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APPLICATION NUMBER:

125359Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125359
Priority or Standard	Priority
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Division / Office	DBOP / OODP
Reviewer Name(s)	Patricia Dinndorf, MD
Medical Team Leader	Suzanne Demko, PA-C
Division Director	Patricia Keegan, MD
Review Completion Date	May 13, 2011
Review Addendum Date	September 28, 2011
Established Name	<i>Erwinia</i> L-asparaginase
(Proposed) Trade Name	Erwinaze®
Therapeutic Class	Enzyme
Applicant	EUSA Pharma (USA), Inc.
Formulation(s)	Lyophilized powder for injection
Dosing Regimen	25,000 IU/m ² IM TIW for 2 weeks to replace a dose of pegaspargase
Indication(s)	Component of a multi-agent chemotherapeutic regimen for treatment of ALL in patients who develop allergic reaction to <i>E. coli</i> - derived asparaginase
Intended Population(s)	ALL patients with allergy to <i>E. coli</i> - derived asparaginase

RAD 9/28/11
10/31/11

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical recommendation for this application, as submitted on November 1, 2010, BLA 125359 is not approvable. A complete response (CR) letter will be issued delineating the deficiencies. The efficacy to support approval of *Erwinia* L-asparaginase in this application was to be based on the pharmacokinetic (PK) endpoint of trough asparaginase activity. Patients who had developed allergic reactions to pegaspargase received *Erwinia* L-asparaginase 25,000 International units (IU)/m² x 6 doses intramuscularly (IM) on a Monday / Wednesday / Friday schedule as a replacement for each scheduled dose of pegaspargase remaining in their original treatment protocol. The Food and Drug Administration (FDA) agreed to accept a PK measurement, trough asparaginase activity of ≥ 0.1 IU/mL at 48 hours, as the outcome supporting efficacy. The FDA Division of Scientific Investigations (DSI) audit of the laboratory responsible for the PK analysis concluded that the PK results were not reliable. Based on this conclusion there is no data to support the efficacy of this agent.

The safety data submitted in this application, were collected from the PK study AALL07P2 "Pharmacology and Toxicity of *Erwinia* L-asparaginase (Erwinase; Crisantaspase: IND 290) Following Allergy to Pegaspargase in Treatment of Children with Acute Lymphoblastic Leukemia (ALL)" and the Erwinaze Master Treatment Protocol (EMTP). The safety data submitted are adequate to support approval of this agent if additional data is collected to confirm efficacy.

ADDENDUM AFTER REVIEW OF 9/16/11 SUBMISSION

The clinical recommendation for this application, BLA 125359 has been amended to approval.

The applicant submitted the results of the PK analysis of archived samples obtained from subjects enrolled on the AALL07P2 trial. The samples were evaluated with a validated assay in a commercial laboratory.

The applicant was able to locate 48 archived samples originally collected to evaluate immunogenicity during the first cycle of *Erwinia* L-asparaginase. These samples were collected prior to the 4th dose of *Erwinia* L-asparaginase. This represents a trough value measured during the middle, after the 3rd of 6 doses, of an *Erwinia* L-asparaginase course rather than at the end of the cycle, after the 5th of six doses as originally specified. The asparaginase activity was greater than 0.1 IU/ml in every sample tested. This analysis adequately demonstrates the activity of *Erwinia* L-asparaginase and supports approval of this application.

1.2 Risk Benefit Assessment

This application is CR. A new study to determine that the trough asparaginase activity is ≥ 0.1 IU/mL at 48 hours in patients who have developed allergic reactions to pegaspargase will be required.

ADDENDUM AFTER REVIEW OF 9/16/11 SUBMISSION

FDA has determined that the analysis of the 48 archived samples adequately demonstrates the activity of *Erwinia* L-asparaginase and supports approval of this application.

The risk benefit analysis of this product supports approval. Asparagine depletion has been demonstrated to be an important component in the overall treatment strategy of childhood ALL. For patients who develop allergies to *E. coli* L-asparaginase, *Erwinia* L-asparaginase provides a substitute asparagine depleting agent. The adverse reaction associated with asparaginase agents are well known, and the profile of *Erwinia* L-asparaginase is comparable that seen with *E. coli* L-asparaginase.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This application is CR. A new study to determine that the trough asparaginase activity is ≥ 0.1 IU/mL at 48 hours in patients who have developed allergic reactions to pegaspargase will be required.

ADDENDUM AFTER REVIEW OF 9/16/11 SUBMISSION

FDA has determined that the analysis of the 48 archived samples adequately demonstrates the activity of *Erwinia* L-asparaginase and supports approval of this application.

There are no specific postmarket risk evaluation and mitigation strategies required

1.4 Recommendations for Postmarket Requirements and Commitments

This application is CR. A new study to determine that the trough asparaginase activity is ≥ 0.1 IU/mL at 48 hours in patients who have developed allergic reactions to pegaspargase will be required.

ADDENDUM AFTER REVIEW OF 9/16/11 SUBMISSION

FDA has determined that the analysis of the 48 archived samples adequately demonstrates the activity of *Erwinia* L-asparaginase and supports approval of this application.

(b) (4)

2 Introduction and Regulatory Background

2.1 Product Information

(copied from submission eCTD 2.2 Introduction page 1)

Erwinia L-asparaginase (Crisantaspase, Erwinase, Erwinaze), contains the (b) (4) enzyme L-asparagine amidohydrolase (L-asparaginase) derived in (b) (4) from the non-human (plant) pathogen *Erwinia chrysanthemi* (nee carotovora). The enzyme is also isolated from a variety of other sources (yeast, animal cells, fungi). Its molecular weight is about 135,000 daltons and is composed of four subunits (tetramers), each subunit having a molecular weight of about 35,000 daltons. *Erwinia* L-asparaginase is freely soluble in water. 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) per milligram of protein.

2.2 Tables of Currently Available Treatments for Proposed Indications

Asparaginase enzymes are an important component in the treatment of childhood ALL. *E. coli* L-asparaginase (Elspar®) an agent derived from *Escherichia coli* was the first agent approved for this indication in the 1970s.

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. 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 1991 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. It should be noted that the methodology for analysis of asparagine depletion was not validated. The trial was not adequately designed or conducted to evaluate superiority or non-inferiority of the event free survival (EFS) or survival but there did not appear to 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.

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

2.3 Availability of Proposed Active Ingredient in the United States

Erwinia L-asparaginase has been available in the US since 1968 under Investigational New Drug (IND) 290 originally held by Ipsen Ltd. In February 2006 Ipsen Ltd transferred all rights and responsibilities of IND 290 to Orphan Pharmaceuticals International (OPi) SA (subsequently EUSA Pharma (US)). *Erwinia* L-asparaginase (Crisantaspase, Erwinase) is available in some countries in Europe and in Canada.

2.4 Important Safety Issues With Consideration to Related Drugs

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* L-asparaginase, but in current clinical practice most patients receive initial therapy with pegaspargase.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 1: Regulatory History of the Submission

Date / Milestone	Summary of Issues
April 1968 / IND 290 submitted	Ipsen Ltd. original sponsor
February 2006 / IND 290 Transferred	IND 290 was transferred from Ipsen Ltd. to OPi SA (OPi)
May 2006 / Pre- BLA meeting	<ul style="list-style-type: none"> OPi proposed an (b) (4) (b) (4) 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 schedule of <i>Erwinia</i> L-asparaginase 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 <i>Erwinia</i> L-asparaginase PK and immunogenicity.
August 2007 / Change sponsor	OPi acquired by EUSA Pharma (US) Inc. (EUSA)
March 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.
July 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 <i>ex vivo</i> 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.
September 2009 / Pre- BLA meeting	<p>EUSA requested a pre-BLA Meeting</p> <ul style="list-style-type: none"> 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 <i>Erwinia</i> L-asparaginase. EUSA planned to include a synopsis of the Erwinaze Master Treatment Protocol (EMTP) that collected additional safety data.

	<ul style="list-style-type: none"> FDA informed EUSA that the application must contain an integrated summary of safety (ISS).
October 2009 / Proprietary name request	<p>FDA Division of Medication Error Prevention and Analysis rejected the proposed proprietary name of (b) (4)</p> <div style="background-color: #cccccc; height: 150px; width: 100%;"></div>
May 2009 / Proprietary name request	The proprietary name Erwinaze was granted 11/10/10
June 2010 / Request fast track status	Fast track status granted 7/15/10
September 2010 / Rolling BLA 125359	Submitted
November 1, 2010 / Final CMC unit	Priority review status granted; PDUFA final action date May 3, 2011
February 28, 2011 / Major amendment	PDUFA final action date revised August 2, 2011
September 16, 2011	<p>The application was not approvable based on the inspection of the clinical laboratory site responsible for the asparaginase activity analysis. At the inspection the data was determined not to be reliable. EUSA submitted an amendment with a new analysis by a laboratory determined to be reliable.</p>

2.6 Other Relevant Background Information

FDA considered asparagine depletion an acceptable surrogate for efficacy of *Erwinia* L-asparaginase in an application supported by a single study. However there is an inherent unreliability of asparagine assays because of *ex vivo* metabolism of asparagine in the collected samples. The sponsor was unable to develop a validated sample collection method for measuring asparagine. FDA agreed to accept a PK measurement, trough asparaginase activity of ≥ 0.1 IU/mL at 48 hours, as the primary endpoint of this submission. This level of asparaginase activity, which can be reliably measured in the clinical setting, is directly related to asparagine depletion.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Submission Quality

There were many problems identified in the original application. The applicant addressed most of the issues in a November 19, 2010 amendment to the application. At the December 14, 2010 Filing Meeting the following deficiencies were identified that were not adequately addressed by the November 19, 2010 submission:

- Case report forms (CRF) for every course of treatment (specimen transfer CRF) were not submitted
- The MedDRA coding was not done correctly for the AALL07P2 study
- The actual dose of *Erwinia* L-asparaginase was not included on the EX.xpt dataset

These were conveyed to the applicant during 2 teleconferences on December 16 and 21, 2010. In response to the FDA requests, on December 31, 2010 the applicant provided specimen transfer CRFs for each course subject received. The applicant submitted revised datasets correcting the MedDRA coding, and datasets providing the actual dose subjects received derived from the specimen transfer CRF. An audit of 20% of the specimen transfer CRFs confirmed the appropriate dose was reported on the EX.xpt dataset.

An audit of the safety data submitted from the EMTP was performed to determine the quality of this data. The CRFs of 122 subjects of the 577 were reviewed and compared to the safety data captured in the ADAE.xpt. Initially 44 subjects were audited but problems were identified in 12 cases and the audit was expanded to more fully ascertain the extent of the problems. Subjects who received first dose of *Erwinia* L-asparaginase in the months of May, August, and November were reviewed. The following problems were identified:

- There were no CRFs for 14 of 122 subjects selected for this audit.
- There were 12 subjects without reported adverse events (AE) with AEs identified on the CRFs.
- There were 3 subjects with AEs reported although no AEs were documented on the CRFs.
- The CRFs were designed as check box queries. The verbatim term generated "AETERM" and the MedDRA term it was mapped to "AECODE" from this form should have been consistent each time an AE was identified from a check box from the form. This was not the case.

For instance Allergic reaction if Local Reaction was checked it was reported as "AETERM" - "skin reaction", "AECODE" – "skin reaction" for Subject EMTP-000000000025579; "urticaria" for Subject EMTP-000000006687270; and "hypersensitivity" for Subject EMTP-000000099999082.

Systemic Allergic reaction grade 1 was coded as "anaphylactic reaction" for Subjects EMTP-000000000779117, and EMTP-000000000790100; "hypersensitivity" for Subject EMTP-0000000001413127.

Systemic Allergic reaction grade 2 was coded as "anaphylactic reaction" for Subjects EMTP-000000099999048; and hypersensitivity" for Subject EMTP-000000000747797.

Systemic Allergic reaction grade 3 was coded as "eyelid edema", for Subject EMTP-000000000004978; "hypotension" for Subject EMTP-0000000001249691.

The applicant was advised to submit revised datasets to correct these deficiencies in the day 74 deficiency letter. After the revised datasets were submitted to the application February 28, 2011, the revised safety datasets included 53 new cases with AEs identified. There were 102 case corrections made to the safety database. The BLA was deemed to be acceptable to allow substantive review of the clinical data.

Submission Integrity

DSI audits were conducted at one clinical site and the nonclinical site of sample evaluation. John Hopkins was chosen as the clinical audit site because it was judged to be a representative institution. There were 31 institutions who contributed from 1 to 6 subjects. John Hopkins contributed 3 subjects. No substantial regulatory violations were identified during the inspection.

The nonclinical site audit was conducted at the laboratory of (b) (4) at (b) (4) laboratory was responsible for the PK and PD analyses. As previously noted, the efficacy analysis was based on a PK endpoint, not a clinical measurement. The inspectional findings included the following problems:

Asparaginase Assay

- Failure to reject analytical run #480 on 4/8/10 when one of the three quality control (QC) samples failed the acceptance criterion. Seven samples were not re-assayed or required dilution.
- Failure to exclude serum samples from clinical sites received in the thawed state.
- Records of freezer temperatures for storage of asparaginase samples were not retrievable in an auditable form.
- Failure to document the times when samples were removed from frozen storage for analysis.
- Failure to adequately document preparation and storage of asparaginase stock solutions.
- Failure to adjust nominal asparaginase concentrations in calibrator and quality control solutions for the actual content of L-asparaginase commercial vials.

- Reported serum asparaginase activities less than the lower limit of quantitation. Specifically, the LLOQ [lower limit of quantitation] of the asparaginase assay was 0.025 IU/mL. However, asparaginase concentrations ranging from 0.009 to 0.024 IU/mL were reported.

Asparagine Assay

- Failure to reject analytical runs on 9 days when the quality control (QC) samples failed the acceptance criterion at one or two of the three QC concentrations.
- Failure to reject chromatograms when no asparagine internal standard was detected or when peaks could not be accurately integrated.
- Failure to exclude plasma samples from clinical sites which were unacidified or were received in the thawed state.
- Failure to demonstrate stability of samples under the conditions of the study.
Examples:
 - a) The blank plasma used in method development, validation, and QC samples for the asparagine assay was citrate-phosphate-dextrose transfusion plasma, not heparin plasma as in study samples.
 - b) There was no evaluation of freeze/thaw or long-term frozen stability of samples for the asparagine assay. Most plasma samples were stored frozen for 3 to 11 months before assay for asparagine.
 - c) Records of freezer temperatures for storage of asparagine samples were not retrievable in an auditable form. The alarm system for temperatures outside -70°C to -90°C did not record the extreme excursions of temperature and durations of the excursions when the alarm triggered, including the event on 3/4/10 when the majority of study asparagine samples were in this freezer.
 - d) Some samples were received thawed (7 shipments), or without acid preservative for asparagine (61 samples), or with documented delays between sample collection and plasma acidification (multiple examples longer than 10 minutes).
 - e) The effectiveness of hydrochloric acid in preserving asparagine in plasma was tested only for *E. coli* asparaginase, not for *Erwinia* asparaginase.
 - f) The times when samples were removed from frozen storage for analysis were not recorded.
- Between-run accuracy and precision for the asparagine assay were not evaluated.
- Failure to evaluate the variability in recovery of asparagine in more than one plasma sample in a run.
- Failure to evaluate the stability of asparagine in stock solutions or extracts.
- Only a single stock solution of asparagine was used for both calibrators and QC samples, rather than independently-prepared stock solutions, in both pre-study validation and within-study conduct.

- Failure to verify (by balance printer or witness) the weights of asparagine used for calibrator and QC stock solutions.

REVIEWER COMMENT:

The clinical pharmacology team determined that given the irregularities identified in the conduct of the PK analysis the data did not allow for substantive review of the primary efficacy endpoint. Without this analysis there is no evidence to support the efficacy of *Erwinia* L-asparaginase for this indication.

There was no validated sample collection methodology for asparagine sample collection. Moreover, because of the irregularities identified in the conduct of asparagine level analysis asparagine depletion can not be reliably assessed. Asparagine depletion data can not be used to support a finding of efficacy for this application.

ADDENDUM AFTER REVIEW OF 9/16/11 SUBMISSION

The applicant submitted the results of the PK analysis of archived samples obtained from 48 subjects enrolled on the AALL07P2 trial. The applicant contracted the evaluation of these samples to (b) (4) (b) (4) conducted a full validation study for the PK assay and FDA agreed to the methodology. DSI inspected the testing site and no adverse findings were identified.

REVIEWER COMMENT;

The results of this analysis can be used to support the efficacy findings of this application.

