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APPLICATION NUMBER:

125359Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

BLA 125359/0 Erwinaze®
Cross-Discipline Team Leader Review

Date	November 07, 2011 11/07/2011
From	Suzanne G. Demko
Subject	Cross-Discipline Team Leader Review
BLA # **Supplement#**	125359 0
Applicant	EUSA Pharma (USA), Inc.
Date of Submission	November 1, 2010
PDUFA Goal Date	May 1, 2011 *After major amendment submission:* August 2, 2011 *After September 16, 2011 submission of efficacy analysis:* November 21, 2011
Proprietary Name / Established names (FDA assigned)	Erwinaze®/ asparaginase *Erwinia chrysanthemi*
Dosage forms / Strength	10,000 International Units/vial lyophilisate for reconstitution
Proposed Indication(s)	Component of a multi-agent chemotherapeutic regimen for treatment of ALL in patients who develop allergic reaction (b) (4)
Recommended:	Approval

1. Introduction

An original Biologic License Application (BLA) for asparaginase *Erwinia chrysanthemi* (Erwinaze®) was submitted under STN 125359/0 as a rolling BLA with the initial unit submitted in September, 2010 and the final unit submitted on November 1, 2010. The application was given a priority review status with a PDUFA date of May 1, 2011. On February 28, 2011, a major amendment was submitted to the application which triggered an extension of the review clock with a revised PDUFA date of August 2, 2011. A Division of Scientific Investigations (DSI) audit of the laboratory that had analyzed the clinical samples supporting the claim of effectiveness for this application took place from (b) (4) The inspection findings included a comprehensive list of deficiencies identified in the application. These were conveyed to the applicant on April 7, 2011. The applicant responded to the inspectional findings on April 27, 2011, then met with FDA on June 23, 2011, at which time they were informed that the results obtained for the primary endpoint would not be acceptable to support an approval for Erwinaze because of the inspectional findings by DSI. FDA also informed the applicant that they were willing to explore another way forward for this application. Subsequently, during a telephone conference on July 12, 2011, FDA agreed with the applicant's proposal to test samples that had been frozen and stored for future antibody analysis to confirm the effectiveness of Erwinaze. The samples had been taken at

trough time points consistent with the asparaginase primary and secondary endpoints. Identified were 35 patients with 48 hour trough levels and 13 patients with 72 hour trough levels for determination of asparaginase activity levels and it was proposed that an independent laboratory experienced in running asparaginase activity assays would perform an analysis of the samples after a full validation study of the assay methods were conducted. The assay methods were validated, the samples were analyzed and a report of the analysis was submitted to the BLA on September 16, 2011.

A list of the CMC deficiencies was sent to the applicant on July 11, 2011. The applicant responded to all CMC deficiencies by August 31, 2011. In addition, during the period July through September, 2011, the CMC primary review teams for drug substance and drug product were in communication with the applicant to convey a number of additional deficiencies in the application which were also resolved.

Both of the sets of results analyzed in support of the finding of effectiveness submitted for this application were from one clinical trial, Study AALL07P2, entitled, "Pharmacology and Toxicity of Erwinia L-asparginase (Erwinaze; Crisantaspase) Following Allergy to Pegaspargase in Treatment of Children with Acute Lymphoblastic Leukemia (ALL). Study AALL07P2 was an open label trial conducted at 31 Children's Oncology Group (COG) institutions. The study was designed to assess the PK, PD, and related toxicities of asparaginase *Erwinia chrysanthemi* when used as replacement therapy for pegaspargase dosing. The indication proposed by the applicant is: "ERWINAZE (asparaginase *Erwinia chrysanthemi*) is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to (b) (4) *E. coli* derived asparaginase." Also under the Erwinaze IND, a compassionate use protocol, the Erwinaze Master Treatment Protocol (EMTP), was conducted to enable US patients to receive Erwinaze outside of the COG AALL07P2 PK/PD study. The results from the EMTP were submitted in support of the safety of Erwinaze.

Asparaginase *Erwinia chrysanthemi* has been available in the United States (US) since 1968 under IND 290 originally held by Ipsen Ltd. On February 10, 2006 Ipsen Ltd transferred all rights and responsibilities of IND 290 to Orphan Pharmaceuticals International (OPi) SA (subsequently EUSA Pharma (US)). Asparaginase *Erwinia chrysanthemi* (Crisantaspase, Erwinaze) is approved in some countries in Europe and in Canada.

L-asparaginase has been a component of multi-agent chemotherapy for childhood ALL for many years. Efficacy has been demonstrated by achieved remissions in both the induction and consolidation phases of therapy. In the US, there are 2 asparaginase preparations approved by the FDA and available for clinical use, native *E. coli* (Elspar®), and pegaspargase (Oncaspar®), a pegylated form of the *E. coli* enzyme. Asparaginase *Erwinia chrysanthemi* has never been commercially available in the United States. Prior to 2002, asparaginase *Erwinia chrysanthemi* was available to patients with hypersensitivity to the *E. coli* derived preparations on a named patient basis. The product was removed from the worldwide market in 2003 because of manufacturing difficulties; however, in 2004, the manufacturing issues were resolved and Erwinaze was again available.

