CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761102Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

BLA Multidisciplinary Review and Evaluation

Application Number	BLA 761102
Application Type	Original 351(a)
Priority or Standard	Standard
Submit Date	12/21/2017
Received Date	12/22/2017
PDUFA Goal Date	12/22/2018
Division/Office	DHP/OHOP
Review Completion Date	12/19/2018
Applicant	Servier Pharmaceuticals LLC
Proper Name	Calaspargase pegol-mknl
(Proposed) Trade Name	Asparlas
Pharmacologic Class	Asparagine-specific enzyme
Formulations	Injection (3,750 Units in 5 mL)
Dosing Regimen	2,500 Units per m^2 intravenously not more frequently than every 21 days
Applicant Proposed Indication/Population	As a component of a multi-agent chemo-therapeutic regimen for the treatment of patients with ALL
Recommendation on Regulatory Action	Regular approval
Recommended Indication/Population	As a component of a multi-agent chemo-therapeutic regimen for the treatment of acute lymphoblastic leukemia in pediatric and young adult patients age 1 month to 21 years.

* For purposes of this review, the proposed product is referred to by either the proposed proprietary name (Asparlas), the proposed proper name (calaspargase pegol-mknl), or the Sponsor's descriptor, calaspargase pegol. The proposed proprietary name and the proposed proper name are only conditionally-accepted until the application is approved.

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Pediatric Rare Disease Voucher	Althea Cuff

Glossary

ADA	anti-drug antibody
ADaM	Analysis Data Model
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AT III	antithrombin III
APC	absolute phagocyte count
ARDS	acute respiratory distress syndrome
BFM	Berlin Frankfurt Münster
BLA	biologics license application
BM	bone marrow
BMI	body mass index
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSA	body surface area
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CVA	cerebrovascular accident
DFCI	Dana Farber Cancer Institute
DFS	disease free survival
DHOT	Division of Hematology Oncology Toxicology
DSMB	data safety monitoring board
ECG	electrocardiogram
eCTD	electronic common technical document
EFS	event free survival
F	Friday

FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GGT / γGT	gamma-glutamyl transferase
GRMP	good review management practice
HLGT	High Level Group Term (MedDRA)
ICH	International Conference on Harmonization
IM	intramuscular
IND	Investigational New Drug
INR	international normalized ratio
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
IT	intrathecal
ITT	intent to treat
IV	intravenous
LL	lymphoblastic lymphoma
M	Monday
M1	marrow remission status - < 5% blasts
M2	marrow remission status – 5-25% blasts
M3	marrow remission status - > 25% blasts
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MRD	minimal residual disease
NDA	New Drug Application
NSAA	nadir serum asparaginase activity
OCS	Office of Computational Science
ODAC	Oncology Drug Advisory Committee
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PCR	polymerase chain reaction
PD	pharmacodynamic
PEG	polyethylene glycol
Ph+	Philadelphia chromosome positive
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PO	*per os* (orally)
PP	per protocol

PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	Preferred Term (MedDRA)
PT	prothrombin time
PTT	partial thromboplastin time
REMS	risk evaluation and mitigation strategy
RER	rapid early responder
SAA	serum asparaginase activity
SAE	serious adverse event
SAP	statistical analysis plan
SC	carbamate (linker)
SER	slow early responder
SOC	System Organ Class (MedDRA)
SS	succinyl succinate (linker)
TEAE	treatment emergent adverse event
US	United States
W	Wednesday

1 Executive Summary

1.1 Product Introduction

Proposed Trade Name:	Asparlas™
Proposed Proper Name:	Calaspargase pegol-mknl
Also Known As:	Calaspargase pegol, EZN-2285, (succinimidyl carbonate-polyethylene glycol) E. coli L-asparaginase, SC-PEG L-asparaginase, PEG-L-ASNase
Molecular Weight:	Approximately 313 kDa
Dosage Forms:	Injection (3,750 units in 5 mL)
Therapeutic Class:	Antineoplastic
Chemical Class:	(b) (4) protein
Structure:	Pegylated L-asparaginase homotetramer
Pharmacologic Class:	Asparagine-specific enzyme
Mechanism of Action:	Depletes L-asparagine by catalyzing conversion to aspartic acid and ammonia.

BLA 761102 for Asparlas was submitted under the 351(a) pathway for the indication "as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL."

1.2 Conclusions on the Substantial Evidence of Effectiveness

The review team recommends regular approval of calaspargase pegol-mknl for the indication "as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia in pediatric and young adult patients age 1 month to 21 years" using a dose of 2,500 units/m^2 given intravenously no more frequently than every 21 days.

The determination of efficacy was based on a demonstration of the achievement and maintenance of nadir serum asparaginase activity (NSAA) above the level of 0.1 U/mL using calaspargase pegol-mknl 2500 U/m^2 intravenously every 3 weeks. The pharmacokinetics of calaspargase pegol-mknl were studied when used in combination with multi-agent chemotherapy in 124 patients with B cell lineage acute lymphoblastic leukemia (ALL) in Study AALL07P4 (NCT00671034). Among these patients, the median age was 11.5 years (range 1 – 26); 62 (50%) were male, 102 (82%) white, 6 (5%) Asian, 5 (4%) Black or African American, 2 (2%) Native Hawaiian or Pacific Islander and 9 (7%) other or unknown. The results showed that 123 (99%, 95% CI: 96% - 100%) of the 124 patients maintained NSAA > 0.1 U/mL at weeks 6, 12, 18, 24 and 30.

1.3 Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• About 80% of children with ALL achieve long-term survival when treated with a multi-agent chemotherapy regimen. • Use of asparaginase in the regimen provides for a significant improvement in survival.	The outcomes for patients with ALL are improved with asparaginase.
Current Treatment Options	• Pegaspargase is the only asparaginase product marketed for 1st line treatment of ALL. • Pegaspargase is administered no more frequently that every 14 days.	There is one asparaginase product marketed for this indication.
Benefit	• Persistent NSAA levels > 0.1 U/mL correlate with outcome. • The PK of calaspargase pegol-mknl was studied in 124 patients with ALL treated with a multi-agent chemotherapy regimen. • The PK analysis for calaspargase pegol-mknl given every 3 weeks demonstrated that the NSAA would be > 0.1 U/mL at weeks 6, 12, 18, 24 and 30 for 99% (95% CI: 96% - 100%).	Adequate NSAA levels are maintained when calaspargase pegol-mknl is given every 3 weeks.
Risks and Risk Management	• In a randomized trial, the toxicity profile of calaspargase pegol-mknl was similar to that of pegaspargase. • The clinical trials included specific monitoring and dose modifications to mitigate serious toxicities. • In a randomized trial, there was no substantial decrement in event-free survival using calaspargase pegol-mknl in comparison to patients treated with pegaspargase	The safety profile of calaspargase pegol-mknl is similar to the available asparaginase product, and risks can be mitigated with appropriate labeling.

Maintaining adequate NSAA levels is critical to successful treatment of ALL. The result of the PK analysis showed that administration of calaspargase pegol-mknl every 3 weeks would maintain NSAA levels adequately. In a randomized comparison to pegaspargase every 2 weeks, the asparaginase available currently, treatment with calaspargase pegol-mknl every 3 weeks had a similar safety profile and no substantial impairment in event-free survival. The results suggest that calaspargase pegol-mknl is an appropriate alternative asparaginase therapy for patients with ALL.

1.4 Patient Experience Data

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
☑	Patient experience data was not submitted as part of this application.	

Donna Przepiorka, MD, PhD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1 Analysis of Condition

ALL is the most common cancer diagnosis in children. ALL originates in T and B lymphocytes in the bone marrow (BM). More than 95% of children with newly diagnosed ALL attain a complete remission (CR) after induction chemotherapy and approximately 80% treated with multi-agent chemotherapy, including asparaginase agents, are expected to be long term survivors.

Asparaginase agents have been an important component of pediatric ALL therapy since the early 1970s. The incorporation of asparaginase agents as a component of therapy has been shown to add a 15% to 20% survival benefit to children with ALL (Sallan 1983). The completion of a patient's entire planned asparaginase treatment has been shown to be important for optimal survival outcome (Vrooman 2010).

2.2 Current Treatment Options

Table 1: FDA-Approved Asparaginase Agents

Product(s) Name / Description	Relevant Indication	Approval Year	Recommended Dose	Efficacy Information	Important Safety and Tolerability Issues
Elspar® asparaginase *Escherichia coli*-derived L-asparaginase	Elspar is an asparagine specific enzyme indicated as a component of a multi-agent chemo-therapeutic regimen for the treatment of patients with ALL	1978	6,000 IU/m^2 Route IM, IV Frequency during induction therapy – Monday (M), Wednesday (W), Friday (F) x 9 doses Subsequent phases of therapy MWF variable number of doses	As a component of multi-agent combination therapy of ALL. Complete remission induction rate of combination chemotherapy with and without Elspar 93% v 86%	Allergic reactions and anaphylaxis; thrombotic events and coagulopathy; immunogenicity; pancreatitis; hepatotoxicity; glucose intolerance
Oncaspar® Pegaspargase *Escherichia coli*-derived L-asparaginase covalently linked to succinyl succinate PEG (SS-PEG)	Pegaspargase is an asparagine-specific enzyme indicated as a component of a multi-agent chemo-therapeutic regimen for treatment of patients with: • First line ALL • ALL with hypersensitivity to asparaginase	1994	2,500 IU/m^2 Route IM, IV Frequency No more frequently than every 14 days	As a component of multi-agent combination therapy of ALL. Based on PK/PD comparison pegaspargase to MWF *Escherichia coli*-derived L- asparaginase	Allergic reactions and anaphylaxis; thrombotic events and coagulopathy; immunogenicity; pancreatitis; hepatotoxicity; glucose intolerance
Erwinaze™ asparaginase *Erwinia chrysanthemi* derived L-asparaginase	Erwinaze is an asparagine specific enzyme indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL who have developed hypersensitivity to E. coli-derived asparaginase.	2011	25,000 IU/m^2 Route IM, IV One dose pegaspargase replaced by 6 doses Erwinaze MWF One dose of Escherichia coli-derived L-asparaginase replaces by one dose of Erwinaze	PK evaluation of the level of asparaginase activity of 6 doses given on a MWF schedule	Allergic reactions and anaphylaxis; thrombotic events and coagulopathy; immunogenicity; pancreatitis; hepatotoxicity; glucose intolerance

Pegaspargase (Oncaspar) was originally approved in 1994 for patients who had developed hypersensitivity to native *Escherichia coli*-derived L-asparaginase (Elspar). In 2006, pegasparagase was approved for the first-line treatment of patients with ALL. The approval was based on the pharmacokinetic (PK) and pharmacodynamic (PD) results of a randomized

comparison of pegasparagase administered as a single dose compared to Elspar administered as 6 to 9 injections three times weekly. The adverse event profiles were similar between arms, and there was no evidence of erosion of long-term event-free survival or overall survival as a result of the replacement of *Escherichia coli*-derived L-asparaginase by pegasparagase. The advantage of providing asparaginase treatment with single-dose therapy rather than multiple injections resulted in pegasparagase becoming the asparaginase of choice for the treatment of children with ALL. Elspar was withdrawn from the United States (US) market in 2012.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

Calaspargase pegol-mknl is not marketed in any country.

3.2 Summary of Presubmission/Submission Regulatory Activity

Table 2: Regulatory History

10/27/2006	Pre-IND (b) (4) Meeting - Discussion with Enzon (original sponsor) of a new pegylated, (b) (4) L-asparaginase intended to replace pegasparagase because of shelf-life instability of pegasparagase. ▪ New product - succinyl succinate (SS) linker is replaced with a succinyl carbamate (SC) linker
6/5/2007	Pre-IND 100594 Meeting – Discussion of Enzon's proposal for a study to support licensure ▪ Enzon's proposals o Children's Oncology Group (COG) to conduct a randomized open label study (AALL07P4) with 60 patients in the ENZ-2285 arm and 30 patients in the pegasparagase arm ▪ FDA Advise o Recommended a limited scope trial to determine an appropriate dose rather than empirically choosing 2500 IU/m^2 prior to starting the definitive licensure trial
11/20/2007	New IND 100594 was allowed to proceed 12/19/2007. Enzon agreed to submit statistical analysis plan (SAP), Plan for QTc study for review prior to patient entry.
4/22/2008	IND 100594 placed on hold because Enzon did not submit information to confirm the methodology for sample collection was adequate to ensure accurate measurement of asparagine concentrations (the PD measurement FDA accepted as the basis for approval).

7/9/2008	Hold removed from IND 100594. ▪ FDA agreed that Enzon demonstrated that the obstacles to accurate measurement of asparagine in clinical samples were insurmountable (b) (4)
5/11/2009 7/28/2009	Meetings to discuss run in PK evaluation and appropriate doses for study. FDA instructed the sponsor that PK comparability should be assessed using the standard bioequivalence criteria, i.e., a 90% confidence interval for the geometric mean ratio should be between 80 to 125% for both C_{max} and AUC. Using this criteria a dose of 2100 IU/m^2 using AUC_{0-25} was appropriate. .
6/4/2010	IND was transferred to Sigma-Tau Pharmaceuticals, Inc., from Enzon Pharmaceuticals, Inc
9/28/12	BLA (b) (4) submitted; Standard Review; Indication: Component of multi-agent chemotherapeutic regimen for (b) (4) treatment of ALL; Trial AALL 07P4
4/30/12	Applicant withdrew BLA (b) (4) (b) (4)
3/4/14	Pre BLA Meeting (b) (4)

	[redacted] (b) (4)
9/2/14	Pre BLA Meeting Sigma Tau proposed a new analysis of AALL07P4 using PK/PD and PK/AE modeling, to support a BLA submission. FDA reiterated the recommendation that any BLA submission should include PK and induction safety data from the Dana Farber study.
12/16/15	IND transferred to Baxalta
8/4/16	Pre BLA Meeting with Baxalta FDA agreed COG AALL07P4 and DFCI 11-001 were appropriate studies to evaluate safety and efficacy. The acceptability of these trials to support approval would be a review issue. [redacted] (b) (4) a full clinical report will be required in the BLA submission. FDA agreed the applicant could use the summary of clinical efficacy and the summary of clinical safety in lieu of the ISS and ISE for the application.
10/25/17	FDA Rare Pediatric Disease (RPD) designation letter (Designation request # RPD-2017-135) issued by the Office of Pediatric Therapeutics (OPT) and Office of Orphan Products Development (OOPD)
12/22/17	BLA 761102 submitted by Baxalta, Inc.
6/7/18	Midcycle Communication
8/8/18	Late Cycle Meeting
12/17/18	Ownership of BLA 761102 transferred to Servier Pharmaceuticals LLC

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) inspected three clinical sites (Sites 1031, 1037 and 1038) and the Applicant for Study DFCI 11-001. The clinical sites chosen for inspection had the highest enrollment or the highest percentage of patients with protocol violations. All inspections were classified as No Action Indicated (NAI). The study data from the clinical sites were considered reliable in support of the requested indication.

The Office of Study Integrity and Surveillance (OSIS) inspected four analytical sites. The final classification for (b) (4) was NAI. The final classifications for (b) (4) and (b) (4) were VAI, and the responses to observations on the Form 483s issued were considered acceptable. It was concluded specifically that the PK data for Study AALL07P4 were acceptable for further Agency review.

The final classification for the inspection at the (b) (4) was VAI; an adequate response to the Form 483 observations was not received within this review cycle. The inspector concluded that the PK data for Study DCFI-11-001 were not reliable to support a regulatory decision and should not be accepted for agency review.

4.2. Product Quality

Calaspargase pegol-mknl drug substance is produced (b) (4) in Escherichia coli. It is comprised of an E. coli L-asparaginase homotetramer and 31-39 molecules of monomethoxypolyethylene glycol (mPEG) with a succinimidyl carbonate (SC) linker. Potency is based on enzyme kinetics.

Asparlas injection drug product is supplied as a clear, colorless, preservative-free, isotonic sterile solution in phosphate buffered saline, pH 7.3. Each single-dose vial contains 3,750 units in 5 mL of solution. Each milliliter contains 750 units of calaspargase pegol-mknl; dibasic sodium phosphate, USP (5.58 mg); monobasic sodium phosphate, USP (1.20 mg); and sodium chloride, USP (8.50 mg) in water for injection, USP. The drug product requires dilution prior to intravenous infusion. The diluted solution may be stored for up to 4 hours at room temperature or refrigerated for up to 24 hours. The recommended duration of infusion is one hour.

The Immunogenicity Reviewer found that the screening, titering and neutralizing assays were validated adequately for cut-point, precision, accuracy, linearity, short-term stability, freeze-thaw stability and drug interference, but the performance of the assays was suboptimal. (b) (4) Two postmarketing commitments for immunogenicity studies were also recommended. The reviewer based the recommended regulatory action on risk assessment.

There were no outstanding safety issues identified for the manufacturing process or from the facilities inspections. OPQ recommended approval of the BLA. They also recommended six additional postmarketing commitments to improve the robustness of the manufacturing process and product quality control strategy.

4.3 Devices and Companion Diagnostic Issues

The Applicant submitted minimal residual disease (MRD) data from Study DFCI11-001 (b) (4) [redacted] Based on the information submitted in the BLA and the response to Information Requests, the CDRH reviewer was not able to verify that the (b) (4) assay has reliable analytical performance at (b) (4) % as performed by (b) (4) The CDRH reviewer also noted that for the (b) (4) Assay, (b) (4) [redacted]

5 Nonclinical Pharmacology/Toxicology

5. 1 Executive Summary

Calaspargase pegol (Asparlas®, EZN-2285) is a conjugate of L-asparaginase and monomethoxy polyethylene glycol (mPEG) similar to the approved product pegaspargase (Oncaspar®, BLA 103411). Pegaspargase is PEGylated via a succinimidyl succinate (SS) linker, while calaspargase pegol uses a shorter and more stable succinimidyl carbonate (SC) linker. The applicant developed calaspargase pegol with the SC linker to extend the shelf life and half-life relative to pegaspargase.

A nonclinical bridging strategy was employed to compare the nonclinical pharmacodynamic (PD), pharmacokinetic (PK), and toxicity profiles of calaspargase pegol to pegaspargase. The applicant conducted single-dose comparative PD, PK, and toxicity studies in rats and dogs; rats, dogs, and humans have similar pharmacologic responses to L-asparaginase, and these species were used in the marketing application for pegaspargase. The applicant also conducted a repeat-dose study in dogs to evaluate the PK and toxicity profiles of calaspargase pegol following weekly administration for 4 weeks.

Single-dose studies were conducted in rats and dogs to evaluate the comparative PD, PK, and toxicity profiles of calaspargase pegol and pegaspargase. In both studies, animals were administered a single intravenous (IV) dose of calaspargase pegol or pegaspargase (100 or 500 IU/kg) followed by a 14-day observation period. Calaspargase pegol and pegaspargase were well-tolerated in both species with no mortality. Clinical signs consisted primarily of transient body weight loss and red discoloration (hemorrhage) of the subcutis (in rats) and increased incidence of soft feces and lacrimation (in dogs). Minor changes in hematology and clinical chemistry parameters were observed; however, there were no meaningful differences between the calaspargase pegol and pegaspargase groups. Decreases in absolute liver, spleen, and heart weights in rats were proportionate to decreases in body weight, and were similar between the calaspargase pegol and pegaspargase groups.

In the repeat-dose study in dogs, three dose levels (150, 500, and 1500 IU/kg) of calaspargase pegol were administered by IV injection once weekly for 4 weeks. Calaspargase pegol was well-tolerated with no mortality and no calaspargase pegol-related clinical signs. Mild decreases in red cell mass (1500 IU/kg) and in leukocyte, lymphocyte, and neutrophil counts (≥ 150 IU/kg, males only) were observed. Minimal decreases in total protein, albumin, and globulin were observed in males and females at ≥ 150 IU/kg. Increased spleen (both sexes) and testes weights were observed with no microscopic correlates.

PK parameters for calaspargase pegol and pegaspargase were inferred by evaluating plasma L-asparaginase activity in all toxicity studies. Calaspargase pegol and pegaspargase demonstrated similar systemic exposure (AUC_{last}, C_{max}), T_{max}, and $t_{1/2}$. Plasma L-asparagine concentrations were measured to assess calaspargase pegol and pegaspargase PD activity. Plasma L-asparagine concentrations were below the limit of quantitation (BLQ) at both dose levels of calaspargase pegol and pegaspargase at nearly all blood collection time points; therefore, no dose-response or potential differences in PD activity between calaspargase pegol and pegaspargase could be determined.

The single-dose comparative studies in rats and dogs demonstrated the PK and toxicity profiles of calaspargase pegol and pegaspargase were similar despite changing the linker from SS to SC. There were also no clear differences in the PD activity of calaspargase pegol and pegaspargase. The absence of effect on PD/PK endpoints may be at least partially attributed to the assay sensitivity, the small cohorts of animals, or the relatively short postdose PD/PK sampling period.

A dose range finding (DRF) embryo-fetal developmental (EFD) toxicity study was conducted in rats. Calaspargase pegol (100, 300, 500, and 1000 IU/kg/dose) was administered by the IV route every 6 days for three doses (on presumed gestation days [GDs] 6, 12, and 18). At ≥ 500 IU/kg, maternal toxicity characterized by decrease in body weight gain was observed, and correlated with reduction in food consumption; effects on body weight gain trended towards reversibility in the period before each subsequent dose administration. At 1000 IU/kg/dose reduced gravid uterine weight correlated with reduced litter weight and reduced mean fetal body weights. Plasma exposure could not be quantified and PK analyses were not performed; therefore, animal:human exposure multiples could not be determined.

The Agency previously agreed the (b) (4) study (b) (4) the applicant indicated this study was (b) (4)

The nonclinical pharmacology and toxicology data submitted to this BLA are adequate to support the approval of calaspargase pegol for the proposed indication.

5.2 Referenced NDAs, BLAs, DMFs

BLA 103411 (pegaspargase); BLA (b) (4) (calaspargase pegol – application withdrawn)

5.3 Pharmacology

Primary Pharmacology

The asparaginase mechanism of action is not impacted by the substitution of the SS linker in pegaspargase with the SC linker in calaspargase pegol; therefore, no dedicated pharmacology studies were conducted with calaspargase pegol.

The PD activity of calaspargase pegol and pegaspargase was evaluated in the single-dose comparative PD, PK, and toxicity studies in rats and dogs (see 5.5.1 General Toxicology). Plasma L-asparagine concentrations were BLQ (200 ng/mL) in calaspargase pegol- and pegaspargase-treated animals at nearly all blood collection time points. No dose-response or differences in PD activity between calaspargase pegol and pegaspargase were observed.

Secondary Pharmacology

Secondary pharmacology studies were not conducted.

Safety Pharmacology

Standalone safety pharmacology studies were not conducted. No effects on the CNS, respiratory, or cardiovascular systems were observed in the repeat-dose toxicity study in dogs (see 5.5.1 General Toxicology).

5.4 ADME/PK

Type of study	**Major findings**
TK data from general toxicology studies	
Single-dose comparative (calaspargase pegol vs pegaspargase) PK, PD, and toxicity study in rats / Study Report 824-015/AD07017	PK parameters were inferred by evaluating L-asparaginase activity. No significant gender differences were observed. Systemic exposure (AUC_{last}, C_{max}) increased in a dose proportional manner, and was similar between calaspargase pegol and pegaspargase. $t_{1/2}$ was similar for calaspargase pegol and pegaspargase. Calaspargase pegol was associated with extended T_{max}, except in females at 100 IU/kg.

<table>
<tr><th>Type of study</th><th>Major findings</th></tr>
<tr><td></td><td>Mean plasma L-asparaginase activity after a single dose of calaspargase pegol or pegaspargase in rats
(Adapted from applicant's submission)
<table>
<tr><th>Test article</th><th>Dose (IU/kg)</th><th>Sex</th><th>AUC_{last} (mIU*h/mL)</th><th>C_{max} (mIU/mL)</th><th>T_{max} (h)</th><th>$t_{1/2}$ (h)</th></tr>
<tr><td rowspan="4">Pegaspargase</td><td rowspan="2">100</td><td>F</td><td>93500</td><td>974</td><td>15.9</td><td>79.5</td></tr>
<tr><td>M</td><td>163000</td><td>1360</td><td>10.7</td><td>68.1</td></tr>
<tr><td rowspan="2">500</td><td>F</td><td>720000</td><td>5910</td><td>15.2</td><td>77.6</td></tr>
<tr><td>M</td><td>726000</td><td>6030</td><td>12.1</td><td>74.9</td></tr>
<tr><td rowspan="4">Calaspargase pegol</td><td rowspan="2">100</td><td>F</td><td>137000</td><td>1230</td><td>12.9</td><td>77.6</td></tr>
<tr><td>M</td><td>177000</td><td>1990</td><td>27.1</td><td>80.0</td></tr>
<tr><td rowspan="2">500</td><td>F</td><td>715000</td><td>6260</td><td>27.3</td><td>79.4</td></tr>
<tr><td>M</td><td>814000</td><td>6140</td><td>39.2</td><td>87.3</td></tr>
</table></td></tr>
<tr><td>Single-dose comparative (calaspargase pegol vs pegaspargase) PK, PD, and toxicity study in dogs / Study Report 824-016/AD07018</td><td>PK parameters were inferred by evaluating L-asparaginase activity. No significant gender differences in systemic exposure (AUC_{last}, C_{max}) were observed. Systemic exposure increased in an approximately dose proportional manner, and was similar between calaspargase pegol and pegaspargase. Variability in mean $t_{1/2}$ (pegaspargase, 500 IU/kg, males) and T_{max} (all groups) may have been the result of small sample size; excluding a single outlying value, $t_{1/2}$ was similar for calaspargase pegol and pegaspargase.
Mean plasma L-asparaginase activity after a single dose of calaspargase pegol or pegaspargase in dogs
(Adapted from applicant's submission)
<table>
<tr><th>Test article</th><th>Dose (IU/kg)</th><th>Sex</th><th>AUC_{last} (mIU*h/mL)</th><th>C_{max} (mIU/mL)</th><th>T_{max} (h)</th><th>$t_{1/2}$ (h)</th></tr>
<tr><td rowspan="4">Pegaspargase</td><td rowspan="2">100</td><td>F</td><td>418000</td><td>2120</td><td>18.3</td><td>184</td></tr>
<tr><td>M</td><td>360000</td><td>1660</td><td>1.8</td><td>206</td></tr>
<tr><td rowspan="2">500</td><td>F</td><td>1660000</td><td>8480</td><td>36.3</td><td>139</td></tr>
<tr><td>M</td><td>2230000</td><td>11400</td><td>30.3</td><td>969</td></tr>
<tr><td rowspan="4">Calaspargase pegol</td><td rowspan="2">100</td><td>F</td><td>319000</td><td>1720</td><td>1.8</td><td>216</td></tr>
<tr><td>M</td><td>351000</td><td>1910</td><td>24.3</td><td>282</td></tr>
<tr><td rowspan="2">500</td><td>F</td><td>1410000</td><td>8540</td><td>6.3</td><td>232</td></tr>
<tr><td>M</td><td>1810000</td><td>8370</td><td>3.1</td><td>307</td></tr>
</table></td></tr>
<tr><td>TK data from reproductive toxicology studies</td><td></td></tr>
<tr><td>EZN-2285 (BAX2303) Calaspargase-Pegol: Preliminary Embryo-Fetal Toxicity Study in Rats via Intravenous Injection / Study Report YW32SL</td><td>Plasma exposure could not be quantified, likely due to sample degradation prior to assay. PK analyses were not performed.</td></tr>
</table>

5.5 Toxicology

5.5.1 General Toxicology

A single intravenous dose comparative pharmacokinetic, pharmacodynamic and toxicity study between EZN-2285 and EZN-002 (Oncaspar®) in rats / Study Report 824-015/AD07017

Key study findings

- The toxicity profiles of calaspargase pegol and pegaspargase were comparable at equivalent dose levels, consisting primarily of transient body weight loss and red discoloration (hemorrhage) of the subcutis.
- Calaspargase pegol and pegaspargase demonstrated similar systemic exposure (AUC_{last}, C_{max}) and $t_{1/2}$ despite different linker technology.
- Both dose levels of calaspargase pegol and pegaspargase resulted in abrogation of plasma L-asparagine; therefore, no dose-response or differences between pegaspargase and calaspargase pegol PD activity were observed.

Conducting laboratory and location:
(b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 100, and 500 IU/kg (single dose)
Route of administration:	IV injection (approximately 30 seconds)
Formulation/vehicle:	Phosphate Buffered Saline (50 mM Phosphate), pH 7.3
Species/strain:	Rat/CD®[Crl:CD®(SD)]
Number/sex/group:	8/sex/group
Age:	9 to 10 weeks
Satellite groups/unique design:	Two satellite groups were included for PK/PD analyses (calaspargase pegol only). Comparative study design (calaspargase pegol and pegaspargase arms).
Deviation from study protocol affecting interpretation of results:	None

Observations and results: changes from control

Parameters	Major findings
Mortality	Four unscheduled deaths (all females) in the satellite study groups. All deaths were attributed to stress or/and associated complications of blood collection.

<table>
<tr><td>Clinical signs</td><td>500 IU/kg calaspargase pegol group: soft feces was observed in one male on Day 5; tremors were observed in one female on Day 1; red material around the nose, decreased activity and breathing difficult/rapid, and sparse hair were observed in another female on Days 2, 11, and 13-14, respectively.</td></tr>
<tr><td>Body weights</td><td>Transient body weight losses were observed in the pegaspargase and calaspargase pegol groups through Day 3; body weight was maintained or increased from Day 4-14, but remained below control animals on Day 14. There were no meaningful differences in body weight between the pegaspargase and calaspargase pegol groups (100 or 500 IU/kg) in males of females.
% Mean difference in body weight vs. concurrent vehicle control (Day 14)
(Adapted from applicant's submission)
<table>
<tr><th></th><th colspan="2">Pegaspargase (IU/kg)</th><th colspan="2">Calaspargase pegol (IU/kg)</th></tr>
<tr><th></th><th>100</th><th>500</th><th>100</th><th>500</th></tr>
<tr><td>Males</td><td>-5.1%</td><td>-14.1%**</td><td>-10.7%**</td><td>-12.6%**</td></tr>
<tr><td>Females</td><td>-5.6%*</td><td>-9.4%**</td><td>-6.2%*</td><td>-6.7%**</td></tr>
</table>
* p<0.05; ** p<0.01</td></tr>
<tr><td>Hematology and coagulation</td><td>No test article-related effects were observed.</td></tr>
<tr><td>Clinical chemistry</td><td>No toxicologically significant changes were observed. Decrease in globulins and total protein, and increase in cholesterol were observed; however, there were no meaningful differences between the pegaspargase and calaspargase pegol groups.</td></tr>
<tr><td>Urinalysis</td><td>No test article-related effects were observed.</td></tr>
<tr><td>Gross pathology</td><td>Mild to severe red discoloration of the subcutis was observed in ≤ 2 animals per group; the frequency and severity of red discoloration was similar between the pegaspargase and calaspargase pegol groups.</td></tr>
<tr><td>Organ weights</td><td>Decreases in absolute organ weights (liver, spleen, heart) were attributed to decreased body weight; there were no meaningful differences between the pegaspargase and calaspargase pegol groups.</td></tr>
<tr><td>Histopathology
Adequate battery: Yes
Peer review: Yes</td><td>Mild to moderate hemorrhage of the subcutis was observed at a similar frequency and severity between the pegaspargase and calaspargase pegol groups; evidence of hemorrhage is consistent with macroscopically-observed red discoloration. Minimal hepatic fatty change was observed in control and test article-treated females, but not in males, and is of unknown toxicological significance.</td></tr>
<tr><td>PD analysis</td><td>Plasma L-asparagine concentrations were BLQ (200 ng/mL) in all pegaspargase- and calaspargase pegol-treated animals at all blood collection time points with two exceptions. Because plasma L-asparagine concentrations were BLQ for nearly all samples, no dose-response or potential differences between pegaspargase and calaspargase pegol could be determined. Plasma L-asparagine concentrations were unaffected in control-treated animals, and plasma L-glutamine concentrations were not depleted at any time point in any animal.</td></tr>
</table>

A single intravenous dose comparative pharmacokinetic, pharmacodynamic, and toxicity study between EZN-2285 and EZN-002 (Oncaspar®) in beagle dogs / Study Report 824-016/AD07018

Key study findings

- The toxicity profiles of calaspargase pegol and pegaspargase were comparable at equivalent dose levels, consisting primarily of increased incidence of soft feces and lacrimation.
- Calaspargase pegol and pegaspargase demonstrated similar systemic exposure (AUC_{last}, C_{max}) despite different linker technology; variability in mean $t_{1/2}$ and T_{max} may have been the result of small sample size.
- Both dose levels of calaspargase pegol and pegaspargase resulted in abrogation of plasma L-asparagine; therefore, no dose-response or differences between pegaspargase and calaspargase pegol PD activity were observed.