3.2 Compliance with Good Clinical Practices

The title page of the Clinical Study Report for AALL07P2 (section 5.3.4.2.3) affirms the study was conducted in accordance with Good Clinical Practices.

3.3 Financial Disclosures

Financial disclosure forms of the principal investigator for each institution were submitted to the application 11/19/10 in amendment 3 to the application. No investigator reported disclosable financial interests.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The final reports for the manufacturing site inspection and product review were not available at the time this review was completed. The determination of the primary manufacturing site inspector is that the application is NA. The product reviewer has not made a final determination.

4.2 Clinical Microbiology

Not applicable for this application.

4.3 Preclinical Pharmacology/Toxicology

The nonclinical studies conducted on *Erwinia* sp asparaginases predated good laboratory practice (GLP) regulations. The information submitted with the application is not GLP compliant. *Erwinia* L-asparaginase is approved in Europe based on these non-GLP compliant studies submitted with the application. FDA reviewed the non-GLP compliant studies. Review of these studies in combination with the extended clinical experience with *Erwinia* L-asparaginase suggests that *Erwinia* L-asparaginase is reasonably safe for use in ALL patients who are allergic to L asparaginases derived from *E. coli*.

Under new controlling legislation (Patient Protection and Affordable Care Act, 2010), FDA can not rely on published literature for developmental and reproductive toxicity studies. The applicant will be required to submit the results of the complete battery of fertility, embryo-fetal and pre-post-natal nonclinical developmental toxicity studies. The applicant has provided plans and protocols to be evaluated for all required studies.

4.4 Clinical Pharmacology

Based on the results of the FDA DSI audit of the laboratory responsible for the PK analysis the clinical pharmacology review team determined that the PK results were not reliable. Therefore there is no efficacy data to support approval of this application.

ADDENDUM AFTER REVIEW OF 9/16/11 SUBMISSION

The applicant submitted the results of the PK analysis of archived samples obtained from 48 subjects enrolled on the AALL07P2 trial. See section 6/1/4.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2: Clinical Trials in the Submission

Clinical Trial	Title	Comment
AALL07P2	Pharmacology and Toxicity of <i>Erwinia</i> L-asparaginase (Erwinase; Crisantaspase: IND 290) Following Allergy to Pegaspargase in Treatment of Children with Acute Lymphoblastic Leukemia (ALL)	Prospective PK (PD) Trial of <i>Erwinia</i> L-asparaginase in Patients with ALL allergic to pegaspargase.
EMTP	Erwinaze Master Treatment Protocol	Additional clinical safety data was prospectively collected for patients treated on this expanded access protocol

5.2 Review Strategy

The design and efficacy results of Trial AALL07P2 will be reviewed in section 6 and the safety information will be reviewed in section 7. The design of the EMTP will be discussed in section 5.3. The safety data from the EMTP will be reviewed in section 7.

5.3 Discussion of Individual Studies/Clinical Trials - EMTP

5.3.1 Methods

The EMTP was instituted as an expanded access program. Collection of safety data on patients enrolled on the EMTP provided a larger safety population available for this application.

For this program the applicant developed CRFs in collaboration with the FDA. The CRFs included sections to gather information regarding demographics, disease and prior treatments, prior asparaginase exposure and toxicity, *Erwinia* L-asparaginase administration, concomitant medications, and *Erwinia* L-asparaginase toxicity.

The toxicity data was captured using a check box format. Investigators were requested to report coagulation test values that were obtained at the onset of a thrombotic or hemorrhagic AE. Investigators were requested to report aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, amylase and lipase associated at the time of onset with hepatic or pancreatic disorders. Three components of the laboratory

values were captured, normal ranges of the testing laboratory, the laboratory value and units of the laboratory value. There were spaces provided to supply additional information about the specific AE captured. There was a section to report any other significant AE not included as a standard inquiry and a section to report information about deaths within 28 days of receiving *Erwinia* L-asparaginase.

In order to increase the compliance of investigators returning CRFs, the applicant offered to pay the investigators \$150 when complete CRFs were returned.

5.3.2 Protocol Amendments

Table 3: Protocol Amendments

December 22, 2006	<ul style="list-style-type: none"> ▪ Original protocol
November 17, 2008	<ul style="list-style-type: none"> ▪ Formatting and editing changes ▪ Allowed T or B cell lymphoma as inclusion criteria ▪ Excluded subjects with only local pain or redness at injection site as an inclusion criteria ▪ Risk inactivation due to neutralizing antibodies associated with an allergic reaction ▪ Added specific dosing recommendations from the Childrens Oncology Group (COG), St Jude's, and Dana-Farber Cancer Institute (DFCI). ▪ Added section describing collection of safety data. ▪ Revised CRFs ▪ Revised consent form
February 9, 2009	<ul style="list-style-type: none"> ▪ Formatting and editing changes
June 25, 2009	<ul style="list-style-type: none"> ▪ Formatting and editing changes

5.3.3 Inclusion and Exclusion Criteria

Inclusion criteria: (copied from final protocol in submission)

- Age: no restrictions
- Patient must give a written informed consent to receive Erwinaze under IND 290
- Patient must be treated for acute lymphoblastic leukemia
- Children with either T or B cell lymphoma being treated with asparaginase.
- Patient must have either systemic hypersensitivity reactions to native or pegylated *E. coli* L-asparaginase. This includes patients with generalized rash with or without anaphylactic symptoms, but not those with only local pain or redness at the site of injection.
- Patients with previously documented local or systemic reactions to *E. coli* derived L-asparaginase.

Exclusion criteria : (copied from final protocol in submission)

- Previous allergic reaction to *Erwinia* L-Asparaginase (Erwinaze).
- Previous acute pancreatitis.

- Pregnant or lactating woman.

5.3.4 Drug Administration

Route of Administration: (copied from final protocol in submission)

May be administered intramuscularly, subcutaneously, or intravenously. The intramuscular route or the subcutaneous route, is the preferred route of administration.

When given according to the scheduled induction regimen, the product is first reconstituted by adding 1 to 2 ml Sodium Chloride Injection USP to the 10,000 U vial.

When given by the IV [intravenous] route reconstitute the product by adding 1 to 2 ml of Sodium Chloride Injection USP to the 10,000 U vial.

Dosing Regimen: (copied from final protocol in submission)

The precise dosing schedules will be conducted according to the recommendations of the treatment protocols.

Children Oncology Group (COG) recommends the following dosing schedule:

- Substitute Erwinaze 25,000 IU/m² intramuscularly x 6 doses on a every other day schedule (including week-ends and holidays) for each dose of pegylated *E. coli* derived L-Asparaginase (Pegaspargase) (days 1, 3, 5, 7, 9,11).

St Jude recommends the following dosing schedule:

- Substitute Erwinaze 20,000 IU/m² intramuscularly for each dose of native *E. coli* derived L-asparaginase during remission, induction or re-induction therapy.
- Substitute Erwinaze 25,000 IU/ m² twice weekly for each dose of native *E. coli* derived L-asparaginase during consolidation therapy.

Dana-Farber Cancer Institute (DFCI) recommends the following dosing schedule:

- Substitute Erwinaze 20,000 IU/ m² intramuscularly twice a week for each dose of native *E. coli* derived L-Asparaginase.
- Substitute Erwinaze® 25,000 IU/ m² intramuscularly twice weekly for two weeks for each dose of pegylated *E. coli* derived L-Asparaginase during consolidation therapy.

5.3.5 Demographics

Subjects enrolled on the EMTP February 2006 through April 2010 were included in this analysis. There were 843 patients who received *Erwinia* L-Asparaginase through this mechanism during this period. There were 574 subjects included in the demographic dataset, DM.xpt. Two subjects were excluded from the safety population. The CRFs of one of these subjects documented the patient did not receive *Erwinia* L-Asparaginase and the CRFs of the second subject indicated he received pegylated asparaginase.

CRFs with complete AE portions were submitted to the application for 543 subjects. CRFs with missing pages of AE information were submitted for 3 subjects. There were 4 subjects with AEs documented by reports but not on CRFs. There were 22 subjects in the demographic dataset (DM.xpt) with no CRFs submitted in the application.

Table 4: Demographics of EMTP

Demographics Safety Population EMTP	
Safety Population N= 572	
Sex	
Male	356 (62%)
Female	215 (38%)
Not reported/Missing CRF	1
Age in Years	
≤ 18	533 (95%)
1 – 5	210 (37%)
6 - 10	118 (21%)
11-18	205 (36%)
> 18	31 (5%)
Mean	9.4
Median	9
Range	1(13 months) – 66 years
Not reported	8
Diagnosis	
ALL B-lineage	450 (83%)
ALL T-lineage	72 (13%)
Lymphoma	16 (3%)
Biphenotypic Leukemia	2 (<1%)

5.3.6 Subject Disposition

Table 5: Subject Disposition of EMTP

Disposition EMTP	
N=574	
Received no therapy	2
Completed planned therapy	434
Discontinued prior to completing planned therapy	98
Adverse Reaction	78
Systemic allergic reaction	56
Local allergic reaction (injection site)	1
Pancreatitis	8
Thrombosis	4
Hyperammonemia	2
Febrile neutropenia (physician decision)	2
Local site reaction	2
Seizure	1
Diarrhea (patient decision)	1
Death (investigator reported possibly related)	1
Other	20
Physician decision	7
Leukemia not controlled	7
Transferred care	3
Parent/patient decision	2
Unable to afford	1
Missing Data	40

5.3.7 Exposure

Accurate details concerning the dosing and dosing schedules were beyond the scope of the data collected on the CRFs and were not systematically collected. The number of doses of *Erwinia* L-asparaginase planned for an individual patient depended on the protocol and the phase in the treatment course the patient was due to receive asparaginase. From the documented information the planned number of doses of *Erwinia* L-asparaginase ranged from 3 doses to 48 doses (20,000 or 25,000 IU/m²/dose). Most patients (434 of 575 (75%)) were able to receive all the planned *Erwinia* L-asparaginase to complete their treatment courses. There were 18 patients who were scheduled to receive between 24 to 48 doses, 16 (89%) of these patients were able to receive all the planned doses. As expected the most common reason patients did not receive the planned therapy with *Erwinia* L-asparaginase was allergic reaction.

6 Review of Efficacy

6.1 Indication

The applicant proposed the following indication for *Erwinia* L-asparaginase in the original BLA submission:

ERWINAZE (*Erwinia* L-asparaginase) 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.

FDA recommended the following indication determined during label review (pending additional data substantiating efficacy):

(b) (4)

6.1.1 Methods

Study AALL07P2 "Pharmacology and Toxicity of *Erwinia* L-asparaginase (Erwinaze; Crisantaspase; IND 290) Following Allergy to Pegaspargase in Treatment of Children with Acute Lymphoblastic Leukemia (ALL)" was an open label trial conducted at 31 COG phase I institutions. This study was designed to assess the PK, PD, and related toxicities of *Erwinia* L-asparaginase used as replacement therapy for pegaspargase dosing. Patients received *Erwinia* L-asparaginase 25,000 IU/m² x 6 doses IM on a three days weekly schedule (Monday / Wednesday / Friday) as a replacement for each scheduled dose of pegaspargase remaining on the original treatment protocol.

Protocol Amendments:

Table 6: Protocol Amendments AALL07P2

Protocol Amendments AALL07P2	
December 13, 2007	▪ Original protocol
September 23, 2008	▪ Formatting and editing changes ▪ Update personnel ▪ Details EKG data collection ▪ Youth information sheet added

Inclusion Criteria: (copied from protocol in submission)

- Age: Patients must be > 1 year and ≤ 30 years of age.

- Diagnosis: Patients must be on a frontline COG ALL treatment study at a participating institution.
- Patients must have had a Grade 2 or higher hypersensitivity reaction (CTCAE v 3.0 [Common Terminology Criteria for Adverse Events]) to PEG-asparaginase. Patients must have 1 or more courses of asparaginase remaining in their treatment protocol.

Exclusion Criteria: (copied from protocol in submission)

- Patients must not have previously received *Erwinia* L-asparaginase
- Patients must not have a history of \geq Grade 2 pancreatitis.

Dosing Regimen:

- *Erwinia* L-asparaginase 25,000 IU/m² x 6 doses IM on a Monday / Wednesday / Friday, Wednesday / Friday / Monday or Friday / Monday / Wednesday schedule as a replacement for each scheduled dose of pegaspargase remaining on the original treatment protocol.
- All other chemotherapy to continue according to the original treatment protocol.

6.1.2 Demographics

Enrollment

- Planned – 55 to have 50 evaluable patients
- Enrolled - 59
- Eligible – 58 - Definition: Subjects who met eligibility criteria
- Evaluable - Definition: Subjects with evaluable samples for the PK/PD analysis available as determined by the study chair
PK population – 53
PD population – 47
- Safety population – 58 – Definition: Eligible subjects who received at least 1 dose of *Erwinia* L-asparaginase

Table 7: Demographics AALL07P2

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	5 (9%)

REVIEWER COMMENT:

The population in this review differs slightly from the population as defined by EUSA in the submission. Subject 797513 is not eligible because he was not registered on a therapeutic COG ALL protocol. EUSA includes him in the safety population because he received one dose of study agent before the ineligibility was noted.

Subject 798213 is included in the safety population because he was removed from the study after he experienced a grade 3 allergic reaction with second dose of *Erwinia* L-asparaginase on April 28, 2010. The applicant excluded this subject because the data

capture form with the clinical information was submitted a week after the cut off date of April 30, 2010.

6.1.3 Subject Disposition

The targeted number of patients who received a full course *Erwinia* L-asparaginase with PK samples for submission of this application was 50. The applicant cut off data for this application on April 30, 2010. Subjects enrolled on this study continued to receive ongoing treatment with *Erwinia* L-asparaginase after submission of the application.

Table 8: Subject Disposition AALL07P2

N= 58	
Completed first course of therapy	57
Completed second course of therapy	39
Completed third course of therapy	29
Completed fourth course of therapy	19
Completed fifth course of therapy	13
Completed sixth course of therapy	6
Completed seventh course of therapy	2
Completed eighth course of therapy	2
Discontinued prior to completing planned therapy	
Adverse Reaction	
Systemic allergic reaction	5
Other	
Physician decision	2
Patient decision	2
Relapse	1

6.1.4 Analysis of Primary Endpoint(s)

Endpoint

The primary endpoint is the proportion subjects with a 48 hour trough serum asparaginase activity is ≥ 0.1 IU/mL.

Planned Analysis

This study is powered to test the hypothesis target level in 70% of patients meeting this trough threshold activity against an alternative of in 50% of patients meeting this trough threshold activity.

Results

REVIEWER COMMENT:

The FDA DSI audit of the laboratory responsible for the PK analysis concluded that the PK results were not reliable. The results can not be evaluated.

ADDENDUM AFTER REVIEW OF 9/16/11 SUBMISSION

The applicant submitted the results of the PK analysis of archived samples obtained from 48 subjects enrolled on the AALL07P2 trial. These samples were originally collected to evaluate immunogenicity during the first cycle of *Erwinia* L-asparaginase. The demographics of these 48 patients are summarized in Table 9 below.

Table 9: Demographics of the 9/16/11 Efficacy Subset

Demographics AALL07P2 Subjects (9/16/11 Efficacy Subset)	
N= 48	
Sex	
Male	27 (56%)
Female	21 (44%)
Age in Years	
2 – 5	15 (31%)
6 - 10	11 (23%)
11 - 18	22 (46%)
Mean	9.5
Median	10
Range	2-18
Race/Ethnicity	
White Not Hispanic or Latino	23 (48%)
White Hispanic or Latino	14 (29%)
Black or African American Not Hispanic or Latino	5 (10%)
Asian	3 (6%)
Other Not Hispanic or Latino	1 (2%)
Other Hispanic or Latino	2 (4%)
Diagnosis	
ALL B-lineage	38 (79%)
ALL T-lineage	5 (10%)
ALL	5 (10%)

The samples for this analysis were collected prior to the 4th dose of *Erwinia* L-asparaginase. This represents a trough value measured during the middle, after the 3rd of 6 doses, of an *Erwinia* L-asparaginase course rather than at the end of the cycle, after the 5th of six doses as originally specified.

The asparaginase activity was ≥ 0.1 IU/ml in every sample tested at either 48-hour (n=35) or 72-hour (n=13) post dose 3. Eighty percent (28/35) of those evaluated at 48 hours and 38% (5/13) evaluated at 72 hours had serum asparaginase activity levels ≥ 0.4 IU/mL.

REVIEWER COMMENT:

This analysis adequately demonstrates the activity of *Erwinia* L-asparaginase and supports approval of this application.

