BLA Multidisciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Application Number	**BLA 761179**
Application Type	Original
Priority or Standard	Standard
Submit Date	4/30/2021
Received Date	4/30/2021
PDUFA Goal Date	4/30/2022
Office/Division	OOD/DHM1
Review Completion Date	6/30/2021
Applicant	Jazz Pharmaceuticals
Established/Proper Name	asparaginase erwinia chrysanthemi (recombinant)-rywn
(Proposed) Trade Name	Rylaze
Pharmacologic Class	Asparagine-specific enzyme
Formulations	Injection (10 mg in 0.5 mL)
Applicant Proposed Indication/Population	As a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in adults and pediatric patients who have developed hypersensitivity or silent inactivation to E. coli-derived asparaginase.
Recommendation on Regulatory Action	Approval
Recommended Indication/Population	As a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in adults and pediatric patients 1 month or older who have developed hypersensitivity to E. coli-derived asparaginase.
SNOMED CT for the Recommended Indication/Population	413440007
Recommended Dosing Regimen	25 mg/m^2 every 48 hours

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GLOSSARY

AC	Advisory Committee
ADA	Antidrug Antibody
ADME	Absorption, Distribution, Metabolism, Excretion
AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
AESIs	Adverse Events of Special Interest
ACS	American Cancer Society
BLA	Biologics License Application
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
COA	Clinical Outcome Assessment
COG	Children's Oncology Group
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	Case Report Form
CRO	Contract Research Organization
CRT	Clinical Review Template
CSR	Clinical Study Report
CSS	Controlled Substance Staff
DCO	Data Cut-Off date
DDI	Drug-Drug interaction
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCTD	Electronic Common Technical Document
EFD	Embryofetal Development
ETASU	Elements To Assure Safe Use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FEED	Fertility and Early Embryonic Development
GCP	Good Clinical Practice

GD	Gestation Day
GLP	Good Laboratory Practice
GRMP	Good Review Management Practice
IA	Interim Analysis
IC	Informed Consent
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IM	Intramuscular
IND	Investigational New Drug
iPSP	Initial Pediatric Study Plan
IRB	Institutional Review Board
ISE	Integrated Summary of Effectiveness
ISS	Integrated Summary of Safety
ITT	Intent To Treat
IU	International Units
IV	Intravenous
LBL	Lymphoblastic Lymphoma
LD	Lactation Day
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent to Treat
MWF	Monday Wednesday Friday
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New Drug Application
NME	New Molecular Entity
NOAEL	No-Observed-Adverse-Effect Level
NSAA	Nadir Serum Asparaginase Activity
ObsRO	Observer Reported Outcome
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PerfO	Performance Outcome
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamics
PI	Prescribing Information
PK	Pharmacokinetics
PMC	Post Marketing Commitment
PMR	Post Marketing Requirement
PP	Per Protocol
PPI	Patient Package Insert
PPK	Population Pharmacokinetic

PPND	Pre- and Post-Natal Developmental
PREA	Pediatric Research Equity Act
PRO	Patient Reported Outcome
PSUR	Periodic Safety Update report
RCP	Recombinant Crisantaspace produced in *Pseudomonas Fluorescens*
REMS	Risk Evaluation and Mitigation Strategy
SAA	Serum Asparaginase Activity
SAE	Serious Adverse Event
SAC	Serum Asparaginase Concentration
SAP	Statistical Analysis Plan
SDRC	Study Data Review Committee
SGE	Special Government Employee
SOC	Standard of Care
SP	Species
$t_{1/2}$	Terminal Elimination Half-Life
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Figures, Listings
TK	Toxicokinetics
U	Units

1 EXECUTIVE SUMMARY

1.1. Product Introduction

Proposed Trade Name:	Rylaze®
Proper Name:	Asparaginase erwinia chrysanthemi (recombinant)-rywn
Also Known As:	JZP-458
Molecular Weight:	140 kDa
Dosage Forms:	Injection (10 mg)
Therapeutic Class:	Antineoplastic
Chemical Class:	Recombinant protein
Structure:	L-asparaginase homotetramer
Pharmacologic Class:	Asparagine-specific enzyme
Mechanism of Action:	Depletes L-asparagine by catalyzing conversion to aspartic acid and ammonia.

BLA 761179 for JZP-458 was submitted for the indication "as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in adults and pediatric patients who have developed hypersensitivity or silent inactivation to E. coli-derived asparaginase" using 25 mg /m^2 intramuscularly (IM) on Monday and Wednesday and 50 mg/m^2 on Friday for a total of six doses every 2 weeks to substitute for each planned dose of long-acting E. coli-derived asparaginase; and 25 mg /m^2 IM on Monday and Wednesday and 50 mg/m^2 on Friday for to substitute for native E. coli-derived asparaginase.

The review team recommends approval of JZP-458 "as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in adults and pediatric patients 1 month or older who have developed hypersensitivity to E. coli-derived asparaginase" under the provisions of Section 351(a) of the Public Health Service Act. The recommended dosage when replacing a long-acting asparaginase product is 25 mg/m^2 IM every 48 hours for the duration of asparaginase activity expected for that product.

The recommended regulatory action is based on the pharmacometric analysis and safety data in patients treated with JZP-458 by the intramuscular route in Study JZP458-201. Additional studies will be needed to determine a safe and effective dosage by the intravenous route and to characterize the incidence and impact of anti-drug antibodies.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Study JZP458-201 (NCT04145531) was an open-label, multicenter, sequential-cohort trial to determine the recommended dosage of JZP-458. Eligible patients had ALL or LBL and had developed hypersensitivity to or silent inactivation after treatment with E. coli-derived asparaginase as a component of a multi-agent chemotherapeutic regimen. A treatment course consisted of JZP-458 at various doses administered intramuscularly every Monday, Wednesday, and Friday for a total of 6 doses. The primary objective was to determine the efficacy defined as the last 72-hour nadir serum asparaginase activity (NSAA) level ≥ 0.1 U/mL during the first course. Achievement and maintenance of NSAA ≥ 0.1 U/mL correlates with depletion of CSF and serum asparagine, and it has been used as an established surrogate of effectiveness for asparaginase class products in combination with chemotherapy for first-line treatment of ALL, so the endpoint was acceptable to establish the appropriateness of dosing with up to 72 hours between administrations.

The planned sample size of 98 patients was calculated to provide 83% probability that the lower bound of the 95% Wald CI exceeds 90%, assuming a true response rate of 96% for the primary efficacy endpoint and a 5% drop out rate. There was one planned interim analysis with 51 patients. For the interim analysis, a sample size of 51 patients was calculated to provide 70% probability that the lower bound of the 95% CI exceeds 90% under the assumption of a 96% true response rate and a 5% drop out rate. Additionally, the probability of observing at least one AE related to asparaginase with an incidence as low as 3% is 79% with 51 patients.

As of the cutoff date for the data provided in the Day-60 Update, 102 patients were accrued, including 33 patients to Cohort 1A (JZP-458 at 25 mg/m^2 MWF x 6), 53 patients to Cohort 1B (JZP-458 at 37.5 mg/m^2 MWF x 6) and 16 patients to Cohort 1C (JZP-458 25-25-50 mg/m^2 MWF x 6). The median age was 10 years (range, 1 - 24 years); 57% were male and 43% were female; 73% were white, 12% were Black/African American, 5% were Asian, and 10% were of other or unknown race. Ninety-seven (94%) patients had experienced a hypersensitivity reaction to pegaspargase, and 6 patients (7%) had reported silent inactivation.

On the basis of the observed data, the objective of a 72-hour NSAA ≥ 0.1 U/mL in at least 90% of patients was not met in any of the three dosage cohorts. In Cohorts 1A and 1B, the point estimate for NSAA response was < 90%. In Cohort 1C, the point estimate for NSAA response was > 90%, but the lower bound of the 95% confidence interval did not meet the objective due to the small sample size. FDA developed a population pharmacokinetic (PopPK) model based on the observed SAA data from the study participants and used the model to test two different dosages in 2,000 virtual subjects in the Applicant's simulation dataset from the National Health and Nutrition Examination Survey (NHANES). The simulations projected that at least 90% of patients would achieve and maintain an NSAA ≥ 0.1 U/mL with JZP-458 at 25 mg/m^2 IM every 48 hours (93.6%; 95% CI 92.6% - 94.6%) or at 25-25-50 mg/m^2 MWF (91.4%; 95% CI 90.2% -

92.7%). The projected high rate of durable success with the high level of confidence (lower 95% CI bound > 90%) was considered substantial evidence of effectiveness.

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. • 10-20% of patients will develop hypersensitivity to available long-acting E. coli-derived asparaginase.	The outcomes for patients with ALL are improved with asparaginase.
Current Treatment Options	• An asparaginase product with a non-cross-reactive structure, such as from a different bacteria, would be an alternative treatment. • There are currently no asparaginase products available other than those derived from E. coli.	There is a need for an asparaginase product not derived from E. coli.
Benefit	• Persistent NSAA levels $\geq$ 0.1 U/mL correlate with clinical efficacy outcomes. • The PK of JZP-458 was studied in 102 patients with ALL treated with a multi-agent chemotherapy regimen. • The PopPK analyses and simulations showed that JZP-458 25 mg/m^2 IM every 48 hours would maintain an NSAA $\geq$ 0.1 U/mL in 93.6% (95% CI: 92.6% - 94.6%) of patients.	Adequate NSAA levels can be maintained using JZP-458 given at 25 mg/m^2 IM every 48 hours.
Risks and Risk Management	• Most common adverse reactions (incidence > 20%) are abnormal liver test, nausea, musculoskeletal pain, fatigue, infection, headache, pyrexia, drug hypersensitivity, febrile neutropenia, decreased appetite, stomatitis, bleeding, and hyperglycemia. • The clinical trials included specific monitoring to mitigate serious toxicities.	The safety profile of JZP-458 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 PopPK analyses and simulations in Study JZP458-201 showed that administration of JZP-458 at 25 mg/m^2 IM every 48 hours (48-hour dosing) or at 25-25-50 mg/m^2 MWF (MWF dosing) would maintain adequate NSAA levels. Although the MWF dosing would be more convenient, concerns were raised regarding the safety of the high dose of JZP-458 given on Fridays in the latter regimen. At the present time, there is no established biomarker for safety of asparaginase class products, so safety can be assessed only with clinical trial experience.

The adverse events of special interest (AESI) for JZP-458 included hepatotoxicity, hypersensitivity, pancreatitis, and thrombosis. In the exposure-safety analyses, there was a trend to earlier onset of hepatotoxicity with higher SAA average concentration (C_{mean}) up to

the first occurrence of the event, but this relationship was not found for the other AESI. Additionally, there were no correlations between PK exposures and incidence of the AESI. In the assessment of AESI by dose, there was a trend for earlier onset of hypersensitivity with the 37.5 mg/m^2 MWF regimen, but too few patients were studied with the 25-25-50 mg/m^2 MWF regimen for a credible analysis of hypersensitivity by dose. There was also a trend for earlier time to onset and a higher incidence numerically for pancreatitis with the 25-25-50 mg/m^2 MWF regimen. It is acknowledged that such trends are difficult to interpret with so few patients treated with the 25-25-50 mg/m^2 MWF regimen, but only empiric data with this regimen would resolve the uncertainty. As such, JZP-458 at 25 mg/m^2 IM every 48 hours is the recommended dose.

Although the recommended dosage was not itself tested in Study JZP458-201, the safety profile is not expected to differ substantially from that in Cohort 1A. The most common adverse reactions (incidence > 20%) of JZP-458 in that cohort were abnormal liver test, nausea, musculoskeletal pain, fatigue, infection, headache, pyrexia, drug hypersensitivity, febrile neutropenia, decreased appetite, stomatitis, bleeding, and hyperglycemia. Overall, the safety profile is similar to that of other asparaginase products, and no unexpected toxicities were encountered in Study JZP458-201. Of the AESI, hepatotoxicity was observed in 70%, drug hypersensitivity in 24%, pancreatitis in 12%, and thrombosis in none.

The incidences of hypersensitivity and pancreatitis are higher than those prespecified in the benchmarks accepted for the safety analysis, but it should be noted that the adverse event reporting plan and the criteria for case ascertainment differed between this analysis for Study JZP458-201 and that for the benchmarks, confounding interpretation of the results. Additionally, no data were available for assessment of anti-drug antibodies (ADA) and their possible correlation with drug hypersensitivity reactions. Hence, mitigation plans for the AESI are warranted until additional data are available, and labeling is considered adequate for this purpose.

The results of Study JZP458-201 suggest that JZP-458 is an appropriate alternative asparaginase therapy for ALL and LBL in adults and pediatric patients 1 month or older who have developed hypersensitivity to E. coli-derived asparaginase ALL. With the mitigation strategies in place, the potential benefits of JZP-458 outweigh the risks.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

X	Patient experience data were not submitted in the application.

2 THERAPEUTIC CONTEXT

2.1. Analysis of Condition

The Applicant's Position:

Acute lymphoblastic leukemia (ALL) is a malignant transformation and proliferation of immature lymphoid cells in the bone marrow, peripheral blood and other organs. The American Cancer Society (ACS) estimates that approximately 5,690 new cases of ALL will be diagnosed in 2021 in the US. The median age at diagnosis for ALL is 15 years, with 55.4% of patients diagnosed at younger than 20 years of age. In contrast, 28% of cases are diagnosed at 45 years or older and only approximately 12.3% of patients are diagnosed at 65 years or older. ALL represents 75 to 80% of acute leukemia's in children, making it the most common form of childhood leukemia; by contrast, ALL represents approximately 20% of all leukemia among adults. (NCCN Guidelines; ALL, version 2, 2020). The risk of developing ALL is highest in children younger than 5 years of age, after which the risk gradually decreases until approximately the mid-twenties, increasing slowly again after the age of 50 years (ACS 2021).

Lymphoblastic lymphoma (LBL) is a rare, fast-growing, aggressive subtype of Non-Hodgkin's lymphoma, most often seen in teenagers and young adults (Leukemia Foundation 2020). Lymphoblastic lymphoma is a cancer of immature lymphoblasts (Dana-Farber Cancer Institute 2021; ACS 2016). Approximately 25% of 30% of NHL in children in the US is due to LBL (ACS 2021).

Asparaginase is an important component of multi-agent chemotherapeutic regimen for the treatment of patients with ALL and LBL (Pui & Evans 2006; Stock 2008; Panosyan 2004). Treatment regimens, especially those including high doses of asparaginase, have significantly improved long-term, event-free survival, specifically in children with ALL (Pieters et al. 2011). The incremental survival benefit associated with asparaginase concomitantly with other chemotherapy has been estimated to be 15% to 20% (Sallan et al. 1983).

L-asparaginase hydrolyzes the nonessential amino acid, asparagine, into aspartic acid and ammonia, thus depleting the circulating pool of serum asparagine (Pieters 2011). It is believed that the depletion of plasma levels of L-asparagine by L-asparaginase selectively kills cancer cells, leaving normal cells unaffected. Serum asparaginase activity levels serve as a surrogate marker for asparagine depletion, and NSAA levels ≥ 0.1 IU/mL is an accepted threshold to provide adequate asparagine depletion in clinical practice (Asselin and Rizzari 2015; Pieters 2011, van der Sluis 2016).

Most asparaginase products approved for treatment of ALL are derived from *E. coli*. Because of their bacterial origin, asparaginases are highly allergenic and immunogenic. The most common toxicity of *E. coli*-derived asparaginases is hypersensitivity, which can manifest as allergic reactions or as "silent inactivation." Several studies indicate that switching patients who

develop clinical hypersensitivity or silent inactivation to *E. coli*-derived asparaginase to alternative non-*E. coli*-derived preparations can maintain outcomes when adequate asparagine depletion is achieved (Panosyan 2004; Vrooman 2010; Woo 2000). Monitoring of asparaginase activity and switching asparaginase preparations in the event of clinical allergy or silent inactivation is therefore strongly recommended by experts and included in many of the US and European ALL treatment protocols (van der Sluis 2016).

Hypersensitivity or silent inactivation to *E.coli*-derived treatments results in reduced effectiveness of the treatment. Studies indicate that switching patients who develop clinical hypersensitivity or silent inactivation to *E. coli*-derived asparaginase to alternative non-*E. coli*-derived preparations can maintain outcomes when adequate asparagine depletion is achieved (Panosyan 2004; Vrooman 2010; Woo 2000). Recent investigations have shown that ALL patients who fail to complete their prescribed asparaginase therapy for any reason have significant inferior survival compared with those who receive all of their planned asparaginase doses (Silverman 2001; Gupta et al, JCO, 2020). This emphasizes the importance of completing planned asparaginase therapy.

Thus, patients with hypersensitivity or silent inactivation to an *E. coli*-derived asparaginase have a critical unmet need for an immunologically distinct asparaginase product that will allow them to continue and complete their optimal treatment plan.

The FDA's Assessment:
The FDA agrees that asparaginase is an important component of multi-agent chemotherapy for patients with ALL or LBL.

2.2. Analysis of Current Treatment Options

Monitoring of asparaginase activity and switching asparaginase preparations in the event of clinical allergy or silent inactivation is strongly recommended by experts and is included in many of the US ALL treatment protocols (van der Sluis 2016).

The L-asparaginase derived from Erwinia chrysanthemi, which lacks cross-reactivity with the *E. coli* preparation, is an approved treatment option for patients with hypersensitivity reactions to *E. coli*-derived asparaginase.

Erwinaze (asparaginase Erwinia chrysanthemi) is currently the only FDA-approved asparaginase indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to *E. coli*-derived asparaginase. It is administered IV or IM on a Monday/Wednesday/Friday schedule over two weeks, with patients receiving 25,000 IU/m^2 of Erwinaze for each dose.
A recombinant crisantaspase (such as JZP-458) with no immunological cross-reactivity to *E. coli*-derived asparaginase, would address the significant current medical need for patients with ALL/ LBL, who have developed hypersensitivity or silent inactivation to *E. coli*–derived asparaginase

and who otherwise might not be able to receive their complete asparagine depleting therapy. This current unmet meet is largely, but not exclusively, to be found in the pediatric age range, since ALL/LBL occurs commonly in the pediatric age range. Because of the outages of the current sole non-*E. coli* asparaginases, this patient need is urgent and has driven the accelerated development of JZP-458.

In addition real world data indicate that with the licensed dose of Erwinaze, 15% to 20% of patients are not achieving SAA levels ≥ 0.1 IU/mL at 72 hours (Vrooman 2010; Panetta 2020; Salzer 2013) and it has been concluded that higher doses of Erwinaze would likely be needed to maintain NSAA levels ≥ 0.1 IU/mL over the 72-hour interval (ASCO poster 2015). Therefore, the applicant has investigated a dosing regimen for JZP-458, which would provide optimal benefit over 48-and 72-hour dosing durations with acceptable safety to allow for MWF dosing in line with current treatment practice.

The Applicant's Position:
ALL/LBL are serious and life-threatening conditions for which asparaginases have been critical in the treatment of these diseases and associated with survival benefit.

JZP-458, recombinant crisantaspase produced in *Pseudomonas fluorescens* (also known as RC-P) has the identical amino acid sequence to native *Erwinia* asparaginase and has been formulated to ensure stability and bioavailability after intramuscular (IM) and intravenous (IV) injection.

JZP-458 is the first recombinant *Erwinia*-based asparaginase intended as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in adults and pediatric patients who have developed hypersensitivity or silent inactivation to *E. coli*-derived asparaginase. Jazz has developed JZP-458 with a dose and dosing regimen, to ensure consistent maintenance of therapeutic SAA levels both at 48-hours and 72-hours.

Due to the unmet medical need that currently exists and is expected to persist for patients who have developed hypersensitivity or silent inactivation to an *E.coli*-derived asparaginase, FDA and the Applicant have been working collaboratively on an appropriate path forward to develop JZP-458 that will support patients as quickly as possible.

The FDA's Assessment:
The FDA agrees that Erwinaze is the only drug approved for patients with ALL or LBL and hypersensitivity to E. coli-derived asparaginase. There are no other drugs used off-label for this indication.

3 REGULATORY BACKGROUND

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
JZP-458 is being submitted for review with BLA number 761179. The BLA is being reviewed under the FDA OCE RTOR pilot program. JZP-458 is not yet marketed in the US or any other country. There is no post-marketing experience.

The FDA's Assessment:
The FDA agrees that JZP-458 is not yet marketed in the US or any other country.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
Applicant has studied JZP-458 with several dosing regimens to meet both 48-hour NSAA levels and 72-hour NSAA levels and to ensure consistent maintenance of the NSAA level at a therapeutic threshold associated with known clinical benefit for the entire duration of treatment. The preferred proposed dosing regimen with a supporting positive benefit risk profile is 25/25/50 mg/m^2.

Ahead of the full development program (including the phase 1 clinical study), Jazz studied the analytical comparability of JZP-458 and Erwinaze. The data obtained demonstrated that JZP-458 and Erwinaze were highly similar proteins in primary structure.

Serum asparaginase activity levels serve as a surrogate marker for asparagine depletion, and NSAA levels ≥ 0.1 IU/mL are the accepted threshold to demonstrate adequate asparagine depletion in clinical practice. Based on the initial phase 1 study data and PPK modeling and simulations, JZP-458 at the IM dose of 25 mg/m^2 and IV dose of 37.5 mg/m^2 is expected to achieve 72-hour NSAA levels ≥ 0.1 IU/mL in 100% of adult or pediatric populations after IM administration, and 80.9% in adult or 94.5% in pediatric populations after IV administration. Therefore, based on the totality of the safety and PK data in this phase 1 study, in agreement with FDA, the recommended phase 2/3 starting dose for the IM route of administration was 25 mg/m^2.

Subjects began to enroll at a dose of 25 mg/m^2 (MWF) beginning in late December of 2019. The dose was later increased to 37.5 mg/$m^{2,}$ (MWF) in a new cohort which enrolled until November 2020.

As agreed with the FDA during the November 6, 2020 Type A meeting, the efficacy and safety results from the initial 2 dose groups of 25 and 37.5 mg/m^2 (Cohorts 1a and 1b) given 3 times/week IM on a Monday-Wednesday-Friday (MWF) schedule in Study JZP458-201 were adequate to support initiation of the BLA with a dosing regimen of 25 mg/m^2 administered every 48-hours. Also, preliminary PPK model using data from 25 and 37.5 mg/m^2 (Cohorts 1a (N = 30) and 1b (N = 32)) predicted that the optimal dose to support a MWF dosing regimen would be a dose of 25/25/50 mg/m^2 administered on MWF for a total of 6 doses to replace every dose

of long-acting *E.coli* asparaginase. Following agreement with the Agency on this approach, and enabled through protocol amendment 2, Cohort 1c was initiated, evaluating a dose of 25 mg/m^2 on Monday/Wednesday and 50mg/m^2 on a Friday in November 2020.

