2.0 \text{ mg/dl}$, usually $30\text{--}60 \mu\text{mol/l}$ or $0.5\text{--}1.0 \text{ mg/dl}$). In humans, however, this metabolic route of elimination is inoperative owing to mutation of the urate oxidase gene during evolution. Thus, when blood levels of uric acid are in the hyperuricemic range due to reduced renal proximal tubular UA excretion, deposition of monosodium urate crystals (MSU) can occur in tissues throughout the body and lead to gout. The individual patient's immune response to MSU crystals determines the range of gout signs and symptoms, with primarily rheumatologic and renal manifestations. The crystals are pathogenic in gout. Pegloticase catalyzes the oxidation of uric acid to allantoin and therefore reduces the blood concentrations of uric acid sufficiently below the solubility limit to bring existing crystal accumulations into solution to alleviate the signs and symptoms of gout.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

The recommended dose and regimen of pegloticase for adult patients is 8 mg given as an intravenous infusion every two weeks. No dosing adjustment for pegloticase is necessary for sex, age, weight or renal impairment. Pegloticase has not been studied in patients with hepatic impairment.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical development program focused on establishing safety, efficacy, and PK characteristics of the product in the gout patients and is supported by six studies: two Phase 1 studies (C0401 and C0402), one Phase 2 study (C0403), and three Phase 3 studies (C0405, C0406 and C0407). Study C0401 investigated the PK and drug effect on symptomatic gout after subcutaneous administration. This study was discontinued due to

adverse events (generalized urticaria in two subjects following 12 mg pegloticase administration). Study C0407 is an ongoing trial to assess the long term safety and efficacy of pegloticase. Both C0401 and C0407 are not included in the current review. Summarized in this review are the remaining four studies: study C0402 assessing the PK, safety and tolerability of pegloticase, study C0403 assessing the PK, safety, efficacy of pegloticase, and studies C0405 and C0406 assessing the PK, efficacy, and safety of pegloticase. The proposed dosing regimen is 8 mg every 2 weeks.

Table 3. Tabular listing of all clinical studies.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	C0401	5.3.5.4	Assess PK, tolerability, safety	Open label, escalating single dose	PEG-uricase; Subcutaneous injection; 4mg, 8 mg, 12 mg, 24 mg	13	Pts. with symptomatic gout despite conventional therapy	1 day; follow-up evaluations for 21 days	Terminated; Full
PK	C0402	5.3.5.2	Assess PK, tolerability, safety	Open label, escalating single dose	PEG-uricase; IV infusion; dose escalation in 6 cohorts: 0.5 mg, 1.0 mg, 2.0 mg, 4.0mg, 8 mg, 12 mg	24	Pts. with symptomatic gout despite conventional therapy	1 day; follow-up evaluations for 8 weeks	Complete; Full
PK and efficacy/safety	C0403	5.3.5.1	Assess multiple dose PK, efficacy, tolerability and safety	Randomized, open-label, parallel group	PEG-uricase; IV infusion; 4 mg every 2 weeks; 8 mg every 2 weeks; 8 mg every 4 weeks; 12 mg every 4 weeks	41	Pts. with symptomatic gout despite conventional therapy	18 weeks	Complete; Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety	C0405 GOUT 1*	5.3.5.1	Demonstrate superiority in response rate vs. placebo in percentage achieving plasma uric acid concentrations <6 mg/dL for at least 80% of the time during months 3 and 6	Randomized, double-blind, placebo controlled, parallel	PEG-uricase IV infusion; 8 mg every 2 weeks; 8 mg every 4 weeks; placebo	104 (84 PEG-uricase; 20 placebo)	Treatment-failure pts. with symptomatic gout	26 weeks	Complete; Full
Efficacy and Safety	C0406 GOUT 2*	5.3.5.1	Demonstrate superiority in response rate vs. placebo in percentage achieving plasma uric acid concentrations <6 mg/dL for at least 80% of the time during months 3 and 6	Randomized, double-blind, placebo controlled, parallel	PEG-uricase IV infusion; 8 mg every 2 weeks; 8 mg every 4 weeks; placebo	108 (85 PEG-uricase; 23 placebo)	Treatment failure pts. with symptomatic gout	26 weeks	Complete; Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety and Efficacy	C0407 GOUT 3*	5.3.5.2	Evaluate long-term safety, treatment effect and durability of response	Open label extension study	PEG-uricase; iv infusion, 8 mg every 2 weeks, 8 mg every 4 weeks, or no treatment (observational arm)	151* (149 PEG-uricase, 2 no treatment)*	Pts. with gout who completed protocol C0405 or C0406	24 months	Ongoing; Interim

2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The primary and secondary efficacy/pharmacodynamic endpoints in the clinical studies are listed in the Table 4 below.

Table 4. Efficacy/pharmacodynamic primary and secondary endpoints.

Study	Primary Endpoint	Secondary Endpoints
C0402 (Phase 1)	PK	Dose effect of pegloticase on plasma uric acid and urine uric acid:creatinine ratio
C0403 (Phase 2)	To assess the effect of multiple doses of pegloticase on uric acid levels, time to normalization of uric acid, and duration of uric acid normalization in the above-mentioned subject population.	PK and Safety
C0405/06 (Phase 3)	To demonstrate superiority of pegloticase vs. placebo in reducing plasma uric acid (PUA) as determined by the percentage of subjects achieving and maintaining PUA concentrations < 6 mg/dL for at least 80% of the time during Months 3 and 6 combined.	To determine the treatment effect in the reduction of tophus burden (using digital photography, image analysis, and a Central Reader), improvement of patient reported outcomes (PROs) using the Medical Outcomes Survey Short Form-36 (SF-36) and Health Assessment Questionnaire (HAQ), the reduction of the number of swollen and tender joints, and incidence and frequency of gout flares in the two pegloticase treatment groups vs. the placebo group.

The therapeutic effect of pegloticase is due entirely to its ability to lower the level of uric acid in plasma by catalyzing the oxidation of uric acid to allantoin. Therefore, quantifying uric acid concentration in the plasma of treated patients is a meaningful pharmacodynamic parameter in a clinical trial. In addition, the following clinical endpoints in the phase 3 trial were assessed, tophus assessment, patient report outcomes (PROs), and number of swollen and tender joints, incidence and frequency of gout flares.

The uric acid level was quantified by a validated HPLC/DAD (High Performance Liquid Chromatograph/Diode Array Detector) method. In study C0402, the relationship of plasma uric acid concentration to plasma uricase activity over time was examined at each pegloticase dose level. In addition, the C_{max} of pegloticase was compared to the C_{min} of uric acid at each pegloticase dose level. Further, the ratio of urine uric acid and urine creatinine concentration was evaluated for a correlation to plasma uric acid concentration and uricase activity. In study C0403, the effect of multiple doses of pegloticase on uric acid levels, time to normalization of uric acid, and duration of uric acid normalization in the above-mentioned subject population was assessed. In studies C0405/06, the percentage of subjects achieving and maintaining PUA concentrations < 6 mg/dL for at least 80% of the time during Months 3 and 6 combined was calculated. In addition, the tophus assessment was based on the reduction of tophus burden by using digital

photography, image analysis and a Central Reader. The improvement of PROs was assessed by using the Medical Outcomes Survey Short Form-36 (SF-36) and Health Assessment Questionnaire (HAQ).

2.2.3 What are the PK characteristics of pegloticase in gout patients?

Following single i.v. infusions of 0.5 to 12.0 mg of pegloticase in 23 patients with symptomatic gout (C0402), pegloticase exposure increased approximately proportionally to the dose administered. Mean terminal half-life ranged from 152 to 332 hours.

Figure 8. Mean plasma concentrations of pegloticase after IV administration of pegloticase 0.5 to 12 mg (study C0402).

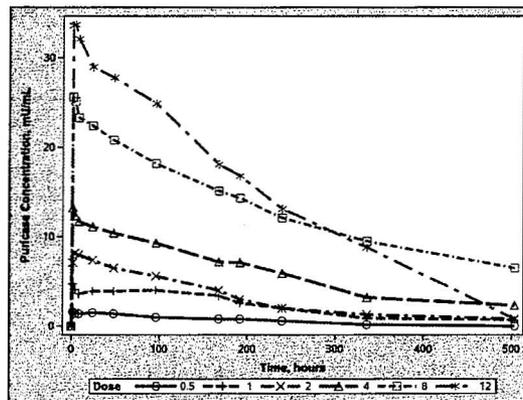


Table 5. Summary statistics (mean and coefficient of variation) of pharmacokinetic parameters for pegloticase after IV administration of pegloticase 0.5 to 12 mg (study C0402).

Parameter	Dose (mg)					
	0.5	1	2	4	8	12
AUC(0-inf) (mU.h/mL)	479.26 (55.27%)	2350.19 (33.13%)	1996.25 (90.32%)	3970.83 (76.64%)	9166.54 (11.39%)	8543.45 (38.74%)
AUC(0-t) (mU.h/mL)	243.12 (55.57%)	997.29 (69.73%)	1510.63 (80.89%)	2839.06 (70.33%)	6325.68 (10.05%)	6271.61 (38.81%)
Cmax (mU/mL)	1.7 (18.18%)	4.8 (32.07%)	8.6 (29.94%)	14.2 (19.44%)	26.0 (10.80%)	36.0 (15.71%)
T1/2 (h)	203.37 (57.50%)	331.88 (15.33%)	152.67 (63.89%)	166.71 (75.63%)	300.45 (7.05%)	162.92 (40.14%)

Note: N=4 per group with the exception of the 1 mg where N =3.

After multiple dose administrations, the accumulation index was 1.42 for AUC and 1.86 for Cmax at the dose of 8 mg every 2 weeks, and the accumulation was minimal for the dose of 8 mg every 4 weeks (study C0403).

Figure 9. Mean pegloticase serum concentrations-time profiles after multiple i.v. infusions (study C0403).

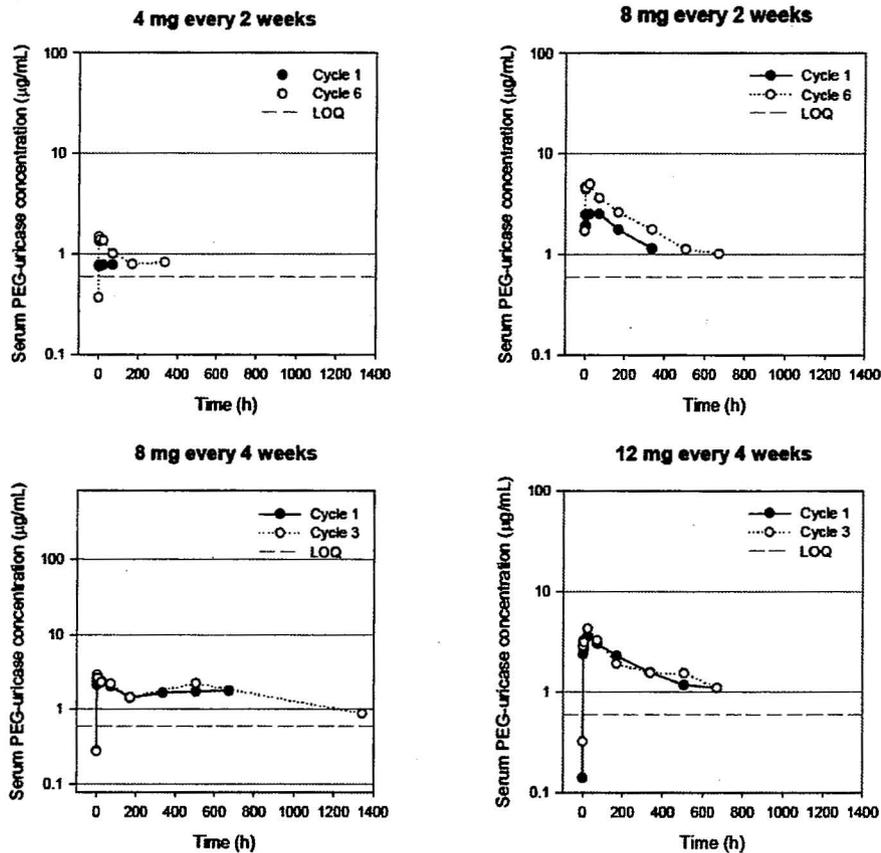


Table 6. Summary of PK parameters of serum pegloticase following multiple i.v. infusions (study C0403).

Treatment	Cycle	Median (Range)								
		AUC ₀₋₂₄ (mcg·h/mL)	AUC ₀₋₁₆₈ (mcg·h/mL)	AUC ₀₋₄ (mcg·h/mL)	AUC _{inf} (mcg·h/mL)	C _{max} (mcg/mL)	T _{max} (h)	Half-life (h)	CL (L/h)	V _{dss} (L)
4 mg every 2 weeks	1	17.0 (15.0-18.9)	NC	18.1 (15.0-17.0)	NC	0.800 (0.768-1.14)	6.5 (1.58-168)	NC	NC	NC
	6	34.2 (22.7-51.9)	251 (132-369)	132 (97.1-657)	1230 (322-2138)	1.62 (1.51-2.94)	1.60 (1.50-23.5)	414 (210-617)	0.00609 (0.00609-0.00609)	NC
8 mg every 2 weeks	1	50.3 (20.5-71.7)	355 (245-489)	608 (264-838)	1090 (568-1494)	2.95 (1.98-4.81)	22.9 (1.50-168)	274 (198-308)	0.00734 (0.00536-0.0141)	2.67 (2.31-3.95)
	6	122 (61.1-186)	710 (326-1034)	1361 (326-2734)	1546 (456-3815)	5.96 (2.87-8.89)	6.00 (1.50-21.9)	160 (95.8-371)	0.00681 (0.00447-0.0114)	NC
8 mg every 4 weeks	1	41.4 (15.7-92.9)	269 (151-759)	304 (151-1751)	1337 (579-2549)	2.50 (1.34-5.14)	23.4 (1.67-71.5)	280 (239-296)	0.00673 (0.00314-0.0138)	2.43 (1.36-5.96)
	3	46.5 (25.4-72.8)	403 (231-577)	231 (81.2-393.6)	1935 (146-6337)	2.81 (1.92-4.56)	23.2 (1.50-70.9)	399 (61.6-940)	0.00349 (0.00349-0.00349)	NC
12 mg every 4 weeks	1	59.6 (30.7-114)	478 (252-765)	1047 (97.6-2574)	1566 (991-3052)	3.52 (1.53-5.79)	23.2 (1.50-71.5)	329 (181-403)	0.00767 (0.00393-0.0121)	3.30 (1.82-4.05)
	3	84.0 (63.5-139)	519 (398-567)	670 (398-1821)	925 (628-2216)	4.64 (3.28-6.18)	14.6 (1.52-23.4)	119 (92.8-282)	0.00671 (0.00659-0.00683)	NC

NC - not calculated.

A population PK analysis was conducted based on data from the two phase 3 studies (C0405 and C0406). A one-compartment model with linear elimination was found to best fit the plasma pegloticase concentration time profiles. Body surface area and overall anti-pegloticase antibody response were identified as significant covariates for PK parameters clearance (CL) and volume of distribution (V). An increase in anti-

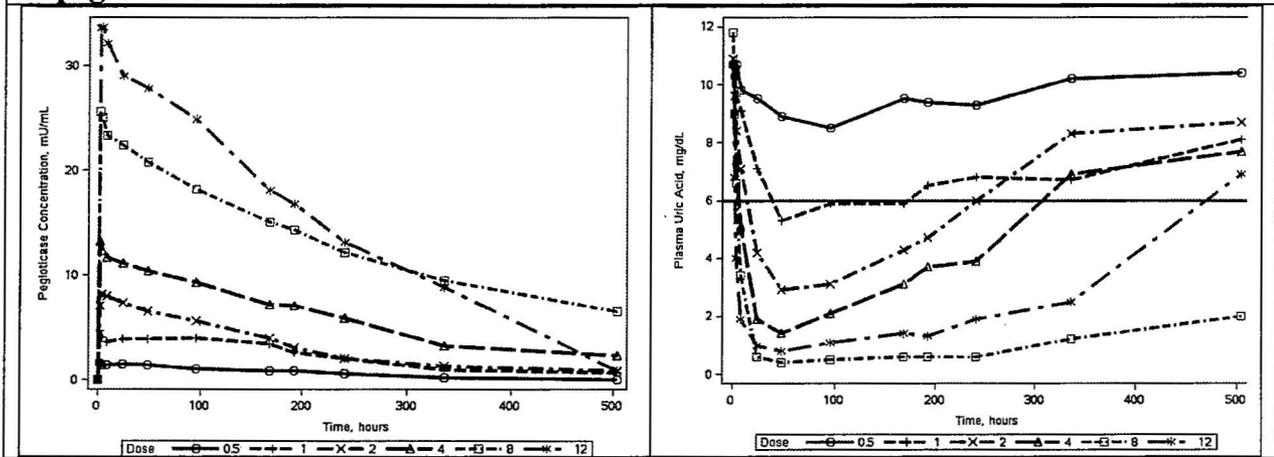
pegloticase antibody response led to 32% increase in CL and 25% increase in V. Body surface area was found to be positively related with CL and V.

2.2.4 Exposure-response

2.2.4.1 Is there evidence of dose and response (reduction in plasma uric acid) relationship?

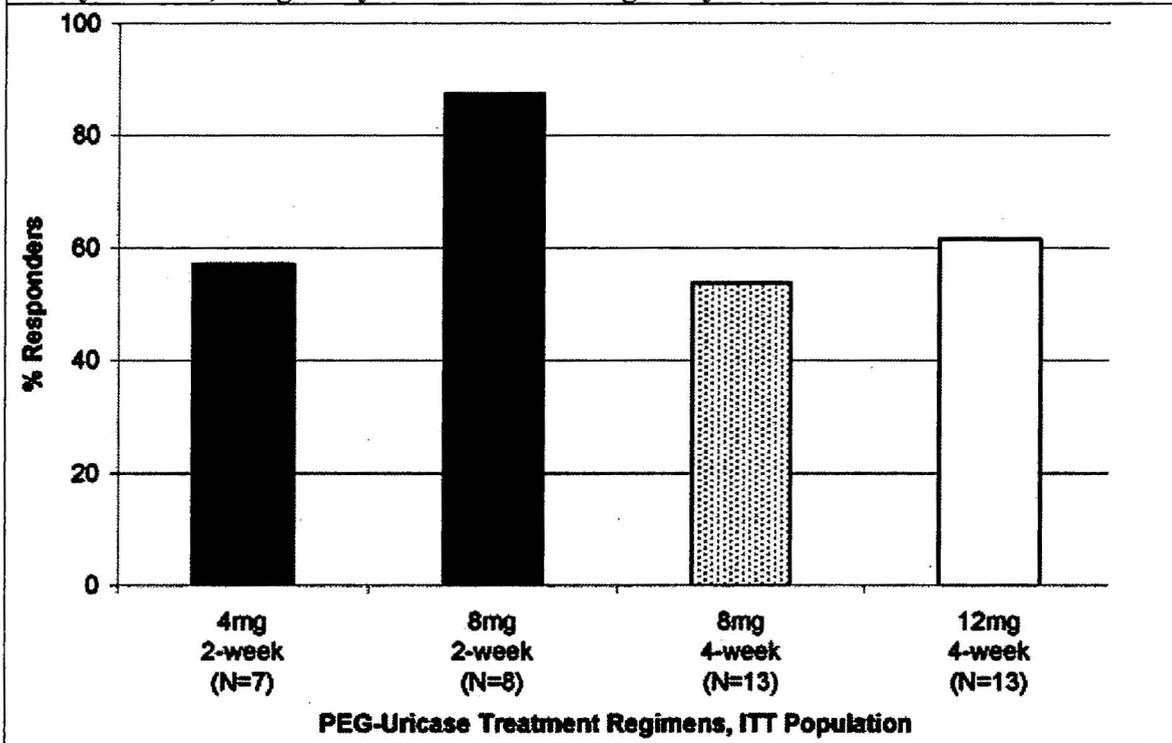
The sponsor characterized the relationship between dose and reduction in plasma uric acid adequately in the Phase 1 study C0402 (A phase 1 study to evaluate the pharmacokinetic profile, tolerability and safety of intravenously administered pegloticase). At dose levels above 1 mg, the mean maximal plasma uric acid (PUA) levels are reduced below the 6 mg/dL (target) as shown in Figure 10.

Figure 10. Mean (A) pegloticase concentrations (mU/mL) vs time (hours) (B) plasma uric acid concentrations after single intravenous dose administration of 0.5, 1, 2, 4, 8, or 12 mg of pegloticase.



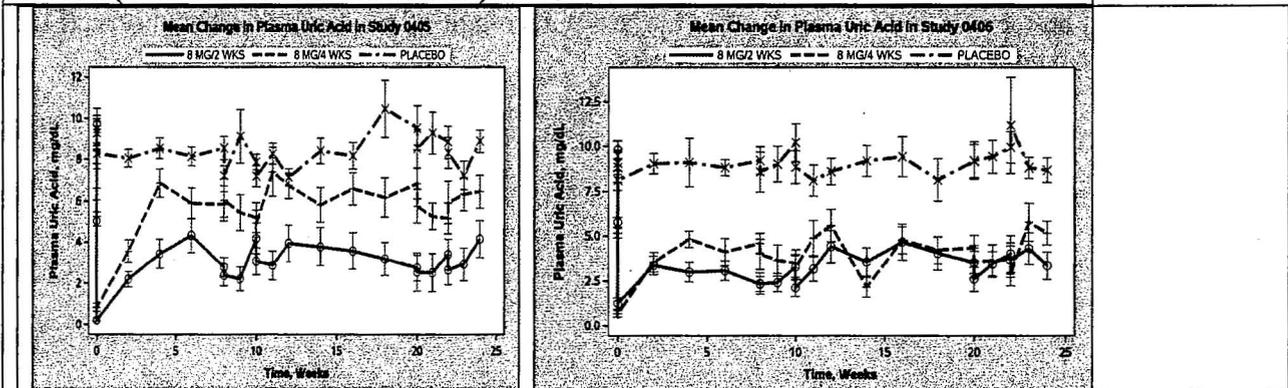
In the Phase 2 study C0403, the uric acid lowering potential of pegloticase was evaluated after drug administered as 4 mg every 2 weeks, 8 mg every 2 weeks, 8 mg every 4 weeks and 12 mg every 4 weeks. The percentage of patients classified as Responders (subjects whose plasma uric acid levels remained ≤ 6 mg/dL for at least 80% of the treatment period) are shown in Figure 11. The highest percentage of responders were observed in the group administered 8 mg every 2 weeks.