6.1.5 Analysis of Secondary Endpoints(s)

Endpoint 1.

Asparagine depletion

Planned Analysis

Adequate asparagine depletion was determined to be plasma asparagine $\leq 3\mu\text{M}$ (0.396 $\mu\text{g/mL}$)

Results

REVIEWER COMMENT:

Samples for evaluation of this endpoint were not collected with a validated methodology. The FDA DSI audit of the laboratory responsible for the PD analysis concluded that the PD results were not reliable. Asparagine depletion data can not be used to support this application.

Endpoint 2.

Incidence of anti-*Erwinia* asparaginase antibodies in children treated with a course(s) of *Erwinia* L-asparaginase following clinical allergy to pegaspargase.

REVIEWER COMMENT:

Validated immunogenicity assays were not developed at the time this application was submitted. The applicant has submitted a schedule to complete assay development, assay validation, and evaluation of the clinical samples. The evaluation of clinical samples can be done as a post marketing requirement or at the time when the application is resubmitted with PK data to support the efficacy of *Erwinia* L-asparaginase in this indication.

Endpoint 3.

Incidence of asparaginase-related toxicities following treatment with *Erwinia* L-asparaginase

See section 7 for safety analysis.

6.1.6 Other Endpoints

No other endpoints were evaluated.

6.1.7 Subpopulations

REVIEWER COMMENT:

The FDA DSI audit of the laboratory responsible for the PK analysis concluded that the PK results were not reliable. The results can not be evaluated.

ADDENDUM AFTER REVIEW OF 9/16/11 SUBMISSION

There were 100% of the samples obtained after dose 3 of *Erwinia* L-asparaginase with a trough asparaginase activity > 0.1 IU/ml. No additional subgroup analysis is feasible.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No relevant information in the submission.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

REVIEWER COMMENT:

The FDA DSI audit of the laboratory responsible for the PK analysis concluded that the PK results were not reliable. The results can not be evaluated.

ADDENDUM AFTER REVIEW OF 9/16/11 SUBMISSION

The analysis supporting approval of this application only included samples obtained after the 3rd dose of *Erwinia* L-asparaginase administered during the first course of therapy, therefore there is no analysis of the persistence of efficacy in this review.

6.1.10 Additional Efficacy Issues/Analyses

REVIEWER COMMENT:

The FDA DSI audit of the laboratory responsible for the PK analysis concluded that the PK results were not reliable. The results can not be evaluated.

ADDENDUM AFTER REVIEW OF 9/16/11 SUBMISSION

No additional efficacy issues were identified.

7 Review of Safety

Safety Summary

The safety database contained data from 630 patients who received *Erwinia* L-asparaginase in the AALL07P2 trial or the EMTP. There were no control subjects for comparison.

Asparaginase is administered as a component of multi agent chemotherapy. This makes attribution of adverse events challenging. Reported adverse events may be related to concomitant therapy or to active leukemia. The toxicity profile of asparaginase is well described as it has been a component of ALL therapy for more than 40 years.

The most significant toxicity is allergic reaction. Rarer but potentially life threatening toxicities include pancreatitis and coagulopathy. Hyperglycemia and liver test abnormalities are associated with asparaginase therapy. Concomitant steroids contribute to the incidence of hyperglycemia and concomitant chemotherapy such as methotrexate, 6-mercaptopurine and anthracyclines contribute to the incidence of liver abnormalities.

In order to assess the safety of *Erwinia* L-asparaginase compared to *E. coli*-derived L-asparaginase the incidence of these adverse event in the safety population was compared to the incidence reported in the pegaspargase label. As would be expected, the incidence of allergic reactions was higher with *Erwinia* L-asparaginase. These patients received *Erwinia* L-asparaginase because they had developed an allergic reaction to *E. coli*-derived L-asparaginase. The incidence of pancreatitis, coagulopathy, hyperglycemia and liver abnormalities was lower in *Erwinia* L-asparaginase treated subjects than the incidence reported for pegaspargase.

The safety profile of *Erwinia* L-asparaginase supports approval of this agent.

ADDENDUM AFTER REVIEW OF 9/16/11 SUBMISSION

No additional safety data was submitted.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 10: Trials Included in Safety Evaluation

Clinical Trial	Title	Comment
AALL07P2	Pharmacology and Toxicity of <i>Erwinia</i> L-asparaginase (Erwinase; Crisantaspase: IND 290) Following Allergy to Pegaspargase in Treatment of Children with Acute Lymphoblastic Leukemia (ALL)	Prospective PK (PD) Trial of <i>Erwinia</i> L-asparaginase in Patients with ALL allergic to pegaspargase. Safety Population N=58
EMTP	Erwinaze Master Treatment Protocol	Additional clinical safety data was prospectively collected for patients treated on this expanded access protocol Safety Population N=572

7.1.2 Categorization of Adverse Events

AALL07P2

AEs were captured on COG standard electronic data sets. There was a query if the subject experienced an AE. If answer was yes the reported was instructed to complete The AALL07P2 AE CRF.

See AE query below:

Figure 1: Format to Query Adverse Events on AALL07P2

• ADVERSE EVENTS			
Did patient experience any reportable adverse events during the indicated period? (Erwinase related adverse events)*	<input type="checkbox"/> - Yes <input type="checkbox"/> - No	• Required field	ExprAclPrd
If yes, complete the AALL07P2 Adverse Event Reporting Screen using CTC version 3.0			

Clinical Review
 Patricia Dinndorf
 BLA 125359 Original
 Erwinia L-asparaginase, Erwinaze

Figure 2: Adverse Event CRF AALL07P2

Institutional Reminders: Adverse events to be reported: All Erwinase-related adverse events including allergic reactions, pancreatitis, coagulopathy (hemorrhage, thrombosis or infarct), hyperbilirubinemia, hyperglycemia, hyperlipidemia, ketoacidosis and CNS events (bleed, thrombosis or infarction, cerebral vein thrombosis). All grades are to be reported. See section 3.3.2 of the NCI Guidelines on Adverse Event Reporting Requirements (<http://ctep.cancer.gov/reporting/adeers.html>) for instructions on reporting Persistent/Recurring Adverse Events.

QUESTIONS (ELEMENTS)	VALID VALUES	RULES & VALIDATIONS	SDC USE ONLY
Serial Number *	Automatically assigned by the system.	<ul style="list-style-type: none"> Required field 	SerialNumber
AALL07P2 Reporting Period: *	Drop down box	<ul style="list-style-type: none"> Required field 	AALL07P2ReportingPeriod
Select the Reporting Period during which the Adverse Event began.			C
CTCAEv3.0 Adverse Event (Select) TYPE *	Drop-down box	<ul style="list-style-type: none"> Required field 	CTCAEv30AESelTYPE
Help Document			C
If other (e.g. pain, other) is selected, Specify adverse event:		<ul style="list-style-type: none"> Required if 'other, specify' selected above. Blank if not 'other, specify' 	SpfAeTxt
CTC Adverse Event Grade *	<input type="checkbox"/> - 1 Mild Adverse Event <input type="checkbox"/> - 2 Moderate Adverse Event <input type="checkbox"/> - 3 Severe or Undesirable Adverse Event <input type="checkbox"/> - 4 Life threatening or Disabling Adverse Event <input type="checkbox"/> - 5 Death Related to Adverse Event	<ul style="list-style-type: none"> Required field 	CTC_AE_GD
			C
CTC Adverse Event Attribution: *	<input type="checkbox"/> - Definite <input type="checkbox"/> - Possible <input type="checkbox"/> - Probable	<ul style="list-style-type: none"> Required field 	CTC_AE_ATTR_SCALE
Adverse Event Onset Date: *	(MM/DD/CCYY)	<ul style="list-style-type: none"> Required field Cannot be a future date Must be greater than or equal to enrollment date 	CTC_AE_ONSET_DT
			DLC
Has the CTC adverse event resolved? *	<input type="checkbox"/> - Yes <input type="checkbox"/> - No	<ul style="list-style-type: none"> Required 	CTCAEResolvedIND
Adverse Event Resolution Date:	(MM/DD/CCYY)	<ul style="list-style-type: none"> Required if yes above Not answered if No above If answered, date must be greater than or equal to date of enrollment If answered, cannot be a future date 	RslAeDt
Help text: Leave this field blank if the AE has not resolved. When the AE is resolved enter the resolution date on this form irrespective of the reporting period in which it resolved.			DLC
Has an AdEERs report been filed? *	<input type="checkbox"/> - No <input type="checkbox"/> - Yes	<ul style="list-style-type: none"> Required field. Must be yes, if AE grade is equal to 5 	AdEERSRptFld
			C
If yes above, what is the AdEERs ticket number: AdEERs reports are to be submitted one per course. If a report was filed for a given course, and subsequent information is found that was not on the initial report, please amend the report. Please do not fill out a new AdEERs report.		<ul style="list-style-type: none"> Required if yes above. Not answered if No above. Numeric values only 	AdEERsTktNbr
			C
Comments:	Text		RSCH_COMMENTS_TXT

The following table maps the AE code to the AE term captured for these electronic data CRFs.

Table 11: Map AE Term to AE Code in AALL07P2

Number*	AETERM
1010000	1010.000: ALLERGIC REACTION/HYPERSENSITIVITY (INCLUDING DRUG FEVER)
1646000	1646.000: LEUKOCYTES (TOTAL WBC)
1664000	1664.000: NEUTROPHILS/GRANULOCYTES (ANC/AGC)
1670000	1670.000: PLATELETS
2810000	2810.000: FATIGUE (ASTHENIA, LETHARGY, MALAISE)
2817000	2817.000: FEVER (IN THE ABSENCE OF NEUTROPENIA, WHERE NEUTROPENIA IS DEFINED AS ANC <1.0 X 10E9/L)
3444001	3444.001: DERMATITIS: RASH: DERMATITIS ASSOCIATED WITH RADIATION - CHEMORADIATION
3458000	3458.000: URTICARIA (HIVES, WELTS, WHEELS)
4062000	4062.000: NAUSEA
4084000	4084.000: VOMITING
5119000	5119.000: FEBRILE NEUTROPENIA (FEVER, UNK. ORIGIN, W/O INFECTION, ANC <1X10E9, FEVER ≥ 38.5°C)
5128077	5128.077: INFECTION (CLINICAL OR MICROBIOLOGICAL DX) W/ GR 3-4 NEUTROPHILS, ANC <1.0X10E9 - BLOOD
5137077	5137.077: INFECTION WITH NORMAL ANC OR GRADE 1 OR 2 NEUTROPHILS - BLOOD
5712000	5712.000: ALBUMIN, SERUM-LOW (HYPOALBUMINEMIA)
5718000	5718.000: ALT, SGPT (SERUM GLUTAMIC PYRUVIC TRANSAMINASE)
5722000	5722.000: AST: AST, SGOT (SERUM GLUTAMIC OXALOACETIC TRANSAMINASE)
5726000	5726.000: BILIRUBIN: BILIRUBIN (HYPERBILIRUBINEMIA)
5742000	5742.000: HYPERGLYCEMIA: GLUCOSE, SERUM-HIGH (HYPERGLYCEMIA)
6346001	6346.001: MOOD ALTERATION - AGITATION
6810018	6810.018: PAIN - HEAD/HEADACHE

EMTP

The applicant developed CRFs in collaboration with the FDA. These forms included sections to gather information regarding *Erwinia* L-asparaginase toxicity.

The toxicity data was captured using a check box format. Investigators were requested to report coagulation test values that were obtained at the onset of a thrombotic or hemorrhagic AE. Investigators were requested to report AST, ALT, bilirubin, amylase

and lipase associated at the time of onset with hepatic or pancreatic disorders. Three components of the laboratory values were captured, normal ranges of the testing laboratory, the laboratory value and units of the laboratory value. There were spaces provided to supply additional information about the specific AE captured. There was a section to report any other significant AE not included as a standard inquiry and a section to report information about deaths within 28 days of receiving *Erwinia* L-asparaginase.

These forms captured the CTCAE version 3 grade 1 through 5 categorization of allergic reactions, liver dysfunction, pancreatitis, and grade 3&4 hyperglycemia. Grade was not captured for other AEs reported. Investigators did not report attribution.

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

The safety data from the AALL07P2 study and the EMTP were combined for an integrated study summary analysis. The ISS safety population contained 633 subjects.

7.2 Adequacy of Safety Assessments

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

Exposure

See section 6.1.4 for AAALL07P2 and section 5.3.7 for the EMTP study.

Demographics

See section 6.1.2 for AAALL07P2 and section 5.3.5 for the EMTP study.

7.2.2 Explorations for Dose Response

These were not done as a component of the developmental plan for this BLA.

7.2.3 Special Animal and/or In Vitro Testing

These were not done as a component of the developmental plan for this BLA.

7.2.4 Routine Clinical Testing

See 7.4.2 Laboratory Findings below.

7.2.5 Metabolic, Clearance, and Interaction Workup

These were not done as a component of the developmental plan for this BLA.

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

AALL07P2

Pegaspargase was given the indication for first line treatment of ALL based on a randomized comparison to native *E. coli* L-asparaginase, the Children's Cancer Group (CCG) 1962 trial. This trial only captured grade 3 or greater toxicity. The per-patient incidence of Grade 3 and 4 adverse reactions was presented in the label. The following table compares the incidence of Grade 3 and 4 adverse reactions associated with *E. coli* L-asparaginase and pegaspargase therapy to the incidence associated with *Erwinia* L-asparaginase therapy in the COG trial AALL07P2.

Table 12: Grade 3&4 Adverse Reactions on AALL07P2 Compared to CCG 1962

Per Patient Incidence of Non Hematologic Non Infectious Grade 3 & 4 Adverse Reactions			
	CCG 1962 N=58 Pegaspargase	CCG 1962 N=59 Native <i>E. coli</i> Asparaginase	COG AALL07P2 N=58 <i>Erwinia</i> Asparaginase
Allergic Reaction / Hypersensitivity	1 (2%)	0	5 (9%)
Pancreatitis	1 (2%)	1 (2%)	0
Hyperglycemia	3 (5%)	2 (3%)	0
Clinical Coagulation Abnormalities - Thrombosis	2 (3%)	2 (3%)	0
Clinical Coagulation Abnormalities - Coagulopathy	1 (2%)	3 (5%)	0
Abnormal Liver Tests	3 (5%)	5 (8%)	1 (2%)
Elevated Transaminases	2 (3%)	4 (7%)	1 (2%)
Hyperbilirubinemia	1 (2%)	1 (2%)	0

EMTP

The safety evaluation of pegaspargase for the indication of initial therapy of ALL was augmented by safety data collected from the CCG 1991 trial. In the CCG 1991 trial pegaspargase was the only asparaginase used. Only grade 3 and 4 non-hematologic toxicities safety data were collected in this trial. The following table compares the per patient incidence of grade 3 and 4 adverse reactions of *Erwinia* L-asparaginase reported in the EMTP to the incidence reported with pegaspargase therapy in the CCG 1991.

Table 13: Grade 3&4 Adverse Reactions on EMTP Compared to CCG 1991

Per Patient Incidence of Non Hematologic Non Infectious Grade 3 & 4 Adverse Reactions		
	CCG 1991 N=2770 Pegaspargase	EMTP N=572 <i>Erwinia</i> Asparaginase
Allergic Reaction / Hypersensitivity	1%	27 (5%)
Pancreatitis	2%	4 (1%)
Hyperglycemia	5%	11 (2%)
Clinical Coagulation Abnormalities		
- Thrombosis / Hemorrhage	2%	7 (1%)
- Coagulopathy	7%	0
Elevated Transaminases	11%	2 (<1%)

REVIEWER COMMENT:

The incidence of known AEs associated with *Erwinia* asparaginase therapy was not greater than that reported for *E. coli* derived asparaginase therapy with the exception of clinical allergic reactions. The higher incidence of allergic reactions is not surprising because subjects receiving *Erwinia* L-asparaginase had previously experienced an allergic reaction to an *E. coli*-derived asparaginase.

7.3 Major Safety Results

7.3.1 Deaths

AALL07P2

There were no deaths.

EMTP

There were 6 reported deaths in the EMTP. None of these were obviously related to *Erwinia* asparaginase exposure. Five subjects had documented disease progression.

The subject without documented disease progression was a 17 year old female initially diagnosed with ALL on (b) (6). She relapsed (b) (6). She received *Erwinia* L-asparaginase between May 10, 2008 and April 22, 2009. She died at home (b) (6).

REVIEWER COMMENT:

It is unlikely that *Erwinia* L-asparaginase was a major contributory factor in this death. The last dose was given 13 days prior to death. No asparaginase toxicities were documented.