Efficacy and safety of JZP-458 is demonstrated by the totality of data observed at the different dose levels tested, and includes observed nadir serum asparaginase activity (NSAA) data at the protocol-specified time points, population pharmacokinetic (PPK) modeling and simulation results, asparagine depletion data, asparaginase enzyme content data, available immunogenicity data, adverse events (AEs), and clinical laboratory results. Based on agreement with the FDA, the Applicant began the submissions for JZP-458 BLA (761179) in December of 2020 based on the data cut-off date of October 14 2020 (25 and 37.5 mg/m^2, Cohort 1a and 1b) with the BLA submission components identified on an agreed RTOR rolling submission schedule. Also based on this agreement with FDA, the applicant will submit data from Cohort 1c to the BLA in support of MWF dosing at dose of 25/25/50 mg/m^2. In parallel, Applicant continued to correspond with FDA on BLA Information Requests and the continuing development program under the IND 129622.

A summary of key pre-submission interactions with the FDA regarding JZP-458 development is provided in Applicant Table 1.

Applicant Table 1: Major Regulatory Milestones for JZP-458 Development in Relation to JZP458-201

Milestone	Date	Description
Type B Pre-IND meeting	May 17, 2016	Feedback received from FDA on the clinical, nonclinical and Quality(CMC) plan for IND filling. Agreement from the agency on the Nonclinical package that consists of publically available data on asparaginase in addition to Applicant sponsored nonclinical studies to support BLA.
Type A Meeting with FDA (Clinical)	Sept 14, 2018	Pre-IND Meeting to agree on the proposed Phase 1 clinical program and CMC program to support BLA.
Type A EOP1 Meeting with FDA	July 9, 2019	EOP1 Meeting to agree on the proposed Phase 2/3 clinical program to support the BLA.
Orphan Drug Designation	July 24, 2020	Designation under review as of March 15, 2020.
Fast Track Designation	Oct 24, 2019	Fast Track Designation Granted for JZP-458.
Pediatric Study Plan	April 21, 2020	FDA agreement on the proposed Pediatric Study Plan (iPSP).

Rare Pediatric Disease Designation Request	Sept 23, 2020	Rare Pediatric Disease Product Designation Granted.
Type A Meeting with FDA (Clinical)	Nov 6, 2020	FDA agreement that based on the totality of the data from Part A IM Cohort 1 (25mg/m^2 and 37.5mg/m^2),-efficacy and safety data of JZP-458 using NSAA data at the protocol specified time points, population pharmacokinetic (PPK) modeling and simulation results, asparagine depletion data, asparaginase enzyme content data, available immunogenicity data, adverse events (AEs), and clinical laboratory results could be submitted in support of a BLA for JZP458.
BLA filling	Dec 18, 2020	BLA 761179 for JZP-458 was initiated under the RTOR pathway on December 18, 2020. The sponsor is seeking full (regular) approval for this application.
Pre-BLA meeting	Mar 29, 2021	Meeting to gain agreement on the complete BLA package required to support proposed dosing regimen

The FDA's Assessment:

In general, FDA agrees with the listing of events above with the following exceptions and/or additions:

- Orphan Designation (DRU-1986-151, Jazz Pharmaceuticals, Inc.) for AEC was granted on July 30, 1986, for "Treatment of acute lymphocytic leukemia." The Office of Orphan Product Development acknowledged the evolution of the diagnosis terminology over time and confirmed that the designation applies to the current WHO classification of lymphoblastic leukemia/lymphoma, which include acute lymphoblastic leukemia and lymphoblastic lymphoma in the vernacular.[1]
- Orphan Drug Designation DRU-1986-151 for AEC was subsequently withdrawn by the Applicant on May 10, 2021.
- Orphan Designation (DRU-2020-7734, Jazz Pharmaceuticals, Inc.) for AEC was granted on June 22, 2021, for "Treatment of pediatric and adult patients with acute lymphoblastic leukemia (ALL) /Lymphoblastic lymphoma (LBL) who have developed hypersensitivity to E. coli derived asparaginase treatment."

Key advice for the clinical development relevant to this supplement included:

[1] IND 129622 Memorandum to File dated 3/24/2021

- The pivotal trial should be open to patients of all ages and not limited to children.
- In order to support a 72-hour interval for dosing, the pivotal study should demonstrate that the 72-hour NSAA should be at least 0.1 IU/mL for at least 90% of patients as determined by the lower bound of the confidence interval.
- To accelerate dose selection, the Applicant should consider an interim PK analysis and adjustment of the dose based on data emerging during the trial.
- A sufficient number of patients must be enrolled at the recommended dosage to exclude a clinically meaningful increase in risks of adverse events of special interest.

The submission of BLA 761179 was completed on April 30, 2021.

- On May 20, 2021, the Applicant notified FDA by email that, in view of the expedited timeline for review of this submission, the Applicant would forgo "procedural mid-cycle and late-cycle meetings for ad hoc meetings as needed".
- An agreed-upon late update was received on May 21, 2021.
- An ad hoc meeting was held on June 10, 2021, to update the Applicant on the review. The agenda included the issues with the safety data needed to support the proposed dosage, the issues to date that would warrant a PMR, the deficiencies in the immunogenicity data, and the additional information needed for Module 3.

4 SIGNIFICANT ISSUES FROM OTHER REVIEW DISCIPLINES PERTINENT TO CLINICAL CONCLUSIONS ON EFFICACY AND SAFETY

4.1. Office of Scientific Investigations (OSI)

As there were no clinical efficacy endpoints to assess, no inspections of the clinical sites were requested. Due to recent inspection history, no additional inspection of the Applicant was considered necessary.

The Office of Study Integrity and Surveillance (OSIS) was also consulted. They noted an inspection of (b) (4) that had a final classification of NAI and indicated that further inspection was not warranted.

During (b) (4), OSIS also conduction a remote record review for (b) (4) where the PK, PD and immunogenicity assays were performed. They identified objectional issues that impacted the reliability of the immunogenicity and serum asparaginase content assays.

4.2. Product Quality

Asparaginase erwinia chrysanthemi (recombinant)-rywn drug substance is produced by fermentation of a genetically engineered *Pseudomonas fluorescens* bacteria containing the DNA which encodes for the L-asparaginase from *Erwinia chrysanthemi*. It is comprised of *Erwinia chrysanthemi* L-asparaginase homotetramers with a molecular mass of 140 kDa. The amino acid sequence, structure, and physiochemical properties of the enzyme are consistent with those of the native *Erwinia chrysanthemi*-derived asparaginase (also known as crisantaspase). The activity of asparaginase erwinia chrysanthemi (recombinant)-rywn is expressed in units, defined as the amount of enzyme that catalyzes the conversion of 1 µmol of L-asparagine per reaction minute, per mg of protein.

Rylaze (asparaginase erwinia chrysanthemi (recombinant)-rywn) injection drug product is supplied as a sterile, clear to opalescent, colorless to slightly yellow, preservative-free solution for intramuscular injection. Each 0.5 mL contains 10 mg asparaginase erwinia chrysanthemi (recombinant)-rywn and the following inactive ingredients: polysorbate 80 (0.1 mg), sodium chloride (1.5 mg), sodium phosphate dibasic anhydrous (0.8 mg), sodium phosphate monobasic monohydrate (0.6 mg), and trehalose (32.1 mg). Sodium hydroxide may be added to adjust the pH. The pH is approximately 7.

The Rylaze drug product vials require storage refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Once drawn into a syringe, If needed, the syringe(s) may be stored at room temperature (15°C to 25°C [59°F to 77°F]) or refrigerated at 2°C to 8°C (36°F to 46°F) for up to 4 hours.

The Immunogenicity Reviewer found that the immunogenicity assays were not sufficiently sensitive to detect anti-JZP-458 antibodies in presence of the expected level of JZP-458 in serum. However, the reviewer did not consider this finding to be an approvability issue given the acceptable safety profile and lack of actionable information based on ADA status.

The OPQ review team noted that the data submitted in this application were adequate to support the conclusion that the manufacture of asparaginase erwinia chrysanthemi (recombinant)-rywn is well-controlled and leads to a product that is pure and potent. They recommended approval of the BLA and agreed with the request for categorical exclusion under 21 CFR 25.31 (c) from preparation of an environmental assessment or an environmental impact statement. They also indicated that additional studies would be needed to complete development of the ADA assays if needed for assessment of the impact of ADA on activity of Rylaze in patients.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

There was no companion device or diagnostic included in this application.

5 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

5.1. Executive Summary

JZP-458 is an *Erwinia chrysanthemi* asparaginase produced recombinantly in a *Pseudomonas fluorescens* expression system. The amino acid sequence of JZP-458 is identical to native *Erwinia chrysanthemi* asparaginase (Erwinaze), and the Applicant conducted analytical comparability studies comparing JZP-458 and Erwinaze. Except as specifically identified, all nonclinical data and information discussed below and necessary for approval of BLA 761179 are owned by Jazz Pharmaceuticals or are data for which Jazz Pharmaceuticals has a right of reference. Any information or data that the Applicant does not own or have a written right to reference is for descriptive purposes only and is not relied upon for approval of this BLA.

Asparaginases are enzymes that hydrolyze asparagine into aspartic acid and ammonia. In biochemical assays, the enzymatic activity of JZP-458 (658-663 U/mg) was comparable to Erwinaze (610 U/mg). The antitumor activity of asparaginases is attributed to the depletion of asparagine in tumor cells. The in vitro cytotoxic activity of JZP-458 was evaluated in a panel of eight leukemia or lymphoma cell lines. All cell lines were sensitive to JZP-458 with IC_{50} values of 0.2-60 mU/mL. No secondary pharmacology or safety pharmacology studies were conducted with JZP-458.

The pharmacokinetics (PK) of JZP-458 were evaluated in single-dose PK studies in mice and rats, and as endpoints in the 2-week repeat-dose toxicology study in rats. Newly conducted studies, i.e. those conducted with JZP-458, used intravenous (IV) injection in animals. Several studies conducted with Erwinaze used intramuscular (IM) injection in animals. The proposed clinical route of administration is IM injection. In the single-dose PK studies with JZP-458, the terminal elimination half-life ($t_{1/2}$) in mice and rats was 2.1 hours and 1.4 hours, respectively. In the 2-week repeat-dose toxicology study with JZP-458 in rats, anti-drug antibodies (ADAs) were observed in some animals, but exposure (C_{max} and AUC_{0-t}) was similar on Days 1 and 14. PK parameters were inferred from serum asparaginase activity (SAA). There were different activity assays for JZP-458 in mice, rats, and rabbits, and for Erwinaze in rats. SAA was determined in each of the studies, but direct comparison across studies should be avoided due to the lack of a universally accepted and validated specific activity assay.

Rats are a pharmacologically relevant species to assess the toxicology of asparaginases, and JZP-458 was evaluated in a 2-week repeat-dose toxicology study in rats. JZP-458 was

administered once daily by the IV route and was not tolerated at the high dose level (30,000 U/kg/day). Rats at the high dose level demonstrated body weight loss and other adverse clinical signs (piloerection, rough haircoat, red skin of the feet, and clear oral discharge) and were prematurely sacrificed in a moribund condition. Histopathological examination of early decedents identified decreased cellularity of the marrow in the femur, myocardial necrosis and hemorrhage in the heart, submucosal edema or abscess and epithelial hyperplasia in the nonglandular stomach, and erosion/ulcer of the stomach or duodenum. There were no adverse findings at the ≤10,000 U/kg/day dose levels. The toxicologic profile of JZP-458 was consistent with that observed for other asparaginases in publicly available toxicology studies.

Reproductive and developmental toxicology studies conducted with Erwinaze were submitted to BLA 761179. Toxicology studies conducted with Erwinaze are relevant to JZP-458 because the Applicant conducted analytical comparability studies comparing JZP-458 and Erwinaze. These studies include a fertility and early embryonic development (FEED) study in rats, embryofetal development toxicity (EFD) studies in rats and rabbits, and a pre- and post-natal developmental (PPND) study in rats. There were no adverse observations in the FEED study, and findings in the EFD study in rats were limited to a slight increase in partially undescended fetal thymic tissue at the high-dose level (2000 IU/kg). The results of the FEED and rat EFD studies should be interpreted with caution due to the formation of neutralizing ADAs. In the EFD study in rabbits, there were maternal effects (body weight changes, post-implantation loss, and decreases in live fetuses) at the 40 IU/kg dose level, decreased gravid uterine weights at the ≥25 IU/kg dose levels, and fetal effects (visceral and skeletal observations) at the ≥10 IU/kg dose levels. The adverse effects in rabbits were observed despite the formation of neutralizing ADAs. There were no adverse observations in the PPND study; ADAs and PK parameters were not measured in this study. Due to the clear findings for Erwinaze in the EFD study in rabbits, JZP-458 should be considered a reproductive and developmental toxicant; these risks will be described in the product label for JZP-458.

Due to the potential for JZP-458 to cause fetal harm, the use of effective contraception is recommended for female patients of reproductive potential while receiving JZP-458 and for 3 months after the last dose. The recommendation for the duration of contraception use is mainly for consistency across asparaginase products.

There are no data on the presence of JZP-458 in human milk, the effects on the breastfed child, or on milk production. Because of the potential for serious adverse events in the breastfed child, the product label for JZP-458 recommends women to avoid breastfeeding during treatment with JZP-458 and for 1 week after the last dose. The recommendation for the duration to avoid breastfeeding is based on the plasma $t_{1/2}$ of JZP-458, rounded up to 1 week.

The nonclinical pharmacology, PK, and toxicology data submitted to BLA 761179, along with the clinical experience with approved asparaginases, are adequate to support the approval of JZP-

458 for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:
No other registration applications are being referenced in BLA 761179.

The FDA's Assessment:
We agree that no other applications are being referenced to support the approval of BLA 761179. Results of several animal studies conducted with Erwinaze were submitted to this BLA. Thus, the JZP-458 nonclinical development program relies on nonclinical studies conducted with JZP-458 and Erwinaze.

5.3. Pharmacology

Primary pharmacology

The FDA's Assessment:
The enzymatic activity of JZP-458 was evaluated in vitro using Nessler's reagent. JZP-458 catalyzed the conversion of asparagine into aspartic acid and ammonia (658-663 U/mg); the enzymatic activity of JZP-458 was comparable to the enzymatic activity of Erwinaze (610 U/mg).

The effect of JZP-458 on the viability of eight leukemia or lymphoma cell lines was evaluated in vitro. Cells were cultured in multiwell plates under standard conditions and incubated with a dilution series of JZP-458 or vehicle control for 72 hours. Cell proliferation was evaluated with a commercially-available luminescence assay. JZP-458 negatively impacted the viability of each cell line tested (see FDA Table 2).

FDA Table 2: Effect of JZP-458 on the viability of various leukemia or lymphoma cell lines

Cell line	IC_{50} (mU/mL)	Max effect (%)
CCRF-CEM	0.6	48
CTV-1	18	100
HSB-2	1.1	46
JM1	20	90
Jurkat E6.1	60	100
MOLT-4	0.3	79
RS4-11	0.2	91
SUP-T1	18	99

Secondary Pharmacology

The Applicant's Position:

Based on the demonstrated analytical comparability between JZP-458 and Erwinaze the secondary pharmacology of JZP-458 is expected to be similar to that of Erwinaze. Data from the published literature on the secondary pharmacology of Erwinia asparaginases are referenced in this BLA application for JZP-458. In agreement with FDA, no new secondary pharmacology studies were required. Applicant believes that the secondary pharmacology is adequately supported by the nonclinical data package presented in BLA.

The FDA's Assessment:
We agree that no secondary pharmacology studies were conducted or are needed to support the approval of BLA 761179. The approval of BLA 761179 does not rely on product-specific published literature or any BLA.

Safety Pharmacology

No safety pharmacology data were identified in the published literature on the safety pharmacology of *Erwinia* asparaginases. In agreement with FDA, no new safety pharmacology studies were required. Applicant believes that the safety pharmacology is adequately supported by the known safety profile of asparaginases in oncology patients as well as long-standing clinical use of asparaginases.

The FDA's Assessment:
We agree that no safety pharmacology studies were conducted or are needed to support the approval of BLA 761179. The approval of BLA 761179 does not rely on product-specific published literature.

5.4. ADME/PK

The Applicant's Position:
The pharmacokinetics of JZP-458 were evaluated in two non-GLP, single dose PK studies in rodents sponsored by the Applicant, study number (b) (4)-350510 and 2018-416-039. It is also supported by published literature on *Erwinia* asparaginases in multiple nonclinical species.

JZP-458 was studied in a single-dose PK study in mice after IV administration (Study (b) (4)-350510); the $t_{1/2}$ in mice was 2.13 hours. A single-dose PK study of JZP-458 was also conducted in rats after IV administration (Study 2018-416-039); the $t_{1/2}$ in rats was 1.35 hours. Volume of distribution values determined for JZP-458 from these two studies are approximately the same as the plasma volume in mouse and rat, suggesting that JZP-458 is mostly confined to the central vascular compartment.

The PK of JZP-458 were determined to be consistent with that of *Erwinia* asparaginase in preclinical species; $t_{1/2}$ determined for JZP-458 in mouse and rat were consistent with data from *Erwinia* asparaginases or *Erwinia cartovora* L-asparaginase.

The FDA's Assessment:
We have additional comments on the studies mentioned above and have reviewed additional

PK data from the general toxicology study in rats. Dosages were based on the specific activity of the asparaginases and reported in International Units (IU) or Units (U); however, there is no universally accepted and validated specific activity assay, and direct comparison across studies should be avoided.

In the two single-dose PK studies in mice and rats, JZP-458 (250 U/kg) was administered by the IV route, while the proposed clinical routes of administration are IV or IM. The C_{max} and AUC_{0-t} in mice were 2,830 U/L and 12,200 U*hr/L, respectively. The C_{max} and AUC_{0-t} in rats were 11,800 mIU/mL and 25,400 mIU*hr/mL, respectively.

TK data from general toxicology studies

The toxicokinetics (TK) of JZP-458 were evaluated in the 2-week toxicology study in rats. In this study, JZP-458 was referred to Recombinant Crisantaspase expressed in *Pseudomonas fluorescens* (RC-P). There were no sex-related differences. ADAs were observed in some animals, but the exposure in surviving animals was similar on Days 1 and 14.

A Good Laboratory Practices (GLP) 2-Week Intravenous Infusion Toxicity and Toxicokinetic Study of Recombinant Crisantaspase expressed in *Pseudomonas fluorescens* (RC-P) in Rats with a 2-Week Recovery Phase (Study/Report No. 8399210)

Summary of JZP-458 TK parameters inferred from SAA

Dose of JZP-458	C_{max} (mIU/mL)		AUC_{0-24h} (h*mIU/mL)		$t_{1/2}$ (h)	
	M	F	M	F	M	F
Day 1						
3,000 U/kg/day (4.6 mg/kg/day)	22,200	21,900	80,800	89,600	2.51	2.66
10,000 U/kg/day (15.2 mg/kg/day)	83,100	103,000	409,000	512,000	3.09	2.24
30,000 U/kg/day (45.6 mg/kg/day)	293,000	251,000	1,740,000	1,400,000	2.35	2.54
Day 14						
3,000 U/kg/day (4.6 mg/kg/day)	26,400	24,100	81,800	76,000	2.48	2.56
10,000 U/kg/day (15.2 mg/kg/day)	82,900	74,900	321,000	322,000	4.63	2.57
30,000 U/kg/day (45.6 mg/kg/day) [#]	-	-	-	-	-	-

C_{max} = maximum observed SAA; AUC_{0-24h} = area under concentration-time curve from time 0 to 24 hours; [#] animals at 30,000 U/kg/day (4.56 mg/kg/day) were euthanized on Day 6

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position

A 2-week GLP toxicity and toxicokinetic study in rats was conducted with JZP-458 (study number 2018-458-032). Additionally, available data from acute and repeat dose toxicity studies with *Erwinia sp*. asparaginases and reproductive and developmental toxicity studies with the native crisantaspase are referenced in the BLA.

In acute and repeated dose toxicity studies with *Erwinia sp*. asparaginases in rats, hamsters, rabbits and monkeys, principal findings included body weight loss, changes in clinical chemistry (electrolytes, blood urea nitrogen [BUN], glucose, creatinine, liver enzymes, triglycerides, lipids), hematology (decreases in erythroid elements and white blood cell counts), and histopathology (hepatocellular vacuolation, bone marrow hypoplasia, increase in oxyphil cells in the parathyroid). At high doses, additional observations in early decedents included muscle weakness, ataxia, tremors, and convulsions (b) (4)-69-00, (b) (4)-71-01, (b) (4)-71-02, (b) (4)-72-05, (b) (4)-72-05).

Similar observations were noted in a 2-week GLP-compliant toxicity and toxicokinetic study with JZP-458 in rats (2018-458-032). Animals receiving 30,000 U/kg/day IV did not survive to their scheduled sacrifice and presented with significant decreases in blood counts, hypocellularity of the femoral bone marrow, thymus and spleen, and decreased extramedullary hematopoiesis. Increased blood glucose and secretory depletion in the pancreas were noted as well, along with serum chemistry (proteins, calcium) and pathology findings in the liver, lungs, gastrointestinal tract, and heart. Based on the observations in recovery animals, these findings appeared to be reversible. There were no adverse findings at ≤ 10,000 U/kg/day, and therefore this dose was considered the no-observed-adverse-effect level (NOAEL). Antidrug antibody (ADA) formation was observed in a number of animals but exposure, as assessed by serum asparaginase activity (SAA), was generally similar between Day 1 and Day 14 at 3,000 and 10,000 U/kg/day (Day 14 data are not available at 30,000 U/kg/day). The toxicology studies with JZP-458 in addition to available literature adequately support a full assessment of the non-clinical profile of JZP-458.

The FDA's Assessment:
In the 2-week toxicology study in rats, JZP-458 was administered by the IV route, while the proposed clinical route of administration is IM. There were no JZP-458-related findings at the IV infusion sites. We agree with the Applicant's overall conclusions for the 2-week toxicology study in rats. In the 2-week toxicology study in rats, the toxicologic profile of JZP-458 was consistent with that observed for other asparaginases in publicly available toxicology studies; however, the approval of BLA 761179 does not rely on the results of the publicly available studies.

5.5.2. Genetic Toxicology

The Applicant's Position:
Genotoxicity studies are not warranted for biotechnology-derived oncology products and were

not performed with JZP-458.

The FDA's Assessment:
Per ICH S6, we agree that genotoxicity studies are not needed to support the approval of BLA 761179.

5.5.3. Carcinogenicity

The Applicant's Position:
Carcinogenicity studies are not warranted for biotechnology-derived oncology products and were not performed with JZP-458.

The FDA's Assessment:
We agree that carcinogenicity studies are not needed to support the approval of BLA 761179.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:
Reproductive and developmental toxicology were not performed with JZP-458. GLP-compliant applicant-sponsored nonclinical studies conducted with the native *Erwinia chrysantemi* asparaginase are referenced in the BLA.

In a GLP-compliant fertility and early embryonic development study in rats, there was a decrease in sperm count in males, but no effects on fertility parameters were noted at any doses. The NOAEL for systemic and fertility effects in both male and female rats was 2000 IU/kg IM when given every other day (QOD) (11-4368).