Figure 11. % responders in study C0403 administered 4 mg every 2 weeks, 8 mg every 2 weeks, 8 mg every 4 weeks and 12 mg every 4 weeks.



In the two registration studies (C0405 and C0406), gout patients were randomized to three treatment groups, 8 mg pegloticase every 2 weeks, 8 mg every 4 weeks, and placebo. Figure 12 shows the mean changes in plasma uric acid in the three groups. Both studies showed that the two dosing regimens were superior to placebo based on the primary endpoint (% of subjects achieving and maintaining PUA concentrations < 6 mg/dL for at least 80% of the time during Months 3 and 6 combined. These patients are classified as responders).

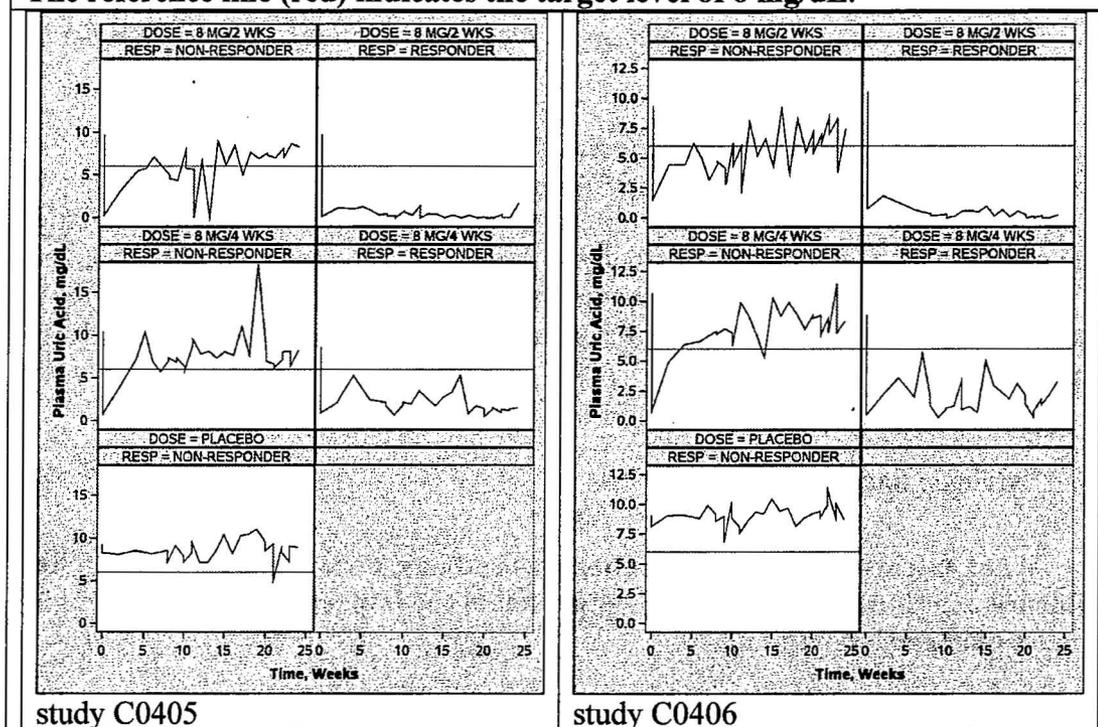
Figure 12. Mean (\pm SE) changes in plasma uric acid in studies C0405 and C0406 (based on actual week data).



In reviewer's analysis, the time course of plasma uric acid in patients who are categorized as responders and non-responders was further explored. Patients who discontinued early

in the study due to tolerability issues were characterized as non-responders. Figure 13 shows the mean time course of plasma uric acid in responders versus non-responders after administration of placebo, 8 mg every 4 weeks and 8 mg every 2 weeks. Patients classified as non-responders did not show sustained reduction in plasma uric acid levels.

Figure 13. Mean changes in plasma uric acid after administration of placebo (PLACEBO), 8 mg every 4 weeks (8 MG/4 WKS), and 8 mg every 2 weeks (8 MG/2 WKS) in responders and non-responders in studies C0405 and C0406. The reference line (red) indicates the target level of 6 mg/dL.



2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Gout flare and infusion reaction were the two outstanding safety signals. The incidence of gout flare was comparable, whereas the infusion reaction (IRs) was much higher in 8 mg every two weeks group (40.5%) than in 8 mg every four weeks group (25.9%).

Overall, two pegloticase related safety signals are identified in the total safety data set. The first is the (expected) increase in gout flares accompanying lowering of PUA, as occurs with all effective urate-lowering therapies. Notably, however, the increased incidence of gout flares with pegloticase persisted for no more than three months, and resulted in very few patient withdrawals (5/85 in the every 2 weeks group and 3/84 in the every 4 weeks group, 1/43 in the placebo group). The second adverse safety signal is the occurrence of infusion reactions. Although the occurrence of IRs in the 8 mg pegloticase every two weeks group (25.9%) approximated that of other biologicals commonly used by Rheumatologists (e.g., infliximab) the incidence of IRs in the every 4 weeks group (40.5%) was higher. (Source: summary of clinical safety module2, 2.7.4, page 10)

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, weight, etc.) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

No specific studies were conducted with regard to intrinsic factors. Based on popPK analysis, anti-pegloticase antibody and body surface area were found to be significant PK covariates.

Although no specific studies were conducted, based on the results of the POP-PK analyses, body surface area and anti-pegloticase antibody were found to be significant PK covariates. A positive relationship was observed between body surface area and the clearance and volume of distribution; as body surface area increased both clearance and volume of distribution increased. The anti-pegloticase antibody increase (APUL =1) was associated with higher volume ($\uparrow 25\%$) and clearance ($\uparrow 32\%$) as compared to antibody no increase (APUL=0).

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

Pharmacokinetics of pegloticase was not studied with regard to interactions with drugs, herbal products, diet, smoking.

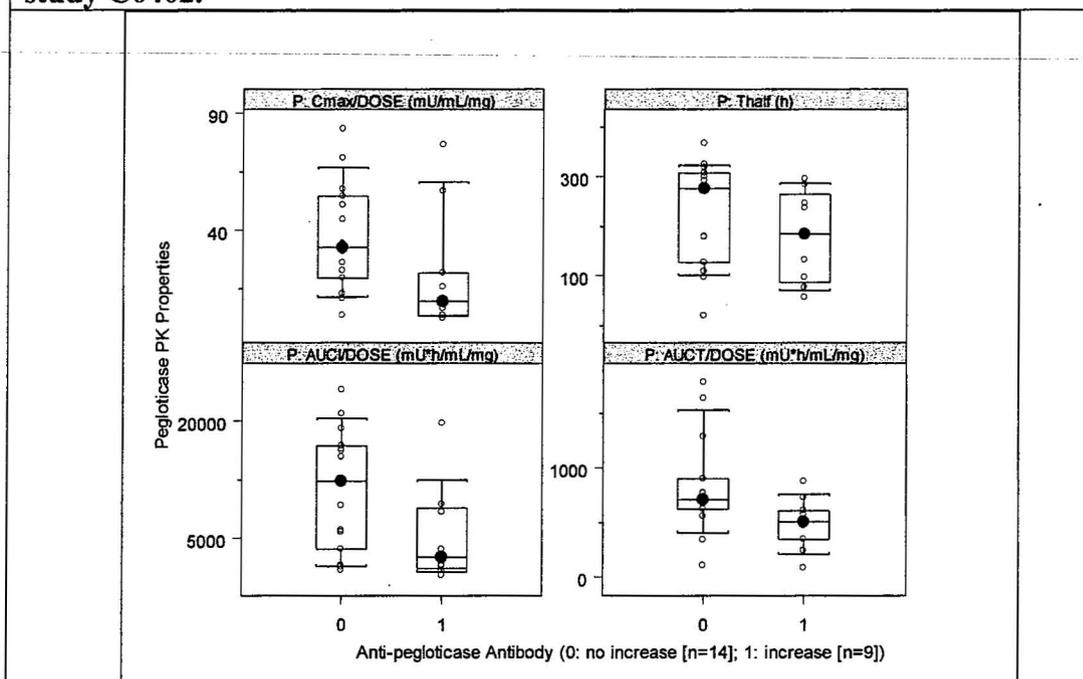
2.5 Immunogenicity

2.5.1 What were the immunogenicity findings for pegloticase? What was the impact of immunogenicity on exposure and efficacy?

The presence of anti-pegloticase antibody was associated with a decrease in the exposure of pegloticase and an increase in plasma uric acid level.

In study C0402, nine subjects developed anti-pegloticase antibody and the rest 14 subjects were either sero-negative or inclusive (positive at baseline). The boxplot of various PK properties versus anti-pegloticase antibody status showed that the presence of antibody was associated with a decrease in both exposure and elimination half-life of pegloticase, as shown in Figure 14.

Figure 14. Pegloticase PK properties (AUC/dose, Cmax/dose, and T-half) in patients who have an increase or no increase of anti-pegloticase antibody in study C0402.



Note: AUCi: AUCinf; AUC0-T

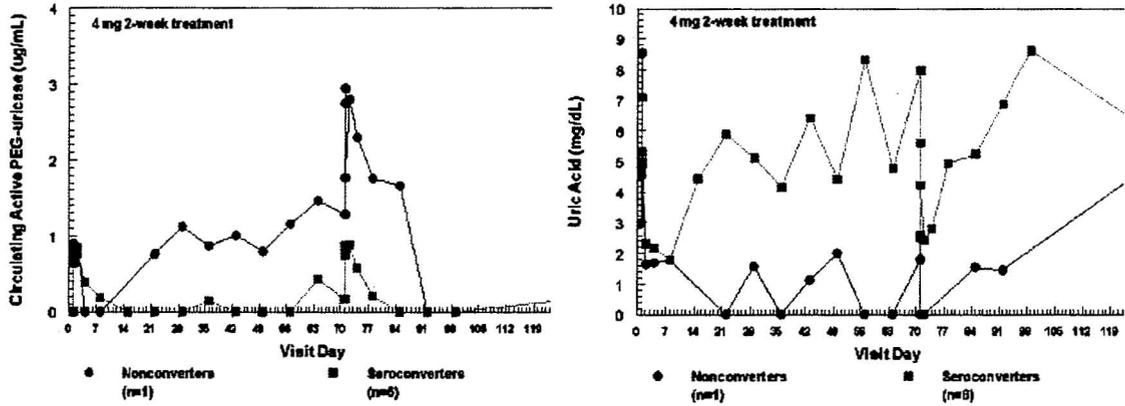
Source: page 49-62 of 521 (1.5 listing of individual pharmacokinetic parameters for uricase grouped by seropositive/seronegative subjects) in Appendix 3.4 of section 9 in Appendix 3.3 pharmacokinetic report of CSR C0402.

In study C0403, seroconversion (an increase in titers at one or more time points after the initial dose) occurred in 31/41 subjects (76%). The distribution of seroconverted subjects across the 4 treatment arms appeared to be random: 6/7 (86%) in the 4 mg every 2 week regimen, 5/8 (63%) in the 8 mg every 2 week regimen, 9/13 (69%) in the 8 mg every 4 week regimen, and in the 11/13 (85%) in the 12 mg every 4 week regimen. Six of the 41 randomized subjects had no anti-pegloticase immunoreactivity at any time point. (Source: page 151 in report body.pdf)

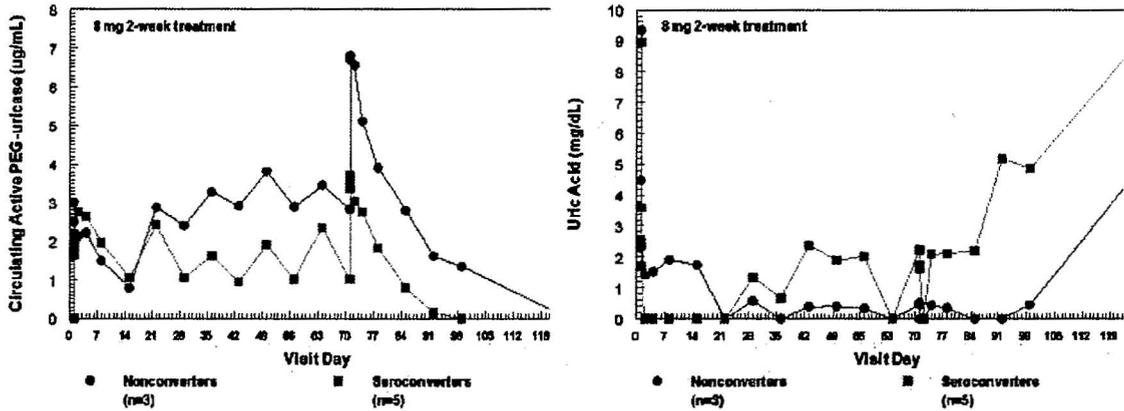
The effect of anti-pegloticase antibody production on pharmacokinetics and plasma uric acid by dose group is presented in Figure 15. These figures depict the mean circulating active pegloticase concentrations ($\mu\text{g/mL}$) and uric acid concentrations (mg/dL) for subjects that seroconverted versus those that did not seroconvert (non-converters) by dose group. There was only one non-converting subject in both the 4 mg 2 week and 12 mg 4 week treatment regimens. The nonconverter in the 12 mg 4 week treatment regimen did not complete treatment. It appears that there may have been an increase in plasma uric acid in subjects who seroconverted. However, the sample size for each dose regimen was small.

Figure 15. Effect of anti-pegloticase antibody on PK and efficacy (plasma uric acid) after 4 mg/2 wk, 8 mg/2 wk, 8 mg/4 wk and 12 mg/2 wk regimens in study C0403.

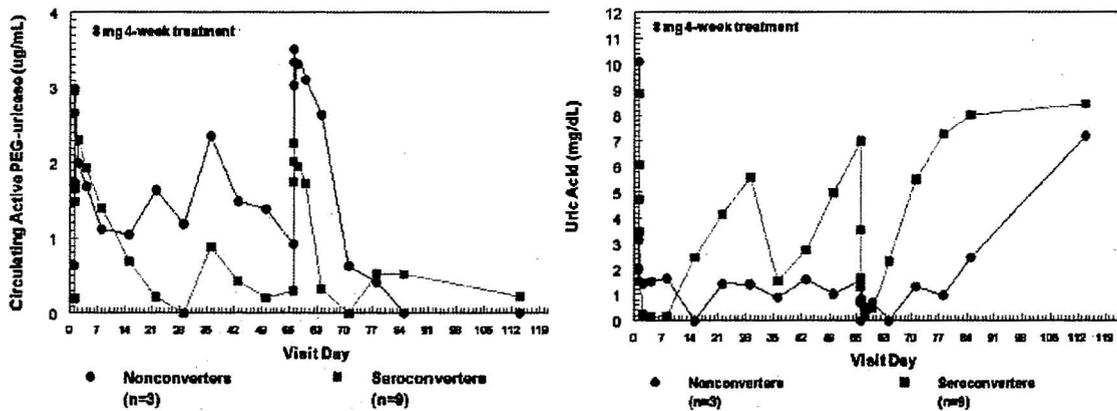
A: 4 mg/2 wk



B: 8 mg/2 wk



C: 8 mg/4 wk



The plasma uric acid (PUA) responder status as a function of the highest antibody titers during Month 3 or 6 for the intend-to-treat (ITT) population is shown in Table 8. Of the 212 subjects in the pooled dataset, 191 had antibody data: 75/85 subjects in the pegloticase 8 mg every 2 week group, 75/84 subjects in the pegloticase 8 mg every 4 week group, and 41/43 subjects in the placebo group. There was a significant association between antibody titer and PUA responder status for both pegloticase treatment groups ($p < 0.001$). In the pegloticase 8 mg every 2 week group, none of the 25 subjects with a high anti-pegloticase antibody titer increase were PUA responders; 36 of 50 (72.0%) subjects with no, low, or moderate anti-pegloticase antibody titer increases were PUA responders. In the pegloticase 8 mg every 4 week group, one of 27 (3.7%) subjects with a high anti-pegloticase antibody titer increase was a PUA responder; 28 of 48 (58.3%) subjects with no, low, or moderate anti-pegloticase antibody titer increases were PUA responders.

Table 8. PUA treatment responses by highest anti-pegloticase antibody titer during Month 3 or 6 (ITT population).

	8 mg Pegloticase		Placebo (N = 43)
	Every 2 Weeks (N = 85)	Every 4 Weeks (N = 84)	
Responders: PUA less than 6 mg/dL for at least 80% of the time in Months 3 and 6 combined			
Anti-Pegloticase Antibody Level	n/N (%)	n/N (%)	n/N (%)
No Increase	7/9 (77.8)	6/7 (85.7)	0/34 (0.0)
Low Increase	19/25 (76.0)	13/24 (54.2)	0/4 (0.0)
Moderate Increase	10/16 (62.5)	9/17 (52.9)	0/3 (0.0)
High Increase	0/25 (0.0)	1/27 (3.7)	0/0 (0.0)
Total Number of Subjects	75	75	41
P-value ¹	<0.001	<0.001	NA

Note: "n" represents the number of subjects that were PUA responders in each anti-pegloticase antibody titer category. "N" within the cells represents the total number of subjects in each anti-pegloticase antibody titer category. NA = Not Applicable.

¹ P-value for test of association between antibody level and responder status using Fisher's exact test.

Source: Page 145 in MODULE 5 integrated summary of efficacy.

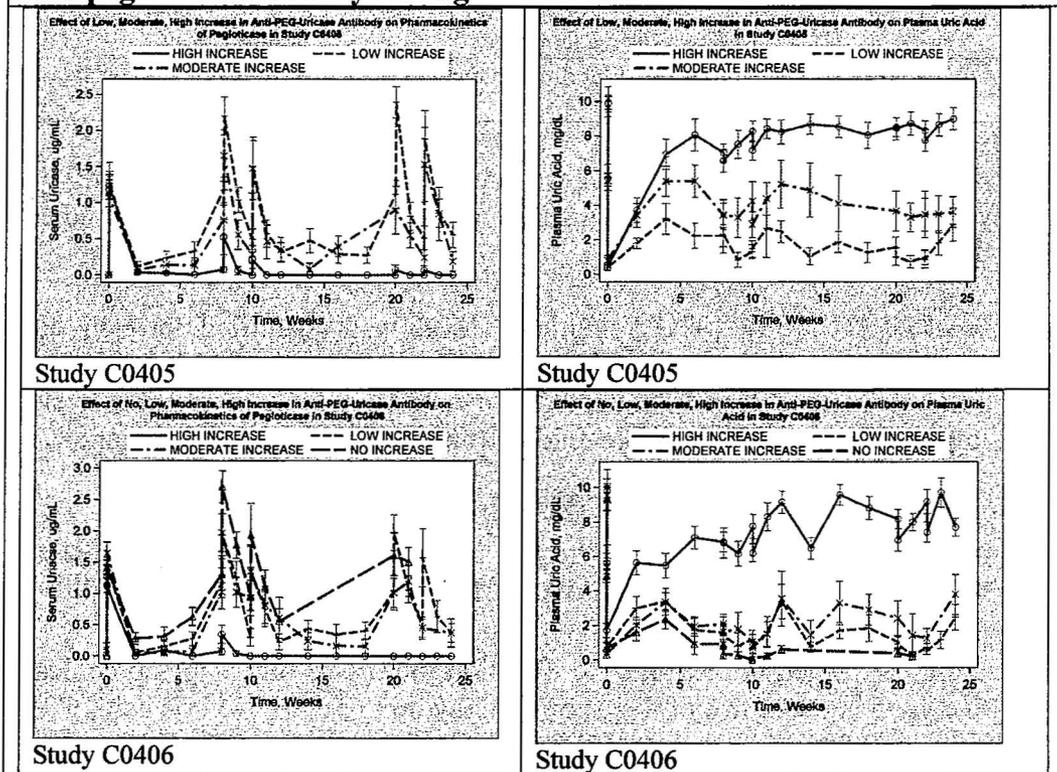
Further analysis showed that in non-responder group in both studies, subjects with high body weight (BMI>30) and being male also appear to have high incidence of high increase in anti-pegloticase antibody, while this trend is not so obvious in the responder group (Table 9).

Table 9. Frequency of the anti-pegloticase antibody by responder status, body mass index and sex from studies C0405 and C0406.