7.3.2 Nonfatal Serious Adverse Events

AALL07P2

AEs were not characterized as serious in the data capture form in the AALL07P2 study. See table of treatment emergent AEs in section 7.4.1 Common Averse Events below.

EMTP

The applicants table summarizing Serious Adverse Events reported in $\geq 1\%$ of patients is presented below:

Table 14: Serious Adverse Events on EMTP

System Organ Class/ Preferred Term	<i>Erwinia</i> asparaginase (N=573)* n (%)
Total Number of Serious TEAE	418
Number of Patients with At Least One Serious TEAE	162 (28.3)
Immune system disorders	69 (12.0)
Anaphylactic reaction	53 (9.2)
Hypersensitivity	16 (2.8)
Gastrointestinal disorders	39 (6.8)
Pancreatitis	20 (3.5)
Vomiting	13 (2.3)
Nausea	10 (1.7)
Abdominal pain	7 (1.2)
Investigations	38 (6.6)
Alanine aminotransferase increased	13 (2.3)
Aspartate aminotransferase increased	10 (1.7)
Lipase increased	8 (1.4)
Blood amylase increased	7 (1.2)
General disorders and administration site conditions	29 (5.1)
Pyrexia	15 (2.6)
Blood and lymphatic system disorders	20 (3.5)
Neutropenia	8 (1.4)
Febrile neutropenia	7 (1.2)
Metabolism and nutrition disorders	14 (2.4)
Hyperglycemia	10 (1.7)

REVIEWER COMMENT:

No unexpected serious events were reported. The table includes allergic reactions, pancreatitis including clinical and laboratory signs of pancreatitis, elevated transaminases, and hyperglycemia. Fever and neutropenia are the known expected AEs in patients being treated for ALL.

7.3.3 Dropouts and/or Discontinuations

AALL07P2

There were 4 subjects that discontinued therapy due to an AE. These were all systemic allergic reactions.

EMTP

See table in 5.3.6 Subject Disposition for discontinuation information on the EMTP.

7.3.4 Significant Adverse Events

AALL07P2

See section 7.2.6 Evaluation for Potential AEs for Similar Drugs in Drug Class above.

EMTP

See section 7.2.6 Evaluation for Potential AEs for Similar Drugs in Drug Class above.

7.3.5 Submission Specific Primary Safety Concerns

See section 7.2.6 Evaluation for Potential AEs for Similar Drugs in Drug Class above.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

AALL07P2

The applicant's table of treatment-emergent AEs is copied below.

Table 15: Treatment Emergent Adverse Events on AALL07P2 by Preferred Term

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)

EMTP

The applicants table summarizing Common Treatment Emergent AEs reported in $\geq 1\%$ of patients is presented below:

Table 16: Treatment Emergent Adverse Events on EMTP by Preferred Term

System Organ Class/ Preferred Term	<i>Erwinia</i> 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)

7.4.2 Laboratory Findings

AALL07P2

The following laboratory parameters were evaluated prior to the first dose of *Erwinia* L-asparaginase (baseline) and following the last dose of *Erwinia* L-asparaginase of each course of therapy (post therapy) in 58 subjects:

Hematology:

- Complete blood cell count (CBC)/differential/platelets.

Coagulation:

- prothrombin time (PT) (normal 8.8 to 14.1 seconds)
- partial thromboplastin time (PTT) (normal 24 to 39 seconds)
- fibrinogen (normal 160 to 420 mg/dL)
- protein C activity (normal 55 to 140%)
- protein S activity (normal 63 to 140%)
- anti-thrombin III (ATIII) (normal 77 to 123%)
- d-dimer (normal 0 to 0.4)
- fibrin degradation products (FDPs) (upper limit normal 4 µg/mL)

Serum chemistry:

- ALT (normal 0 to 55 IU/L)
- AST (normal 0 to 40 IU/L)
- bilirubin (normal 0.1 to 1.2 mg/dL)
- blood urea nitrogen (BUN) (normal 5 to 26 mg/dL)
- creatinine (normal 0.5 to 1.5 mg/dL) [These are inappropriate normal values for a pediatric population]
- cholesterol (normal 100 to 169 mg/dL)
- triglycerides (normal 0 to 149 mg/dL)
- amylase (normal 28 to 100 U/L)
- lipase (normal 0 to 59 U/L)

Results:

Coagulation Battery:

PT

There were 4 subjects with post therapy prolongation of PT. These were at levels that were clinically insignificant, that is 14.3 to 15 seconds. There were no hemorrhagic or thrombotic AEs documented in these subjects.

PTT

The baseline PTT was prolonged in 18 subjects. There were 25 subjects with prolonged PTTs greater than the baseline PTT at the post therapy timepoint. These results must be interpreted with caution because PTT is exquisitely sensitive to heparin and these studies were most likely drawn from heparinized central catheters. There were no hemorrhagic or thrombotic AEs documented in these subjects.

Fibrinogen

The baseline fibrinogen was low in 6 subjects. There were 44 subjects with abnormal post therapy fibrinogen determinations lower than baseline. There were no hemorrhagic or thrombotic AEs documented in these subjects.

Protein C Activity

The baseline protein C activity was low in 1 subject. There were 29 subjects with abnormal post therapy protein C activity lower than baseline. There were no hemorrhagic or thrombotic AEs documented in these subjects.

Protein S Activity

The baseline protein S activity was low in 7 subjects. There were 43 subjects with abnormal post therapy protein S activity lower than baseline. There were no hemorrhagic or thrombotic AEs documented in these subjects.

ATIII

The baseline AT III activity was low in 4 subjects. There were 51 subjects with abnormal post therapy AT III activity lower than baseline. There were no hemorrhagic or thrombotic AEs documented in these subjects.

D-Dimer

There were 35 subjects with elevated d-dimer determination at baseline. There were 18 subjects with post therapy elevated d-dimer determinations higher than baseline. There were no hemorrhagic or thrombotic AEs documented in these subjects.

FDPs

There were 16 subjects with elevated FDPs at baseline. . There were 10 subjects with post therapy elevated FDP determinations higher than baseline. There were no hemorrhagic or thrombotic AEs documented in these subjects.

REVIEWER COMMENT:

The following coagulation proteins were decreased in the majority of subjects after a 2 week course of *Erwinia* L-asparaginase: fibrinogen, protein C activity, protein S activity, and AT III. The effect of *Erwinia* L-asparaginase treatment on PT and PTT was not clearly demonstrated. There was no effect on d-dimers or FDPs. Importantly no subjects with abnormalities in these coagulation tests were reported to experience a hemorrhagic or thrombotic AE.

Serum Chemistry Battery:

Hepatic:

ALT

There were no subjects with \geq grade 3 ALT elevation documented at the post therapy evaluation.

AST

There were no subjects with \geq grade 3 ALT elevation documented at the post therapy evaluation.

Bilirubin

There was one subject with a grade 3 elevation of bilirubin after course 1 of *Erwinia* L-asparaginase. This subject received 3 additional course of *Erwinia* L-asparaginase with normal bilirubin at the end of each course.

Renal:

BUN

There were 2 subjects with post therapy mild elevation in BUN.

Creatinine

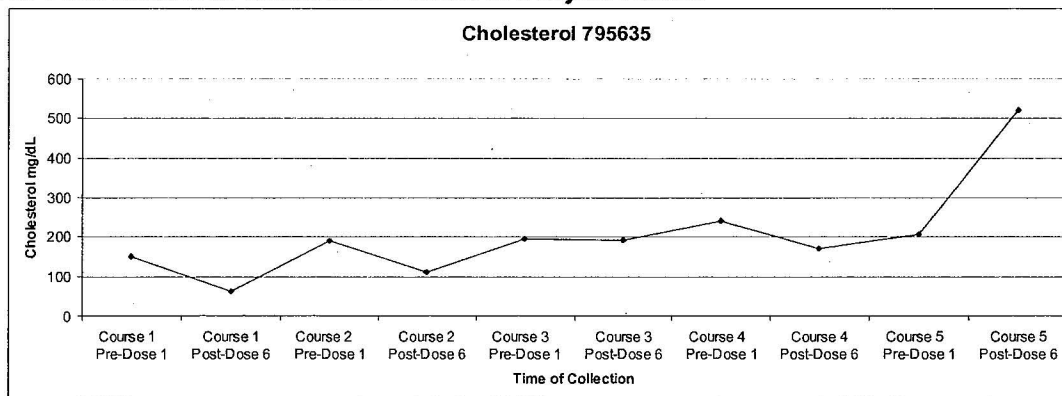
There were no subjects with post therapy abnormalities in creatinine.

Metabolic:

Cholesterol

No grade 3 toxicity was identified. One subject had a single grade 4 cholesterol determination after the 5th course of *Erwinia* L-asparaginase.

Figure 3: Time Course of Cholesterol Levels in Subject 795635



Triglycerides

Five subjects demonstrated grade 3 and 4 elevations in triglycerides at post therapy evaluations.

Figure 4: Time Course of Triglyceride in Subject 791637

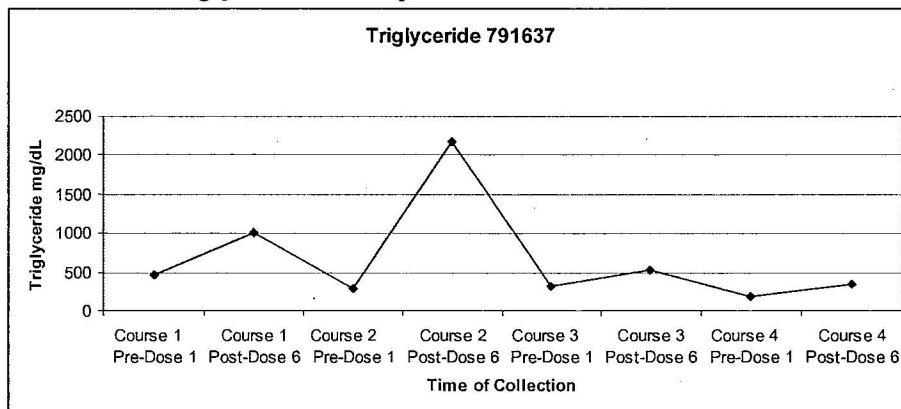


Figure 5: Time Course of Triglyceride in Subject 795635

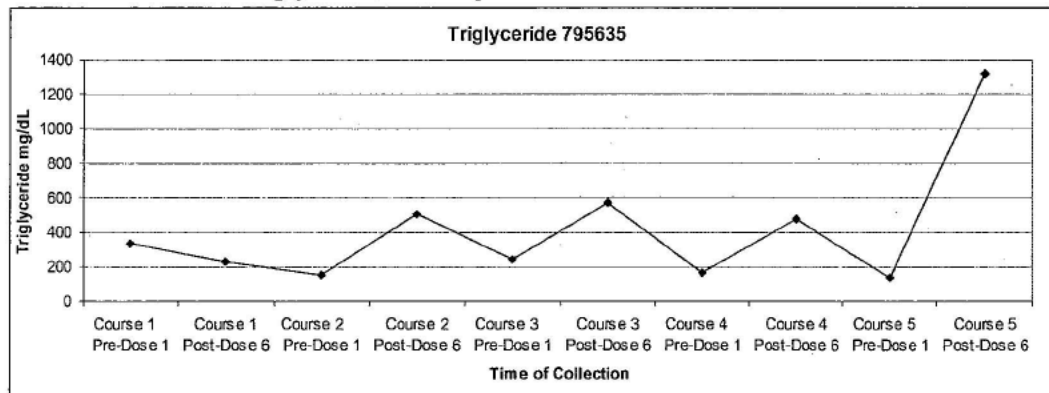


Figure 6: Time Course of Triglyceride in Subject 794765

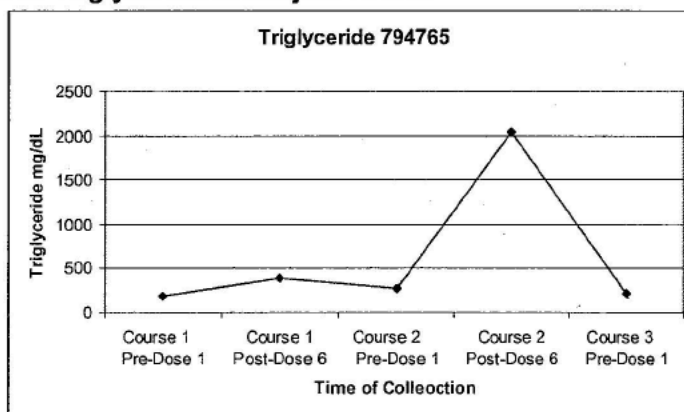


Figure 7: Time Course of Triglyceride in Subject 789794

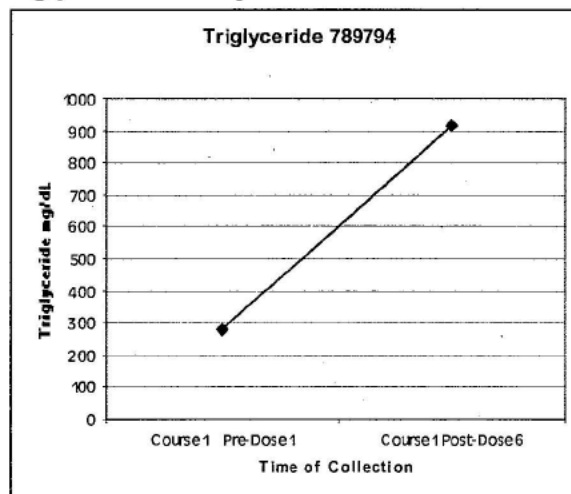
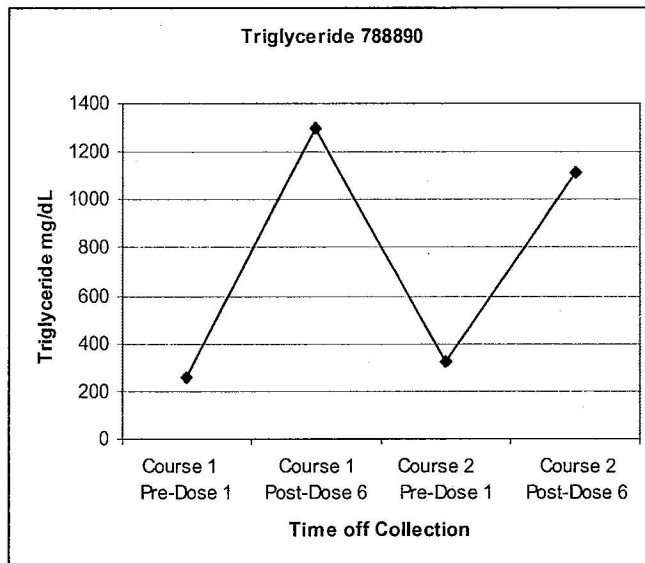


Figure 8: Time Course of Triglyceride in Subject 788890



Pancreas:

Amylase

There were no subjects with post therapy evaluation of amylase \geq to grade 3.

Lipase.

There were 3 subjects with post therapy evaluation of lipase \geq to grade 3. These subjects were not reported to have pancreatitis or symptoms such as abdominal pain associated with pancreatitis.

REVIEWER COMMENT:

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

EMTP

Laboratory data was not systematically collected in the EMTP.

7.4.3 Vital Signs

7.4.4 Electrocardiograms (ECGs)

AALL07P2

According to the Interdisciplinary Review Team (IRT) for QT studies no definitive conclusions regarding the QTc effects due to *Erwinia* L-asparaginase are possible from the data submitted. The assessment involved single post-treatment, locally read ECGs

collected at 1 hour post-dose 6 with categorical analysis only. The IRT team usually recommends in this circumstance that an ECG sub-study with intensive PK and time-matched ECGs and central over-read be conducted. However they defer to the clinical review team to determine the feasibility of this approach.

REVIEWER COMMENT:

Given the long history of this agent and related asparaginase agents and the absence of any cardiac signals associated with these agent I do not think additional studies are justified.

EMTP

ECGs were not evaluated in the EMTP.

7.4.5 Special Safety Studies/Clinical Trials

These were not necessary or done for this application.

7.4.6 Immunogenicity

Validated immunogenicity assays were not developed at the time this application was submitted. The applicant has submitted the following schedule to complete assay development, assay validation, and evaluation of the clinical samples. The evaluation of clinical samples will be done as a post marketing requirement.

Table 17: Schedule for Proposed Immunogenicity Testing

(b) (4)



7.5 Other Safety Explorations

These were not necessary or done for this application.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

These were not done as a component of the developmental plan for this BLA.

7.6.2 Human Reproduction and Pregnancy Data

These were not done as a component of the developmental plan for this BLA.