In a GLP-compliant embryofetal toxicity study in rats, the NOAEL for maternal effects was 1000 IU/kg IM QOD due to decreases in body weights and food consumption at 2000 IU/kg IM QOD. There were no gross external, visceral, or skeletal malformations observed in the offspring. Based on the slight increase in partially undescended thymic tissue in the 2000 IU/kg dose group, the NOAEL for developmental effects was also considered to be 1000 IU/kg IM QOD. There were no effects on the reproductive parameters and thus the corresponding NOAEL was 2000 IU/kg IM QOD (11-4370).

In a GLP embryofetal toxicity study in rabbits, the NOAEL for maternal effects was 10 IU/kg IM QOD due to decreases in body weights and food consumption observed at higher doses. There were no gross external, visceral, or skeletal malformations observed in the offspring. However, a NOAEL for reproductive or fetal effects could be determined due to increased resorptions and post-implantation loss, fewer live fetuses, decreased gravid uterine and fetal/litter weights,

increased fetal visceral abnormalities, and delays in fetal skeletal ossification at all doses (11-4372).

In a GLP-compliant pre- and postnatal developmental toxicity study in rats, there were no effects on gestation, delivery, viability and lactation indices, pup body weight or clinical signs during and after the lactation period. Therefore, the NOAEL for maternal effects and effects in offspring (pre and postnatal development) were 2400 IU/kg IM QOD (11-4373).

Although there were no effects on the reproductive parameters or significant fetal observations in reproductive and developmental toxicity studies in rats, the presence of neutralizing ADAs in the majority of animals complicates the interpretation of these studies. Nevertheless, despite the presence of ADAs, there were clear findings in the rabbit developmental toxicity study.

Therefore, JZP-458 should be considered a potential reproductive and developmental toxicant.

The FDA's Assessment:
Reproductive and developmental toxicology studies conducted with Erwinaze were submitted to BLA 761179. Toxicology studies conducted with Erwinaze are relevant to JZP-458 because the Applicant conducted analytical comparability studies comparing JZP-458 and Erwinaze.

We agree with the Applicant's overall conclusions for the reproductive and developmental toxicology studies. We have further reviewed these studies. The reproductive and developmental toxicology studies were conducted by the IM route; there were no adverse local tolerance findings.

Embryo-fetal toxicity was observed at all dose levels in the embryofetal toxicity study in rabbits. The Applicant's Position contains a typographical error stating no reproductive or fetal effects were observed in rabbits.

Fertility and Early Embryonic Development
Erwinaze: An intramuscular study of fertility and early embryonic development to implantation in rats / study number 11-4368

Key study findings

- No toxicologically significant fertility or early embryonic developmental effects were observed in this study.
- The development of ADAs (including those capable of neutralizing asparaginase activity) were detected in asparaginase *Erwinia chrysanthemi*-treated rats.

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 500, 1000, or 2000 IU/kg (0, 3000, 6000, or 12000 IU/m^2) Animals were dosed every other day. For males and satellite females, dosing started on Day 1 and ended on Day 73 for males and Day 71 for satellite females. Dosing for females started two weeks prior to pairing for mating (Day 1), was continued throughout cohabitation/mating period (maximum duration 3 weeks), and continued until presumed gestation day (GD) 6 (inclusively).
Route of administration:	IM injection
Formulation/Vehicle:	Preservative free physiological saline (0.9%), USP
Species/Strain:	Rat/Crl:CD (SD)
Number/Sex/Group:	22/sex/group
Satellite groups:	TK and immunogenicity: 0, 500, 1000, or 2000 IU/kg (0, 3000, 6000, or 12000 IU/m^2)
Study design:	Main study: males treated with vehicle or asparaginase *Erwinia chrysanthemi* every other day for 4 weeks prior to pairing were paired with females treated with vehicle or asparaginase *Erwinia chrysanthemi* every other day for 2 weeks prior to pairing. Cesarean section was performed on GD 14. TK and ADA animals were dosed every other day from Study Days 1 to 71. TK samples were taken on Day 1 and at termination of dosing. ADA samples were taken pretest and at termination.
Parameters and endpoints evaluated:	Males and females: clinical signs (cageside and detailed), body weights, food consumption, mating index, copulatory interval, fertility index, TK, immunogenicity/neutralizing antibodies, necropsy, and organ weights. Females only: estrous cycle determination, corpora lutea, viable embryos, resorptions, total implantations, and % pre- and % post-implantation loss.

Deviation from study protocol affecting interpretation of results: No

Observations and results

Parameters	Major findings
Mortality	Males and females: there were no asparaginase *Erwinia chrysanthemi*-related mortalities
Clinical signs	Males and females: there were no asparaginase *Erwinia chrysanthemi*-related clinical observations
Body weights	Males and females: unremarkable
Food consumption	Males and females: unremarkable
Estrous cycle, mating, and fertility indices	Males and females: unremarkable

Estrous cycle data from rats

Endpoint	Dose level (IU/kg every other day)			
	0	500	1000	2000
Number of animals examined	22	21	21	22
Regular cycles (total)	12	18	16	14
4 day	10	16	15	12
4/5 day	2	2	1	2
5 day	0	0	0	0
Irregular cycle*	7	3	2	4
Extended estrus**	0	0	1	0
Acyclic***	3	0	2	4

*at least one cycle of two, three, or six to ten days; **at least four consecutive days of estrus; ***at least ten days without estrus.

Mating and fertility indices in rats

Endpoint	Dose level (IU/kg every other day)			
	0	500	1000	2000
Females paired with males	22	21	21	22
Total number mated	22	21	21	22
Female mating index (%)	100.0	100.0	100.0	100.0
Total number pregnant	21	19	21	22
Female fertility index (%)	95.5	90.5	100.0	100.0
Males placed with females	24	21	22	23
Total number mated	22	21	21	22
Male mating index (%)	91.7	100.0	95.5	95.7
With females pregnant	21	19	21	22
Male fertility index (%)	87.5	90.5	95.5	95.7
Females with defined GD 0	22	21	21	22
Number of days to mating	2.6	2.8	2.9	3.2
Day 1 to 4	22	21	20	20
Day 5 to 8	0	0	0	0
Day 9 to 14	0	0	1	2

Summary of pregnancy in rats

Endpoint	Dose level (IU/kg every other day)			
	0	500	1000	2000
Number of females on study (mated)	22	21	21	22
Not pregnant	1	2	0	0
Pregnant	21	19	21	22
Pregnant with termination before scheduled date	0	0	0	0
Pregnant at scheduled termination	21	19	21	22

With total implantation loss	0	0	0	0
With viable fetuses	21	19	21	22

Sperm evaluations

There were no toxicologically significant effects of asparaginase *Erwinia chrysanthemi* on sperm motility or morphology. Sperm counts (millions/gram of right testis) were minimally suppressed (↓ 12 to 15%) at doses ≥500 IU/kg; however, this was likely due to slightly higher testis weights in treated animals compared to controls, as there were no meaningful histopathological correlates. Sperm counts in cauda epididymal (right) tissue were unaffected.

Necropsy findings

Males: slightly higher absolute weight of the left epididymis and bilateral testis was observed at ≥1000 IU/kg.

Summary of absolute organ weight changes (% difference) relative to control

Organ	Dose level (IU/kg every other day)		
	500	1000	2000
Left epididymis	3.0	6.5	2.4
Left testis	4.9	8.8	5.9
Right testis	3.9	8.2	5.6*

* Excludes animals with small/soft epididymis and testis, which were attributed to unilateral or bilateral blockage and unrelated to the test article.

Females: unremarkable

Caesarean section

Unremarkable

Cesarean section data (means) from rats

Endpoint	Dose level (IU/kg every other day)			
	0	500	1000	2000
Corpora lutea	15.1	14.5	15.6	15.4
Implantations	13.5	13.4	14.4	14.1
Early resorptions	1.1	1.1	0.9	1.0
Late resorptions	0.0	0.0	0.0	0.0
Total resorptions	1.1	1.1	1.0	1.0
Dead fetuses	0.0	0.0	0.0	0.0
Live fetuses	12.4	12.3	13.4	13.1
Pre-implantation loss (%)	10.4	7.9	7.9	8.7
Post-implantation loss (%)	7.9	7.9	7.4	6.8

Embryo-Fetal Development

Erwinaze: Embryo-fetal toxicity study via intramuscular injection in rats / study number 11-4370

Key study findings

- Maternal toxicity: slight but statistically significant decreases in body weight change, accompanied by decreases in food consumption, were observed in females exposed to 2,000 IU/kg (high dose) compared to controls.
- Abnormal fetal examination findings were limited to slightly increased litter/fetal incidences of partially undescended thymus gland at 2,000 IU/kg.
- The development of anti-asparaginase *Erwinia chrysanthemi* antibodies (including those capable of neutralizing asparaginase activity) were detected in essentially all asparaginase *Erwinia chrysanthemi*-treated rats.

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 500, 1000, or 2000 IU/kg (0, 3000, 6000, or 12000 IU/m^2) Once every other day from GD 6 to 16
Route of administration:	IM injection
Formulation/Vehicle:	Preservative free physiological saline (0.9%), USP
Species/Strain:	Rat/Crl:CD (SD)
Number/Sex/Group:	22 females/group
Satellite groups:	TK and immunogenicity: 3 control females and 9 females/treatment group
Study design:	22 females/group were dosed every other day from GD 6 to 16 and euthanized on GD 20
Parameters and endpoints evaluated:	Females: clinical signs, body weight, food consumption, necropsy, gravid uterine and placental weights, TK, and immunogenicity Fetuses: fetal weights and external, visceral, and skeletal examinations
Deviation from study protocol affecting interpretation of results:	No

Observations and results

Parameters	**Major findings**
Mortality	None
Clinical signs	Statistically significant decreases in food consumption were observed in animals receiving 2000 IU/kg for intervals GD 6-9 and GD 6-18.
Body weights	Statistically significant decreases in body weight change were observed in animals receiving 2,000 IU/kg compared to controls; decreases in body weight change correlated with decreases in food consumption.
Necropsy findings Cesarean section data	

Mean maternal body weight change (g)

Study interval (GD)	Dose level (IU/kg every other day)			
	0	500	1000	2000
4-6	12.3	9.0	10.2	8.9*
6-9	17.1	14.6	13.3*	4.7**
9-12	19.5	18.5	20.9	18.8
12-15	15.2	18.9	16.8	9.7**
15-18	38.9	36.6	38.1	38.8
18-20	28.2	31.7	29.7	28.5
6-18	90.7	88.6	89.1	72.0**
6-20	118.8	120.2	118.7	100.5**

*Significant different from control ($p<0.05$), **Significant different from control ($p<0.01$)

Mean gravid uterine weight and adjusted body weight and body weight change

Study interval (GD)	Dose level (IU/kg every other day)			
	0	500	1000	2000
Body weight Day 6	270	261	264	262*
Body weight Day 20	389	382	383	362**
Gravid uterine weight	79.3	79.2	76.7	73.1

	Adjusted body weight Day 20: 309 / 302 / 306 / 289** Adjusted body weight change GD 6-20: 40 / 41 / 42 / 27** *Significant different from control (p<0.05), **Significant different from control (p<0.01) **Uterine examination data**

Endpoints		Dose level (IU/kg every other day) 0	500	1000	2000
# of females mated		22	22	22	22
# of pregnant females		22	22	22	21
# of females with viable fetuses		22	22	22	21
Corpora lutea		14.8	13.7	14.3	13.6
Implantations		13.4	13.1	13.0	12.2
Pre-implantation loss (%)		8.7	3.7	9.3	10.2
Post-implantation loss (%)		6.4	4.0	6.5	3.3
Resorptions	Early	0.7	0.5	0.9	0.4
	Late	0	0	0	0
	Total	0.7	0.5	0.9	0.4
Live fetuses	Male	6.6	6.6	5.1	6.0
	Female	6.0	6.0	7.0	5.8
	Total	12.7	12.6	12.1	11.8

Necropsy findings Offspring	There were no changes in fetal sex ratio or fetal weights. There were no fetal external or skeletal observations. **Select fetal visceral observations**

	Dose level (IU/kg every other day) 0	500	1000	2000
Number of litters evaluated	22	22	22	21
Number of external examinations	140	137	131	123
No abnormality detected	21/100	22/102	20/103	20/92
Cervical				
Thymus gland, partially undescended	2/3	4/4	3/3	7/10
Thymus gland, undescended	0/0	1/1	1/1	1/1

Litter incidence/fetal incidence

Erwinaze: Embryofetal toxicity and toxicokinetic study via intramuscular injection in rabbits / study number 11-4372

Key study findings

- Maternal toxicity: statistically significant decreases in body weight and weight change, accompanied by decreases in food consumption, were observed in females exposed to 40 IU/kg (high dose) compared to controls.
- Gravid uterine weights were dose-dependently decreased, reaching the level of statistical significance at ≥ 25 IU/kg.
- Embryo-fetal toxicity: resorptions (early, late, and total) and % post-implantation loss were increased in animals exposed to ≥ 10 IU/kg; decreases in the number of total live fetuses were also observed at ≥ 10 IU/kg.
- Fetal visceral observations: increased incidences of absent kidney, absent or rudimentary accessory lung lobe, and additional subclavian artery.
- Fetal skeletal observations: delays in skeletal ossifications parameters.

- The development of anti-asparaginase *Erwinia chrysanthemi* antibodies (including those capable of neutralizing asparaginase activity) were detected in essentially all asparaginase *Erwinia chrysanthemi*-treated rabbits.

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 10, 25, or 40 IU/kg (0, 120, 300, or 480 IU/m^2) Once every other day from GD 6 to 18
Route of administration:	IM injection
Formulation/Vehicle:	Preservative free physiological saline (0.9%), USP
Species/Strain:	Rabbit/New Zealand White
Number/Sex/Group:	22 females/group
Satellite groups:	TK and immunogenicity: 3 females/group
Study design:	22 females/group were dosed every other day from GD 6 to 18 and euthanized on GD 29
Parameters and endpoints evaluated:	Females: clinical signs, body weight, food consumption, necropsy, gravid uterine and placental weights, TK, and immunogenicity Fetuses: fetal weights and external, visceral, and skeletal examinations
Deviation from study protocol affecting interpretation of results:	No

Observations and results

Parameters	Major findings
Mortality	None
Clinical signs	Decreases in food consumption were observed in animals receiving 40 IU/kg for most intervals; however, increased food consumption was observed for intervals GD 23-26 and GD 26-29.
Body weights	Statistically significant decreases in body weight change were observed in animals receiving 40 IU/kg compared to controls; decreases in body weight change correlated with decreases in food consumption.

Mean maternal body weight change (g)

Study interval (GD)	Dose level (IU/kg every other day)			
	0	10	25	40
4-6	100.8	95.0	92.9	115.7
6-9	40.9	27.9	17.6	-98.0**
9-12	47.8	50.8	10.1	-8.1*
12-15	69.1	72.1	48.5	7.5
15-18	36.1	35.1	56.2	25.1
18-20	26.1	17.0	32.1	29.3
20-23	45.3	74.0	52.4	103.7*
23-26	43.2	23.0	17.6	69.1

26-29	52.4	51.1	60.6	60.8
6-20	220.0	202.8	164.4	-44.3**
20-29	140.9	148.1	130.7	233.6*
6-29	360.9	350.9	295.1	189.4**

*Significant different from control (p<0.05), **Significant different from control (p<0.01)

Necropsy findings
Cesarean section data

Mean gravid uterine weight and adjusted body weight and body weight change

Study interval (GD)	Dose level (IU/kg every other day)			
	0	10	25	40
Body weight Day 6	3844	3941	3898	3845
Body weight Day 29	4204	4292	4194	4034
Gravid uterine weight	547	505	451*	433**
Adjusted body weight Day 29	3657	3787	3743	3607
Adjusted body weight change GD 6-29	-186	-154	-156	-227

*Significant different from control (p<0.05), **Significant different from control (p<0.01)

Adverse maternal necropsy findings

Endpoints	Dose level (IU/kg every other day)			
	0	10	25	40
# of females in subgroups	22	22	22	22
Within normal limits	19	20	21	20
Lungs, absent accessory lobe	0	0	0	1
Placenta, cyst	0	0	0	1
Uterus w/ Cervix, cyst	0	0	0	1

Uterine examination data

Endpoints		Dose level (IU/kg every other day)			
		0	10	25	40
# of females mated		22	22	22	22
# of pregnant females		21	19	18	20
# of females with total implantation loss		0	0	0	1
# of females with viable fetuses		21	19	18	19
Corpora lutea		10.9	10.8	10.6	10.9
Implantations		9.7	9.5	9.1	8 8
Pre-implantation loss (%)		11.6	12.4	13.9	22.8
Post-implantation loss (%)		2.6	8.3*	12.3	15.6*
Resorptions	Early	0.1	0.6	0.9	1.1
	Late	0.1	0.3	0.4	0 3
	Total	0.3	0.8	1.3	1.4
Live fetuses	Male	5.0	3.7	3.8	3 2
	Female	4.4	4.9	4.1	4 6
	Total	9.4	8.6	7.8*	7.7*

*Significant different from control (p<0.05), **Significant different from control (p<0.01)

Necropsy findings
Offspring

There were no fetal external observations.

Fetal sex ratio and weights

Endpoints		Dose level (IU/kg every other day)			
		0	10	25	40
Fetal sex ratio (mean % male fetuses per female)		54.9	43.5	46.9	38.7
Mean fetal weight (g)	Male	39.4	38.0	37.0	36.1
	Female	37.6	37.7	38.0	35.4
	Total	39.1	37.9	37.4	36.0

Select fetal visceral observations

	Dose level (IU/kg every other day)			
	0	10	25	40
Number of litters evaluated	21	19	18	19
Number of external examinations	198	125	106	147
No abnormality detected	21/171	18/125	18/106	17/84
Abdomen				

Spleen, small	0/0	0/0	0/0	3/4
Kidney/ureter				
Kidney, absent	0/0	0/0	1/1	6/8
Lungs				
Accessory lung lobe, absent	6/7	12/28	10/22	15/43
Accessory lung lobe, rudimentary	0/0	0/0	0/0	2/3
Thorax				
Subclavian artery, additional	0/0	3/4	3/3	3/4

Litter incidence/fetal incidence

Select fetal skeletal observations

	Dose level (IU/kg every other day)			
	0	**10**	**25**	**40**
Number of litters evaluated	21	19	18	20
Number of external examinations	198	164	141	147
No abnormality detected	11/16	7/9	5/9	4/6
Cervical vertebrae				
Cervical vert. centrum, asymmetrically ossified	0/0	4/5	3/4	5/7
Cervical vert. centrum(a), bipartite ossified	0/0	0/0	0/0	2/2
Cervical vert. centrum(a), dumbbell ossified	0/0	0/0	1/1	2/2
Cervical vert. centrum(a), hemicentric	0/0	3/3	5/5	7/16
Cervical vert. centrum(a), incompletely ossified	4/6	10/34	9/18	8/9
Cervical vert. centrum(a), unossified	1/1	5/9	2/4	1/1
Odontoid process, incompletely ossified	0/0	0/0	0/0	2/2
Odontoid process, misshapen	0/0	0/0	1/1	1/1
Head				
Frontal, unossified area(s)	0/0	0/0	0/0	1/1
Hyoid cornua, bent inwards	0/0	0/0	0/0	1/2
Interparietal, supraoccipital, partially fused	0/0	0/0	0/0	1/1
Interparietal, bipartite	0/0	0/0	1/1	3/4
Parietal, fissure(s)	0/0	0/0	1/1	2/3
Premaxilla, incompletely ossified	0/0	1/1	1/1	1/1
Limb bones				
2nd phalanx, bilateral forelimb, incompletely ossified	3/5	5/6	2/4	6/14
2nd phalanx, bilateral forelimb, unossified	8/17	12/41	13/34	16/61
2nd phalanx, bilateral forelimb, incompletely ossified	0/0	0/0	1/1	3/3
2nd phalanx, right forelimb, incompletely ossified	0/0	0/0	1/1	3/3
2nd phalanx, right forelimb, unossified	1/1	2/2	4/4	4/5
2nd phalanx, right hind limb, unossified	0/0	0/0	0/0	2/2
Epiphyses, incompletely ossified	17/48	16/72	17/63	16/75
Epiphyses, unossified	5/6	3/9	3/9	7/10
Metacarpal, bilateral forelimb, unossified	7/14	6/18	6/28	14/39
Phalanx, unossified	0/0	0/0	0/0	1/1
Lumbar vertebrae				

	Lumbar vertebral arch(es), isolated ossification site	2/2	3/6	0/0	4/4
	Lumbar vertebral arch(es), fused	0/0	0/0	1/1	1/1
	Lumbar vertebral centrum(a), additional oss site, between	0/0	0/0	1/1	1/1
	Ribs				
	Costal cartilage, partially fused	0/0	2/2	0/0	3/3
	Bilateral rib(s), distal, associated costal cartilage	14/60	19/88	18/95	17/97
	Bilateral rib(s), distal, thickened	0/0	1/1	3/4	2/2
	Left rib, intercostal rib, between	0/0	0/0	0/0	2/2
	Left rib, branched	0/0	0/0	0/0	2/2
	Sternebrae				
	Costal cartilage(s), misaligned	0/0	0/0	3/4	1/1
	Sternebral center(s), bipartite ossified, misaligned	0/0	0/0	1/1	1/1
	Sternebral center(s), incompletely ossified	3/3	4/5	6/11	8/12
	Thoracic vertebrae				
	20 thoracolumbar vertebrae, present	14/39	18/79	14/43	19/66
	Thoracic region, fused, 9th, 10th	0/0	0/0	1/1	1/1
	Variants				
	13th bilateral rib, present	17/74	19/108	18/106	18/117
	13th right rib	0/0	0/0	1/1	1/1

Litter incidence/fetal incidence; Vert.=vertebrae/vertebral; oss=ossified

Pre- and Post-natal Development

Erwinaze: Pre- and Postnatal Development Study in Rats via Intramuscular Injection / study number 11-4373

Key study findings

- No toxicologically significant maternal effects were observed.
- No toxicologically significant pre- or post-natal effects were observed.
- NOAEL = 2,400 IU/kg Erwinaze (14,400 IU/m^2) for both maternal effects and effects on the offspring.