Responder	Yes				No			
	F		M		F		M	
SEX	F		M		F		M	
BMI	<30	>30	<30	>30	<30	>30	<30	>30
Study C0405								
No increase	0	0	0	0	1	4	6	8
Low increase	2	7	5	7	0	3	3	5
Moderate increase	1	1	6	1	0	1	1	13
High increase	0	0	0	0	0	6	9	15
Study C0406								
No increase	0	1	5	5	1	2	12	5
Low increase	1	3	3	8	0	0	4	7
Moderate increase	1	4	4	3	0	1	4	3
High increase	0	0	1	0	1	2	9	15

The formation of anti-pegloticase antibody appeared to be associated with a decrease in plasma pegloticase level and the loss of effect on plasma uric acid (Figure 16).

Figure 16. Mean (\pm SE) changes in plasma concentrations of pegloticase and uric acid in patients who have no, mild, moderate or severe increase in anti-pegloticase antibody during studies C0405 and C0406.



2.6 General Biopharmaceutics

Pegloticase is a protein based drug delivered by intravenous infusion. The formulation has remained consistent during the course of pegloticase clinical development, with the same excipients used throughout. Therefore, no biopharmaceutic studies were conducted.

2.7 Analytical Section

2.7.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology studies?

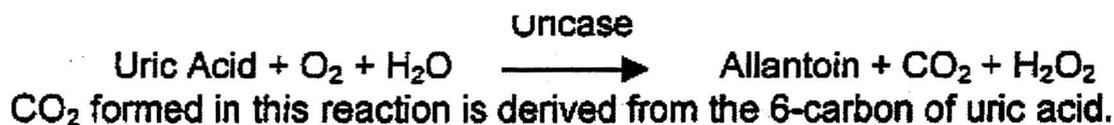
Different validated analytical methods were used in the clinical studies to determine the concentrations of pegloticase and uric acid in human plasma (or serum) samples. A summary of different assays used in clinical studies are listed in the Table 10. Enzyme-linked immunosorbent assay (ELISA) was used to detect the presence of anti-pegloticase antibody and neutralizing pegloticase antibody.

Table 10. Summary of the Various Assays used in the Clinical Studies

Analytes	C0402	C0403	C0405/06
Pegloticase	Radiochemical-HPLC	Coupled enzymatic/fluorescent reaction assay	Coupled enzymatic/fluorescent reaction assay
Uric acid	HPLC couple with diode array detector	Fluorimetric method	Enzymatic colorimetric method

Pegloticase was quantified in human plasma was done by a validated radiochemical-HPLC in study C0402 and a coupled enzymatic/fluorescent reaction assay in studies C0403 and C0405/06.

Radiochemical-HPLC Assay The Pegloticase level was quantified through the assessment of uricase activity. Assaying urate oxidase activity is a specific means of measuring Pegloticase in the plasma of treated subjects because human plasma and tissues lack endogenous urate oxidase. Urate oxidase (uricase) catalyzes the reaction:



(b) (4)

2.7.2 How was the assay performed for the analytes?

The analytical assay for all the analytes for studies C0403, C0405 and C0406 appears adequate and validated.

The assay performance for all the analytes are displayed in the tables below.

Table 11. Assay performance of pegloticase.

Study	C0402	C0403, C0405 and C0406
Sensitivity	0.2 mU/mL	0.5 µg/mL
Selectivity	No uricase activity in the blank plasma. No interference by allopurinol and oxypurinol. However, moderate or gross hemolysis has a significant interference and increased (>20%) the apparent uricase activity of the test sample.	There was some matrix interference with pegloticase in human serum for the undiluted samples. After diluting the samples (standards, QC samples, and test samples) 40-fold, the matrix interference problem was overcome.
Accuracy	acceptable	86.3-123.4%
Precision	<5%	1.1-18.5%
recovery	acceptable	acceptable
Linearity range	5-80 ng/mL with r^2 of 0.9995 150-2970 ng/mL with r^2 of 0.999	0.6 to 10.00 µg/mL based on 0.25 mL of serum
Ruggedness	acceptable	-

Study	C0402	C0403, C0405 and C0406
Stability	pass	pass
Freeze/thaw cycle	3 cycles	10 cycles
Post-operative stability	Up to 34 hours	Up to 72 hours
Long term stability at -70°C	415 days	573 days

Table 12. Assay performance of uric acid in studies C0402 and C0403.

Study	C0402	C0403
method	HPLC couple with diode array detector	Fluorimetric method
Sensitivity	0.5 mg/dL	5.0 µg/mL
Selectivity	-	No interference
Accuracy	acceptable	82.2-106.4% (intra-assay) 86.7-99.5% (inter-assay)
Precision	<19%	1.7-11.5% (intra-assay) 5.3-12.4% (inter-assay)
recovery	acceptable	acceptable
Linearity range	-	5.00 to 100.00 µg/mL
Ruggedness	-	-
Stability	-	pass
Freeze/thaw cycle		3 cycles
Post-operative stability		Up to 5 hours
Long term stability at -70°C		-

Table 13. Assay performance of uric acid in studies C0405 and C0406.

Validation Parameter	Acceptance Criteria or Expected Result	Obtained Result
8 Non-zero standards (0.50-12.00 mg/dL) calibration working range	% Nominal of each standard must be 85%-115% except for the LLOQ 80% - 120%	16 out of the 17 curves met the acceptance criteria
Precision/accuracy at the LLOQ (0.50 mg/dL) and ULOQ (12.00 mg/dL)	LLOQ: %CV ≤20% % Nominal: 80%-120% ULOQ: %CV ≤15% % Nominal: 85%-115%	LLOQ: %CV = 1.9% % Nominal = 106% ULOQ: %CV = 0.9% % Nominal = 98.3%
Recovery of uric acid from plasma acidification procedure	Not applicable	% Recovery of 89.1% to 95.6% (n = 7) with an overall mean (n = 21) of 93.2%
Limit of detection	Not applicable	0.20 mg/dL
Specificity and linearity of dilution	Recovery of spiked and diluted samples: 85%-115% r ≥ 0.9800	Recovery of spiked samples = 101%-103%, (n = 6) Recovery of diluted samples = 90.0%-103% (n = 42) r: 0.9998-0.9999 (n = 6)
Carry-over	≤ 2%	1.0%
Accuracy	Mean (n = 36) % N: 85% - 115% for LQC, MQC and HQC	LQC: % N = 97.0%-103%, overall mean of 99.6% MQC: % N = 99.1%-104%, overall mean of 101% HQC: % N = 99.2%-104%, overall mean of 101%
Intra-Assay Precision	% CV ≤ 15%	LQC: 0.5%-1.3% (n = 6) MQC: 0.5%-1.0% (n = 6) HQC: 0.2%-0.5% (n = 6)
Inter-Assay Precision	% CV ≤ 15%	LQC: 2.3% (n = 36) MQC: 1.8% (n = 36) HQC: 1.7% (n = 36)
Stability	% Nominal: 85-115%	Stock Solution 15 mg/dL in human acidified plasma and 1500 mg/dL in NaOH 1M: 48 hours at ca. -20°C LQC and HQC: 24 hours at 37°C LQC and HQC: 3 freeze/thaw cycles LQC and HQC: 9 Months at ca. -20°C

Source: bioanalytical report: Study No. 600191

Table 14. Assay performance of Anti-pegloticase antibody.

Validation No.	Study	300913	300572	300569
Analytes		IgE antibody	IgG and IgM antibody	Neutralizing antibody
Method		ELISA	ELISA	ELISA
Recovery		Not performed	acceptable	Not performed
Drug interference		Not performed		Not performed
Sensitivity		Not performed		Not performed
Prozone		Not performed	No prozone effect was observed after dilution of 20 fold.	Not performed
Titration		Not performed		Not performed
Drug competition test				Not performed
Stability		Not performed	Acceptable for both	Not performed

Validation No.	Study	300913	300572	300569
			short and long term stability test. Benchtop ~4°C, 4 freeze-thaw cycles at -20°C Long term stability at -20°C for 19.5 mth	
Cut-point (CPF)	factor	1.123		0.701
Negative (NCO)	cu-off	-	0.218	mean RFU values between 2058.118 and 3374.992
Specificity		acceptable	acceptable	acceptable
Precision		Acceptable	Intra-assay precision: 1.2-5.9% (pass) inter-assay precision: 8.9%-29.7% (failed)	The intra-batch precision was in the range of 3.5 to 7.9, and the inter-assay precision was 20.1%.
Detection report		Study No. 300914 for Study C0405/06	Study no. 301044 for study C0405/06	

3 Detailed Labeling Recommendations



(b) (4)

24 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

4.2. Individual Study Review

C0402

Study Title: A Phase I study to evaluate the pharmacokinetic profile, tolerability and safety of intravenously administered pegloticase

Objectives: **Primary objective** to determine the single dose pharmacokinetic profile and safety of intravenously administered Pegloticase at six ascending dose levels. **Secondary objective** to evaluate the dose effect on plasma uric acid level.

Study Design: This was an open-label, single-dose pharmacokinetic study of escalating intravenous doses of pegloticase, administered by infusion, in subjects with symptomatic gout. Subjects were administered single intravenous doses of 0.5, 1, 2, 4, 8, and 12 mg pegloticase (n=4 subjects/dose group). Plasma samples for the determination of pegloticase were obtained predose (sample 1), and at the following times after the initiation of the infusion of pegloticase (samples 2-12): 1.5 hours, 4 ± 0.25 hours, 8 ± 0.25 hours, 24 ± 0.5 hours, 2 days, 3 or 4 days (depending on whether infusion was on a Tuesday or a Monday, respectively), 7 ± 1 days, 8 ± 1 days, 10 ± 1 days, 14 ± 1 days, and 21 ± 2 days. Sampling times for plasma uric acid in relation to dosing were: 0, 1.5, 4, 8, and 24 hours, 2, 4, 7, 8, 10, 14, and 21 days.

Study Population: A total of 24 male (n=20) and female (n=4) subjects between 28 and 73 years of age were enrolled in this study. Ethnic origin was 75.0% white (n=18) and 25% black (n=6). All subjects completed the study and were included in the PK analysis.

Bioanalytical Analysis: Pegloticase in human plasma was measured by an assay for urate oxidase activity performed by a radiochemical-HPLC method. Plasma uric acid concentrations in 24 subjects following administration of pegloticase at the different dose levels were assayed by a validated HPLC/DAD method. The antibody levels were detected with an ELISA method. The assay performance is summarized in Table 1:

Table 1. Summary of assay performance for pegloticase and uric acid.

Analytes	Method	SC range (ng/mL)	SC precision (%CV)	SC mean recovery (% of theoretical)	QC levels (ng/mL)	QC precision (%CV)	QC mean recovery (%of theoretical)
Pegloticase	radiochemical-HPLC for urate oxidase activity	150-1780	0.9-4.9	97.3-107.1	150, 1200, and 2600	7.1 to 10.4	94.9-99.6
Uric acid	HPLC with DAD detector	5-500 uM	-	-	12.10 mg/dL	19	99.9

The short term stability for freeze-thaw at -70°C was acceptable (within 15% of the activity determined prior to storage). The stability after thawing from -70°C (11 days) and storage at 4°C for 4 days was acceptable (within 20% of the “control” at the lowest

concentrations, and within 15% at the two higher concentrations). The stability after long term storage at -70°C for both concentrations of 294 and 2940 ng/mL was acceptable (within 20% of the activity in the unfrozen sample)

Data Analysis: The values for the PK variables were determined by using non-compartmental methods based on the individual plasma concentration-time data of uricase concentration.

Pharmacokinetic Results: In the dose range studied, 0.5 mg to 12 mg, the increase of mean C_{max} and AUC appeared to be dose related.

Figure 1. Mean (SD) plasma pegloticase concentrations versus time.

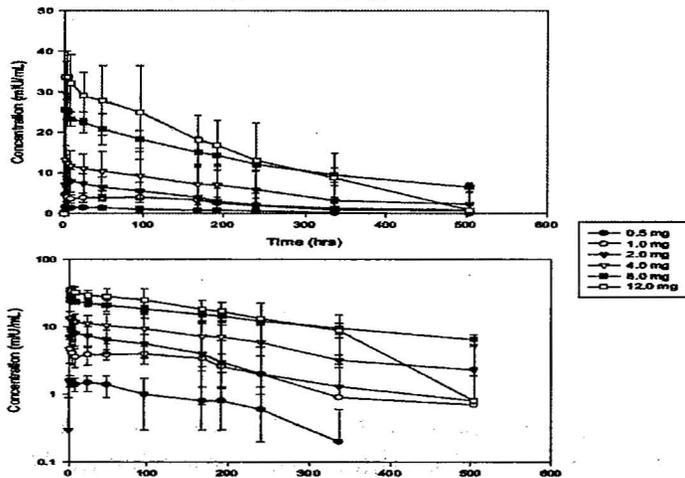
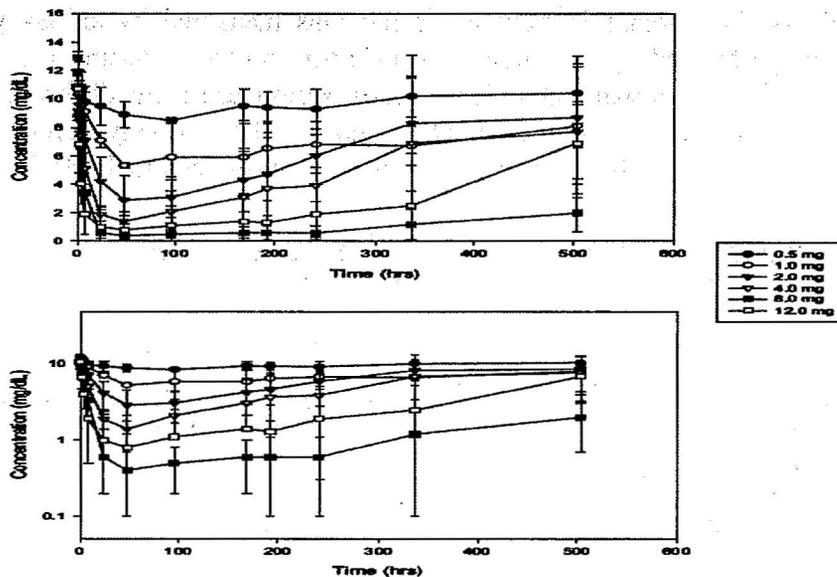


Figure 2. Mean (SD) plasma uric acid concentration versus time.



Uric acid levels decreased with increasing pegloticase dose or concentrations; the decrease was rapid up to 2 mg dose, more gradual up to 4 mg dose and appeared to reach

a plateau at higher doses. The mean (% CV) values for the parameters derived from the analyses of plasma samples are summarized in Table 2.

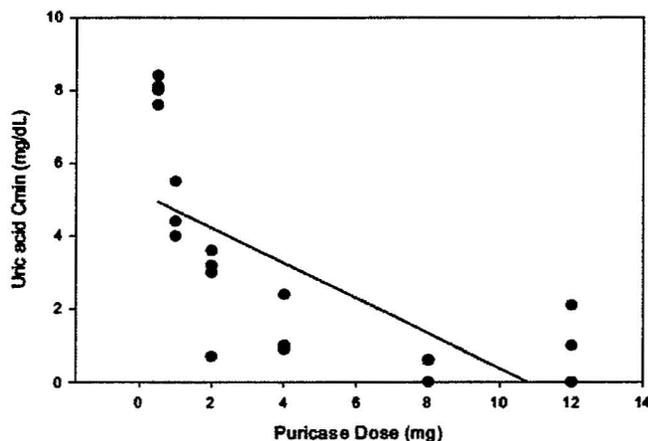
Table 2. Summary of pegloticase PK parameters and uric acid C_{min} values.

Analyte	Parameter	Dose (mg)					
		0.5	1	2	4	8	12
Uricase	AUC(0-Inf) (mIU.hr/mL)	479.26 (55.27%)	2350.19 (33.13%)	1996.25 (90.32%)	3970.83 (76.64%)	9166.54 (11.39%)	8543.45 (38.74%)
	AUC(0-t) (mIU.hr/mL)	243.12 (55.57%)	997.29 (69.73%)	1510.63 (80.89%)	2839.06 (70.33%)	6325.68 (10.05%)	6271.61 (38.81%)
	C _{max} (mIU/mL)	1.7 (18.18%)	4.8 (32.07%)	8.6 (29.94%)	14.2 (19.44%)	26.0 (10.80%)	36.0 (15.71%)
	t _{1/2} (hr)	203.37 (57.50%)	331.88 (15.33%)	152.67 (63.89%)	166.71 (75.63%)	300.45 (7.05%)	162.92 (40.14%)
	Kel (1/hr)	0.0047 (67.52%)	0.0021 (15.33%)	0.0064 (67.50%)	0.0116 (134.3%)	0.0023 (7.07%)	0.0048 (39.32%)
	t _{max} * (hr)	12.75 (1.50-58.13)	1.50 (1.50-71.92)	2.75 (1.50-7.83)	4.72 (1.50-72.00)	2.75 (1.50-4.00)	2.90 (1.50-72.50)
Uric Acid	C _{min} (mg/dL)	8.0 (4.12%)	4.6 (16.76%)	2.6 (49.80%)	1.3 (54.20%)	0.5 (66.67%)	0.8 (129.2%)

Note: N = 4 per group with the exception of the 1 mg group where N = 3.
* Median (range)

The variability in the half-lives is so great that it is not possible to determine the effect of dose on half-life. In all cases however, the mean half-life was close to or greater than 1 week. In sponsor's analysis, a one-compartment PK model and a sigmoidal E_{max} model inhibitory effect effectively explain the postdose relationship between plasma uricase and uric acid. The results of PK-PD modeling indicate that a pegloticase dose of 2 mg or greater is required to maintain mean uricase levels above EC₅₀ and consequently uric acid levels below the solubility limit of 7 mg/dL in serum for up to one week.

Figure 3. Plasma uric acid C_{min} versus pegloticase dose.



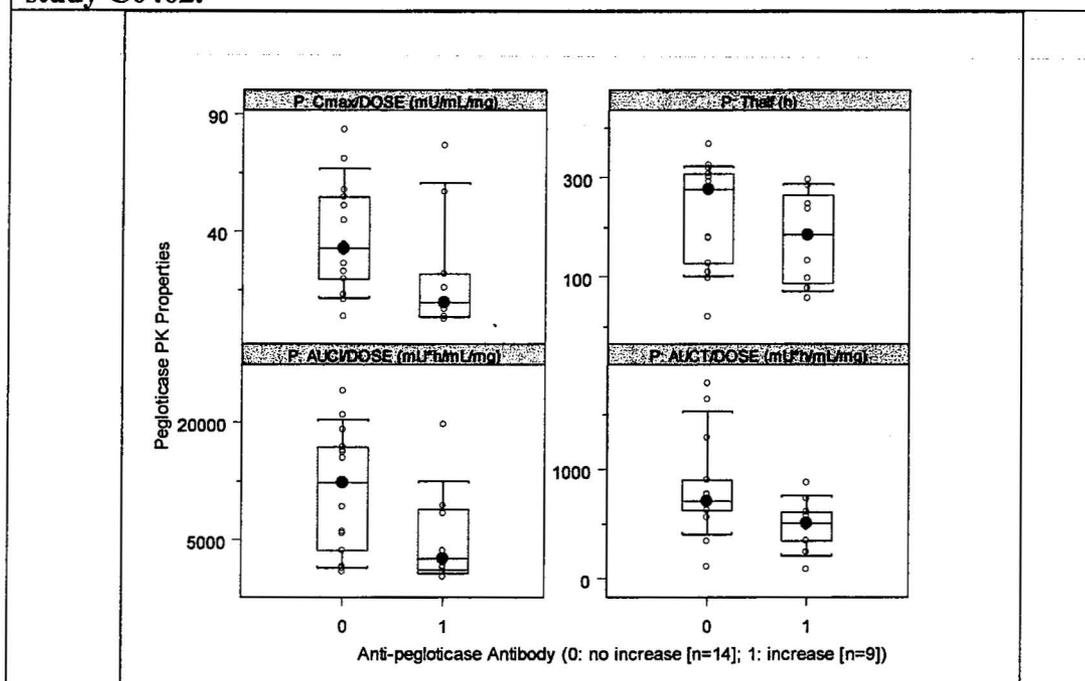
Of the 24 subjects in the study, 9 are judged to have "sero-converted", and 13 are judged to have remained "sero-negative". For 15 of these 22 subjects, for every sample tested the result (positive or negative) obtained with pegloticase as antigen was concordant with that for 10KPEG on every day tested. In a 16th subject judged to be sero-negative, the ELISA with pegloticase was transiently positive only on day 14, and the 10 KPEG ELISA was negative on all days tested. Of the 9 subjects who sero-converted, 7 were positive with both pegloticase and 10KPEG. One subject became positive only for 10KPEG, and another only for pegloticase. In two subjects, the results did not permit a judgment regarding sero-conversion. In the case of subject #113 the ELISA with pegloticase was positive on day 0 and the response did not change on subsequent days; the ELISA with 10KPEG was negative on all days tested. In the case of subject #105 the ELISAs with both pegloticase and 10KPEG were clearly positive on day 0 (pre-dose) and the responses changed only slightly on subsequent days of testing. The possible basis for these results may be subject to further investigation. However, the results obtained in the initial ELISAs were considered to be valid and did not meet criteria for reassay of these samples.

Conclusions: The results of this study indicate that intravenously infused pegloticase is well tolerated and in doses of 2 mg or greater is effective in lowering plasma uric acid to levels below the solubility limit in subjects with active gout.

Reviewer's comments: It is the opinion of the reviewer that the model chosen for describing the effect of pegloticase on the plasma uric acid levels is not the right model based on mechanistic reasons. The sponsor described the PK/PD relationship under the assumption that pegloticase suppresses the production of uric acid. However, the mechanism of action of pegloticase indicates that it stimulates the degradation of uric acid.