7.6.3 Pediatrics and Assessment of Effects on Growth

The AALL07P2 study was conducted in children 1 to 18 years of age. The majority of subjects included in the EMTP study were children.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no risk of drug abuse for this agent.

7.7 Additional Submissions / Safety Issues

None identified.

8 Postmarket Experience

There is no US post marketing experience. *Erwinia* L-asparaginase is licensed in some countries in Europe and in Canada. There is an extensive, greater than 50 years, experience in Europe and North America.

9 Appendices

9.1 Literature Review/References

None

9.2 Labeling Recommendations

This application will not be approved at this time. A new study to determine that the trough asparaginase activity is ≥ 0.1 IU/mL at 48 hours in patients who have developed allergic reactions to pegaspargase will be required. Therefore label content regarding efficacy will be addressed after appropriate data supporting efficacy has been submitted.

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 *Erwinia* L-asparaginase. The recommended changes as of 9/28/11 are summarized below:

(b) (4)

9.3 Advisory Committee Meeting

Not required.

9.4 Abbreviations

Table 20: Abbreviations

Abbreviations	
AE	Adverse event
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CCG	Children's Cancer Group
COG	Children's Oncology Group
CR	Complete response
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DFCI	Dana-Farber Cancer Institute
DSI	Division of Scientific Investigations
ECG	Electrocardiograms
EFS	Event free survival
EMTP	Erwinaze Master Treatment Protocol
EUSA	EUSA Pharma (US) Inc.
FDA	Food and Drug Administration
GLP	Good laboratory practice
IND	Investigational New Drug
IM	Intramuscularly
IRT	Interdisciplinary Review Team (for QT studies)
ISS	Integrated summary of safety
IU	International Units
IV	Intravenous
OPi	OPi SA
QC	Quality control
PD	Pharmacodynamic
PK	Pharmacokinetic
USAN	United States Adopted Names

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125359
Priority or Standard	Priority
Submit Date(s)	November 1, 2010
Received Date(s)	November 1, 2010
PDUFA Goal Date	May 3, 2011, Revised August 2, 2011
Division / Office	DBOP / OODP
Reviewer Name(s)	Patricia Dinndorf, MD
Medical Team Leader	Suzanne Demko, PA-C
Division Director	Patricia Keegan, MD
Review Completion Date	May 13, 2011
Established Name	<i>Erwinia</i> L-asparaginase
(Proposed) Trade Name	Erwinaze®
Therapeutic Class	Enzyme
Applicant	EUSA Pharma (USA), Inc.
Formulation(s)	Lyophilized powder for injection
Dosing Regimen	25,000 IU/m ² IM TIW for 2 weeks to replace a dose of pegaspargase
Indication(s)	Component of a multi-agent chemotherapeutic regimen for treatment of ALL in patients who develop allergic reaction to (b) (4)
Intended Population(s)	ALL patients with allergy to pegaspargase


 6/17/11
6/17/2011

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical recommendation for this application, BLA 125359 is not approvable as submitted. A complete response (CR) letter will be issued delineating the deficiencies. The efficacy to support approval of *Erwinia* L-asparaginase in this application was to be based on the pharmacokinetic (PK) endpoint of trough asparaginase activity. Patients who had developed allergic reactions to pegaspargase received *Erwinia* L-asparaginase 25,000 International units (IU)/m² x 6 doses intramuscularly (IM) on a Monday / Wednesday / Friday schedule as a replacement for each scheduled dose of pegaspargase remaining in their original treatment protocol. The Food and Drug Administration (FDA) agreed to accept a PK measurement, trough asparaginase activity of ≥ 0.1 IU/mL at 48 hours, as the outcome supporting efficacy. The FDA Division of Scientific Investigations (DSI) audit of the laboratory responsible for the PK analysis concluded that the PK results were not reliable. Based on this conclusion there is no data to support the efficacy of this agent.

The safety data submitted in this application, were collected from the PK study AALL07P2 "Pharmacology and Toxicity of *Erwinia* L-asparaginase (Erwinase; Crisantaspase: IND 290) Following Allergy to Pegaspargase in Treatment of Children with Acute Lymphoblastic Leukemia (ALL)" and the Erwinaze Master Treatment Protocol (EMTP). The safety data submitted are adequate to support approval of this agent if additional data is collected to confirm efficacy.

1.2 Risk Benefit Assessment

This application is CR. A new study to determine that the trough asparaginase activity is ≥ 0.1 IU/mL at 48 hours in patients who have developed allergic reactions to pegaspargase will be required.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This application is CR. A new study to determine that the trough asparaginase activity is ≥ 0.1 IU/mL at 48 hours in patients who have developed allergic reactions to pegaspargase will be required.

1.4 Recommendations for Postmarket Requirements and Commitments

This application is CR. A new study to determine that the trough asparaginase activity is ≥ 0.1 IU/mL at 48 hours in patients who have developed allergic reactions to pegaspargase will be required.

2 Introduction and Regulatory Background

2.1 Product Information

(copied from submission eCTD 2.2 Introduction page 1)

Erwinia L-asparaginase (Crisantaspase, Erwinase, Erwinaze), contains the (b) (4) enzyme L-asparagine amidohydrolase (L-asparaginase) derived in (b) (4) from the non-human (plant) pathogen *Erwinia chrysanthemi* (nee carotovora). The enzyme is also isolated from a variety of other sources (yeast, animal cells, fungi). Its molecular weight is about 135,000 daltons and is composed of four subunits (tetramers), each subunit having a molecular weight of about 35,000 daltons. *Erwinia* L-asparaginase is freely soluble in water. 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) per milligram of protein.

2.2 Tables of Currently Available Treatments for Proposed Indications

Asparaginase enzymes are an important component in the treatment of childhood ALL. *E. coli* L-asparaginase (Elspar®) an agent derived from *Escherichia coli* was the first agent approved for this indication in the 1970s.

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. 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 1991 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. It should be noted that the methodology for analysis of asparagine depletion was not validated. The trial was not adequately designed or conducted to evaluate superiority or non-inferiority of the event free survival (EFS) or survival but there did not appear to 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.

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

2.3 Availability of Proposed Active Ingredient in the United States

Erwinia L-asparaginase has been available in the US since 1968 under Investigational New Drug (IND) 290 originally held by Ipsen Ltd. In February 2006 Ipsen Ltd transferred all rights and responsibilities of IND 290 to Orphan Pharmaceuticals International (OPI) SA (subsequently EUSA Pharma (US)). *Erwinia* L-asparaginase (Crisantaspase, Erwinase) is available in some countries in Europe and in Canada.

2.4 Important Safety Issues With Consideration to Related Drugs

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* L-asparaginase, but in current clinical practice most patients receive initial therapy with pegaspargase.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 1: Regulatory History of the Submission

Date / Milestone	Summary of Issues
April 1968 / IND 290 submitted	Ipsen Ltd. original sponsor
February 2006 / IND 290 Transferred	IND 290 was transferred from Ipsen Ltd. to OPi SA (OPi)
May 2006 / Pre- BLA meeting	<ul style="list-style-type: none"> OPi proposed an (b) (4) (b) (4) 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 schedule of <i>Erwinia</i> L-asparaginase 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 <i>Erwinia</i> L-asparaginase PK and immunogenicity.
August 2007 / Change sponsor	OPi acquired by EUSA Pharma (US) Inc. (EUSA)
March 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.
July 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.
September 2009 / Pre- BLA meeting	<p>EUSA requested a pre-BLA Meeting</p> <ul style="list-style-type: none"> 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 <i>Erwinia</i> L-asparaginase. EUSA planned to include a synopsis of the Erwinaze Master Treatment Protocol (EMTP) that collected additional safety data.

	<ul style="list-style-type: none"> FDA informed EUSA that the application must contain an integrated summary of safety (ISS).
October 2009 / Proprietary name request	FDA Division of Medication Error Prevention and Analysis rejected the proposed proprietary name of (b) (4) <div style="background-color: black; width: 100%; height: 100%; min-height: 100px;"></div>
May 2009 / Proprietary name request	The proprietary name Erwinaze was granted 11/10/10
June 2010 / Request fast track status	Fast track status granted 7/15/10
September 2010 / Rolling BLA 125359	Submitted
November 1, 2010 / Final CMC unit	Priority review status granted; PDUFA final action date May 3, 2011
February 28, 2011 / Major amendment	PDUFA final action date revised August 2, 2011

2.6 Other Relevant Background Information

FDA considered asparagine depletion an acceptable surrogate for efficacy of *Erwinia* L-asparaginase in an application supported by a single study. However there is an inherent unreliability of asparagine assays because of *ex vivo* metabolism of asparagine in the collected samples. The sponsor was unable to develop a validated sample collection method for measuring asparagine. FDA agreed to accept a PK measurement, trough asparaginase activity of ≥ 0.1 IU/mL at 48 hours, as the primary endpoint of this submission. This level of asparaginase activity, which can be reliably measured in the clinical setting, is directly related to asparagine depletion.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Submission Quality

There were many problems identified in the original application. The applicant addressed most of the issues in a November 19, 2010 amendment to the application. At the December 14, 2010 Filing Meeting the following deficiencies were identified that were not adequately addressed by the November 19, 2010 submission:

- Case report forms (CRF) for every course of treatment (specimen transfer CRF) were not submitted
- The MedDRA coding was not done correctly for the AALL07P2 study
- The actual dose of *Erwinia* L-asparaginase was not included on the EX.xpt dataset

These were conveyed to the applicant during 2 teleconferences on December 16 and 21, 2010. In response to the FDA requests, on December 31, 2010 the applicant provided specimen transfer CRFs for each course subject received. The applicant submitted revised datasets correcting the MedDRA coding, and datasets providing the actual dose subjects received derived from the specimen transfer CRF. An audit of 20% of the specimen transfer CRFs confirmed the appropriate dose was reported on the EX.xpt dataset.

An audit of the safety data submitted from the EMTP was performed to determine the quality of this data. The CRFs of 122 subjects of the 577 were reviewed and compared to the safety data captured in the ADAE.xpt. Initially 44 subjects were audited but problems were identified in 12 cases and the audit was expanded to more fully ascertain the extent of the problems. Subjects who received first dose of *Erwinia* L-asparaginase in the months of May, August, and November were reviewed. The following problems were identified:

- There were no CRFs for 14 of 122 subjects selected for this audit.
- There were 12 subjects without reported adverse events (AE) with AEs identified on the CRFs.
- There were 3 subjects with AEs reported although no AEs were documented on the CRFs.
- The CRFs were designed as check box queries. The verbatim term generated "AETERM" and the MedDRA term it was mapped to "AECODE" from this form should have been consistent each time an AE was identified from a check box from the form. This was not the case.

For instance Allergic reaction if Local Reaction was checked it was reported as "AETERM" - "skin reaction", "AECODE" – "skin reaction" for Subject EMTP-000000000025579; "urticaria" for Subject EMTP-000000006687270; and "hypersensitivity" for Subject EMTP-000000099999082.

Systemic Allergic reaction grade 1 was coded as "anaphylactic reaction" for Subjects EMTP-000000000779117, and EMTP-000000000790100; "hypersensitivity" for Subject EMTP-000000001413127.

Systemic Allergic reaction grade 2 was coded as "anaphylactic reaction" for Subjects EMTP-000000099999048; and hypersensitivity" for Subject EMTP-000000000747797.

Systemic Allergic reaction grade 3 was coded as "eyelid edema", for Subject EMTP-000000000004978; "hypotension" for Subject EMTP-000000001249691.

The applicant was advised to submit revised datasets to correct these deficiencies in the day 74 deficiency letter. After the revised datasets were submitted to the application February 28, 2011, the revised safety datasets included 53 new cases with AEs identified. There were 102 case corrections made to the safety database. The BLA was deemed to be acceptable to allow substantive review of the clinical data.

Submission Integrity

DSI audits were conducted at one clinical site and the nonclinical site of sample evaluation. John Hopkins was chosen as the clinical audit site because it was judged to be a representative institution. There were 31 institutions who contributed from 1 to 6 subjects. John Hopkins contributed 3 subjects. No substantial regulatory violations were identified during the inspection.

The nonclinical site audit was conducted at the laboratory of (b) (4) at (b) (4) laboratory was responsible for the PK and PD analyses. As previously noted, the efficacy analysis was based on a PK endpoint, not a clinical measurement. The inspectional findings included the following problems:

Asparaginase Assay

- Failure to reject analytical run #480 on 4/8/10 when one of the three quality control (QC) samples failed the acceptance criterion. Seven samples were not re-assayed or required dilution.
- Failure to exclude serum samples from clinical sites received in the thawed state.
- Records of freezer temperatures for storage of asparaginase samples were not retrievable in an auditable form.
- Failure to document the times when samples were removed from frozen storage for analysis.
- Failure to adequately document preparation and storage of asparaginase stock solutions.
- Failure to adjust nominal asparaginase concentrations in calibrator and quality control solutions for the actual content of L-asparaginase commercial vials.

- Reported serum asparaginase activities less than the lower limit of quantitation. Specifically, the LLOQ [lower limit of quantitation] of the asparaginase assay was 0.025 IU/mL. However, asparaginase concentrations ranging from 0.009 to 0.024 IU/mL were reported.

Asparagine Assay

- Failure to reject analytical runs on 9 days when the quality control (QC) samples failed the acceptance criterion at one or two of the three QC concentrations.
- Failure to reject chromatograms when no asparagine internal standard was detected or when peaks could not be accurately integrated.
- Failure to exclude plasma samples from clinical sites which were unacidified or were received in the thawed state.
- Failure to demonstrate stability of samples under the conditions of the study.

Examples:

- a) The blank plasma used in method development, validation, and QC samples for the asparagine assay was citrate-phosphate-dextrose transfusion plasma, not heparin plasma as in study samples.
 - b) There was no evaluation of freeze/thaw or long-term frozen stability of samples for the asparagine assay. Most plasma samples were stored frozen for 3 to 11 months before assay for asparagine.
 - c) Records of freezer temperatures for storage of asparagine samples were not retrievable in an auditable form. The alarm system for temperatures outside -70°C to -90°C did not record the extreme excursions of temperature and durations of the excursions when the alarm triggered, including the event on 3/4/10 when the majority of study asparagine samples were in this freezer.
 - d) Some samples were received thawed (7 shipments), or without acid preservative for asparagine (61 samples), or with documented delays between sample collection and plasma acidification (multiple examples longer than 10 minutes).
 - e) The effectiveness of hydrochloric acid in preserving asparagine in plasma was tested only for *E. coli* asparaginase, not for *Erwinia* asparaginase.
 - f) The times when samples were removed from frozen storage for analysis were not recorded.
- Between-run accuracy and precision for the asparagine assay were not evaluated.
 - Failure to evaluate the variability in recovery of asparagine in more than one plasma sample in a run.
 - Failure to evaluate the stability of asparagine in stock solutions or extracts.
 - Only a single stock solution of asparagine was used for both calibrators and QC samples, rather than independently-prepared stock solutions, in both pre-study validation and within-study conduct.

- Failure to verify (by balance printer or witness) the weights of asparagine used for calibrator and QC stock solutions.

REVIEWER COMMENT:

The clinical pharmacology team determined that given the irregularities identified in the conduct of the PK analysis the data did not allow for substantive review of the primary efficacy endpoint. Without this analysis there is no evidence to support the efficacy of *Erwinia* L-asparaginase for this indication.

There was no validated sample collection methodology for asparagine sample collection. Moreover, because of the irregularities identified in the conduct of asparagine level analysis asparagine depletion can not be reliably assessed. Asparagine depletion data can not be used to support a finding of efficacy for this application.

3.2 Compliance with Good Clinical Practices

The title page of the Clinical Study Report for AALL07P2 (section 5.3.4.2.3) affirms the study was conducted in accordance with Good Clinical Practices.

3.3 Financial Disclosures

Financial disclosure forms of the principal investigator for each institution were submitted to the application 11/19/10 in amendment 3 to the application. No investigator reported disclosable financial interests.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The final reports for the manufacturing site inspection and product review were not available at the time this review was completed. The determination of the primary manufacturing site inspector is that the application is NA. The product reviewer has not made a final determination.

4.2 Clinical Microbiology

Not applicable for this application.

4.3 Preclinical Pharmacology/Toxicology

The nonclinical studies conducted on *Erwinia* sp asparaginases predated good laboratory practice (GLP) regulations. The information submitted with the application is not GLP compliant. *Erwinia* L-asparaginase is approved in Europe based on these non-GLP compliant studies submitted with the application. FDA reviewed the non-GLP compliant studies. Review of these studies in combination with the extended clinical experience with *Erwinia* L-asparaginase suggests that *Erwinia* L-asparaginase is reasonably safe for use in ALL patients who are allergic to L asparaginases derived from *E. coli*.