The review cycle for this application has been extended and the PDUFA action date was missed intentionally in order to accommodate the applicant and allow them to rectify the application's deficiencies during the initial review cycle. Each review discipline performed and submitted an original primary review addressing the application as originally filed on November 1, 2010, and amended on February 28, 2011. Based on the results of a Division of Scientific Investigations (DSI) audit of the laboratory responsible for the endpoint analysis for Study AALL07P2, and the issues arising from the CMC reviews of both drug substance and drug product, the majority of the review disciplines involved with this application as deemed completely filed on November 1, 2010 agreed that the data upon which the determination of efficacy was based were flawed and they could not be relied upon to determine that Erwinaze is an effective product for the indication sought. In addition, in order for the application to be approved, the CMC issues would have to be resolved to FDA's satisfaction. The only caveat to this determination was the safety review. In the opinion of Dr. Dinndorf, the primary clinical reviewer, the safety data reviewed from the original application were adequate to support approval for Erwinaze if adequate additional data was submitted to support the effectiveness of the product, and all CMC issues were resolved. The Clinical, Clinical Pharmacology, and CMC review teams also reviewed a number of other amendments to the application submitted by the applicant in response to communications from FDA regarding the application's deficiencies. For each of these disciplines, addenda were submitted to the original reviews.

2. Background

The information in this section was derived from the review of Dr. Patricia Dinndorf, Division of Biologic Oncology Products as well as the applicant's submission. Revisions were made for the purposes of this review.

Asparaginase *Erwinia chrysanthemi* (Erwinaze), contains the (b) (4) enzyme L-asparagine amidohydrolase (L-asparaginase) derived in (b) (4) (b) (4) from the plant pathogen *Erwinia chrysanthemi* (nee carotovora). The enzyme can also be isolated from a variety of other sources (yeast, animal cells, and fungi). The molecular weight of Erwinaze is about 135,000 daltons and it is composed of four subunits (tetramers), each subunit having a molecular weight of about 35,000 daltons. Asparaginase *Erwinia chrysanthemi* is freely soluble in (b) (4) Its activity is expressed in terms of International Units (IU) according to the rules of the International Union of Biochemistry. The specific activity of the enzyme is at least (b) (4) (b) (4) of protein.

Asparaginase enzymes are an important component in the treatment of childhood ALL. L-asparaginase (Elspar®) an agent derived from *Escherichia coli* was the first agent approved for this indication in 1994. Asparaginase is an enzyme that catalyzes the hydrolysis of asparagine to aspartic acid. The mechanism of action of asparaginase in the treatment of ALL is thought to be based on the inability of leukemia cells to make asparagine due to lack of asparagine synthetase activity. The lymphoid leukemic cells depend on an exogenous source of the amino acid asparagine for their protein metabolism and survival. Hydrolysis of circulating asparagine deprives leukemic cells of this amino acid and results in cell death.

The use of *E. coli* L-asparaginase is limited due to the incidence of allergic reactions. Clinical studies suggest that the prognosis of children with ALL who do not receive a full course of

scheduled asparaginase treatment due to allergic reactions is inferior to that of children who are able to receive the full intended treatment course.

Pegaspargase (Oncaspar®), a pegylated formulation of *E. coli* L-asparaginase, was initially approved in 1994 for patients with ALL who require L-asparaginase in their treatment regimen, but have developed hypersensitivity to the native forms of L-asparaginase. In 2006, pegaspargase was approved as a component of a multi-agent chemotherapeutic regimen for the first line treatment of patients with ALL. Confirmation of clinical benefit was based on a comparison of serum asparagine depletion, asparaginase activity, and immunogenicity of pegaspargase and native *E. coli* L-asparaginase. The trial was not adequately designed or conducted to evaluate superiority or non-inferiority of event free survival (EFS) or survival, but there did not appear the be erosion of EFS of patients treated with pegaspargase compared to patients treated with *E. coli* L asparaginase. A compelling supporting factor in the approval of Oncaspar in first line treatment of ALL is the dosing schedule. A single intramuscular injection of pegaspargase can be substituted for 6 to 9 intramuscular injections of native *E. coli* L-asparaginase. Intramuscular injections are a traumatic component of ALL therapy for children.

Asparaginase *Erwinia chrysanthemi* (Crisantaspase, Erwinaze can be tolerated in patients who have developed hypersensitivity or allergic reactions to *E. coli* derived asparaginase. Asparaginase *Erwinia chrysanthemi* is expected to contribute to the overall success of ALL therapy by allowing patients who develop hypersensitivity/allergic reactions to *E. coli* derived L-asparaginase to continue to receive an asparagine depleting agent as a part of their ALL therapy.

There are no related drugs that can be administered to patients who become allergic to pegaspargase. Pegaspargase can be given to patients who develop allergic reactions to native *E. coli* asparaginase, but in current clinical practice most patients receive initial therapy with pegaspargase.

The table below, copied from Dr. Dinndorf's primary clinical review and updated for this review, summarizes the regulatory history of the Erwinaze application.