Reviewer further evaluated the effect of anti-pegloticase antibody on the exposure of pegloticase. The boxplot of various PK properties versus anti-pegloticase antibody status showed that the presence of antibody was associated with a decrease in both exposure and elimination half-life of pegloticase.

Figure 4. Pegloticase PK properties (AUC/dose, Cmax/dose, and T-half) in patients who have an increase or no increase of anti-pegloticase antibody in study C0402.



Note: AUCi: AUCinf; AUC0-T

Source: page 49-62 of 521 (1.5 listing of individual pharmacokinetic parameters for uricase grouped by seropositive/seronegative subjects) in Appendix 3.4 of section 9 in Appendix 3.3 pharmacokinetic report of CSR C0402.

C0403 (aa24807)

Study Title: A Phase II Study of Multiple Doses of Intravenous Pegloticase in Subjects with Hyperuricemia and Refractory Gout

Objectives: **Primary** to assess the effect of multiple doses of pegloticase on uric acid levels, time to normalization of uric acid (ie, ≤ 6 mg/dL of uric acid in plasma), and duration of uric acid normalization in the above-mentioned population. **Secondary** to assess the pharmacokinetics and pharmacodynamics of multiple doses of pegloticase in the above-mentioned population.

Study Design: This study was a randomized, open-label, multi-center, parallel-group study of multiple doses of pegloticase, administered by i.v. infusion to research subjects with symptomatic treatment-failure gout. All dosages were administered as i.v. infusions over a period of 30min initially or 60min after the protocol amendment. Eligible subjects were randomized to one of 4 dosing groups (ie, 2-week infusion regimens consisting of 6 infusions of either 4mg or 8mg of pegloticase or 4-week infusion regimens consisting of 3 infusions of either 8mg or 12mg of pegloticase). During the treatment and the follow-up periods, subjects were evaluated on a routine basis for plasma and urine uric acid concentrations, urine creatinine concentrations, gout flares, plasma uricase concentration,

and vital signs. All subjects received the same lot of pegloticase (ie, Lot #26890051, expiration date: April 2005). The blood sampling schedule is listed in the table below.

Table 3. Blood sampling schedule.

Regimen		Cycle			
Frequency	Dose (mg)	1	2	3*	6
Every 2 weeks	4 and 8	- Pre-dose - Post-dose: 1.5, 4, 6, 24, 72, 168 h	- Pre-dose - Post-dose: 168 h	- Pre-dose - Post-dose: 168 h	- Pre-dose - Post-dose: 1.5, 4, 6, 24, 72, 168, 336, 504, 672, 1344 h
Every 4 weeks	8 and 12	- Pre-dose - Post-dose: 1.5, 4, 6, 24, 72, 168, 336, 504 h	- Pre-dose - Post-dose: 168, 336, 504 h	- Pre-dose - Post-dose: 1.5, 4, 6, 24, 72, 168, 336, 504, 672, 1344 h	N/A

*Includes Cycles 4 and 5 for treatments given every 2 weeks.

N/A: Not applicable

Study Population: A total of 41 healthy male (n=35) and female (n=6) subjects between 22 and 83 years of age were enrolled in this study. Ethnic origin was 82.9% white (n=34), 12.2% black (n=5), and 4.9% others (n=2). Of the 41 subjects enrolled, 15 discontinued the study. Most of the discontinuations (ie, 14 subjects) were withdrawn due to an adverse event or an SAE. One subject in the 12mg 4 week regimen withdrew consent for further participation in the trial.

Bioanalytical Analysis: Pegloticase in human plasma was measured by an assay for urate oxidase activity performed by a coupled enzymatic/fluorimetric assay method. Plasma uric acid concentrations were assayed by a fluorimetric method. The assay performance is summarized in the table below.

Table 4. Summary of assay performance.

Analytes	Method	SC range (µg/mL)	SC precision (%CV)	SC mean recovery (% of theoretical)	Nominal pegloticase activity in QC (mg/dL)	QC precision (%CV)	QC mean recovery (%of theoretical)
Pegloticase	Coupled Enzymatic/fluorimetric assay	0.5-10	0.7-7.9	96.8-105.6	1.50, 3.50, and 7.50	5.5 to 15.7	101.7-114.0
Uric acid	fluorimetric method	2.53-122.36	2.2-8.1	98.2-114.1	15.00, 35.00, and 70.00	7.7-13.2	92.1-102.7

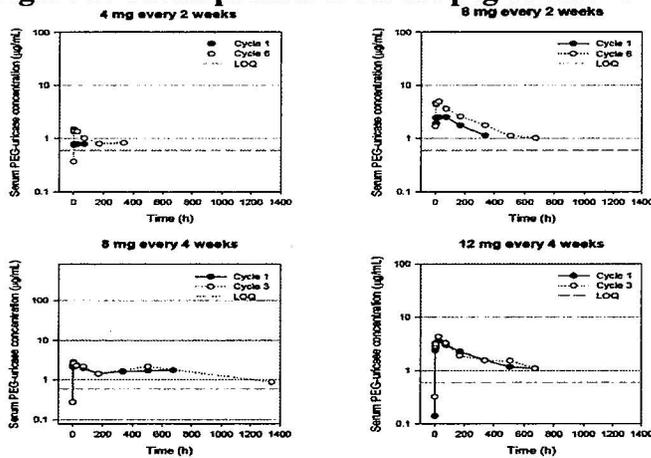
Source: Pegloticase study no. 340391 p15 and p19

The anti-pegloticase IgG and IgM antibodies in human serum samples were measured by a qualitative enzyme linked immunosorbent assay (ELISA) (Study no. 300573).

Data Analysis: Multiple compartmental models were constructed and their ability to fit serum pegloticase were first evaluated using ADAPT-II®. The model discrimination process was performed by computing the Akaike Information Criterion (AIC) and by looking at pertinent graphical representations of goodness of fit. Following the selection of the final structural PK model in ADAPT-II®, various covariates were tested for potential inclusion in the model using regression analyses and population PK analyses were performed with IT2S® using this model. Once the structural PK model for serum pegloticase was determined, various PK-PD models were tested using ADAPT-II®. The inhibitory effect of pegloticase on uric acid was tested using various models, including direct and indirect models with both Emax and sigmoidal Emax effects. Using prior estimates obtained from the ADAPT-II® compartmental analysis, population PK-PD analyses were then conducted using IT2S®.

Pharmacokinetic Results: Mean profiles for serum pegloticase are presented by treatment below.

Figure 5. Mean profiles of serum pegloticase for all patients.



The summary statistics for the pharmacokinetic parameters are summarized in Table 5:

Table 5. Summary of PK parameters of serum pegloticase for all patients following single and multiple doses (n=40).

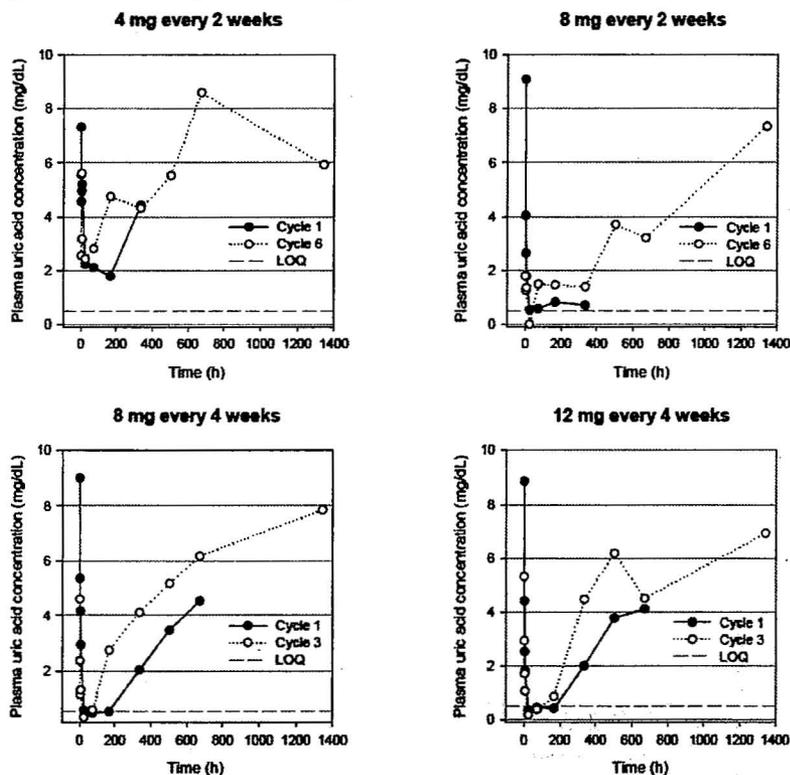
Treatment	Cycle	Median (Range)								
		AUC ₀₋₂₄ (mcg·h/mL)	AUC ₀₋₁₆₈ (mcg·h/mL)	AUC ₀₋₄ (mcg·h/mL)	AUC _{inf} (mcg·h/mL)	C _{max} (mcg/mL)	T _{max} (h)	Half-life (h)	CL (L/h)	Varia (L)
4 mg every 2 weeks	1	17.0 (15.0-18.9)	NC	18.1 (15.0-17.0)	NC	0.800 (0.768-1.14)	6.5 (1.58-168)	NC	NC	NC
	6	34.5 (22.7-51.9)	251 (132-369)	132 (97.1-657)	1230 (322-2138)	1.62 (1.51-2.94)	1.60 (1.50-23.5)	414 (210-617)	0.00609 (0.00609-0.00609)	NC
8 mg every 2 weeks	1	50.3 (20.5-71.7)	355 (245-489)	608 (264-838)	1090 (568-1494)	2.95 (1.98-4.81)	22.9 (1.50-168)	274 (198-308)	0.00734 (0.00536-0.0141)	2.67 (2.31-3.95)
	6	122 (61.1-186)	710 (326-1034)	1361 (326-2734)	1546 (456-3815)	5.96 (2.87-8.89)	6.00 (1.50-21.9)	160 (95.8-371)	0.00681 (0.00447-0.0114)	NC
8 mg every 4 weeks	1	41.4 (15.0-18.9)	269 (151-759)	304 (151-751)	1337 (579-2549)	2.50 (1.34-5.14)	23.4 (1.67-71.5)	280 (239-296)	0.00673 (0.00314-0.0138)	2.43 (1.36-5.96)
	3	46.3 (25.4-72.8)	463 (231-577)	281 (81.2-393.6)	1935 (146-6337)	2.81 (1.92-4.56)	23.2 (1.50-70.9)	359 (61.6-940)	0.00349 (0.00349-0.00349)	NC
12 mg every 4 weeks	1	39.6 (30.3-114.4)	478 (252-765)	1047 (97.6-2574)	1566 (991-3052)	3.32 (1.53-5.79)	23.2 (1.50-71.5)	329 (181-403)	0.00767 (0.00393-0.0121)	3.30 (1.82-4.05)
	3	84.0 (63.5-139)	519 (398-567)	670 (398-1821)	925 (628-2216)	4.64 (3.28-6.18)	14.6 (1.52-23.4)	119 (92.8-282)	0.00671 (0.00659-0.00683)	NC

NC – not calculated.

BEST AVAILABLE COPY

In the dose range studied, 0.5 mg to 12 mg, the increase of mean C_{max} and AUC appeared to be dose related. There may be some accumulation of pegloticase following dosing every 2 weeks. Pegloticase administered every 4 weeks appeared to be associated with less accumulation. T_{max} values were highly variable for all treatments. Although half-life values were also highly variable, results suggest that serum pegloticase has a long half-life. Mean profiles for plasma uric acid are presented by treatment in 7.

Figure 6. Mean profiles of plasma uric acid.



The profiles depicted above demonstrate the rapid decline in plasma uric acid concentrations following dosing with pegloticase. For all treatment groups, uric acid levels remained below the target level of 6 mg/dL until approximately 300 hours post-dose. Table 6 presents median PD parameters calculated for plasma uric acid:

Table 6. Summary of pharmacodynamic parameters of plasma uric acid following single and multiple doses.

Treatment	Cycle	Median (Range)		
		C0 (mg/dL)	Cmin (mg/dL)	tmin (h)
4 mg every 2 weeks	1	6.87 (5.51-10.3)	1.24 (0.00-3.96)	71.5 (23.5-504)
	6	5.17 (1.51-13.0)	0.67 (0.00-4.61)	22.3 (1.50-1343)
8 mg every 2 weeks	1	9.55 (6.63-11.3)	0.00 (0.00-3.11)	22.5 (1.58-167)
	6	0.00 (0.00-9.77)	0.00 (0.00-3.21)	2.83 (1.50-791)
8 mg every 4 weeks	1	8.75 (4.31-14.9)	0.00 (0.00-2.93)	23.4 (1.67-71.5)
	3	3.91 (0.00-13.3)	0.00 (0.00-8.61)	14.3 (0.00-23.5)
12 mg every 4 weeks	1	8.24 (4.58-13.2)	0.00 (0.00-1.10)	22.8 (2.50-335)
	3	3.08 (0.00-18.6)	0.00 (0.00-3.31)	1.51 (1.50-23.2)

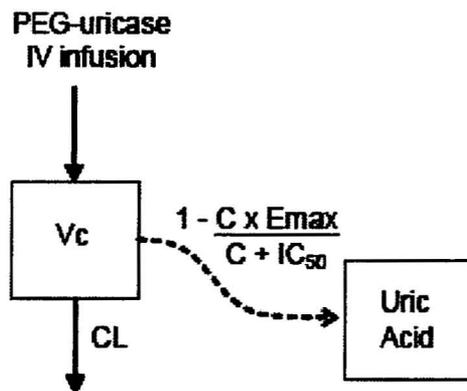
NC – not calculated.

Treatment	Cycle	Median (Range)				
		AUEC0-24 (mg-h/dL)	Cav 0-24 (mg/dL)	AUEC0-168 (mg-h/dL)	Cav 0-168 (mg/dL)	AUEC0-t (mg-h/dL)
4 mg every 2 weeks	1	82.2 (43.7-177)	3.43 (1.82-7.37)	313 (43.7-673)	1.86 (0.260-4.00)	840 (330-1959)
	6	34.4 (18.6-196)	1.43 (0.774-8.17)	522 (158-1315)	3.11 (0.941-7.83)	6726 (9.9-8189)
8 mg every 2 weeks	1	37.2 (26.5-109)	1.55 (1.10-4.54)	48.0 (36.6-569)	0.286 (0.218-3.39)	34.9 (21.8-569)
	6	0.00 (0.00-3.26)	0.00 (0.00-0.136)	0.00 (0.00-1604)	0.00 (0.00-9.55)	3271 (687-11611)
8 mg every 4 weeks	1	52.8 (21.6-93.8)	2.20 (0.902-3.91)	75.0 (25.3-566)	0.447 (0.151-3.37)	1038 (14.7-4317)
	3	29.9 (0.00-111)	1.25 (0.00-4.64)	94.6 (0.00-648)	0.563 (0.00-3.86)	7281 (1143-12323)
12 mg every 4 weeks	1	36.5 (12.1-114)	1.52 (0.505-4.74)	36.5 (12.1-331)	0.217 (0.0722-1.97)	841 (18.3-4477)
	3	2.57 (0.00-76.0)	0.107 (0.00-3.17)	80.0 (1.77-252)	0.476 (0.011-1.50)	4245 (26.0-17167)

NC – not calculated.

The PD parameters above also indicate that pegloticase was able to provide marked suppression of uric acid concentrations, as demonstrated by the difference between C0, Cmin and average concentrations at 24 and 168 hours. The Cmin parameter suggests that complete suppression of uric acid was obtained when doses of 8 mg every 2 or 4 weeks or doses of 12 mg every 4 weeks were administered. In all treatment groups, average concentrations of uric acid remained well below 6 mg/dL at 168 hours post-dose.

The model that best described the PK of pegloticase in serum following intravenous administration was a 1-compartment model with linear elimination. The best model that described the inhibitory effect of pegloticase on uric acid was a direct inhibitory Emax model. The final model is depicted below.



C = PEG-uricase concentration
V_c = Central volume of distribution for PEG-uricase
CL = Systemic clearance of PEG-uricase
E_{max} = Maximum inhibitory capacity
IC₅₀ = Concentration of PEG-uricase where 50% of maximal inhibitory effect is attained

Mean values for the pharmacokinetic and pharmacodynamic parameters of pegloticase along with inter-individual variability (CV%) are presented below.

Parameters	Mean (CV%)
CL (L/month/kg)	0.0615 (28.2%)
V _c (L/kg)	0.0449 (21.2%)
Half-life (h)	404 (44.2%)
Baseline uric acid (mg/dL)	10.7 (12.5%)
E _{max} (%)	82.5 (18.1%)
IC ₅₀ (µg/mL)	0.104 (65.1%)
IC ₉₀ (µg/mL)*	0.932 (65.1%)

*IC₉₀: Concentration of PEG-uricase where 90% of maximal inhibitory effect on uric acid levels is attained.

The results of PK-PD modeling indicate that a pegloticase dose of 2 mg or greater is required to maintain mean uricase levels above EC50 and consequently uric acid levels below the solubility limit of 7 mg/dL in serum for up to one week.

Covariates investigated for inclusion in the PK/PD model included: age, gender, race, body weight, ideal body weight and antibody levels. Neither age, race, gender were significant covariates for PK or PD parameters. Body weight was the only covariate influencing the PK parameters CL and V_c.

Conclusions:

- A compartmental model was developed to simultaneously describe serum concentrations of pegloticase and plasma concentrations of uric acid. A one-compartment model with linear elimination best described the PK of pegloticase.

- The PK-PD model included an inhibitory Emax effect (as a function of pegloticase concentration) resulting in a decrease in uric acid levels with increasing pegloticase concentrations.
- Weight was the only significant covariate for the PK parameters CL and Vc. There were no covariates that influenced PD parameters in a significant manner.
- According to this model, pegloticase was generally able to suppress uric acid concentrations up to 83%, and maximal suppression was attained at very low serum concentrations of pegloticase.
- Based on predictive simulations performed using this model, pegloticase given as 2-hour IV infusions every 2 or 4 weeks at 8 mg maintained uric acid levels well below 6 mg/dL. In addition, the long half-life of pegloticase supports the use of a less frequent dosing regimen.

Reviewer's comments: As commented in the review of study C0402, it is the opinion of the reviewer the sponsor's PKPD model is mechanistically inappropriate. The sponsor described the PK/PD relationship under the assumption that pegloticase suppresses the production of uric acid. However, the mechanism of action of pegloticase indicates that it stimulates the degradation of uric acid.

C0405/6 (including Pop PK report Aa41382 and PD report Aa41382-2)

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

Objectives: To demonstrate superiority in the response rate of subjects receiving designed to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of report describes the pharmacokinetics (PK) of pegloticase in serum using a population PK pegloticase vs. those receiving placebo in achieving control of plasma uric acid (PUA).

Study Design: Each subject received 8 mg pegloticase IV every 2 weeks or 8 mg pegloticase IV every 4 weeks or matching placebo control. All subjects received an intravenous infusion (pegloticase or placebo) every two weeks in order to maintain the blind throughout the study. Placebo was alternated with 8 mg pegloticase infusions throughout the study in the 8 mg every 4 week dose group. Treatment was administered for 24 weeks. Subjects were randomized to one of the three treatment arms in a 2:2:1 ratio: 8 mg pegloticase every 2 weeks; 8 mg pegloticase every 4 weeks; or placebo. Randomization was balanced across all centers and was stratified by the presence (or absence) of tophi. Samples for PK analysis were collected before each dose administration, as well as 2 and 24 hours after the end of dose administration following Doses 1 (Week 1), 5 (Week 9) and 11 (Week 21). Additional samples were also collected 7 days after the end of dose administration following Doses 5 and 11, 2 hours and 7 days after the end of dose administration following Doses 6 and 12, and 14 days after the end of dose administration following Dose 12 (Week 25). In the event of an early termination, a sample was also collected at this time. Samples for analysis of antibodies to pegloticase

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

Study Population: In study C0405, 128 subjects were screened and 109 subjects were randomized. In study C0406, 134 subjects were screened and 116 subjects were randomized. A total of 212 subjects were dosed (104 from C0405 and 108 from C0406) and 157 subjects completed the study per protocol (76 from C0405 and 81 from C0406).

A total of 163 subjects (131 men; 32 women) were included in the pharmacokinetic analysis. Only subjects who received active drug and who had at least one detectable pegloticase concentration were included in the population PK analysis.

The following table summarizes the demographic characteristics of the subjects included in this analysis.

Table 7. Demographic characteristics of study subjects.

Subject Demographics	Mean (CV%)	Median (Range)
Age (years)	55.6 (26.0%)	57 (23 - 89)
Body Weight (kg)	99.1 (25.1%)	96.2 (48.2 - 191)
Height (cm)	174 (6.28%)	175 (145 - 193)
Body mass index (kg/m ³)	32.8 (22.5%)	31.5 (15.0 - 65.9)
Body surface area (m ²)	2.12 (13.3%)	2.12 (1.44 - 2.88)
Ideal body weight (kg)	68.2 (16.3%)	70.5 (38.6 - 86.8)
Screening creatinine clearance (mL/min)*	92.4 (55.4%)	84.5 (17 - 264)
Pre-dose serum uric acid (mg/dL)	9.80 (17.7%)	9.80 (5.40 - 14.9)

*Creatinine clearance was calculated using the Cockcroft-Gault equation

Bioanalytical Analysis: Bioanalytical assays were conducted at (b) (4) Serum pegloticase was measured as pegloticase activity. This assay comprised a coupled enzymatic/fluorescent reaction. The analytical range was 0.5 to 10 µg/mL. The enzymatic colorimetric method was used to obtain uric acid concentrations. The plasma uric acid concentrations ranged from <LLOQ to 30.07 mg/dL. The serum uric acid concentrations ranged from <LLOQ to 16.06 mg/dL. Antibody levels were also analyzed using an ELISA assay. The neutralizing antibody assay was not fully validated. The assay performance is summarized in the table below:

Table 8. Summary of assay performance.