Conducting laboratory and location:
(b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 100, and 500 IU/kg (single dose)
Route of administration:	IV injection (approximately 3 minutes)
Formulation/vehicle:	Phosphate Buffered Saline (50 mM Phosphate), pH 7.3
Species/strain:	Dog/beagle
Number/sex/group:	4/sex/group
Age:	5 to 6 months
Satellite groups/unique design:	No/comparative study design (calaspargase pegol and pegaspargase arms)
Deviation from study protocol affecting interpretation of results:	None

Observations and results: changes from control

Parameters	Major findings
Mortality	There were no unscheduled deaths.
Clinical signs	Increased incidence of soft feces was observed in males and females treated with both dose levels of calaspargase pegol and pegaspargase. The frequency of soft feces was not dose dependent and was similar between the pegaspargase and calaspargase pegol groups. Increased incidence of lacrimation was observed in males (calaspargase pegol, 500 IU/kg) and females (calaspargase pegol and pegaspargase, 500 IU/kg). Increased incidence of scleral injection (bloodshot eyes) was observed in males (pegaspargase, 100 IU/kg) and females (calaspargase pegol and pegaspargase, 100 and 500 IU/kg).

Body weights	Unremarkable
ECG	Unremarkable
Hematology and coagulation	Decreased erythrocytes, hemoglobin, and hematocrit (13-19%) were observed in calaspargase pegol-treated males; hemoglobin was statistically lower ($p<0.05$) than pegaspargase at 100 IU/kg. Reticulocytes (males) and lymphocytes (males and females) were sporadically decreased across the treatment groups, with no meaningful differences between the pegaspargase and calaspargase pegol groups. No test article-related effects on coagulation parameters were observed.
Clinical chemistry	Decreased albumin and total protein were observed in males; however, there were no meaningful differences between the pegaspargase and calaspargase pegol groups.
Urinalysis	No test article-related effects were observed.
Gross pathology	Unremarkable
Organ weights	Unremarkable
Histopathology **Adequate battery:** Yes **Peer review:** Yes	Minimal to mild inflammation and hyperplasia of the trachea was observed in calaspargase pegol-treated males. Sporadic cases of minimal to mild inflammation and histiocytosis of the lung were observed in the pegaspargase and calaspargase pegol groups (males and females).
PD analysis	Plasma L-asparagine concentrations were BLQ (200 ng/mL) in all pegaspargase- and calaspargase pegol-treated animals at all but two blood collection time points. No dose-response or potential differences between pegaspargase and calaspargase pegol could be determined. Plasma L-asparagine concentrations were unaffected in control-treated animals, and plasma L-glutamine concentrations were not depleted at any time point in any animal.

General toxicology; additional studies

A 4-Week Intravenous Toxicity Study in Beagle Dogs / Study Report 824-026/AD09001
This study was conducted to evaluate the PK and toxicity profiles of calaspargase pegol following weekly IV administration for 4 weeks (total of five doses) in beagle dogs; the doses of calaspargase pegol evaluated were 150, 500, and 1500 IU/kg. Calaspargase pegol was well-tolerated with no unscheduled deaths and no test article-related clinical signs. Slightly reduced body weights were not dose-related and were not statistically significant. Mild decreases in red cell mass (erythrocytes, hemoglobin, and hematocrit) were observed at 1500 IU/kg, and decreases in leukocyte, lymphocyte, and neutrophil counts (males only) were observed at ≥ 150 IU/kg. Minimal decreases in total protein, albumin, and globulin were observed in males and females at ≥ 150 IU/kg. Increased spleen (both sexes) and testes weights were observed, which was statistically significant at 1500 IU/kg; however, there were no microscopic correlates for organ weight changes. PK parameters were inferred by evaluating L-asparaginase activity; there were no gender differences in PK, and exposure increased dose-proportionally between 150 and 1500 IU/kg. Mean $t_{1/2}$ was similar on Day 22 and was slightly longer at ≤ 500 IU/kg on Day 1; mean T_{max} was similar at all doses on both days. Modest accumulation (1.7-2.6) was observed on Day 22 relative to Day 1.

5.5.2 Genetic Toxicology

Not conducted per ICH S6(R1).

5.5.3 Carcinogenicity

Not conducted per ICH S6(R1), S1, and S9.

5.5.4 Reproductive and Developmental Toxicology

Embryo-Fetal Development

EZN-2285 (BAX2303) Calaspargase-Pegol: Preliminary Embryo-Fetal Toxicity Study in Rats via Intravenous Injection / Study Report YW32SL

Key study findings:

- Calaspargase pegol caused maternal toxicity at ≥ 500 IU/kg/dose characterized by decrease in body weight gain; effects on body weight gain trended towards reversibility in the period before each subsequent dose administration and correlated with reduction in food consumption.
- At 1000 IU/kg/dose reduced gravid uterine weight correlated with reduced litter weight and reduced mean fetal body weights.
- There were no calaspargase pegol-related effects on maternal macroscopic observations, pregnancy or cesarean section parameters, or fetal external abnormalities.
- Plasma exposure could not be quantified, likely due to sample degradation prior to assay. PK analyses were not performed.

Conducting laboratory and location:
(b) (4)
GLP compliance: No

Methods

Dose and frequency of dosing:	0, 100, 300, 500, and 1000 IU/kg/dose; test article was administered every 6 days for three doses (on presumed GDs 6, 12, and 18)
Route of administration:	IV injection
Formulation/vehicle:	Phosphate Buffered Saline (50 mM Phosphate), pH 7.4, without Calcium and Magnesium
Species/strain:	Rat/CD®[Crl:CD®(SD)BR]
Number/sex/group:	8/females/group
Age:	7 to 12 weeks
Satellite groups:	Satellite groups were included for PK/PD analyses

	(3-6/females/group)
Study design:	Time-mated female rats were administered calaspargase pegol on GDs 6, 12, and 18, with necropsy/cesarean on GD 21
Deviation from study protocol affecting interpretation of results:	None

Observations and results

Parameters	Major findings
Mortality	None
Clinical signs	None
Body weights (values are BW gain over treatment period, % relative to control group)	**100 IU/kg/dose**: 72% **300 IU/kg/dose**: 70% **500 IU/kg/dose**: 62% **1000 IU/kg/dose**: 65%
Necropsy findings Cesarean section data	None
Necropsy findings Offspring (values are % relative to control group)	**500 IU/kg/dose**: mean fetal body weights 83.6%; **1000 IU/kg/dose**: gravid uterine weight 73%, mean fetal body weights 80.3%;

5.5.5 Other Toxicology Studies

None

Michael L. Manning, PhD
Primary Reviewer

Christopher Sheth, PhD
Team Leader

6 Clinical Pharmacology

6.1 Executive Summary

Calaspargase pegol (CalPEG), a pegylated form of L-asparaginase with a succinimidyl carbamate (SC) linker, is proposed to be used in combination with multi-agent chemotherapic regimens for the treatment of acute lymphoblastic leukemia (ALL), which is the same indication as currently approved product pegaspargase (Oncaspar®, BLA 103411). Due to the more stable SC linker used for conjugation, CalPEG is intended to have a longer half-life and extended shelf life than that of Oncaspar. The proposed dosing regimen of CalPEG is 2,500 U/m^2 for intravenous (IV) infusion (b) (4) no more frequently than every 21 days (Q3W). The recommended dosing regimen for Oncaspar is 2500 IU/m^2 IV infusion no more frequently than every 14 days (Q2W). The clinical development of CalPEG was based on a pivotal Study DFCI 11-001 and a supportive Study AALL 07P4. Oncaspar was used as a comparator in both studies. The primary objective in both studies includes the determination and comparison of asparaginase

acitivity levels between CalPEG and Oncaspar following a single induction dose and at steady state during the post-induction phase. The asparaginase activity is the basis of pharmacokinetic (PK) assessment in the clinical pharmacology program.

The PK data and population PK (PPK) analysis indicated that at the same dose of 2500 U/m^2 the nadir serum asparaginase activity (NSAA) at steady state are comparable between CalPEG Q3W and Oncaspar Q2W. Both drugs and regimens maintained the NSAA above the therapeutic threshold of 0.1 U/mL and is expected to have similar effect on asparagine depletion.

The immunogenicity of CalPEG is not sufficiently evaluated due to the failure of suitability of the immunogenicity assays. Applicant agreed to conduct post marketing commitments (PMCs) studies regarding re-development and validation of immunogenicity methods and re-evaluation of immunogenicity samples stored from the clinical studies.

6.1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in BLA 761102. This BLA is approvable from a clinical pharmacology perspective, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling language. The key review issues with specific recommendations and comments are summarized:

Review Issue	**Recommendations and Comments**
Pivotal and Supportive evidence of effectiveness	The evidence of effectiveness comes from the combination of observed valid PK data in the pivotal Study DFCI 11-001 and the estimated NSAA data based on a population PK model validated for both Study DFCI11-001 and Study AALL 07P4. PK data showed that asparaginase activity of CalPEG can be sustained ≥ 0.1 U/mL up to 25 days after single dose in the induction phase and maintained at steady state during the post-induction phase. PPK estimated data indicated comparable level of NSAA at steady state between CalPEG Q3W and Oncaspar Q2W at the same dose of 2500 U/m^2.
General dosing instructions	OCP agrees with the proposed dosing regimen of CalPEG: 2,500 U/m^2 IV infusion for (b) (4) with no more frequently than every 21 days (Q3W).
Dosing in patient subgroups (intrinsic and extrinsic factors)	Dose of CalPEG is based on body surface area (BSA) as the PPK model showed that the volume of distribution and clearance of CalPEG are dependent on BSA. No dose individualization is recommended for patients with renal and hepatic impairment.

Immunogenicity	Not sufficiently evaluated due to the failure of suitability of the immunogenicity assays. Post marketing commitments (PMCs) regarding re-development and validation of immunogenicity methods and re-evaluation of immunogenicity samples are communicated to the Applicant.
Labeling	The review team included the observed valid PK data in both CalPEG and Oncaspar arms in Study DFCI 11-001 and imputed NSAA data of CalPEG in section 14.1. (b) (4) PD data in Study AALL07P4 are added in section 12.2.

6.1.2 Postmarketing Requirements and Commitments

(b) (4) requested by OBP/CMC review teams.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

CalPEG is a pegylated form of L-asparaginase using a succinimidyl carbamate (SC) linker. CalPEG is proposed to be used in combination with multi-agent chemotherapeutic regimens for the treatment of acute lymphoblastic leukemia (ALL).

The clinical pharmacology program includes two clinical studies DFCI 11-001 and AALL07P4. Oncaspar at a dose of 2500 IU/m^2 was used as a comparator in both studies. CalPEG was administered at 2500 U/m^2 in the pivotal Study DFCI 11-001 and at two dose levels of either 2100 U/m^2 or 2500 U/m^2 in the supportive Study AALL07P4. Regarding the dosing interval, CalPEG was administered Q3W and Oncaspar was dosed Q2W for 30 weeks in Study DFCI 11-001, whereas, the dosing interval of CalPEG was the same as Oncaspar in study AALL07P4, which ranged from 2 to 5.5 weeks.

Absorption: A mean maximum concentration after a single IV infusion of 2500 U/m^2 is 1622 mU/mL with a standard deviation (SD) of 373 mU/mL. Steady state has been reached around the 4^{th} dose of CalPEG and NSAA is maintained $\geq$ 0.1 U/mL. The mean $AUC_{0\text{-}inf}$ is 25470 mU*day/mL with a SD of 7752 mU*day/mL.

Distribution: A mean volume of distribution is 3.0 L with a SD of 2.5 L after a single dose of 2500 U/m^2.

Metabolism: CalPEG is a pegylated enzyme so it is expected to be metabolized by proteolytic degradation.

Excretion: A mean elimination half-life is 16 days with a SD of 8.3 days after a single dose of 2500 IU/m^2. The range from minimum to maximum is 2.5 to 50 days.

Immunogenicity: The suitability of the immunogenicity assays for intended use has not been adequately demonstrated (b) (4)

Population PK: The population PK model was updated based on the valid PK measurements. In addition, the steady-state NSAA of CalPEG were imputed under the dosing regimen of 2500 U/m^2 Q3W based on the updated population PK model. The proportions of subjects that could maintain NSAA above the protocol-specified level of 0.1 U/mL is above 99% up to 30 weeks.

6.2.2 General Dosing and Therapeutic Individualization

General Dosing

CalPEG is proposed for IV infusion (b) (4) no more frequently than Q3W at a dose of 2,500 U/m^2. PK data showed that the mean elimination half-life of CalPEG (16 days) is more than 3 times longer than that of Oncaspar (5 days) after a single IV dose, which supports a longer dosing interval for CalPEG (Q3W) than that of Oncaspar (Q2W). In addition, both valid PK data in Study DFCI 11-001 and the imputation of NSAA data showed the NSAA at steady state given CalPEG Q3W and Oncaspar Q2W at the same dose of 2500 U/m^2 are comparable and maintained $\geq$ 0.1 U/mL. Therefore, CalPEG is expected to have similar effect on asparagine depletion to Oncaspar with the proposed less dosing frequency. Moreover, the safety profiles between CalPEG Q3W arm and Oncaspar Q2W arm in Study DFCI 11-001 appear comparable and acceptable.

Therapeutic Individualization

CalPEG is dosed using body surface area (BSA) and BSA was a significant covariate on the volume of distribution and clearance according to the population PK analysis. There is no clinically meaningful difference in CalPEG exposures among age and BMI subgroups. The PPK modeling and simulation suggested that the dosing regimen of 2500 U/m^2 Q3W would be sufficient to maintain the NSAA at steady-state above 0.1 U/mL regardless of age. For further details, see appendix 14.4.3 pharmacometrics review.

Outstanding Issues

None

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

The clinical pharmacology and pharmacokinetics characteristics of CalPEG at the dose of 2500 U/m^2 are summarized in the following table.

Pharmacology	
Mechanism of Action	CalPEG is an E.coli derived L-asparaginase which is covalently conjugated to monomethoxy polyethylene glycol (mPEG) using a succinimidyl carbamate (SC) linker. The molecular weight is approximately 313 kDa. L-asparaginase is an enzyme that catalyzes the conversion of the amino acid L-asparagine into aspartic acid and ammonia. CalPEG, as an asparaginase treatment, is thought to selectively kill leukemic cells due to depletion of plasma asparagine because the survival of leukemic cells are highly dependent on exogenous asparagine in the blood.
Pharmacodynamics	CalPEG treatment suppresses plasma and cerebrospinal fluid (CSF) asparagine concentrations to a similar extent as Oncaspar. Depletion of plasma and CSF asparagine concentrations following the single induction dose and the first consolidation dose of CalPEG and Oncaspar were assessed in Study AALL07P4. During the induction phase, plasma asparagine concentrations were rapidly depleted to below the assay lower limit of quantitation at 5 minutes post dose regardless of treatment groups and remained below the LLOQ for the entire sampling duration up to 25 days post dose. The depletion of asparagine occurred in the same trend following the first dose in the consolidation phase. CSF asparagine concentrations were suppressed to near or below the LLOQ after the single induction dose and the first consolidation dose regardless of treatment groups.
QT Prolongation	CalPEG is not expected to prolong the QT interval to a clinically relevant extent as it is an enzyme.
General Information	
Dose and Dosage Form	The proposed dose is 2,500 U/m^2 given IV infusion for (b) (4) (b) (4) no more frequently than Q3W. Each single-dose vial contains 3,750 Unites/5 mL (750 Unites/mL) injection solution. CalPEG activity is expressed in Units. (b) (4)

	(b) (4)
Bioanalysis	The bioanalytical method and validation reports were submitted to both Study DFCI 11-001 and AALL07P4. A coupled enzymatic spectrophotometric assay was applied to measure L-asparaginase activity in human serum or plasma at each PK sampling time for Oncaspar or CalPEG. The lower limit of quantification (LLOQ) was (b) (4) IU/ml in Study DFCI 11-001 and 12.86 mIU/mL in Study AALL07P4. The calibration curve ranged from (b) (4) IU/ml (8 standards) in Study DFCI 11-001 and ranged from 12.86 to 150 mIU/mL (8 standards) in Study AALL07P4. Three QC levels were prepared in each study. However, the core lab to assess the PK samples in Study DFCI 11-001 failed the FDA inspection, which impacted the validity of the PK data. The lab inspection for Study AALL07P4 appears acceptable. For details, see appendix section 14.4.1.
Drug exposure following a single dose	Following a single dose of CalPEG 2500 U/m^2 in the induction phase in Study AALL07P4, mean C_{max}, $AUC_{(0\text{-}25d)}$ and $AUC_{(0\text{-}inf)}$ were 1622 mU/mL, 16870 mU*day/mL and 25470 mU*day/mL, respectively.
Absorption	
C_{max} and AUC	A mean maximum concentration (C_{max}) after a single IV infusion of 2500 U/m2 is 1622 mU/mL with a standard deviation (SD) of 373 mU/mL. The mean $AUC_{0\text{-}inf}$ is 25470 mU*day/mL with a SD of 7752 mU*day/mL.
Accumulation	Steady state has been reached around the 4th dose of CalPEG and NSAA is maintained $\geq$ 0.1 U/mL.
Dose proportionality	$AUC_{(0\text{-}25d)}$ of CalPEG in Study AALL07P4 at 2100 U/m^2 and 2500 U/m^2 increased approximately proportional to dose while C_{max} and $AUC_{(0\text{-}inf)}$ increased slightly greater than proportionally with dose.
Distribution	
Volume of Distribution	A mean value of 3.0 L with a SD of 2.5 L for CalPEG 2500 U/m^2 in Study AALL07P4.
Elimination	
Mean terminal elimination half-life	A mean value of 16 days with a SD of 8.3 days after a single dose of 2500 U/m^2 in the induction phase in Study AALL07P4. The range from minimum to maximum is 2.5 to 50 days

Clearance	A mean value of 0.15 L/day with a SD of 0.1 L/day after a single dose of 2500 U/m^2 in the induction phase in Study AALL07P4.
Metabolism	
Primary metabolic pathway (*in vitro*)	CalPEG is a pegylated enzyme so it is expected to be metabolized by proteolytic degradation.
Immunogenicity	
Incidence	The OBP review team informed the applicant that the suitability of the immunogenicity assays for intended use has not been adequately demonstrated (b) (4) For details, see question 3.3.3.
Impact on PK	NA

6.3.2 Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. Maintaining nadir serum asparaginase activity (NSAA) above 0.1 U/mL and the PK comparability assessment between CalPEG and ONCOSPAR are the pivotal evidence of effectiveness in this development program. Safety analyses also suggest that the overall benefit/risk profile is unlikely to differ between CALPEG Q3W and ONCOSPAR Q2W. The evidence of effectiveness are summarized below:

- Comparable safety profiles between CALPEG Q3W and ONCASPAR Q2W in pivotal Study DFCI 11-001

- After single dose in induction phase in Study DFCI 11-001, eight out of the 11 evaluable patients in CalPEG arm had sustained SAA ≥ 0.1 U/mL up to 25 days in contrast to none of the patients in Oncaspar arm

- During post-induction phase in Study DFCI 11-001, all 5 evaluable patients in CalPEG arm (Q3W) and 3 evaluable patients in Oncaspar arm (Q2W) had maintained NSAA ≥ 0.1 for 30 weeks

- Imputations based on the population PK analysis with valid PK data from 124 subjects (13 from study DFCI 11-001 and 111 from study AALL07P4) indicated that more than 99% of the subjects (123 out of 124) would maintain NSAA ≥ 0.1 U/mL from Week 6 to

Week 30 during the post-induction phase, suggesting a sufficient level of NSAA at steady state under the proposed CalPEG dosing regimen of 2500 U/m^2 Q3W (details refer to pharmacometrics review in section 14.4.3).

- Plasma asparagine concentrations were rapidly depleted to below the assay lower limit of quantitation (LLOQ, 0.05 μg/mL) at 5 minutes post dose regardless of treatment groups and remained below the LLOQ for the entire sampling duration up to 25 days post dose. \

The exposure to asparaginase activity is utilized for PK assessment and is one of the primary endpoints in Study DFCI 11-001 and Study AALL07P4. The protocol specified therapeutic threshold of asparaginase activity either after a single dose or at steady state is set as ≥ 0.1 U/mL, which is considered to be associated with complete asparagine depletion based on in vitro data and clinical studies. The determination of effectiveness is to demonstrate sufficient asparagine depletion, which is considered as a valid surrogate PD endpoint for clinical efficacy of asparaginase treatment.

Study DFCI 11-001 and Study AALL07P4 are two randomized trials in pediatrics and adults with newly diagnosed ALL or lymphoblastic lymphoma. Oncaspar at a dose of 2500 IU/m^2 was used as a comparator in both studies. CalPEG was administered at 2500 U/m^2 in the pivotal Study DFCI 11-001 and at two dose levels of either 2100 U/m^2 or 2500 U/m^2 in the supportive Study AALL07P4. Another difference in treatment between two studies is the dosing interval of CalPEG during the post induction phase. In Study DFCI 11-001, CalPEG was administered Q3W for 30 weeks, while the dosing interval of CalPEG was the same as Oncaspar in study AALL07P4, which ranged from 2 to 5.5 weeks. See detailed study descriptions for two studies in the section of clinical review.

During the review process, the PK bioanalysis inspection team reported that the bioanalytical validation method used in Study DFCI 11-001 to determine the asparaginase activity is not reliable, which leads to > 90% observed PK data can not be used for PK analysis. For detailed description of bioanalytical method failure, see the report of analytical inspection of (b) (4)

Subsequently, there are 11 evaluable patients in CalPEG arm and 16 evaluable patients in Oncaspar arm during induction phase. Eight out of the 11 evaluable patients in CalPEG arm had sustained SAA ≥ 0.1 U/mL up to 25 days after a single dose in contrast to none of the patients in Oncaspar arm. During post-induction phase, all 5 evaluable patients in CalPEG arm and 3 evaluable patients in Oncaspar arm had maintained NSAA ≥ 0.1 for 30 weeks. Because the low evaluable observed PK data is lack of power for any decision making, the review team utilized an imputation method based on the population PK modeling and simulation, and combined it with the limited observed PK data to support an approval of the proposed dosing regimen of CalPEG Q3W. Specifically, the population PK (PPK) model was updated by re-assessing the PPK model originally developed by the applicant based on the retained valid PK data from 124 subjects (111 from study AALL07P4, and 13 from study DFCI 11-001). All subjects from studies AALL07P4 and DFCI 11-001 with at least one valid PK observation were included in the

imputation. Each subject's PK parameters (empirical Bayes estimates) were estimated by the updated population PK model. The subject's PK at any time point, including NSAA at steady-state, under the proposed dosing regimen of 2500 U/m^2 Q3W could then be imputed. For detailed description of imputation method and its appropriateness, see the pharmacometrics section in appendix14.4. Imputation data showed that more than 99% of the subjects (123 out of 124) would maintain NSAA ≥ 0.1 U/mL from Week 6 to Week 30 during the post-induction phase, which indicated sufficient level of NSAA at steady state with CalPEG given the proposed dose regimen of 2500 U/m^2 Q3W.

Moreover, the clinical review team indicates the safety profiles between CalPEG Q3W arm and Oncaspar Q2W arm appear comparable and acceptable in the pivotal study DFCI 11-001.

As supportive evidence of effectiveness, depletion of plasma and cerebrospinal fluid (CSF) asparagine concentrations following the single induction dose and the first consolidation dose were assessed in Study AALL07P4. During the induction phase, plasma asparagine concentrations were rapidly depleted to below the assay lower limit of quantitation (LLOQ, 0.05 μg/mL) at 5 minutes post dose regardless of treatment groups and remained below the LLOQ for the entire sampling duration up to 25 days post dose. Similarly, the median plasma asparagine concentrations were below the LLOQ for all three treatment groups following the first dose in the consolidation phase at all PK sampling timepoints. CSF asparagine concentrations were suppressed to near or below the LLOQ after the single induction dose and the first consolidation dose regardless of treatment groups. The applicant also reported the mean CSF asparagine levels immediately prior to the consolidation phase appeared to achieve approximately pre-induction levels in the Oncaspar group while CSF asparagine rose considerably slowly in both CalPEG arms indicating the CSF asparagine depletion was more persistent in CalPEG arms comparing to Oncaspar arm. In summary, CalPEG treatment suppresses plasma and CSF asparagine concentrations to a similar extent as Oncaspar.

In conclusion, combined valid PK data in Study DFCI 11-001 together with the imputation of NSAA data support the evidence that majority of subjects would maintain steady-state NSAA above 0.1 U/mL and comparable asparaginase activity between CalPEG Q3W and Oncaspar Q2W given the same dose level of 2500 U/m^2. CalPEG is expected to have similar effect on asparagine depletion to Oncaspar with less dosing frequency because NSAA are ≥ 0.1 U/mL for both CalPEG Q3W and Oncaspar Q2W.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dose and dosing interval of CalPEG is acceptable in the target patient population. The population PK analysis indicated that BSA is the only significant covariate for clearance and volume distribution. Therefore, the proposed dosing regimen is BSA based dose (2500 U/m2). The PK comparison between CalPEG Q3W and Oncaspar Q2W provided the primary evidence for the effectiveness. The longer mean half life of CalPEG (16 days) than Oncaspar (5 days) supports the proposed Q3W dosing regimen. The change of asparaginase activity vs. time profile after a single dose in induction phase or the first dose in consolidation

phase in Study AALL07P4 demonstrated that asparaginase activity in CalPEG arm had a longer time to sustain ≥ 0.1 U/mL up to 25 days post dose than in Oncaspar arm, which supports the less frequent dosing interval of CalPEG can maintain the similar asparagine depletion to Oncaspar. Although, only 11 evaluable patients in CalPEG arm and 16 evaluable patients in Oncaspar arm during induction phase are available for PK analysis, the same trend was observed.

Moreover, imputations of NSAA based on the updated population PK analysis indicated that more than 99% of the subjects (123 out of 124) would maintain NSAA ≥ 0.1 U/mL for CalPEG treatment from Week 6 to Week 30 during the post-induction phase, suggesting a sufficient level of NSAA at steady state under the proposed CalPEG dosing regimen of 2500 U/m2 Q3W.

In addition, the clinical review team indicates comparable and acceptable safety profiles between CalPEG Q3W arm and Oncaspar Q2W arm in the pivotal study DFCI 11-001.

Overall, the proposed dosing regimen of CalPEG at 2500 U/m2 IV infusion no more frequently than Q3W appears acceptable based on the PK profile, the NSAA comparison with Oncaspar, and safety profile.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. There is no need for an alternative dose or dosing regimen for subpopulation based on the intrinsic factors as described below.

CalPEG is a pegylated enzyme with a molecular weight of 313 kDa so it is unlikely to be renally filtered and therefore the effect of renal impairment is unlikely to result in PK alteration of CalPEG. In addition, CalPEG is not metabolized by hepatic enzymes, therefore hepatic impairment is unlikely to alter PK of CalPEG, either. No dedicated renal impairment or hepatic impairment study was conducted.

The influence of intrinsic factors such as body size, sex, age, and anti-drug antibody status were evaluated as part of a population PK evaluation. The final population PK model demonstrated a proportional relationship between body surface area (BSA) and the volume of distribution and clearance of CalPEG, which supports the proposed dosing of calaspargase pegol based on BSA (i.e., 2500 U/m^2). In addition, imputed NSAA at steady-state were compared across different BMI or age sub-groups, and did not show clinically meaningful difference. The magnitudes of effects on CalPEG PK from other intrinsic factors are not considered clinically important in terms of the change in asparaginase activity. For detailed description of population PK model and covariates analysis, see the pharmacometrics section in appendix 14.4.3.

Immunogenicity

Immunogenicity assessment of CalPEG and Oncaspar included the detection of both binding and neutralizing anti-drug antibodies (ADA) and the detection of binding anti-PEG antibodies. Immunogenicity analysis including method validation and sample analyses for Studies AALL07P4 and DFCI 11- 001 were conducted at (b) (4)

[redacted]

According to OBP review, the data provided in "Summary of In-study ADA Assay Performance" showed that approximately 54 % of the samples tested for anti-CalPEG antibodies and 12% for anti-Oncaspar antibodies in the DFCI 11-001 study failed the system suitability acceptance criteria. For these reasons, the suitability of the immunogenicity assays for intended use has not been adequately demonstrated [redacted]

Consequently, the Applicant agreed to conduct the following post marketing commitments (PMC) studies:

1. To develop and validate screening, confirmatory, [redacted] assays for the evaluation of anti-calaspargase antibodies. Develop an assay to determine whether the anti-calaspargase antibodies are anti-PEG, [redacted]
2. [redacted]

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food-drug interaction is not applicable as CalPEG is administered intravenously.

Drug-drug interaction is unlikely as CalPEG is developed as a pegylated enzyme.