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 600, 1200, or 2400 IU/kg (0, 3600, 7200, or 14400 IU/m^2)
Every other day from GD 6 to lactation day (LD) 20

Route of administration: IM injection

Formulation/Vehicle: Preservative free physiological saline (0.9%), USP

Species/Strain: Rat/Crl:CD (SD)

Number/Sex/Group: 22 time-mated females/group

Satellite groups:	None
Study design:	Mated F_0 females were dosed every other day via IM injection from the time of implantation (GD 6) through the time of offspring weaning (LD 20). F_0 dams were sacrificed on LD 21, or as convenient thereafter. Since manifestations of effects induced during this period could have been delayed, observations of the F_1 offspring continued through sexual maturity, mating and establishment of pregnancy.
Deviation from study protocol affecting interpretation of results:	No

Observations and results

Generation	Major Findings
F_0 generation	There were two premature sacrifices. One female at 0 IU/kg had not delivered by GD 25 and was euthanized (not pregnant at necropsy). One female at 600 IU/kg was sacrificed in moribund condition (clinical signs of thinness and decreased activity) on LD 18. Statistically significant reductions in F_0 female body weight gains observed at 2400 IU/kg (↓44% on GD 6-9 and ↓23% on GD 12-15) led to lower mean body weights for this group compared to controls, reaching the level of statistical significance on GD 9 (↓4%) and GD 15 (↓5%). Of note, mean body weights of the high dose (2400 IU/kg) group were within 1% of the control values at the end of gestation, 4% of controls on LD 1, and 2% of controls at the end of lactation. The transient reductions in body weight did not adversely affect any of the delivery or litter endpoints. Food consumption, uterine content, and necropsy observations were unremarkable.
F_1 generation	In the pre-weaning functional assessment, numerical increases in the number of days to acquisition of righting reflex were observed; surface righting reflex acquisition occurred at 3.2, 3.4, 3.6, and 3.5 days for animals in the 0, 600, 1200, and 2400 IU/kg groups, respectively. Statistically significant delays in acquisition of mid-air righting were observed; however, the small delays may not be toxicologically significant: it took 16.3 days for controls and 16.8 days and 16.7 days for animals at 1200 and 2400 IU/kg, respectively.
F_2 generation (F_1 uterine examination)	Unremarkable

5.5.5. Other Toxicology Studies

The Applicant's Position:

There was no definitive evidence of diabetogenic potential or fatty liver and bromosulfophthalein retention following daily administration of 2000 IU/kg Erwinia species asparaginase for 5 days to one monkey or of a single dose of 10,000 IU/kg to one rabbit.

The development of ADAs was observed in four of the five GLP-compliant studies conducted with Erwinia chrysanthemi-derived asparaginases (2018-458-032, 11-4368, 11-4370, 11-4372, 11-4373).

Specifically, in the 2-week study with JZP-458 in rats, the incidence of ADA induction was observed at all doses in treated and recovery animals. In the reproductive and developmental toxicity studies with Erwinia chrysanthemi asparaginase, the majority of the rats and rabbits evaluated for ADAs were positive. These observations are consistent with the known immunogenic potential of bacterial asparaginases.

The FDA's Assessment:
These studies are not needed to support the approval of BLA 761179.

6 CLINICAL PHARMACOLOGY

6.1. Executive Summary

The FDA's Assessment:

JZP-458, a recombinant asparaginase derived from *Erwinia chrysanthemi*, is proposed for use as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in adults and pediatric patients who have developed hypersensitivity or silent inactivation to *E. coli*-derived asparaginase. JZP-458 has an identical amino acid sequence to ERWINAZE (asparaginase *Erwinia chrysanthemi*) which is currently 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.

Clinical development of JZP-458 included a single-dose Phase 1 study in adult healthy volunteers (JZP458-101) and a pivotal Phase 2/3 study in patients with ALL or LBL who had developed hypersensitivity reaction or silent inactivation to prior *E. coli*-derived asparaginase (JZP458-201). Serum asparaginase activity (SAA) is an established surrogate endpoint for asparaginase products and was utilized for pharmacokinetic (PK) analyses of JZP-458. The primary objective of the Study JZP458-201 was the proportion of patients with 72-hour nadir serum asparaginase activity (NSAA) $\geq$0.1 IU/mL.

The first two studied dosing regimens in Study JZP458-201, 25 mg/m^2 and 37.5 mg/m^2 intramuscularly (IM) on Monday, Wednesday, and Friday (MWF) for a total of 6 doses per 2-week course, failed to meet the primary endpoint. Based on modeling and simulation of SAA data, the following dosing regimens were proposed for JZP-458:

- 25 mg/m^2 IM on Mondays and Wednesdays and 50 mg/m^2 IM on Fridays for a total of 6

doses every 2 weeks (25/25/50 mg/m^2 IM MWF x 6)

- 25 mg/m^2 IM every 48 hours (Q48H) for a total of 7 doses every 2 weeks

The Office of Clinical Pharmacology has reviewed the information contained in BLA 761179. This BLA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized in the table below.

REVIEW ISSUE	RECOMMENDATIONS/COMMENTS
Pivotal or supportive evidence of effectiveness	The evidence of JZP-458 effectiveness comes from observed SAA data in Study JZP458-201 and modeling and simulation of SAA for the two proposed dosing regimens. The dosing regimens of 25 mg/m^2 IM Q48H for a total of 7 doses per 2-week course and 25/25/50 mg/m^2 IM MWF for a total of 6 doses per 2-week course are predicted to meet the goal NSAA ($\geq$0.1 IU/mL) in 93.6% of patients [95% CI 92.6, 94.6] and 91.4% of patients [95% CI 90.2, 92.7], respectively.
General dosing instructions	The recommended dosage regimen of JZP-458 is 25 mg/m^2 IM Q48H for a total of 7 doses per 2-week course.
Dosing in patient subgroups (intrinsic and extrinsic factors)	*Pediatric Patients $\geq$1 month of age:* BSA is a statistically significant covariate for JZP-458 apparent clearance (CL/F) and apparent volume of distribution (V/F), supporting the BSA-based dosing regimen. The recommended dosage regimen is predicted to meet the goal NSAA in >90% of patients, regardless of age. *Race and Ethnicity:* Black (n=10) and Asian (n=5) patients had a 29% lower CL/F compared to White patients (n=61), but there were no clinically significant differences in NSAA or safety between race groups. There were no differences in CL/F between Hispanic (n=28) and Non-Hispanic (n=53) patients. No dosage modification is recommended based on race or ethnicity. *Renal and Hepatic Impairment:* No dedicated studies were conducted for patients with renal or hepatic impairment.
Immunogenicity	Treatment-emergent ADA against JZP-458 were detected in 40/99 (40.4%) evaluable patients in Study JZP458-201; 4 patients (4%) had neutralizing antibodies against JZP-458. However, the immunogenicity assays used in the current BLA submission did not have adequate drug tolerance for the drug concentration present at the time of ADA sampling and therefore the observed results underestimate the true incidence of ADA against JZP-458. A PMC will be issued to assess binding and neutralizing ADA responses with a validated assay capable of sensitively detecting ADA responses in the presence of JZP-458 levels that are present in the serum at the time of patient sampling.

Labeling	The proposed labeling recommendations are acceptable upon the Applicant's agreement to the FDA revisions to the label.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

JZP-458 clinical pharmacology includes two clinical studies: a completed phase 1 study in healthy adult participants (JZP458-101) that facilitated the selection of starting dose for the pivotal phase 2/3 study (JZP458-201) and an ongoing phase 2/3 study (JZP458-201) in pediatric and adult participants with ALL/LBL who have developed hypersensitivity or silent inactivation to *E. coli* derived asparaginases.

Information presented in the Clinical Pharmacology section 6.2.1 is based on JZP458-201 initial interim analysis (IA) data cutoff date (DCO) October 14, 2020, and is being submitted to the BLA. Updated analyses for JZP458-201 will continue through the end of the study.

JZP-458 clinical pharmacology has been characterized by population pharmacokinetic (PPK) analyses in ALL/LBL patients who have developed hypersensitivity or silent inactivation to *E. coli* derived asparaginases. PK of JZP-458 was evaluated based on SAA.

A population PK approach was used to characterize the PK of JZP-458 in ALL/LBL patients who have developed hypersensitivity or silent inactivation to *E. coli* derived asparaginases. At the time of the initial IA, SAA data from 85 patients were used for the model development, with 32 patients dosed intramuscularly at 25 mg/m^2 (Cohort 1a) and 53 patients dosed intramuscularly at 37.5 mg/m^2 (Cohort 1b) on a Monday, Wednesday and Friday schedule for 6 doses per course of treatment. The PK of JZP-458 is described by a 1-compartment IM model with linear elimination and sequential mixed order absorption, with weight included as an allometric covariate on CL and V.

Absorption: Slow absorption is observed for JZP-458 after IM administration. The estimated median (range) Tmax of JZP-458 after the 6th dose of JZP-458 is 13.1 (5.85-20.2) hours in ALL/LBL patients from JZP458-201 based on the 85 patients at 25mg/m^2 and 37.5mg/m^2.

Distribution: Population estimate of apparent volume of distribution (V/F) for JZP-458 in a 40 kg patient is 3.35 (standard error: 0.46) L in ALL/LBL patients from Study JZP458-201 based on 85 patients at 25mg/m^2 and 37.5mg/m^2.

Metabolism: JZP-458 is an enzyme and it is expected to be metabolized by proteolytic degradation.

Elimination: The estimated mean (SD) of individual predicted terminal elimination half-life ($t_{1/2}$) of JZP-458 following a single dose simulation out to 96 hours postdose is 16.1 (1.38) hours, and the population PK estimate of CL/F for JZP-458 in a 40 kg patient is 0.416 (standard error: 0.0193) L/h in ALL/LBL patients from JZP458-201 based on the 85 patients from cohort 1a and 1b (25 and 37.5 mg/m^2).

Dose proportionality: Dose proportionality for JZP-458 was evaluated in studies JZP458-101 and JZP458-201. In JZP458-101, JZP-458 exposures increased with increasing doses based on SAA, and the increases in JZP-458 SAA exposures (C_{max} and AUC) were approximately dose-proportional between the dose range of 12.5 to 25 mg/m^2 for IM administration (JZP458-101 CSR).

In JZP458-201, based on population PK analyses model predicted C_{max} and AUC values are provided below after the 1st and 6th doses of JZP-458. With a dose increase of 1.5-fold from 25 to 37.5 mg/m^2, ratios of (C_{max} 37.5/C_{max} 25) were 1.63 and 1.62 for mean $C_{max,1}$ and $C_{max,6}$, respectively, and ratio of (AUC 37.5/AUC 25) was 1.69, suggesting the increases in JZP-458 SAA exposures (C_{max} and AUC) were approximately dose-proportional between the dose range of 25 to 37.5 mg/m^2 for IM administration, see Applicant Table 3.

Applicant Table 3: Dose proportionality determination for JZP-458 from study JZP458-201

Dose (mg/m^2)	**Mean $C_{max,1}$ (IU/mL)**	**Mean $C_{max,6}$ (IU/mL)**	**AUC_{0-336} (IU*h/mL)**
25	1.2501	1.4704	283
37.5	2.0328	2.3760	478
DP (C_{max} or AUC 37.5/C_{max} or AUC 25)	1.63	1.62	1.69

Accumulation: Accumulation for JZP-458 was evaluated in study JZP458-201. Based on dosing frequency and half-life (16.1 hours) determined, the accumulation ratio for IM JZP-458 is estimated at 1.15 assuming a dosing interval of 48-hours. Based on population PK analyses, in JZP-458-201, model predicted C_{max} values are provided below after the 1st and 6th doses of JZP-458. Accumulation ratios (calculated as $C_{max,6}/C_{max,1}$) were 1.18 and 1.17 for 25 and 37.5 mg/m^2, respectively, suggesting very little accumulation, see Applicant Table 4.

Applicant Table 4: Accumulation information for JZP-458 from Study JZP458-201

Dose (mg/m^2)	**Mean $C_{max,1}$ (IU/mL)**	**Mean $C_{max,6}$ (IU/mL)**	**Accumulation Ratio**
25	1.2501	1.4704	1.18
37.5	2.0328	2.3760	1.17

The Applicant's Position:

JZP-458 clinical pharmacology has been characterized by a population pharmacokinetic (PPK) approach in ALL/LBL patients who have developed hypersensitivity or silent inactivation to *E. coli* derived asparaginases. SAA data from 85 patients were used for the PPK model development, with 32 patients dosed IM at 25 mg/m^2 and 53 patients dosed IM at 37.5 mg/m^2 on a Monday, Wednesday and Friday schedule for 6 doses per course of treatment. A discussion of patients who developed ADA within this dataset is in Section **Error! Reference source not found.** under Immunogenicity.

PK parameters were derived from the population PK analysis. The population estimates of apparent clearance (CL/F) and apparent volume of distribution (V/F) for JZP-458 in a 40 kg patient is 0.416 L/h and 3.35 L, respectively, and the mean (SD) of individual predicted terminal elimination half-life (t1/2) of JZP-458 following a single dose simulation out to 96 hours postdose is 16.1 (1.38) hours. The increases in JZP-458 SAA exposures (C_{max} and AUC) were approximately dose-proportional between the dose range of 25 to 37.5 mg/m^2 for IM administration, and there was very little accumulation observed after the 6th dose.

The FDA's Assessment:

FDA identified issues with the Applicant's PopPK analysis and therefore considers the results of the Applicant's PopPK modeling and simulation unreliable (See details in **Section 6.2.2.1** and **Appendix 14.4.2**). FDA conducted an independent PopPK analysis based on all available SAA data from Studies JZP458-101 and JZP458-201 (including 32 patients in Cohort 1a and 53 patients in Cohort 1b) with cut-off date of 14 Oct 2020 (See details in **Appendix 14.4.3**).

Based on FDA's final PopPK model, JZP-458 PK (based on SAA) was described by a 1-compartment model with sequential zero-order and first-order absorption and first-order elimination. BSA was a significant covariate for both CL/F and V/F. JZP-458 C_{max} and AUC are dose proportional over a dosage range from 12.5 to 50 mg/m^2 administered IM.

Absorption

The median t_{max} of JZP-458 is 10 hours after IM administration. The mean absolute bioavailability for IM administration is 37% in healthy adult subjects.

Distribution

The geometric mean (%CV) V/F of JZP-458 is 1.48 L/m^2 (49%).

Elimination

The geometric mean (%CV) CL/F of JZP-458 is 0.31 L/hour/m^2 (36%) and the apparent half-life is

18.2 hours (16%) following IM administration.

Late during the review cycle, the Applicant submitted additional SAA data. FDA conducted a sensitivity analysis by combining updated data from Study JZP458-201 with a data cut-off date of 11 Jan 2021 (including 33, 53 and 16 patients in Cohort 1a, 1b and 1c respectively) with the PopPK dataset. The inclusion of the updated data did not result in any remarkable changes in the FDA's final PopPK model and PK parameters. Unless otherwise specified, the FDA's assessment throughout Section 6 is based on final PopPK model with data from the cut-off date of 14 Oct 2020.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:
JZP458-201 is a pivotal phase 2/3 study in patients with ALL/LBL who have developed hypersensitivity or silent inactivation to *E. coli*-derived asparaginases. The recommended phase 2/3 starting dose for the IM route of administration was 25 mg/m^2 on a M/W/F dosing schedule. This was based on the JZP458-101 study data and PPK modeling and simulations indicating JZP-458 at the IM dose of 25 mg/m^2 and IV dose of 37.5 mg/m^2 is expected to achieve 72-hour NSAA levels ≥ 0.1 IU/mL in 100% of adult or pediatric populations after IM administration, and 80.9% in adult or 94.5% in pediatric populations after IV administration. This information is found in Version 1 of the JZP458-101 CSR. An updated CSR addendum and dataset (not available at the time of preparation of this document) will be submitted to the BLA.

This initial BLA application utilizes a combination of observed safety and efficacy data from participants in the investigational cohorts in the ongoing phase 2/3 study and a PPK modeling and simulation results. The PPK model provides critical supporting data to establish the optimal efficacy of JZP-458 at the proposed dosing regimen of 25 mg/m^2 on Monday and Wednesday and 50 mg/m^2 on Friday.

The PPK analysis provides support of the observed data and for the total data package for the BLA because the model uses pooled participant data from all dose levels, all time points, and across all courses, and it uses continuous rather than categorical data. Applicant believes that the PPK model results illustrate more accurately the SAA exposures of JZP-458 than does the primary analysis methodology in the protocol (since the protocol specified endpoint relies solely on a binary determination using the last 72-hour NSAA levels), and the PPK model provides reliable predictions of NSAA levels at 48- and 72-hour timepoints. This combined approach provides for a data package to support the registration of JZP-458 with efficacy based on NSAA level ≥ 0.1 U/mL at 48 and 72 hours. Supporting data, such as asparagine depletion, is also included in the BLA.

JZP458-201 Observed efficacy data from 25 mg/m^2 and 37.5 mg/m^2 Initial IA

JZP-458 IM dose of 25 mg/m^2 and 37.5 mg/m^2 have been studied in JZP458-201 on MWF/WFM/FMW dosing schedule for 6 doses per course of treatment. The primary efficacy endpoint of Study JZP458-201 is to determine the proportion of patients with the last 72-hour NSAA level ≥ 0.1 IU/mL during the first course of JZP-458 IM administration. The key secondary endpoint is to determine the proportion of patients with the last 48-hour NSAA level ≥ 0.1 IU/mL during the first course of IM JZP-458.

Observed SAA results show that at JZP-458 IM dose levels of 25mg/m^2 and 37.5 mg/m^2, mean and median SAA levels at the last 72 and 48 hours postdose were > 0.1 IU/mL (See Applicant Table 5)

The observed SAA results in Course 1 show that at the JZP-458 IM dose level of 25 mg/m^2, the mean NSAA level at the last 72 and 48 hours postdose was 0.1543 (95% CI: 0.1162, 0.1924) and 0.4489 (95% CI: 0.3730, 0.5258), respectively. At the JZP-458 IM dose level of 37.5 mg/m^2, the mean SAA level at the last 72 and 48 hours postdose was 0.3000 (95% CI: 0.2269, 0.3730) and 0.8376 (95% CI: 0.6813, 0.9939), respectively.

Applicant Table 5: Study JZP458-201 – Summary of SAA Results (IU/mL) with JZP-458 IM in Course 1 (Efficacy Analysis Set as of October 14 2020)

Route/ Dose Level	Time Point	N	Mean (95% CI) NSAA (IU/mL)	Median (Q1, Q3) NSAA (IU/mL)
IM 25 mg/m^2 MWF	Last 48-hour	32	0.4489 (0.3720, 0.5258)	0.4091 (0.2742, 0.6545)
	Last 72-hour	29	0.1543 (0.1162, 0.1924)	0.1331 (0.0886, 0.2178)
IM 37.5 mg/m^2 MWF	Last 48-hour	53	0.8376 (0.6813, 0.9939)	0.7161 (0.3741, 1.0612)
	Last 72-hour	51	0.3000 (0.2269, 0.3730)	0.2145 (0.1222, 0.4101)

Abbreviations: IM = intramuscular; MWF = Monday, Wednesday, Friday; Q1 = first quartile; Q3 = third quartile; NSAA = nadir serum asparaginase activity.
The Efficacy Analysis Set includes participants who received at least 1 dose of JZP-458 with at least one 48-hour or 72-hour NSAA assessment collected within the protocol-defined sample collection window (± 2 hours) in Course 1.
Source: Initial IA TFL Table 9.2.2.5 DCO October 14 2020

At 25 mg/m^2 (N = 32) and 37.5 mg/m^2 (N = 53) JZP-458 IM administered MWF/WFM/FMW, the percentage of participants achieving NSAA levels ≥ 0.1 IU/mL at the last 48-hour assessment in Course 1 was 96.9% (95% CI: 90.8%, 100%) and 98.1% (95% CI: 94.5%, 100.0%), respectively.

The lower bound of the 95% CI exceeds 90%, which supports the efficacy of 25 mg/m^2 and 37.5 mg/m^2 JZP-458 dosing every 48-hours (See Applicant Table 6).

At 25 mg/m^2 (N = 29) and 37.5 mg/m^2 (N = 51) JZP-458 IM administered MWF/WFM/FMW, the percentage of participants achieving NSAA levels ≥ 0.1 IU/mL at the last 72-hour assessment in Course 1 was 65.5% (95% CI: 48.2%, 82.8%) and 80.4% (95% CI: 69.5%, 91.3%), respectively (See Applicant Table 6).

Applicant Table 6: Proportion of Participants with Last 72- and 48-hour NSAA Levels ≥ 0.1 IU/mL during the First Course of JZP-458 (Efficacy Analysis Set DCO October 14 2020)

NSAA Level	Time Point	IM 25 mg/m^{2}a (N = 33)			IM 37.5 mg/m^{2}a (N = 53)		
		N	n (%)	95% CI	N	n (%)	95% CI
≥ 0.1 IU/mL	Last 48-hour	32	31 (96.9)	90.8, 100.0	53	52 (98.1)	94.5, 100.0
	Last 72-hour	29	19 (65.5)	48.2, 82.8	51	41 (80.4)	69.5, 91.3

Abbreviations: CI = confidence interval; IM = intramuscular; NSAA = nadir serum asparaginase activity
a Doses were administered on a Monday, Wednesday, Friday schedule.
Percentages were calculated with the number of participants for each course and schedule as a denominator.
The Efficacy Analysis Set at 72-hour (primary efficacy endpoint) includes participants administered who received at least one dose of JZP 458 with at least one 72-hour NSAA assessment collected within the protocol-defined sample collection window (± 2 hours) in Course 1. The Efficacy Analysis Set at 48-hour (key secondary efficacy endpoint) includes participants who received at least one dose of JZP-458 with at least one 48-hour NSAA assessment collected within the protocol-defined sample collection window (± 2 hours) in Course 1.
95% CI was calculated by the Wald method.
Source: Initial IA TFL Tables 9.2.1.1 and 9.2.1.2 DCO October 14 2020

Population PK analysis was performed to support dosing of JZP-458 in participants with ALL and LBL who developed hypersensitivity to *E. coli*-derived asparaginase. As there were significant differences between observed in the SAA levels between healthy volunteers in Study JZP458-101 and ALL/LBL patients in Study JZP458-201 (based on the initial dataset), the initial datasets were not pooled. The mechanism for this difference is still unknown and considered multifactorial. Therefore, the data used for the PPK model development of JZP-458 were limited to JZP458-201. PPK modeling and simulation data submitted to the initial BLA were based on observed efficacy data from JZP458-201 (25mg/m^2 and 37.5mg/m^2) DCO October 14 2020. Updated data and information are being provided to the BLA as available. The PPK model

fits the observed data from the JZP458-201 study very well and supports clinical analysis and development of JZP-458.

An initial PPK modeling analysis was performed using SAA data from JZP458-201 at 25mg/m^2 and 37.5mg/m^2 (Cohorts 1a and 1b DCO October 14 2020). A validated PPK model was developed; SAA data across all courses from 85 patients who received IM JZP-458 were included in the population PK model development. The covariate model developed for JZP-458 was a 1-compartment IM-only model with linear elimination and sequential mixed order absorption, with weight included as an allometric covariate on CL and V.

PPK modeling and simulation data (Initial PPK report dated February 9, 2020 with data from the initial IA) suggested that:

- JZP458 administered IM at a dose 50/25/25 mg/m2 on a FMW schedule: 97.7% of patients (95% CI: 97.0%, 98.4%) are expected to achieve the last 72-hour NSAA levels ≥ 0.1 IU/mL, and 99.8% of patients (95% CI: 99.6%, 100%) are expected to achieve the last 48-hour NSAA level ≥ 0.1 IU/mL (See Applicant Table 7 and Applicant Figure 1).