Under new controlling legislation (Patient Protection and Affordable Care Act, 2010), FDA can not rely on published literature for developmental and reproductive toxicity studies. The applicant will be required to submit the results of the complete battery of fertility, embryo-fetal and pre-post-natal nonclinical developmental toxicity studies. The applicant has provided plans and protocols to be evaluated for all required studies.

4.4 Clinical Pharmacology

Based on the results of the FDA DSI audit of the laboratory responsible for the PK analysis the clinical pharmacology review team determined that the PK results were not reliable. Therefore there is no efficacy data to support approval of this application.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2: Clinical Trials in the Submission

Clinical Trial	Title	Comment
AALL07P2	Pharmacology and Toxicity of <i>Erwinia</i> L-asparaginase (Erwinase; Crisantaspase: IND 290) Following Allergy to Pegaspargase in Treatment of Children with Acute Lymphoblastic Leukemia (ALL)	Prospective PK (PD) Trial of <i>Erwinia</i> L-asparaginase in Patients with ALL allergic to pegaspargase.
EMTP	Erwinaze Master Treatment Protocol	Additional clinical safety data was prospectively collected for patients treated on this expanded access protocol

5.2 Review Strategy

The design and efficacy results of Trial AALL07P2 will be reviewed in section 6 and the safety information will be reviewed in section 7. The design of the EMTP will be discussed in section 5.3. The safety data from the EMTP will be reviewed in section 7.

5.3 Discussion of Individual Studies/Clinical Trials - EMTP

5.3.1 Methods

The EMTP was instituted as an expanded access program. Collection of safety data on patients enrolled on the EMTP provided a larger safety population available for this application.

For this program the applicant developed CRFs in collaboration with the FDA. The CRFs included sections to gather information regarding demographics, disease and prior treatments, prior asparaginase exposure and toxicity, *Erwinia* L-asparaginase administration, concomitant medications, and *Erwinia* L-asparaginase toxicity.

The toxicity data was captured using a check box format. Investigators were requested to report coagulation test values that were obtained at the onset of a thrombotic or hemorrhagic AE. Investigators were requested to report aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, amylase and lipase associated at the time of onset with hepatic or pancreatic disorders. Three components of the laboratory values were captured, normal ranges of the testing laboratory, the laboratory value and

units of the laboratory value. There were spaces provided to supply additional information about the specific AE captured. There was a section to report any other significant AE not included as a standard inquiry and a section to report information about deaths within 28 days of receiving *Erwinia* L-asparaginase.

In order to increase the compliance of investigators returning CRFs, the applicant offered to pay the investigators \$150 when complete CRFs were returned.

5.3.2 Protocol Amendments

Table 3: Protocol Amendments

December 22, 2006	<ul style="list-style-type: none"> Original protocol
November 17, 2008	<ul style="list-style-type: none"> Formatting and editing changes Allowed T or B cell lymphoma as inclusion criteria Excluded subjects with only local pain or redness at injection site as an inclusion criteria Risk inactivation due to neutralizing antibodies associated with an allergic reaction Added specific dosing recommendations from the Childrens Oncology Group (COG), St Jude's, and Dana-Farber Cancer Institute (DFCI). Added section describing collection of safety data. Revised CRFs Revised consent form
February 9, 2009	<ul style="list-style-type: none"> Formatting and editing changes
June 25, 2009	<ul style="list-style-type: none"> Formatting and editing changes

5.3.3 Inclusion and Exclusion Criteria

Inclusion criteria: (copied from final protocol in submission)

- Age: no restrictions
- Patient must give a written informed consent to receive Erwinaze under IND 290
- Patient must be treated for acute lymphoblastic leukemia
- Children with either T or B cell lymphoma being treated with asparaginase.
- Patient must have either systemic hypersensitivity reactions to native or pegylated *E. coli* L-asparaginase. This includes patients with generalized rash with or without anaphylactic symptoms, but not those with only local pain or redness at the site of injection.
- Patients with previously documented local or systemic reactions to *E. coli* derived L-asparaginase.

Exclusion criteria: (copied from final protocol in submission)

- Previous allergic reaction to *Erwinia* L-Asparaginase (Erwinaze).
- Previous acute pancreatitis.
- Pregnant or lactating woman.

5.3.4 Drug Administration

Route of Administration: (copied from final protocol in submission)

May be administered intramuscularly, subcutaneously, or intravenously. The intramuscular route or the subcutaneous route, is the preferred route of administration.

When given according to the scheduled induction regimen, the product is first reconstituted by adding 1 to 2 ml Sodium Chloride Injection USP to the 10,000 U vial.

When given by the IV [intravenous] route reconstitute the product by adding 1 to 2 ml of Sodium Chloride Injection USP to the 10,000 U vial.

Dosing Regimen: (copied from final protocol in submission)

The precise dosing schedules will be conducted according to the recommendations of the treatment protocols.

Children Oncology Group (COG) recommends the following dosing schedule:

- Substitute Erwinaze 25,000 IU/m² intramuscularly x 6 doses on a every other day schedule (including week-ends and holidays) for each dose of pegylated *E. coli* derived L-Asparaginase (Pegaspargase) (days 1, 3, 5, 7, 9,11).

St Jude recommends the following dosing schedule:

- Substitute Erwinaze 20,000 IU/m² intramuscularly for each dose of native *E. coli* derived L-asparaginase during remission, induction or re-induction therapy.
- Substitute Erwinaze 25,000 IU/ m² twice weekly for each dose of native *E. coli* derived L-asparaginase during consolidation therapy.

Dana-Farber Cancer Institute (DFCI) recommends the following dosing schedule:

- Substitute Erwinaze 20,000 IU/ m² intramuscularly twice a week for each dose of native *E. coli* derived L-Asparaginase.
- Substitute Erwinaze® 25,000 IU/ m² intramuscularly twice weekly for two weeks for each dose of pegylated *E. coli* derived L-Asparaginase during consolidation therapy.

5.3.5 Demographics

Subjects enrolled on the EMTP February 2006 through April 2010 were included in this analysis. There were 843 patients who received *Erwinia* L-Asparaginase through this mechanism during this period. There were 574 subjects included in the demographic dataset, DM.xpt. Two subjects were excluded from the safety population. The CRFs of one of these subjects documented the patient did not receive *Erwinia* L-Asparaginase and the CRFs of the second subject indicated he received pegylated asparaginase.

CRFs with complete AE portions were submitted to the application for 543 subjects. CRFs with missing pages of AE information were submitted for 3 subjects. There were 4 subjects with AEs documented by reports but not on CRFs. There were 22 subjects in the demographic dataset (DM.xpt) with no CRFs submitted in the application.

Table 4: Demographics of EMTP

Demographics Safety Population EMTP	
Safety Population N= 572	
Sex	
Male	356 (62%)
Female	215 (38%)
Not reported/Missing CRF	1
Age in Years	
≤ 18	533 (95%)
1 – 5	210 (37%)
6 - 10	118 (21%)
11-18	205 (36%)
> 18	31 (5%)
Mean	9.4
Median	9
Range	1(13 months) – 66 years
Not reported	8
Diagnosis	
ALL B-lineage	450 (83%)
ALL T-lineage	72 (13%)
Lymphoma	16 (3%)
Biphenotypic Leukemia	2 (<1%)

5.3.6 Subject Disposition

Table 5: Subject Disposition of EMTP

Disposition EMTP	
N=574	
Received no therapy	2
Completed planned therapy	434
Discontinued prior to completing planned therapy	98
Adverse Reaction	78
Systemic allergic reaction	56
Local allergic reaction (injection site)	1
Pancreatitis	8
Thrombosis	4
Hyperammonemia	2
Febrile neutropenia (physician decision)	2
Local site reaction	2
Seizure	1
Diarrhea (patient decision)	1
Death (investigator reported possibly related)	1
Other	20
Physician decision	7
Leukemia not controlled	7
Transferred care	3
Parent/patient decision	2
Unable to afford	1
Missing Data	40

5.3.7 Exposure

Accurate details concerning the dosing and dosing schedules were beyond the scope of the data collected on the CRFs and were not systematically collected. The number of doses of *Erwinia* L-asparaginase planned for an individual patient depended on the protocol and the phase in the treatment course the patient was due to receive asparaginase. From the documented information the planned number of doses of *Erwinia* L-asparaginase ranged from 3 doses to 48 doses (20,000 or 25,000 IU/m²/dose). Most patients (434 of 575 (75%)) were able to receive all the planned *Erwinia* L-asparaginase to complete their treatment courses. There were 18 patients who were scheduled to receive between 24 to 48 doses, 16 (89%) of these patients were able to receive all the planned doses. As expected the most common reason patients did not receive the planned therapy with *Erwinia* L-asparaginase was allergic reaction.

6 Review of Efficacy

6.1 Indication

The applicant proposed the following indication for *Erwinia* L-asparaginase in the original BLA submission:

ERWINAZE (*Erwinia* L-asparaginase) 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.

FDA recommended the following indication determined during label review (pending additional data substantiating efficacy):

(b) (4)

6.1.1 Methods

Study AALL07P2 "Pharmacology and Toxicity of *Erwinia* L-asparaginase (Erwinaze; Crisantaspase; IND 290) Following Allergy to Pegaspargase in Treatment of Children with Acute Lymphoblastic Leukemia (ALL)" was an open label trial conducted at 31 COG phase I institutions. This study was designed to assess the PK, PD, and related toxicities of *Erwinia* L-asparaginase used as replacement therapy for pegaspargase dosing. Patients received *Erwinia* L-asparaginase 25,000 IU/m² x 6 doses IM on a three days weekly schedule (Monday / Wednesday / Friday) as a replacement for each scheduled dose of pegaspargase remaining on the original treatment protocol.

Protocol Amendments:

Table 6: Protocol Amendments AALL07P2

Protocol Amendments AALL07P2	
December 13, 2007	▪ Original protocol
September 23, 2008	▪ Formatting and editing changes ▪ Update personnel ▪ Details EKG data collection ▪ Youth information sheet added

Inclusion Criteria: (copied from protocol in submission)

- Age: Patients must be > 1 year and ≤ 30 years of age.

- Diagnosis: Patients must be on a frontline COG ALL treatment study at a participating institution.
- Patients must have had a Grade 2 or higher hypersensitivity reaction (CTCAE v 3.0 [Common Terminology Criteria for Adverse Events]) to PEG-asparaginase. Patients must have 1 or more courses of asparaginase remaining in their treatment protocol.

Exclusion Criteria: (copied from protocol in submission)

- Patients must not have previously received *Erwinia* L-asparaginase
- Patients must not have a history of \geq Grade 2 pancreatitis.

Dosing Regimen:

- *Erwinia* L-asparaginase 25,000 IU/m² x 6 doses IM on a Monday / Wednesday / Friday, Wednesday / Friday / Monday or Friday / Monday / Wednesday schedule as a replacement for each scheduled dose of pegaspargase remaining on the original treatment protocol.
- All other chemotherapy to continue according to the original treatment protocol.

6.1.2 Demographics

Enrollment

- Planned – 55 to have 50 evaluable patients
- Enrolled - 59
- Eligible – 58 - Definition: Subjects who met eligibility criteria
- Evaluable - Definition: Subjects with evaluable samples for the PK/PD analysis available as determined by the study chair
PK population – 53
PD population – 47
- Safety population – 58 – Definition: Eligible subjects who received at least 1 dose of *Erwinia* L-asparaginase

Table 7: Demographics AALL07P2

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%)

REVIEWER COMMENT:

The population in this review differs slightly from the population as defined by EUSA in the submission. Subject 797513 is not eligible because he was not registered on a therapeutic COG ALL protocol. EUSA includes him in the safety population because he received one dose of study agent before the ineligibility was noted.

Subject 798213 is included in the safety population because he was removed from the study after he experienced a grade 3 allergic reaction with second dose of *Erwinia* L-asparaginase on April 28, 2010. The applicant excluded this subject because the data

capture form with the clinical information was submitted a week after the cut off date of April 30, 2010.

6.1.3 Subject Disposition

The targeted number of patients who received a full course *Erwinia* L-asparaginase with PK samples for submission of this application was 50. The applicant cut off data for this application on April 30, 2010. Subjects enrolled on this study continued to receive ongoing treatment with *Erwinia* L-asparaginase after submission of the application.

Table 8: Subject Disposition AALL07P2

N= 58	
Completed first course of therapy	57
Completed second course of therapy	39
Completed third course of therapy	29
Completed fourth course of therapy	19
Completed fifth course of therapy	13
Completed sixth course of therapy	6
Completed seventh course of therapy	2
Completed eighth course of therapy	2
Discontinued prior to completing planned therapy	
Adverse Reaction	
Systemic allergic reaction	5
Other	
Physician decision	2
Patient decision	2
Relapse	1

6.1.4 Analysis of Primary Endpoint(s)

Endpoint

The primary endpoint is the proportion subjects with a 48 hour trough serum asparaginase activity is ≥ 0.1 IU/mL.

Planned Analysis

This study is powered to test the hypothesis target level in 70% of patients meeting this trough threshold activity against an alternative of in 50% of patients meeting this trough threshold activity.

Results

REVIEWER COMMENT:

The FDA DSI audit of the laboratory responsible for the PK analysis concluded that the PK results were not reliable. The results can not be evaluated.

6.1.5 Analysis of Secondary Endpoints(s)

Endpoint 1.

Asparagine depletion

Planned Analysis

Adequate asparagine depletion was determined to be plasma asparagine $\leq 3\mu\text{M}$ (0.396 $\mu\text{g/mL}$)

Results

REVIEWER COMMENT:

Samples for evaluation of this endpoint were not collected with a validated methodology. The FDA DSI audit of the laboratory responsible for the PD analysis concluded that the PD results were not reliable. Asparagine depletion data can not be used to support this application.

Endpoint 2.

Incidence of anti-*Erwinia* asparaginase antibodies in children treated with a course(s) of *Erwinia* L-asparaginase following clinical allergy to pegaspargase.

REVIEWER COMMENT:

Validated immunogenicity assays were not developed at the time this application was submitted. The applicant has submitted a schedule to complete assay development, assay validation, and evaluation of the clinical samples. The evaluation of clinical samples can be done as a post marketing requirement or at the time when the application is resubmitted with PK data to support the efficacy of *Erwinia* L-asparaginase in this indication.

Endpoint 3.

Incidence of asparaginase-related toxicities following treatment with *Erwinia* L-asparaginase

See section 7 for safety analysis.

6.1.6 Other Endpoints

No other endpoints were evaluated.

6.1.7 Subpopulations

REVIEWER COMMENT:

The FDA DSI audit of the laboratory responsible for the PK analysis concluded that the PK results were not reliable. The results can not be evaluated.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No relevant information in the submission.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

REVIEWER COMMENT:

The FDA DSI audit of the laboratory responsible for the PK analysis concluded that the PK results were not reliable. The results can not be evaluated.

6.1.10 Additional Efficacy Issues/Analyses

REVIEWER COMMENT:

The FDA DSI audit of the laboratory responsible for the PK analysis concluded that the PK results were not reliable. The results can not be evaluated.

7 Review of Safety

Safety Summary

The safety database contained data from 630 patients who received *Erwinia* L-asparaginase in the AALL07P2 trial or the EMTP. There were no control subjects for comparison.

Asparaginase is administered as a component of multi agent chemotherapy. This makes attribution of adverse events challenging. Reported adverse events may be related to concomitant therapy or to active leukemia. The toxicity profile of asparaginase is well described as it has been a component of ALL therapy for more than 40 years.

The most significant toxicity is allergic reaction. Rarer but potentially life threatening toxicities include pancreatitis and coagulopathy. Hyperglycemia and liver test abnormalities are associated with asparaginase therapy. Concomitant steroids contribute to the incidence of hyperglycemia and concomitant chemotherapy such as methotrexate, 6-mercaptopurine and anthracyclines contribute to the incidence of liver abnormalities.

In order to assess the safety of *Erwinia* L-asparaginase compared to *E. coli*-derived L-asparaginase the incidence of these adverse event in the safety population was compared to the incidence reported in the pegaspargase label. As would be expected, the incidence of allergic reactions was higher with *Erwinia* L-asparaginase. These patients received *Erwinia* L-asparaginase because they had developed an allergic reaction to *E. coli*-derived L-asparaginase. The incidence of pancreatitis, coagulopathy, hyperglycemia and liver abnormalities was lower in *Erwinia* L-asparaginase treated subjects than the incidence reported for pegaspargase.