Runyan Jin Ph.D.	***Xianhua (Walt) Cao Ph.D***
Ruojing Li Ph.D.	***Chao Liu Ph.D.***
Primary Reviewers	***Team Leaders***

7 Sources of Clinical Data and Review Strategy

7.1 Table of Clinical Studies

Table 3: Clinical Trials

Summary of Clinical Studies					
Trial Id. NCT No.	**Title**	**Design**	**Regimen**	**Endpoints**	**Number of Patients Countries**
DFCI 11-011 NCT01574274 Initiated 6/4/12 Data Cut Off 10/15/16	Randomized Study of Intravenous Calaspargase Pegol (SC-PEG-L-asparaginase) and Intravenous Oncaspar® in Children and Adolescents with Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma	Phase 2 Randomized Stratified by disease type, age and initial risk group classification	Multi-agent Chemotherapy calaspargase vs pegasparagase 2500 IU/m^2 IV Induction Day 7 CNS Therapy /Consolidation calaspargase 10 doses (q3wk) pegasparagase 15 doses(q2wk)	PK Endpoints Induction SAA level ≥0.10 IU/mL at Induction d7/11/18/25/32 NSAA level ≥0.10 IU/mL during the post-induction phase NSAA wk 7 Efficacy Induc d32 MRD/CR/EFS/DFS OS Safety AEs/Infections/ADA	n=239 Calaspargase n=119 Pegasparagase n=120 USA n=148 Canada n=91
AALL07P4 No NCT ID Initiated 10/14/08 Data Cut Off 12/31/15 FSR	A Pilot Study of Intravenous EZN-2285 (SC PEG *E. coli* L asparaginase, IND 100594) or Intravenous Oncaspar® in the Treatment of Patients with High-Risk Acute Lymphoblastic Leukemia (ALL): A Limited Institution Pilot Study	Pilot study Open-label Randomized	Multi-agent Chemotherapy pegasparagase 2500 IU/m^2 vs calaspargase 2500 IU/m^2 AND calaspargase 2100 IU/m^2	Primary PK (including Cmax and AUC) of calaspargase pegol and pegasparagase during Induction and Consolidation. Secondary PD (asparagine depletion), MRD, and immunogenicity Safety (no erosion) DFS, EFS, OS	n=166 Pegasparagase n=55 Calaspargase 2500 IU/m^2 n=42 Calaspargase 2100 IU/m^2 n=69 USA all

Abbreviations: ADA anti-drug antibody; AE – adverse event; CR - complete remission; DFS – disease free survival; EFS -event free survival; MRD – minimal residual disease; PD – pharmacodynamic; PK -pharmacokinetic; NSAA – nadir serum asparaginase activity; SAA - serum asparaginase activity; OS – overall survival

7.2 Review Strategy

Two clinical trials were considered for the review of this application. The tables and figures presented in the clinical review are the FDA analysis unless stated otherwise.

DFCI 11-001

DFCI 11-001 was evaluated to support efficacy and safety. The DFCI 11-001 study was designed to determine whether an every-3-week regimen of calaspargase pegol provided nadir serum asparaginase activity (NSAA) comparable to pegasparagase administered every 2 weeks, with comparable safety and no erosion in event-free survival (EFS) and overall survival (OS). The DFCI 11-001 study was not designed or powered to demonstrate clinical superiority or non-inferiority of EFS or OS with calaspargase pegol compared to pegasparagase. Non-erosion of EFS, DFS and OS were considered safety objectives for the purposes of this review.

AALL07P4

The clinical study report of AALL07P4 was submitted 9/28/12 to support (b) (4)

(b) (4)

Because the calaspargase regimen in AALL07P4 differed from the regimen currently proposed by the Applicant, the review of AALL07P4 will focus on the safety information.

8 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. DFCI 11-001

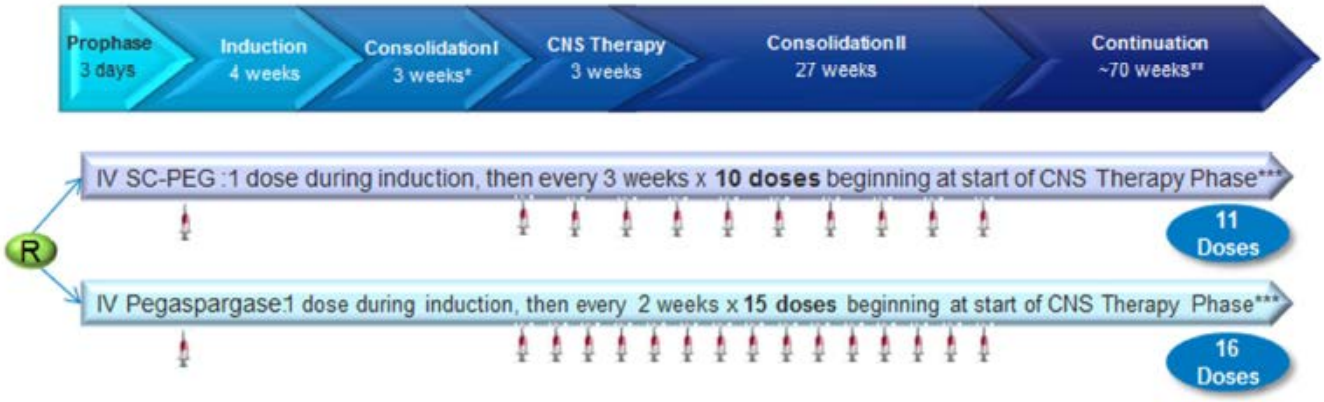
Title
"Randomized Study of Intravenous Calaspargase Pegol (SC-PEG-L-asparaginase) and Intravenous Oncaspar® in Children and Adolescents with Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma"

INVESTIGATIONAL PLAN

Trial Design
Phase 2, randomized, multicenter trial (conducted under IND (b) (4))

DFCI 11-001 was a phase 2, randomized multicenter study to determine the safety and feasibility of administering calaspargase pegol, compared with pegasparagase, in children and adolescents with newly diagnosed acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LL) treated with the DFCI ALL Consortium therapeutic backbone.

Figure 1: DFCI 11-001 Schema
(copied from submission)



*~9 weeks for VHR subjects
**Until 104 weeks (24 months) of CCR
***Post-induction asparaginase begins during Consolidation I phase in VHR subjects. The asparaginase dose for both groups is 2500 IU/m^2 as an intravenous infusion over 1 hour.

Treatment Plan

See appendix 14.6 for treatment details of DFCI 11-001

Monitoring Plan

See Section 8.3 for details of the safety monitoring plan.

Study Objectives

DFCI 11-001 was not originally designed as a study to support a regulatory submission. The original protocol objectives were modified for this BLA application. The following study objectives are derived from the statistical analysis plan (SAP) submitted by Baxalta 6/21/16, amended 7/23/17.

- Primary Objective - To assess the safety and feasibility associated with the administration of calaspargase pegol 2500 IU/m^2 given intravenously (IV) as a single dose during remission induction and then every 3 weeks for 30 weeks during post-induction therapy in children and adolescents with newly diagnosed ALL.
    - To assess the toxicity associated with calaspargase pegol administration and determine if it is different from the toxicity associated with pegasparagase 2500 IU/m^2 given a single dose during remission induction and then every 2 weeks for 30 weeks during post-induction therapy.
    - To determine the serum asparaginase activity (SAA) levels associated with calaspargase pegol administered as a single dose during remission induction and every 3 weeks for 30 consecutive weeks during post-induction therapy, and to compare them to the SAA associated with pegasparagase administered as a single dose during remission induction and every 2 weeks for 30 consecutive weeks during post-induction therapy.
- Secondary Objectives
    - To assess the frequency of bacteremia, fungemia and invasive fungal infections during the remission induction phase in patients receiving antibiotic prophylaxis.
    - To determine end of Induction therapy minimal residual disease
    - To determine the complete remission (CR) rate
    - To assess event-free survival, disease-free survival from complete remission and overall survival
    - To assess the immunogenicity

Endpoints

- Safety Endpoints
    - Serious adverse event (SAEs) and laboratory adverse events (AEs), especially AEs of interest related to asparaginase toxicity
    - Bacteremia, fungemia and invasive fungal infection during the remission induction phase in patients treated with antibiotic prophylaxis.
    - Positive post-baseline anti-drug antibodies
    - Physical exam: height, weight, BSA and BMI

- Pharmacokinetic Endpoints
  - SAA level ≥0.10 IU/mL at Induction phase Days 7 (immediately post-asparaginase dose), 11, 18, 25 and 32.
  - NSAA level ≥0.10 IU/mL during the post-induction phase overall and by visit day.
  - NSAA level at the week 7

- Efficacy Endpoints
  - Day 32 end-induction MRD status.
  - CR
  - EFS
  - DFS from achievement of CR
  - OS

CLINICAL REVIEWER COMMENT:
The comparison of toxicity, including infections, will be evaluated in section 8.3. The pharmacokinetic profile will be evaluated by the clinical pharmacology reviewer in section 7. The efficacy endpoints will be presented in section 8.1.1. but evaluated as a safety issues.

Statistical Analysis Plan
As noted below, DFCI 11-001 was designed to assess the safety and feasibility of IV administration of calaspargase pegol 2500 IU/m^2. It was not designed to assess efficacy with respect to clinical endpoints such as

- Minimal residual disease
- Complete remission
- Overall survival
- Disease free survival
- Event free survival

STATISTICAL REVIEWER COMMENT
While the statistical analysis plan discusses how these endpoints are to be analyzed, there are no prespecified criteria from which a determination of efficacy is to be made. For example, there were no agreed-up margins on which non-inferiority between IV calaspargase pegol 2500 IU/m2 and pegasparagase can be determined. Furthermore, the amount of statistical information for time-to-event endpoints is insufficient for making statements about OS, DFS, and EFS.

Protocol Amendments (notable amendments)

Original Protocol 3/12/12
Amendment #1 12/27/12

- The complete remission criterion for the percentage of allowable malignant lymphoblasts was changed from fewer than 5% to fewer than 1%.

- Timing of immunogenicity samples
- Sample required for patients switched to intramuscular (IM)
- Details regarding timing and dose of Erwinia added.

Amendment # 2 5/6/13

- Supportive care guidelines not related to asparaginase

Amendment #3 8/20/13

- Eligibility was revised to increase upper age limit from 18 years to < 22 years.
- Noted total bilirubin of <1.4 mg/dL was sufficient to meet the bilirubin criteria for enrollment, starting and continuing therapy.
- No immunogenicity testing after switch to Erwinia
- Requirement for real-time asparaginase samples on day 25 and 32 eliminated

Amendment #4 5/14/14

- MRD methodology for patient with MRD indeterminate by polymerase chain reaction (PCR) was added and included for risk stratification
- Clarification direct bilirubin criteria (≤1.4 mg/dL) to administer asparaginase
- Clarification regarding administration of asparaginase schedule during consolidation

Amendment #5 11/17/14

- The required direct bilirubin level was specified for all doses of asparaginase.
- Dose modifications in the case of elevated bilirubin levels were specified.
- Erwinia IV allowed

Amendment #6 12/30/14

- Bilirubin testing during Erwinia weekly
- Guidelines for IV Erwinia administration

Amendment #7 3/6/15

- Vincristine and dexamethasone specifications

Amendment #8 7/16/15

- Requirement PK samples for patients on Erwinia treated patients removed
- Guidelines for Erwinia dosing in subjects with silent inactivation to pegylated asparaginase added

Amendment #9 2/24/16

- Retroactive collection of additional AEs related to asparaginase added with reporting guidelines

Major Inclusion Criteria

Inclusion:

- Confirmed diagnosis of acute lymphoblastic leukemia or lymphoblastic lymphoma
- No prior therapy with the exception of
    - Limited corticosteroids (≤ 7days)
    - A single dose of intrathecal (IT) cytosine arabinoside prior to registration
    - Emergent radiation to the mediastinum or other life-threatening masses
- Age: 365 days to ≤ 22 years
- Direct or total bilirubin < 1.4 mg/dL

Exclusion:

- Patients with mature B-cell (Burkitt's) ALL

STUDY RESULTS

Compliance with Good Clinical Practices
The cover page of the study report includes the statement: "This study was conducted in accordance with the standards of Good Clinical Practice (GCP) in effect at the time of the study. All records have been attached per GCP requirements."

Financial Disclosure
Financial disclosure information was included in the submission. No investigators with disclosable financial interests were identified. See Appendix 14.2.

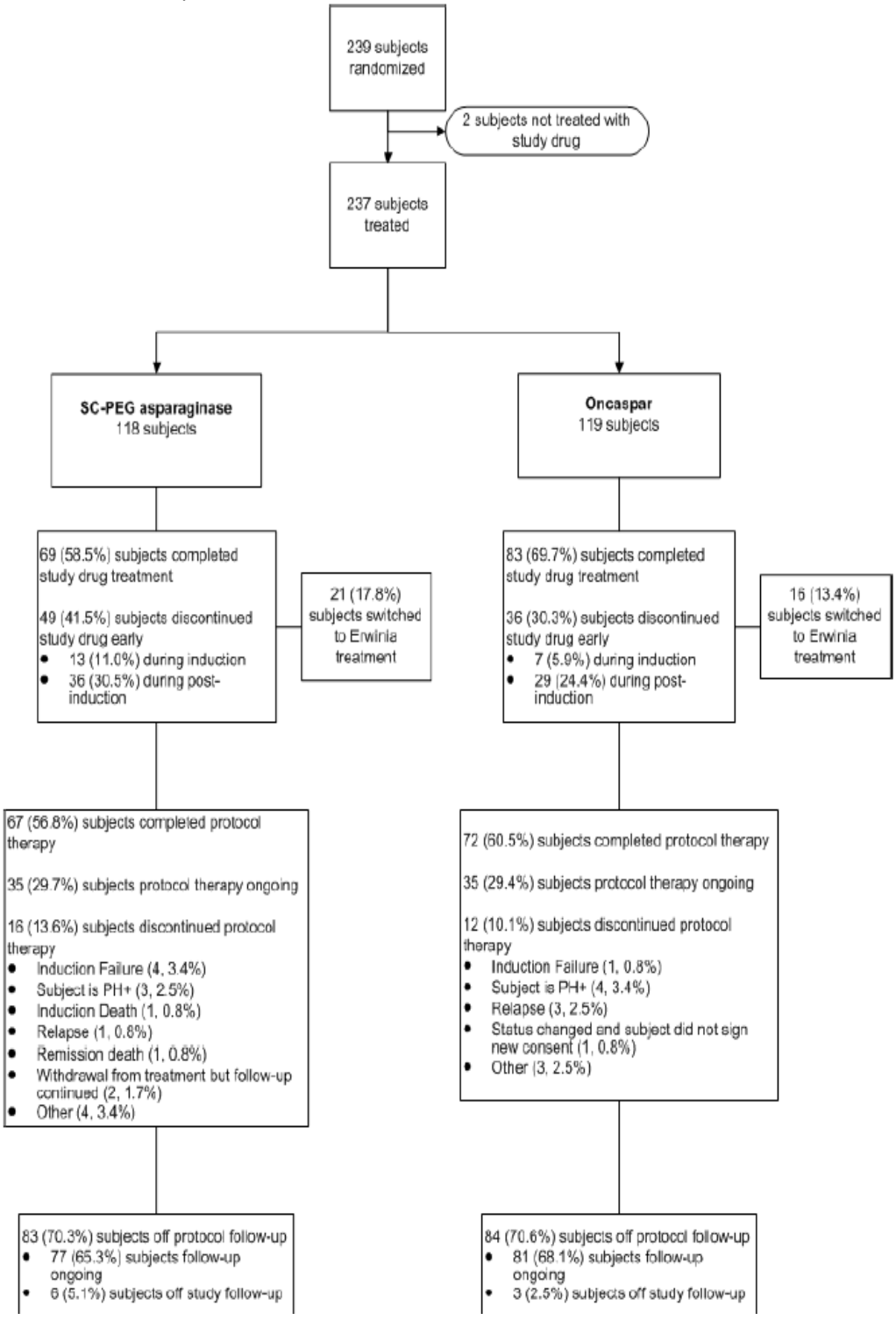
Data Quality and Integrity
The quality and integrity of the submitted data were sufficient for the reviewers to review the application.

Study Timeline

Original Protocol Open for Entry:	3/12/12
First Subject Enrolled:	6/4/12
Last Subject Completed Asparaginase:	2/18/16
Data Cut-Off Date:	10/5/16
Planned Enrollment:	Total n = 240
Actual Enrollment:	n = 239

Patient Disposition

Figure 2: DFCI 11-001 Patient Disposition
(copied from submission)



Protocol Violations/Deviations

There were 47 (20%) subjects who had at least 1 major protocol deviation during the study, 26 (22%) were in the calaspargase pegol group and 21 (18%) were in the pegasparagase group.

CLINICAL REVIEWER COMMENT:
Overall, the protocol violations described do not prevent interpretation of the study results.

Demographic and Disease Characteristics

There were 2 patients included in the intent to treat (ITT) population who did not receive study drug, one in each arm.

Table 4: DFCI 11-001 Demographics - ITT Population

DFCI 11-001 Demographics (ITT)			
	Pegasparagase n = 120	**Calaspargase n = 119**	**Total n = 239**
Gender n (%)			
Male	71 (59)	76 (64)	147 (62)
Female	49 (41)	43 (36)	92 (38)
Age (years)			
Mean	6.2	6.5	6.4
Median	4.5	5	5
Range	1 to 18	1 to 20	1 to 20
1 – 10 n (%)	93 (78)	90 (76)	182 (76)
11 – 15 n (%)	20 (17)	23 (19)	43 (18)
16 – 20 n (%)	7 (6)	6 (5)	13 (5)
Race / Ethnicity n (%)			
White / Not Hispanic or Unknown	80 (67)	72 (61)	152 (64)
White / Hispanic	10 (8)	6 (5)	16 (7)
Black / Not Hispanic	2 (2)	9 (8)	11 (5)
Asian	4 (3)	6 (5)	10 (4)
More than one / Hispanic	3 (3)	3 (3)	6 (3)
More than one / Not Hispanic	3 (3)	2 (2)	5 (2)
Other / Hispanic	11 (9)	9 (8)	20 (8)
Other / Not Hispanic or Unknown	7 (6)	12 (10)	19 (8)
Country n (%)			
US	72 (60)	76 (64)	148 (62)
Canada	48 (40)	43 (36)	91 (38)

Disease Characteristics

Table 5: DFCI 11-001 Disease Characteristics - ITT Population

DFCI 11-001 Disease Characteristics (ITT)			
	Pegasparagase n = 120	**Calaspargase n = 119**	**Total n = 239**
Disease n (%)			
Acute Lymphoblastic Leukemia	116 (97)	114 (96)	230 (96)
Lymphoblastic Lymphoma	4 (3)	5 (4)	9 (4)
Acute Lymphoblastic Leukemia - Phenotype n (% [n/230])			
B-cell lineage	104 (90)	100 (88)	204 (89)
T-cell lineage	12 (10)	14 (12)	26 (11)
Acute Lymphoblastic Leukemia – Initial Risk Category n (% [n/230])			
Standard risk	71 (61)	68 (60)	139 (60)
High risk	45 (39)	46 (40)	91 (40)
Acute Lymphoblastic Leukemia – Final Risk Category n (% [n/230])			
Standard risk	63 (54)	61 (54)	124 (54)
High risk	35 (30)	35 (31)	70 (30)
Very high risk	12 (10)	8 (7)	20 (9)
Philadelphia chromosome positive	4 (3)	3 (3)	7 (3)
Not evaluated	2 (2)	7 (6)	9 (4)
Acute Lymphoblastic Leukemia – CNS Disease Category n (% [n/230])			
CNS 1	96 (83)	90 (79)	186 (81)
CNS 2	14 (12)	18 (16)	32 (14)
CNS 3	3 (3)	1 (1)	4 (2)
Traumatic Tap with Blasts	2 (2)	3 (3)	5 (2)
Not evaluated	1 (1)	2 (2)	3 (1)
Karyotype n (% [n=239])			
Normal	8 (7)	16 (13)	24 (10)
Abnormal	111 (92)	100 (84)	211 (88)
Not evaluable	1 (1)	3 (3)	4 (2)
Specific Cytogenetic Abnormalities n (% [n=239])			
Philadelphia Chromosome (BCR-ABL) (removed from study)	4 (3)	3 (3)	7 (3)
MLL rearranged (unfavorable - changed risk category)	0	3 (3)	3 (1)
Hypodiploidy (unfavorable - changed risk category)	1 (1)	1 (1)	2 (1)
Intrachromosomal amplification of chromosome 21 (unfavorable)	10 (8)	2 (2)	12 (5)
t(1;19) (unfavorable)	2 (2)	1 (1)	3 (1)
9p deletion (unfavorable)	14 (12)	17 (14)	31 (13)
Monosomy 7	(1)	1 (1)	2 (1)
12p deletion (average)	4 (3)	9 (8)	13 (5)
TEL/AML1 (average, favorable)	18 (15)	32 (27)	50 (21)
Hyperdiploidy (favorable)	36 (30)	36 (30)	72 (30)

CLINICAL REVIEWER COMMENT:
Overall the favorable and unfavorable demographic and disease characteristics were balanced between arms.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
Asparaginase therapy was administered at study site. Actual exposure to asparaginase agent is reflected in datasets.

Regarding the concomitant multi-agent chemotherapy, the sponsor identified to 2 subjects on the calaspargase arm with potentially significant non-compliance with oral study treatment.

Concomitant Medications
See Appendix 14.6 for the schedule of concomitant therapy in DFCI 11-001.

Efficacy Results – Primary Endpoint
Clinical efficacy endpoints were not the primary endpoints of this study. The primary analysis to support efficacy is a comparison of the pharmacokinetic profile of calaspargase pegol compared to pegasparagase which will be evaluated by the clinical pharmacology reviewer in section 7.

Efficacy Results – Secondary and Other Relevant Endpoints
The study was not powered to demonstrate superiority or non-inferiority and the efficacy endpoints are secondary endpoints. The efficacy analysis is presented using the full analysis set (FAS). Two subjects in the ITT population were excluded from the FAS. A subject randomized to calaspargase who died prior to drug exposure and a subject randomized to pegasparagase who withdrew consent prior to drug exposure. There were 7 patients with Philadelphia chromosome positive (Ph+) ALL removed from the study per protocol, 3 on the calaspargase pegol arm and 4 on the pegasparagase arm.

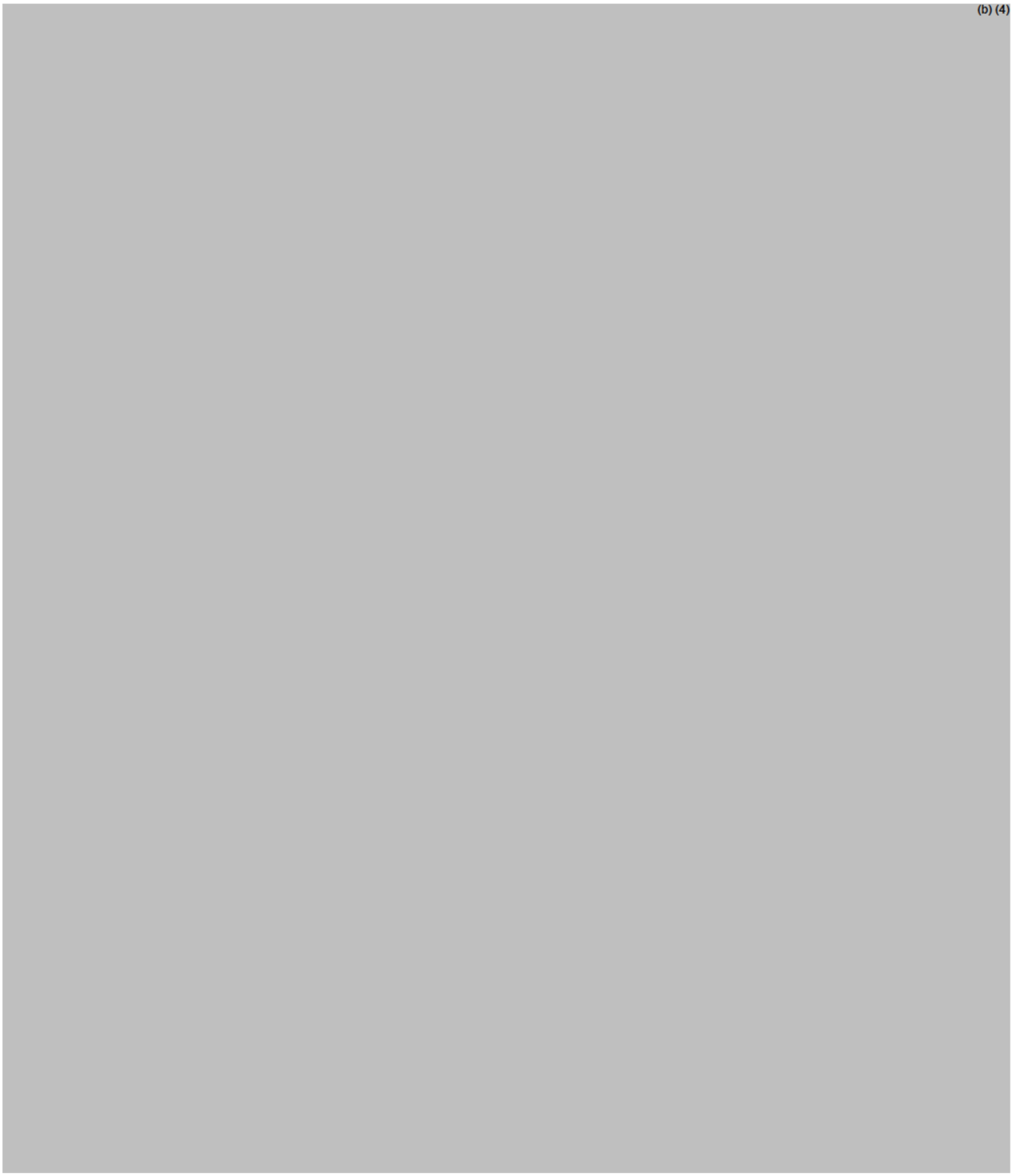
In patients with ALL, end-induction CR rate on Day 32 and end-induction MRD status on Day 32 endpoints reflect a direct comparison of a single dose of asparaginase, either calaspargase pegol 2500 IU/m^2 or pegasparagase 2500 IU/m^2 on day 7 of induction.

The efficacy endpoints are also evaluated in the subset of patients with B-cell lineage ALL entered on this study, this is the largest subpopulation of patients entered on DFCI 11-001 with a relatively uniform clinical course.

<u>Remission Induction Evaluation in ALL</u>
The analysis of end-induction CR rate is restricted to the FAS population of patients with ALL (excludes 9 LL patients) and excludes 7 patients identified by day 15 with Ph+ ALL. Complete remission of leukemia was defined as an interpretable BM (a specimen with normal marrow elements present) with fewer than 1% malignant lymphoblasts by microscopic examination and peripheral blood without lymphoblasts, and an absolute phagocyte count (APC) ≥ 1000/mm^3

and platelets > 100,000/mm^3, and no evidence of extramedullary leukemia, (no blasts in spinal fluid, at least 70% reduction in size of masses noted on imaging at diagnosis).

(b) (4)



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CLINICAL REVIEWER COMMENT:

(b) (4)

8.1.2 AALL07P4

Title

A Pilot Study of Intravenous EZN-2285 (SC-PEG *E. coli* L-asparaginase, IND 100594) or Intravenous Oncaspar in the Treatment of Patients with High-Risk Acute Lymphoblastic Leukemia (ALL): A Limited Institution Pilot Study

INVESTIGATIONAL PLAN

Trial AALL07P4 was an open label randomized trial conducted at 23 COG phase I institutions. Subjects were randomized 2:1 to calaspargase pegol versus pegasparagase. This study was designed as a registration trial to assess and compare the PK of intravenous calaspargase to intravenous pegasparagase during induction and consolidation therapy in patients with high risk B-cell precursor ALL.

The FDA recommended the sponsor conduct a limited scope trial to identify an appropriate dose of calaspargase pegol rather than empirically choosing a dose of 2500 IU/m^2. In lieu of this this limited scope trial; AALL07P4 included a run-in, real-time pharmacokinetics evaluation which was to be submitted to FDA for concurrence of the calaspargase pegol dose when 10 patients had been treated with calaspargase pegol. In May of 2009, after 44 patients had been enrolled, the sponsor submitted the PK data from 11 patients treated with calaspargase pegol and 8 patients treated with pegasparagase. The FDA clinical pharmacology reviewer determined the agents did not meet the formal criteria for bioequivalence, defined as the 90% confidence interval for the geometric mean ratio between 80 to 125% for both C_{max} and AUC. Review of the available safety data suggested there was excessive toxicity in the calaspargase pegol arm. Based on the PK analysis the recommended dose for evaluation was 2100 IU/m^2 using $AUC_{0\text{-}25}$.

(b) (4)

In May 2011, the protocol was revised to randomize patients 2:1 to calaspargase pegol 2500 IU/m^2 or pegasparagase 2500 IU/m^2 and the remaining asparaginase doses in patients previously randomized to calaspargase pegol 2100 IU/m^2 were changed to pegasparagase 2500 IU/m^2.

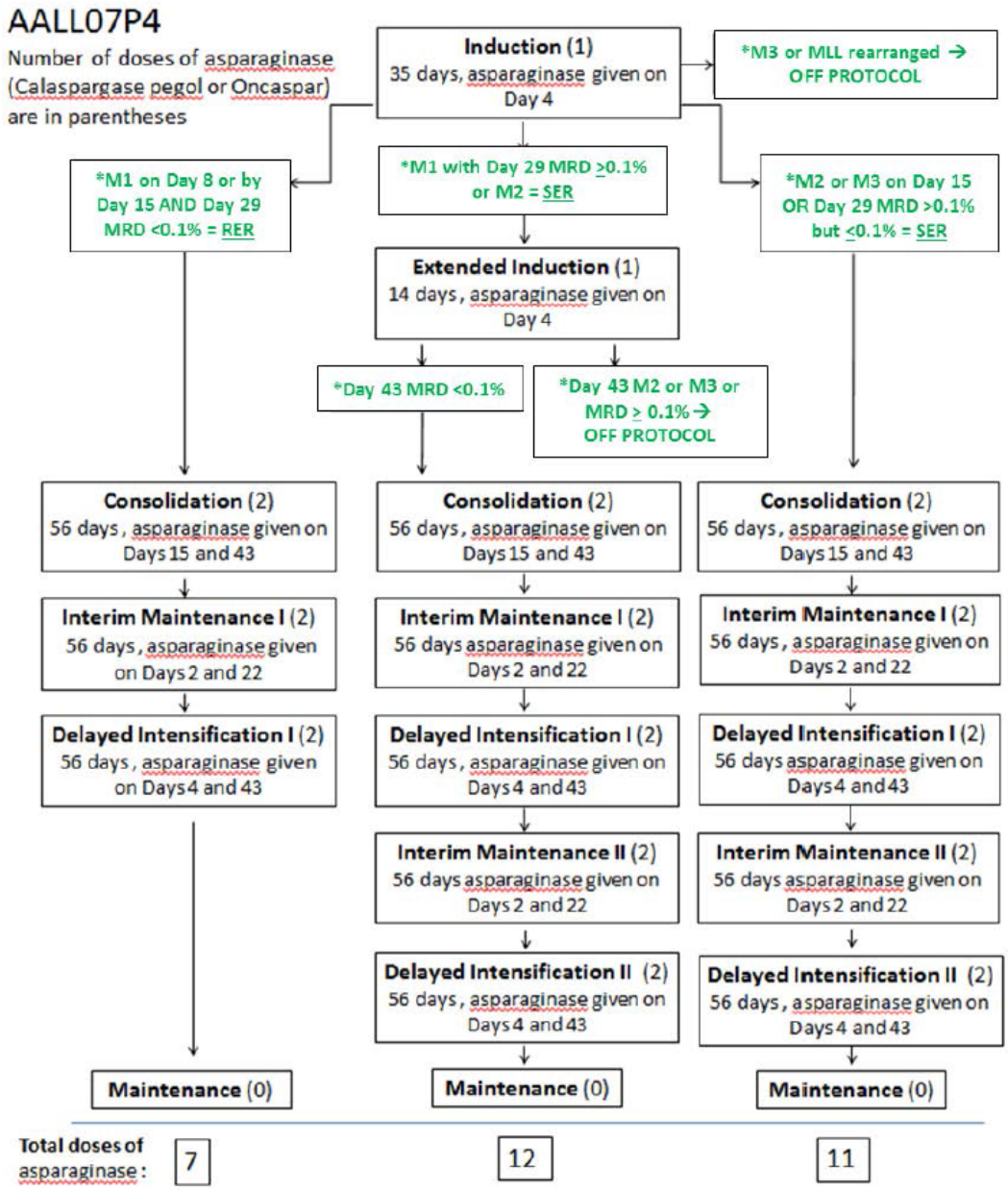
CLINICAL REVIEWER COMMENT:

(b) (4)

(b) (4)

Trial Design

Figure 7: AALL07P4 Schema
(copied from submission; see appendix 14.7 for treatment details of AALL07P4)



Abbreviations: M1 – Bone marrow <5% blasts; M2 – Bone marrow 5 – 25% blasts; M3 – Bone marrow > 25% blasts; MRD – minimal residual disease; RER – rapid early responder; SER – slow early responder

Endpoints
(From Statistical Analysis Plan Dated 12/14/16, Revised from Original)
Safety

- Adverse events, especially for those with special interest
- Laboratory abnormalities
- ECG
- Immunogenicity
- Physical exam: height, weight, BSA and BMI

Pharmacokinetics

- Plasma concentration of asparaginase and PK parameters, including but not limited to AUC, Cmax, Tmax, Kel, T1/2, CL, Vss
- Asparaginase level ≥0.10 IU/mL and ≥0.40 IU/mL during the induction and consolidation phase

Pharmacodynamics

- Depletion of asparagine from the blood and the CSF during the induction and consolidation phase

Efficacy

- Day 29 end-induction minimal residual disease (MRD) status.
- Complete remission (CR)
- Event free survival (EFS)
- Disease free survival (DFS) from achievement of complete remission
- Overall survival (OS)

Study Objectives

Primary Objective

- To determine the pharmacokinetic (PK) comparability of calaspargase pegol compared to pegasparagase given intravenously during Induction and Consolidation in patients with high-risk ALL receiving augmented Berlin Frankfurt Münster (BFM) therapy.