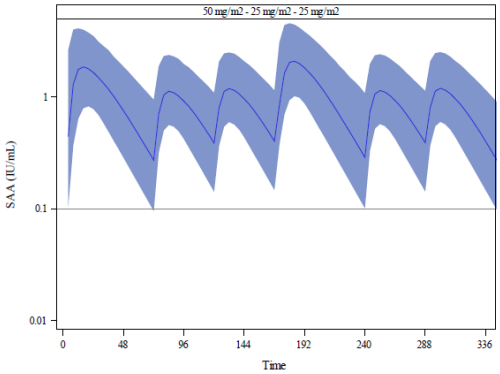
- JZP-458 administered IM at a dose of 25 mg/m2 every 48 hours: ≥ 99.7% of patients (95% CI: 99.5%, 99.9%) are expected to achieve any 48-hour NSAA level ≥ 0.1 IU/mL (See Applicant Table 8 and Applicant Figure 2)

Applicant Table 7: Simulation Summary Results - Proportion of JZP-458 Subjects Expected to Achieve Target SAA Trough Levels (50-25-25 FMW Dosing Schedule) – Patient Phase 2/3 IM Model (Initial PPK report DCO October 14 2020)

	Proportion of subjects ≥ 0.1 IU/mL (95% CI)		
FMW Dosing Schedule	Dose 1 72-hour trough	Dose 4* 72-hour trough	Dose 5 72-hour trough
50 mg/m^2 – 25 mg/m^2 – 25 mg/m^2	96.9 (96.1, 97.6)	97.7 (97.0,98.4)	99.8 (99.6, 100)

Notes: Proportion represents the number calculated for 2000 simulated subjects per dose level. FMW = A dosing schedule of Friday, Monday, and Wednesday. Patient population age range was 2 to 85 years.
* indicates the last 72h, which is the primary endpoint in the JZP458-201 protocol. The 95% Wald CI for the proportions was calculated using SAS proc freq with the following option: / binomial (CL = WALD). The 95% PI = prediction interval based on the percentiles (2.5 and 97.5 percentiles) for the simulated data.
Source: Initial PPK report dated 09Feb2021 DCO October 14 2020

Applicant Figure 1: Simulated JZP-458 Median SAA Profiles with 95% Prediction Intervals – Semi-log scale (50-25-25 FMW Dosing Schedule) – Patient Phase 2/3 IM Model (Initial PPK report DCO October 14 2020)



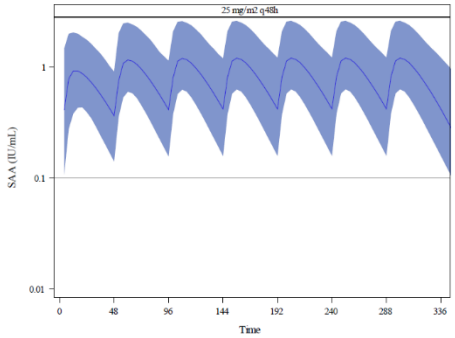
Notes: Center lines are the median value; bands (95% prediction interval) represent the 2.5th (lower) and 97.5th (upper) percentiles. The x-axis is displayed out to 336 hours. Dashed line indicates target trough level of 0.1 IU/mL
Source: Initial PPK report dated 09Feb2021

Applicant Table 8: Simulation Summary Results - Proportion of JZP-458 Subjects Expected to Achieve Target SAA Trough Levels (25 mg/m^2 every 48 hours) – Patient Phase 2/3 IM Model (Initial PPK report DCO October 14 2020)

	Proportion of subjects ≥ 0.1 IU/mL (95% CI)		
Every 48-Hours (q48h) Dosing Schedule	Dose 1 48-hour trough	Dose 4* 48-hour trough	Dose 7 48-hour trough
25 mg/m^2	99.7 (99.5, 99.9)	99.9 (99.8, 100)	99.9 (99.8, 100)

Notes: Proportion represents the number calculated for 2000 simulated subjects per dose level. q48h = every 48 hours. Patient population age range was 2 to 85 years. The 95% Wald CI for the proportions was calculated using SAS proc freq with the following option: / binomial (CL = WALD). The 95% PI =prediction interval based on the percentiles (2.5 and 97.5 percentiles) for the simulated data.
Source: Initial PPK report dated 09Feb2021 DCO October 14 2020

Applicant Figure 2: Simulated RC-P Median SAA Profiles with 95% Prediction Intervals – Semi-log scale (25 mg/m^2 every 48 hours) – Patient Phase 2/3 IM Model (Initial PPK report DCO October 14 2020)



Notes: Center lines are the median value; bands (95% prediction interval) represent the 2.5th (lower) and 97.5th (upper) percentiles. The x-axis is displayed out to 336 hours. Dashed line indicates target trough level of 0.1 IU/mL.
Source: Initial PPK report dated 09Feb2021 DCO October 14 2020

JZP458-201 Observed efficacy data from Cohort 1c at 25/25/50 mg/m^2 (DCO 11 January 2021)
A total of 17 participants (including 1 participant who did not receive JZP-458) were enrolled in Cohort 1c at DCO January 11 2021. Efficacy results from these 17 patients enrolled at 25/25/50 mg/m^2 Cohort 1c (N=16 as one patient enrolled but not dosed) DCO January 11 2021 will be presented in the Update Report following the initial BLA submission along with additional safety and efficacy information.

An updated PPK modeling and simulation analysis based on data from 25 mg/m^2 (n = 32), 37.5 mg/m^2 (n = 53), and 25/25/50 mg/m^2 (n = 16) through data cut date of January 11, 2021 is targeted for submission to the BLA in late April 2021.

The Applicant's Position:

The efficacy of JZP-458 is demonstrated by the totality of data, which includes observed nadir serum asparaginase activity (NSAA) data at the protocol-specified time points, population pharmacokinetic (PPK) modeling and simulation results of NSAA, asparagine depletion data, asparaginase enzyme content data, available immunogenicity data, adverse events (AEs) including adverse events of special interest known to be associated with asparaginase treatment, and clinical laboratory results.

The proposed dose regimen for JZP-458 is:

- (Preferred option) JZP-458 25 mg/m^2 administered intramuscularly Mondays and Wednesdays and 50 mg/m^2 on Fridays for a total of 6 doses every 2 weeks. This is the preferred dosing regimen because it provides optimal benefit:risk profiles for JZP-458, with sustained SAA levels ≥ 0.1 IU/mL over 48- and 72-hour dosing

durations with acceptable safety to provide meaningful benefit to patients, and to allow for MWF dosing in line with current treatment practice.

- The data also support JZP-458 being given as 25 mg/m^2 administered intramuscularly every 48-hours for 2 weeks for a total of 7 doses.

Jazz believes that the totality of data from Study JZP458-201, including observed efficacy data at 25 and 37.5 mg/m^2 in addition to the data from 25/25/50 mg/m^2 (which will be included in update report) and the PPK modeling and simulation results supports both dosing regimens.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of observed data from the initial IA of Study JZP458-201. FDA does not agree with Applicant's PopPK modeling and simulation results, as it overpredicted the SAA and SAA response rate compared to the observed data (**Table 11**).

FDA identified potential reasons for the overprediction including:

- Inclusion of sparse SAA data from study JZP458-201 only, which is insufficient to characterize the absorption process
- Exclusion of SAA data below the lower limit of quantitation (BLQ, 0.0035 IU/mL), representing ~9% of the PopPK dataset

FDA conducted an independent PopPK analysis using SAA data from Studies JZP458-101 and JZP458-201. The results showed that SAA time profiles were best described by a one-compartment model with sequential zero- and first-order absorption and first-order elimination. Body surface area (BSA) was identified as a statistically significant covariate on both CL/F and V/F in patients with ALL and LBL, supporting the BSA-based dosing regimen. Based on FDA's modeling and simulation results, administration of either JZP-458 25/25/50 mg/m^2 IM MWF x 6 doses per 2-week course or 25 mg/m^2 IM Q48H x 7 doses per 2-week course is predicted to meet the primary endpoint of NSAA $\geq$0.1 IU/mL in at least 90% of patients. Refer to **Section 6.3.2.1** and **Appendix 14.4.3** for additional details on FDA's independent PopPK analysis.

6.2.2.2. Therapeutic Individualization

Data:

Age, sex, height, body weight, body surface area (BSA), ethnicity, race, primary disease – ALL and LBL, disease subtype (B or T-cell), and ADA status were evaluated as potential covariates on JZP-458 PK within the JZP-458 Population PK analysis. Only weight was identified as a statistically significant covariate for JZP-458 clearance (CL) and volume (V).

Renal impairment: JZP-458 is an enzyme with a molecular weight of 140 kDa, which is unlikely to be renally eliminated; therefore, the effect of renal impairment is unlikely to result in changes in the PK of JZP-458.

Hepatic impairment: JZP-458 is an enzyme and is not metabolized by hepatic enzymes; therefore, hepatic impairment is unlikely to alter the PK of JZP-458.

Drug-drug interaction (DDI): Drug-drug interaction (DDI) are unlikely as JZP-458 is an enzyme and is not metabolized by hepatic cytochrome P450 enzymes.

The Applicant's Position:

JZP-458 is dosed per m^2, no dose adjustment is necessary based on demographic or other covariates.

The FDA's Assessment:

There were no clinically significant differences in the PK of JZP-458 based on weight (9 to 131 kg) or sex after the dose was adjusted by body surface area (BSA).

Pediatric Patients ≥1 Month of Age: BSA (range 0.44 to 2.53 m^2) was a significant covariate for JZP-458 V/F and CL/F. After adjusting for BSA, there were no significant differences in JZP-458 PK based on age (1 to 52 years). See **Section 6.3.2.3**.

Race and Ethnicity: Black (n=10) and Asian (n=5) patients had 29% decreased CL/F compared to White patients (n=61). There were no differences in CL/F between Hispanic (n=28) and Non-Hispanic (n=53) patients. No dosage modification is recommended based on race or ethnicity.

Renal and Hepatic Impairment: FDA agrees with the Applicant's position.

Drug-Drug Interactions: FDA agrees with the Applicant's position.

6.2.2.3. Outstanding Issues

Data:
There is no data available at this time.

The Applicant's Position:
An updated PPK modeling and simulation analysis based on data from 25 mg/m^2 (N = 32), 37.5 mg/m^2 (N = 53), and 25/25/50 mg/m^2 (N = 16) through data cut date of January 11, 2021 is targeted for submission to the BLA in late April 2021. The PK parameters estimated for JZP-458 listed in section 6.2.1 may be updated after this analysis becomes available and the updated parameters will be provided to this BLA with Update Report. PPK modeling based on the JZP458-201 initial analysis data cut (October 14 2020) provides strong evidence that the 25/25/50 mg/m^2 MWF dosing regimen meets the criteria for providing appropriate SAA level coverage over 48 and 72-hour intervals, which will be confirmed with the addition of observed data from 25/25/50 mg/m^2.

Additional safety, efficacy, and immunogenicity data at 25/25/50 mg/m^2 through January 11, 2021 as detailed in section 7.2 will be submitted to BLA in an Update Report.

The FDA's Assessment:

Issues were identified with the immunogenicity assays used in Study JZP458-201. Development of ADA has been associated with incidence of clinical hypersensitivity reactions and reduction of SAA for other asparaginase products. Inadequate assessment of immunogenicity confounds the risk assessment for potential effects of ADA and NAb on safety (clinical hypersensitivity reactions) and efficacy (SAA as surrogate endpoint for efficacy). A PMC will be issued to assess binding and neutralizing ADA responses with a validated assay capable of sensitively detecting ADA responses in the presence of JZP-458 levels that are present in the serum at the time of patient sampling.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:
The clinical pharmacology and pharmacokinetics characteristics of JZP-458 are summarized in Applicant Table 9

Applicant Table 9: Summary of General Pharmacology, Pharmacokinetic, and Other Information for JZP-458

PHYSICOCHEMICAL PROPERTIES	
Chemical structure and molecular weight	The structure of JZP-458 is a non-disulfide bonded, tetrameric protein consisting of 4 identical subunits with a combined molecular weight of 140 kDa. JZP-458 has the identical amino acid sequence to native *Erwinia asparaginase.* The amino acid sequence of crisantaspase is published in the Swiss Prot database (reference number P06608), see Module 3.2.S. 2.
PHARMACOLOGY	
Mechanism of Action	JZP-458 is an asparaginase enzyme that hydrolyzes asparagine into aspartic acid and ammonia, depriving leukemia cells of a critical amino acid. The mechanism of action of JZP-458 is thought to be based on the inability of leukemic cells to synthesize asparagine due to lack of asparagine synthetase activity, resulting in cytotoxicity specific for leukemic cells that depend on exogenous asparagine for their protein metabolism and survival.
Pharmacodynamics	At IM doses of 25 and 37.5 mg/m^2 JZP-458, complete depletion of plasma asparagine levels was observed after IM administration of JZP-458. Plasma asparagine levels declined rapidly from predose levels to levels below or near the assay lower limit of quantitation (0.025 µg/mL), and lasted throughout the treatment duration of Course 1 up to predose 6, where the last sample was collected. Four participants had transient low level increases in plasma asparagine (3 from cohort 1a (25 mg/m^2) and 1 from cohort 1b (37.5 mg/m^2), see data in Section 6.2.2.1.
Active Moiety	Recombinant Erwinia asparaginase produced in *Pseudomonas fluorescens.*
QT/QTc prolongation	JZP-458 is an enzyme, and is not expected to have an effect on the QT interval. FDA advice (14 September 2018) indicated that it was not necessary to conduct a formal assessment of JZP-458 for QTc prolongation.
GENERAL INFORATION	

<table>
<tr><td>Bioanalytical Assay</td><td>The bioanalytical methods used to quantify JZP-458 serum asparaginase activity (SAA), serum asparaginase concentration (SAC), plasma L-asparagine and L- glutamine levels, anti-drug antibody (ADA) levels, and neutralizing antibody (NAb) levels in human serum (Details to be provided by Applicant, see Appendix 14.4)

These methods support pharmacokinetics (SAA and SAC), pharmacodynamics (asparagine and glutamine) and immunogenicity (ADA and NAb) assessment of the JZP-458 clinical studies.</td></tr>
<tr><td>Patient PK vs Healthy subject PK</td><td>There are significant differences in the initial dataset of PK of for JZP-458 as reflected by the SAA levels between ALL patients vs. healthy volunteers due to yet undetermined reasons.

<table>
<tr><th>Population (Study)</th><th></th><th>1st C_{48h} (IU/mL)</th><th>1st C_{72h} (IU/mL)</th></tr>
<tr><td colspan="4">(b) (4)</td></tr>
<tr><td>HV (JZP458-101), (b) (4)</td><td></td><td>1.3150</td><td>0.6723</td></tr>
<tr><td rowspan="3">Patient (JZP458-201)</td><td>MWF</td><td>0.5243</td><td>NA</td></tr>
<tr><td>WFM</td><td>0.4412</td><td>NA</td></tr>
<tr><td>FMW</td><td>NA</td><td>0.2169</td></tr>
<tr><td colspan="4">(b) (4)</td></tr>
<tr><td>SAA Ratio (Patient/HV), (b) (4)</td><td></td><td>0.34 – 0.40</td><td>0.32</td></tr>
</table>
Source: response to FDA IR dated March 08 2021

As the JZP458-101 population did not reflect the JZP458-201 population and historical expectations across these populations has not been established, it was determined that merging these 2 datasets would not be appropriate at that time. Therefore, the PPK model was constructed using only data from study JZP458-201 to support the development of JZP-458. The target population is well reflected in JZP458-201 and, the number of participants and data-points</td></tr>
</table>

<table>
<tr><td></td><td>used to construct the model were robust. The PPK model that was developed fits the observed data very well.</td></tr>
<tr><td>Minimal effective dose</td><td>25 mg/m^2</td></tr>
<tr><td>Maximum tolerated dose of exposure</td><td>37.5 mg/m^2 (cohort 1c is currently testing 50 mg/m^2 IM to support a 72 hour (weekend) period.</td></tr>
<tr><td>Dose proportionality</td><td>Dose proportionality for JZP-458 was evaluated in the phase 1 single dose healthy volunteer Study JZP458-101 and the phase2/3 patient Study JZP458-201.

In JZP458-101, initial data on JZP-458 exposures increased with increasing doses based on SAA, and the increases in JZP-458 SAA exposures (C_{max} and AUC) were approximately dose-proportional between the dose range of 12.5 to 25 mg/m^2 for IM administration.

In JZP458-201, based on population PK analyses, model predicted C_{max} and AUC values are provided below after the 1st and 6th doses of JZP-458. With a dose increase of 1.5-fold from 25 to 37.5 mg/m^2, ratios of (C_{max} 37.5/C_{max} 25) were 1.63 and 1.62 for mean $C_{max,1}$ and $C_{max,6}$,, respectively, and ratio of (AUC 37.5/AUC 25) was 1.69, suggesting the increases in JZP-458 SAA exposures (C_{max} and AUC) were approximately dose-proportional between the dose range of 25 to 37.5 mg/m^2 for IM administration.

<table>
<tr><th>Dose (mg/m^2)</th><th>Mean $C_{max,1}$ (IU/mL)</th><th>Mean $C_{max,6}$ (IU/mL)</th><th>AUC_{0-336} (IU*h/mL)</th></tr>
<tr><td>25</td><td>1.2501</td><td>1.4704</td><td>283</td></tr>
<tr><td>37.5</td><td>2.0328</td><td>2.3760</td><td>478</td></tr>
<tr><td>DP (C_{max} or AUC 37.5/C_{max} or AUC 25)</td><td>1.63</td><td>1.62</td><td>1.69</td></tr>
<tr><td colspan="4">Source: Cmax and AUC from PPK report planned for submission with initial BLA</td></tr>
</table></td></tr>
<tr><td>Accumulation</td><td>Accumulation for JZP-458 was evaluated in the phase2/3 patient Study JZP458-201.
In JZP458-201, based on dosing frequency and half-life (16.1 hour) determined, the accumulation ratio for IM JZP-458 is estimated at 1.15 assuming a dosing interval of 48 hours.</td></tr>
</table>

<table>
<tr><td></td><td>Based on population PK analyses, in Study JZP-458-201, model predicted C_{max} values are provided below after the 1st and 6th doses of JZP-458. Accumulation ratios (calculated as $C_{max,6}/C_{max,1}$) were 1.18 and 1.17 for 25 and 37.5 mg/m^2, respectively, suggesting very little accumulation.
<table>
<tr><th>Dose (mg/m^2)</th><th>Mean $C_{max,1}$ (IU/mL)</th><th>Mean $C_{max,6}$ (IU/mL)</th><th>Accumulation Ratio</th></tr>
<tr><td>25</td><td>1.2501</td><td>1.4704</td><td>1.18</td></tr>
<tr><td>37.5</td><td>2.0328</td><td>2.3760</td><td>1.17</td></tr>
<tr><td colspan="4">Source: Cmax from PPK report planned for submission with initial BLA</td></tr>
</table></td></tr>
<tr><td>Variability</td><td>In the JZP458-201 patient Study JZP458-201, %CV for observed 48h and 72h NSAA levels was 43.3-58.8% and 43.6-76.8%, respectively, at 25 mg/m^2 and 40.3-77.8% and 69.9-96.3%, respectively, at 37.5 mg/m^2
Source: IA Table 9.2.2.1</td></tr>
<tr><td>Immunogenicity</td><td>The immunogenicity of IM JZP-458 following repeat administration has been evaluated in the initial Interim Analysis of ongoing Study JZP458-201.

In this initial IA, 30 of 86 participants (34.9%) were confirmed with positive ADA toward JZP-458. Of these 30 ADA positive participants, 1 participant experienced a hypersensitivity reaction during the study (1.2%; 1 of 86), and 3 participants had neutralizing antibodies (3.5%; 3 of 86). ADA samples will be collected until the end of the study. Further assessments of ADA results, including patients at 25/25/50 mg/m^2, will be provided once available, and are intended to support the positive benefit: risk profile for the use of JZP-458 in all patients.</td></tr>
<tr><td colspan="2">ABSORPTION</td></tr>
<tr><td>Bioavailability</td><td>Bioavailability of JZP-458 is not available in the patient population; IV data is not available as enrollment for IV cohort is ongoing.

Bioavailability for IM JZP-458 was estimated at 36.8% based on SAA data in JZP458-101 study.</td></tr>
</table>

T_{max}	The median (range) of individual predicted T_{max} of JZP-458 after the 6th dose of JZP-458 is 13.1 (5.85-20.2) hours in ALL/LBL patients from Study JZP458-201 based on 85 patients from 25 and 37.5 mg/m^2. Source: Initial PPK report dated February 09 2021 DCO October 14 2020
Food Effect	Not applicable (JZP-458 is administered IM)
DISTRIBUTION	
Apparent Volume of distribution	Population estimate of V/F for JZP-458 in a 40 kg patient is 3.35 (standard error: 0.46) L in ALL/LBL patients from Study JZP458-201 based on 85 patients from 25 and 37.5 mg/m^2 *Source:* : Initial PPK report dated February 09 2021 DCO October 14 2020
ELIMINATION	
Half-life and apparent clearance	The PK of JZP-458 is described by a 1-compartment IM model with linear elimination and sequential mixed order absorption, with weight included as an allometric covariate on CL and V. The mean (SD) of individual predicted terminal elimination half-life (t1/2) of JZP-458 following a single dose simulation out to 96 hours postdose is 16.1 (1.38) hours, and the population estimate of CL/F for JZP-458 in a 40 kg patient is 0.416 (standard error: 0.0193) L/h in ALL/LBL patients from Study JZP458-201 based on 85 patients from 25 and 37.5 mg/m^2. *Source: CL/F from i*nitial PPK report dated February 09 2021 DCO October 14 2020*1; t1/2 from PPK report DCO January 11 2021.*
Metabolism	JZP-458 is an enzyme and it is expected to be metabolized by proteolytic degradation.
EXCRETION	No mass balance study has been conducted.

The Applicant's Position:

The data generated from the clinical pharmacology program sufficiently characterizes the pharmacokinetics of JZP-458 and guided effective administration of JZP-458 to patients. Assessments included determination of the ADME profile, dose proportionality, accumulation, patient PK vs healthy subject PK, pharmacodynamic data (asparagine depletion), immunogenicity.

The FDA's Assessment:

FDA agrees that the observed data provided by the Applicant sufficiently characterize the PK of JZP-458; however, the Applicant's PopPK analysis was insufficient. FDA's assessment of JZP-458 General Pharmacology and Pharmacokinetic Characteristics is summarized the in the table below based on FDA's independent analysis. PK parameters are presented based on SAA following administration of 25 mg/m^2 IM Q48H x 7 doses per 2-week course in pediatric and young adult patients (1 to 24 years), unless otherwise specified.