Analytes	Method	SC range (µg/mL)	SC precision (%CV)	SC mean recovery (% of theoretical)	Nominal Pegloticase activity in QC (mg/dL)	QC precision (%CV)	QC mean recovery (% of theoretical)
Pegloticase	Coupled enzymatic/fluorescent	0.5-10	2.1-9.8	97.3-107.1	1.50, 3.50, and 7.50	7.1 to 10.4	94.9-99.6

	rimetric method							
Uric acid	enzymatic colorimetric method	0.5-12	92-110	-	4.00, 9.00	6.00,	1.08-2.48	99.8%-100.8%

Source: Study No. 340648 p26 and p48
Study No. 600168 (uric acid, c0406)
Study No. 600141 (uric acid, c0405)

Anti-IgE pegloticase was monitored in human serum by an ELISA (report 300914)
Anti-IgG and IgM pegloticase was monitored in human serum by an ELISA (report 301043)
Neutralizing pegloticase was monitored in human serum by an ELISA (report 301045)

Data Analysis: A total of 2199 study samples from Study No. C0405 were analyzed. The serum active pegloticase concentrations measured in this study ranged from below the lower limit of quantitation (LLOQ, 0.500 µg/mL) to 5.693 µg/mL, with 1646 study samples giving results < LLOQ. A total of 2271 study samples from Study No. C0406 were analyzed. The serum active Pegloticase concentrations measured in this study ranged from < LLOQ to 5.298 µg/mL, with 1644 study samples giving results < LLOQ. In all, 163 subjects (131 men and 32 women) were included in the pharmacokinetic analysis.

Using NONMEM VI, various structural PK models were tested, such as one- and two-compartment models with linear and non-linear elimination processes. Quality of fit and selection of the final model was determined using objective function, Akaike information criterion, residual variability, other indicators of goodness of fit and by visual inspection of pertinent graphs (i.e., fitted and observed concentrations versus time, weighted residuals versus fitted values). Following the selection of the final structural PK model, various covariates were tested for potential inclusion in the model using regression analyses.

Covariates investigated for inclusion in the model were: weight, height, body mass index, body surface area, ideal body weight, sex, presence of tophi, creatinine clearance, baseline serum uric acid level, number of gout flare ups, antibody levels (against PEG and pegloticase), the presence of co-morbidities (such as hypertension and diabetes) and allergy or gastrointestinal intolerance to allopurinol. Based on the individual pharmacokinetic parameters obtained from the population PK analysis, additional parameters such as AUC_{0-τ}, C_{max}, T_{max}, Kel and terminal elimination half-life were calculated for each subject.

Pharmacokinetic Results: The model that best described the PK of pegloticase in serum following IV administration was a 1-compartment model with linear elimination. The only significant covariates included in the PK model were body surface area and overall anti-pegloticase antibody level on V_c and CL.

Efficacy Results: The primary efficacy endpoint was the proportion of subjects whose PUA was normalized to less than 6 mg/dL for at least 80% of the time during the

treatment assessment period: Month 3, Month 6, and Months 3 and 6 combined (PUA responders). In the ITT population, the proportion of subjects whose PUA remained below 6 mg/dL for at least 80% of the time during Month 3 was 58.1% of the subjects in the 8 mg/2 weeks group, 31.7% in the 8 mg/4 weeks group, and 5.0% in the placebo group ($p \leq 0.024$ for each pegloticase group vs. the placebo group). Similar results were observed during Month 6: 46.5% of the subjects in the 8 mg/2 weeks group, 26.8% in the 8 mg/4 weeks group, and 0.0% in the placebo group had PUA below 6 mg/dL for at least 80% of the time ($p \leq 0.011$ for each pegloticase group vs. the placebo group).

Significantly greater proportions of subjects also reached the primary efficacy endpoint in the two pegloticase treatment groups compared to placebo at Month 3 and Month 6 combined (i.e., were PUA responders): 46.5%, 19.5%, and 0.0% in the pegloticase 8 mg/2 weeks group, pegloticase 8 mg/4 weeks group, and placebo group, respectively ($p \leq 0.044$ for each pegloticase group vs. the placebo group).

In the pegloticase treatment groups, the PUA responder rates based on the PP population were higher than those in the ITT population: 66.7% of the subjects in the pegloticase 8 mg/2 weeks group and 30.8% of the subjects in the pegloticase 8 mg/4 weeks group were responders (i.e., maintained PUA concentrations below 6 mg/dL for at least 80% of the time during Month 3 and Month 6 combined). Both pegloticase treatment groups achieved significantly higher responder rates compared to placebo ($p \leq 0.014$ for each pegloticase group vs. placebo).

Table 9. Treatment Response for intent-to-treat (ITT) and per-protocol (PP) Populations.

	ITT Population			PP Population		
	8 mg Pegloticase		Placebo (N = 20)	8 mg Pegloticase		Placebo (N = 18)
	Every 2 Weeks (N = 43)	Every 4 Weeks (N = 41)		Every 2 Weeks (N = 30)	Every 4 Weeks (N = 26)	
PUA less than 6 mg/dL for at least 80% of the time in Month 3						
n (%)	25 (58.1)	13 (31.7)	1 (5.0)	23 (76.7)	9 (34.6)	1 (5.6)
95% CI ¹	35.6, 70.7	9.6, 43.9		52.6, 89.6	7.9, 50.2	
P-value ²	<0.001	0.024		<0.001	0.031	
PUA less than 6 mg/dL for at least 80% of the time in Month 6						
n (%)	20 (46.5)	11 (26.8)	0 (0.0)	20 (66.7)	11 (42.3)	0 (0.0)
95% CI ¹	31.6, 61.4	13.3, 40.4		49.8, 83.5	23.3, 61.3	
P-value ²	<0.001	0.011		<0.001	<0.001	
Responders: PUA less than 6 mg/dL for at least 80% of the time in Months 3 and 6 combined						
n (%)	20 (46.5)	8 (19.5)	0 (0.0)	20 (66.7)	8 (30.8)	0 (0.0)
95% CI ¹	31.6, 61.4	7.4, 31.6		49.8, 83.5	13.0, 48.5	
P-value ²	<0.001	0.044		<0.001	0.014	

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

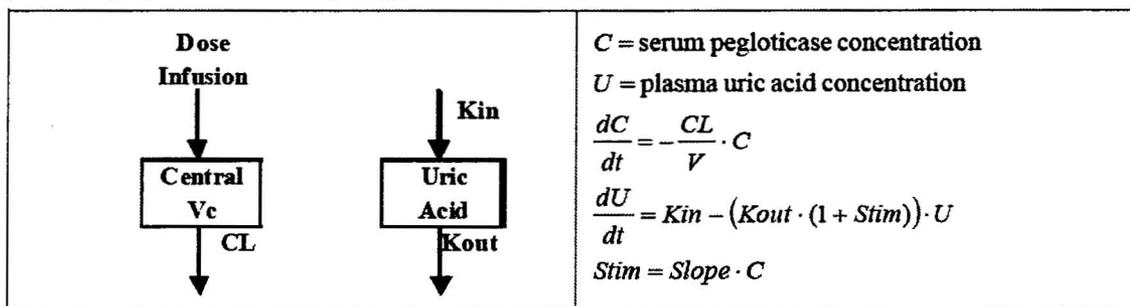
²P-value using Fisher's exact test to compare corresponding pegloticase group vs. placebo.

³ITT: intend to treat population comprised all randomized subjects who received at least 1 dose of study medication and had at least one post-dose observation.

⁴PP: per-protocol population comprised all subjects in the ITT population who had no major protocol deviations.

Conclusions: A compartmental model was developed to describe serum concentrations of pegloticase. A one compartment model with linear elimination best described the PK of pegloticase. Body surface area and overall anti-pegloticase antibody response were the only covariates included for the PK parameters CL and Vc. Seroconversion was associated with an increase in CL and Vc. The mean half-life for the population of subjects was approximately 221 hours (median value of 217 hours). Based on Bayesian estimates, the mean (median) half-life of subjects with no increase in anti-pegloticase antibody levels was approximately 234 hours (median 216 hours) while it was around 220 hours (median 217 hours) in subjects with an increase in anti-pegloticase antibody levels.

Population PD Analysis: In sponsor's population PD analysis (study report: aa41382-2 [5.3.4.2 population PD report]), the following model was used.



Vc = Central volume of distribution for pegloticase; CL = Systemic clearance of pegloticase; Kin = rate of uric acid presentation to plasma; Kout = rate of uric acid depletion from plasma; Slope = linear relationship between serum pegloticase and stimulation of Kout; Stim = stimulation of Kout.

The key findings from sponsor's population PD analysis based on Phase 3 clinical studies (c0405 and c0406) are summarized below:

- An indirect response model with linear stimulation of PUA elimination provided the best fit to the data.
- Based on estimated serum pegloticase levels and population PD parameter estimates, PUA elimination could be stimulated up to 2358% of normal endogenous function following the IV administration of pegloticase (4 mg every 2 weeks or 8 mg every 4 weeks).
- The level of stimulation was inversely related to the levels of circulating antibodies to pegloticase. However, even in the subjects with high increases in antibodies to pegloticase, circulating pegloticase elicited a 32% increase in the rate of PUA elimination.

Reviewer's Comments: Sponsor's population PK analysis is generally adequate and the significant covariates identified by the sponsor were verified. An indirect response model instead of direct response model was used in sponsor's PD analysis in this report. The use of indirect response model reflects the mechanism of action of pegloticase, i.e., stimulating the degradation of uric acid.

4.3 Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Application Number	BLA125293
Submission Number (Date)	0000 (Oct 31, 2008) 0008 (Feb 5, 2009)
Clinical Division	Division of Anesthesia, Analgesia, and Rheumatology
Primary PM Reviewers	Bhattaram Atul Venkatesh, Ph.D., Ping Ji, Ph.D.
Team Leader	Yaning Wang, Ph.D.

1	Summary of Findings.....	71
1.1	Key Review Questions.....	71
1.1.1	Is there evidence of dose and response (reduction in plasma uric acid) relationship?.....	72
1.1.2	What is the relationship between severity of anti-pegloticase antibody formation (none, low, moderate, high) and response (PK, Plasma Uric Acid).	74
1.1.3	What is the effect of dose/exposure on safety of pegloticase?	80
1.2	Recommendations.....	80
1.3	Labeling Statements.....	81
12.2	Pharmacodynamics	81
2	Pertinent regulatory background.....	83
3	Results of Sponsor’s Analysis	83
4	Reviewer’s Analysis	86
4.1	Introduction.....	86
4.2	Objective	86
4.3	Methods.....	86
4.3.1	Data Sets	86
4.3.2	Software	86
4.3.3	Covariates investigated	86
4.4	Results.....	87
4.4.1	Population Pharmacokinetic Analysis	87
4.4.2	Population Pharmacodynamic Analysis	88
Appendix 1.	Listing of Analyses files and Output Files.....	90

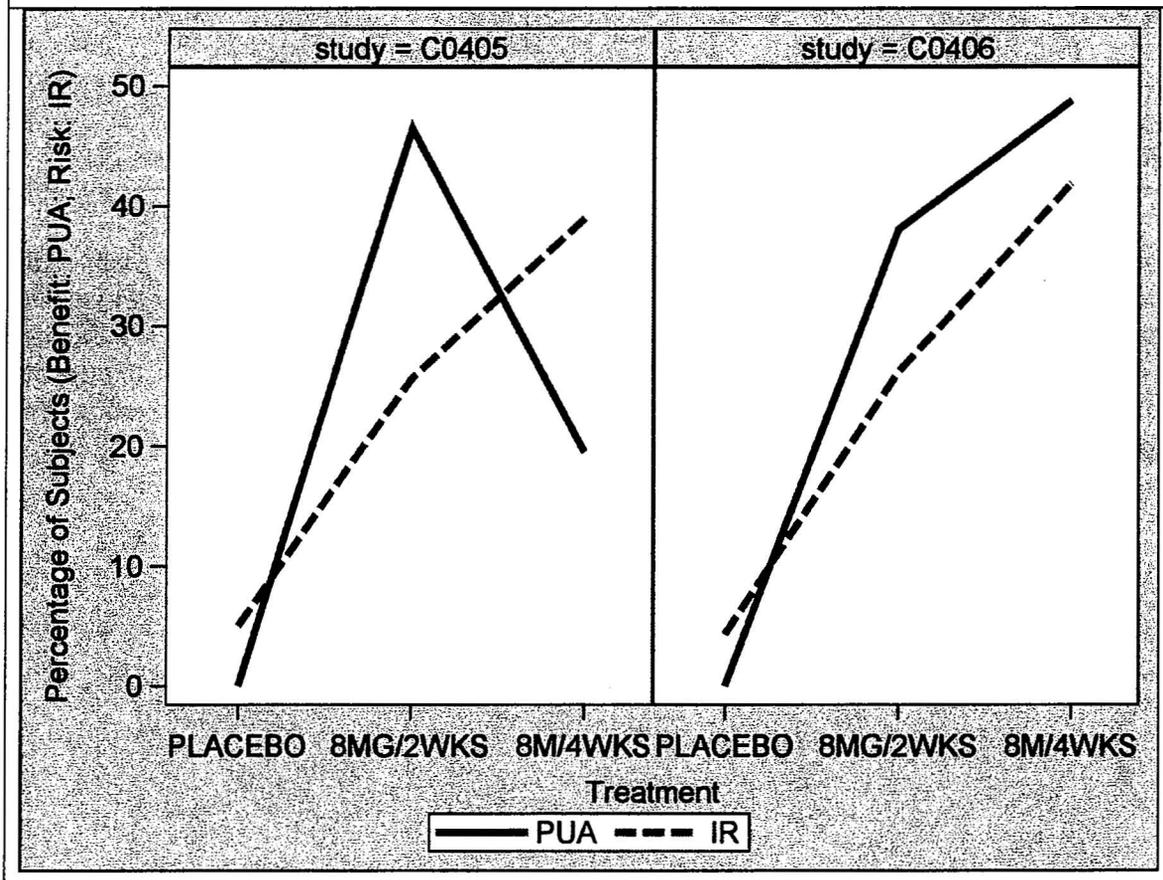
Appendix 2. Model Parameter Estimates for the Final Pharmacokinetic Model (final_1.mod)	91
Appendix 3. Scatter plots of goodness of fit of final pharmacokinetic model.	92
Appendix 4. Model Parameter Estimates for the Final Pharmacodynamic Model (runR1.mod).....	93
Appendix 5. Scatter plots of goodness of fit of the reviewer's final pharmacodynamic model.....	94
Appendix 6. Scatter plots of goodness of fit of Sponsor's pharmacodynamic model run709.mod.	95
Appendix 7. Individual Subject observed uric acid level or predicted uric acid level vs time profiles.	96

1 SUMMARY OF FINDINGS

The key pharmacometric findings from Pegloticase BLA125293 submission are:

- Clear dose/concentration-response relationship for reduction in plasma uric acid.
- A one-compartment model with linear elimination was found to best fit the plasma pegloticase concentration time profiles. An indirect response model with drug stimulation on the output was found to best fit the pharmacodynamic (plasma uric acid concentration versus time) profiles.
- Anti-pegloticase antibody was associated with the lowering of the plasma pegloticase concentrations and the loss of effect on plasma uric acid.
- Based on benefit-risk assessment (as shown in **Figure 1** below), the sponsor is seeking approval for 8 mg every 2 week dosing regimen.

Figure 1. Percentage of patients with benefit (Plasma Uric Acid; PUA less than 6 mg/dL for at least 80% of the time in Months 3 and 6 combined) and risk (Infusion reaction) in placebo, 8 mg every 2 weeks (8MG/2WKS), 8 mg every 4 weeks (8MG/4WKS).



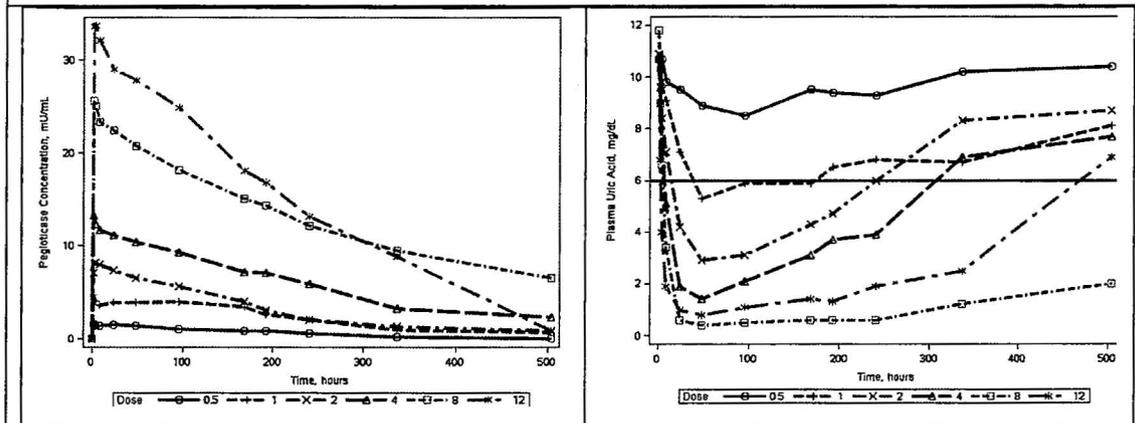
1.1 Key Review Questions

The purpose of the pharmacometrics review is to address the following key questions.

1.1.1 Is there evidence of dose and response (reduction in plasma uric acid) relationship?

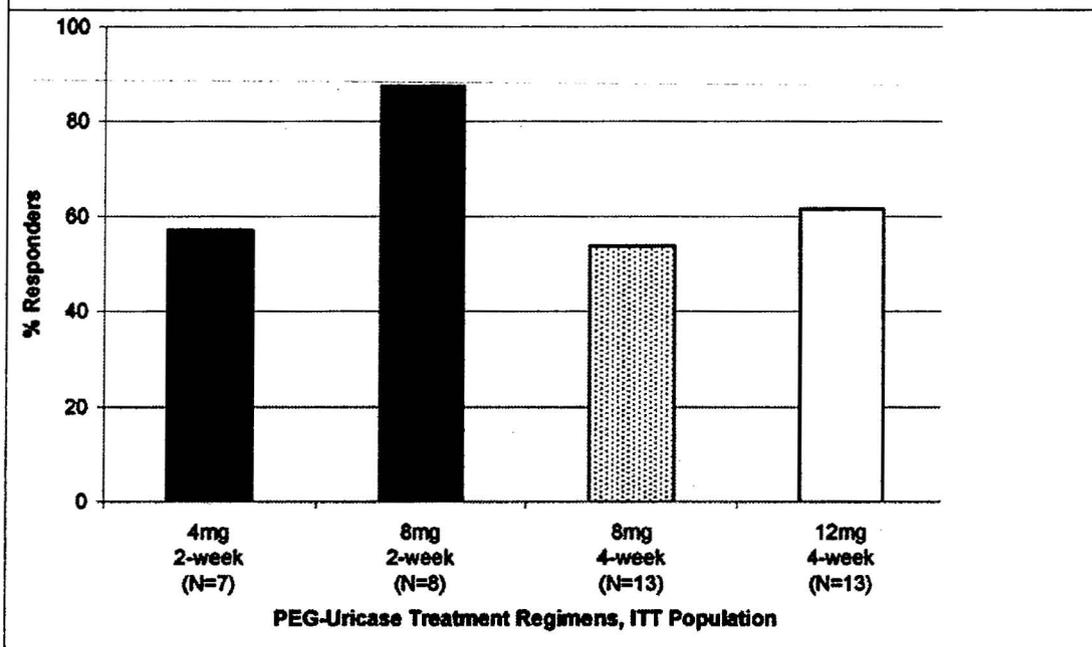
The sponsor characterized the relationship between dose and reduction in plasma uric acid adequately in the Phase 1 study C0402 (A phase 1 study to evaluate the pharmacokinetic profile, tolerability and safety of intravenously administered pegloticase). At dose levels above 1 mg, the mean plasma uric acid (PUA) levels are reduced below the 6 mg/dL (target) as shown in **Figure 2**.

Figure 2. Mean (A) pegloticase concentrations (mU/mL) vs time (hours) (B) plasma uric acid concentrations after single intravenous dose administration of 0.5, 1, 2, 4, 8, or 12 mg of pegloticase.