Secondary Objectives

- To describe the pharmacodynamics (PD) of calaspargase pegol compared to pegasparagase given intravenously during Induction and Consolidation in patients with high-risk ALL receiving augmented BFM therapy.
- To determine end of Induction therapy Day 29 minimal residual disease (MRD) for patients randomized to the calaspargase pegol containing regimen compared to the pegasparagase containing regimen.
- To determine the complete remission (CR) rates for patients receiving calaspargase pegol by Day 29 of Induction compared to pegasparagase.
- To assess event-free survival (EFS) associated with the administration of calaspargase pegol given during augmented post-Induction intensification therapy to patients with high-risk ALL compared to pegasparagase.

- To determine the proportion of calaspargase pegol treated patients with an asparaginase level of at least 0.1 IU/mL and the proportion with at least 0.4 IU/mL on Days 4, 15, 22, and 29 of Induction compared to pegasparagase treated patients.
- To determine the serum and CSF concentrations of asparagine after administration of calaspargase pegol compared to pegasparagase.
- To assess the immunogenicity of calaspargase pegol including the detection of binding and neutralizing antibodies compared to pegasparagase.

Protocol Amendments (notable amendments)

Amendment #1 4/2/09
- Revised to blind laboratories to patient assignment

Amendment #2 8/7/09
- Revised dose calaspargase pegol from 2500 IU/m² to 2100 IU/m².

Amendment #3 5/26/10
- Company changed from Enzon to Sigma Tau

Amendment #4A (#4) 5/20/11
Amendment 4 was revised to 4A prior to any formal change in the protocol.
- Incorporate changes to the study therapy as a result of the findings of planned interim analysis of AALL07P4. (b) (4) Recent analyses have shown that these differences have crossed pre-defined safety monitoring boundaries.
- Enrollment to AALL07P4 was closed temporarily to accrual on December 22, 2010.
- Patients randomized to receive intravenous calaspargase pegol at the 2100 IU/m² dose changed therapy to receive intravenous pegasparagase at the 2500 IU/m² dose.
- Patients randomized to receive intravenous calaspargase pegol at the 2500 IU/m² dose continued therapy as assigned.
- Patients currently randomized to receive intravenous pegasparagase at the 2500 IU/m² dose continued therapy as assigned.

Amendment #6 10/5/11
- A total of 123 eligible, evaluable patients to be randomized to the dose of calaspargase pegol 2500 IU/m^2 versus pegasparagase in a 2:1 randomization. To ensure that 90 RER patients are available for evaluations at the end of the trial.
- No PD data to be collected for this new cohort of patients
- PK data collection to be limited to fewer time points
- Analyses to include descriptive comparisons between the 2 arms of the remission rate

and MRD negativity rates at the end of Induction in addition to the exploratory estimation and comparison of EFS between the 2 arms.

- The incidence and level of anti- calaspargase pegol antibodies and anti- calaspargase pegol neutralizing antibodies to be summarized. The relation between the terminal PK of calaspargase pegol and the presence of antibodies will be explored as appropriate.
- Asparaginase immunogenicity will be compared between calaspargase pegol and pegasparagase using appropriate statistical methods.

Amendment #6A 4/23/12

- To evaluate the safety endpoint (no erosion of efficacy [EFS]) the trial reverted to the original trial design, 2:1 randomization to calaspargase pegol 2500 IU/m²/dose or pegasparagase 2500 IU/m²/dose.

Amendment #7A 4/30/13

- Updated diagram to clarify protocol changes with amendment 4A.

STUDY RESULTS

Study Timeline	
Original Protocol Open for Entry:	7/21/08
First Subject Enrolled:	10/14/08
Last Subject Enrolled:	12/17/10
Data Cut-Off Date:	12/31/15 (Final Clinical Study Report)
Planned Enrollment:	Total n = 123; RER n = 90 (calaspargase pegol n = 60 pegasparagase n = 30 available for 3 year EFS comparison); Revised 8/7/09 after dose change n = 186
Actual Enrollment Randomized Subjects:	n = 166

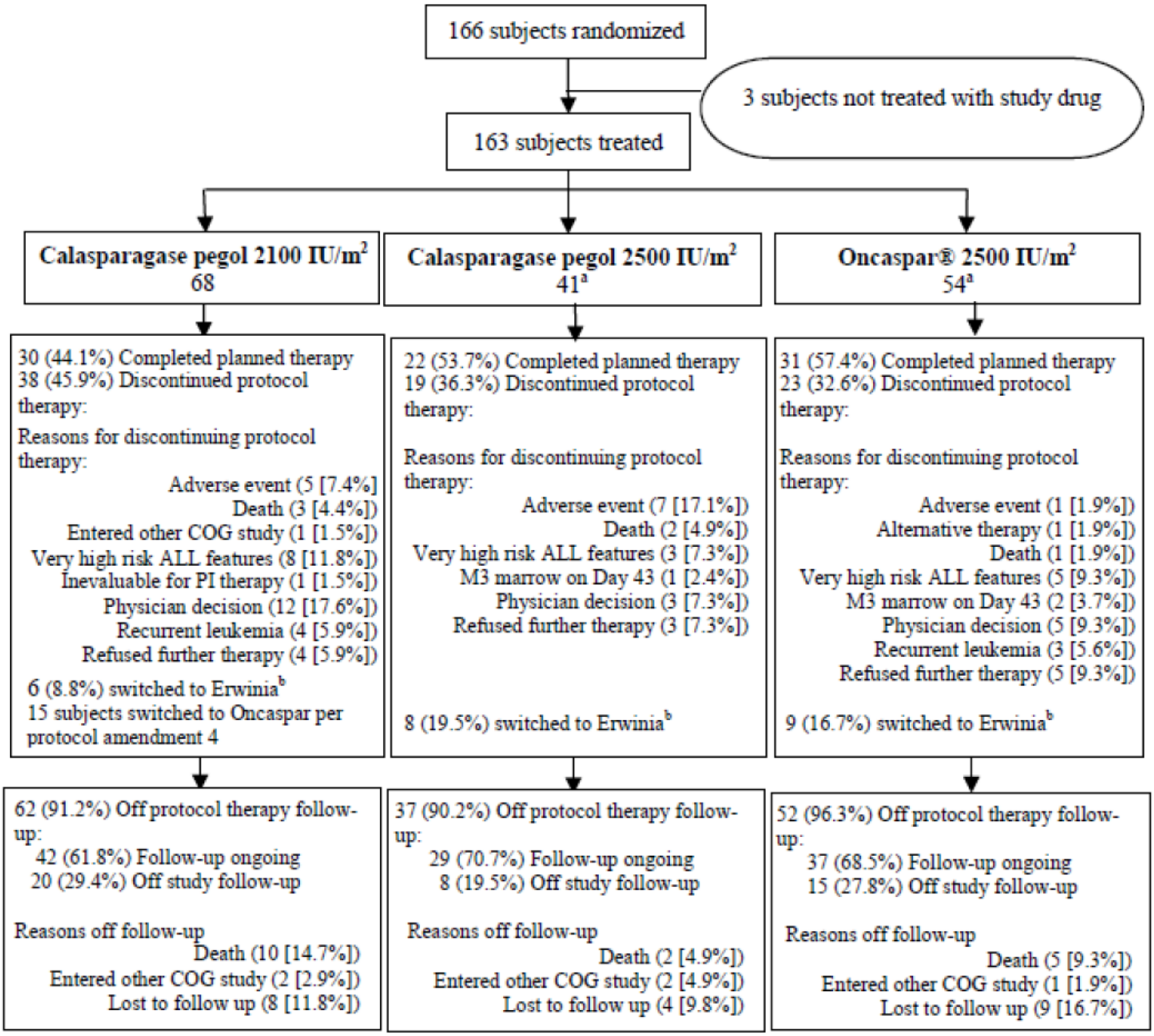
Compliance with Good Clinical Practices
The title page information of the Clinical Study Report for AALL07P4 includes the following statement. “This study was conducted in accordance with the standards of Good Clinical Practice (GCP) in effect at the time of the study. All records have been attached per GCP requirements.”

Financial Disclosure
Financial disclosure information was included in the submission. No investigators with disclosable financial interests were identified. See Appendix 14.2.

Data Quality and Integrity
The quality and integrity of the submitted data were sufficient to review the application.

Patient Disposition
(copied from submission)

Figure 8: AALL07P4 Disposition
(copied from submission)



Protocol Violations/Deviations
There were 2 major protocol violations subjects [redacted] (b) (6) who were randomized to pegasparagase but received calaspargase pegol 2500 IU/m^2.

Demographics and Disease Characteristics

Table 9: AALL07P4 Demographic and Disease Characteristics (ITT Population)

AALL07P4 Demographics and Disease Characteristics ITT				
	Total n = 163	Randomized Pegaspargase 2500 IU/m^2 n = 54	Randomized Calaspargase 2500 IU/m^2 n = 41	Randomized Calaspargase 2100 IU/m^2 n = 68
Gender n (%)				
Male	83 (51)	31 (57)	14 (34)	38 (56)
Female	80 (49)	23 (43)	27 (66)	30 (44)
Age (years)				
Mean	10.6	10.4	9.4	11.4
Median	11	11	11	12.5
Range	1 to 26	1 to 23	1 to 26	1 to 21
1 – 10 n (%)	69 (42)	24 (44)	20 (49)	25 (37)
11 – 17 n (%)	81 (50)	26 (48)	19 (46)	36 (53)
18 – 26 n (%)	13 (8)	4 (7)	2 (5)	7 (10)
Race (Ethnicity) n				
White (Hispanic)	134 (82)	43 (80)	35 (11)	56 (12)
Black/ African American	11 (7)	6 (11)	1	4
Asian	5 (3)	1 (2)	1	3
Pacific Islander	2 (1)	0	1	1
Unknown (Hispanic)	11 (6)	4 (7)	3 (1)	4 (2)
WBC at Diagnosis x 10^3/µL				
Mean	72	66	90	67
Median	34.2	27.2	59	34
Range	0.5 to 610	0.5 to 610	0.8 to 509	0.9 to 308
< 10 x 10^3/µL	55 (34)	18 (33)	10 (24)	27 (40)
≥ 10 < 50 x 10^3/µL	32 (20)	15 (28)	9 (22)	8 (12)
≥ 50 < 100 x 10^3/µL	39 (24)	12 (22)	10 (24)	17 (25)
≥ 100 x 10^3/µL	37 (23)	9 (17)	12 (29)	16 (24)
CNS Status n (%)				
CNS 1 - No blasts in CSF	129 (79)	46 (85)	35 (85)	48 (71)
CNS 2 - < 5 WBC/µL + blasts	28 (17)	8 (15)	5 (12)	16 (24)
CNS 3 - ≥ 5 WBC/µL + blasts	5 (3)	0	1 (3)	4 (6)
Exposure to Steroids n (%)				
Yes	9 (6)	1 (2)	3 (7)	5 (7)
ALL Risk Classification n (%)				
High Risk	142 (87)	47 (87)	37 (90)	58 (85)
Very High Risk	21 (13)	7 (13)	4 (10)	10 (15)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
Study drug was administered at the research sites by qualified study personnel.

Efficacy Results – Primary Endpoint (analyzed during review of BLA (b) (4)

(b) (4)

(b) (4)

Efficacy Results – Secondary and Other Relevant Endpoints (analyzed during review of BLA (b) (4))

Secondary clinical endpoints evaluating efficacy in this study included:

- Day 29 end-induction minimal residual disease (MRD) status.
- Complete remission (CR)
- Event free survival (EFS)
- Disease free survival (DFS) from achievement of complete remission
- Overall survival (OS)

This study was not adequately powered to evaluate these clinical efficacy endpoints. (b) (4)

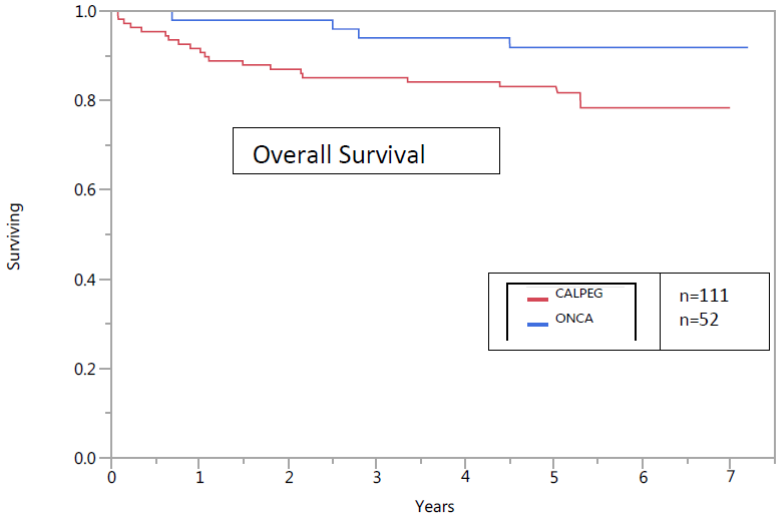
CLINICAL REVIEWER COMMENT:

(b) (4)

Survival

This submission includes the final survival data from the AALL07P4 study. The final study OS analysis follows.

Figure 9: AALL07P4 Kaplan Meier Analysis of Overall Survival as Treated



The planned COG analysis was evaluation of EFS in the subset of RER patients, the largest subset of patients in a relatively homogenous risk category. The Kaplan Meier analysis that follows is EFS and OS as treated during induction calaspargase pegol compared to pegasparagase.

Figure 10: AALL07P4 RER Population Kaplan Meier Analysis of Event Free Survival as Treated

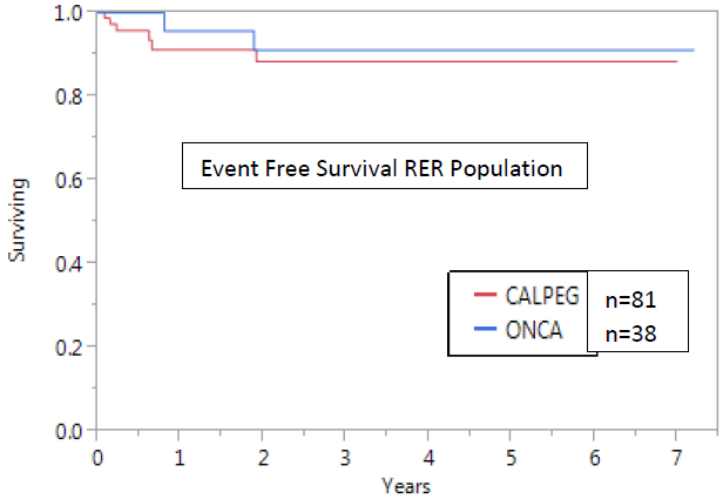
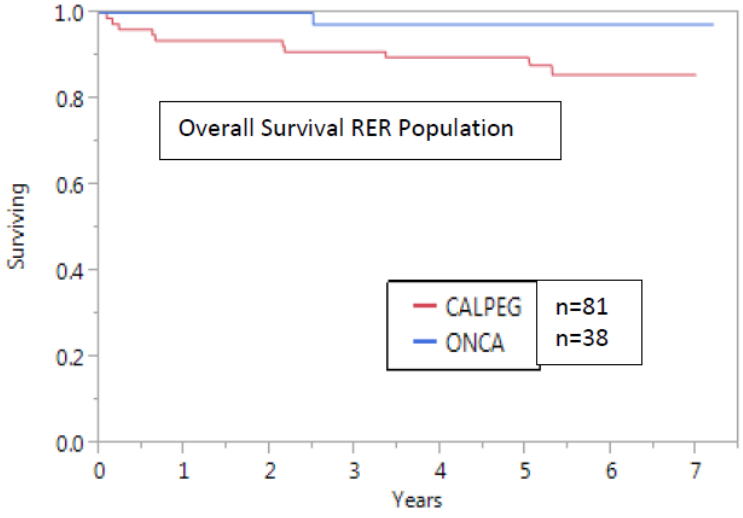


Figure 11: AALL07P4 RER Population Kaplan Meier Analysis of Overall Survival as Treated



CLINICAL REVIEWER COMMENT:
The Kaplan Meier analysis of EFS in the RER population as treated during induction is similar in both treatment groups, although the analysis of OS in the RER population and the entire patient population suggests the outcome in patients treated with calaspargase during induction may be inferior.

8.2 Integrated Review of Effectiveness

The indication proposed by the Applicant for calaspargase pegol-mknl was "as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL." The results of Study DFCI 11-001 were submitted to support the indication. The primary objective of Study DFCI 11-001 was to determine the pharmacokinetic (PK) comparability of calaspargase pegol-mknl compared to pegasparagase given intravenously during Induction and Consolidation in patients with high-risk ALL receiving augmented Berlin Frankfurt Münster (BFM) therapy.

The use of the pharmacodynamic endpoint nadir serum asparaginase activity (NSAA) has been used as the basis of approvals of asparaginase products as discussed in Section 2.2. However, as reported in Section 4.1, FDA did not find the clinical pharmacology results of Study DFCI 11-001 to be credible.

(b) (4)

The clinical pharmacology data from Study AALL07P4 were considered credible. See Section 6.3.2 for the discussion of the clinical pharmacology assessment used to establish the efficacy of calaspargase pegol-mknl.

8.3 Review of Safety

8.3.1. Safety Review Approach

The safety of calaspargase pegol compared to pegasparagase will primarily be evaluated separately in the 2 studies. However, results of induction therapy will be compared side by side as the background therapy of induction is essentially the same in the 2 studies. In contrast, the treatment schedules and exposure to concomitant therapy in post induction phases of therapy are markedly different in the 2 studies; therefore, it is not informative to simultaneously compare the adverse event profiles of the 2 agents during the post induction phases of therapy.

Neither the DFCI 11-001 study nor the AALL07P4 study were powered to evaluate superiority or non-inferiority, and potential erosion of efficacy is a safety issue. The secondary clinical endpoints associate with efficacy are reviewed in sections 8.1.1 and 8.1.2. There was no evidence of erosion in the DFCI 11-001 study of remission induction evaluations or survival evaluations. In the AALL07P4 trial the Kaplan Meier analysis of EFS in the RER population as treated during induction is similar in both treatment groups, although the analysis of OS in the

RER population and the entire patient population suggests the outcome in patients treated with calaspargase during induction may have been inferior.

There was insufficient information to allow completion of Section 8.3.6 - 8.3.9, so these sections are omitted.

8.3.2. Review of the Safety Database

Overall Exposure

There were 229 patients with ALL and LL exposed to calaspargase pegol and 171 exposed to pegasparagase.

Table 10: Safety Database – Exposure

Exposure					
Trial Id. NCT No.	**Regimen**	**Pegaspargase** 2500 IU/m^2	**Calaspargase** (any dose)	**Calaspargase** 2500 IU/m^2	**Calaspargase** 2100 IU/m^2
DFCI 11-011	Induction - Day 7 CNS/Consolidation Calaspargase 10 doses (q3wk) Pegaspargase 15 doses (q2wk)	n=119 no. doses range 1 - 17 median 16	n=118 no. doses range 1 – 11 median 11	n=118 no. doses range 1 – 11 median 11	
AALL07P4	Induction - Day 4 Extended Induction - Day 4 Consolidation - Days 15,43 Interim Maintenance 1 - Days 2, 22 Delayed Intensification 1 - Days 4, 42 Interim Maintenance 2 - Days 2, 22 Delayed Intensification 2 - Day 4, 43	n=52 no. doses range 1-12 median 4.5	n=111 no. doses range 1-11 median 3	n=43 no. doses range 1-11 median 4	n=68 no. doses range 1-11 median 2

Relevant characteristics of the safety population

See Table 4: DFCI 11-001 Demographics - ITT Population and Table 5: DFCI 11-001 Disease Characteristics - ITT Population.

In the DFCI 11-001 Study the ITT and safety population are essentially the same with the exception that 2 patients randomized to pagaspargase did not receive study drug.

Table 11: AALL07P4 Demographics and Disease Characteristics Safety Population

AALL07P4 Demographics and Disease Characteristics Safety Population			
	Total n = 163	Pegaspargase n = 52	Calaspargase n = 111
Gender n (%)			
Male	83 (51)	30 (58)	53 (48)
Female	80 (49)	22 (42)	58 (52)
Age (years)			
Mean	10.6	10.3	10.7
Median	11	11	12
Range	1 to 26	1 to 23	1 to 26
1 – 10 n (%)	69 (42)	24 (46)	45 (41)
11 – 17 n (%)	81 (50)	24(46)	57 (51)
18 – 26 n (%)	13 (8)	4 (8)	9 (8)
Race (Ethnicity) n			
White (Hispanic)	134 (82)	41 (79)	93 (84)
Black/ African American	11 (7)	6 (11)	5 (5)
Asian	5 (3)	1 (2)	4 (4)
Pacific Islander	2 (1)	0	1 (1)
Unknown (Hispanic)	11 (6)	4 (8)	7 (6)
WBC at Diagnosis x 10^3/µL			
Mean	72	68	80
Median	34.2	28.6	55.5
Range	0.5 to 610	0.5 to 610	0.8 to 509
< 10 x 10^3/µL	55 (34)	17 (33)	38 (34)
≥ 10 < 50 x 10^3/µL	32 (20)	14 (27)	18 (16)
≥ 50 < 100 x 10^3/µL	39 (24)	12 (23)	27 (25)
≥ 100 x 10^3/µL	37 (23)	9 (17)	28 (25)
CNS Status n (%)			
CNS 1 - No blasts in CSF	129 (79)	44 (85)	85 (76)
CNS 2 - < 5 WBC/µL + blasts	29 (18)	8 (15)	21 (19)
CNS 3 - ≥ 5 WBC/µL + blasts	5 (3)	0	5 (5)
Exposure to Steroids n (%)			
Yes	9 (6)	1 (2)	8 (7)
ALL Risk Classification n (%)			
High Risk	142 (87)	45 (87)	97 (87)
Very High Risk	21 (13)	7 (13)	14 (13)

Adequacy of the Safety Database

The safety database is adequate to compare the safety profiles of the 2 asparaginase products.

8.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality
The quality of the safety data submitted was adequate to allow substantial primary review. The submission includes appropriate hyperlinks. The datasets are in standard Analysis Data Model (ADaM) format. Case report forms are submitted for all subjects.

Categorization of Adverse Events

DFCI 11-001 (derived from submission)
Adverse Event (AE)
AEs were defined as any undesirable sign, symptom or medical condition, or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study drug.

Serious Adverse Event (SAE)
A serious adverse event (SAE) is any adverse event, regardless of causality that:

- Results in death
- Is life-threatening
- Requires intensive inpatient medical interventions
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

By the original protocol definition, the following expected toxicities related to the diagnosis and treatment of ALL and considered to be unrelated to asparaginase were not to be recorded as AEs, unless they met definition of an SAE.

- Blood count abnormalities (any grade)
- Electrolyte abnormalities (any grade)
- Uric Acid (any grade)
- Transaminitis without clinical symptoms
- Mucositis (grade 2 or below)
- Nausea (any grade)
- Vomiting (any grade)
- Fatigue (any grade)
- Anorexia (any grade)

- Fever (any grade)
- Constipation (any grade)
- Diarrhea (any grade)
- Hypertension thought to be related to steroids (grade 1)
- Hyperglycemia related to steroids that does not require the use of insulin
- Neuropathy – sensory, motor, or cranial (grade 3 or below and thought to be related to Vincristine)
- Vascular access complication (grade 2)
- Allergic reactions that are not related to asparaginase (grade 2 or below) (Note: all asparaginase-related allergic reaction were to be reported, regardless of grade.)
- Any grade 1 or grade 2 expected toxicities that are not related to asparaginase

After February 2016 the following additional AEs related to asparaginase were to be collected retrospectively on all participants through 30 days after their final dose of asparaginase.

- All grades:
    - Allergic reaction (only asparaginase related)
    - Injection site reaction (only related to Erwinia asparaginase)
    - Seizure
    - Intracranial hemorrhage
    - Thromboembolic Event
    - Pancreatitis –grade 2 and above, collect all forms (such as Pancreatitis enzymatic, Pancreatitis Necrosis, Pancreatitis Hemorrhagic, Pancreatic fistula, Pancreatic Duct Stenosis)
- Grade 2 and above:
    - Alanine Aminotransferase (ALT) Increased
    - Alkaline Phosphatase Increased
    - Aspartate Aminotransferase (AST)Increased
    - Blood Bilirubin Increased
    - Hypoalbuminemia (low blood albumin levels)
    - Creatinine Increased
    - Abnormal Glucose Levels (hyperglycemia & hypoglycemia)
    - Hypertriglyceridemia
    - Abnormal Potassium Levels (hyperkalemia & hypokalemia)
    - Abnormal Sodium Levels (hypernatremia & hyponatremia)
    - Serum Amylase Increased
    - Lipase Increased
    - Activated Partial Thromboplastin Time (PTT) Prolonged
    - International normalized ratio (INR) Increased
    - Fibrinogen Decreased
- Grade 3-4:
    - Anaphylaxis
    - Erythema multiforme
    - Nervous system disorders – other, specify

- Peripheral sensory neuropathy – Grade 4 only
- Peripheral motor neuropathy – Grade 4 only
- Dizziness
- Encephalopathy (all forms)
- Syncope
- Leukoencephalopathy
- Depression
- Confusion
- Hallucinations
- Hematuria
- Hematoma
- Abdominal pain
- Mucositis/stomatitis (all forms)
- Epistaxis
- Hepatic failure
- Ventricular Arrhythmias
- Myocarditis
- Heart failure
- Sepsis
- Pneumonia – Grade 4 only
- Febrile neutropenia

AEs were to be assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0. AEs were categorized using Medical Dictionary for Regulatory Activities (MedDRA) version 19.

AALL07P4 (derived from submission)

The following toxicities and other adverse events were reported

- All (Grade 1 to 5) asparaginase [pegasparagase or calaspargase pegol] specific adverse events.
- All Grade 3 and 4 non-hematologic toxicities
- All Grade 3 and 4 hematologic toxicities that result in hospitalization or a delay in therapy of > 1week
- All CNS toxicities, Grade 2 and greater
- All osteonecrosis
- All grades peripheral neuropathies
- All Grade 3 and higher infection toxicities

No other Grade 1 or 2 toxicities were reported.

Routine Clinical Tests

DFCI 11-001

Routine laboratory results obtained as a component of clinical care were evaluated locally but not centrally collected. Abnormal laboratory values or diagnostic test results that induced clinical signs or symptoms or required treatment or further diagnostic tests were reported as AEs.

These included:

- Alanine aminotransferase increased
- Aspartate aminotransferase increased
- Blood bilirubin increased
- Bilirubin conjugated increased
- Lipase increased
- Amylase increased
- Blood fibrinogen decreased
- Activated partial thromboplastin time prolonged
- Blood alkaline phosphatase increased
- International normalised ratio increased
- Blood culture positive
- Blood creatinine increased

AALL07P4

Clinical laboratory was collected at the following timepoints:

- Baseline
- Induction Day 4
- Induction Day 15
- Consolidation Day 15
- Consolidation Day 29

These included:

- Chemistry
    - Alanine Aminotransferase
    - Amylase
    - Aspartate Aminotransferase
    - Blood Urea Nitrogen
    - Cholesterol
    - Creatinine
    - Serum Glutamic Pyruvic Transaminase
    - Total Bilirubin
    - Triacylglycerol Lipase
    - Triglycerides

- Hematology
    - Activated Partial Thromboplastin Time
    - Anti-thrombin III
    - D-dimers
    - Fibrin degradation products
    - Fibrinogen
    - Lymphocytes
    - Neutrophils Band Form
    - Neutrophils Segmented
    - Protein C activity
    - Protein S activity
    - Protein S Antigen, free
    - Prothrombin Intl. Normalized Ratio
    - Prothrombin Time
    - Red Blood Cells

The following abnormal laboratory values were collected as adverse events in the Investigations System Organ Catyegory (SOC).

- Neutrophil count decreased
- Blood bilirubin increased
- Alanine aminotransferase increased
- Platelet count decreased
- White blood cell count decreased
- Aspartate aminotransferase increased
- Activated partial thromboplastin time prolonged
- International normalised ratio increased
- Lipase increased
- Gamma-glutamyltransferase increased
- Weight decreased
- Blood fibrinogen decreased
- Blood cholesterol increased
- Amylase increased
- Lymphocyte count decreased
- Blood creatinine increased
- Blood alkaline phosphatase increased

8.3.4. Safety Results

Deaths - Induction Combined DFCI 11-001 and AALL07P4

Review of induction toxicity will be consolidated because induction therapy was similar on the 2

studies. Induction therapy included daily steroid, weekly vincristine, anthracycline (DFCI 11- 001 –doxorubicin day 4&5; AALL07P4 daunorubicin day 1, 8,15, 22), asparaginase (DFCI 11- 001 – day 7; AALL07P4 day 4) IT chemotherapy. The DFCI 11-001 induction also included methotrexate 40 mg/m^2.

There were 5 deaths that occurred in the safety population after induction therapy; all patients received calaspargase pegol. Infection was the major contributing factor to death in all 5 cases.