PHYSICOCHEMICAL PROPERTIES	
Chemical structure and molecular weight	FDA agrees with the Applicant's position.
PHARMACOLOGY	
Mechanism of Action	FDA agrees with the Applicant's position.
Pharmacodynamics	The bioanalytical methods used to quantify L-asparagine and L-glutamine in plasma were inadequate (Refer to **Appendix 14.4.1**). Therefore, FDA did not assess effects of JZP-458 on L-asparagine and L-glutamine plasma concentrations.
Active Moiety	FDA agrees with the Applicant's position.
QT/QTc prolongation	FDA agrees with the Applicant's position.
GENERAL INFORATION	
Bioanalytical Assay	• FDA agrees with the bioanalytical methods used to quantify JZP-458 SAA and SAC. However, the potential effects of antidrug antibodies' interference on the SAA and SAC analytical methods were not evaluated (Refer to **Appendix 14.4.1**). • The bioanalytical methods used to quantify L-asparagine and L-glutamine in plasma were inadequate (Refer to **Appendix 14.4.1**). • The bioanalytical methods used to evaluate ADA and NAb in human serum had insufficient drug tolerance to detect ADA or NAb in the presence of JZP-458 at clinically observed concentrations (Refer to OBP Review).

	Therefore, results of the ADA and NAb assays may underestimate the true incidence of immunogenicity.
Patient PK vs Healthy subject PK	Based on the FDA's independent analysis, patients with ALL/LBL (n=85) had higher CL/F (0.31 L/hour/m^2 [36%] vs. 0.15 L/hour/m^2 [CV% = 18%]) and smaller V/F (1.48 L/m^2 [49%] vs. 3.04 L/m^2 [12%]) than healthy subjects (n=12), following IM dosing of JZP-458.
Minimal effective dose	A dosing regimen of 25 mg/m^2 IM Q48H is predicted to maintain NSAA $\geq$0.1 IU/mL at 48-hours post-dose in >90% of patients.
Maximum tolerated dose of exposure	The dosing regimen of 37.5 mg/m^2 IM MWF x 6 doses per 2-week course was acceptable from a safety perspective. Limited data are available from patients treated with 25/25/50 mg/m^2 IM MWF x 6 doses per 2-week course. Refer to **Section 8.3** for a review of safety data.
Dose proportionality	JZP-458 AUC and C_{max} increase dose proportionally over a dose range from 12.5 to 50 mg/m^2 IM.
Accumulation	In patients treated with 25 mg/m^2 IM Q48H x 7 doses, the predicted accumulation ratio after the seventh dose is 1.24-fold for C_{max}, 1.21-fold for C_{48h}, and 1.28-fold for $AUC_{0\text{-}48h}$.
Variability	FDA agrees with the Applicant's presentation of the observed data as of the IA for Study JZP458-201. Based on FDA's PopPK analysis, the %CV was 36% for BSA-normalized CL/F and 49% for BSA-normalized Vd/F.
Immunogenicity	Treatment-emergent ADA against JZP-458 were detected in 40/99 (40.4%) patients in Study JZP458-201 with a baseline and at least one post-baseline ADA sample; 4 patients (4%) had neutralizing antibodies against JZP-458. However, as described above, the immunogenicity assays were inadequate and therefore the observed results may underestimate the true incidence of ADA against JZP-458 due to potential false negatives.
ABSORPTION	
Bioavailability	FDA agrees with the Applicant. Based on FDA's PopPK analysis, the bioavailability for IM JZP-458 was estimated at 36.5% based on SAA data from healthy adult subjects in JZP458-101 study.

T_{max}	The PK of JZP-458 was described by a 1-compartment model with sequential zero- and first-order absorption and first-order elimination. Based on FDA's PopPK analysis, the median (range) of individual predicted T_{max} of JZP-458 after IM administration is 10 (10-12) hours in patients with ALL and LBL.
Food Effect	FDA agrees with the Applicant.
DISTRIBUTION	
Apparent Volume of distribution	Based on FDA's PopPK analysis, the geometric mean (%CV) V/F of JZP-458 is 1.48 L/m^2 (49%) in patients with ALL and LBL. BSA is a significant covariate on JZP-458 V/F.
ELIMINATION	
Half-life and apparent clearance	Based on FDA's PopPK analysis, the geometric mean (%CV) CL/F of JZP-458 is 0.31 L/hour/m^2 (36%) and the apparent half-life is 18.2 hours (16%) in patients with ALL and LBL following IM administration. BSA is a significant covariate on JZP-458 CL/F.
Metabolism	FDA agrees with the Applicant.
EXCRETION	FDA agrees with the Applicant.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:
Clinical pharmacology program for JZP-458 includes two clinical studies: JZP458-101 and JZP458-201, See Applicant Table 13.
For observed efficacy data from 25 and 37.5 mg/m^2 (DCO October 14, 2020), see section 6.2.2.1.

Population PK analysis of JZP-458 from Cohorts 1a and 1b (25 and 37.5 mg/m^2)
Population PK analysis was performed to support dosing of JZP-458 in participants with ALL and LBL who developed hypersensitivity to *E. coli*-derived asparaginase. As there were significant differences observed in the SAA levels between healthy volunteers in Study JZP458-101 and ALL/LBL patients in Study JZP458-201 (based on the initial dataset), the initial datasets were not pooled. The mechanism for this difference is still unknown and considered multifactorial. Data limited to the JZP458-201 study were used for the PPK model development of JZP-458. PPK modeling and simulation data submitted to the initial BLA were based on observed efficacy data

from JZP458-201 (25mg/m^2 and 37.5mg/m^2) DCO October 14 2020. Updated data and information are being provided to the BLA as available. The PPK model established fits the observed data from the JZP458-201 study very well and supports clinical analysis and development of JZP-458.

An initial PPK modeling analysis was performed using SAA data from 25 and 37.5 mg/m^2 from Study JZP458-201 (DCO October 14 2020). A validated PPK model has been developed. SAA data across all courses from 85 patients (32 patients at 25 mg/m^2 [cohort 1a] and 53 patients at 37.5 mg/m^2 [cohort 1b]) who received intramuscular (IM) JZP-458 were included in the population PK model development. Models were fit to the SAA data to identify a structural model. Age, sex, height, body weight, body surface area (BSA), ethnicity, race, primary disease – ALL and LBL, disease subtype (B or T-cell), and ADA status were evaluated as potential covariates on JZP-458 PK. Only weight was identified as a statistically significant covariate for JZP-458 clearance (CL) and volume (V). The covariate model developed for JZP-458 was a 1-compartment IM-only model with linear elimination and sequential mixed order absorption, with weight included as an allometric covariate on JZP-458 SAA CL and V, and a proportional residual error model. Model diagnostics showed good fits based on the predicted versus the observed data. PPK modeling and simulation.

Pharmacokinetic parameters estimated from the PPK modeling are presented in Applicant Table 10

Applicant Table 10: JZP458-201 – Population PK Parameters for JZP-458 (Initial PPK report DCO October 14 2020)

Parameters	Model Form	Estimate	CV %	Standard error	Relative standard error	Lower CI	Upper CI	Shrinkage
Apparent Clearance (mL/h)		416		19.3	4.65	378	454	
Apparent Central Compartment Volume of distribution (mL)		3350		460	13.7	2450	4250	
Absorption Rate Constant (1/h)		0.0457		0.00204	4.46	0.0417	0.0497	
Zero Order Rate (IU/h)		7780		886	11.4	6040	9520	

Wt Cov On Cl		0.993		0.0674	6.79	0.861	1.13	
Wt Cov On V		1.16		0.136	11.8	0.893	1.43	
BSV Clearance (CL)	Exponential	0.108	33.8%	0.0159	14.7	0.0768	0.139	6.68%
BSV Volume (V)	Exponential	0.4	70.1%	0.0993	24.8	0.205	0.595	13.4%
Within Subject Variability	Exponential	0.18	42.4%	0.0148	8.22	0.151	0.209	6.45%

Footnote: CI = Confidence interval; CV = Coefficient of variation; SD = standard deviation; WT = Weight; CL/F = 416 * (WT/40) ^ 0.993;
V/F = 3350 * (WT/40) ^ 1.16
Source: Initial PPK report dated February 09 2021 DCO October 14 2020

The covariate model was used to simulate SAA profiles (2000 participants) to determine the proportion of participants achieving a therapeutic NSAA level of ≥ 0.1 IU/mL using different dosing regimens; See Section 6.2.2.1

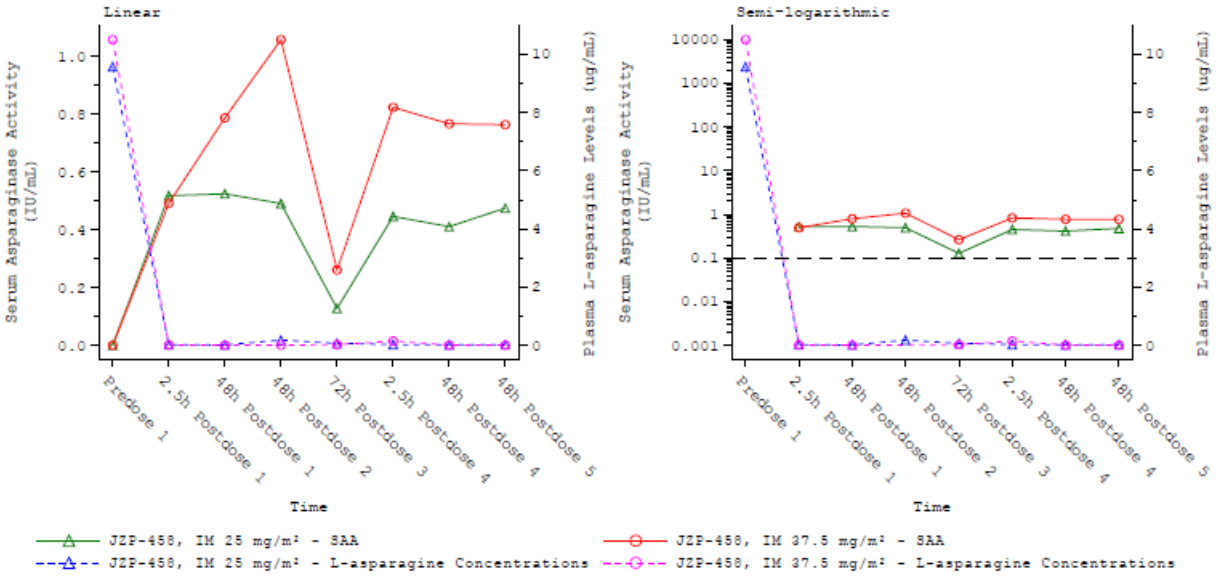
PPK modeling and simulation data from the initial PPK analysis dated February 09 2021 suggested that when:

- JZP458 administered IM at a dose 50/25/25 mg/m2 on a FMW schedule, 97.7% of patients (95% CI: 97.0%, 98.4%) are expected to achieve the last 72-hour NSAA levels ≥ 0.1 IU/mL, and 99.8% of patients (95% CI: 99.6%, 100%) are expected to achieve the last 48-hour NSAA level ≥ 0.1 IU/mL (See Applicant Table 7 and Applicant Figure 1).
- JZP-458 administered IM at a dose of 25 mg/m^2 every 48-hours, ≥99.7% of patients (95% CI: 99.5%, 99.9%) are expected to achieve any 48-hour NSAA level ≥ 0.1 IU/mL (See Applicant Table 9 and Applicant Figure 2). The PPK modeling and simulation will be updated from the February 9, 2021 version (based on 25 and 37.5 mg/m^2 at the Initial IA DCO) to include the 25/25/50 mg/m^2 N=17 observed data for submission to the BLA in April 2021, pending FDA agreement at the late March 2021 pre-submission meeting.

<u>PD (Asparagine Depletion) Data from Cohorts 1a and 1b (25 and 37.5 mg/m^2, DCO October 14, 2020)</u>
Depletion of asparagine after IM JZP-458 was also evaluated in JZP458-201 study. Asparagine concentrations were assayed using a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method. Administration of IM JZP-458 at 25 (N=32) and 37.5 mg/m^2 (N=53) resulted in complete depletion of plasma asparagine levels. Plasma asparagine levels declined rapidly from predose levels to levels below or near the assay lower limit of

quantitation (0.025 µg/mL), and lasted throughout the treatment duration of Course 1 up to predose 6, where the last sample was collected (Applicant Figure 3). Four participants had transient low-level increases in plasma asparagine (3 from cohort 1a (25mg/m^2) and 1 from cohort 1b (25 and 37.5 mg/m^2).

Applicant Figure 3 Mean SAA vs Time Profiles for Corresponding Mean Plasma L-Asparagine Levels with IM JZP-458 in Course 1 on Linear and Semi-logarithmic Scales (PD Analysis Set) (MWF schedule only); JZP458-201 DCO October 14 2020



Abbreviations: IM = Intramuscular injection; SAA = Serum asparaginase activity
Lower limit of quantitation (LLOQ): SAA 0.0350 IU/mL, L-asparagine = 0.0250 µg/mL. Values below the LLOQ were set to 0. For the semi-logarithmic plot, only SAA is on a semi-logarithmic scale.
Source: Initial IA Figure 9.2.4.3

JZP458-201 Observed efficacy data from 25/25/50 mg/m^2 Cohort 1c (DCO 11 January 2021)
A total of 17 participants (including 1 participant who was never dosed) were enrolled in cohort 1c (25/25/50 mg/m^2 administered IM on MWF). Additional safety and efficacy information through January 11, 2021 will be submitted to BLA in the Update Report.

The Applicant's Position:
JZP-458 clinical pharmacology program provides critical evidence of effectiveness demonstrated by the totality of data, which includes observed NSAA data at the protocol-specified time points, population pharmacokinetic (PPK) modeling and simulation results, asparagine depletion, and safety data.

Evidence of effectiveness was obtained from the pivotal phase 2/3 Study JZP458-201, based on a combination of observed data and PPK modeling and simulation results. The PPK model provides critical supporting data to establish the optimal efficacy of JZP-458 at the proposed dosing regimen of 25 mg/m^2 on Monday and Wednesday and 50 mg/m^2 on Friday or 25 mg/m^2 every 48-hours. The PPK analysis provides robust support of the observed data and for the total data package for the BLA because the model uses pooled participant data from all dose levels, all time points, and across all courses, and it uses continuous rather than categorical data. Applicant believes that the PPK model results illustrate more accurately the SAA exposures of JZP-458 than does the primary analysis methodology in the protocol (because protocol specified endpoint relies solely on a binary determination based on the last 72-hour NSAA level). The PPK model provides reliable predictions of NSAA levels at the 48- and 72-hour timepoints. This combined approach of supplying both observed and modeled data provides for a robust data package to support the registration of JZP 458 with efficacy based on NSAA level ≥ 0.1 U/mL at 48 and 72 hours.

PPK modeling and simulation data from the initial PPK analysis based on N=85 from the initial IA at 25mg/m^2 and 37.5mg/m^2 (initial PPK report dated 09 February 2021) suggested that when JZP-458 is administered IM at a dose 50/25/25 mg/m^2 on a FMW schedule, 97.7% of patients (95% CI: 97.0%, 98.4%) are expected to achieve the last 72-hour NSAA levels ≥ 0.1 IU/mL, and 99.8% of patients (95% CI: 99.6%, 100%) are expected to achieve the last 48-hour NSAA level ≥ 0.1 IU/mL (See Applicant Table 7 and Applicant Figure 1) when JZP-458 is administered IM at a dose of 25 mg/m^2 every 48-hours, ≥99.7% of patients (95% CI: 99.5%, 99.9%) are expected to achieve any 48-hour NSAA level ≥ 0.1 IU/mL (See Applicant Table 9 and Applicant Figure 2).

The updated PPK modeling and simulation analysis with data from 25mg/m^2 [cohorts 1a (N = 32)], 37.5 mg/m2 [cohort 1b (N = 53)], and 25/25/50 mg/m^2 [cohort 1c (N = 16)] of the will be available for submission to the BLA in April pending agreement in the pre-submission meeting.

The observed SAA data from 25/25/50 mg/m^2 N=17(DCO January 11 2021), which will be provided to FDA in an update report is intended to support the efficacy of IM JZP-458 administered 25/25/50 mg/m^2 on MWF schedule. In a preliminary review, these data fit with the initial 25/25/50 mg/m^2 projections based on the 25 mg/m^2 (cohort 1a) and 37.5 mg/m^2 (cohort 1b) and supported the PPK modeling and simulation results for the 25/25/50 mg/m^2 administered IM on MWF regimen as discussed in data section above.

The FDA's Assessment:

The clinical pharmacology program provides pivotal evidence of effectiveness for JZP-458. SAA is an established surrogate endpoint for efficacy of asparaginase products with a goal of NSAA ≥0.1 IU/mL in at least 90% of patients. In Study JZP458-201, the first two studied dosage regimens (25 mg/m^2 and 37.5 mg/m^2 IM MWF x 6 doses per 2-week course) both failed the primary endpoint (Refer to **Applicant Table 6**); however 25mg/m^2 IM Q48H x 7 doses and

25/25/50 mg/m^2 IM MWF x 6 doses per 2-week courses were identified as JZP-458 dosage regimens predicted to achieve NSAA ≥0.1 IU/mL in >90% of patients after 48 and 72 hours, respectively.

FDA conducted an independent analysis of SAA data. Refer to **Appendix 14.4.3** for details of FDA's independent PopPK analysis. In brief, FDA's final PopPK model was a one-compartment model with sequential mixed order absorption and linear elimination, with BSA included as an allometric covariate on both CL/F and V/F, with inter-individual variability (IIV) expressed as an exponential term on CL/F, V/F, zero-order absorption rate (R1) and first-order absorption rate constant (Ka), and a mixed proportional and additive residual error model.

Using FDA's final PopPK model, simulations of SAA were conducted based on a virtual population generated by resampling with replacement from the National Health and Nutrition Examination Survey (NHANES) database. The virtual population included 2,000 subjects ranged from 2 to 85 years of age with a median [range] BSA of 1.68 [0.47, 2.92] m^2 and a median [range] body weight of 62.7 [8.9, 174.6] kg.

Table 11 shows a comparison of the observed, Applicant simulated, and FDA simulated NSAA response rates for each dosing regimen. For the 25/25/50 mg/m^2 MWF x 6 regimen, two simulated scenarios are presented: first dose starting on a Friday to represent the worst-case scenario and first dose starting on a Monday to represent the best-case scenario.

FDA Table 11: Observed and Simulated NSAA Response Rates

NSAA Response Rate	JZP-458 Dosing Regimen IM				
	25 mg/m^2 MWF x 6	**37.5 mg/m^2 MWF x 6**	**50/25/25 mg/m^2 FMW x 6**	**25/25/50 mg/m^2 MWF x 6**	**25 mg/m^2 Q48H x 7**
Observed at Last 72-hour* % (n/N) [95% CI]	65.5% (19/29) [48.2, 82.8]	80.4% (41/51) [69.5, 91.3]	93.3% (14/15) [80.7, 100]		N/A
Observed at Last 48-hour % (n/N) [95%) CI]**	96.9% (31/32) [90.8, 100]	98.1% (52/53) [94.5, 100]	93.8% (15/16) [81.9, 100]		N/A
Applicant's Simulation [95% CI]	72.6% [70.6, 74.6]	94.2% [93.1, 95.2]	96.4% [95.6, 97.2]	97.2% [96.5, 97.9]	99.7% [99.5, 99.9]
FDA's Simulation [95% CI]	67.2% [64.7, 69.1]	83.7% [82.1, 85.4]	90.6% [89.2, 91.9]	91.4% [90.2, 92.7]	93.6% [92.6, 94.6]

NSAA Response Rate defined as proportion of patients maintaining NSAA ≥0.1 IU/mL at specified timepoint. For simulation results, NSAA response rate is based on the last 72 hour interval for MWF regimens or last 48 hour interval for Q48H regimen; N/A – not applicable; IM – intramuscularly; *Study JZP458-201 primary endpoint; **Study JZP458-201 key secondary endpoint

Source: JZP458-201 CSR Version 2, Table 7; Applicant's PopPK report dated 8 Apr 2021 Tables 8.12 and 8.15; Applicant's PopPK report dated 18 Mar 2021 Tables 5 and 6; and FDA's analysis (Appendix 14.4.3 **Table 70**)

FDA's simulations agree well with the observed NSAA response rates for the three studied dosing regimens. For both proposed dosing regimens (25 mg/m^2 IM Q48H x 7 doses or 25/25/50 mg/m^2 IM MWF x 6 doses per 2-week course), >90% of patients will achieve NSAA response (NSAA ≥0.1 IU/mL at last 72-hour or last 48-hour interval).

In summary, administration of either JZP-458 25/25/50 mg/m^2 IM MWF x 6 doses per 2-week course or 25 mg/m^2 IM Q48H x 7 doses per 2-week course is predicted to meet the primary endpoint of NSAA ≥0.1 IU/mL in at least 90% of patients.

The Applicant's asparagine depletion data was not reviewed due to inadequacy of the bioanalytical methods (Refer to **Appendix 14.4.1**).

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

Data:
Refer to Section 6.3.1 on observed efficacy data, asparagine depletion, and PPK modeling and simulation results

The Applicant's Position:
Population PK analysis indicated that body size is the only significant patient specific factor shown to impact JZP-458 clearance and volume distribution. Therefore, the proposed BSA based dosing regimen is appropriate. The PPK modeling and simulation predicted that JZP-458 administered IM at a dose 50/25/25 mg/m^2 on a FMW schedule, 97.7% of patients (95% CI: 97.0%, 98.4%) are expected to achieve the last 72-hour NSAA levels ≥ 0.1 IU/mL, and 99.8% of patients (95% CI: 99.6%, 100%) are expected to achieve the last 48-hour NSAA level ≥ 0.1 IU/mL.

In addition, as of the DCO October 14 2020, adverse events of interest such as allergic reactions, thrombosis and pancreatitis have remained within acceptable, pre-specified thresholds, consistent with the known safety profile of asparaginases.

The JZP-458 clinical pharmacology program provides critical evidence of effectiveness demonstrated by the totality of data, which includes observed NSAA data at the protocol-specified time points, population pharmacokinetic (PPK) modeling and simulation results, asparagine depletion data, and safety data.

Applicant confirms that the proposed dosing regimen for JZP-458 as described below is appropriate for the target patient population for which the indication is being sought:

> JZP-458 administered IM at 25 mg/m^2 on Mondays and Wednesdays and 50 mg/m^2 on Fridays for a total of 6 doses every 2 weeks. This is the preferred dosing regimen because it provides optimal benefit:risk profiles for JZP-458, with sustained SAA levels ≥ 0.1 IU/mL over 48- and 72-hour dosing durations with acceptable safety to provide meaningful benefit to patients, and to allow for MWF dosing in line with current treatment practice.