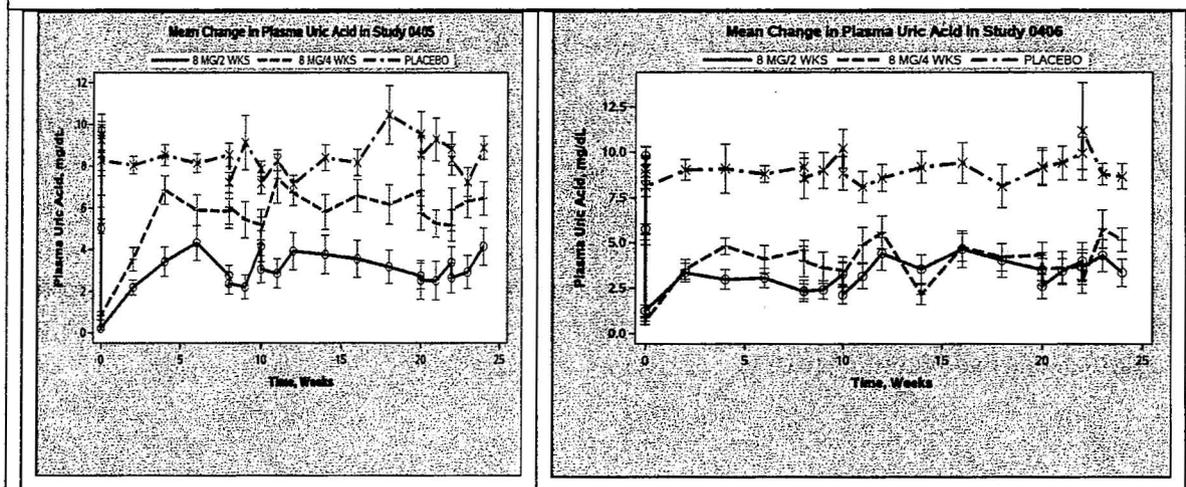
In the Phase 2 study C0403, the uric acid lowering potential of pegloticase was evaluated after drug administered as 4 mg every 2 weeks, 8 mg every 2 weeks, 8 mg every 4 weeks and 12 mg every 4 weeks. The percentage of patients classified as Responders (subjects whose plasma uric acid levels remained ≤ 6 mg/dL for at least 80% of the treatment period) is shown in **Figure 3**. The highest percentage of responders was observed in the group administered 8 mg every 2 weeks.

Figure 3. % responders in study C0403 administered 4 mg every 2 weeks, 8 mg every 2 weeks, 8 mg every 4 weeks and 12 mg every 4 weeks.



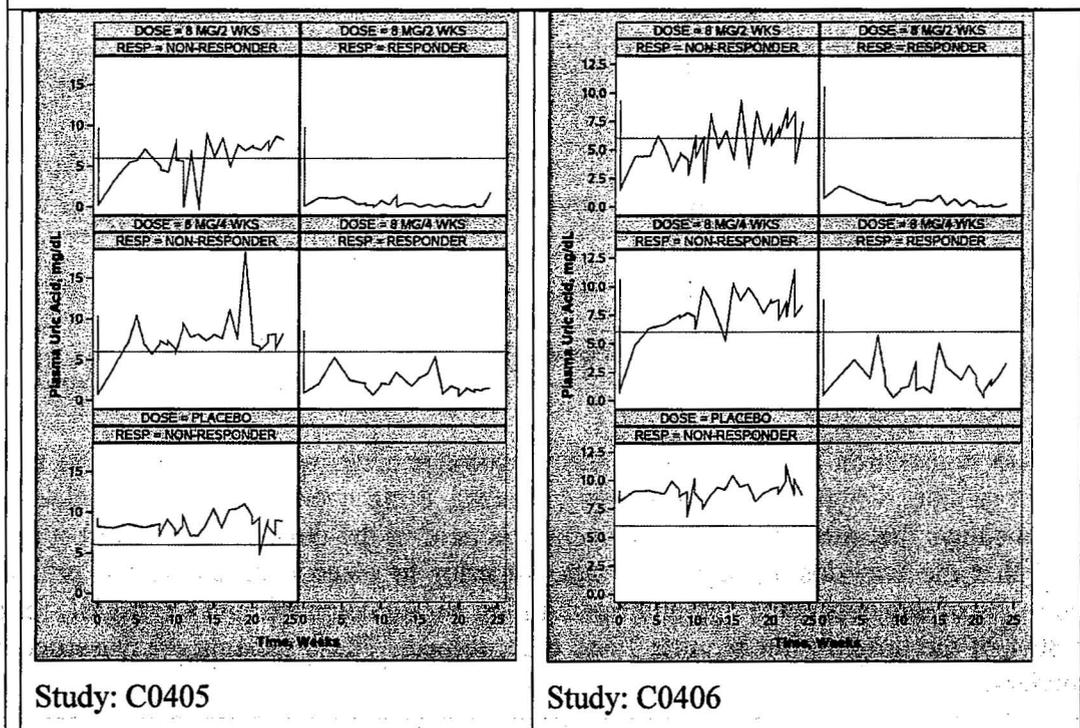
In the two registration studies (C0405 and C0406), patients were randomized to three treatment groups, 8 mg pegloticase every 2 weeks, 8 mg every 4 weeks, and placebo. **Figure 4** shows the mean changes in plasma uric acid in the three groups. Both studies showed that the two dosing regimens were superior to placebo based on the primary endpoint (% of subjects achieving and maintaining PUA concentrations < 6 mg/dL for at least 80% of the time during Months 3 and 6 combined. These patients are classified as responders).

Figure 4. Mean (\pm SE) changes in plasma uric acid in studies C0405 and C0406 (Based on actual week data)



In reviewer's analysis, the time course of plasma uric acid in patients who are categorized as responders and non-responders was further explored. Patients who discontinued early in the study due to tolerability issues were characterized as non-responders. **Figure 5** shows the mean time course of plasma uric acid in responders versus non-responders after administration of placebo, 8 mg every 4 weeks and 8 mg every 2 weeks. Patients classified as non-responders did not show sustained reduction in plasma uric acid levels.

Figure 5. Mean changes in plasma uric acid after administration of placebo (PLACEBO), 8 mg every 4 weeks (8 MG/4 WKS), and 8 mg every 2 weeks (8 MG/2 WKS) in responders and non-responders in studies C0405 and C0406. The reference line (red) indicates the target level of 6 mg/dL.

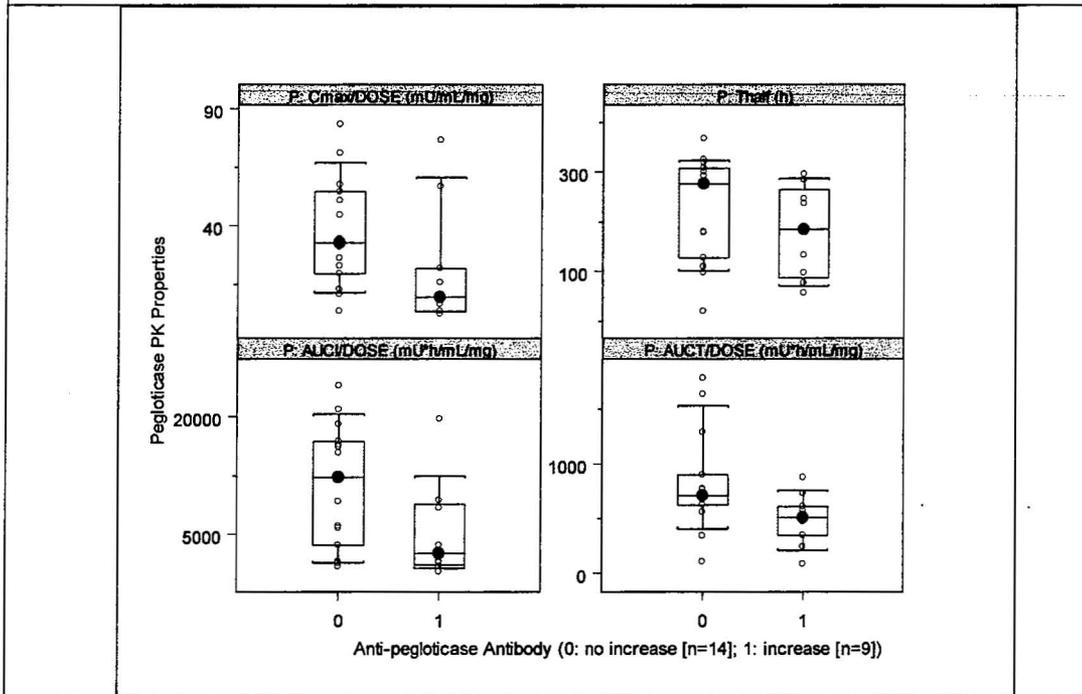


1.1.2 What is the relationship between severity of anti-pegloticase antibody formation (none, low, moderate, high) and response (PK, Plasma Uric Acid).

The presence of anti-pegloticase antibody was associated with a decrease in the exposure of pegloticase and an increase in plasma uric acid level.

In study C0402, nine subjects developed anti-pegloticase antibody and the rest 14 subjects were either sero-negative or inclusive (positive at baseline). The boxplot of various PK properties versus anti-pegloticase antibody status showed that the presence of antibody was associated with a decrease in both exposure and elimination half-life of pegloticase, as shown in **Figure 6**.

Figure 6. Pegloticase PK properties (AUC/dose, C_{max}/dose, and T_{1/2}) in patients who have an increase or no increase of anti-pegloticase antibody in study C0402.



Note: AUC_i: AUC_{inf}; AUCT: AUC_{0-T}

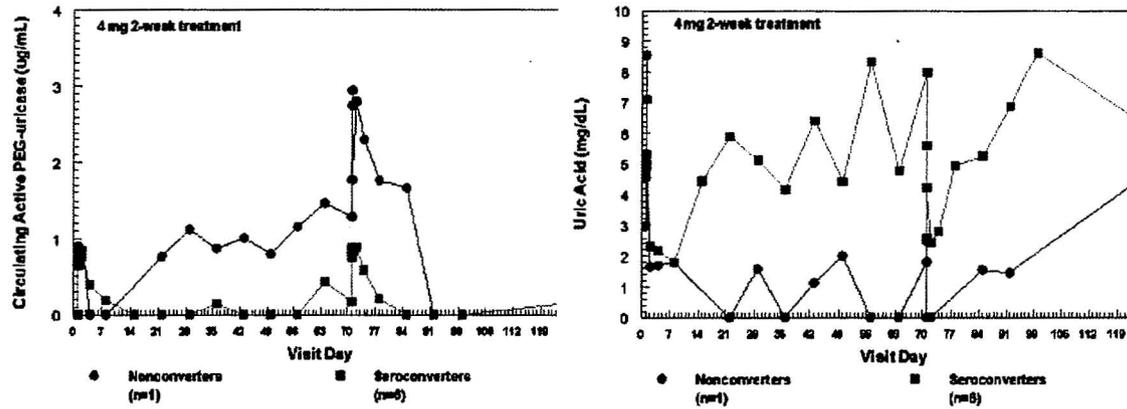
Source: page 49-62 of 521 (1.5 listing of individual pharmacokinetic parameters for uricase grouped by seropositive/seronegative subjects) in Appendix 3.4 of section 9 in Appendix 3.3 pharmacokinetic report of CSR C0402.

In study C0403, seroconversion (an increase in titers at one or more time points after the initial dose) occurred in 31/41 subjects (76%). The distribution of seroconverted subjects across the 4 treatment arms appeared to be random: 6/7 (86%) in the 4 mg every 2 week regimen, 5/8 (63%) in the 8 mg every 2 week regimen, 9/13 (69%) in the 8 mg every 4 week regimen, and in the 11/13 (85%) in the 12 mg every 4 week regimen. Six of the 41 randomized subjects had no anti-pegloticase immunoreactivity at any time point. (Source: page 151 in report body.pdf)

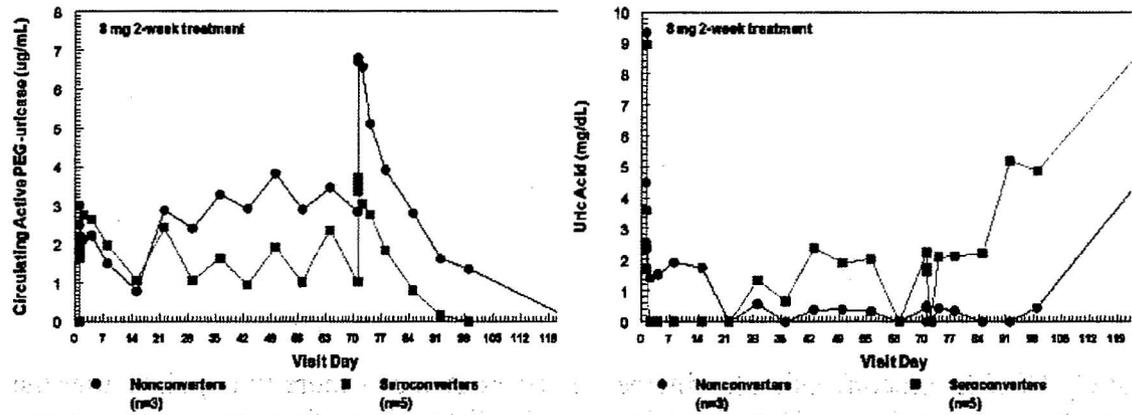
The effect of anti-pegloticase antibody production on pharmacokinetics and plasma uric acid by dose group is presented in Figure 7. These figures depict the mean circulating active pegloticase concentrations (µg/mL) and uric acid concentrations (mg/dL) for subjects that seroconverted versus those that did not seroconvert (non-converters) by dose group. There was only one non-converting subject in both the 4 mg 2 week and 12 mg 4 week treatment regimens. The nonconverter in the 12 mg 4 week treatment regimen did not complete treatment. It appears that there may have been an increase in plasma uric acid in subjects who seroconverted. However, the sample size for each dose regimen was small.

Figure 7. Effect of anti-pegloticase antibody on PK and efficacy (plasma uric acid) after 4 mg/2 wk, 8 mg/2 wk, 8 mg/4 wk and 12 mg/2 wk regimens in study C0403.

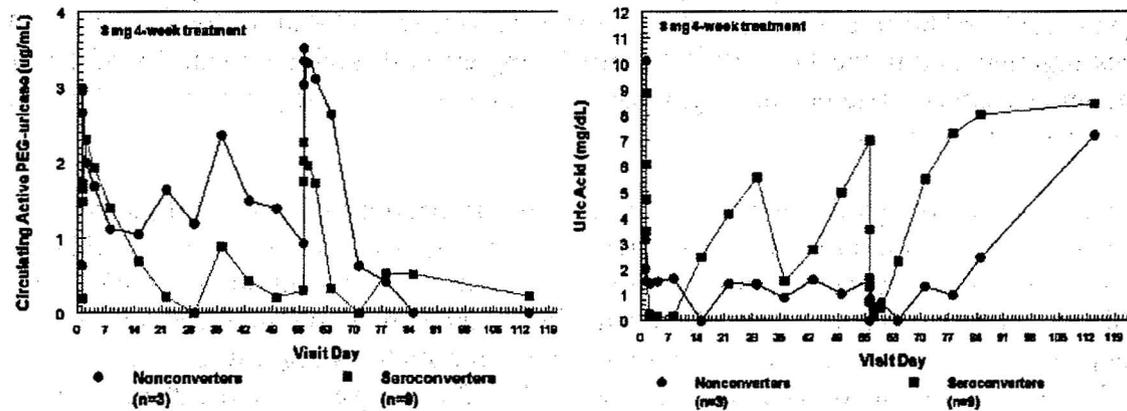
A: 4 mg/2 wk



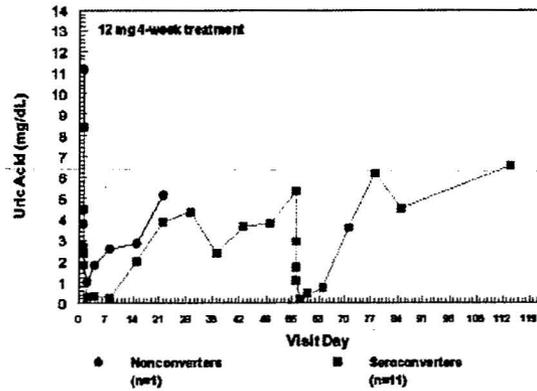
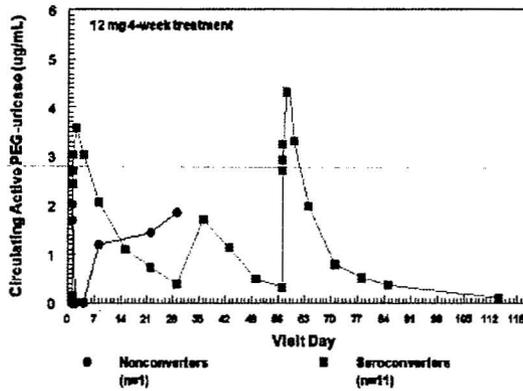
B: 8 mg/2 wk



C: 8 mg/4 wk



D: 12 mg/2 wk



Note the lower pegloticase (PEG-Uricase) concentrations and higher uric acid concentrations in seroconverters in comparison to nonconverters.

Source: Pages 153-156 in report body.pdf

The frequency of anti-pegloticase antibody and its effect on response was further investigated in Phase 3 studies. Anti-pegloticase antibody response was treated as a categorical variable, which included no increase, low increase, moderate increase, or high increase. No increase included subjects whose anti-pegloticase response was negative at baseline, Months 3 and 6 (no titer), or whose anti-pegloticase response was positive at baseline but with no increase from baseline in titer during Months 3 and 6 (no increase in titer); low increase if titer was > 0 and ≤ 810 at Month 3 or Month 6; moderate increase if titer was > 810 and ≤ 7290 at Month 3 or Month 6; high increase if titer > 7290 at Month 3 or Month 6. **Table 1** shows the percentage of patients with no, low, moderate or high increase in anti-pegloticase antibody during month 3 and month 6.

Table 1. Percentage of patients with no, mild, moderate or high increase in anti-pegloticase antibody during month 3 and month 6 (antilevl) in Study C0405 and C0406.

Description of Planned Arm=PLACEBO		Description of Planned Arm=6 MG PEG-URICASE EVERY 2 WEEKS		Description of Planned Arm=8 MG PEG-URICASE EVERY 4 WEEKS	
2	10.00	2	10.00	14	38.89
18	90.00	20	100.00	14	38.89
				28	77.78
				8	22.22
				36	100.00
Study C0405					
Description of Planned Arm=PLACEBO		Description of Planned Arm=6 MG PEG-URICASE EVERY 2 WEEKS		Description of Planned Arm=8 MG PEG-URICASE EVERY 4 WEEKS	
4	19.05	4	19.05	13	33.33
1	4.76	5	23.81	10	25.64
				23	58.97
				9	23.08
				32	82.05
				7	17.95
				39	100.00
Study C0406					

BEST AVAILABLE COPY

The plasma uric acid (PUA) responder status as a function of the highest antibody titers during Month 3 or 6 for the intend-to-treat (ITT) population is shown in **Table 2**. Of the 212 subjects in the pooled dataset, 191 had antibody data: 75/85 subjects in the pegloticase 8 mg every 2 week group, 75/84 subjects in the pegloticase 8 mg every 4 week group, and 41/43 subjects in the placebo group. There was a significant association between antibody titer and PUA responder status for both pegloticase treatment groups ($p < 0.001$). In the pegloticase 8 mg every 2 week group, none of the 25 subjects with a high anti-pegloticase antibody titer increase were PUA responders; 36 of 50 (72.0%) subjects with no, low, or moderate antipegloticase antibody titer increases were PUA responders. In the pegloticase 8 mg every 4 week group, one of 27 (3.7%) subjects with a high anti-pegloticase antibody titer increase was a PUA responder; 28 of 48 (58.3%) subjects with no, low, or moderate anti-pegloticase antibody titer increases were PUA responders.

Table 2. PUA treatment responses by highest anti-pegloticase antibody titer during Month 3 or 6 (ITT population).

	8 mg Pegloticase		Placebo (N = 43)
	Every 2 Weeks (N = 85)	Every 4 Weeks (N = 84)	
Responders: PUA less than 6 mg/dL for at least 80% of the time in Months 3 and 6 combined			
Anti-Pegloticase Antibody Level	n/N (%)	n/N (%)	n/N (%)
No Increase	7/9 (77.8)	6/7 (85.7)	0/34 (0.0)
Low Increase	19/25 (76.0)	13/24 (54.2)	0/4 (0.0)
Moderate Increase	10/16 (62.5)	9/17 (52.9)	0/3 (0.0)
High Increase	0/25 (0.0)	1/27 (3.7)	0/0 (0.0)
Total Number of Subjects	75	75	41
P-value ¹	<0.001	< 0001	NA

Note: "n" represents the number of subjects that were PUA responders in each anti-pegloticase antibody titer category. "N" within the cells represents the total number of subjects in each anti-pegloticase antibody titer category. NA = Not Applicable.

¹ P-value for test of association between antibody level and responder status using Fisher's exact test.

Source: Page 145 in *MODULE 5 integrated summary of efficacy*.