Table 12: DFCI 11-001 & AALL07P4 Clinical History of Induction Deaths

Trial Patient ID	Induction Deaths
AALL07P4 (b) (6)	This was a 17 year old Hispanic white male with high risk B-lineage ALL who presented with a WBC of 9 x 10^3/µL. The patient was randomized to and received calaspargase 2100 IU/m^2 on day 4 of induction. On day 16 he developed pancreatitis. On day 21 he was diagnosed with *Pseudomonas* sepsis and transferred to ICU. On day 29, day 25 from calaspargase exposure, he experienced an intracranial hemorrhage and died.
AALL07P4 (b) (6)	This was a 26 year old white female with high risk B-lineage ALL who presented with a WBC of 2x10^3/µL. At diagnosis the patient was pregnant and was delivered by C-section 4 days prior to starting protocol. She was randomized to and received calaspargase 2500 IU/m^2 day 4 of induction. On day 29, 25 days from calaspargase, she developed sepsis with necrotizing fasciitis of the chest wall (*clostridium perfringens).* She of died septic shock on day 31, 27 days from calaspargase exposure.
AALL07P4 (b) (6)	This was a 12 year old white female with high risk B-lineage ALL who presented with a WBC of 2 x 10^3/µL. The patient developed tumor lysis requiring dialysis. She was randomized to and received calaspargase 2100 IU/m^2 day 4 of induction. On day 10 she developed hyperglycemia requiring insulin; day 19 she developed hypotension requiring resuscitation and pressors; day 22 there was a positive *Staphylococcus aureus* culture and she was diagnosed with ARDS. She died day 54, 48 days from calaspargase exposure.
AALL07P4 (b) (6)	This was a 12 year old white female who presented with a WBC of 25 x 10^3/µL. The patient was randomized to pegaspargase but received calaspargase 2500 IU/m^2 on day 4 of induction. She was hospitalized in ICU Day 18 with sepsis. She completed induction therapy and achieved a remission. However she progressively deteriorated in the ICU with hyperglycemia requiring insulin, renal failure, pancreatitis, hypertriglyceridemia, hyperbilirubinemia, erythema multiforme. She died of fungal sepsis day 78 82 days from calaspargase exposure.
DFCI 11-001 (b) (6)	This was a 4 year old black female with standard risk B-lineage ALL who presented with a WBC of 1 x 10^3/µL. The patient was randomized to and received calaspargase 2500 IU/m^2 on day 8 of the study. The patient was diagnosed with a Beta-hemolytic streptococci infection at the time of presentation and her hospital course was complicated by renal insufficiency due to sepsis. She developed multisystem organ failure secondary to disseminated a fungal infection (Scedosporium) and died day 37, 28 days from calaspargase exposure.

One additional patient on DFCI 11-001 ID (b) (6) died during induction. This was a 15 yo Hispanic male who was randomized to calaspargase pegol but died prior to receiving the investigational agent. The patient received steroids, IT cytosine arabinoside and a single dose of vincristine. The patient had a catheter-related fungal infection and died on day 15.

Table 13: DFCI 11-001 & AALL07P4 Summary of Induction Deaths

Deaths during Asparaginase Therapy		Deaths n (%)	Major Cause of Death
DFCI Induction Pegaspargase	**n=119**	0	
DFCI Induction Calaspargase	**n=118**	1 (0.8)	• Sepsis; Fungal infection
AALL Induction Pegaspargase	**n=52**	0	
AALL Induction Calaspargase	**n=111**	4 (3.6)	• Pancreatitis; *Pseudomonas* sepsis • Necrotizing fasciitis (*clostridium perfringens*); Septic shock • Shock; ARDS; *Staphylococcus aureus* pneumonia • Sepsis; Pancreatitis

Deaths - DFCI 11-001 Post-Induction

The deaths that occurred on study after induction and up to day 292, 30 days after the last protocol scheduled asparginase, are presented in Table 14

Table 14: DFCI 11-001 Post-Induction Deaths

Patient ID DFCI	Treatment	Study Day of Deaths	Deaths after Induction
(b) (6)	Calaspargase pegol	81	19 month boy with standard risk ALL who died in remission after accidental administration of intrathecal vincristine.
	Calaspargase pegol	155	3 year old boy with standard risk ALL who died in remission due to pancreatitis. The patient received a total of 4 doses of calaspargase, the last was administered on study day 104.

CLINICAL REVIEWER COMMENT:
There was one death was due to an asparaginase related event of pancreatitis on the calaspargase pegol arm.

Deaths - AALL07P4 Post-Induction

The deaths that occurred on study after induction and up to day 359, 30 days after the last protocol scheduled asparginase, are presented in Table 15.

Table 15: AALL07P4 Post-Induction Deaths

Patient ID COG	Treatment	Study Day of Deaths	Deaths after Induction
(b) (6)	Calaspargase pegol (immediately prior to death 2 doses of pegaspargase)	224	13 yo girl with high risk ALL was randomized to calaspargase. She received calaspargase during induction and 6 additional doses. Per protocol amendment, the asparginase was changed to pegaspargase. She received 2 doses of pegaspargase on days 179 and 217. She died at home suddenly, possibly due to a CNS bleed on day 224.
	Calaspargase pegol	237	15 year old girl with high risk ALL, she received the day 4 calaspargase dose. On day 45 she developed grade 3 pancreatitis. After induction she subsequently received 6 doses of calaspargase the last dose on day 224. She subsequently developed sepsis and acute renal failure and progressed to multi-organ failure and died day 237.

Grade 3 and 4 Adverse Events - Induction Combined DFCI 11-001 and AALL07P4

Table 16: DFCI 11-001 & AALL07P4 Induction Grade 3&4 TEAEs

Induction TEAE Grade 3&4 AEs				
SOC PT n(%)	DFCI 11-001		AALL07P4	
	Pegaspargase n=119	Calaspargase n=118	Pegaspargase n=52	Calaspargase n=111
Investigations	59 (50)	41 (35)	15 (29)	47 (42)
Increased AST /ALT /GGT	33 (28)	25 (21)	9 (17)	17 (15)
(Abnormal Coagulation) inc aPTT /inc INR /dec Fibrinogen	18 (15)	10 (8)	0	11 (10)
Increased Amylase /Lipase	11 (9)	5 (4)	2 (4)	10 (9)
Increased Bilirubin	13 (11)	8 (7)	3 (6)	13 (12)
Metabolism and nutrition disorders	41 (34)	39 (33)	11 (21)	41 (37)
Hyperglycemia	14 (12)	14 (12)	4 (8)	26 (23)
Hypoalbuminemia	12 (10)	6 (5)	0	10 (9)
Immune system disorders	1 (1)	0	4 (8)	3 (3)
Anaphylactic reaction (definitely related to asparaginase)	0	0	3 (6)	1 (1)
Infections and infestations	18 (15)	15 (13)	10 (19)	27 (24)
Sepsis /Bacteremia	5 (4)	5 (4)	4 (8)	15 (14)
Gastrointestinal disorders	22 (18)	18 (15)	5 (10)	19 (17)
Pancreatitis/ Pancreatic necrosis	2 (2)	2 (2)	1 (2)	7 (6)
Vascular disorders	9 (8)	5 (4)	2 (4)	9 (8)
Hypotension	4 (3)	1 (1)	0	4 (4)
Embolism /Venous thrombosis	1 (1)	0	0	4 (4)

The table above presents a comparison of the induction grade 3&4 asparaginase-associated treatment emergent adverse events (TEAE)s reported on the AALL07P4 and DFCI 11-001 trials. The adverse events with an incidence ≥ 3% in any arm are highlighted.

CLINICAL REVIEWER COMMENT:

(b) (4)

Treatment Emergent Adverse Events - DFCI 11-001 Post-Induction

The following table presents an analysis of TEAEs during CNS, consolidation 2, and modified consolidation 2 phases of therapy. There were 105 patients exposed to calaspargase pegol and 112 patients exposed pegasparagase during these phases of therapy. The table includes SOCs with at least 10 subjects and preferred terms (PT)s in SOCs where the difference in the incidence is ≥ 3% between arms or PTs that were identified as safety concerns in the previous review of AALL07P4. For the SOC "Infections and infestations" rather than multiple PT categories the results are presented in high level group term (HLGT) categories. The adverse events with an incidence ≥ 3% in any arm are highlighted.

Table 17: DFCI 11-001 Post-Induction TEAEs

DFCI TEAE CNS / Consolidation 2 / Modified Consolidation 2				
SOC *HLGT* PT n (%)	Pegaspargase n=112		Calaspargase n=105	
	Any Grade	Grade 3 & 4	Any Grade	Grade 3 & 4
Investigations	87 (78)	70 (63)	77 (73)	56 (53)
AST / ALT inc	78 (70)	57 (51)	71 (68)	41 (39)
Bilirubin inc	49 (44)	18 (16)	41 (39)	15 (14)
Amylase / lipase inc	24 (21)	20 (18)	22 (21)	17 (16)
Alkaline phosphatase inc	5 (4)	1 (1)	7 (7)	2 (2)
Metabolism and nutrition disorders (exclude electrolytes)	87 (78)	59 (53)	78 (74)	54 (51)
Hypoalbuminemia	66 (59)	22 (20)	66 (63)	25 (22)
Hypoglycemia	38 (34)	14 (13)	32 (30)	6 (6)
Hypertriglyceridemia	34 (30)	34 (30)	19 (18)	19 (18)
Hyperglycemia	16 (14)	10 (9)	16 (15)	11 (10)
Blood and lymphatic system disorders	31 (28)	31 (28)	25 (22)	25 (22)
Febrile neutropenia	31 (28)	31 (28)	25 (22)	25 (22)
Gastrointestinal disorders	21 (19)	18 (16)	20 (19)	19 (18)
Pancreatitis	17 (15)	11 (10)	12 (11)	14 (13)
Infections and infestations	17 (15)	14 (13)	18 (17)	17 (16)
Bacterial infectious disorders	10 (9)	9 (8)	5 (5)	5 (5)
Viral infectious disorders	3 (3)	2 (2)	3 (3)	1 (1)
Fungal infectious disorders	0	0	1 (1)	1 (1)
Infections - pathogen unspecified	8 (7)	7 (6)	14 (13)	14 (13)
Sepsis	1 (1)	1 (1)	2 (2)	2 (2)
Vascular disorders	11 (10)	5 (4)	15 (14)	9 (9)
Embolism / Thrombosis	9 (8)	6 (5)	12 (11)	3 (3)
Hypotension	4 (4)	3 (3)	2 (2)	2 (2)
Immune system disorders	14 (13)	7 (6)	15 (14)	8 (8)
Anaphylaxis / hypersensitivity (related to asparaginase)	14 (13)	7 (6)	15 (14)	8 (8)
Respiratory, thoracic and mediastinal disorders	9 (8)	8 (7)	5 (5)	4 (4)
Hypoxia	0	0	2 (2)	2 (2)
Pulmonary embolism	2 (2)	2 (2)	0	0
Nervous system disorders	3 (3)	2 (2)	7 (7)	6 (6)
Seizure	1 (1)	1 (1)	2 (2)	2 (2)
Thromboembolic event / stroke	0	0	2 (2)	2 (2)

Treatment Emergent Adverse Events - AALL07P4 Post-Induction

The following table presents an analysis of TEAEs during the post induction phases of therapy that included asparaginase treatment were consolidation, interim maintenance 1 &2, and delayed intensification 1 & 2. The adverse events with an incidence ≥ 3% in any arm are highlighted.

Table 18: AALL07P4 Post-Induction TEAEs

AALL07P4 TEAE Consolidation / Interim Maintenance I&II / Delayed Intensification I&II				
SOC HLGT PT	Pegaspargase n=40		Calaspargase n=80	
	Any Grade	Grade 3 & 4	Any Grade	Grade 3 & 4
Investigations (exclude hematologic)	25 (63)	20 (50)	59 (74)	41 (51)
AST / ALT / γGT inc	18 (45)	18 (45)	25 (31)	24 (30)
Bilirubin inc	19 (48)	3 (8)	48 (60)	13 (16)
Amylase / lipase inc	3 (8)	3 (8)	13 (16)	13 (16)
Alkaline phosphatase inc	0	0	2 (3)	2 (3)
Metabolism and nutrition disorders (exclude electrolytes)	25 (63)	18 (45)	65 (81)	48 (60)
Hyperglycemia	22 (55)	7 (18)	53 (66)	15 (19)
Hypertriglyceridemia	5 (13)	4 (10)	18 (23)	9 (11)
Hypoalbuminemia	3 (8)	2 (5)	15 (19)	13 (16)
Blood and lymphatic system disorders (exclude cytopenias / anemia)	21 (53)	21 (53)	53 (66)	52 (65)
Febrile neutropenia	19 (48)	19 (48)	48 (60)	48 (60)
Gastrointestinal disorders	11 (28)	11 (28)	39 (49)	37 (45)
Abdominal pain	5 (13)	5 (13)	18 (23)	14 (18)
Pancreatitis	3 (8)	2 (5)	12 (15)	9 (11)
Nausea / vomiting	5 (13)	5 (13)	13 (16)	12 (15)
Diarrhea	1 (3)	1 (3)	10 (13)	10 (13)
Infections and infestations	10 (25)	9 (23)	37 (46)	37 (46)
Bacterial infectious disorders	4 (10)	4 (10)	24 (30)	24 (30)
Viral infectious disorders	4 (10)	4 (10)	10 (13)	10 (13)
Fungal infectious disorders	1 (3)	1 (3)	6 (8)	6 (8)
Infections - pathogen unspecified	6 (15)	5 (13)	16 (20)	16 (20)
Sepsis / bacteremia	2 (5)	2 (5)	22 (28)	22 (28)
Vascular disorders	5 (13)	2 (5)	19 (24)	18 (23)
Embolism / Thrombosis	1 (3)	1 (3)	3 (4)	2 (3)
Hypotension	2 (5)	0	14 (18)	13 (16)
Immune system disorders	10 (25)	6 (15)	25 (31)	20 (25)
Anaphylaxis / hypersensitivity (related to asparaginase)	9 (23)	6 (15)	22 (28)	19 (24)
Respiratory, thoracic and mediastinal disorders	6 (15)	3 (8)	22 (28)	19 (24)
Hypoxia	4 (10)	3 (8)	8 (10)	8 (10)
ARDS / respiratory failure	0	0	4 (5)	4 (5)
Nervous system disorders (exclude headache / neuropathy)	15 (38)	10 (25)	37 (46)	26 (33)
Seizure	2 (5)	0	6 (8)	2 (3)
CVA / Cerebral ischemia	0	0	2 (3)	1 (1)

CLINICAL REVIEWER COMMENT:
The comparison of the asparaginase associated AEs of safety concern that were identified at a higher incidence in the calaspargase pegol arm of AALL07P4 trial were pancreatitis, allergic reactions, and hyperglycemia. In addition, the incidence of infections appeared to be greater in the calaspargase pegol arm. An increased incidence of these safety signals was not

identified in the DFCI 11-001 trial. See section 8.3.5 for further analysis of asparaginase-associated adverse reactions, including immunogenicity and allergic reactions, pancreatitis, hepatotoxicity, thrombosis and coagulopathy, and hyperglycemia. The incidence of infections will also be evaluated.

Dropouts and/or Discontinuations Due to Adverse Effects - DFCI 11-001

Table 19: DFCI 11-001 Discontinuation of Study Agent for Adverse Events

DFCI 11-001 Discontinued Study Drug Due to Adverse Event - Safety Population			
n (%)	Total n = 239	Pegaspargase n = 120	Calaspargase n = 119
Total	68 (28)	29 (24)	39 (33)
Allergic reactions, infusion reactions	33 (14)	15 (13)	18 (15)
Silent inactivation	2 (1)		2 (2)
Pancreatitis	29 (12)	13 (11)	16 (13)
Thrombus / bleeding	2 (1)		2 (2)
Other liver toxicity; Portal hypertension	2 (1)	1 (1)	1 (1)

Dropouts and/or Discontinuations Due to Adverse Effects – AALL07P4

Table 20: AALL07P4 Discontinuation of Study Agent for Adverse Events

AALL07P4 Discontinued Study Drug Due to Adverse Event - Safety Population			
n (%)	Total n = 163	Pegaspargase n = 52	Calaspargase n = 111
Total	44 (27)	13 (25)	31 (28)
Allergic reactions including urticaria	31 (19)	9 (17)	22 (20)
Pancreatitis	8 (5)	3 (6)	5 (5)
Thrombus / bleeding	2 (1)		2 (2)

CLINICAL REVIEWER COMMENT:
The incidence of discontinuation of the experimental agent was higher in the calaspargase pegol arms with more discontinuations due to allergic reactions in both studies.

8.3.5 Analysis of Submission-Specific Safety Issues

Immunogenicity, Allergic Reactions (anaphylaxis / hypersensitivity)
OBP determined that the assays to evaluate immunogenicity were not valid. See OBP review. The incidence of allergic reactions (anaphylaxis / hypersensitivity) after the induction therapy was similar in the calaspargase pegol arms compared to the pegaspargase arms of both trials. See Table 17: DFCI 11-001 Post-Induction TEAEs and Table 18: AALL07P4 Post-Induction TEAEs.

Pancreatitis - DFCI -11-001

The incidence of pancreatitis based on clinical diagnosis of pancreatitis, pancreatitis-associated

laboratory values, and a standardized MedDRA query for pancreatitis between arms are presented in the following table.

Table 21: DFCI 11-001 Pancreatitis

DFCI 11-001 Pancreatitis – TEAE n (%)		
Induction		
	Pegaspargase n=119	**Calaspargase n=118**
Pancreatitis (any grade) PTs Pancreatitis	4	3
Pancreatitis (grade 3 and 4)	2	2
Laboratory PTs Amylase increased Lipase increased	16	8
Standardised MedDRA Queries (pancreatitis) PTs Abdominal pain Amylase increased Blood bilirubin increased Hyperbilirubinemia Lipase increased Pancreatitis	41	32
CNS / Consolidation 2 / Modified Consolidation 2		
	Pegaspargase n=112	**Calaspargase n=105**
Pancreatitis (any grade) PTs Pancreatic necrosis Pancreatitis Pancreatitis relapsing	17 (15)	12 (11)
Pancreatitis (grade 3 and 4)	14 (13)	11 (10)
Laboratory PTs Amylase increased Lipase increased	24 (21)	22 (21)
Standardised MedDRA Queries (pancreatitis) PTs Abdominal pain Amylase increased Ascites Blood bilirubin increased Hyperbilirubinaemia Lipase increased Pancreatic necrosis Pancreatitis Pancreatitis relapsing	92 (82)	88 (84)

Pancreatitis – AALL07P4

The incidence of pancreatitis based on clinical diagnosis of pancreatitis, pancreatitis-associated laboratory values, and a standardized MedDRA query for pancreatitis between arms is presented in Tables 22. The AALL07P4 study also included a central laboratory prospective evaluation of amylase and lipase during the induction and consolidation phases of therapy. An analysis of this evaluation is presented in Table 23.

Table 22: AALL07P4 Pancreatitis

AALL07P4 Pancreatitis – TEAE n (%)		
Induction		
	Pegaspargase n=52	**Calaspargase n=111**
Pancreatitis (any grade) PTs Pancreatic necrosis Pancreatitis	1 (2)	8 (7)
Pancreatitis (grade 3 and 4)	1 (2)	7 (6)
Laboratory PTs Amylase increased Lipase increased	2 (4)	13 (12)
Standardised MedDRA Queries (pancreatitis) PTs Abdominal pain Amylase increased Ascites Blood bilirubin increased Lipase increased Nausea Pancreatic necrosis Pancreatitis Vomiting	27 (52)	88 (79)
Consolidation / Interim Maintenance I&II / Delayed Intensification I&II		
	Pegaspargase n=40	**Calaspargase n=80**
Pancreatitis (any grade) PTs Pancreatitis	3 (8)	12 (15)
Pancreatitis (grade 3 and 4)	2 (5)	9 (11)
Laboratory PTs Amylase increased Lipase increased	4 (10)	11 (14)
Standardised MedDRA Queries (pancreatitis) PTs Abdominal pain Amylase increased Ascites Blood bilirubin increased Lipase increased Nausea Pancreatitis Vomiting	22 (55)	55 (69)

Table 23: AALL07P4 Prospective Amylase and Lipase Evaluation

AALL07P4 Abnormalities Amylase and Lipase – Central Laboratory Analysis		
Induction Day 15 Consolidation Day 15 and Day 29		
n (%)	Pegaspargase n=49	Calaspargase n=109
Elevated Amylase		
Any grade (and > grade at baseline)	4 (8)	12 (11)
Grade 3 & 4 (and > grade at baseline)	0	3 (27)
Elevated Lipase		
Any grade (and > grade at baseline)	2 (4)	13 (12)
Grade 3 & 4 (and > grade at baseline)	1 (2)	8 (7)

CLINICAL REVIEWER COMMENT:
In the DFCI 11-001 study there was not an increased incidence of pancreatitis or laboratory tests associated with pancreatitis in either the induction or post induction phases of therapy in the calaspargase arm compared to the pegasparagase arm. This contrasts with analysis of the AALL07P4 study, the incidence of pancreatitis and laboratory tests associated with pancreatitis were higher in the calaspargase pegol arm. In the prospectively collected amylase and lipase samples analyzed in the reference laboratory as a component of the AALL07P4 study the incidence of abnormal values was higher in the calaspargase pegol arm compared to pegasparagase arm.

Hepatotoxicity - DFCI 11-001
Evaluation of hepatotoxicity in the DFCI 11-001 study is presented for the asparaginase arms including clinical diagnoses from the hepatobiliary disorder SOC and laboratory values associated with liver toxicity in the following table.

Table 24: DFCI 11-001 Hepatotoxicity

DFCI 11-001 Hepatotoxicity – TEAE n (%)		
Induction		
	Pegaspargase n=119	Calaspargase n=118
Hepatobiliary disorders PT Acute hepatitis	0	1 (1)
Investigations		
HGLT Hepatobiliary Investigations		
PT AST / ALT / γGT increased	54 (45)	54 (46)
PT Bilirubin increased	34 (29)	28 (24)
CNS / Consolidation 2 / Modified Consolidation 2		
	Pegaspargase n=112	Calaspargase n=105
Hepatobiliary disorders PT Drug-induced liver injury, Hepatic failure	0	2 (2)
Investigations		
PT AST / ALT increased	78 (70)	71 (68)
PT Bilirubin increased	37 (33)	38 (36)

Hepatotoxicity - AALL07P4

Hepatotoxicity in the AALL07P4 study is compared between the asparaginase arms including clinical diagnoses from the hepatobiliary disorder SOC and laboratory values associated with liver toxicity in the following table. The table also includes an analysis of data from special research laboratory tests, related to hepatotoxicity (AST, ALT, and bilirubin) which were prospectively collected on day 15 of the induction period, 11 days after the asparaginase dose and on day 29 of the consolidation period, 14 days after the asparaginase dose.

Table 25: AALL07P4 Hepatotoxicity

AALL07P4 Hepatotoxicity – TEAE n (%)		
Induction		
	Pegaspargase n=52	**Calaspargase n=111**
SOC Hepatobiliary disorders (liver only)	0	0
HGLT Hepatobiliary Investigations		
PT AST / ALT / γGT increased	10 (19)	17 (15)
PT Bilirubin increased	17 (33)	43 (39)
Consolidation / Interim Maintenance I&II / Delayed Intensification I&II		
	Pegaspargase n=40	**Calaspargase n=80**
SOC Hepatobiliary disorders (liver only)	0	0
HGLT Hepatobiliary Investigations	25 (63)	51 (64)
PT AST / ALT / γGT increased	18 (45)	24 (30)
PT Bilirubin increased	19 (48)	48 (60)
Reference Laboratory		
AST and/or ALT Induction Day 15 Grade 3	4 (8) [47 tested]	1 (<1) [104 tested]
Bilirubin Induction Day 15 Grade 2 or 3	5 (11) [45 tested]	10 (9) [106 tested]
AST and/or ALT Consolidation Day 29 Grade 3	3 (9) [32 tested]	1 (2) [57 tested]
Bilirubin Consolidation Day 29 Grade 2 or 3	0 [32 tested]	0 [56 tested]

CLINICAL REVIEWER COMMENT:
There is no signal of excess hepatotoxicity in the calaspargase pegol arm of either trial.

Coagulopathy Bleeding and Thrombosis - DFCI 11-001

TEAEs reported in the DFCI 11-001 study associated with bleeding and thrombosis are presented in the following table.

Table 26: DFCI 11-001 Coagulopathy, Bleeding and Thrombosis

DFCI 11-001 Coagulopathy – TEAE n (%)		
Induction		
	Pegaspargase n=119	Calaspargase n=118
Bleeding PTs Melena	1 (1)	0
Thrombosis / Embolism PTs Cerebrovascular accident, Device related thrombosis, Embolism, Thrombophlebitis superficial, Thrombosis in device, Venous thrombosis, Venous thrombosis limb	8 (7)	4 (3)
Laboratory Blood fibrinogen decreased, International normalised ratio increased	25 (21)	18 (15)
CNS / Consolidation 2 / Modified Consolidation 2		
	Pegaspargase n=112	Calaspargase n=105
Bleeding PTs Epistaxis, Esophageal ulcer hemorrhage	2 (2)	0
Thrombosis / Embolism PTs Cerebrovascular accident, Disseminated intravascular coagulation, Embolism, Intracardiac thrombus. Intracranial venous sinus thrombosis, Pulmonary embolism, Superior sagittal sinus thrombosis, Vena cava embolism, Venous thrombosis	13 (12)	12 (11)
Laboratory Activated partial thromboplastin time prolonged, Blood fibrinogen decreased, International normalised ratio increased	10 (9)	11 (10)

Coagulopathy Bleeding and Thrombosis - AALL07P4

TEAEs reported in the AALL07P4 study associated with bleeding and thrombosis are presented in Table 27. Table 28 "AALL07P4 Prospectively Evaluated Clotting Factors" presents the analysis of the special research laboratory tests evaluated at a central laboratory, related to coagulation

and thrombosis. These samples were collected on Days 4 (prior to asparaginase) and 15 of the induction period and included prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, protein C, protein S, antithrombin III (ATIII), d-dimers, and fibrin degradation products (FDP). Paired samples were evaluated and the percent of the patients with normal baseline samples that subsequently became abnormal are presented for each arm.

Table 27: AALL07P4 Coagulopathy, Bleeding and Thrombosis

AALL07P4 Coagulopathy – TEAE n (%)		
Induction		
	Pegaspargase n=52	**Calaspargase n=111**
Bleeding **PTs Hematemesis,** **Hematoma,** **Hemorrhage intracranial,** **Medical device site hemorrhage,** **Mouth hemorrhage,** **Subdural hemorrhage**	0	7 (6)
Thrombosis / Embolism **PTs Embolism,** **Subclavian vein thrombosis,** **Disseminated intravascular coagulation**	1(2)	5 (5)
Consolidation / Interim Maintenance I&II / Delayed Intensification I&II		
	Pegaspargase n=40	**Calaspargase n=80**
Bleeding **PTs Hematoma,** **Haematuria,** **Lower gastrointestinal haemorrhage,** **Purpura,** **Uterine haemorrhage,** **Vitreous haemorrhage**	2 (5)	3 (4)
Thrombosis / Embolism **PTs Cerebral ischaemia,** **Cerebrovascular accident,** **Disseminated intravascular coagulation,** **Embolism,** **Hemiparesis,** **Subclavian vein thrombosis**	2 (5)	9 (11)

Table 28: AALL07P4 Prospectively Evaluated Clotting Factors

AALL07P4 Paired Samples Induction Day 4, 15			Pegaspargase	Calaspargase
PT	normal to prolonged	n=85	22%	17%
PTT	normal to prolonged	n=102	38%	30%
Fibrinogen	normal/elevated to low	n=97	71%	73%
Protein C	normal/elevated to low	n=101	3%	4%
Protein S (activity)	normal/elevated to low	n=101	24%	36%
Protein S (antigen)	normal/elevated to low	n=101	62%	51%
ATIII	normal/elevated to low	n=101	79%	71%

CLINICAL REVIEWER COMMENT:
There is no signal of excess adverse events related to bleeding or thrombosis in the calaspargase pegol arm in the DFCI 11-001 study. There was nominal increase in bleeding and thrombosis in the AALL07P4 study. The proportion of samples of clotting factors with normal values at baseline and subsequently and subsequently became abnormal was similar in the treatment arms of the AALL07P4 study.

Hyperglycemia - DFCI 11-011 and AALL07P4

An evaluation of grade 3 and 4 hypergycemia is presented in the table below.

Table 29: DFCI 11-001 & AALL07P4 Hyperglycemia

Hyperglycemia TEAE				
SOC Metabolism and nutrition disorders PT Hyperglycemia				
	Any grade	Grade 3 & 4	Any grade	Grade 3 & 4
	Pegaspargase n=119		Calaspargase n=118	
DFCI 11-001 Induction	17 (14)	14 (12)	24 (20)	14 (12)
	Pegaspargase n=112		Calaspargase n=105	
DFCI 11-001 Post-induction treatment	16 (14)	10 (9)	16 (15)	11 (10)
	Pegaspargase n=52		Calaspargase n=111	
AALL07P4 Induction	12 (23)	4 (8)	49 (44)	26 (23)
	Pegaspargase n=40		Calaspargase n=80	
AALL07P4 Post-induction treatment	22 (55)	7 (18)	53 (66)	15 (19)

CLINICAL REVIEWER COMMENT:
There is no signal of an excess incidence of grade 3 and 4 hyperglycemia in the calaspargase pegol arm of the DFCI 11-001 study. During the induction phase of the AALL07P4 study there

was an increase in grade 3 and 4 hyperglycemia in the calaspargase pegol arm which was not seen during the post induction therapy of this study.

Infections - DFCI 11-011 and AALL07P4

The incidence of infections during induction and post induction phases of therapy in the 2 studies are presented in the following table. Arms in the individual study with an incidence > 3% are highlighted.

Table 30: DFCI 11-001 & AALL07P4 Comparison of the Incidence of Infections

Comparison of the Incidence of Infections				
	DFCI 11-001		AALL07P4	
Induction	Pegaspargase n=119	Calaspargase n=118	Pegaspargase n=52	Calaspargase n=111
SOC Infection	21 (18)	17 (14)	11 (21)	28 (25)
Serious (SOC Infection)	4 (3)	4 (3)	NA	NA
Grade 3 and 4 (SOC Infection)	18 (15)	15 (13)	10 (19)	27 (24)
HGLT Bacterial (SOC Infection)	8 (7)	8 (7)	5 (10)	19 (17)
HGLT Fungal (SOC Infection)	3 (3)	4 (3)	2 (4)	5 (5)
HGLT Viral (SOC Infection)	1 (1)	1 (1)	3 (6)	0
F&N Grade 3 and 4 (SOC Blood Disorders)	20 (17)	14 (12)	6 (12)	12 (11)
Post-Inductions Asparaginase Phases of Therapy	Pegaspargase n=112	Calaspargase n=105	Pegaspargase n=40	Calaspargase n=80
SOC Infection	17 (15)	18 (17)	10 (25)	37 (46)
Serious (SOC Infection)	2 (2)	5 (5)	NA	NA
Grade 3 and 4 (SOC Infection)	14 (13)	17 (16)	9 (23)	37 (46)
HGLT Bacterial (SOC Infection)	10 (9)	5 (5)	4 (10)	24 (30)
HGLT Fungal (SOC Infection)	0	1 (1)	1 (3)	6 (8)
HGLT Viral (SOC Infection)	3 (3)	3 (3)	4 (10)	10 (13)
F&N Grade 3 and 4 (SOC Blood Disorders)	31 (28)	25 (24)	19 (48)	48 (60)

CLINICAL REVIEWER COMMENT:
The stark difference in the incidence of infections identified in the calaspargase pegol arms of the AALL07P4 study was not repeated in the DFCI 11-001 study.

Lipid Abnormalities – AALL07P4

The table below presents an analysis of the data derived from special research laboratory tests collected in the AALL07P4 study. Triglycerides and cholesterol levels were prospectively collected at baseline, on day 15 of the induction period, 11 days after the initial asparaginase dose and on day 15 and 29 of the consolidation period. The table presents the incidence of elevated levels that were higher than the baseline grade.