The FDA's Assessment:

The recommended dosage regimen for JZP-458 is 25 mg/m^2 IM Q48H x 7 doses per 2-week course. As described above in **Section 6.3.2.1**, this dosage regimen is predicted to achieve NSAA ≥0.1 IU/mL in >90% of patients. The safety of this regimen is supported by the observed safety profile in patients administered 25 mg/m^2 or 37.5 mg/m^2 IM MWF x 6 doses per 2-week course in Study JZP458-201 (Refer to **Section 8.3**) and exposure-response analyses for safety.

The Applicant's proposed dosage regimen of 25/25/50 mg/m^2 IM MWF x 6 doses per 2-week course is also predicted to achieve NSAA ≥0.1 IU/mL in >90% of patients (Refer to **Section 6.3.2.1** and **Appendix 14.4.3**); however, due to the small number of patients and limited follow-up as of the 11 Jan 2021 data cut-off, there was insufficient safety data to support this regimen (Refer to **Section 8.3**).

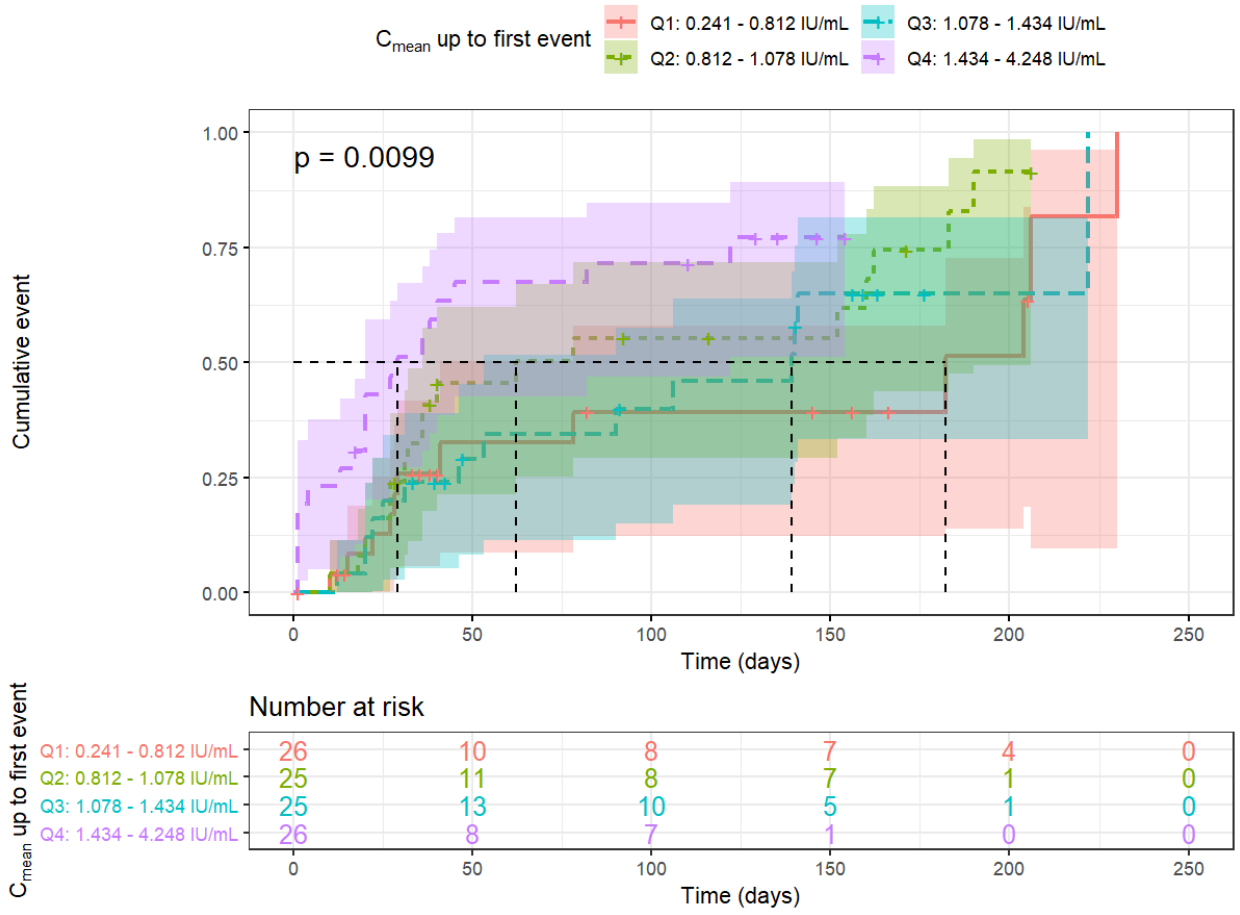
Exposure-Response for Safety:

Exposure-response (E-R) analyses for selected safety events (drug hypersensitivity, pancreatitis, hepatotoxicity, and thrombosis) were conducted based on SAA PK metrics derived from FDA's updated PopPK model and safety data from the first 102 patients treated with JZP-458 in Study JZP458-201 through the 11 Jan 2021 data cut-off. The E-R database included SAA data from 33 patients treated with 25 mg/m^2 IM MWF x 6 doses, 53 patients treated with 37.5 mg/m^2 IM MWF x 6 doses, and 16 patients treated with 25/25/50 mg/m^2 IM MWF x 6 doses per 2-week courses.

Based on Kaplan-Meier curves of the time to first event stratified by exposure quartiles, there appear to be a trend of E-R towards significantly earlier onset of hepatotoxicity (**FDA Figure** 4) with higher SAA C_{mean} from the first JZP-458 dose up to the occurrence of the first adverse event. This trend was not observed for hypersensitivity, pancreatitis, or thrombosis. The observed E-R relationship is potentially confounded by considerable heterogeneity among patients receiving JZP-458. In general, treatment of patients with ALL or LBL utilizes multiple blocks of multiagent chemotherapy with varying intensity and medications per block. Patients in Study JZP458-201 had varying chemotherapy treatment plans (see **FDA Table 22**), began treatment with JZP-458 at differing points in their overall treatment regimens, and received

each course of JZP-458 at varying intervals. Given the variability in overall treatment plans among patients treated with JZP-458, the relative contribution of JZP-458 dosage regimens to the observed E-R relationship is not clear. Refer to **Appendix 14.4.6** for more details regarding FDA's independent E-R analysis for safety.

FDA Figure 4: FDA's Kaplan-Meier Curves of the Time to the First Hepatotoxicity Adverse Event Stratified by the SAA Average Concentration Up to the First Event



Source: FDA's analysis.

Based on logistic regression analysis, no significant E-R relationships were identified for the incidence of selected safety events vs. any of the SAA PK metrics ($AUC_{0\text{-}336h}$ in Cycle 1, C_{max} in Cycle 1, or C_{mean} during treatment). Exposure of JZP-458 after administration of the recommended dosage regimen (25 mg/m^2 IM Q48H x 7 doses per 2-week course) is well within the range of observed exposure. The C_{max} of JZP-458 after administration of 50 mg/m^2 (in the 25/25/50 mg/m^2 IM MWF x 6 doses per 2-week course regimen) is at the top of the observed exposure range. Given the limited number of patients treated with this regimen, short duration of follow-up, and low incidence of some events, a clinically meaningful increase in the incidence

of the selected safety events cannot be excluded for administration of 25/25/50 mg/m^2 IM MWF x 6 doses per 2-week course. Refer to **Section 8.3** for additional review of the available safety data.

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

Data:
Based on PPK analysis, the influence of intrinsic factors such as age, sex, height, body weight, body surface area (BSA), ethnicity, race, primary disease – ALL and LBL, disease subtype (B or T-cell), and ADA status were evaluated as potential covariates on JZP-458 PK. Only weight was identified as a statistically significant covariate for JZP-458 clearance (CL) and volume (V)

Data on the impact of renal or hepatic Impairment or DDI interactions on JZP-458 PK is described in Section 6.2.2.2.

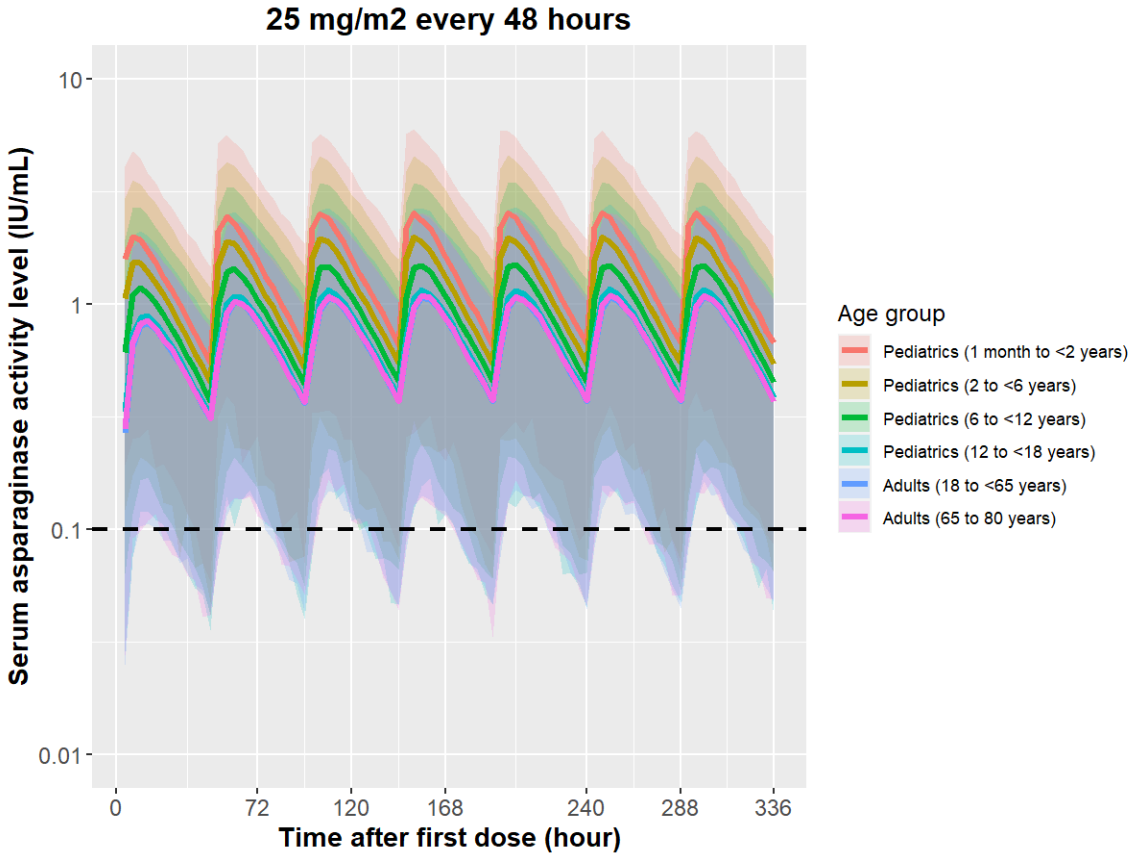
The Applicant's Position:
JZP-458 does not require an alternative dose or dosing regimen for subpopulations based on the intrinsic patient factors. JZP-458 is an enzyme with a molecular weight of 140kDa, which is unlikely to be renally eliminated and is not metabolized by hepatic enzymes. Renal and hepatic impairment are unlikely to alter the PK of JZP-458. Drug-drug interactions (DDIs) are unlikely as JZP-458 is an enzyme and is not metabolized by cytochrome P450 enzymes.

The FDA's Assessment:

Body Surface Area: As described above, BSA is a significant covariate on JZP-458 V/F and CL/F, supporting the BSA-based dosing regimen.

Pediatric Patients ≥1 Month of Age: In Study JZP458-201, the majority of patients treated with JZP-458 were pediatric patients. As of the data cut-off date of 11 Jan 2021, there were 2 infants (≥1 month to <2 years), 72 children (≥2 years to <12 months), 26 adolescents (≥12 years to <18 years), and 12 adult patients (≥18 years) with exposure to JZP-458. Simulations for SAA profile were performed for 2,000 patients ranging from 1 month of age to 80 years of age (155 from 1 month to <2 years of age, 248 from 2 to <6 years of age, 328 from 6 to <12 years of age, and 269 from 12 to <18 years of age, 739 from 18 to <65 years of age, and 261 from 65 to 80 years of age). For all age groups, the SAA profiles were similar (**F FDA** igure 5) and proportions of patients with predicted NSAA ≥0.1 IU/mL were >90% (**FDA Table** 12).

FDA Figure 5: FDA's Simulated Median and 95% Prediction Intervals of SAA Time Profiles in Subjects Following 25mg/m2 Every 48 Hours for 7 Doses per 2-Week Course Stratified by Six Age Groups



Source: *FDA's analysis.*

FDA Table 12: FDA's Simulated Median and 95% Confidence Intervals of Response Rate of Achieving a Therapeutic NSAA in Subjects Following 25mg/m^2 Every 48 Hours for 7 Doses per 2-Week Course Stratified by Six Age Groups

Dosing Regimen	Age group	Simulated response rate Median [95% CI]
25 mg/m^2 every 48 hours for 7 doses per 2-week course	1 month - <2 years of age	96.8% [94.2%, 98.7%]
	2 - <6 years of age	96.0% [93.1%, 98.0%]
	6 - <12 years of age	94.5% [91.8%, 96.6%]
	12 - <18 years of age	93.3% [89.6%, 95.5%]
	18 - <65 years of age	92.6% [90.8%, 94.5%]
	65 - <80 years of age	92.5% [89.7%, 95.4%]

Source: *FDA's analysis.*

Race and Ethnicity: In FDA's PopPK analysis, Black (n=10) and Asian (n=5) patients had 29% decreased CL/F compared to White patients (n=61). There were no differences in CL/F between Hispanic (n=28) and Non-Hispanic (n=53) patients. Regardless of race or ethnicity, at least 90% of patients are predicted to meet the primary endpoint (NSAA ≥0.1 IU/mL) after administration of the recommended dosage regimen. In addition, race or ethnicity was not a significant covariate in the E-R relationships for safety. Therefore, no dosage modification is recommended based on race or ethnicity. Refer to **Appendix 14.4.3** and **Appendix 14.4.6** for more details on FDA's independent PopPK analysis and E-R analysis for safety, respectively.

Renal and Hepatic Impairment: FDA agrees with the Applicant's position.

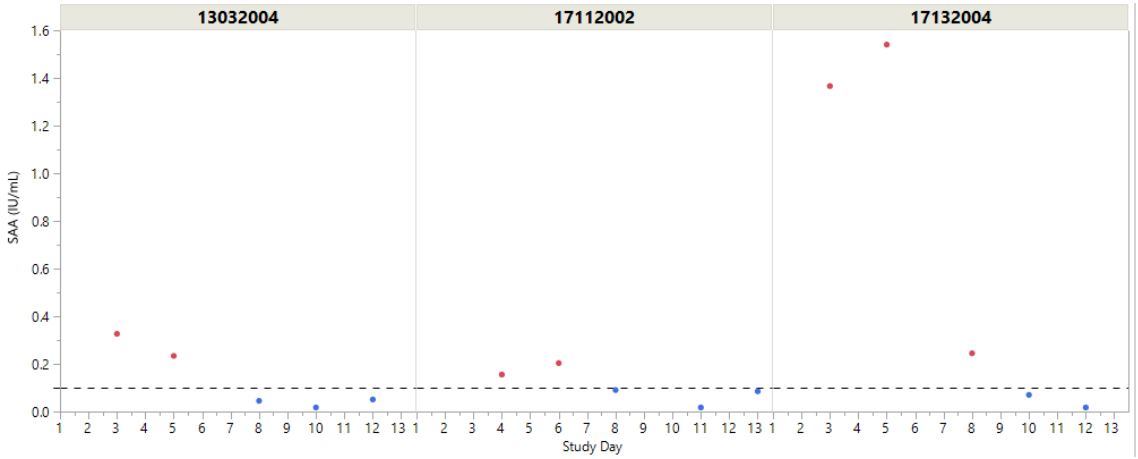
Immunogenicity: The immunogenicity assays were inadequate and therefore the observed results may underestimate the true incidence of ADA against JZP-458 due to potential false negatives. Immunogenicity samples with time-matched PK had JZP-458 concentrations above the established drug tolerance of the assay for 119/416 (28.6%) screening ADA samples, 22/101 (21.8%) confirmatory ADA samples, and 10/70 (14.3%) neutralizing ADA samples.

Using the available assays, treatment-emergent ADA against JZP-458 were detected in 40/99 (40.4%) patients in Study JZP458-201 with a baseline and at least one post-baseline ADA sample; 4 patients (4%) had neutralizing antibodies against JZP-458. Three additional patients were ADA positive at baseline with either the same or decreased titer post-baseline or no sample post-baseline.

In FDA's PopPK model, presence of NAb was not a significant covariate on JZP-458 PK; however, the analysis was limited by the small number of patients with NAb (n=2).

Three patients were identified with reduced SAA coinciding with development of ADA against JZP-458 in Course 1 (**FDA Figure** 6). All three patients were ADA- at baseline and ADA+ prior to Dose 6 in Course 1. All three patients were negative in the NAb assay.

FDA Figure 6: SAA and ADA Profiles in ADA+ Patients with NSAA <0.1 IU/mL During Course 1



Notes: The black dashed line is set at SAA = 0.1 IU/mL; red points represent NSAA ≥0.1 IU/mL and blue points represent NSAA <0.1 IU/mL
Source: *Reviewer's Analysis*

Of the 40 patients with treatment-emergent ADA, 10 (25%) had an adverse event of drug hypersensitivity compared to 16/56 (28.6%) evaluable patients who were never ADA+.

Given the limited data and inadequacy of the immunogenicity assays, the effects of anti-JZP-458 antibodies on the safety and PK (SAA also as surrogate endpoint for efficacy) of JZP-458 are inconclusive. Immunogenicity data from validated assays with sufficient drug tolerance are needed to appropriately evaluate potential effects of anti-JZP-458 antibodies on JZP-458 safety and PK. A PMC will be issued to assess binding and neutralizing ADA responses with a validated assay capable of sensitively detecting ADA responses in the presence of JZP-458 levels that are present in the serum at the time of patient sampling. Refer to OBP review for additional information on the immunogenicity assays and relevant PMCs.

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

Data:
There is no data available at this time.

The Applicant's Position:
Clinical food-drug interaction study was not conducted because JZP-458 is administered IM. JZP-458 is an enzyme administered IM so food-drug interaction is not expected. Clinical drug-drug interaction (DDI) study was not conducted because JZP-458 is an enzyme and is not metabolized by hepatic CYP450 enzymes. JZP-458 metabolism is presumed to occur via proteolytic degradation, therefore, DDIs involving CYPs are not expected. Thus, no

management strategy is needed for food-drug or drug-drug interactions.

The FDA's Assessment:
FDA agrees with the Applicant's position.

7 SOURCES OF CLINICAL DATA

7.1. Clinical Studies

Studies pertinent to efficacy and safety evaluation for JZP-458 include the completed Phase 1 study (JZP458-101) and an ongoing Phase 2/3 study (JZP458-201 Part A) that currently includes 3 IM cohorts (cohort 1a (25mg/m^2), 1b (37.5 mg/m^2) and 1c 25/25/50 mg/m^2) as detailed in Applicant Table 13, and a recently opened portion evaluating JZP-458 administered intravenously.

Applicant Table 13: Listing of Clinical Trials Relevant to this BLA

Trial Design and Trial Identity	NCT No.	Study status	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
Pivotal Phase 2/3 JZP458-201	04145531	Ongoing	Part A, (IM) - 3 subcohort Cohort 1a: 25 mg/m^2 M/W/F Cohort 1b:37.5 mg/m^2 M/W/F Cohort 1c:25/25/50 mg/m^2 M/W/F <u>Part B, IV</u> 25/25/50 mg/m^2 M/W/F	<u>Part A</u> <u>Primary endpoint</u>: The primary efficacy endpoint of the study is the response rate, defined as the proportion of participants with the last 72-hour NSAA level ≥ 0.1 IU/mL during the first course of IM JZP-458. Depending on the JZP-458 start day for a participant, this could be predose 4 if the first course of JZP-458 started on a Monday; predose 6 if the first course of JZP-458 started on a Wednesday; or predose 5 if the first course of JZP-458 started on a Friday. <u>Key Secondary Endpoints</u> The proportion of participants with the last 48-hour NSAA level ≥ 0.1 IU/mL during the first course of IM administration of JZP-458.	Part A (IM) Cohort 1a: 33 Cohort 1b: 84* Cohort 1c: 52 as of 08 March 2021 Part B (IV) ongoing	ALL/ LBL, Adult or Pediatric patients who have developed hypersensitivity to *E. coli* derived asparaginases	66 centers in 2 countries (US and Canada)

				Other secondary endpoints included characterization of the PK of IM JZP-458 based on SAA using a population PK approach and exposure-response correlations, and assessment of immunogenicity			
Phase 1 JZP458-101	N/A	Completed	JZP458 Cohort 1: 25mg/m^2 (IV or IM) Cohort 2: 37.5mg/m^2 IV or 12.5mg/m^2 IM	PK, Safety, tolerability	30	Healthy Adult Subjects	1 center in US

Abbreviations: MWF=Monday/Wednesday/Friday, US=United States, F/u=Follow up for safety assessment, IM=Intramuscular, IV= Intravenous, PK= Pharmacokinetics *a total of 53 patients enrolled in the Cohort1b as of the DCO 14 October 2021
Basis of BLA filling is IM only, IV study is exploratory

7.2. Review Strategy

The Applicant's Position:

This BLA application is supported by a comprehensive data package from the completed Phase 1 healthy volunteer study and the Pivotal Phase 2/3 study, including the observed NSAA data at the protocol-specified time points, PPK modeling and simulation results, asparagine depletion data, asparaginase enzyme content data, immunogenicity data, AEs, and clinical laboratory results.

In agreement with FDA, ahead of the phase 1 clinical study, Jazz studied the analytical comparability of JZP-458 and Erwinaze. This data was originally generated to support the strategy for nonclinical program for JZP-458. This data obtained demonstrated that JZP-458 and Erwinaze were highly similar proteins in primary structure.

Study JZP458-101

Phase 1 Study JZP458-101 was a randomized, single-center, open-label study to evaluate the safety, tolerability, and pharmacokinetics (PK) of a single dose of JZP-458 in healthy adult participants via either IV infusion or an IM administration. An Erwinaze dosing arm was included.

Serum asparaginase activity levels serve as a surrogate marker for asparagine depletion, and NSAA levels ≥ 0.1 IU/mL are the accepted threshold to demonstrate adequate asparagine depletion in clinical practice. Based on the phase 1 study data and PPK modeling and simulations, JZP-458 at the IM dose of 25 mg/m^2 and IV dose of 37.5 mg/m^2 were expected to achieve 72-hour NSAA levels ≥ 0.1 IU/mL in 100% of adult or pediatric populations after IM administration, and 80.9% in adult or 94.5% in pediatric populations after IV administration. Therefore, based on the totality of the safety and PK data in this phase 1 study, the recommended phase 2/3 starting dose for the IM route of administration was 25 mg/m^2.