Regulatory History

Date /Milestone	Submission/Summary of Issues
Apr 1968/IND 290 submitted	Ipsen Ltd. original sponsor
Feb 2006 /IND 290 transferred	IND 290 was transferred from Ipsen Ltd. to OPi SA (OPi)
May 2006 /Pre- BLA meeting	▪ OPi proposed (b) (4) [redacted] ▪ FDA did not agree because it would be necessary to demonstrate comparability of currently manufactured product to that used in published studies. ▪ FDA suggested a limited (50 patient) pharmacodynamics (PD) trial in patients hypersensitive to pegaspargase to determine a dose and

Date /Milestone	Submission/Summary of Issues
	schedule of *Erwinia* L-asparginase that results in depletion of asparagine to a degree similar to that provided by the labeled dose of pegaspargase in non-hypersensitive patients. Information would also be required on *Erwinia* L-asparginase PK and immunogenicity.
Aug 2007/Change sponsor	OPi acquired by EUSA Pharma (US) Inc. (EUSA)
Mar 2008 /Partial clinical hold	Proposed clinical trial AALL07P2, to support license approval, did not include a validated method to collect clinical samples to measure asparagine levels.
Jul 2008 /Remove clinical hold	FDA acknowledged EUSA's submission documenting their diligent attempt to develop a validated collection method to obtain samples to measure asparagine levels. The results of asparagine assays are inherently unreliable due to the inability to control for *ex vivo* metabolism. FDA agreed that asparaginase activity, which can be reliably measured, could serve as the primary PK study endpoint. Asparaginase activity is directly related to asparagine depletion.
Sep 2009 /Pre- BLA meeting	EUSA requested a pre-BLA Meeting ▪ EUSA planned to institute a data lock when 50 patients completed the primary endpoint assessments of AALL07P2 the trial conducted to confirm efficacy and safety of *Erwinia* L-asparginase. ▪ EUSA planned to include a synopsis of the Erwinaze Master Treatment Protocol (EMTP) that collected additional safety data. ▪ FDA informed EUSA that the application must contain an integrated summary of safety (ISS).
Oct 2009/Proprietary name request	FDA Division of Medication Error Prevention and Analysis rejected the proposed proprietary name of (b) (4) [redacted] (b) (4)
May 2009/ Proprietary name request	The proprietary name Erwinaze was granted 11/10/10
Jun 2010 /Fast Track request	Fast track status granted 7/15/10
Sep 2010 /Rolling BLA	Submitted
Nov 1, 2010 /Final CMC unit	Priority review status granted; PDUFA final action date May 3, 2011
Feb 28, 2011/Major amendment	PDUFA final action date revised to August 2, 2011
June 23, 2011/Meeting	FDA Requested Meeting ▪ Applicant informed FDA of the strong possibility for discontinuation of the Erwinaze treatment protocol should this application receive an action of CR ▪ Applicant believes that all CMC issues can be rectified as

Date /Milestone	Submission/Summary of Issues
	postmarketing commitments ▪ Applicant believes that asparagine assay is a loss and cannot be rectified ▪ Applicant believes that asparaginase assay is reliable ▪ FDA informed applicant that since there were issues with the controls for the asparaginase assay, the data submitted to support the efficacy claim are not reliable ▪ There will be additional communication between FDA and the sponsor to clarify the issues remaining and suggest a way forward for this application
July 12, 2011/Teleconference	CMC deficiencies communicated to applicant. Applicant's proposal for testing of new samples agreed upon
July 22, 2011	Applicant's response to CMC deficiencies submitted
August 5, 2011/Teleconference	CMC Deficiencies resolved, data and information submissions agreed
September 16, 2011	Analysis of new samples submitted to support efficacy claims

3. CMC/Device

The information in this section was derived from the reviews of Drs. Cristina Ausin-Moreno, Jacek Cieslak, and Nikolay Spiridonov, Division of Therapeutic Proteins, Office of Biologic Products, and Anastasia Lolas, M.S. and Dr. Mary Farbman, Office of Compliance, Division of Manufacturing and Product Quality, Manufacturing Assessment and Pre-Approval Compliance Branch. Revisions were made for the purposes of this review.

The application as originally filed was not acceptable for approval as a result of deficiencies identified and remaining after the initial primary CMC review had been completed. Specifically, deficiencies remained in the drug substance (DS) and drug product (DP) manufacturing processes, in DS and DP microbial control, CMC sterility assurance. and microbiology product quality. The CMC review team communicated a comprehensive list of deficiencies to the applicant on July 12, 2011. FDA received a response from the applicant on July 22, 2011 to all CMC questions, and a request for a meeting. The meeting (teleconference) took place on August 5, 2011 and a plan for resolution of all CMC issues was agreed upon during the meeting. It was established that the applicant would submit additional material for review in 2 portions, by the end of September and the end of October, 2011. The bulk of the required data and information was submitted in September, 2011. In addition during the meeting, FDA requested additional stability data, this data was submitted on August 31, 2011. Based on their review of all CMC data submitted to support this application to date, the CMC review teams recommend that the Biologic License Application for Erwinaze be approved with PMCs noted later in this review. I concur with their recommendation.

Facilities Review/Inspection

A single facility, the (b) (4) manufactures drug substance and drug product. This facility was inspected (b) (4) by BMT and OBP. There were 17 Form FDA 483 observations and the initial recommendation

was VAI – non-concur approval for the BLA until identified issues were resolved. (b) (4) (b) (4) conducted sterility testing of the drug product. The testing site is under the surveillance program and was inspected in early (b) (4) (b) (4) The previous inspection was conducted in (b) (4). (b) (4) (b) (4) performs labeling, packaging and distribution of the drug product and was inspected by the field on (b) (4) Initial classification was VAI-acceptable. However, there were 9 Form 483 observations.