Table 31: AALL07P4 Lipid Abnormalities

AALL07P4 Lipid Abnormalities – Central Laboratory Analysis		
Induction Day 15 Consolidation Day 15 and Day 29		
n (%)	Pegaspargase n=49	Calaspargase n=109
Elevated Triglyceride		
Any grade (and > grade at baseline)	17 (35)	28 (26)
Grade 3 & 4 (and > grade at baseline)	8 (16)	8 (7)
Elevated Cholesterol		
Any grade (and > grade at baseline)	14 (29)	22 (20)
Grade 3 & 4 (and > grade at baseline)	2 (4)	1 (1)

CLINICAL REVIEWER COMMENT:
Based on the analysis of the prospectively collected samples in the AALL07P4 study, calaspargase pegol treatment is not associated with a higher incidence of triglyceride or cholesterol elevation compared to pegasparagase.

Erosion of Efficacy

The DFCI 11-001 study was not powered to evaluate superiority or non-inferiority. For this study, an erosion of efficacy is a safety issue. In the subgroup of patients with B-cell lineage ALL the complete remission rate in the calaspargase pegol arm was 98% (95/97) compared to 99% (98/99) in the pegaspargase arm; the estimated Kaplan-Meier analysis of overall survival was comparable between treatment arms. The results do not signal a potential lack of efficacy.

8.3.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable.

Expectations on Safety in the Postmarket Setting

There are no new safety issues expected to arise in the postmarket setting.

8.3.11 Integrated Assessment of Safety

Overall, the data suggest that the safety profile of calaspargase pegol-mknl does not differ substantially from that of the comparator pegaspargase.

SUMMARY AND CONCLUSIONS

8.4 Statistical Issues

The following comments pertain to Study DFCI 11-001. As noted in Section 8.1.1, DFCI 11-001 was designed primarily to evaluate the safety and feasibility of IV administration of calaspargase pegol 2500 IU/m^2, where feasibility refers to the evaluation of pharmacokinetic endpoints. It was not designed to assess efficacy with respect to clinical endpoints (MRD, CR, EFS, DFS, OS) either in the sense of superiority or in the sense of non-inferiority to pegasparagase. And while the denominator and numerator data for MRD and CR are reasonably large for making statistical inference and while both the MRD negativity rates and the CR rates appear to be similar between IV calaspargase pegol 2500 IU/m^2 and pegasparagase, there is no agreed upon margin from which to formally conclude similarity.

To the extent that the technology for assessing MRD is reasonably reliable, (b) (4) however, the CDRH reviewer could not confirm the validity of the MRD data (see Section 4.3).

(b) (4)

For time-to-event endpoints, (b) (4), the available statistical information is insufficient for making statistical inference.

8.5 Conclusions and Recommendations

This review team defers to the Clinical Pharmacology reviewers' assessment of NSAA as an established surrogate for efficacy. There are no clinical data that signal erosion of efficacy, and there is no unexpected or unacceptable safety issue. Approval is recommended.

Kunthel By, PhD
Primary Statistical Reviewer

Yuan-Li Shen, DrPh
Statistical Team Leader

Patricia Dinndorf, MD
Primary Clinical Reviewer

Donna Przepiorka, MD, PhD
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

This application was not discussed by an advisory committee.

10 Pediatrics

On 10/20/1989, the Applicant was granted Orphan Designation for pegaspargase for treatment of acute lymphocytic leukemia. The Office of Orphan Products Development confirmed that the designation was applicable to calaspargase pegol-mknl.[1] As such, the application is exempt from the requirement of a pediatric assessment under the Pediatric Research Equity Act (PREA). The data herein are adequate to support labeling for pediatric patients down to the age of 1 month.

On 10/25/2017, calaspargase pegol for treatment of acute lymphoblastic leukemia (ALL) was designated as a drug for a rare pediatric disease. At the time of submission of the BLA, the Applicant requested a Rare Pediatric Disease Priority Review Voucher for calaspargase pegol-mknl as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL). Since the application was not given priority review, it is not eligible for the voucher.

11 Labeling Recommendations

11.1 Prescribing Information

Section	Major Changes in Approved Labeling
1	• Revised to include the ages of the approved intended patient population.
2	• Added instructions for safety monitoring and dose modifications.
5	• Added a warning for hemorrhage due to the drug-induce coagulopathy. • (b) (4) • (b) (4)
6	• Updated to display only grades 3 or greater adverse reactions due to the limitations in data collection.

[1] Email from Soumya Patel, PharmD, dated December 14, 2018.

[redacted] (b) (4)	
8	• Added clinically relevant nonclinical data section based on literature assessment. • Added instructions for pregnancy testing. • Provided more detail for the experience in the pediatric population.
[redacted] (b) (4)	
12	• Added specific pharmacodynamic data that were credible. • Revise to include only the credible pharmacokinetics data.
14	[redacted] (b) (4) • Added data on nadir serum asparaginase activity used to as the basis for establishing efficacy.

12 Risk Evaluation and Mitigation Strategies (REMS)

Review determined that a REMS is not necessary to ensure that the benefits of calaspargase pegol-mknl outweigh its risks. Labeling, including Warnings and Precautions, will be used to communicate the safety issues and management of toxicities associated with calaspargase pegol-mknl.

13 Postmarketing Requirements and Commitments

Recommended PMC-1
To develop and validate screening and confirmatory assays for the evaluation of anti-calaspargase antibodies. Develop an assay to determine whether any anti-calaspargase antibodies are anti-PEG. [redacted] (b) (4) Submit information in accordance with 21 CFR 601.12.

Recommended PMC-2
[redacted] (b) (4)

Recommended PMC-3
Complete the qualification of bioburden and endotoxin test methods using two additional batches of (b) (4) drug substance and submit the information and summary data.

Recommended PMC-4
Validate the maximum crimping parameter using a container closure integrity test capable of detecting ≤ 20 µm breaches and submit the validation data.

Recommended PMC-5
Complete the qualification of endotoxin test method for the DP release sample using one additional calaspargase pegol DP lot and submit the endotoxin method qualification data.

Recommended PMC-6
To perform a leachables study to evaluate leachables from the container closure system of calapargase pegol drug product and assess the potential impact of leachables on product quality at the end of the shelf life. The analysis will be performed using one drug product lot and/or a representative sample (e.g. formulation buffer) analyzed at the end of shelf life. Appropriate methods will be used to detect, identify, and quantify organic non-volatile, volatile and semi-volatile species, and metals. Characterization of the potential impact on product quality will be assessed using adequate analytical methods. Complete data and the risk evaluation for the potential impact of leachables on product safety and quality will be submitted in accordance with 21 CFR 601.12.

Recommended PMC-7
To perform a shipping validation study under real time shipping conditions (i.e. temperature, mode of transport, shipping duration, and shipping containers and packing representative of the minimum and maximum load) using a representative commercial (b) (4) lot in the final commercial container closure and packaging systems to evaluate the ability of the shipping containers to maintain the recommended temperature and to evaluate the impact of shipping on the quality the of (b) (4). The shipping validation data will be submitted in accordance with 21 CFR 601.12.

Recommended PMC-8
To perform a shipping validation study under real time shipping conditions (i.e. temperature, mode of transport, shipping duration, and shipping containers and packing representative of the minimum and maximum load) using a representative commercial Calaspargase pegol drug product lot in the final commercial container closure and packaging systems to evaluate the ability of the shipping containers to maintain the recommended temperature and to evaluate the impact of shipping from the manufacturing site(s) to the distribution site(s) on the physical integrity and product quality of Calaspargase pegol drug product. The shipping validation data will be submitted in accordance with 21 CFR 601.12.

14 Appendices

14.1 References

Sallan SE, Hitchcock-Bryan S, Gelber R, et al. Influence of intensive asparaginase in the treatment of childhood non-T-cell acute lymphoblastic leukemia. Cancer Res 1983;43:5601-7.

Vrooman LM, Supko JG, Neuberg DS, et al. *Erwinia* asparaginase after allergy to *E. coli* asparaginase in children with acute lymphoblastic leukemia. Pediatr Blood Cancer 2010;54:199-205.

14.2 Financial Disclosure

Covered Clinical Study: DFCI 11-001

Covered Clinical Study (Name and/or Number):

Was a list of clinical investigators provided:	Yes x ☐	☐
Total number of investigators identified: 91 (9 centers)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: ___ Significant payments of other sorts: _ Proprietary interest in the product tested held by investigator: ___ Significant equity interest held by investigator in S Sponsor of covered study: ____ NOT APPLICABLE		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Not applicable	
Is a description of the steps taken to minimize potential bias provided:	Not applicable	
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Not applicable	

14.3 Nonclinical Pharmacology/Toxicology

None

14.4 OCP Appendices

14.4.1. Bioanalytical Method Review

Study DFCI 11-001

The [redacted] (b) (4) was the central analytical laboratory responsible for determining asparaginase activity in serum samples obtained from patients enrolled in this clinical study DFCI 11-001.

Bioanalytical Method

[redacted] (b) (4)

2 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

Reviewer's Comment:
According to the FDA Guidance for Industry on Bioanalytical Method Validation, the establishment of calibration method appears reasonable and the accuracy and precision for each calibration standard, QC sample and diluted QC sample appears acceptable. However, significant objectionable conditions were observed during the FDA inspection, which may impact the validity of the PK data. Following is the inspection summary.

Form FDA 483 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI).

Significant objectionable conditions were observed during this inspection that impacted the reliability of the audited study. Specifically:

(b) (4)

(b) (4)

We conclude that the data from study DCFI-11-001 are unreliable to support a regulatory decision and should not be accepted for agency review.

A clinical pharmacology IR was conveyed to the applicant on May 25, 2018 for data clean. The following criteria are used to flag the subject data in the raw data worksheets for analytical runs of asparaginase activity in Study DFCI 11-001 as rejected or unacceptable samples.

(b) (4)

The applicant responded to IR on June 27, 2018. Based on the above criteria for data clean, 315 samples were flagged due to (b) (4); 4 samples were flagged due to (b) (4); 3534 samples were flagged (b) (4) and 242 samples were flagged due to (b) (4). Overall, more than 90% of the PK data cannot be used for PK analysis. Therefore, only 11 patients in CalPEG arm and 16 patients in Oncaspar arm are evaluable for the PK analysis during the induction phase and only 5 patiens in CalPEG arm and 3 patients in Oncaspar arm are evaluable for the PK analysis at steady state.

Study AALL07P4

The (b) (4) was the central analytical laboratory responsible for determining asparaginase activity in plasma samples obtained from patients enrolled in this clinical study AALL07P4.

Same coupled enzyme assay is applied to determine the asparaginase acitivity for Oncaspar and CalPEG samples.

Standard Curve

Separate standard curves were prepared fresh daily using both Oncaspar and CalPEG and were prepared in pooled, normal human plasma (sodium heparin). Calibration standards ranged from 12.86 through 150 mIU/mL. The LOD (limit of detection) for the assay is 6.43 mIU/mL. The lower limit of quantification (LLOQ) for the assay is 12.86 mIU/mL. For a standard curve to be acceptable, a minimum of seven standards must be acceptable (±25% of nominal concentration at the LOD and ±20% for all other standards).

QC Sample

Three levels of QCs were included in each assay. Two separate sets of QC samples were prepared fresh daily using both Oncaspar and CalPEG. QCs were prepared at three concentrations (37.5, 75, and 115 mIU/mL).

Accuracy and Precision

As shown in the **Table 35** and **Table 36**, the accuracy and precision of the analytical method at the LLOQ of 12.86 mIU/mL were determined to be 99.6% and 7.81% for Oncaspar, and 101% and 9.85% for CalPEG. The accuracy at all other standards (STD1 to STD7) were ranged from 98.9% to 102% for Oncaspar, and from 98.8% and 101% for CalPEG. The precision at all other standards (STD1 to STD7) were ranged from 1.86% to 5.06% for Oncaspar and from 1.83% and 5.63% for CalPEG.

Table 35: Summary of Calibration Standards for Oncaspar

	STD1	STD2	STD3	STD4	STD5	STD6	STD7	STD8
Nominal (mIU/mL)	150	125	104.2	86.8	57.9	38.6	25.7	12.86
N	247	248	248	248	248	247	248	247
Mean	150.8	123.64	103.82	88.23	57.25	38.34	26.14	12.81
SD	2.81	3.11	2.2	2.04	1.32	1.35	1.32	1.00
%CV	1.86	2.51	2.12	2.31	2.30	3.51	5.06	7.81
%Mean $(A_{assay})/A_{true}$	101%	98.9%	99.6%	102%	98.9%	99.3%	102%	99.6%
% Difference from Nominal	0.54	-1.09	-0.37	1.64	-1.12	-0.68	1.69	-0.37

Table 36: Summary of Calibration Standards for CalPEG

	STD1	STD2	STD3	STD4	STD5	STD6	STD7	STD8
Nominal (mIU/mL)	150	125	104.2	86.8	57.9	38.6	25.7	12.86
N	248	248	248	248	248	248	248	248
Mean	150.53	124.4	103.47	87.92	57.21	38.54	25.93	12.93
SD	2.75	2.44	2.32	2.16	1.47	2.17	1.28	1.27
%CV	1.83	1.96	2.24	2.45	2.57	5.63	4.93	9.85
%Mean $(A_{assay})/A_{true}$	100%	99.5%	99.3%	101%	98.8%	99.8%	101%	101%
% Difference from Nominal	0.35	-0.48	-0.7	1.29	-1.19	-0.16	0.9	0.54

Table 37 and **Table 38** showed that the accuracy of three levels of QC ranged from 90% to 97% for Oncaspar and ranged from 91% to 103% for CalPEG. The precision of three levels of QC ranged from 4.74% to 9.81% for Oncaspar and ranged from 5.53% to 9.34% for CalPEG.

Table 37: Summary of QC Results for Oncaspar

	High QC	Mid QC	Low QC
Nominal (mIU/mL)	115	75	37.5
N	494	494	494
Mean	111.65	69.95	33.78
SD	8.02	3.32	3.31
%CV	7.18	4.74	9.81
%Mean $(A_{assay})/A_{true}$	97%	93%	90%
% Difference from Nominal	-2.91	-6.73	-9.93

Table 38: Summary of QC Results for CalPEG

	High QC	Mid QC	Low QC
Nominal (mIU/mL)	115	75	37.5
N	494	494	494
Mean	118.13	73.12	34.26
SD	10.11	4.04	3.2
%CV	8.56	5.53	9.34
%Mean $(A_{assay})/A_{true}$	103%	97%	91%
% Difference from Nominal	2.72	-2.51	-8.63

Reviewer's Comment:
According to the FDA Guidance for Industry on Bioanalytical Method Validation, the accuracy and precision for each calibration standard and QC sample appears within the acceptable crietria. Following is the inspection summary provided by the FDA inspection team.

Form FDA 483 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI).

Although objectionable conditions were observed during this inspection, the findings did not impact the reliability of the data from the audited studies. Thus, I recommend that the analytical data from **Studies AALL07P4** and **DFCI 11-001** (**BLA 761102**) and other studies using similar methods (**Attachment 1**) be accepted for further Agency review.

14.4.2. Clinical PK Assessment

CalPEG and Oncaspar are both pegylated form of L-asparaginase. The covalently bound polyethylene glycol (PEG) in CalPEG is the same size (5000 Da) as the PEG used in Oncaspar. The difference is that the L-asparaginase enzyme is conjugated with PEG by a more stable succinimidyl carbonate (SC) linker in CalPEG than the succinimidyl succinate (SS) linker used in Oncaspar.

Single Dose PK

The PK paramters following a single induction dose of CalPEG and Oncaspar calculated by the noncompartmental analysis (NCA) analyses in Study AALL07P4 are listed in **Table 39**. The mean C_{max} , T_{max} and $AUC_{(0\text{-}25d)}$ are similar between CalPEG 2500 U/m^2 and Oncaspar 2500 IU/m^2, whereas mean $AUC_{(0\text{-}inf)}$ is much higher for CalPEG 2500 U/m^2 comparing with that of Oncaspar 2500 IU/m^2. In addition, the mean terminal plasma half-life of CalPEG (16 days) is more than three times longer than that of Oncaspar (5 days). Consistent with the longer half-life, CalPEG has a relative lower mean CL (0.15 L/day) to Oncaspar (0.22 L/day). It should be noted that the variability of each PK parameter is high regardless of treatment group. The PK profiles of CalPEG and Oncaspar after the first consolidation dose were similar to those in the induction phase. From the reviwer's view, given the mean calculated terminal half-life of CalPEG is about 16 days, the protocol pre-specified PK sampling time up to day 25 in the induction phase doesn't adequately cover the duration of 3-5 times half-life, which represents about 95-99% of drug elimination phase. It explains the discrepancy that the mean $AUC_{(0\text{-}25d)}$ is similar between CalPEG and Oncaspar at 2500 IU/m^2, while the mean $AUC_{(0\text{-}inf)}$ is about 1.5 times higher for CalPEG than that of Oncaspar. The true terminal half-life of CalPEG might be longer than 16 days if the PK sampling time could cover most of the elimination phase.

Table 39: PK Parameters after A Single Dose of CalPEG and Oncaspar in the Induction Phase in Study AALL07P4

Mean (CV%)	CalPEG 2500 U/m^2 (N=43)	Oncaspar 2500 IU/m^2 (N=47)
C_{max} (mU/mL)	1622 (23%)	1639 (28%)
T_{max} (hr)*	1.2 (1, 97)	1.3 (1, 26)
$AUC_{(0\text{-}25d)}$ (mU*day/mL)	16870 (23%)	15460 (23%)
$AUC_{(0\text{-}inf)}$ (mU*day/mL)	25470 (30%)	16570 (29%)
$T_{1/2}$ (day)	16 (52%)	5.3 (44%)
CL (L/day)	0.15 (76%)	0.22 (56%)
Vss (L)	3.0 (84%)	2.0 (58%)
*Note: T_{max} is expressed as median (min, max).		

(Source: Table 21 on page 299 in the clinical study report of Study AALL07P4)

In addition, the ratio of geometric means (GMR) for C_{max}, $AUC_{(0\text{-}25d)}$ and $AUC_{(0\text{-}inf)}$ of CalPEG to Oncaspar following a single dose of 2500 IU/m^2 are listed in **Table 40** as well as the corresponding two-sided 90% confidence intervals (CIs). Overall, CalPEG and Oncasapr are not considered to be bioequivalent at dose of 2500 U/m^2 because the mean $AUC_{(0\text{-}inf)}$ of CalPEG was 1.5 times higher than that of Oncaspar and the lower limit of the 90% CI (137%, 167%) of the GMR $AUC_{(0\text{-}inf)}$ for CalPEG exceeded 125%.

Table 40: Ratio of PK Parameters Between CalPEG and Oncaspar at Dose of 2500 U/m2

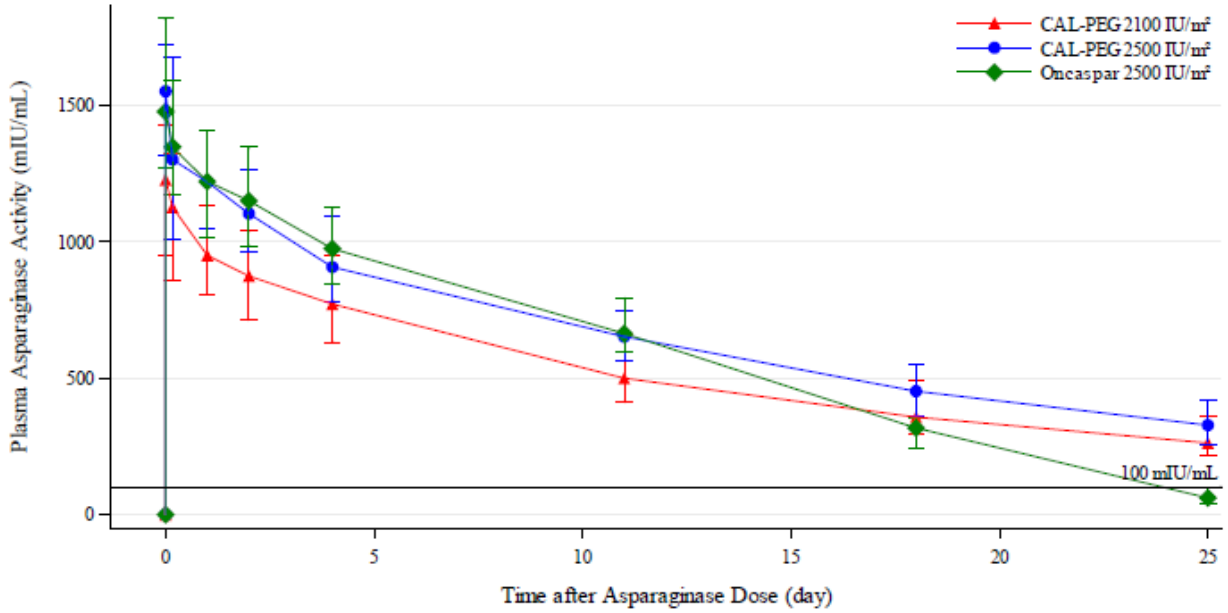
PK Parameters	Treatment	Number	Geometric Mean	GMR (%) of CalPEG vs. Oncaspar	90% CI (Lower, Upper)
C_{max} (mU/mL)	CalPEG 2500	43	1552	99.6	92, 108
	Oncaspar 2500	47	1559		
$AUC_{(0\text{-}25d)}$ (mU*day/mL)	CalPEG 2500	42	16140	108	100, 117
	Oncaspar 2500	46	14890		
$AUC_{(0\text{-}inf)}$ (mU*day/mL)	CalPEG 2500	42	23930	151	137, 167
	Oncaspar 2500	46	15810		

(Source: In-text Table 17 on page 102 in the clinical study report of Study AALL07P4)

The change of asparaginase activity vs. time profile after a single dose of either CalPEG or Oncasapr in Study AALL07P4 [redacted] (b) (4) are shown in **Figure 12**. The level of asparaginase activity in Oncaspar arm had a steep decline and dropped under the therapeutic threshold of 0.1 U/mL before Day 25 postdose, while CalPEG, regardless of dose levels of 2100 or 2500 U/m^2, had a sustained asparaginase acitivity ≥ 0.1 U/ml from Day 1 to Day 25 post dose [redacted] (b) (4) Therefore, the longer time of asparaginase activity ≥ 0.1 U/mL in CalPEG arm than in Oncaspar arm supports the less frequent dosing interval for CalPEG.

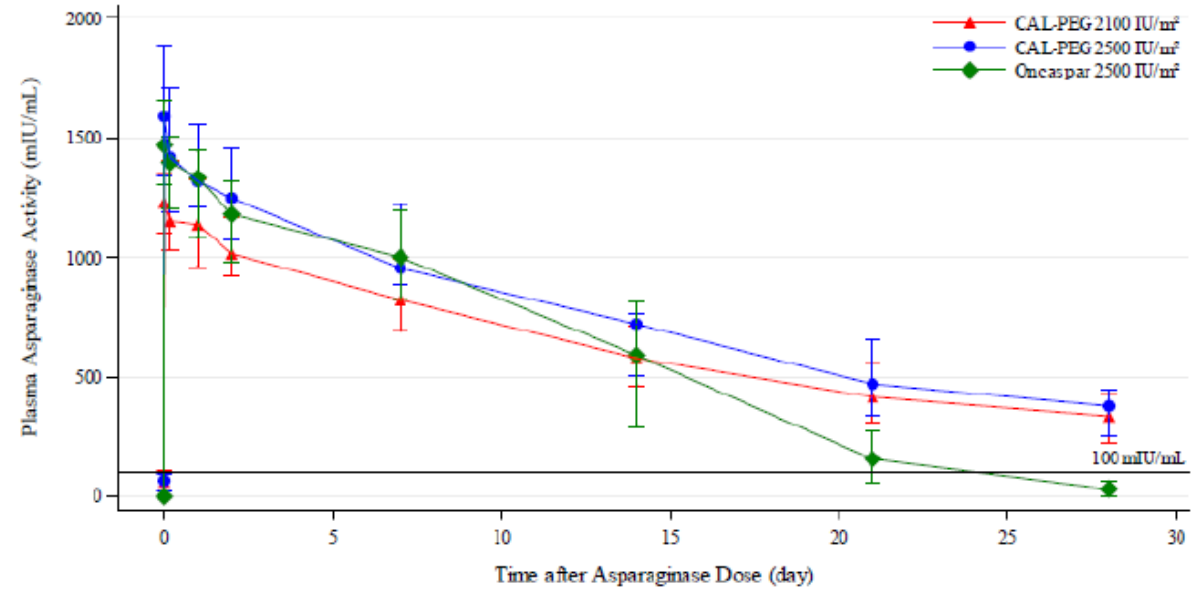
Figure 12: Asparaginase Activity Over Time after A Single Dose of CalPEG or Oncaspar

Figure 12a: Plasma Asparaginase Activity (25th, 75th percentile) Over Time during Induction Phase in Study AALL07P4



(Source: In-text Figure 3 on page 98 in the clinical study report of Study AALL07P4)

Figure 12b: Plasma Asparaginase Activity (25th, 75th percentile) Over Time during Consolidation Phase in Study AALL07P4



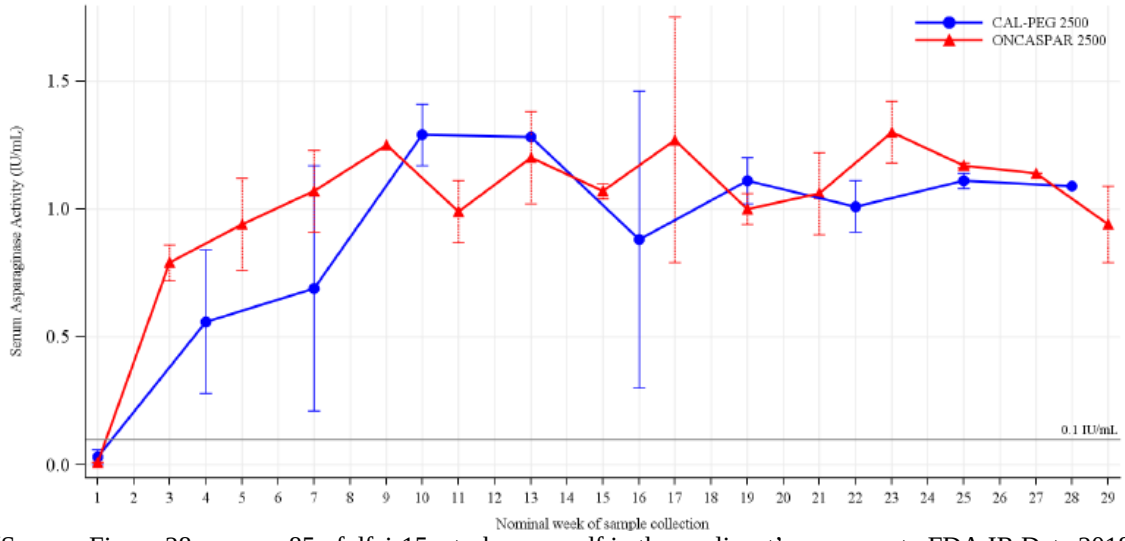
(Source: In-text Figure 5 on page 108 in the clinical study report of Study AALL07P4)

(b) (4)

Multiple Dose PK

The PK parameters after multiple dose are not calculated in either study. **Figure 13** describes the nadir serum asparaginase activity (NSAA) over time profiles of CalPEG Q3W and Oncasapr Q2W after multiple doses of 2500 U/m2 during post-induction phase in Study DFCI 11-001 based on the valid observed PK data. Once steady state has been reached in both treatment arms around Week 13 (i.e., 4th dose of CalPEG and 6th dose of Oncaspar), comparative average NSAA for CalPEG Q3W and Oncaspar Q2W was demonstrated. NSAA had been maintained ≥ 0.1U/mL through the 30-week treatment period for both drugs.

Figure 13: Mean (SD) NSAA levels of CalPEG and Oncaspar during Post-Induction Phase in Study DFCI 11-001



(Source: Figure 28 on page 85 of dfci-15pct-pk-rerun.pdf in the applicant's response to FDA IR Date 2018 May 25)

Simulations of Asparaginase Activity

The applicant reported that four different dosing regimens (Q2W, Q3W, Q4W and Q6W) of CalPEG and Oncaspar at 2500 U/m^2 were simulated to describe the individual predictions of asparaginase activity for 10000 individuals per treatment and dosing regimen sampling from the National Health and Nutrition Examination Survey (NHANES) database. The predicted trough asparaginase activity at steady-state for the majority of the subjects are above the thresholds of 0.4 (orange line, applicant specified threshold) and 0.1 U/mL (red line) for CalPEG 2500 U/m^2 Q3W and Oncaspar 2500 IU/m^2 Q2W.

All together, the PK profile of CalPEG after a single dose, the comparative NSAA at steady state between CalPEG and Oncaspar and the results of predicted asparaginase activity at four different dosing regimens of CalPEG 2500 U/m^2 are in agreement that the proposed dosing regimen of CalPEG 2500 U/m^2 Q3W appears appropriate in target patient population.

CalPEG 2100 U/m^2 vs 2500 U/m^2

CalPEG was administered at the dose of 2100 U/m^2 to 69 subjects after Study AALL07P4 amendment 2 in August 2009 because a planned interim PK analysis in 18 patients (b) (4) However, an interim efficacy analysis in late 2010 showed (b) (4) Consequently, the enrollment to CalPEG 2100 U/m^2 arm was halted in December 2010 (study amendment 4) and subjects randomized to receive CalPEG 2100 U/m^2 were switched to receive Oncaspar 2500 IU/m^2.

The $AUC_{(0\text{-}25d)}$ of asparaginase activity appears to be approximately dose propotional from CalPEG 2100 to 2500 U/m^2. C_{max} and $AUC_{(0\text{-}inf)}$ were lightly more than dose propotional, while the T_{max}, $T_{1/2}$ and CL were similar between two dose levels (**Table 41**). Comparing to the PK parameter of Oncaspar (**Table 39**), CalPEG 2100 U/m^2 had an approximately 20% lower mean T_{max}, 10% lower mean $AUC_{(0\text{-}25d)}$ and 20% higher mean $AUC_{(0\text{-}inf)}$ (**Table 42**), which did not support the PK comparability between CalPEG 2100 U/m^2 and Oncaspar 2500 IU/m^2.

Table 41: PK Parameters after A Single Dose of CalPEG 2100 U/m2 and 2500 U/m2 in the Induction Phase in Study AALL07P4

Mean (CV%)	CalPEG 2500 U/m^2 (N=43)	CalPEG 2100 U/m^2 (N=67)
C_{max} (mU/mL)	1622 (23%)	1283 (29%)
T_{max} (hr)*	1.2 (1, 97)	1.2 (0.1, 49)
$AUC_{(0\text{-}25d)}$ (mU*day/mL)	16870 (23%)	13650 (27%)
$AUC_{(0\text{-}inf)}$ (mU*day/mL)	25470 (30%)	20020 (39%)

Mean (CV%)	CalPEG 2500 U/m^2 (N=43)	CalPEG 2100 U/m^2 (N=67)
$T_{1/2}$ (day)	16 (52%)	14 (41%)
CL (L/day)	0.15 (76%)	0.18 (83%)
Vss (L)	3 (84%)	3.3 (60%)
*Note: Tmax is expressed as median (min, max).		