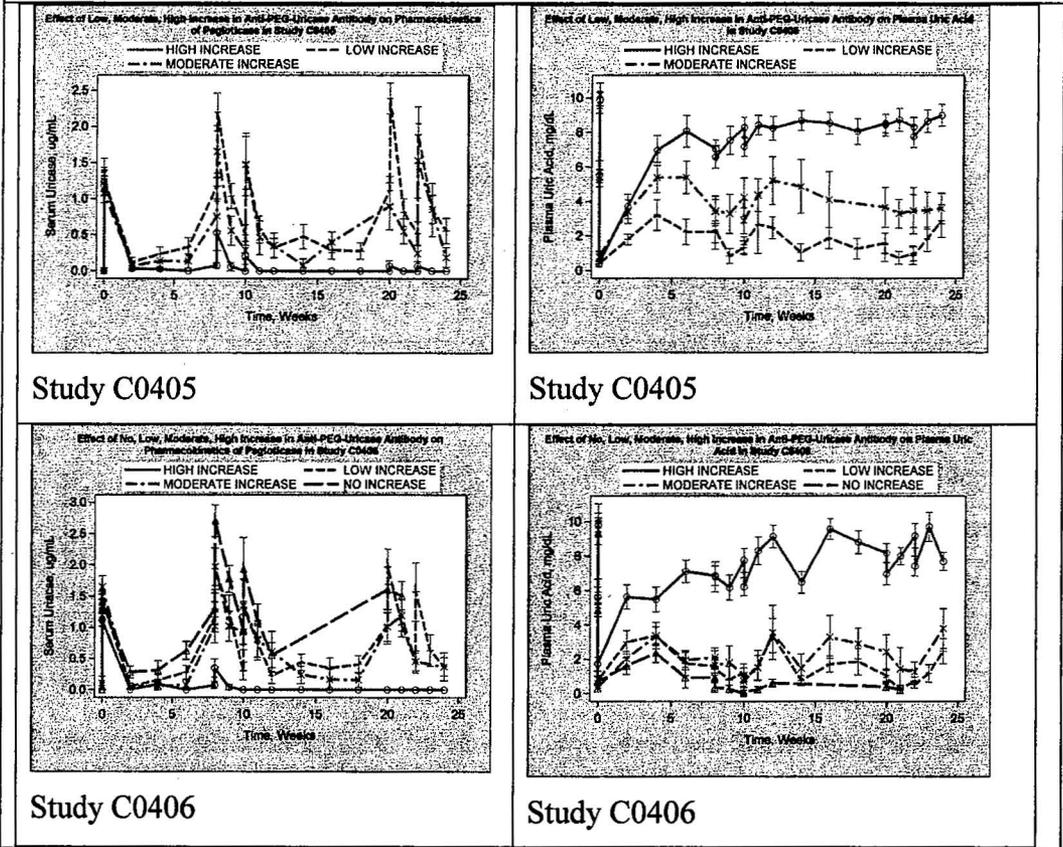
Further analysis showed that in non-responder group in both studies, subjects with high body weight (BMI>30) and being male also appear to have high incidence of high increase in anti-pegloticase antibody, while this trend is not so obvious in the responder group (**Table 3**).

Table 3. Frequency of the anti-pegloticase antibody by responder status, body mass index and sex from studies C0405 and C0406.

Responder	Yes				No			
	F		M		F		M	
	<30	>30	<30	>30	<30	>30	<30	>30
Study C0405								
No increase	0	0	0	0	1	4	6	8
Low increase	2	7	5	7	0	3	3	5
Moderate increase	1	1	6	1	0	1	1	13
High increase	0	0	0	0	0	6	9	15
Study C0406								
No increase	0	1	5	5	1	2	12	5
Low increase	1	3	3	8	0	0	4	7
Moderate increase	1	4	4	3	0	1	4	3
High increase	0	0	1	0	1	2	9	15

The formation of anti-pegloticase antibody appeared to be associated with a decrease in plasma pegloticase level and the loss of effect on plasma uric acid (**Figure 8**).

Figure 8. Mean (\pm SE) changes in plasma concentrations of pegloticase and uric acid in patients who have no, mild, moderate or severe increase in anti-pegloticase antibody during studies C0405 and C0406.



1.1.3 What is the effect of dose/exposure on safety of pegloticase?

The main safety events of interest identified by the Medical Officer (Dr Neuner Rosemarie) were related to cardiovascular. Please refer to her review for more details. In addition to the cardiovascular safety events, it was also shown that administration of 8 mg pegloticase every 4 weeks resulted in more infusion related reactions in comparison to 8 mg every 2 weeks. Please refer to Dr Neuner Rosemarie's review for more details.

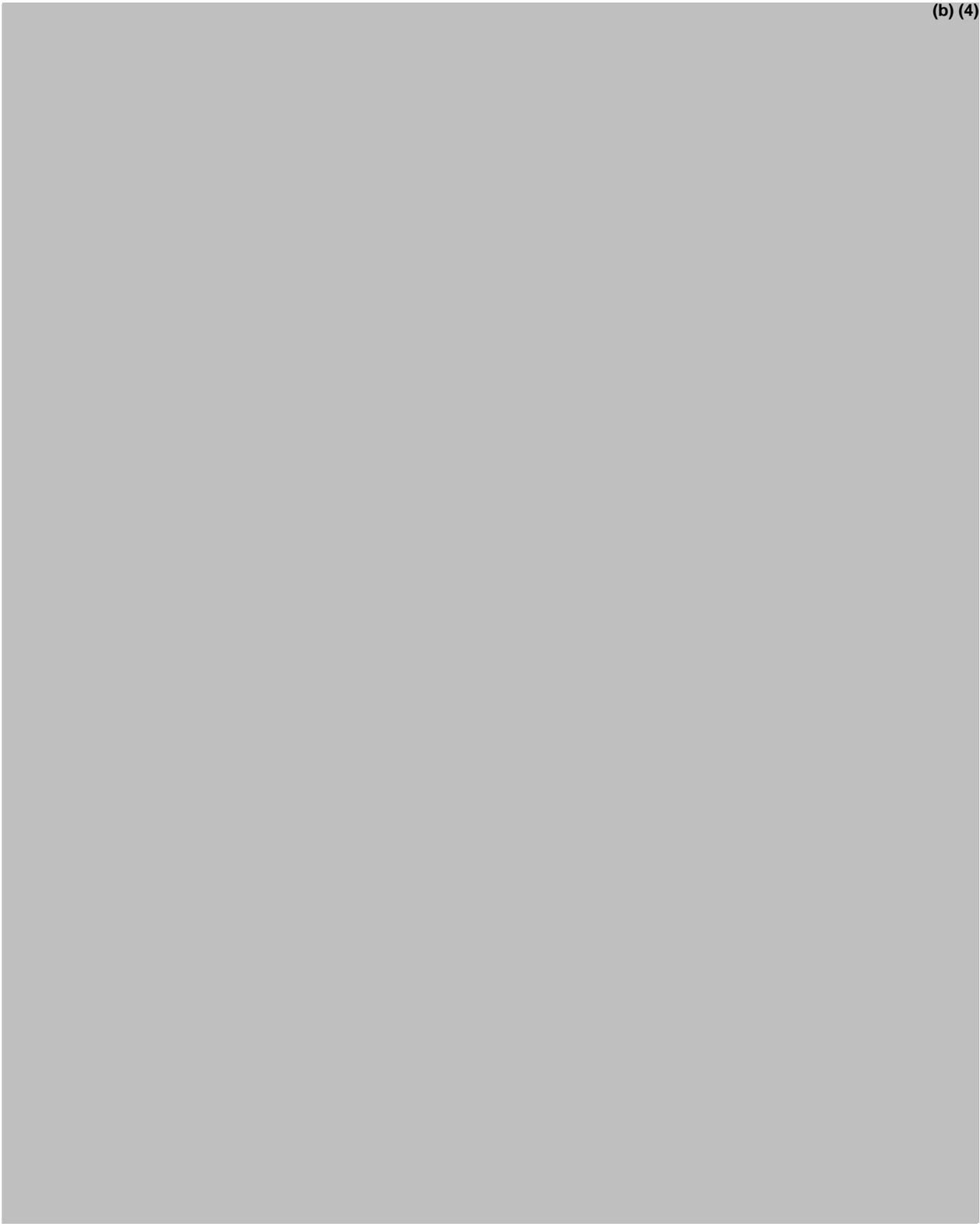
1.2 Recommendations

None.

1.3 Labeling Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

(b) (4)



1 Page has been Withheld in Full immediately following this page as B4 (CCI/TS)

2 PERTINENT REGULATORY BACKGROUND

Pegloticase is a bio-uricolytic agent indicated for treatment failure gout (TFG) to control hyperuricemia and to manage the signs and symptoms of gout. Treatment failure gout is gout in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with conventional urate-lowering therapy at the maximum medically appropriate dose or for whom conventional urate-lowering therapy is contraindicated.

3 RESULTS OF SPONSOR'S ANALYSIS

The key findings from sponsor's population PKPD analysis (study report: aa24807) based on Phase 2 clinical study (c0403) are summarized below:

- A compartment model was developed to simultaneously describe serum concentrations of PEG-uricase and plasma concentrations of uric acid. A one-compartment model with linear elimination best described the PK of PEG-uricase (Pegloticase).
- The PK-PD model included an inhibitory E_{max} effect (as a function of PEG-uricase concentration) resulting in a decrease in uric acid levels with increasing PEG-uricase concentrations.
- Weight was the only significant covariate for the PK parameters CL and V_c. There were no covariates that influenced PD parameters in a significant manner.
- According to this model, PEG-uricase was generally able to suppress uric acid concentrations up to 83%, and maximal suppression was attained at very low serum concentrations of PEG-uricase.
- Based on predictive simulations performed using this model, PEG-uricase given as 2-hour IV infusions every 2 or 4 weeks at 8 mg maintained uric acid levels well below 6 mg/dL. In addition, the long half-life of PEG-uricase supports the use of a less frequent dosing regimen.

Reviewer's comments:

The sponsor analyzed the relationship between concentrations of pegloticase and plasma uric acid levels using various PK/PD models. However, it is the opinion of the reviewer that the model chosen for describing the effect of pegloticase on the plasma uric acid levels is not the right model based on mechanistic reasons. The sponsor described the PK/PD relationship under the assumption that pegloticase suppresses the production of uric acid. However, the mechanism of action of pegloticase indicates that it stimulates the degradation of uric acid.

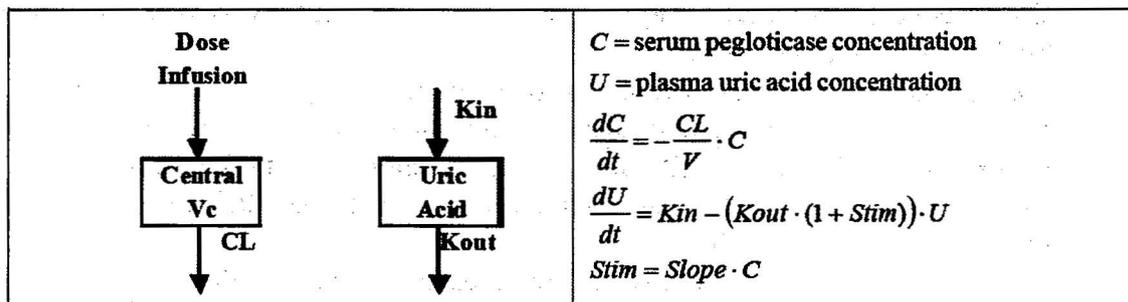
The key findings from sponsor's population PK analysis (study report: aa41382) based on Phase 3 clinical studies (c0405 and c0406) are summarized below:

- A compartmental model was developed to describe serum concentrations of pegloticase. A one compartment model with linear elimination best described the PK of pegloticase.
- Body surface area and overall anti-pegloticase antibody response were the only covariates included for the PK parameters CL and Vc.
- Seroconversion was associated with an increase in CL and Vc.
- The mean half-life for the population of subjects was approximately 221 hours (median value of 217 hours).
- Based on Bayesian estimates, the mean (median) half-life of subjects with no increase in anti-pegloticase antibody levels was approximately 234 hours (median 216 hours) while it was around 220 hours (median 217 hours) in subjects with an increase in anti-pegloticase antibody levels.

Reviewer's comments:

Sponsor's population PK analysis is generally adequate and the significant covariates identified by the sponsor were verified. However, the covariance step in the population PK model was not successful. In addition, the model predicted half-life appeared to be comparable between subjects with no increase in anti-pegloticase antibody levels and an increase in anti-pegloticase antibody levels. This conclusion is contradictory to the results from results from study C0402 as shown in Figure 5.

In sponsor's population PD analysis (study report: aa41382-2 [5.3.4.2 population PD report]), the following model was used.



Vc = Central volume of distribution for pegloticase; CL = Systemic clearance of pegloticase; Kin = rate of uric acid presentation to plasma; Kout = rate of uric acid depletion from plasma; Slope = linear relationship between serum pegloticase and stimulation of Kout; Stim = stimulation of Kout.

The key findings from sponsor's population PD analysis based on Phase 3 clinical studies (c0405 and c0406) are summarized below:

- An indirect response model with linear stimulation of PUA elimination provided the best fit to the data.
- Based on estimated serum pegloticase levels and population PD parameter estimates, PUA elimination could be stimulated up to 2358% of normal endogenous function following the IV administration of pegloticase (4 mg every 2 weeks or 8 mg every 4 weeks).
- The level of stimulation was inversely related to the levels of circulating antibodies to pegloticase. However, even in the subjects with high increases in antibodies to pegloticase, circulating pegloticase elicited a 32% increase in the rate of PUA elimination.

Reviewer's comments:

An indirect response model instead of direct response model was used in sponsor's PD analysis in this report. The use of indirect response model reflects the mechanism of action of pegloticase, i.e., stimulating the degradation of uric acid.

4 REVIEWER'S ANALYSIS

4.1 Introduction

In sponsor's PD analysis, a linear stimulation of the output was used and the nonlinear stimulation in the indirect response model was not being considered as a potential mechanism. In reviewer's analysis, the nonlinear stimulation of the output in the indirect response model was tried and compared with the linear stimulation of the output. In addition, the reviewer also conducted independent analysis on the dose-response and anti-peglyticase antibody-response relationship as shown in section 1.

4.2 Objective

- To assess the proposed labeling claims based on the population pharmacokinetic and population pharmacodynamic analysis.

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table .

Table 3. Analysis Data Set

Study Number	Name	Link to EDR
C0405	Ab.xpt, Adef.xpt, Adlab.xpt, Ae.xpt, Pc.xpt	\\Cbsap58\m\CTD_Submissions\STN125293\0000\m5\datasets\c0405\tabulations
C0406	Ab.xpt, Adef.xpt, Adlab.xpt, Ae.xpt, Pc.xpt	\\Cbsap58\m\CTD_Submissions\STN125293\0000\m5\datasets\c0406\tabulations
aa41382	pk.csv	\\Cbsap58\m\CTD_Submissions\STN125293\0000\m5\datasets\aa41382-1\analysis

4.3.2 Software

SAS 9.1, SAS9.2 (Linux), S-PLUS, NONMEM were used for the reviewer's analyses.

4.3.3 Covariates investigated

In sponsor's population analysis, covariate effects had been extensively investigated, including gender, body mass index, body surface area, and body weight. Only body surface area and anti-peglyticase antibody were shown to be significant covariates for CL and Vc and anti-peglyticase antibody was also found to be a significant PD covariate. These results were reexamined in reviewer's analysis.

4.4 Results

4.4.1 Population Pharmacokinetic Analysis

The listing of base and covariate model development is displayed in the Appendix 1. The parameter estimates and goodness-of-fit graphs for the reviewer's final PK model are presented in Appendices 2 and 3, respectively.

Similar to sponsor's population PK findings, a one-compartment disposition model with first-order absorption and elimination was found to adequately describe the pegloticase concentration-time profiles for the dosing regimens studies (8 mg every 2 weeks and 8 mg every 4 weeks). Body surface area and anti-pegloticase antibody were found to be significant PK covariates (**Figure 9**) consistent with sponsor's findings. A positive relationship was observed between body surface area and the clearance and volume of distribution; as body surface area increased both clearance and volume of distribution increased. The anti-pegloticase antibody increase (APUL =1) was associated with higher volume ($\uparrow 25\%$) and clearance ($\uparrow 32\%$) as compared to antibody no increase (APUL=0). Age, sex, weight, and creatinine clearance were not identified significant PK covariates (**Figure 10**).

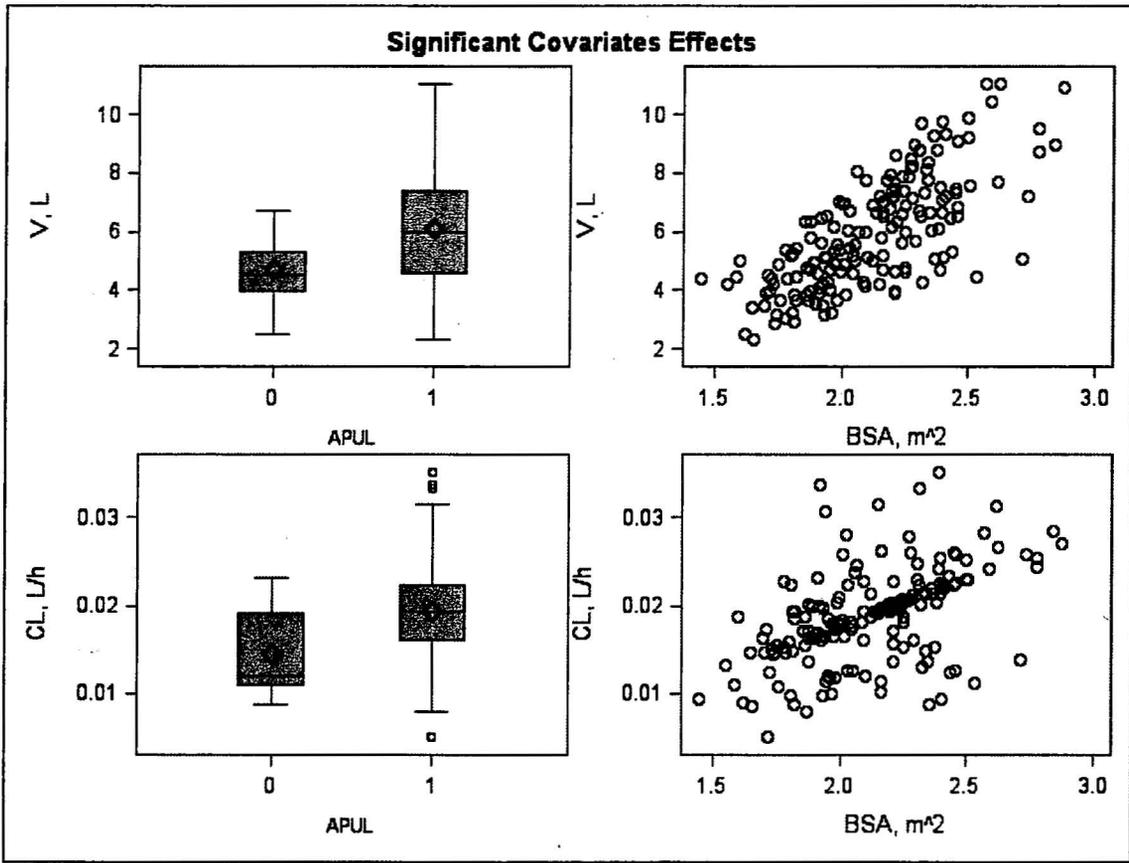
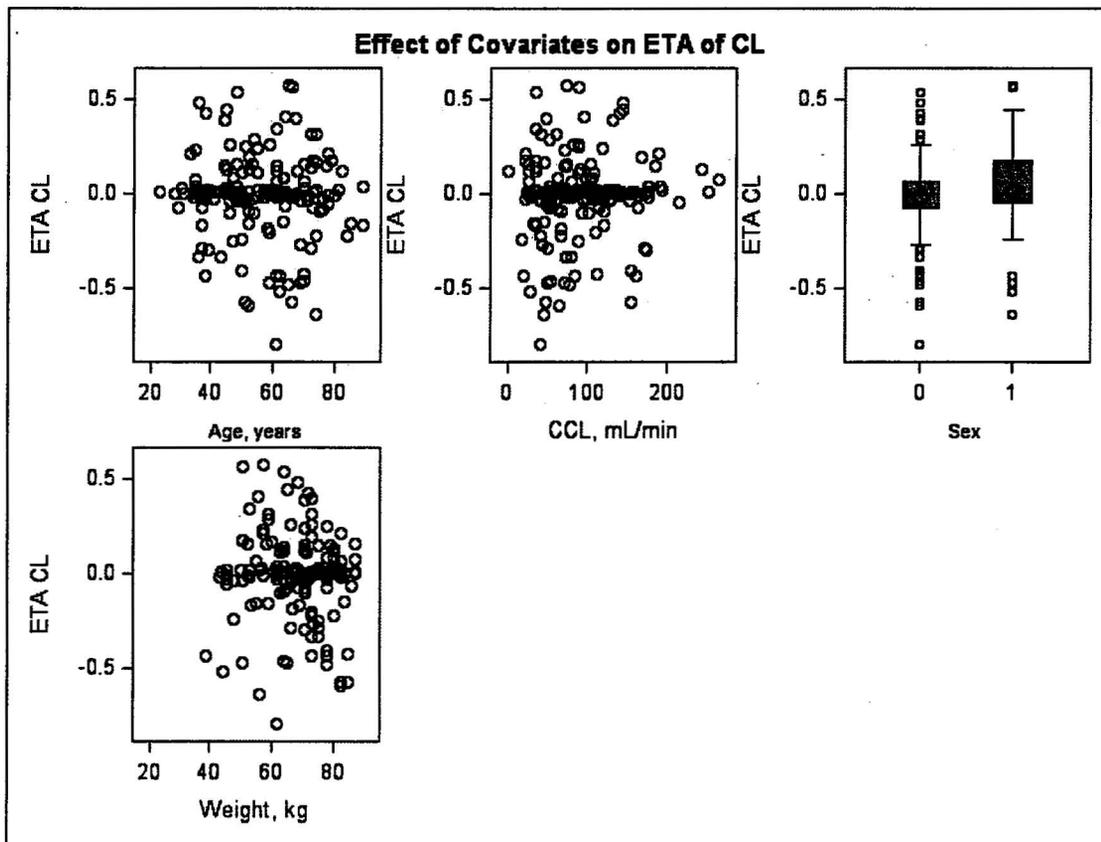


Figure 9. Relationship between anti-pegloticase antibody status (APUL), volume of distribution, clearance and body surface area.