Erwinaze is an approved drug product in the UK with the name Crisantaspase. Approval was granted in 1985. Development of the manufacturing process began in 1968. The drug product is also marketed in several other countries. However, there were deficiencies that initially precluded approval of this BLA from a product quality and sterility assurance perspective.

All facilities inspection issues were addressed during the review cycle and the current recommendation for this BLA is approval.

4. Nonclinical Pharmacology/Toxicology

The information in this section was derived from the review of Dr. Dubravka Kufrin, Division of Biologic Oncology Products. Revisions were made for the purposes of this review.

The nonclinical studies submitted for the Erwinaze application predated GLP regulations. The original IND submission for Erwinaze took place in 1968 under IND 290. The Erwinaze nonclinical program consisted of a review of previously conducted toxicology studies on *Erwinia sp* asparaginases, generally from the 1960's and 1970's, combined with a review of the open literature on *Erwinia sp* asparaginase studies. FDA's nonclinical pharmacology/toxicology review consisted of a review of these studies. It is the recommendation of the nonclinical primary reviewer that this application be approved with PMRs noted later in this review. I concur with this recommendation.

Acute toxicity of *Erwinia sp.* was assessed in six animal studies, with the maximum nonlethal doses administered between 100,000 and 200,000 IU/kg. Maximum lethal doses were between 200, 000 and 500, 000 IU/kg. Lower tolerance rates were seen in rabbit studies, where maximum nonlethal dose was 1 000 IU/kg while the minimum lethal dose was ~2 000 IU/kg. Subdural hemorrhages were observed in some early deceased rabbits, although the true cause of death was not elucidated. In the acute studies done in both species, rodents and rabbits, muscle weakness and ataxia were observed in early animal deaths.

Rabbit, dog and monkeys repeat dose studies could not establish a dose response relationship, since three of the studies used only one dose. One rabbit that received 1 000 IU/kg died 12 days post dosing, of uncertain causes, while the rest of four identically treated rabbits were well tolerated the studied experience.

The single and repeat dose studies submitted with the application were conducted using a peritoneal or venous injection route which differs from the intramuscular route used for clinical development.

Teratogenicity, effects on fertility, and juvenile reproductive studies have not been submitted with this BLA. The applicant has been informed that the full range of reproductive-toxicity studies will be a post approval requirement. Carcinogenicity and mutagenicity studies have not been requested as per ISH S9 and ISH S6 guidelines.

5. Clinical Pharmacology/Biopharmaceutics

The majority of information in this section is an excerpt from the review of Dr. Jun Yang, Office of Clinical Pharmacology, Division of Clinical Pharmacology V. Revisions were made for the purposes of this review.

There were two sets of results analyzed in support of the finding of effectiveness submitted for this application. Both were from one clinical trial, Study AALL07P2, entitled, "Pharmacology and Toxicity of Erwinia L-asparginase (Erwinaze; Crisantaspase) Following Allergy to Pegaspargase in Treatment of Children with Acute Lymphoblastic Leukemia (ALL). Study AALL07P2 was an open label trial conducted at 31 Children's Oncology Group (COG) institutions. The study was designed to assess the PK, PD, and related toxicities of asparaginase *Erwinia chrysanthemi* when used as replacement therapy for pegaspargase dosing. The indication proposed by the applicant is: "ERWINAZE (asparaginase *Erwinia chrysanthemi*) is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to (b) (4) *E. coli* derived asparaginase." The endpoint intended to demonstrate the clinical benefit of the trial was a 48-hour trough L-asparaginase activity level of ≥0.1 IU/mL in patients with pegaspargase allergy. The primary and key secondary endpoints of this trial were based on the expected PK and PD parameters for pegaspargase, i.e., adequate depletion of asparagine is achieved with serum L-asparaginase activity levels ≥0.1 IU/mL; and therapeutic depletion of asparagine requires an asparagine concentration ≤3 μM.

As a result of the primary endpoint agreed upon by FDA and the applicant to support a regulatory filing for Erwinaze, i.e., the percent of patients with a 48-hour trough serum asparaginase activity ≥0.1 IU/mL, there is no efficacy data to be reviewed in this application. The clinical pharmacology review of the PK and PD findings is the primary review for this application.

The original clinical samples intended for testing to support the effectiveness of Erwinaze were analyzed by an academic laboratory at the (b) (4) (b) (4) DSI audited the laboratory from (b) (4) FDA's data verification inspection identified major issues and deficiencies with the sample handling and assay performance of the serum asparaginase assay. At a face to face meeting between the FDA and the applicant held on June 23, 2011, FDA informed the applicant that the asparaginase activity results were not acceptable to support the effectiveness of Erwinaze because of the inspection findings. Subsequently, FDA agreed with the Sponsor's proposal to use frozen immunogenicity samples stored for analysis to determine the trough level of asparaginase activity. A Contract-Research Organization, (b) (4) was proposed for testing the samples. The stated objective would be to assess the primary clinical endpoint, trough asparaginase activity levels ≥0.1 IU/mL.