(Source: Table 21 on page 299 in the clinical study report of Study AALL07P4)

Table 42: Ratio of PK Parameters between CalPEG 2100 U/m2 and Oncaspar 2500 IU/m2 in Study AALL07P4

PK Parameters	Treatment	Number	Geometric Mean	GMR (%) of CalPEG vs. Oncaspar	90% CI (Lower, Upper)
C_{max} (mU/mL)	CalPEG 2100	66	1264	81	76, 87
	Oncaspar 2500	47	1559		
$AUC_{(0\text{-}25d)}$ (mU*day/mL)	CalPEG 2100	66	13380	90	83, 97
	Oncaspar 2500	46	14890		
$AUC_{(0\text{-}inf)}$ (mU*day/mL)	CalPEG 2100	64	18990	120	109, 133
	Oncaspar 2500	46	15810		

(Source: In-text Table 17 on page 102 in the clinical study report of Study AALL07P4)

14.4.3 Pharmacometrics Review

1. Executive Summary

1.1 Recommendations

Calaspargase Pegol is approvable from pharmacometrics perspective.

2. Applicant's Population PK and PK/PD Analysis

Text with gray shadow indicates that the content was copied from the applicant's study report.

2.1 Data

Data from two studies targeting ALL patient populations were utilized for the population PK and PKPD analysis. Both studies included newly diagnosed, asparaginase naïve patients. Study AALL07P42 included high risk (white blood cell (WBC) criteria: Age 1-9.9 years: WBC count ≥ 50000/µL or Age 10-30.9 years: Any WBC or Prior steroid therapy: Any WBC), whereas study DFCI-11-0014 targeted standard risk (WBC criteria: Age: 365 days to < 10 years and WBC count < 50000/µL) and high-risk patients (WBC criteria: Age: 10 to < 22 years or WBC count: Highest pre-treatment WBC > 50000/µL). The summary of number of subjects and number of calaspargase

pegol PK observations in the PK analysis data set and samples below LLOQ used for graphical exploration and diagnostics are presented in **Table** 43.

Table 43: Number of subjects with included PK observations and number of calaspargase pegol PK observations in the PK analysis data set and samples below LLOQ used for graphical exploration and diagnostics

Study / Arm[a]	Number of subjects (N)[b]	Number of PK observations		
		PK analysis data set	Below LLOQ[c,d]	Total
AALL07P4				
Calaspargase pegol 2100 IU/m2	68	832	38	870
Calaspargase pegol 2500 IU/m2	43	535	24	559
All	111	1 367	62	1 429
DFCI-11-001				(b) (4)
Calaspargase pegol 2500 IU/m2	117			
All				
All	228			

[a] Arm denotes the actual arm.
[b] Number of subjects with included PK observations.
[c] LLOQ is the lower limit of quantification and was 12.86 IU/L in AALL07P4 and (b) (4) IU/L in DFCI-11-001.
[d] Samples below LLOQ used for graphical exploration and diagnostics.

Source: Applicant's population PK report page 19 Table 1.

The summaries of baseline continuous and categorical covariates and the summary of anti-drug antibodies and neutralizing antibody per subject in the PK analysis data set for the final population PK model of calaspargase pegol are presented in **Table** 44 and **Table** 45, respectively.

Table 44: Baseline continuous covariate statistics for the PK analysis data set, stratified by study

Covariate		AALL07P4	DFCI-11-001	All
Age (years)	min **median** max	1.00 **12.0** 26.0		(b) (4)
	mean (SD)	10.7 (5.83)		
	N	111		
Body weight (kg)	min **median** max	8.45 **47.0** 143		
	mean (SD)	48.6 (30.5)		
	N	111		
Height (cm)	min **median** max	71.5 **150** 199		
	mean (SD)	143 (34.0)		
	N	111		
BSA (m^2)	min **median** max	0.420 **1.44** 2.80		
	mean (SD)	1.36 (0.580)		
	N	111		
Total bilirubin (mg/dL)	min **median** max	0.0500 **0.300** 1.90		
	mean (SD)	0.405 (0.339)		
	N	111		

SD: standard deviation; BSA: body surface area; N: number of subjects

Source: Applicant's population PK report page 21 Table 3.

Table 45: Baseline categorical covariate statistics for the PK analysis data set, stratified by study

Covariate			AALL07P4	DFCI-11-001	All
Sex	Female	N	58	(b) (4)	
		Percent (%)	52.3		
	Male	N	53		
		Percent (%)	47.7		
Race	Asian	N	4		
		Percent (%)	3.6		
	Black or African American	N	5		
		Percent (%)	4.5		
	Native Hawaiian or Other Pacific Islander	N	2		
		Percent (%)	1.8		
	White	N	93		
		Percent (%)	83.8		
	Other	N	0		
		Percent (%)	0.0		
	Unknown	N	7		
		Percent (%)	6.3		
	Multiple	N	0		
		Percent (%)	0.0		
Risk at baseline	Standard risk	N	0		
		Percent (%)	0.0		
	High risk	N	111		
		Percent (%)	100.0		

N: number of subjects

Source: Applicant's population PK report page 21 Table 4.

For both studies AALL07P4 and DFCI-11-001, binding antibodies against Oncaspar® pegaspargase or calaspargase pegol (according to the treatment group of the subject) were tested. All assays were validated with respect to cut-point, precision, linearity, short-term stability, freeze-thaw stability and drug interference. (b) (4)

2.2 Methods

The methods used in this population PK and PKPD analysis consisted of the following main steps:

1. Exploratory graphical analysis of asparaginase activity versus.
2. Development of a population PK model for calaspargase pegol, which included:
   - Evaluation of the previously developed structural model developed for Oncaspar to describe the typical calaspargase pegol PK profile.
   - Further development of the model structure to fit specifically the calaspargase pegol PK profiles in studies AALL07P4 and DFCI-11-001.
   - Investigation and characterization of patient factors that influence the PK of calaspargase pegol.
   - Assessment of the impact of anti-calaspargase pegol binding antibodies, anti-PEG binding antibodies, on clearance-related PK parameters.

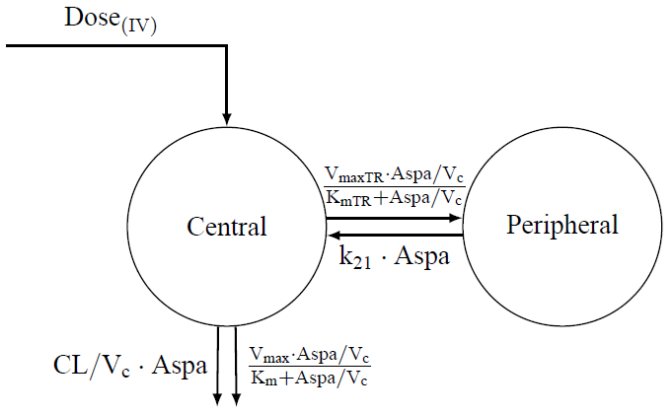
3. Use the empirical Bayes estimates (EBE) of the PK parameters of the final calaspargase pegol population PK model for the subjects in studies AALL07P4 and DFCI-11-001 to produce individual predictions (IPRED) of asparaginase activity.
4. Exploration of a potential relationship between asparaginase exposure following calaspargase pegol treatment and MRD levels at the end of remission induction therapy in study AALL07P4 and DFCI-11-001.
5. Exploration of potential relationships between asparaginase exposure following calaspargase pegol treatment and selected AEs of interest.
6. Simulations based on the final population PK models developed for calaspargase pegol and Oncaspar.

2.3 Results

2.3.1 Population PK model

The base model for calaspargase pegol was a two-compartment model with saturable transport to the peripheral compartment and combined saturable elimination and linear clearance from the central compartment. IIV terms were supported on Vc, CL and k21. The RUV for calaspargase pegol was described by a combined RUV model, similar in structure to the RUV model for the final Oncaspar model. The structure of the base model for calaspargase pegol is depicted in **Figure** 14.

Figure 14: Illustration of the base model with saturable transport to the peripheral compartment and combined saturable elimination and linear clearance from the central compartment for calaspargase pegol after IV administration.



Note: Vc is the central volume of distribution, CL is the absolute clearance, Vmax is the maximum elimination capacity, Km is the concentration at half maximum elimination capacity, VmaxTR is the maximum peripheral distribution capacity, KmTR is the concentration at half maximum peripheral distribution capacity and k21 is the inter-compartmental rate constant. Aspa is short for Asparaginase activity in IU.

Source: Applicant's population PK report page 43 Figure 9.

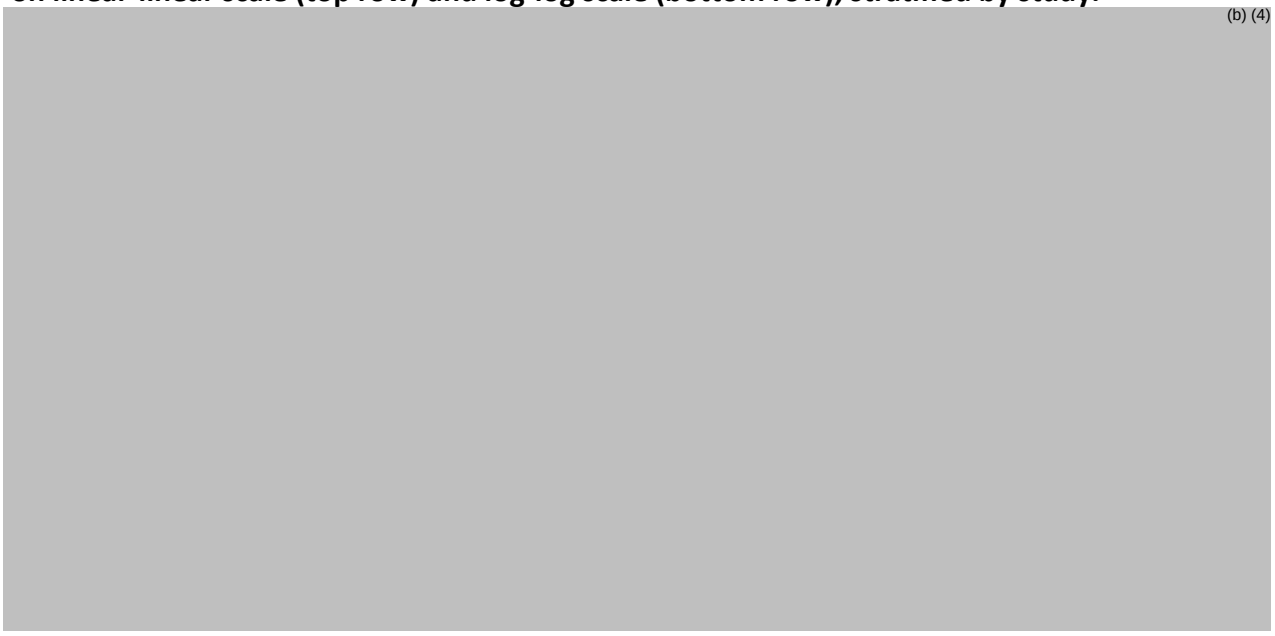
The final model provided a good description of the dose-exposure relationship in studies AALL07P4 and DFCI-11-001, as illustrated by the plots of observed asparaginase activity versus model population predictions in **Figure** 15 and versus individual predictions in **Figure** 16. The final model performed satisfactorily in the VPC, for AALL07P4, stratified by arm and dose occasion, presented in **Figure** 17, except for a slight under-prediction for the first dose in the calaspargase pegol 2100 IU/m^2 arm in study AALL07P4 at the end of the dosing interval.
The parameter estimates of the final population PK model (run23) are present in **Table** 46.

Table 46: Parameter estimates of the final population PK model

(b) (4)

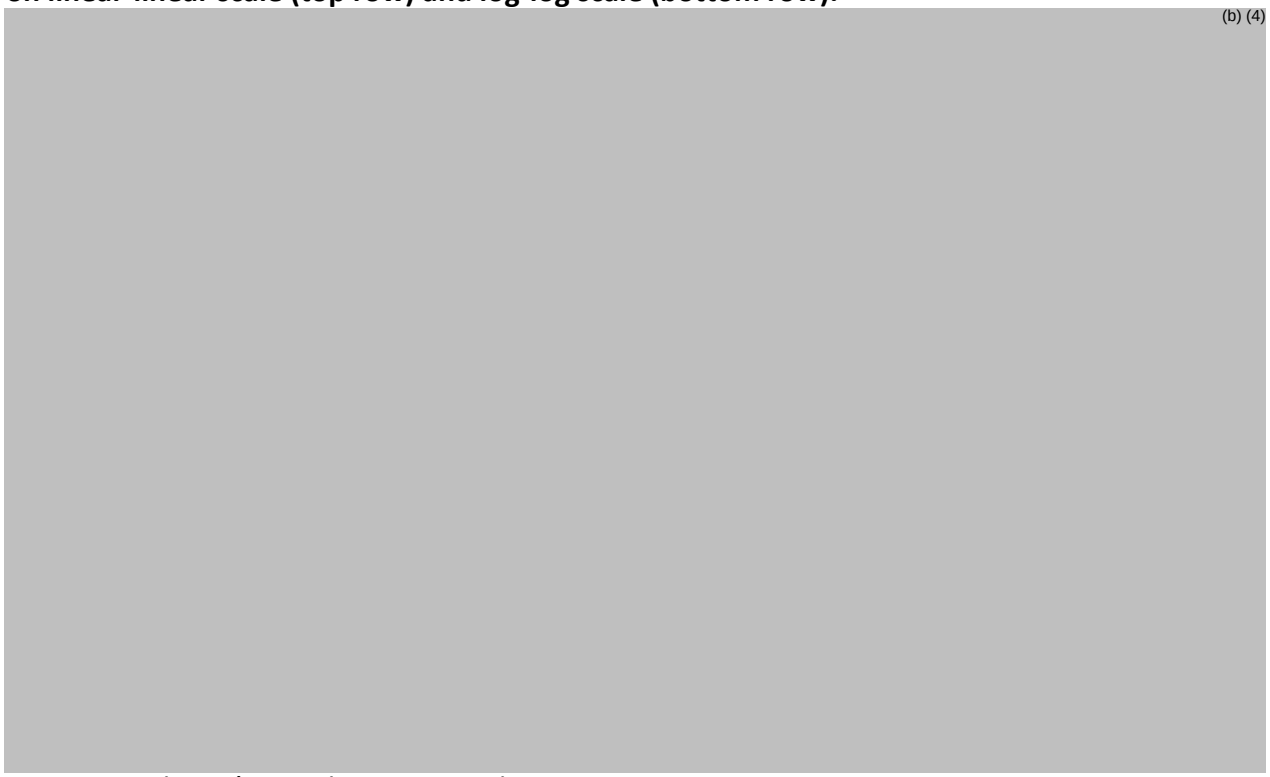
Source: Applicant's population PK study report Page 45 Table 14.

Figure 15: Observations versus population predictions based on the final population PK model on linear-linear scale (top row) and log-log scale (bottom row), stratified by study.



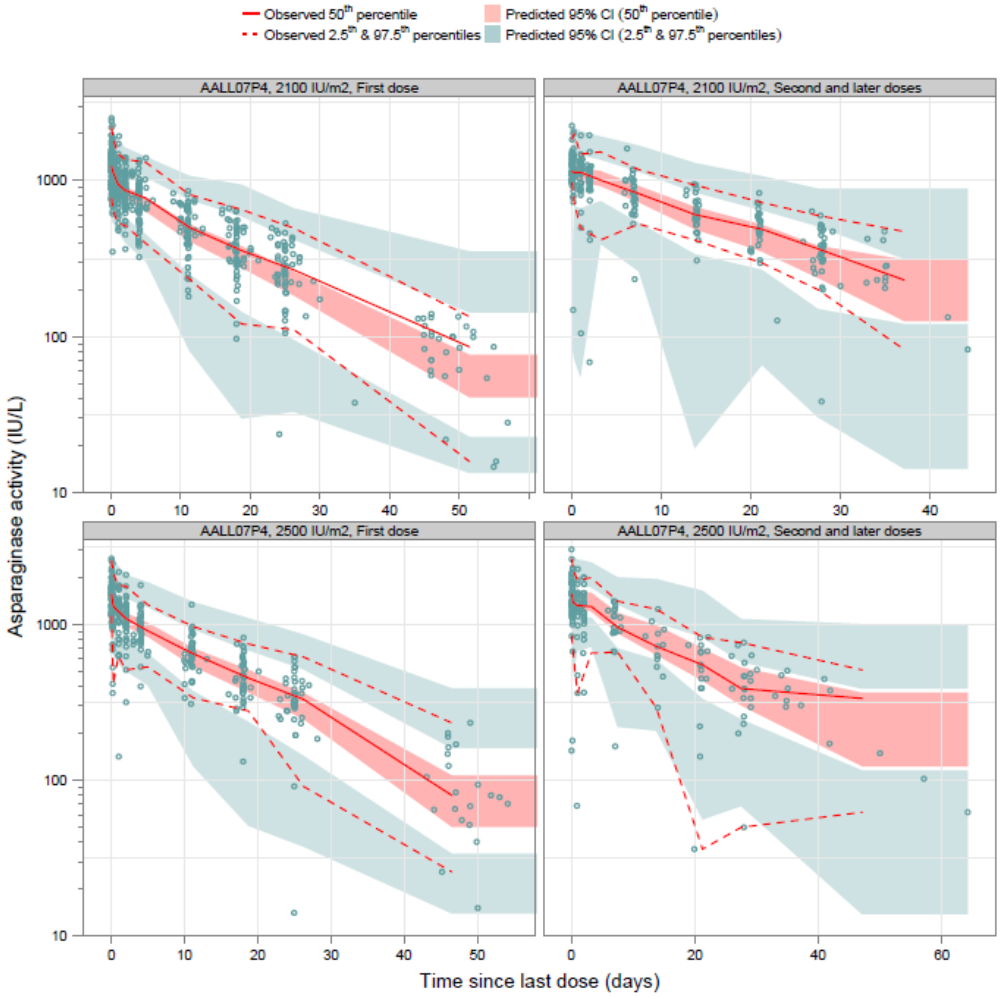
Source: Applicant's population PK study report page 46 Figure 10.

Figure 16: Observations versus individual predictions based on the final population PK model on linear-linear scale (top row) and log-log scale (bottom row).



Source: Applicant's population PK study report page 47 Figure 11.

Figure 17: Visual predictive check for the final population PK model for study AALL07P4 using time after dose as independent variable and stratified by arm and occasion.



Note: The red lines are the 2.5th, 50th (solid) and 97.5th percentile based on the observed data, indicated by open circles. The shaded areas are 95% confidence intervals for the 2.5th, 50th (red) and 97.5th percentile prediction intervals based on 1000 simulated data sets. The asparaginase activity is presented on a logarithmic y-axis.

Source: Applicant's population PK study report page 51 Figure 16.

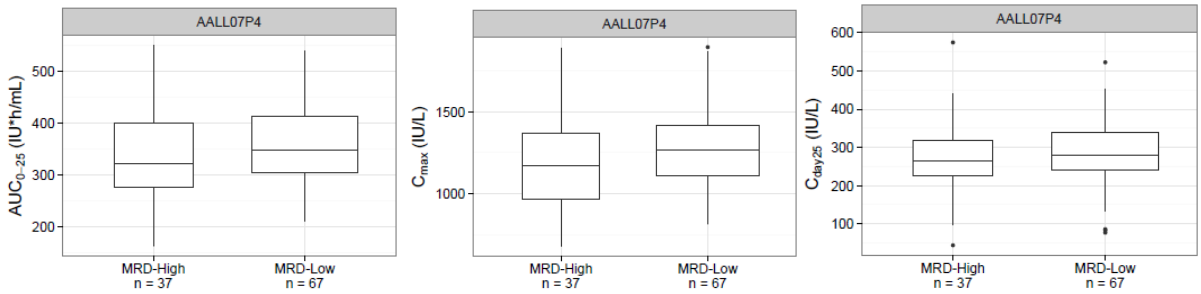
Reviewer's comment: The applicant's final population PK model appears to be able to describe the calaspargase pegol PK data collected from study AALL07P4 and DFCI-11-001. However, because majority of PK data from study DFCI-11-001 were removed due to the inspection failure, the population PK model and parameter estimates are needed to be updated only based on the remained valid PK data. Therefore, FDA reviewer conducted independent analysis using pooled PK data from original AALL07P4 PK data and updated DFCI-11-001 PK data provided by the applicant to update the population PK parameters. The results are summarized in section 3.

2.3.2 PK-MRD model

The applicant conducted analyses for PK-MRD relationship.

A graphical assessment of the relationship between the induction phase asparaginase exposure versus the MRD response at the end of the induction is present in Figure 18.

Figure 18: Graphs exploring the correlation between induction phase asparaginase activity AUC0-25, Cmax, Cday25 and MRD response for Study AALL07P4



Note: The horizontal line within each box represents the median. The box edges represent the lower (25th) and upper (75th) quartiles. The whiskers extend from the lower and upper quartiles to the furthest data points still within a distance of 1.5 interquartile ranges from the lower and upper quartiles. The width of the boxes is proportional to the square-roots of the number of observations (n).

Source: Applicant's population PK and PK/PD study report page 53-55 Figure 18-20.

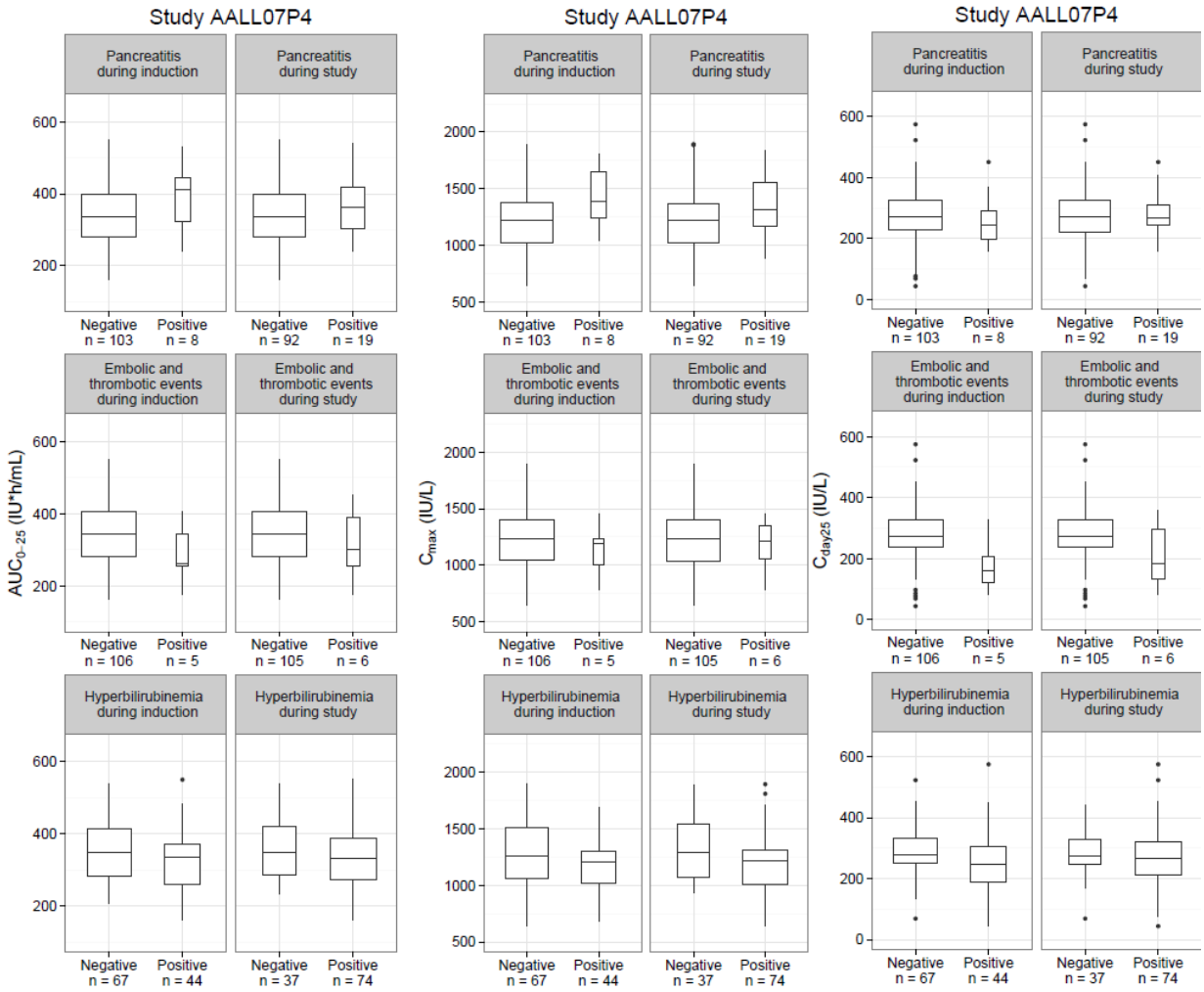
Reviewer's comment: All the PK data from study AALL07P4 passed the inspection. The applicant's PK-MRD analysis for study AALL07P4 is based on the univariate analysis, the potential confounding effects from may not be adjusted if there were some. In the updated DFCI-11-001 PK dataset provided by the applicant, only the PK data from a few subjects were retained. Thus, the PK-MRD analysis results for study DFCI-11-001 are inconclusive.

2.3.3 PK-AE models

The applicant conducted analyses to evaluate the relationship between PK and AEs of interest. Because majority of PK data from study DFCI-11-001 were not valid, PK/PD analyses based on the PK data from study DFCI-11-001 were not conclusive.

For Study AALL07P4, a graphical assessment of induction phase asparaginase exposure for patients that experienced particular AEs or not was conducted to explore potential exposure response relationships. The assessment focused on asparaginase exposure during the induction phase to limit the potential for reverse relationships Figure 19.

Figure 19: Boxplot for induction phase asparaginase AUC0-25, Cmax and Cday25 for patients with and without specific AEs for Study AALL07P4



Note: Separate panels for specific AE types either experienced during the induction phase or any time during the study. Each panel is stratified on patients with event and patients without event (positive/negative). The horizontal line within each box represents the median. The box edges represent the lower (25th) and upper (75th) quartiles. The whiskers extend from the lower and upper quartiles to the furthest data points still within a distance of 1.5 interquartile ranges from the lower and upper quartiles. Data beyond the end of the whiskers are plotted as points. The width of the boxes is proportional to the square-roots of the number of observations (n).

Source: Applicant's population PK and PK/PD study report Page 61 Figure 25, Page 62 Figure 26 and Page 63 Figure 27.

Univariate logistic regression was used to screen for potential effect of asparaginase exposure (AUC0-25, Cmax and C_{day25}) and Age on the incidence of the selected AEs. Focus was primarily on identifying a potential increased probability of occurrence of an AE with higher exposure.

No statistically significant relationships indicating an increased probability for an AE with increasing asparaginase activity exposure were found. A statistically significant negative correlation with asparaginase exposure between at least one of the asparaginase activity exposure metrics ($AUC_{0\text{-}25}$, Cmax or C_{day25}) was seen for Embolic and thrombotic events during the induction phase and Hyperbilirubinemia (induction phase and full study). Pancreatitis and Hyperbilirubinemia (induction phase and full study) were both positively correlated with Age.

Reviewer's comment: Applicant's PK/PD analyses for MRD and AEs are inconclusive due to the inspection failure of PK data for study DFCI-11-001. All the PK data from study AALL07P4 were reliable after the inspection. PK/PD analysis for study AALL07P4 is based on the univariate analysis, the potential confounding effects from may not be adjusted if there were some.

3. Reviewer's Analyses

3.1 Introduction

The PK, efficacy and safety of calaspargase pegol (CalPEG) were evaluated in two clinical trials (studies AALL07P4 and DFCI-11-001). The applicant conducted analysis to describe the population pharmacokinetic (PK) and the pharmacokinetic-pharmacodynamic (PK/PD) characteristics of CalPEG. However, majority of PK data from study DFCI-11-001 were invalid due to the inspection failure. As a result, the applicant updated the PK data set by removing the unacceptable PK observations from study DFCI-11-001 without updating the population PK model.

In this review, the pharmacometrics reviewer performed independent analyses to update the population PK model only based on the valid PK measurements. In addition, the reviewer evaluated whether the steady-state nadir serum asparaginase activity (NSAA) could be maintained above 0.1 U/mL under the dosing regimen of 2500 U/m^2 Q3W via imputation and simulation based on the updated population PK model.

3.2 Objectives

1. Update applicant's population PK model for ALL patients.
2. Conduct imputation to evaluate nadir asparaginase activity at steady state for CalPEG (2500 U/m^2 every 3 weeks).
3. Conduct simulation to evaluate and compare nadir asparaginase activity at steady state for CalPEG (2500 U/m^2 every 3 weeks) and ONCASPAR (2500 U/m^2 every 2 weeks).

3.3 Methods

3.3.1 Data sets

The dataset for population PK analysis in ALL patients was generated by combining the PK data for study AALL07P4 from the applicant's original data set for population PK model development with the updated PK data from study DFCI-11-001. The datasets used for generating population PK dataset are summarized in ***Table 47***. The updated PPK dataset includes 124 subjects with 1448 PK observations.

Table 47: Analysis Datasets

Study Number	File name	Description	Link to EDR
AALL07P4	dpkpmx2.xpt	Population PK dataset that the applicant used to develop the PPK model. Data for study AALL07P4 was filtered.	\\cdsesub1\evsprod\bla761102\0001\m5\datasets\pop-pk\analysis\legacy\datasets\dpkpmx2.xpt
DFCI-11-001	DFCI11-001 ADPC.xpt	Updated PK dataset to remove unacceptable bioanalytic results.	\\cdsesub1\evsprod\bla761102\0001\m5\datasets\dfci11-001\analysis\adam\datasets\adpc.xpt

3.3.2 Software

NONMEM (Version 7.3) was used for all population PK analyses. The R software was used for data table generation and post-NONMEM graphing and reporting.

3.3.3 Models

The applicant's final population PK model was used as the start point for update. Testing the fitting adequacy and evaluating the parameter estimates were conducted on the updated population PK model.

3.4 Results

3.4.1 Population PK analysis

The updated population PK model was based on applicant's two compartment model with saturable transport to the peripheral compartment and combined linear and non-linear elimination from the central compartment.