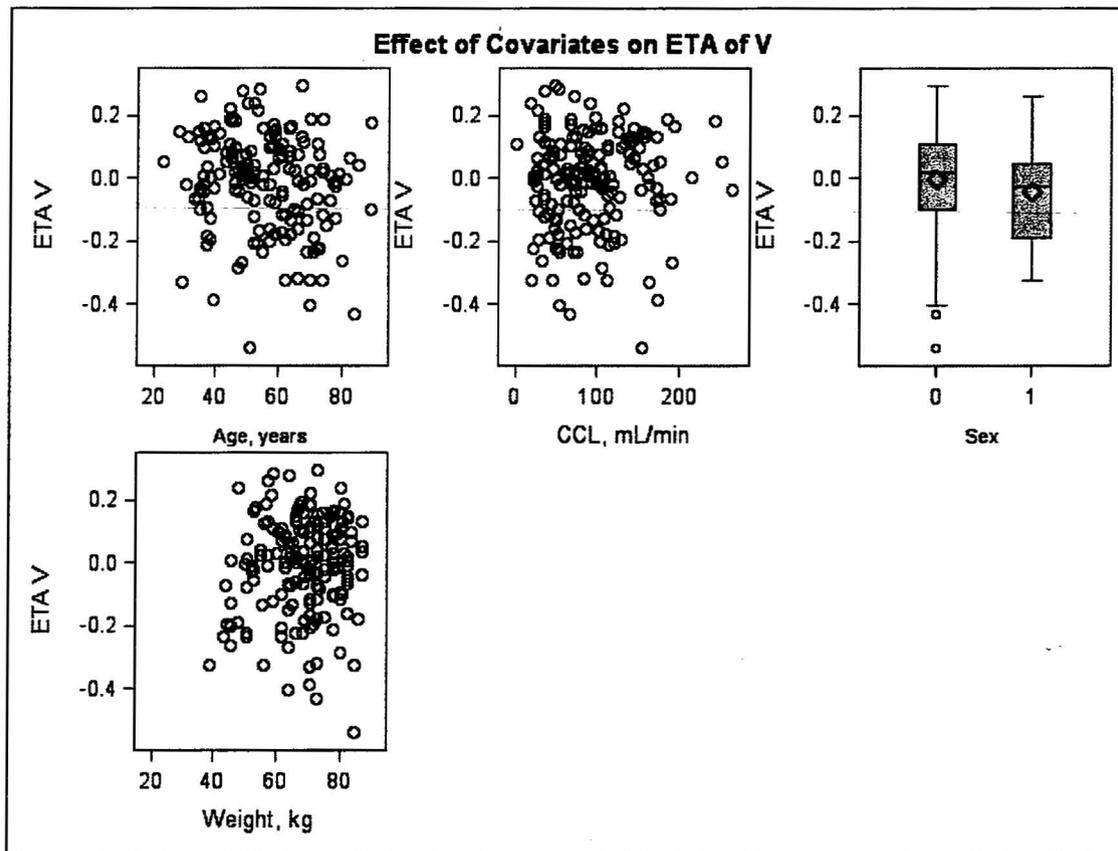


Figure 10. Effects of covariates (age, CCL, sex, and weight) on Eta V and Eta CL.

4.4.2 Population Pharmacodynamic Analysis

The listing of base and covariate model development is displayed in the Appendix 1. The parameter estimates and goodness-of-fit graphs for the reviewer's final pharmacodynamic model are presented in Appendices 4 and 5, respectively. The listing of individual subject observed uric acid level and predicted uric acid level is presented in Appendix 7.

An indirect response model with drug stimulation on kout was found to adequately describe the pegloticase pharmacodynamic effects. In sponsor's PD analysis, a linear stimulation of the output in the indirect response model was used (diagnostic plot shown in Appendix 6). Reviewer also explored the Emax function for the output in the indirect response model. With the Emax function, the OBJ decreased from 10760 to 10697. Although adding anti-pegloticase antibody (APUL) as a covariate in the pharmacodynamic model reduces the OFV significantly, there appears lack of mechanism-based explanation to this reduction. Therefore, anti-pegloticase antibody was not considered as a covariate in the PD model in reviewer's analysis.

APPENDIX 1. LISTING OF ANALYSES FILES AND OUTPUT FILES

Listing of Analyses files and Output Files					
No.	File Name	Output files	Description	OFV	Comments
1	Peg11c0.mod	Peg11c0.lst	1-compt	-252.229	
2	Peg21c0.mod	Peg21c0.lst	2-compt	-252.406	
3	Peg11c1.mod	Peg11c1.lst	Peg11c0.txt with BSA added to CL	-262.042	
4	Peg11c2.mod	Peg11c2.lst	Peg11c0.txt with BSA added to V	-310.685	
5	Final.mod	Final.lst	Antibody added to both CL and V	-353.592	Covariance step successful
6	Finals.mod	Finals.lst	Sponsor's final model, laplacian	-646.758	Covariance step stopped
7	Peg11c3.mod	Peg11c3.lst	Peg11c0.mod with BSA to both CL and V	-317.432	
8	Peg11c4.mod	Peg11c4.lst	Peg11c3.mod with AB added to CL	-330.566	
9	Peg11c5.mod	Peg11c5.lst	Peg11c3.mod with AB added to V	-318.793	
10	Peg11c6.mod	Peg11c6.lst	Peg11c3.mod with AB added to V (reduced AB category)	-317.432	
11	Peg11c7.mod	Peg11c7.lst	Peg11c3.mod with AB added to CL (reduce AB category)	-317.432	
12	Peg11c8.mod	Peg11c8.lst	Peg11c8.mod CL and V correlate	-344.075	
13	run736.mod	run736.lst	Sponsor's final model	10584.823	
14	runR1.mod	runR1.lst	Emax on stimu	10696.662	Reviewer's final model
15	run709.mod	run709.lst	Linear on stimu	10759.752	
16	runR8.mod	runR8.lst	add APUL on EC50	10529.926	Terminated
17	Final_1.mod	Final_1.lst	Remove exponent factor on CL in Final.mod	-353.592	Covariance step successful

APPENDIX 2. MODEL PARAMETER ESTIMATES FOR THE FINAL PHARMACOKINETIC MODEL (FINAL_1.MOD)

Model Parameter Estimates for the Final Covariate Pharmacokinetic Model				
Parameter	θ	Estimate	RSE%	BSV%
V if APUL=0 (L)	$\theta 1$	5.02	6.8	19.3
CL if APUL=0 (L/h)	$\theta 2$	0.0128	9.7	39.5
Exponential factor on BSA for V	$\theta 3$	1.44	13.5	--
V if APUL>0 (L)	$\theta 4$	5.79	2.6	19.3
CL if APUL>0 (L/h)	$\theta 5$	0.0161	5.1	39.5
Residual additive error	-	0.0867	31	-
Residual proportional error	-	0.037	40	-

The final PK model was a one compartment model with linear elimination.

APPENDIX 3. SCATTER PLOTS OF GOODNESS OF FIT OF FINAL PHARMACOKINETIC MODEL.

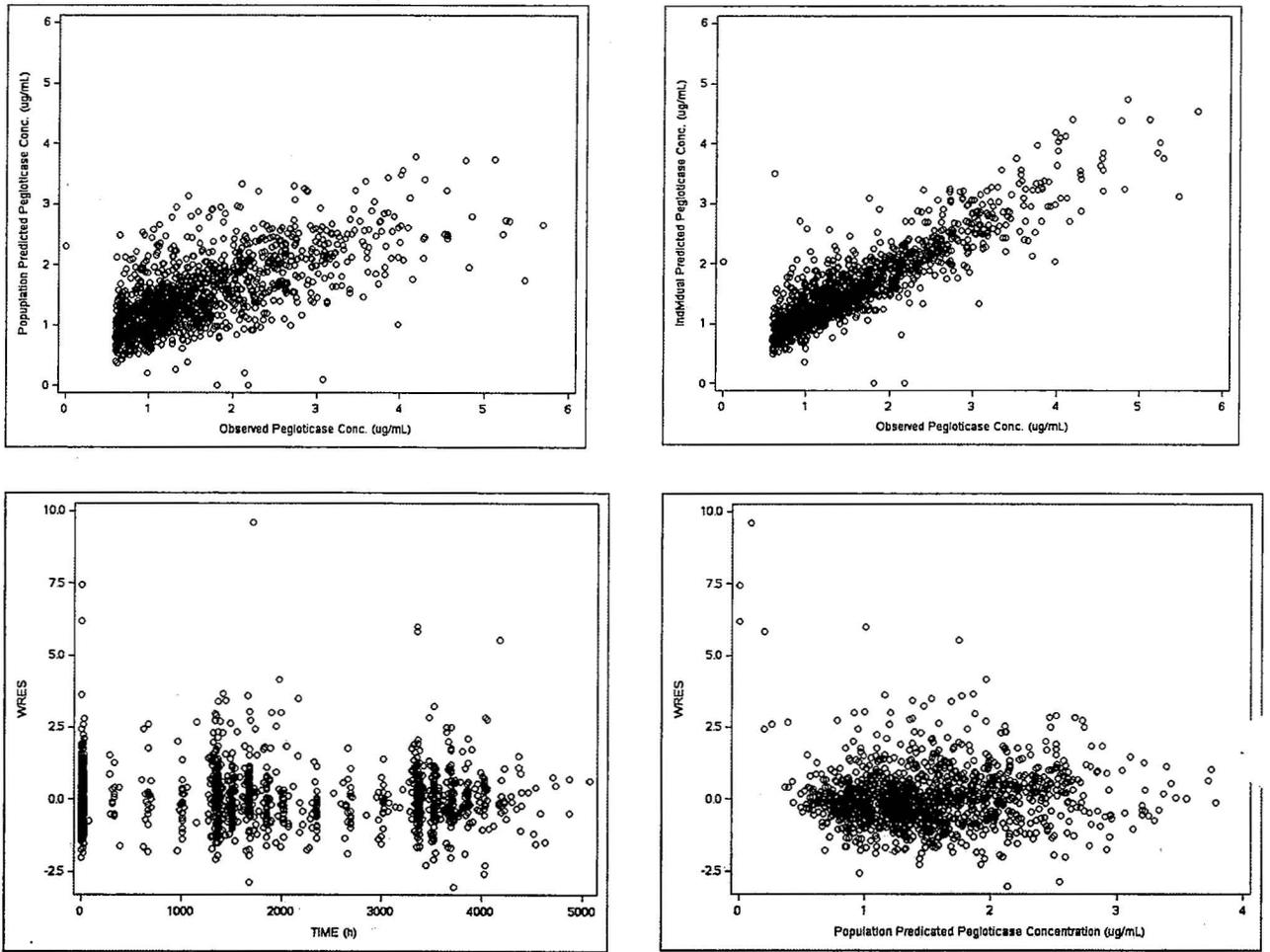


Figure 11. Scatter plots of goodness of fit of final pk model (final_1.mod)

APPENDIX 4. MODEL PARAMETER ESTIMATES FOR THE FINAL PHARMACODYNAMIC MODEL (RUNR1.MOD)

Model Parameter Estimates for the Final Covariate Pharmacodynamic Model				
Parameter	θ	Estimate	RSE%	BSV%
Kin (ug/mL/h)	θ_1	0.423	0.27	1.72
Kout (1/h)	θ_2	0.0461	0.39	12.4
Emax (-)	θ_3	10.4	0.13	-
EC50 (ug/mL)	θ_4	16.4	0.44	248.5
Residual variability		7.67		

The final model was an indirect response model with stimulation effect on the output

APPENDIX 5. SCATTER PLOTS OF GOODNESS OF FIT OF THE REVIEWER'S FINAL PHARMACODYNAMIC MODEL.

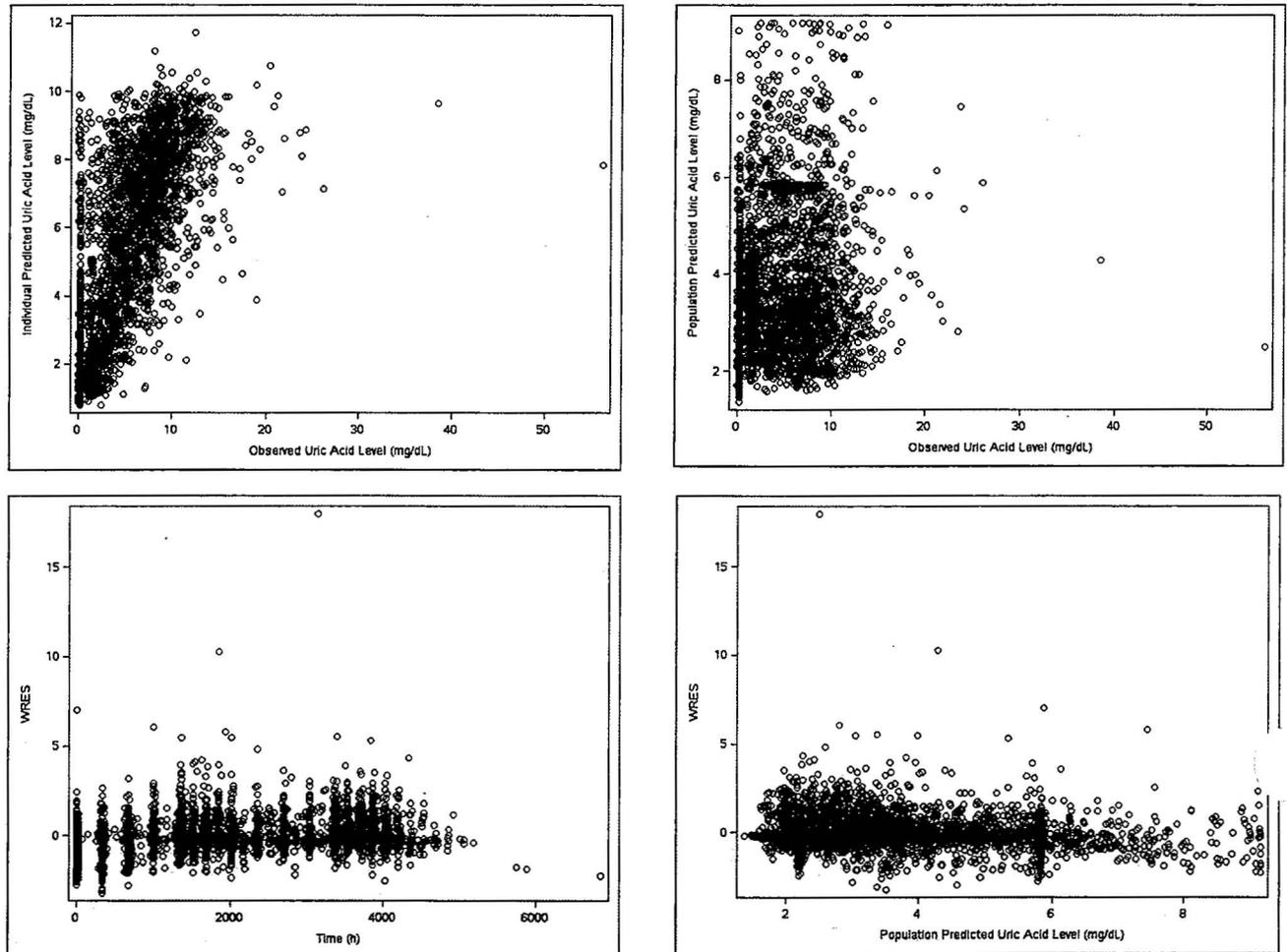


Figure 12. Scatter plots of goodness of fit of final PD model (runR1.mod).

APPENDIX 6. SCATTER PLOTS OF GOODNESS OF FIT OF SPONSOR'S PHARMACODYNAMIC MODEL RUN709.MOD.

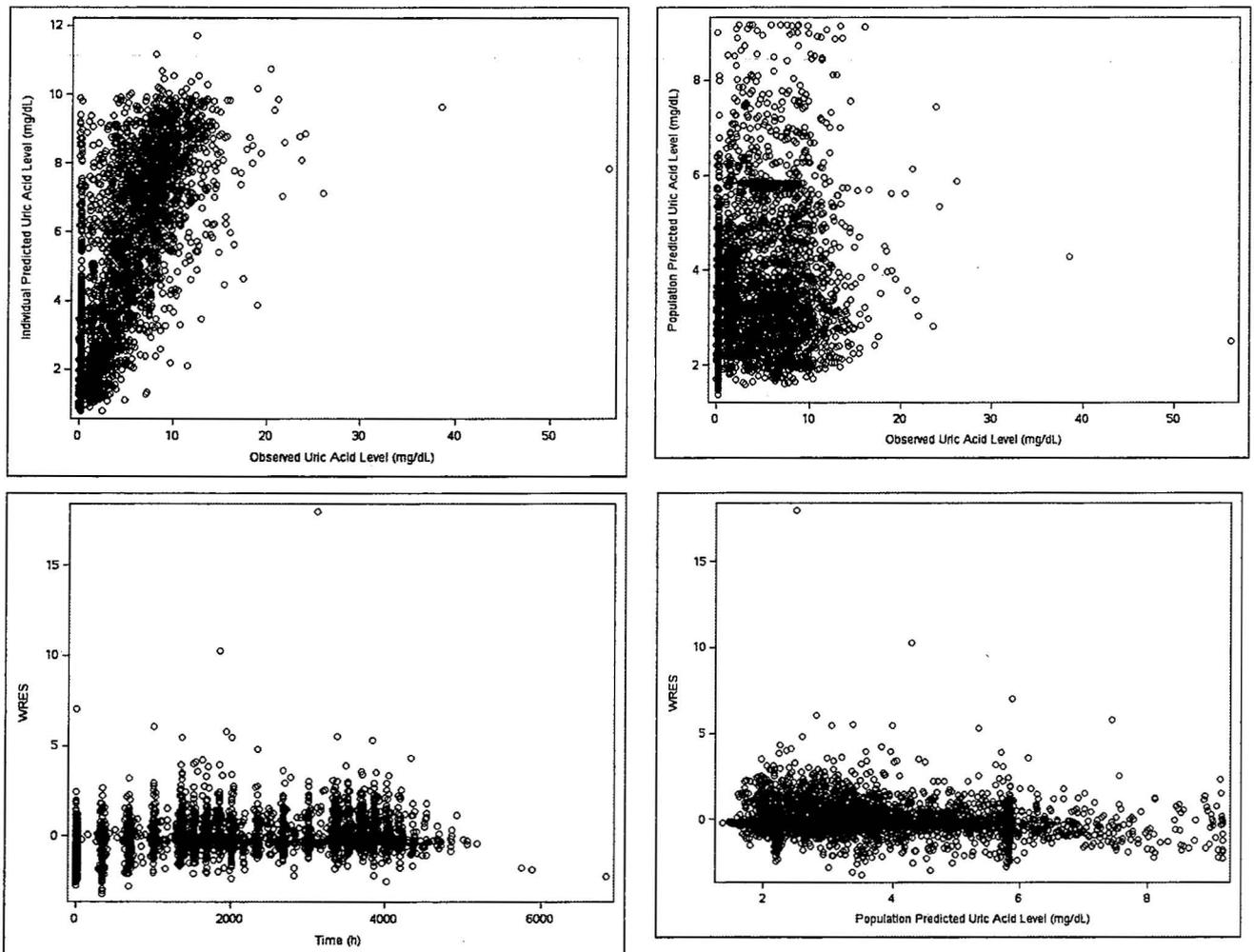


Figure 13. Scatter plots of goodness of fit of sponsor's model run709.mod.

4.4 Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology				
New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA/BLA Number	125293		Brand Name	██████
OCP Division (I, II, III, IV, V)	II		Generic Name	Pegloticase
Medical Division	DAARP		Drug Class	Biologic
OCP Reviewer	Ping Ji		Indication(s)	Gout
OCP Team Leader	Doddapaneni, Suresh		Dosage Form	Liquid
Pharmacometrics Reviewer			Dosing Regimen	8 mg every 2 or 4 wks
Date of Submission	Oct 31, 2008		Route of Administration	IV infusion
Estimated Due Date of OCP Review			Sponsor	Savient Pharmaceuticals, Inc
Medical Division Due Date			Priority Classification	P
PDUFA Due Date	April 30, 2009			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	x			
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	20	8	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				

Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
Patients-				
single dose:	x	1	1	
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	x	1	1	
Phase 3:	x	2	2	
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	x	2	2	
Data sparse:	x	2	2	
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				

traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		28	16	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					

Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? y_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Please provide the complete datasets and control streams for PPK/PD analysis

All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

Reviewing Clinical Pharmacologist

Date

Team Leader/Supervisor

Date

**APPEARS THIS WAY ON
ORIGINAL**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA/BLA Number	125293		Brand Name	TBD
OCP Division (I, II, III, IV, V)	II		Generic Name	Pegloticase
Medical Division	DAARP		Drug Class	bio-uricolytic agent
OCP Reviewer	Ping Ji		Indication(s)	treatment failure gout (TFG)
OCP Team Leader	Doddapaneni, Suresh		Dosage Form	Liquid
Pharmacometrics Reviewer	Bhattaram Atul		Dosing Regimen	8 mg every 2 or 4 wks
Date of Submission	Oct 31, 2008		Route of Administration	IV infusion
Estimated Due Date of OCP Review	March 15, 2009		Sponsor	Savient Pharmaceuticals, Inc
Medical Division Due Date			Priority Classification	P
PDUFA Due Date	April 30, 2009			
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	█			
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	2	2	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Patients-				
single dose:	x	1	1	
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	x	1	1	
Phase 3:	x	2	2	
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	x	2	2	
Data sparse:	x	1	1	
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		9	9	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On initial review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	
----	---	--	--	---	--

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

y_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None

Ping Ji



Dec 11, 08

Reviewing Clinical Pharmacologist

Date



12-16/08

Team Leader/Supervisor

Date