Per agreement between FDA and the applicant, the immunogenicity samples collected at 48 hours (dosing started on Wednesday or Friday) and at 72 hours (dosing started on Monday) pre-dose 4 on Day 8 in Course 1 were tested for asparaginase enzyme activity by (b) (4) As part of the AALL07P2 study, the remaining immunogenicity samples collected during course 1 and all other courses will be analyzed once the anti-product antibody assays are validated. According to the applicant, the samples were stored at (b) (4), (b) (4).

Asparaginase activity was determined in serum samples from 35 patients with 48 hour trough samples and 13 patients with 72 hour trough samples on Day 8 (pre-Dose 4) in Course 1 of treatment. Of this population, the results of all patient samples tested met the prespecified criterion of ≥0.1 IU/mL trough level of asparaginase activity. Since a trough asparaginase activity level ≥0.4 IU/mL was used for another asparaginase product activity assessment, the proportion of patients having a trough asparaginase activity ≥0.4 IU/mL was also assessed. The proportion of patients having trough asparaginase levels ≥0.1 IU/mL and ≥0.4 IU/mL are shown in tabular format below.

Trough Time	≥0.1 IU/mL	≥0.4 IU/mL
48 hours (n=35)	35/35 (100%)	28/35 (80%)
72 hours (n=13)	13/13 (100%)	5/13 (39%)

The FDA Division of Bioequivalence and GLP Compliance (DBGC) audited bioanalytical portions of the study conducted at (b) (4) on (b) (4) According to the DBGC report, there were no objectionable findings, and no Form FDA 483 was issued.

It is the conclusion of the primary clinical pharmacology reviewer that the tested patient trough asparaginase samples (N=48) at pre-dose 4 in course 1, for both the 48-hour samples and 72-hour samples, all met the prespecified clinical endpoint (≥0.1 IU/mL). I concur with this conclusion and further would note that having met this endpoint, Erwinaze has demonstrated both effectiveness as a replacement for pegaspargase and clinical benefit.

A key secondary endpoint, plasma asparagine concentration, was only measured once and the results were submitted with the original rolling BLA. Plasma asparagine level was measured at 5 different time points during course 1 of treatment. In subsequent courses of treatment, samples were collected at 3 different time points. The time points varied slightly depending on whether the patient started Erwinaze treatment on Monday, Wednesday, or Friday. As a secondary objective, plasma asparagine depletion, defined as a trough serum asparagine level ≤3μM, was determined for all subjects who had PD data for Day 12 if their treatment course started on Monday and Day 13 if their treatment course started on Wednesday or Friday. PD measurements were taken for a total of 47 patients. Because of the instability of asparagine, the applicant's results for asparagine were deemed unreliable by the primary clinical pharmacology reviewer. Therefore, whether the PD results met the pre-defined criteria is inconclusive. I concur with this conclusion.

QT/QTc Evaluation: Electrocardiograms (ECGs) were performed prior to Erwinaze dose 1, and at 1 hour following dose 6 in course 1. For the ECG at the pre-dose time point, no patient had a QTc interval > 500 msec, and one patient had both a > 500 msec value and a change in QTc ≥60 msec. For the ECG performed one hour after dose 6, two patients had a QTc interval > 500 msec, and 2 different patients had a change in QTc ≥60 msec. A consult by the FDA QT-IRT team recommended that no language related to QT liability needs to be included in future labeling. I concur with this recommendation.

6. Clinical Microbiology

Not applicable to this application.

7. Clinical/Statistical- Efficacy

Noted previously for this application is the fact that no statistical review was performed because the primary trial results did not require one. Instead, the primary efficacy review was performed by the clinical pharmacology review team and is discussed under section 5 above.

8. Safety

The information in this section was derived from the review of Dr. Patricia Dinndorf, Division of Biologic Oncology Products. Revisions were made for the purposes of this review.

In the opinion of the primary clinical reviewer, Dr. Dinndorf, the safety data submitted with this application are adequate to support approval of Erwinaze since additional data to confirm efficacy was submitted to this application on September 16, 2011. I concur in this opinion.

The safety data from the clinical trial submitted to support the effectiveness of Erwinaze, AALL07P2, and the Erwinaze Master Treatment Protocol (EMTP) were combined to assess the safety profile of Erwinaze in the Integrated Summary of Safety (ISS). The EMTP was conducted to enable US patients being treated for ALL to receive Erwinaze as a component of treatment with multi-agent chemotherapy, but outside of the COG AALL07P2 PK/PD trial. The EMTP was an expanded access protocol for any patient who developed hypersensitivity to native *E. coli* L-asparaginase or pegaspargase. Patients providing informed consent were treated with Erwinaze 25,000 IU/m^2 X 6 doses intramuscular (IM) on a Monday/Wednesday/Friday schedule for 2 weeks as replacement for each scheduled dose of native or pegylated L-Asparaginase remaining on the original treatment protocol. There was no preplanned number of patients. As part of EMTP, FDA required the applicant to collect demographic, medical history, and safety data on case report forms, the design of which was approved in advance by FDA. Safety was reported by summary statistics of data acquired from February, 2006 through April, 2010. At the time the BLA was submitted, the EMTP was still ongoing.

The ISS safety population included 633 patients who received at least one dose of Erwinaze. The demographics of the treated population follow in tabular format.