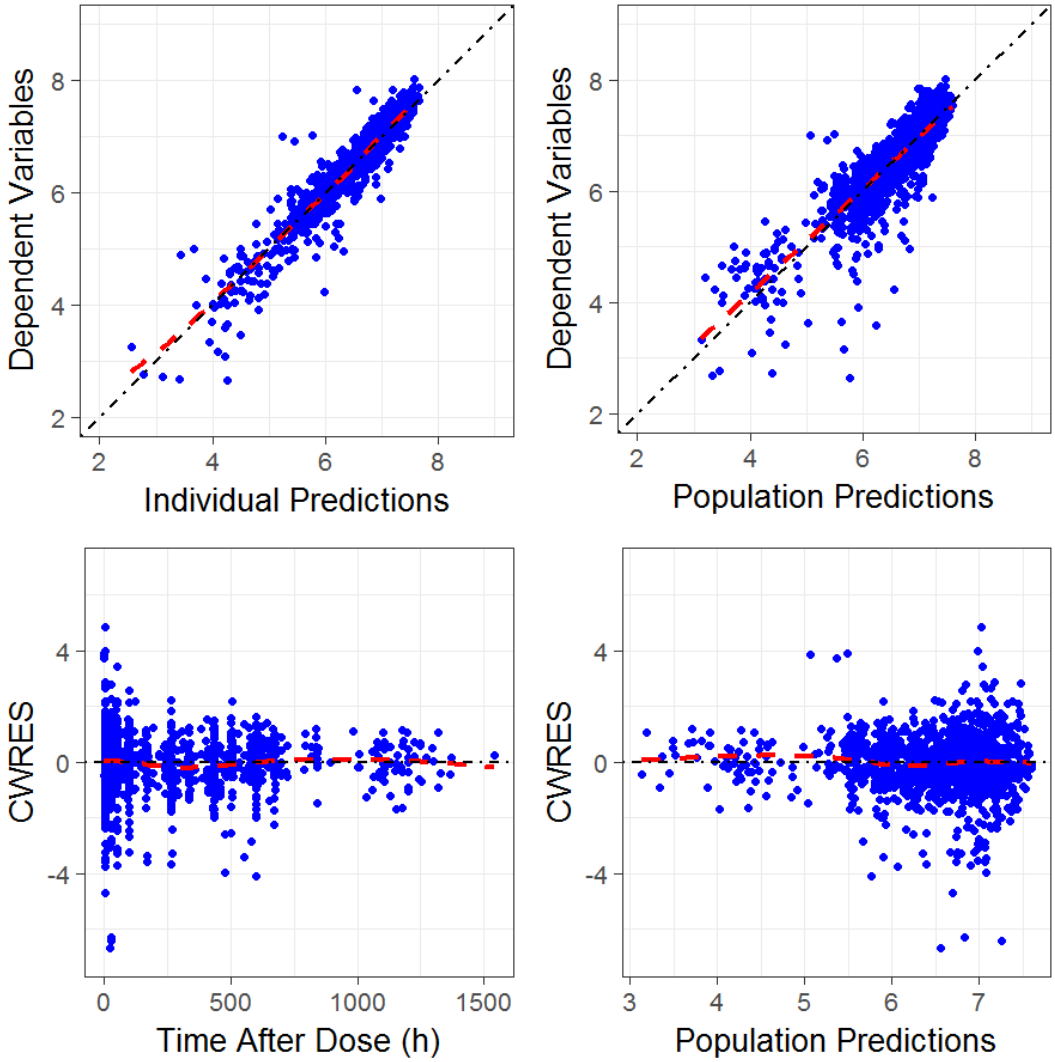
The reviewer's final population PK parameter estimates with the updated population PK dataset are summarized in Table 48.

Table 48: Parameter estimates of the reviewer's final population PK model.

Parameter	Description	Estimate	95% CI	SHR (%)
V_c (L)	Central volume of distribution	1.72	(1.36, 1.82)	--
CL (L/h)	Linear clearance	0.00242	(0.00203, 0.00282)	--
V_{maxTR} (IU/h)	Maximum peripheral distribution capacity	39	(19, 727)	--
K_{mTR} (IU/L)	Concentration at half maximum peripheral distribution capacity	110	(77, 207)	--
K_{21} (h^{-1})	Inter-compartmental rate constant	0.062	(0.027, 0.810)	--
V_{max} (IU/h)	Maximum elimination capacity	0.698	(0.518, 0.842)	--
K_m (IU/L)	Concentration at half maximum elimination capacity	0.001	(FIX)	--
BSA on V_c	Power coefficient of BSA on Vc	1.28	(1.12, 1.34)	--
BSA on CL	Power coefficient of BSA on CL	1.17	(0.84, 1.52)	--
BSA on V_{maxTR}	Power coefficient of BSA on V_{maxTR}	0.795	(0.544, 1.383)	--
BSA on V_{max}	Power coefficient of BSA on V_{max}	0.978	(0.564, 1.402)	--
Sex on V_c		-0.0832	(-0.1330, -0.0071)	--
IIV-V_c	Inter-individual variability	0.024	(0.006, 0.030)	11
IIV-CL	Inter-individual variability	0.203	(0.123, 0.282)	12.2
IIV-k_{21}	Inter-individual variability	0.117	(0.056, 0.242)	24.6
RUV_1	Log-additive RUV	0.142	(0.100, 0.187)	7.4
RUV_2	Additional contribution to the log-additive RUV for a zero prediction	0.823	(0.567, 2.608)	7.4
$RUVC_{50}$ (IU/L)	Prediction at which the additional contribution is half RUV_2	190	(29, 378)	7.4

The goodness-of-fit plots using the reviewer's final population PK model for ALL patients included in the updated population PK dataset are shown in Figure 20. Based on these diagnostic plots, there was a good agreement between observed and model-predicted asparaginase activity.

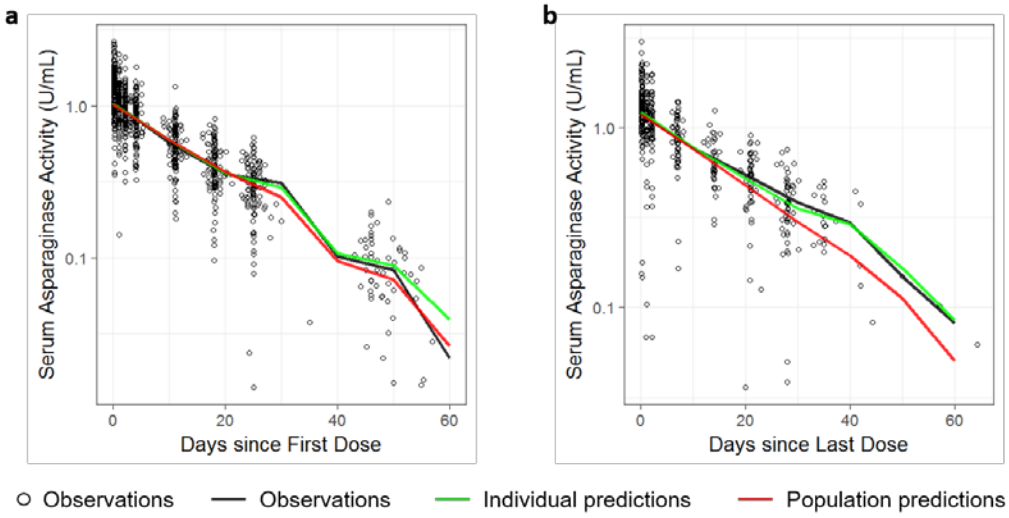
Figure 20: Goodness-of-fit plots for reviewer's final population PK model in all subjects



Note: the red lines are smooth lines showing the trend

The goodness of fit was also evaluated by plotting observations and predictions against days since first dose after the induction dose and time since last dose after the first consolidation dose (Figure 21). No evident deviation was found between observations and model predictions based on individual EBE parameter. The population predictions showed a trend of underestimation of asparaginase activity. This would give a slightly lower nadir serum asparaginase activity (NSAA) in the simulation compared to observations. However, it will produce a conservative assessment on efficacy in terms of NSAA greater than 0.1 IU/mL.

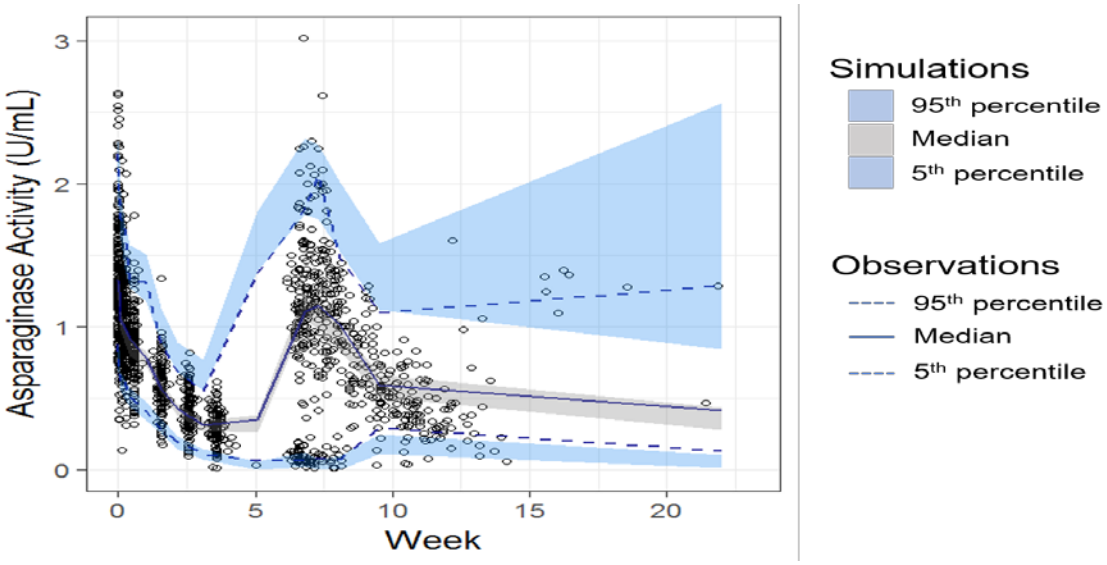
Figure 21: Observations and predictions versus days since induction dose or the 1st consolidation dose



Note: Observations and predictions versus days since induction dose (a) and days since the 1st consolidation dose (b) based on the updated population PK model on log-linear scale. Observed individual data points are indicated by dots. The black, green and red lines are medians for the observations, individual predictions and population predictions, respectively.

The updated model was satisfied in the VPC based on the pooled data from studies AALL07P4 and DFCI-11-001 as well (Figure 22). The median of the observed data mostly fell into the 95% CI for the predictions.

Figure 22: Visual predictive check for the updated population PK model for pooled data from studies AALL07P4 and DFCI-11-001



3.4.2 Evaluation of nadir serum asparaginase activity at steady-state for efficacy

The primary determination of effectiveness is that the nadir serum asparaginase activity (NSAA) could be maintained above 0.1 U/mL. Due to the removal of unacceptable bioanalytical PK measurements, only 5 subjects with valid observed NSAA at steady-state were retained from CalPEG arm in study DFCI-11-001. It was difficult to assess the NSAA at steady-state based on the limited valid PK observations. Thus, the reviewer conducted independent assessment to determine whether NSAA under the applicant proposed CalPEG dosing regimens could pass 0.1 U/mL cut-off, based on imputation and simulation of steady-state NSAA.

3.4.2.1 Imputation of asparaginase activity at steady-state

To evaluate whether the NSAA at steady-state could be maintained above 0.1 U/mL in more than 100 subjects (details please see discussion below), imputation was employed. All subjects from studies AALL07P4 and DFCI-11-001 with at least one valid PK observation were included in the imputation. Each subject's PK parameters (empirical Bayes estimates) were estimated by the updated population PK model. The subject's PK at any time point, including NSAA at steady-state, could then be imputed.

A total of 124 subjects with at least one valid PK observation were included (13 from study DFCI-11-001, 111 from study AALL07P4). The CalPEG dosing regimens for the imputation are described as below:

- Induction phase (Day 0 to 46): single dose (2500 U/m^2) on Day 0.

- Consolidation phase (30 weeks from Day 47):

    - 1st consolidation dose (2500 U/m^2) on Day 47.
    - Dosing (2500 U/m^2) every 3 weeks for 30 weeks.

As the majority of the subjects included in the imputation were not dosed every 3 weeks, the following considerations are laid out to evaluate the robustness of imputation in this case: 1. The PK sampling used to develop the population PK model are rich, and the exposure range can adequately cover the imputed steady-state NSAA, which is interpolation, not extrapolation; 2. The population PK model is robust according to the model's diagnostic plots as discussed above; 3. The empirical Bayesian PK parameters estimated by the population PK model were used to impute their steady-state NSAA. With rich PK, they would be less dependent on the pre-defined

model structure but more on observations. Taken together, using imputation to evaluate whether NSAA at steady-state could be maintained above 0.1 U/mL under 2500 U/m2 Q3W is acceptable.

The NSAA at steady-state was imputed and the result is shown in **Table 49**. The proportions of subjects that could maintain NSAA above the protocol-specified level of 0.1 U/mL are shown in **Table 50**. The result shows that more than 99% of imputed subjects were able to maintain the steady-state NSAA above 0.1 U/mL.

Table 49: Imputed NSAA at steady-state

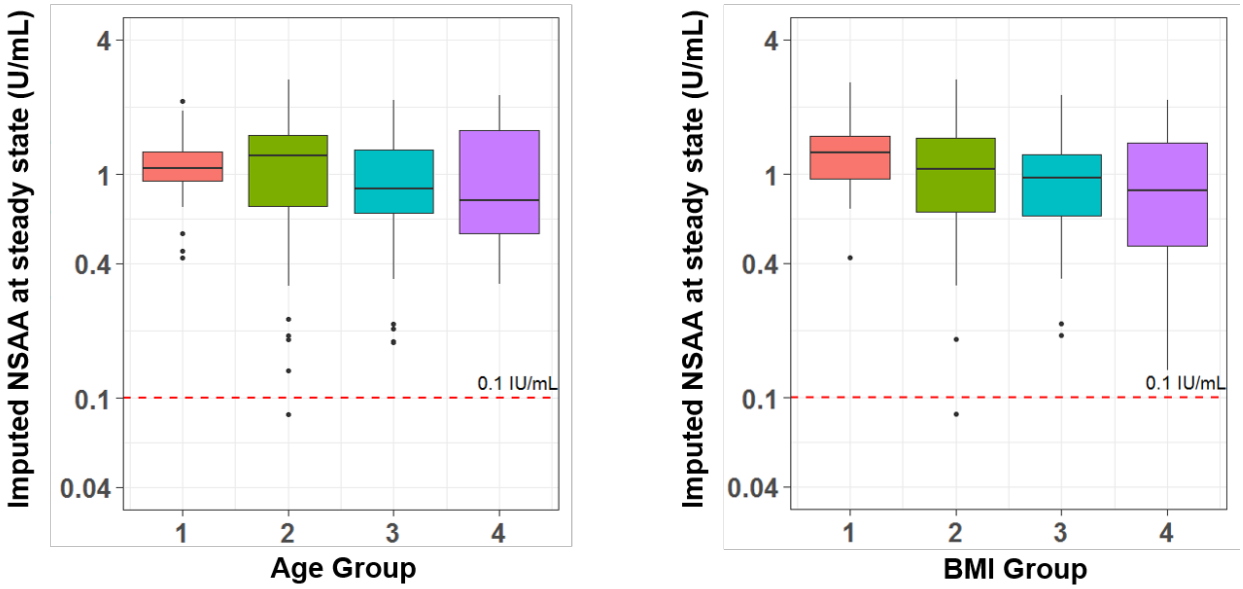
Post-induction weeks	NSAA Median (5^{th}, 95^{th}) (U/mL)
6	0.855 (0.290, 1.338)
12	1.078 (0.313, 1.838)
18	1.150 (0.315, 2.078)
24	1.168 (0.315, 2.220)
30	1.173 (0.315, 2.291)

Table 50: Proportions of imputed subjects with NSAA ≥ 0.1 U/mL

Post-induction weeks	Number of subject with NSAA ≥ 0.1 U/mL (Percentage %)
6	123/124 (99.19 %)
12	123/124 (99.19 %)
18	123/124 (99.19 %)
24	123/124 (99.19 %)
30	123/124 (99.19 %)

The imputed NSAA at steady-state was compared across BMI and age subgroups (Figure 23), and the proportion of subjects who maintains NSAA above 0.1 IU/mL appears similar among different groups.

Figure 23: Imputed nadir asparaginase activity (NSAA) at steady-state across age or BMI groups



Note: Age Group: 1. 1 to 2 years old (n=22); 2. 2 to 12 years old (n=50); 3. 12 to 17 years old (n=36); 4. 17 to 26 years old (n=16). BMI Group: 1. 12.98 to 16.10 kg/m^2 (n=31); 2. 16.10 to 18.46 kg/m^2 (n=31); 3. 18.46 to 23.98 kg/m^2 (n=31); 4. 23.98 to 39.39 kg/m^2 (n=31).

3.4.2.2 Simulations of asparaginase activity at steady-state

Next, simulations were conducted for pseudo-subjects that were generated from the NHANES database (N=10,000). The demographic of the pseudo-subjects used in the simulation is shown in Table 51. The NSAA for both CalPEG and Oncaspar was simulated.

The dosing regimens for CalPEG are described as below:

- Induction phase (Day 0 to 46): single dose (2500 U/m^2) on Day 0.
- Consolidation phase (30 weeks from Day 47):
  - 1st consolidation dose (2500 U/m^2) on Day 47.
  - Dosing (2500 U/m^2) every 3 weeks for 12 weeks.

The dosing regimens for Oncaspar are described as below:

- Induction phase (Day 0 to 46): single dose (2500 U/m^2) on Day 0.
- Consolidation phase (30 weeks from Day 47):
  - 1st consolidation dose (2500 U/m^2) on Day 47.
  - Dosing (2500 U/m^2) every 2 weeks for 12 weeks.

Predicted NSAA at steady-state for both arms is shown in Table 52. The proportions of simulated subjects that maintained NSAA above 0.1 U/mL are shown in Table 53. The result shows that more than 99% of simulated subjects in CalPEG arm were able to maintain the steady-

state NSAA above 0.1 U/mL, further supporting the proposed CalPEG dosing regimens. Based on the reviewer's updated population PK model, the population predictions were underestimated (Figure 21). Thus, the simulated NSAA tend to be lower than the observations. The simulated results would therefore provide a conservative estimation for the efficacy. Even in this scenario, more than 99% of the simulated subjects were still able to maintain their steady-state NSAA above 0.1 U/mL, suggesting a sufficient NSAA to maintain efficacy.

Table 51: Age and BSA groups for the simulation dataset, stratified by Sex

Covariate		Female N (Percent)	Male N (Percent)	All N (Percent)
Age	1-4 years	670 (13%)	680 (14%)	1350 (14%)
	5-8 years	529 (10%)	525 (11%)	1054 (11%)
	9-12 years	573 (11%)	577 (12%)	1150 (12%)
	13-18 years	1234 (24%)	1270 (26%)	2504 (25%)
	19-50 years	2119 (41%)	1823 (37%)	3942 (39%)
BSA	< 1 m^2	1075 (21%)	1038 (21%)	2113 (21%)
	1-2 m^2	3631 (71%)	2738 (56%)	6369 (64%)
	> 2 m^2	419 (8%)	1099 (23%)	1518 (15%)

Table 52: Simulated NSAA at steady-state under the treatment of CalPEG or Oncaspar

Post-induction weeks	CalPEG 2500 U/m^2 Q3W Median (5^{th}, 95^{th}) (U/mL)	Oncaspar 2500 U/m^2 Q2W Median (5^{th}, 95^{th}) (U/mL)
6	0.800 (0.278, 1.476)	0.981 (0.657, 1.351)
12	0.848 (0.305, 2.141)	1.201 (0.821, 1.550)

Table 53: Proportions of simulated subjects with steady-state NSAA ≥ 0.1 U/mL

Post-induction weeks	Number of subjects with NSAA ≥ 0.1 U/mL (Percent)	
	CalPEG 2500 U/m^2 Q3W	Oncaspar 2500 U/m^2 Q2W
6	9958/10000 (99.58 %)	10000/10000 (100 %)
12	9960/10000 (99.60 %)	10000/10000 (100 %)

In summary, the FDA reviewer conducted independent analyses to update population PK model based on the retained valid PK data after the inspection. The updated model was able to adequately describe the CalPEG PK, which was supported by the goodness-of-fit plots, observed/predicted concentrations versus time plots and VPC plots. Due to the limited observed PK data of NSAA at steady-state, the reviewer compared the NSAA at steady-state with the 0.1

U/mL cut-off by employing imputation and simulation. The results suggested that the dosing regimen of 2500 U/m^2 Q3W would be sufficient to maintain the NSAA at steady-state above 0.1 U/mL. In addition, there is no clinically meaningful difference in CalPEG exposures among age and BMI subgroups.

14.5 Additional Clinical Outcomes Assessment Analyses

None

14.6 Treatment Details of DFCI 11-001

Table 54: DFCI 11-001 Schedule of Chemotherapy

DFCI 11-001 Schedule of Chemotherapy		
Phase of therapy	Agent	Day of Therapy
Standard Risk Steroid Prophase (Day 1 – 3) Induction (4 weeks)	IT cytosine arabinoside	Day 1
	Methylprednisolone IV Methylprednisolone and/or prednisone PO	Day 1-3 Day 4-32 then taper
	Vincristine (IV)	Day 4, 11, 18, 25
	Doxorubicin (IV)	Day 4, 5
	Methotrexate (IV)	Day 6
	IT Triple (methotrexate, cytosine arabinoside, hydrocortisone)	Day 18
	IT methotrexate	Day 32
	Asparaginase (IV)	Day 7
OR		
High or Very High Risk Steroid Prophase (Day 1 – 3) Induction (4 weeks)	IT cytosine arabinoside	Day 1
	Methylprednisolone (IV) Methylprednisolone (IV) or prednisone (PO)	Day 1-3 Day 4-32 then taper
	Vincristine (IV)	Day 4, 11, 18, 25
	Doxorubicin/dexrazoxane (IV)	Day 4, 5
	Methotrexate IV	Day 6
	IT Triple (methotrexate, cytosine arabinoside, hydrocortisone)	Day 18
	IT methotrexate	Day 32
	Asparaginase (IV)	Day 7
Standard Risk Consolidation 1 (3 weeks)	Vincristine (IV)	Day 1
	Mercaptopurine (PO)	Day 1-14
	IT methotrexate	Day 1
	High dose methotrexate (5 gm) with leucovorin rescue (IV)	Day 1
OR		
High Risk Consolidation 1 (3 weeks)	Vincristine (IV)	Day 1
	Mercaptopurine (PO)	Day 1-14
	Doxorubicin/dexrazoxane (IV)	Day 1
	IT methotrexate	Day 1
	High dose methotrexate (5 gm) with leucovorin rescue (IV)	Day 1
OR		
Very High Risk Consolidation 1 (9 weeks)	Vincristine (IV)	IA Day 1
	Mercaptopurine (PO)	IA Day 1-14
	Doxorubicin/dexrazoxane (IV)	IA Day 1
	IT methotrexate	IA Day 1
	High dose methotrexate (5 gm) with leucovorin rescue (IV)	IA Day 1
	Cyclophosphamide (1 gm) (IV)	IB Day 1
	Cytosine arabinoside (IV)	IB Day 2- 5, 9-12
	Mercaptopurine (PO)	IB Day 1-14
	IT methotrexate	IB Day 1
	High Dose cytosine arabinoside (IV)	IC Day 1, 2
	Etoposide (IV)	IC Day 3, 4, 5
	Asparaginase (IV)	IC Day 8 (Start of 30 week course)

DFCI 11-001 Schedule of Chemotherapy (continued)		
Phase of therapy	Agent	Day of Therapy
Standard Risk CNS Phase (3 weeks)	Vincristine (IV)	Day 1
	Mercaptopurine (PO)	Day 1-14
	Dexamethasone (PO)	Day 1-5
	Asparaginase (IV)	Day 1 (Start of 30 week course)
	IT Triple (methotrexate, cytosine arabinoside, hydrocortisone)	Twice weekly 4 doses
OR		
High or Very High Risk CNS Phase (3 weeks)	Vincristine (IV)	Day 1
	Doxorubicin/dexrazoxane (IV)	Day 1
	Mercaptopurine (PO)	Day 1-14
	Dexamethasone (PO)	Day 1-5
	Asparaginase (IV)	30 week course
	IT Triple (methotrexate, cytosine arabinoside, hydrocortisone)	Twice weekly 4 doses
	[Cranial radiation to selected patients]	
Standard Risk Consolidation 2	Vincristine (IV)	Day 1 every 3 weeks
	Dexamethasone (PO)	Day 1-5 every 3 weeks
	Mercaptopurine (PO)	Day 1-14 every 3 weeks
	Methotrexate(IV)	Day 1, 8, 15 every 3 weeks
	IT Triple (methotrexate, cytosine arabinoside, hydrocortisone)	Every 9 weeks total 6 doses
	Asparaginase (IV)	30 week course
OR		
High or Very High Risk Consolidation 2	Vincristine (IV)	Day 1 every 3 weeks
	Dexamethasone (PO)	Day 1-5 every 3 weeks
	Mercaptopurine (PO)	Day 1-14 every 3 weeks
	Doxorubicin/dexrazoxane (IV)	Day 1 every 3 weeks
	Methotrexate(IV)	Day 1, 8, 15 every 3 weeks
	IT Triple (methotrexate, cytosine arabinoside, hydrocortisone)	Schedule depends of Radiation Status
	Asparaginase (IV)	30 week course
All patients Continuation Phase (Continue until 2 year of continuous complete remission)	Vincristine (IV)	Day 1 every 3 weeks
	Dexamethasone (PO)	Day 1-5 every 3 weeks
	Mercaptopurine (PO)	Day 1-14 every 3 weeks
	Methotrexate(IV)	Day 1, 8, 15 every 3 weeks
	IT Triple (methotrexate, cytosine arabinoside, hydrocortisone)	Schedule depends of Radiation Status

Abbreviations: IT – intrathecal; IV – intravenous; PO – per os (orally)

14.7 Treatment Details of AALL07P4

Table 55: AALL07P4 Schedule of Chemotherapy

AALL07P4 Schedule of Chemotherapy			
Phase of therapy	Agent		Day of Therapy
Induction (35 days)	IT cytosine arabinoside		Day 1
	Steroid (PO/IV)	Prednisone	Days 1-28
		Dexamethasone	Days 1-14
	Vincristine (IV)		Day 1, 8, 15, 22
	Daunorubicin (IV)		Day 1, 8, 15, 22
	IT methotrexate	CNS negative	Day 8, 29
		CNS positive	Day 8, 15, 22, 28
	Asparaginase		Day 4
Extended Induction (14 days)	Vincristine (IV)		Day 1, 8
	Daunorubicin (IV)		Day 1
	Steroid (PO)	Prednisone	Days 1-14
		Dexamethasone	Days 1-14
	Asparaginase		Day 4
Consolidation (56 days)	Cyclophosphamide (IV)		Day 1, 29
	Cytosine arabinoside (IV)		Days 1-4, 8-11, 29-32, and 36-39
	Mercaptopurine (PO)		Days 1-14 and 29-42
	Vincristine (IV)		Day 15, 22, 43, 50
	IT methotrexate	CNS negative	Day 1, 8, 15, 22
		CNS positive	Day 1, 8
	Asparaginase		Day 15, 43
Interim Maintenance I (Capizzi Methotrexate) (56 days)	Vincristine (IV)		Day 1, 11, 21, 31, 41
	Methotrexate (IV)		Day 1, 11, 21, 31, 41
	IT methotrexate		Day 1, 31
	Asparaginase		Day 2, 22
OR			
Interim Maintenance I (High Dose Methotrexate) (56 days)	Vincristine (IV)		Day 1, 15, 29, 43
	Methotrexate (IV)		Day 1, 15, 29, 43
	Mercaptopurine (PO)		Days 1-56
	IT methotrexate		Day 1, 29
Delayed Intensification I (56 days)	Vincristine (IV)		Day 1, 15, 29, 43
	Dexamethasone (PO)		Days 1-7, 15-21
	Doxorubicin (IV)		Day 1, 8, 15
	Cyclophosphamide (IV)		Day 29
	Cytosine arabinoside (IV/SQ)		Days 29-32, 36-39
	Thioguanine (PO)		Days 29-42
	IT methotrexate		Day 1, 29, 36
	Asparaginase		Day 4, 43
Interim Maintenance II (56 days)	Vincristine (IV)		Day 1, 11, 21, 31, 41
	Methotrexate (IV)		Day 1, 11, 21, 31, 41
	IT methotrexate		Day 1, 31
	Asparaginase		Day 2, 22
Delayed Intensification II (56 days)	Vincristine (IV)		Day 1, 15, 29, 43, 50
	Dexamethasone (PO)		Days 1-7, 15-21
	Doxorubicin (IV)		Day 1, 8, 15
	Cyclophosphamide (IV)		Day 29
	Cytosine arabinoside (IV/SQ)		Days 29-32, 36-39
	Thioguanine (PO)		Days 29-42
	IT methotrexate	No cranial XRT	Day 1, 29, 36
	Asparaginase		Day 4, 43
Maintenance (12 week cycle; 84 days)	Vincristine (IV)		Day 1, 29, 57
	Prednisone		Days 1-5, 29-33, 57-61
	Mercaptopurine (PO)		Days 1-84
	Methotrexate (PO)		Day 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78
	IT methotrexate		Day 1

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(This review is based in part on the reviews of Drs. Donna Przepiorka, Patricia Dinndorf and Kunthel By.)

On December 21, 2017, Baxalta, US, Inc. submitted BLA 761102 in which approval of calaspargase pegol-mknl (Asparlas), a succinimidyl carbonate-polyethylene glycol *E. Coli* L-asparaginase (L-ASP), was requested for the following indication: as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphocytic leukemia (ALL) in pediatric and young adult patients age 1 month to 21 years. The recommended dose and schedule is 2,500 units/m^2 administered as an intravenous infusion no more frequently that every 21 days.

Background: Calaspargase pegol (CP) is identical to Oncaspar (ONS), another earlier FDA approved pegylated L-ASP, in which a linker (succinyl succinate) which was less stable than the succinimidyl carbonate linker in CP, was used to attach the polyethylene glycol to the L-ASP. ONS was originally approved in 1994 for patients who had developed hypersensitivity to native *E. coli* derived L-ASP (Elspar). CP is a (b) (4) biological product comprised of an *E. coli* L-ASP homotetramer and 31-39 molecules of monomethyxpolyethylene glycol (mPeg) attached to the L-asp by the relatively stable succinimidyl carbonate linkage which is associated with a half-life which is longer than that of ONS.

BLA 761102 relied on COG Study AALL07P4 (NCT00671034), which studied doses of 2,100 units/m^2 and 2,500 units/m^2 given at every 2-week intervals, and DFCI 11-001, which studied CS at a dose of 2,500 units/m^2 given every three weeks.

Efficacy and Safety: The results from AALL07P4 suggested that a dose of CP of 2,500 units/m^2 given at every 2-week intervals was associated with unacceptable toxicity while the results from DFCI 11-001 suggested that a dose of CP of 2,500 units/m^2 given at every 3-week intervals was associated with acceptable toxicity. Analysis of the PK/PD results from AALL07P4 suggested that a dose of CP of 2,500 units/m^2 given at every 3-week intervals would be associated with the nadir serum asparaginase activity (NSAA) > 0.1 U/mL at weeks 6, 12, 18, 24 and 30 (a NSAA of >0.1U/mL is associated with a survival and event free survival advantage when added to the ALL backbone therapy.

Recommended Regulatory Action: On the basis of these considerations, this Supervisory Associate Division Director is in agreement with the recommendation of the reviewers for a regular approval of CP for the following indication: as a component of a multi-agent chemotherapeutic regimen for the treatment of ALL in pediatric and young adult patients age 1 month to 21 years. The recommended dose and schedule of CP is 2,500 units/m^2 administered as an intravenous infusion no more frequently that every 21 days.

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director,
Division of Hematology Products (DHP)

19 Office Director (or designee)

This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. The risk-benefit of calaspargase pegol-mknl was also assessed by Drs. Przepiorka and Dinndorf, and I concur with their recommendation to approve this biologic. My signature below also represents an approval recommendation for the clinical portion of this application under CDER.

Amy McKee, MD
Acting Associate Director, Office of Hematology and Oncology Products (OHOP)
Deputy Director, Oncology Center of Excellence (OCE)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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RUOJING LI on behalf of CHAO LIU
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XIANHUA W CAO
12/19/2018

NAM ATIQUR RAHMAN
12/19/2018
I concur.

KUNTHEL BY
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THOMAS E GWISE on behalf of YUAN L SHEN
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