The safety profile of *Erwinia* L-asparaginase supports approval of this agent.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 9: Trials Included in Safety Evaluation

Clinical Trial	Title	Comment
AALL07P2	Pharmacology and Toxicity of <i>Erwinia</i> L-asparaginase (Erwinase; Crisantaspase: IND 290) Following Allergy to Pegaspargase in Treatment of Children with Acute Lymphoblastic Leukemia (ALL)	Prospective PK (PD) Trial of <i>Erwinia</i> L-asparaginase in Patients with ALL allergic to pegaspargase. Safety Population N=58
EMTP	Erwinaze Master Treatment Protocol	Additional clinical safety data was prospectively collected for patients treated on this expanded access protocol Safety Population N=572

7.1.2 Categorization of Adverse Events

AALL07P2

AEs were captured on COG standard electronic data sets. There was a query if the subject experienced an AE. If answer was yes the reported was instructed to complete The AALL07P2 AE CRF.

See AE query below:

Figure 1: Format to Query Adverse Events on AALL07P2

• ADVERSE EVENTS			
Did patient experience any reportable adverse events during the indicated period? (Erwinase related adverse events)*	<input type="checkbox"/> - Yes <input type="checkbox"/> - No	• Required field	ExprAelPd
If yes, complete the AALL07P2 Adverse Event Reporting Screen using CTC version 3.0			

Clinical Review
 Patricia Dinndorf
 BLA 125359 Original
 Erwinia L-asparaginase, Erwinaze

Figure 2: Adverse Event CRF AALL07P2

Institutional Reminders: Adverse events to be reported: All Erwinaze-related adverse events including allergic reactions, pancreatitis, coagulopathy (hemorrhage, thrombosis or infarct), hyperbilirubinemia, hypoglycemia, hyperlipidemia, ketoacidosis and CNS events (bleed, thrombosis or infarction, cerebral vein thrombosis). All grades are to be reported. See section 3.3.2 of the NCI Guidelines on Adverse Event Reporting Requirements (<http://ctep.cancer.gov/reporting/adeers.html>) for instructions on reporting Persistent Recurring Adverse Events.

QUESTIONS (ELEMENTS)	VALID VALUES	RULES & VALIDATIONS	SDC USE ONLY
Serial Number *	Automatically assigned by the system.	<ul style="list-style-type: none"> Required field 	SerialNumber
AALL07P2 Reporting Period: *	Drop down box	<ul style="list-style-type: none"> Required field 	AALL07P2ReportingPeriod
Select the Reporting Period during which the Adverse Event began.			C
CTCAEv3.0 Adverse Event (- Select) TYPE *	Drop-down box	<ul style="list-style-type: none"> Required field 	CTCAEv3.0.AESelTYPE
Help Document			C
If other (e.g. pain, other) is selected. Specify adverse event:		<ul style="list-style-type: none"> Required if 'other, specify' selected above. Blank if not 'other, specify' 	SpfAeTxt
CTC Adverse Event Grade *	<input type="checkbox"/> 1 Mild Adverse Event <input type="checkbox"/> 2 Moderate Adverse Event <input type="checkbox"/> 3 Severe or Undesirable Adverse Event <input type="checkbox"/> 4 Life threatening or Disabling Adverse Event <input type="checkbox"/> 5 Death Related to Adverse Event	<ul style="list-style-type: none"> Required field 	CTC AE GD
CTC Adverse Event Attribution: *	<input type="checkbox"/> Definite <input type="checkbox"/> Possible <input type="checkbox"/> Probable	<ul style="list-style-type: none"> Required field 	CTC AE ATTR SCALE
Adverse Event Onset Date: *	(MM/DD/YYYY)	<ul style="list-style-type: none"> Required field Cannot be a future date Must be greater than or equal to enrollment date 	CTC AE ONSET DT
			DLC
Has the CTC adverse event resolved? *	<input type="checkbox"/> Yes <input type="checkbox"/> No	<ul style="list-style-type: none"> Required 	CTCAEResolvedIND
Adverse Event Resolution Date:	(MM/DD/YYYY)	<ul style="list-style-type: none"> Required if yes above Not answered if No above If answered, date must be greater than or equal to date of enrollment If answered, cannot be a future date 	RslAeDt
Help text: Leave this field blank if the AE has not resolved. When the AE is resolved enter the resolution date on this form irrespective of the reporting period in which it resolved.			DLC
Has an AdEERs report been filed? *	<input type="checkbox"/> No <input type="checkbox"/> Yes	<ul style="list-style-type: none"> Required field. Must be yes, if AE grade is equal to 5 	AdEERSRptFld
If yes above, what is the AdEERs ticket number: AdEERs reports are to be submitted one per course. If a report was filed for a given course, and subsequent information is found that was not on the initial report, please amend the report. Please do not fill out a new AdEERs report.		<ul style="list-style-type: none"> Required if yes above. Not answered if No above. Numeric values only 	AdEERsTrkNbr
			C
Comments:	Text		RSCH_COMMENTS_TXT

The following table maps the AE code to the AE term captured for these electronic data CRFs.

Table 10: Map AE Term to AE Code in AALL07P2

Number*	AETERM
1010000	1010.000: ALLERGIC REACTION/HYPERSENSITIVITY (INCLUDING DRUG FEVER)
1646000	1646.000: LEUKOCYTES (TOTAL WBC)
1664000	1664.000: NEUTROPHILS/GRANULOCYTES (ANC/AGC)
1670000	1670.000: PLATELETS
2810000	2810.000: FATIGUE (ASTHENIA, LETHARGY, MALAISE)
2817000	2817.000: FEVER (IN THE ABSENCE OF NEUTROPENIA, WHERE NEUTROPENIA IS DEFINED AS ANC <1.0 X 10E9/L)
3444001	3444.001: DERMATITIS: RASH: DERMATITIS ASSOCIATED WITH RADIATION - CHEMORADIATION
3458000	3458.000: URTICARIA (HIVES, WELTS, WHEELS)
4062000	4062.000: NAUSEA
4084000	4084.000: VOMITING
5119000	5119.000: FEBRILE NEUTROPENIA (FEVER, UNK. ORIGIN, W/O INFECTION, ANC<1X10E9, FEVER>=38.5°C)
5128077	5128.077: INFECTION (CLINICAL OR MICROBIOLOGICAL DX) W/ GR 3-4 NEUTROPHILS, ANC<1.0X10E9 - BLOOD
5137077	5137.077: INFECTION WITH NORMAL ANC OR GRADE 1 OR 2 NEUTROPHILS - BLOOD
5712000	5712.000: ALBUMIN, SERUM-LOW (HYPOALBUMINEMIA)
5718000	5718.000: ALT, SGPT (SERUM GLUTAMIC PYRUVIC TRANSAMINASE)
5722000	5722.000: AST: AST, SGOT(SERUM GLUTAMIC OXALOACETIC TRANSAMINASE)
5726000	5726.000: BILIRUBIN: BILIRUBIN (HYPERBILIRUBINEMIA)
5742000	5742.000: HYPERGLYCEMIA: GLUCOSE, SERUM-HIGH (HYPERGLYCEMIA)
6346001	6346.001: MOOD ALTERATION - AGITATION
6810018	6810.018: PAIN - HEAD/HEADACHE

EMTP

The applicant developed CRFs in collaboration with the FDA. These forms included sections to gather information regarding *Erwinia* L-asparaginase toxicity.

The toxicity data was captured using a check box format. Investigators were requested to report coagulation test values that were obtained at the onset of a thrombotic or hemorrhagic AE. Investigators were requested to report AST, ALT, bilirubin, amylase

and lipase associated at the time of onset with hepatic or pancreatic disorders. Three components of the laboratory values were captured, normal ranges of the testing laboratory, the laboratory value and units of the laboratory value. There were spaces provided to supply additional information about the specific AE captured. There was a section to report any other significant AE not included as a standard inquiry and a section to report information about deaths within 28 days of receiving *Erwinia* L-asparaginase.

These forms captured the CTCAE version 3 grade 1 through 5 categorization of allergic reactions, liver dysfunction, pancreatitis, and grade 3&4 hyperglycemia. Grade was not captured for other AEs reported. Investigators did not report attribution.

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

The safety data from the AALL07P2 study and the EMTP were combined for an integrated study summary analysis. The ISS safety population contained 633 subjects.

7.2 Adequacy of Safety Assessments

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

Exposure

See section 6.1.4 for AAALL07P2 and section 5.3.7 for the EMTP study.

Demographics

See section 6.1.2 for AAALL07P2 and section 5.3.5 for the EMTP study.

7.2.2 Explorations for Dose Response

These were not done as a component of the developmental plan for this BLA.

7.2.3 Special Animal and/or In Vitro Testing

These were not done as a component of the developmental plan for this BLA.

7.2.4 Routine Clinical Testing

See 7.4.2 Laboratory Findings below.

7.2.5 Metabolic, Clearance, and Interaction Workup

These were not done as a component of the developmental plan for this BLA.

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

AALL07P2

Pegaspargase was given the indication for first line treatment of ALL based on a randomized comparison to native *E. coli* L-asparaginase, the Children's Cancer Group (CCG) 1962 trial. This trial only captured grade 3 or greater toxicity. The per-patient incidence of Grade 3 and 4 adverse reactions was presented in the label. The following table compares the incidence of Grade 3 and 4 adverse reactions associated with *E. coli* L-asparaginase and pegaspargase therapy to the incidence associated with *Erwinia* L-asparaginase therapy in the COG trial AALL07P2.

Table 11: Grade 3&4 Adverse Reactions on AALL07P2 Compared to CCG 1962

Per Patient Incidence of Non Hematologic Non Infectious Grade 3 & 4 Adverse Reactions			
	CCG 1962 N=58 Pegaspargase	CCG 1962 N=59 Native <i>E. coli</i> Asparaginase	COG AALL07P2 N=58 <i>Erwinia</i> Asparaginase
Allergic Reaction / Hypersensitivity	1 (2%)	0	5 (9%)
Pancreatitis	1 (2%)	1 (2%)	0
Hyperglycemia	3 (5%)	2 (3%)	0
Clinical Coagulation Abnormalities - Thrombosis	2 (3%)	2 (3%)	0
Clinical Coagulation Abnormalities - Coagulopathy	1 (2%)	3 (5%)	0
Abnormal Liver Tests	3 (5%)	5 (8%)	1 (2%)
Elevated Transaminases	2 (3%)	4 (7%)	1 (2%)
Hyperbilirubinemia	1 (2%)	1 (2%)	0

EMTP

The safety evaluation of pegaspargase for the indication of initial therapy of ALL was augmented by safety data collected from the CCG 1991 trial. In the CCG 1991 trial pegaspargase was the only asparaginase used. Only grade 3 and 4 non-hematologic toxicities safety data were collected in this trial. The following table compares the per patient incidence of grade 3 and 4 adverse reactions of *Erwinia* L-asparaginase reported in the EMTP to the incidence reported with pegaspargase therapy in the CCG 1991.

Table 12: Grade 3&4 Adverse Reactions on EMTP Compared to CCG 1991

Per Patient Incidence of Non Hematologic Non Infectious Grade 3 & 4 Adverse Reactions		
	CCG 1991 N=2770 Pegaspargase	EMTP N=572 <i>Erwinia</i> Asparaginase
Allergic Reaction / Hypersensitivity	1%	27 (5%)
Pancreatitis	2%	4 (1%)
Hyperglycemia	5%	11 (2%)
Clinical Coagulation Abnormalities		
- Thrombosis / Hemorrhage	2%	7 (1%)
- Coagulopathy	7%	0
Elevated Transaminases	11%	2 (<1%)

REVIEWER COMMENT:

The incidence of known AEs associated with *Erwinia* asparaginase therapy was not greater than that reported for *E. coli* derived asparaginase therapy with the exception of clinical allergic reactions. The higher incidence of allergic reactions is not surprising because subjects receiving *Erwinia* L-asparaginase had previously experienced an allergic reaction to an *E. coli*-derived asparaginase.

7.3 Major Safety Results

7.3.1 Deaths

AALL07P2

There were no deaths.

EMTP

There were 6 reported deaths in the EMTP. None of these were obviously related to *Erwinia* asparaginase exposure. Five subjects had documented disease progression.

The subject without documented disease progression was a 17 year old female initially diagnosed with ALL on (b) (6). She relapsed (b) (6). She received *Erwinia* L-asparaginase between May 10, 2008 and April 22, 2009. She died at home (b) (6).

REVIEWER COMMENT:

It is unlikely that *Erwinia* L-asparaginase was a major contributory factor in this death. The last dose was given 13 days prior to death. No asparaginase toxicities were documented.

7.3.2 Nonfatal Serious Adverse Events

AALL07P2

AEs were not characterized as serious in the data capture form in the AALL07P2 study. See table of treatment emergent AEs in section 7.4.1 Common Averse Events below.

EMTP

The applicants table summarizing Serious Adverse Events reported in $\geq 1\%$ of patients is presented below:

Table 13: Serious Adverse Events on EMTP

System Organ Class/ Preferred Term	<i>Erwinia</i> asparaginase (N=573)* n (%)
Total Number of Serious TEAE	418
Number of Patients with At Least One Serious TEAE	162 (28.3)
Immune system disorders	69 (12.0)
Anaphylactic reaction	53 (9.2)
Hypersensitivity	16 (2.8)
Gastrointestinal disorders	39 (6.8)
Pancreatitis	20 (3.5)
Vomiting	13 (2.3)
Nausea	10 (1.7)
Abdominal pain	7 (1.2)
Investigations	38 (6.6)
Alanine aminotransferase increased	13 (2.3)
Aspartate aminotransferase increased	10 (1.7)
Lipase increased	8 (1.4)
Blood amylase increased	7 (1.2)
General disorders and administration site conditions	29 (5.1)
Pyrexia	15 (2.6)
Blood and lymphatic system disorders	20 (3.5)
Neutropenia	8 (1.4)
Febrile neutropenia	7 (1.2)
Metabolism and nutrition disorders	14 (2.4)
Hyperglycemia	10 (1.7)

REVIEWER COMMENT:

No unexpected serious events were reported. The table includes allergic reactions, pancreatitis including clinical and laboratory signs of pancreatitis, elevated transaminases, and hyperglycemia. Fever and neutropenia are the known expected AEs in patients being treated for ALL.

7.3.3 Dropouts and/or Discontinuations

AALL07P2

There were 4 subjects that discontinued therapy due to an AE. These were all systemic allergic reactions.

EMTP

See table in 5.3.6 Subject Disposition for discontinuation information on the EMTP.

7.3.4 Significant Adverse Events

AALL07P2

See section 7.2.6 Evaluation for Potential AEs for Similar Drugs in Drug Class above.

EMTP

See section 7.2.6 Evaluation for Potential AEs for Similar Drugs in Drug Class above.

7.3.5 Submission Specific Primary Safety Concerns

See section 7.2.6 Evaluation for Potential AEs for Similar Drugs in Drug Class above.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

AALL07P2

The applicant's table of treatment-emergent AEs is copied below.

Table 14: Treatment Emergent Adverse Events on AALL07P2 by Preferred Term

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)

EMTP

The applicants table summarizing Common Treatment Emergent AEs reported in $\geq 1\%$ of patients is presented below:

Table 15: Treatment Emergent Adverse Events on EMTP by Preferred Term

System Organ Class/ Preferred Term	<i>Erwinia</i> 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)

7.4.2 Laboratory Findings

AALL07P2

The following laboratory parameters were evaluated prior to the first dose of *Erwinia* L-asparaginase (baseline) and following the last dose of *Erwinia* L-asparaginase of each course of therapy (post therapy) in 58 subjects:

Hematology:

- Complete blood cell count (CBC)/differential/platelets.

Coagulation:

- prothrombin time (PT) (normal 8.8 to 14.1 seconds)
- partial thromboplastin time (PTT) (normal 24 to 39 seconds)
- fibrinogen (normal 160 to 420 mg/dL)
- protein C activity (normal 55 to 140%)
- protein S activity (normal 63 to 140%)
- anti-thrombin III (ATIII) (normal 77 to 123%)
- d-dimer (normal 0 to 0.4)
- fibrin degradation products (FDPs) (upper limit normal 4 µg/mL)

Serum chemistry:

- ALT (normal 0 to 55 IU/L)
- AST (normal 0 to 40 IU/L)
- bilirubin (normal 0.1 to 1.2 mg/dL)
- blood urea nitrogen (BUN) (normal 5 to 26 mg/dL)
- creatinine (normal 0.5 to 1.5 mg/dL) [These are inappropriate normal values for a pediatric population]
- cholesterol (normal 100 to 169 mg/dL)
- triglycerides (normal 0 to 149 mg/dL)
- amylase (normal 28 to 100 U/L)
- lipase (normal 0 to 59 U/L)

Results:

Coagulation Battery:

PT

There were 4 subjects with post therapy prolongation of PT. These were at levels that were clinically insignificant, that is 14.3 to 15 seconds. There were no hemorrhagic or thrombotic AEs documented in these subjects.