Demographics AALL07P2 Subjects (Safety)	
N= 58	
Sex	
Male	34 (59%)
Female	24 (41%)
Age in Years	
2 – 5	17 (29%)
6 - 10	13 (22%)
11 - 18	28 (48%)
Mean	9.5
Median	10
Range	2 -18
Race/Ethnicity	
White Not Hispanic or Latino	28 (48%)
White Hispanic or Latino	17 (29%)
Black or African American Not Hispanic or Latino	6 (10%)
Asian	3 (5%)
Other Not Hispanic or Latino	1 (2%)
Other Hispanic or Latino	2 (3%)
Unknown Hispanic or Latino	1 (2%)
Diagnosis	
ALL B-lineage	46 (79%)
ALL T-lineage	7 (12%)
ALL	4 (7%)
Leukemia NOS	1 (2%)

There were no deaths occurring during the conduct of the clinical trial and 6 deaths reported for the EMTP. None of the deaths were obviously related to Erwinaze exposure.

There were no unexpected serious adverse events reported in either the clinical trial or the EMTP. The incidence of known adverse events associated with *Erwinaze* therapy in both trials was not greater than that reported in the label for *E. coli* derived asparaginase therapy with the exception of clinical allergic reactions. The higher incidence of allergic reactions (AALL07P2:

Erwinaze 9%, pegaspargase 2%, native *E. coli* asparaginase 0; EMTP: Erwinaze 5%, pegaspargase 1%) is expected because subjects receiving Erwinaze had previously experienced an allergic reaction to an *E. coli* derived asparaginase.

A summary table of common treatment emergent adverse events reported in patients treated on Study AALL07P2 (copied from the applicant's submission) is presented in Table 1; and a summary table of common treatment emergent adverse events reported in ≥1% of patients treated under the EMTP (copied from the applicant's submission) is presented in Table 2.

Table 1 Common Adverse Events Study AALL07P2

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Preferred Term[a]	Number of Patients (%) (N=58)
Hypersensitivity	5 (8.6)
Hyperglycemia	3 (5.2)
Sepsis	3 (5.2)
Vomiting	3 (5.2)
Nausea	2 (3.4)
Hypoalbuminemia	2 (3.4)
Hyperbilirubinemia	2 (3.4)
Alanine aminotransferase increased	1 (1.7)
Alanine aminotransferase abnormal	1 (1.7)
Abdominal pain	1 (1.7)
Upper respiratory tract infection	1 (1.7)
Anxiety	1 (1.7)
Confusional state	1 (1.7)
Depression	1 (1.7)
Mood altered	1 (1.7)
Febrile neutropenia	1 (1.7)
Platelet disorder	1 (1.7)
White blood cell disorder	1 (1.7)
Aspartate aminotransferase increased	1 (1.7)
Aspartate aminotransferase abnormal	1 (1.7)
Neutrophil count abnormal	1 (1.7)
Ataxia	1 (1.7)
Encephalopathy	1 (1.7)
Headache	1 (1.7)
Speech disorder	1 (1.7)
Dermatitis	1 (1.7)
Urticaria	1 (1.7)
Fatigue	1 (1.7)
Pyrexia	1 (1.7)
Hypoxia	1 (1.7)

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Table 2 Common Adverse Events EMTP

System Organ Class/ Preferred Term	*Erwinia* asparaginase (N=573)* n (%)
Total Number of TEAE	**482**
Number of Patients with At Least One TEAE	**202 (35.3)**
Immune system disorders	**96 (16.8)**
Anaphylactic reaction	67 (11.7)
Hypersensitivity	31 (5.4)
Investigations	**46 (8.0)**
Alanine aminotransferase increased	17 (3.0)
Aspartate aminotransferase increased	11 (1.9)
Lipase increased	9 (1.6)
Blood amylase increased	7 (1.2)
Gastrointestinal disorders	**42 (7.3)**
Pancreatitis	22 (3.8)
Vomiting	14 (2.4)
Nausea	11 (1.9)
Abdominal pain	7 (1.2)
General disorders and administration site conditions	**32 (5.6)**
Pyrexia	15 (2.6)
Blood and lymphatic system disorders	**22 (3.8)**
Neutropenia	9 (1.6)
Febrile neutropenia	7 (1.2)
Metabolism and nutrition disorders	**15 (2.6)**
Hyperglycemia	11 (1.9)
Skin and subcutaneous tissue disorders	**15 (2.6)**
Urticaria	9 (1.6)

The following coagulation proteins were decreased in the majority of patients after a 2 week course of Erwinaze: fibrinogen, protein C activity, protein S activity, and AT III. The effect of treatment on PT and PTT was not clearly demonstrated. There was no effect noted on d-dimers or FDPs. No patients with coagulation abnormalities reported a hemorrhagic or thrombotic adverse event.

There was no evidence of post therapy hepatic, renal, or pancreatic laboratory abnormalities greater than grade 3 in the 58 subjects who received 175 courses of *Erwinaze*. Five patients (9%) demonstrated grade 3 and 4 elevations in triglycerides at post therapy evaluations.

Immunogenicity: Immunogenicity samples from all 59 patients treated in clinical trial AALL07P2 were collected at pre-dose on days 8 and 22 during course 1and on days 6 and 15 in subsequent courses. The antibody results were not included in the BLA submission because the assays have not been adequately validated. According to the applicant, the remaining immunogenicity samples collected during course one and all other courses of therapy during the clinical trial will be analyzed once the anti-product antibody assays are validated. These samples continue to be stored at (b) (4)

9. Advisory Committee Meeting

No Advisory Committee meeting was held for this application.

10. Pediatrics

Study AALL07P2 was conducted in children 1 to 18 years of age. The majority of subjects included in the EMTP study were children. These two trials were submitted to support the efficacy and safety of Erwinaze for this application.

11. Other Relevant Regulatory Issues

Orphan Drug Status/Exclusivity

Erwinaze was developed as an orphan drug [redacted] (b) (4) [redacted] (b) (4)

Financial Disclosures

Financial disclosure forms for the principal investigator for each institution participating in the clinical trial were submitted to the application on November 11, 2010 in amendment 3 to the application. No investigator reported disclosable financial interests.

DSI audits

Bioanalytical Data: FDA's Division of Scientific Investigations (DSI) audited the bioanalytical data from the study intended to support the effectiveness of Erwinaze (AALL07P2) from [redacted] (b) (4) Inspected was the laboratory of [redacted] (b) (6) [redacted] (b) (4) A number of deficiencies with regard to both the asparaginase and asparagine assays were identified and communicated to both the laboratory director and the applicant. After discussions with the applicant, the data resulting from the assays was deemed by DSI to be unreliable and no corrective measures were identified that could remedy the situation. Subsequently, the applicant identified additional stored samples from the study, retrieved them from storage and proposed to have them tested. FDA agreed to have the samples tested because they had been taken at trough time points consistent with the asparaginase primary and secondary endpoints of the trial submitted to support efficacy. The testing was conducted at [redacted] (b) (4) [redacted] (b) (4) following a cross-validation of an existing assay to use *E. coli* asparaginase for the calibrators, and both *E coli* and Asparaginase *Erwinia chrysanthemi* for quality control samples. DSI (now OSI) conducted an inspection of [redacted] (b) (4) on [redacted] (b) (4) [redacted] (b) (4) No deficiencies were noted in the inspection and the data resulting from the [redacted] (b) (4) [redacted] (b) (4) assays was deemed acceptable for FDA review.

Clinical Site Data: *The information in this section was derived from the review of Robert Young, Good Clinical Practices Branch II, Division of Scientific Investigations. Revisions were made for the purposes of this review.*

A single clinical site which enrolled three patients to the trial was inspected for this application. Reviewed was study conduct including proper dosing, sample collection and adverse event reporting. There were no significant regulatory violations identified in the inspection. The data generated were deemed acceptable to support the application.

12. Labeling

Proprietary name

A proprietary name request for "Erwinaze" was submitted to the IND n May, 2009 and approved on November 10, 2010.

ADDENDUM AFTER REVIEW OF 9/16/11 SUBMISSION

This application will be approved based on the PK data submitted on 48 patients during the first course of asparaginase *Erwinia chrysanthemi*. The recommended changes to the label as of 9/28/11 are summarized below:

1. INDICATIONS AND USAGE

1.1. Acute Lymphoblastic Leukemia (ALL)

(b) (4)

To:

ERWINAZE (asparaginase *Erwinia chrysanthemi*) is an asparagine specific enzyme indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of (b) (4) (b) (4) patients with Acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to E. coli derived asparaginase

2. DOSAGE AND ADMINISTRATION

2.1. Acute Lymphoblastic Leukemia

(b) (4)

To:

For replacement of pegaspargase:

The recommended dose is 25,000 International Units/m^2 administered intramuscularly three times a week (Monday/Wednesday/Friday) for six doses to replace each dose of pegaspargase.

For replacement of native E. coli asparaginase:

The recommended dose is 25,000 International Units/m^2 administered intramuscularly for each dose of native *E. coli* asparaginase (b) (4)

2.2. Preparation Instructions

(b) (4)

12 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

(b) (4) (b) (4)

[redacted]

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

Based on a full review of the data submitted to support this application, it is the recommendation of all review teams that the original Biologic License Application for Erwinaze be approved. I concur with these recommendations.

Risk Benefit Assessment

Based on all data submitted to the application, there is a favorable risk: benefit assessment for Erwinaze. The activity of Erwinaze was adequately demonstrated by analysis of 48 patient samples which demonstrated the achievement of adequate depletion of asparagine as measured by serum L-asparaginase activity levels ≥0.1 IU/mL based on a validated assay. Therapeutic depletion of asparagine was unable to be demonstrated directly because of plasma aspargine instability. Aspargine depletion is an important component in the overall treatment strategy for childhood ALL. For patients who are unable to receive a full course of asparagine depleting treatment (historically, approximately 2/3), studies suggest poorer prognosis compared to patients who receive a full course. Heretofore, for patients who developed allergies to native *E. coli* L-asparaginase, only pegaspargase (Oncaspar®), a pegylated form of the *E. coli* enzyme, was FDA approved. With the approval of Erwinaze, another effective agent will be added to the armamentarium of treatment for childhood ALL. In addition, the safety of Erwinaze compares favorably to pegaspargase. The incidence of common adverse events reported for Erwinaze, notably pancreatitis, coagulopathy, hyperglycemia and liver abnormalities, was lower in Erwinaze treated subjects than the incidence reported for pegaspargase. Only the incidence reported for allergic reactions in Erwinaze treated patients was higher than that reported for pegaspargase, which would be expected.