PTT

The baseline PTT was prolonged in 18 subjects. There were 25 subjects with prolonged PTTs greater than the baseline PTT at the post therapy timepoint. These results must be interpreted with caution because PTT is exquisitely sensitive to heparin and these studies were most likely drawn from heparinized central catheters. There were no hemorrhagic or thrombotic AEs documented in these subjects.

Fibrinogen

The baseline fibrinogen was low in 6 subjects. There were 44 subjects with abnormal post therapy fibrinogen determinations lower than baseline. There were no hemorrhagic or thrombotic AEs documented in these subjects.

Protein C Activity

The baseline protein C activity was low in 1 subject. There were 29 subjects with abnormal post therapy protein C activity lower than baseline. There were no hemorrhagic or thrombotic AEs documented in these subjects.

Protein S Activity

The baseline protein S activity was low in 7 subjects. There were 43 subjects with abnormal post therapy protein S activity lower than baseline. There were no hemorrhagic or thrombotic AEs documented in these subjects.

ATIII

The baseline AT III activity was low in 4 subjects. There were 51 subjects with abnormal post therapy AT III activity lower than baseline. There were no hemorrhagic or thrombotic AEs documented in these subjects.

D-Dimer

There were 35 subjects with elevated d-dimer determination at baseline. There were 18 subjects with post therapy elevated d-dimer determinations higher than baseline. There were no hemorrhagic or thrombotic AEs documented in these subjects.

FDPs

There were 16 subjects with elevated FDPs at baseline. There were 10 subjects with post therapy elevated FDP determinations higher than baseline. There were no hemorrhagic or thrombotic AEs documented in these subjects.

REVIEWER COMMENT:

The following coagulation proteins were decreased in the majority of subjects after a 2 week course of *Erwinia* L-asparaginase: fibrinogen, protein C activity, protein S activity, and AT III. The effect of *Erwinia* L-asparaginase treatment on PT and PTT was not clearly demonstrated. There was no effect on d-dimers or FDPs. Importantly no subjects with abnormalities in these coagulation tests were reported to experience a hemorrhagic or thrombotic AE.

Serum Chemistry Battery:

Hepatic:

ALT

There were no subjects with \geq grade 3 ALT elevation documented at the post therapy evaluation.

AST

There were no subjects with \geq grade 3 ALT elevation documented at the post therapy evaluation.

Bilirubin

There was one subject with a grade 3 elevation of bilirubin after course 1 of *Erwinia* L-asparaginase. This subject received 3 additional course of *Erwinia* L-asparaginase with normal bilirubin at the end of each course.

Renal:

BUN

There were 2 subjects with post therapy mild elevation in BUN.

Creatinine

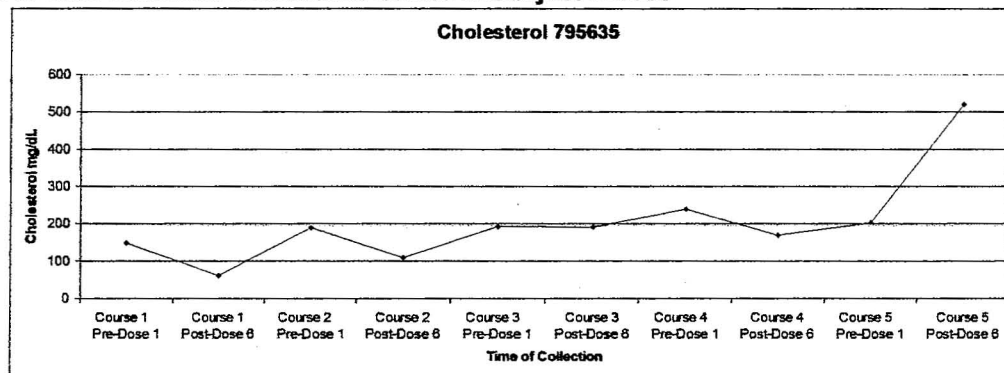
There were no subjects with post therapy abnormalities in creatinine.

Metabolic:

Cholesterol

No grade 3 toxicity was identified. One subject had a single grade 4 cholesterol determination after the 5th course of *Erwinia* L-asparaginase.

Figure 3: Time Course of Cholesterol Levels in Subject 795635



Triglycerides

Five subjects demonstrated grade 3 and 4 elevations in triglycerides at post therapy evaluations.

Figure 4: Time Course of Triglyceride in Subject 791637

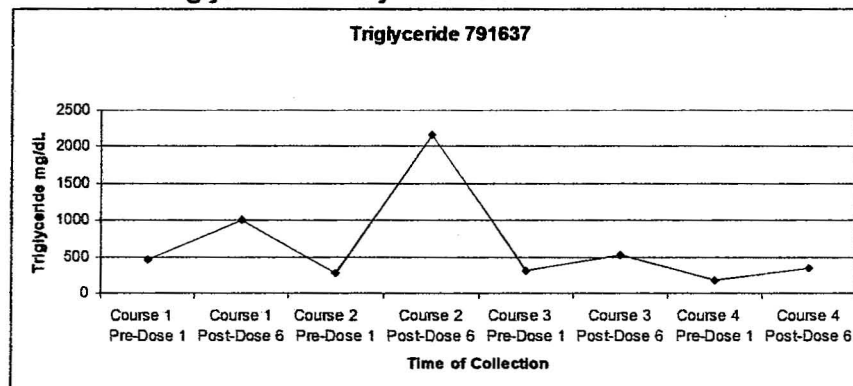


Figure 5: Time Course of Triglyceride in Subject 795635

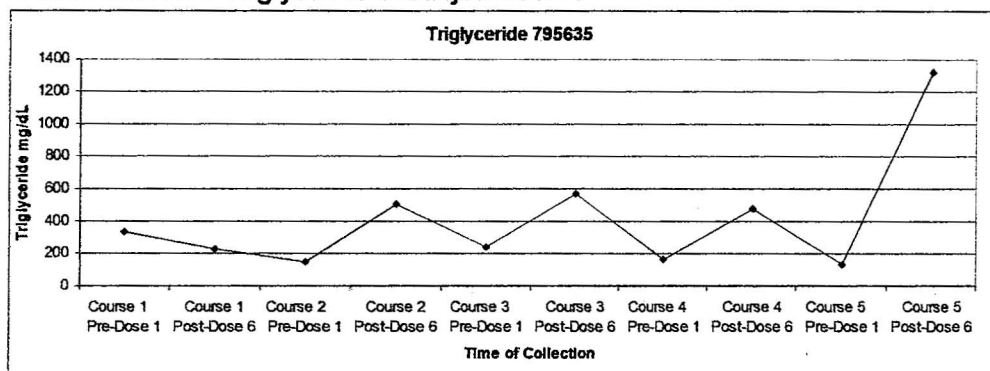


Figure 6: Time Course of Triglyceride in Subject 794765

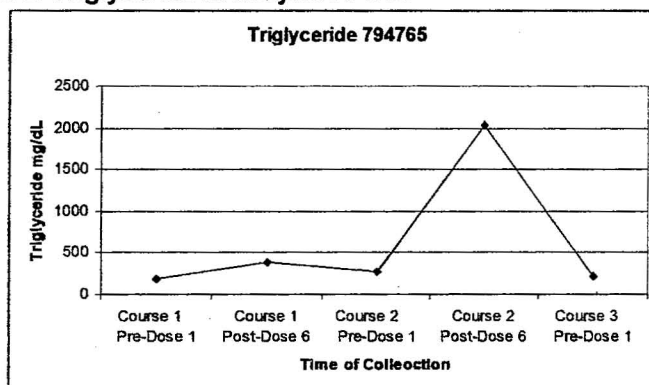


Figure 7: Time Course of Triglyceride in Subject 789794

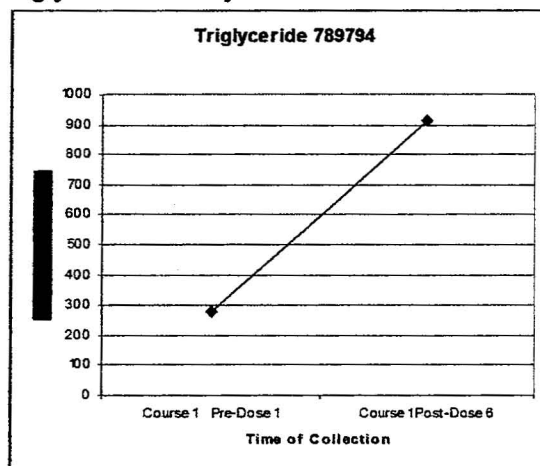
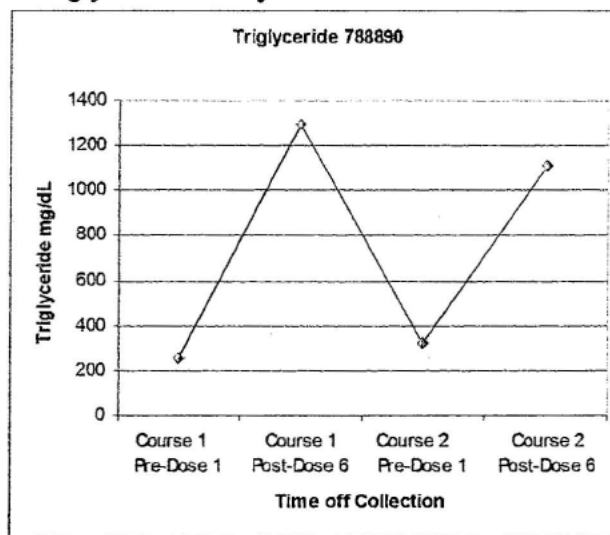


Figure 8: Time Course of Triglyceride in Subject 788890



Pancreas:

Amylase

There were no subjects with post therapy evaluation of amylase \geq to grade 3.

Lipase.

There were 3 subjects with post therapy evaluation of lipase \geq to grade 3. These subjects were not reported to have pancreatitis or symptoms such as abdominal pain associated with pancreatitis.

REVIEWER COMMENT:

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

EMTP

Laboratory data was not systematically collected in the EMTP.

7.4.3 Vital Signs

7.4.4 Electrocardiograms (ECGs)

AALL07P2

According to the Interdisciplinary Review Team (IRT) for QT studies no definitive conclusions regarding the QTc effects due to *Erwinia* L-asparaginase are possible from the data submitted. The assessment involved single post-treatment, locally read ECGs

collected at 1 hour post-dose 6 with categorical analysis only. The IRT team usually recommends in this circumstance that an ECG sub-study with intensive PK and time-matched ECGs and central over-read be conducted. However they defer to the clinical review team to determine the feasibility of this approach.

REVIEWER COMMENT:

Given the long history of this agent and related asparaginase agents and the absence of any cardiac signals associated with these agent I do not think additional studies are justified.

EMTP

ECGs were not evaluated in the EMTP.

7.4.5 Special Safety Studies/Clinical Trials

These were not necessary or done for this application.

7.4.6 Immunogenicity

Validated immunogenicity assays were not developed at the time this application was submitted. The applicant has submitted the following schedule to complete assay development, assay validation, and evaluation of the clinical samples. The evaluation of clinical samples will be done as a post marketing requirement.

Table 16: Schedule for Proposed Immunogenicity Testing

(b) (4)



7.5 Other Safety Explorations

These were not necessary or done for this application.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

These were not done as a component of the developmental plan for this BLA.

7.6.2 Human Reproduction and Pregnancy Data

These were not done as a component of the developmental plan for this BLA.

7.6.3 Pediatrics and Assessment of Effects on Growth

The AALL07P2 study was conducted in children 1 to 18 years of age. The majority of subjects included in the EMTP study were children.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no risk of drug abuse for this agent.

7.7 Additional Submissions / Safety Issues

None identified.

8 Postmarket Experience

There is no US post marketing experience. *Erwinia* L-asparaginase is licensed in some countries in Europe and in Canada. There is an extensive greater than 50 years, postmarketing experience in Europe and North America.

9 Appendices

9.1 Literature Review/References

None

9.2 Labeling Recommendations

This application will not be approved at this time. A new study to determine that the trough asparaginase activity is ≥ 0.1 IU/mL at 48 hours in patients who have developed allergic reactions to pegaspargase will be required. Therefore label content regarding efficacy will be addressed after appropriate data supporting efficacy has been submitted.

The safety data is adequate to support approval of this agent. After review of the submitted data the following suggestions for change in the label will be suggested to the applicant as of March 15, 2011.

(b) (4)

9.3 Advisory Committee Meeting

Not required.

9.4 Abbreviations

Table 19: Abbreviations

Abbreviations	
AE	Adverse event
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CCG	Children's Cancer Group
COG	Children's Oncology Group
CR	Complete response
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DFCI	Dana-Farber Cancer Institute
DSI	Division of Scientific Investigations
ECG	Electrocardiograms
EFS	Event free survival
EMTP	Erwinaze Master Treatment Protocol
EUSA	EUSA Pharma (US) Inc.
FDA	Food and Drug Administration
GLP	Good laboratory practice
IND	Investigational New Drug
IM	Intramuscularly
IRT	Interdisciplinary Review Team (for QT studies)
ISS	Integrated summary of safety
IU	International Units
IV	Intravenous
OPi	OPi SA
QC	Quality control
PD	Pharmacodynamic
PK	Pharmacokinetic
USAN	United States Adopted Names

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

BLA Number: 125359

Applicant: EUSA Pharma
(USA), Inc.

Stamp Date: 9/8/10

Drug Name: *Erwinia* L-
asparaginase (Erwinaze)

NDA/BLA Type: BLA

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		X		Not necessary for this application
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			In 2.5 clinical Overview
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	BLA not NDA
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	X			This agent has been given to patients since the 1970s. The PK characteristics have been extensively studied.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 AALL07P2 Indication: ALL allergic to pegaspargase requiring	X			FDA agreed that a single PK study demonstrating asparaginase activity ≥ 0.1 IU/mL at 48

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	treatment with an asparaginase agent. Pivotal Study #2 – not required				hours, and additional safety data from a Treatment Protocol would be adequate to support approval of this application.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?		X		There are problems with MedDRA coding.
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			Page 95 of AALL07P2 study Report.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			5.3.5.3.22 (16.2.7.3)
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Study done in pediatric population. PREA does not apply because it has orphan status
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?		X		Actual dose and date of medicine not included
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			CDISC but not done correctly
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?		X		Actual dose and date of medicine not included
34.	Are all datasets to support the critical safety analyses available and complete?		X		There are problems with MedDRA coding.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?		X		Actual dose and date of medicine not included
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?		X		Update received 11/19/20, included all patients requested but not all worksheets for PK analysis
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?		X		Update received 11/19/10, included all patients requested but not all worksheets for PK analysis
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			Financial Disclosure information on PI from all institutions submitted 11/19/10 amendment
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?				

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

Provided the Applicant provides the following revisions to the application no later than January 11, 2011.

The Safety data is not presented in an acceptable format that will allow substantive review.

- Regarding the AE.xpt and ADAE.xpt datasets for AALL07P2 - These were prepared incorrectly. There are multiple entries in the AEBODSYS column designated "uncoded." The data in the column AETERM should be the verbatim term. The data supplied by COG for the AALL07 P2 trial, or the adverse events reported in sections 8 through 12 of the case report forms for the EMTP. The terms in the AEDECODE should be coded by EUSA Pharma matching the verbatim term in the AETERM column to preferred terms from the MedDRA coding dictionary. Once the AEDECODE term has been identified the rest of the MedDRA hierarchy is defined. Please include all MedDRA hierarchy in the revised datasets, that is SOC, HLGT, HLT, and PT(AEDECODE). FDA advises you to identify a consultant who is familiar with MedDRA coding to assist.

The PK data is not presented in an acceptable format that will allow substantive review.

- Provide Specimen Transfer CRFs for every course of therapy the patients received not just the initial course.
- Revise the EX.xpt dataset. The EXDOSE should be the "Amount of EXTRT administered or given." This is the dose from the Specimen Transfer CRF documented in the "Calculated Dose" space. There should be one line of data for each administration of Erwinaze with the date and the time of administration.

Reviewing Medical Officer

Date

12/20/10

Clinical Team Leader

Date

12/21/10