In summary, the risk: benefit ratio for Erwinaze favors benefit owing to its safety profile, its ability to deplete aspargine as demonstrated by serum L-asparaginase activity levels ≥0.1 IU/mL, and its availability as an alternative treatment for patients who develop allergies to native *E. coli aspargine* depleting products of which there are two currently approved by FDA.

Recommendation for Postmarketing Risk Evaluation and Management Strategies: None

Recommendation for other Postmarketing Requirements:

1. To conduct non-clinical embryo-fetal development and toxicity (EFT; ICH S5(R2) Harmonized Segment C) studies of ERWINAZE in rats and rabbits.

2. To conduct non-clinical fertility and early pregnancy (Segment I; ICH S5(R2) Harmonized Segment A-B) studies of ERWINAZE in rats.

3. To conduct non-clinical peri-postnatal developmental (PPND; Segment III; ISC S5(R2) Harmonized Segment D-F) studies of ERWINAZE in rats.

4. To develop a validated, sensitive, and accurate assay for the detection of binding antibodies to ERWINAZE, including procedures for accurate detection of antibodies to ERWINAZE in the presence of ERWINAZE levels that are expected to be present in the serum at the time of patient sampling. A summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay SOP will be provided to FDA.

5. To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ERWINAZE, including procedures for accurate detection of neutralizing antibodies to ERWINAZE in the presence of ERWINAZE levels that are expected to be present in the serum at the time of patient sampling. A summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay SOP will be provided to FDA.

6. To conduct an assessment of anti-drug antibody (ADA) binding response and neutralizing ADA response to ERWINAZE with validated assays (required under PMR 4 and 5) capable of sensitively detecting ADA responses in the presence of ERWINAZE levels that are expected to be present at the time of patient sampling. The ADA response will be evaluated in all archived sampling time points available from all patients in the COG Study AALL07P2.

Recommendation for other Postmarketing Commitments:

1. To conduct a container closure integrity study and determine the sensitivity of the test methods.

2. To conduct performance qualification of the Erwinaze lyophilization process.

3. To provide validation data from the executed protocol for shipping ERWINAZE drug product from the (b) (4) to the US market.

4. To conduct a study to substantiate the use of (b) (4) (b) (4) as the (b) (4) (b) (4)

5. To collect data from rabbit pyrogen testing on three lots of thawed and diluted drug substance solution prior to (b) (4). The final validation report should contain a description of the method, the rabbit pyrogen test results, and an

assessment of the impact of [redacted] (b) (4) on drug product quality and the drug product manufacturing.

6. Implement the proposed process improvements described in the March 4, 2011, BLA amendment and re-assess the bioburden and endotoxin limits based on data from three extraction batches.

7. To monitor bioburden and endotoxin levels in CM6 pooled fractions, CM8 pooled fractions, and DEAE pooled fractions held for more than 24 hours at scale from three runs, demonstrating that acceptance criteria are met.

8. To complete the qualification of bioburden and endotoxin in-process test methods:
   - The final reports for the bioburden and endotoxin assay will each provide data on two additional batches of drug substance.

9. To review the specifications for all release and stability test methods when the manufacture of a statistically significant number of Erwinaze DS and DP lots is completed. The final report of this analysis together with any revised release and stability specifications will be submitted in accordance with 21 CFR 601.12.

10. To validate hold times for each DS process intermediate, where applicable, in order to demonstrate that the quality of Erwinaze DS is not affected. This study should include a worst case hold scenario, defined by the cumulative maximal time for each hold step along with an evaluation of the purity and potency of process intermediates and of the resulting DS. The complete hold times validation report and supporting test results will be submitted in accordance with 21 CFR 601.12.

11. To increase the assay sensitivity for SDS-PAGE. The revised assay will be submitted together with the validation report and supporting test results.

12. To perform SEC and AUC testing in a side-by-side analysis of Erwinaze DS samples that have been subjected to stress conditions. Results of these studies together with any revisions to your control strategy will be submitted as a final report in accordance with 21 CFR 601.12.

13. To provide a revised protocol for qualification of the current and future Erwinaze reference standards.

14. To submit an experimental plan for evaluating and, if appropriate, implementing L-asparagine as the substrate for measuring the K_m and k_{cat} of Erwinaze DS and DP.

15. To provide an experimental plan to assess the types and amounts of smaller sub-visible particulates [redacted] (b) (4) in the final drug product under real-time and stress stability conditions along with a timetable for this work. The plan and a timescale for the subsequent assessment of the impact sub-visible particles may

have on the quality, clinical safety and efficacy of Erwinaze DP along with a control strategy will be provided.

16. To revise the peptide mapping method used for DS and DP release testing in order to enable chromatographic base-line resolution of most peptide fragments while accounting for ~98% of the protein sequence. The revised assay will be submitted together with the validation report.

Recommended Comments to Applicant: In order to better characterize Erwinaze, a PK study should be conducted and the results should be submitted as a supplement to the BLA in order to update labeling.