Study JZP458-201

The primary efficacy endpoint of the ongoing Study JZP458-201 is to determine the proportion of patients with the last 72-hour NSAA level ≥ 0.1 IU/mL during the first course of JZP-458 IM administration. The key secondary endpoint is to determine the proportion of patients with the last 48-hour NSAA level ≥ 0.1 IU/mL during the first course of IM JZP-458.

Part A of JZP458-201 study is conducted to provide evidence on the safety, tolerability, and efficacy of repeated doses of IM JZP-458 in participants with ALL/LBL who are hypersensitive to *E. coli*-derived asparaginases (See Section 8.1.1 for details on the trial design). In each part of the study, 6 doses of JZP-458 are substituted for each dose of a long-acting *E. coli*-derived asparaginase. Two consecutive weeks of treatment with JZP-458 is defined as 1 course. A course of JZP-458 (6 doses over 2 weeks) starts on either a Monday, Wednesday, or a Friday;

the number of courses per participant depends on their individual treatment plan and at what point they developed hypersensitivity to an *E. Coli*-derived product. The objectives of the study are:

- To determine the efficacy of IM JZP-458 administration as measured by the last 48- and 72-hour nadir serum asparaginase activity (NSAA) level ≥ 0.1 IU/mL during the first course
- To assess the safety and tolerability of IM JZP-458 in patients with ALL/LBL who are hypersensitive to *E. coli*-derived asparaginases
- To characterize the pharmacokinetics (PK) of IM JZP-458 using a population PK approach, and to explore exposure-response correlations
- To assess the immunogenicity of IM JZP-458 following repeat administration of JZP-458

In addition to the observed data, the PPK model (See Section 6.2.2.1 for details on the PPK model) provides critical supporting data to demonstrate the efficacy of JZP-458. The PPK analysis provides robust support of the observed data and for the total data package for the BLA because the model uses available data across all participants, all timepoints, and all dose levels, and it uses continuous rather than categorical data. The PPK model results illustrate more accurately the SAA exposures of JZP-458 than does the primary analysis methodology in the protocol, and the PPK model provides reliable predictions of NSAA levels at the 48- and 72-hour timepoints. The efficacy and safety of JZP-458 is demonstrated by the totality of data, which includes observed nadir serum asparaginase activity (NSAA) data at the protocol-specified time points, population pharmacokinetic (PPK) modeling and simulation results, asparagine depletion data, asparaginase enzyme content data, available immunogenicity data, adverse events (AEs), adverse events of special interest including pancreatitis, thrombosis and hypersensitivity known to be associated with asparaginase therapy, and clinical laboratory results.

Under the Real Time Oncology Review pathway, the clinical package including safety and efficacy data for cohorts 1a and 1b (25 and 37.5 mg/m^2) as of DCO October 14 2020 is being submitted to the initial BLA. Following the initial BLA submission, in support of the proposed dosing regimen of 25/25/50mg/m^2 on M/W/F an Update Report will be submitted to the BLA. The clinical data package provided in the Update Report will include additional safety data from cohorts 1a and 1b (25 and 37.5 mg/m^2) and efficacy and safety from 16 patients from cohort 1c (25/25/50 mg/m^2) 17 enrolled, one not dosed and only 13 were evaluable) through DCO January 11 2021, data for PPK analysis (DCO February 26 2021) along with the observed clinical and ADA data (DCO April 30 2021). Available ADA data for 25/25/50 mg/m^2 is planned for submission to the BLA with the Update Report. In addition to these specified endpoints, Applicant has collected data on asparagine and glutamine depletion in all participants in Study JZP458-201 to supplement the full efficacy profile for JZP-458. These data will be summarized in

the initial BLA submission and in the Update Report.

The combined safety data from 25 and 37.5 mg/m^2 (N = 86) included in the Initial BLA demonstrates that JZP-458 is well tolerated and that the safety profile of JZP-458 is consistent with the well-established safety profile of asparaginases. Cumulative safety data (by cohort and overall) as of 11 January 2021 for participants in cohorts 1a (25mg/m^2, 33 participants), 1b (37.5 mg/m^2, 53 participants), and 1c (25/25/50 mg/m^2, 16 participants) (total N = 102) from the Update Report to FDA following the initial BLA submission will provide evidence to support the review of the preferred dose and regimen for JZP-458: 25/25/50 mg/m^2 administered IM on MWF.

The FDA's Assessment:

The FDA agrees that studies JZP458-101 and JZP458-201 are the studies submitted with this BLA. We agree with the summary of these Studies presented in Applicant Table 13 above.

The FDA used submitted datasets, clinical study reports, case report forms, narratives, responses to information requests, published literature, and relevant information in the public domain for the independent review of this application. The key materials used for the review of efficacy and safety included:

- BLA datasets, clinical study reports, case report forms, and responses to IRs

- Relevant published literature

- Relevant information in the public domain

The submission and amendments reviewed are listed below. It should be noted that in this document, FDA's position is based on analyses of data included in the agreed upon late submission of updated data.

Date of Submission	SDN	Material
January 28, 2021	5	Top-line Results, JZP458-201 Cohorts 1A and 1B (data cut-off October 2020)
February 10, 2021	6	Analysis and Tabulation Datasets, JZP458-201, Cohorts 1A and 1B (data cut-off October 2020)
March 5, 2021	12	JZP458-201 Case Report Forms
March 15, 2021	17	JZP458-201, Cohort 1C SDRC Meeting Materials

April 12, 2021	24	JZP458-201 CSR and Narratives (data cut-off October 2020)
April 30, 2021	25	Completion of RTOR BLA Submission: Study Report and Datasets for JZP458-101; Integrated Summary of Immunogenicity
May 11, 2021	29	Integrated Summary of Efficacy; Integrated Summary of Safety
May 14, 2021	31	Response to IR: Missing Narrative
May 21, 2021	33	Response to IR: Missing Narrative, updated adlb.xpt
May 21, 2021	34	Agreed upon late submission: Datasets and Patient CRFs for JZP458-201: Cohorts 1A, 1B, and 1C (data cut-off January 2021)
May 25, 2021	35	Resubmission of Above Datasets
May 26, 2021	36	Submission of updated adsl.xpt
June 2, 2021	39	Submission of updated adae.xpt
June 17, 2021	47	Submission of Day 60 Update: CSR Version 2, Updated Narratives

Summaries of data and safety analyses by the clinical reviewer were performed using JMP version 15.0 (SAS Institute, Inc., Cary, NC), MedDRA Adverse Events Diagnostic version 3.0 (MAED, FDA, Silver Spring, MD), and Palantir (Palantir Technologies, Denver, CO ©2021).

8 STATISTICAL AND CLINICAL EVALUATION

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The clinical development program for JZP-458 includes 2 studies: a completed Phase 1 study in adult healthy participants (JZP458-101) and an ongoing pivotal Phase 2/3 study (JZP458-201) in in patients with ALL/LBL who have developed hypersensitivity or silent inactivation to *E. coli*-derived asparaginases

8.1.1. JZP458-201

An Open-Label, Multicenter Study of RC-P in Patients with Acute Lymphoblastic Leukemia (ALL)/Lymphoblastic Lymphoma (LBL) Following Hypersensitivity to E. coli

INVESTIGATIONAL PLAN

Trial Design

The Applicant's Description:

Study JZP458-201 was designed to support registration. This pivotal study is a phase 2/3 open-label; multicenter, dose confirmation, and PK study of JZP-458 in participants (of any age) with ALL/LBL who are hypersensitive to *E. coli*-derived asparaginases (allergic reaction or silent inactivation). This study is designed to assess the tolerability and efficacy of JZP-458, as measured by asparaginase activity.

In this participant population, 6 doses of JZP-458 are substituted for each dose of a long-acting *E. coli*-derived asparaginase. Doses were administered on a Monday, Wednesday, Friday (MWF) schedule.

Study Duration

The treatment duration for individual patients will vary depending on the number of doses of a long-acting *E. coli*-derived asparaginase remaining on a patient's original treatment protocol (completion of each patient's planned asparaginase treatment). The overall total study duration to complete enrollment and all patient courses, including 30 days of safety follow-up and additional time as needed for follow-up assessments, for Part A (IM) and Part B (IV) at the investigative sites will be approximately 2 years.

This study consists of two parts:

- Part A is designed to determine the dose of JZP-458 for IM administration and to confirm safety and efficacy (Applicant Figure 7);
- Part B is designed to define the optimal dose and schedule of IV JZP-458. Part B was initiated post data cut-off date of October 14 2020.

Thus, only Part A is discussed and Part B is not described further herein.

Study population

Pediatric and adult patients with ALL or LBL, who have developed a moderate or severe allergic reaction to or have silent inactivation of an *E. coli*-derived asparaginase.

Trial Location

Sites in US and Canada (North America)

Schedule of Assessment

Applicant Table 14 below outlines the schedule of assessment for start dates of Monday, Wednesday or Friday. Blood samples are collected for serum asparaginase activity (SAA) level determination, other PK/Pharmacodynamics (PD), immunogenicity, and laboratory evaluations as defined in JZP458-201 Protocol Appendix 1 and 2.

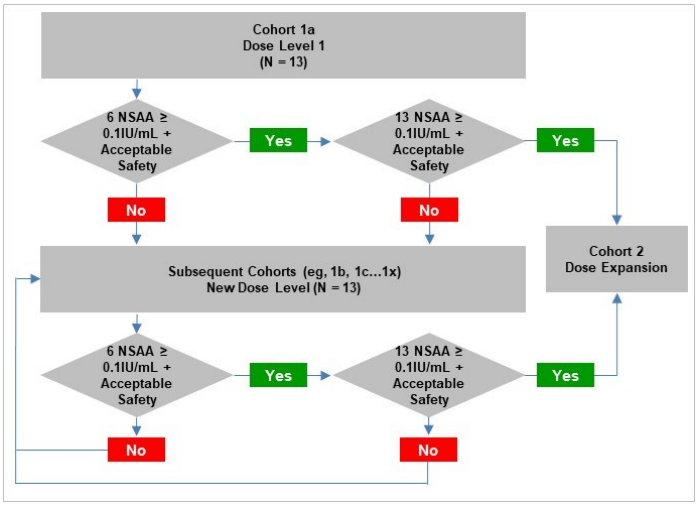
Applicant Table 14: Schedule of Assessment (Start dates of Monday only)

Assessment[a]	**Scre**	**Course 1 and Subsequent Courses**													**EOS** [h]
Study Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**30 days (±3) after last dose**
Weekday		**M**	**T**	**W**	**Th**	**F**	**Sa**	**Su**	**M**	**T**	**W**	**Th**	**F**	**Sa**	**Su**	**M-F**
Informed consent	X															
Prior Medications	X															
Demographics	X															
Medical History	X															
Height	X	X[b]														
Weight	X	X[b]														
Physical	X	X[d]														X
Vital Signs and	X	X		X		X			X		X		X			X
Local Lab Urine Pregnancy Test	X[g]	X[e]														X
Local Lab Serum Chemistry[f]	X[g]	X														X
Local Lab		X														X
Local Lab		X														
JZP-458 Drug		X		X		X			X		X		X			
Pharmacokinetics	Refer to Appendix 2 of Protocol															
Pharmacodynamics	Refer to Appendix 2of Protocol															
Immunogenicity	Refer to Appendix 2 of Protocol															
Adverse Event	X	X		X		X			X		X		X			X
Concomitant	X	X		X		X			X		X		X			X

[a] When multiple procedures are scheduled for the same time point, PK and PD samples will be taken at the protocol assigned time point as specified in Appendix 2 of the protocol and other non-PK and non-PD measurements will be taken before (ie, vital signs) or after (ie, AE review, clinical laboratory evaluation) the protocol-specified PK and PD time point. The window for PK and PD assessments is specified in Appendix 2 of Protocol. Unless otherwise specified, all procedures are to be completed prior to dosing with JZP458. [b] Performed at the beginning of each course with a -3 day window. [c] A complete physical examination, including a description

of a review of systems, external signs of any relevant disease, and co-morbidities should be performed. Physical examinations are to be completed by a physician or other health professional licensed to perform such examinations. Findings will be documented in the patient's medical record and recorded. Blood pressure, pulse rate, and temperature should be measured after the patient has been resting for 5 minutes in a supine position; respiratory rate is not required per protocol but may be collected if it is a standard of care at the study center. Blood pressure (systolic and diastolic) and pulse rate will be measured at Screening, predose, and as per the institutional standard of care. Temperature is measured only at Screening, predose, and at EOS. [d] Physical Examination can be done within 3 days prior to each course (initial and subsequent courses). [e] If a Screening urine pregnancy test was performed within 7 days of Day 1, it need not be repeated on Day 1. [f] Clinical laboratory tests include serum chemistry (albumin, alkaline phosphatase, ALT, amylase, AST, calcium, chloride, creatinine, glucose, lipase, phosphorus, potassium, sodium, total bilirubin, direct bilirubin, total cholesterol [fasting], and triglycerides [fasting]) and CBC with differential. Lipid panel analytes are not required at Screening. Coagulation tests are to be performed at Day 1 of Course 1 and at any time the patient is symptomatic; testing will include the following: PT, aPTT, ATIII activity and antigen, and Fg. See Table 3 of Protocol for additional information. Any laboratory parameter that is out of range and considered clinically significant (as determined by the Investigator) at the end of treatment of RC-P (last dose of the last course) must be re-evaluated until resolution. Windows for the above laboratory tests: 7 days prior to Dose 1. [g] Screening laboratory testing should be completed within 7 days of enrollment. Any Screening laboratory tests performed within 7 days of check in on Day -1 need not be repeated on Day -1. [h] For ADA positive patients, their follow-up ADA samples will be their End of Study samples
Source: Appendix 1 of the protocol amendment 2 dated September 2020

Applicant Figure 7: Part A IM JZP458 Dose Cohorts



Note: The SDRC assesses the safety and tolerability issues for participants in Cohort 1 to determine if additional participants at different dose levels are needed or if the appropriate IM JZP-458 dose level to proceed to the Expansion Cohort (Cohort 2) has been determined. Note: The SDRC are to review NSAA and safety and tolerability data when 6 and 13 evaluable participants in each subcohort complete Course 1; enrollment does not stop at the specified time points for SDRC review. Abbreviations: IM = intramuscular; IU = International Units; NSAA = nadir serum asparaginase activity; SDRC = Study Data Review Committee

As per protocol, participants in this cohort received 6 doses of IM JZP-458 on a MWF schedule over 2 weeks with the initial dose starting either on a Monday or Wednesday or Friday (depending on the participant's planned chemotherapy schedule).

Efficacy and safety data are being assessed by a Study Data Review Committee (SDRC) at frequent intervals as described in the SDRC study charter included in the initial BLA. The SDRC includes members of Children's Oncology Group (COG) and Jazz Pharmaceuticals' personnel. The SDRC will make recommendations and have oversight of the study as described in Protocol Section 9.6.

Part A – IM JZP-458:

- Cohort 1a was initiated at an IM dose of 25 mg/m^2 on a MWF schedule over 2 weeks. The SDRC evaluations for Cohort 1a occurred after 6 evaluable participants enrolled at this dose and again with cumulative data from 16 evaluable participants.
- Cohort 1b was initiated at an IM dose of 37.5 mg/m^2 on a MWF schedule over 2 weeks, as the percentage of participants with NSAA levels at the last 72-hours postdose in cohort 1a were below the protocol-defined threshold, and due to the acceptable safety profile at the IM 25 mg/m^2 dose level.
- Cohort 1c was initiated to evaluate a dose of 25 mg/m^2 on Mondays and Wednesdays and a dose of 50 mg/m^2 on Fridays with agreement from the FDA. Preliminary PPK model using participant data from Course 1 of cohorts 1a (N = 30) and 1b (N = 32) predicted that the optimal dose to support a MWF dosing schedule is a dose of 25/25/50 mg/m^2 administered on MWF for a total of 6 doses to replace every dose of long-acting *E.coli* asparaginase. In order to assess this predicted dose and schedule, cohort 1c was initiated under Protocol Amendment 02 in Study JZP458 201 in November 2020.

Diagnosis and Main Criteria for Inclusion and Exclusion:
The study population includes pediatric and adult participants with ALL or LBL, who have developed a moderate or severe allergic reaction to or have silent inactivation of an *E. coli*-derived asparaginase.

Key inclusion criteria are as follows:

- Pediatric and adult participants with a diagnosis of ALL or LBL

- Have had a ≥ Grade 3 allergic reaction (Common Terminology Criteria for Adverse Events [CTCAE] v5.0) to a long-acting *E. coli*-derived asparaginase or have silent inactivation
- Have 1 or more courses of *E. coli*-derived asparaginase (ie, to allow for at least 6 doses of JZP-458) remaining in his/her treatment plan
- Have, in the opinion of the Investigator, fully recovered from their prior allergic reaction to *E. coli*-derived asparaginase with undetectable SAA levels prior to enrollment in the study, except for participants who received < 10% of an *E. coli*-derived asparaginase IV infusion prior to the reaction.

Key exclusion criteria are as follows:

- Have previously received asparaginase *Erwinia chrysanth*emi or JZP-458.
- Have relapsed ALL or LBL.
- Are concurrently receiving another investigational agent and/or are being treated with an investigational device at the same time as JZP-458 (within 48 hours) during Course 1 of JZP-458.
- Have a history of ≥ Grade 3 pancreatitis (per CTCAE v5.0).
- Prior history of asparaginase-associated ≥ Grade 3 (per CTCAE v5.0) hemorrhagic event or asparaginase-associated thrombus requiring anticoagulation therapy, excluding catheter-related thrombotic events.

The FDA's Assessment:

The FDA agrees with the trial design overview, inclusion and exclusion criteria, and description of study assessments .

Study Endpoints

It is widely accepted that NSAA levels ≥ 0.1 IU/mL is an acceptable surrogate endpoint for treatment effect in patients with ALL. The primary efficacy endpoint of the study is the response rate, defined as the proportion of patients with the last 72-hour NSAA level ≥ 0.1 IU/mL during the first course of IM JZP-458. Depending on the JZP-458 start day for a patient, this could be predose 4 if the first course of JZP-458 started on a Monday; predose 6 if the first course of JZP-458 started on a Wednesday; or predose 5 if the first course of JZP-458 started on a Friday. Key Secondary Endpoint of the study is the response rate, defined as the proportion of participants with the last 48-hour NSAA level ≥ 0.1 IU/mL during the first course of IM administration of JZP-458.

Secondary Endpoints: Secondary endpoints include characterization of the PK of IM JZP-458 based on serum asparaginase activity (SAA) using a population PK approach and exposure-response correlations, and assessment of immunogenicity

The FDA's Assessment:

The FDA agrees that NSAA levels are an acceptable surrogate efficacy endpoint for asparaginase products. NSAA level ≥ 0.1 IU/mL at 72 hours was the agreed upon primary endpoint. The FDA agrees with the description of primary and secondary endpoints.

Statistical Analysis Plan and Amendments

The Applicant's Description:
The SAP was amended four times as described in Applicant Table 15. SAP v1.4 was approved prior to the database freeze for the initial interim analysis.

Applicant Table 15: Summary of Key SAP Amendments

SAP version	Version Date	Information on SAP update
SAP Version 1.0	18Dec2019	Original
SAP Version 1.1	07Apr2020 (last signature 08Apr2020)	Clarification on the Efficacy/PK/PD Analysis Sets and sample size at the interim analysis
SAP Version 1.2	08Jun2020	Further clarification and language update on the sample size at the interim analysis
SAP Version 1.3	24Sep2020	Update study design per protocol amendment 1 and 2 Clarification on the sample size at the primary analysis Addition of the sensitivity analyses to assess COVID-19 impact on the primary and key secondary efficacy endpoints
SAP Version 1.4	16Dec2020	Added the term of pulmonary embolism to the list of preferred terms for the AE of special interest of thrombosis. A population PK model will be used to characterize the JZP458 PK profiles in patients with ALL/LBL following hypersensitivity to *E. coli* derived asparaginases, and to explore exposure-response correlations.

The final analysis is planned when the overall study (IM and IV) is complete and all enrolled patients have completed all of their planned courses, including end of study procedures.

The FDA's Assessment:

The FDA agrees that these were the submitted SAP amendments for JZP458-201. FDA also notes that there was not a clear plan for adaptive modifications based on prespecified interim analyses of PK and PD.

Protocol Amendments

The Applicant's Description:
There were two protocol amendments to Study JZP458-201. Applicant Table 16 below summarizes relevant changes to the protocol. These changes have not impacted the trial integrity or interpretation of the results.

Applicant Table 16: Protocol Amendments

Number (date of internal approval)	**Reasons for Amendment**
Amendment 1.0 (North America) 18 Aug 2020	To allow dose escalation > 37.5 mg/m2 not to exceed 80 mg/m2 To allow enrollment into Part B (IV) to begin before completion of Part A (IM) To allow a higher dose to be given on a Friday over a 72 hour interval versus a Monday or Wednesday dose given every 48 hours
Amendment 2.0 (North America) 03 Sept 2020	To remove dose cap of 80 mg/m^2

The FDA's Assessment:

The FDA agrees that these are the submitted protocol amendments.

RESULTS

Compliance with Good Clinical Practices
Data:
The following audits planned/conducted by the Applicant to evaluate the study conduct and compliance with the ICH E6 Guideline for Good Clinical Practice, and applicable regulations and local laws.

Applicant Table 17: JZP458-201 Audits conducted at Investigator sites and Service providers

AUDITEE(S)	TYPE OF AUDIT(S)	AUDIT DATE*
Vinod Gidvani-Diaz (Site 1713) Methodist Hospital - San Antonio 7700 Floyd Curl Drive	Investigator Site Audit	06-07 Jan 2021
Michael Richards (Site 1505) Children's Minnesota 2525 Chicago Avenue	Investigator Site Audit	16-17 Feb 2021
Mark Ranalli (1401) Nationwide Children's Hospital 700 Children's Drive Columbus Ohio 43205	Investigator Site Audit	(22-23 Mar 2021)
Anne Angiolillo (Site 1211) Center for Cancer & Blood Disorders Children's National Health System 111 Michigan Ave, NW	Investigator Site Audit	(16-18 Mar 2021)
Kasey Leger (Site 1926) Seattle Children's Hospital 4800 Sand Point Way	Investigator Site Audit	(05-06 Apr 2021)
(b) (4)	Qualification Vendor Audit	24-25 Sep 2019
	Routine Vendor Audit	18-20 May 2020
	Routine Vendor Audit	12-13 Mar 2019
	Routine Vendor Audit	11-12 Mar 2020
	Routine Vendor Audit	02-03 Jun 2020

*Planned or Conducted

The Applicant's Position:
Study JZP458-201 is being conducted in compliance with current ICH Good Clinical Practice and other applicable regional regulations, and in accordance with ethical principles from the Declaration of Helsinki. At each trial site, an institutional review board (IRB) or independent ethics committee (IEC) reviewed and approved the clinical trial protocol, the current Investigator's Brochure, and informed consent form (IC). The IRB/IEC subsequently approved protocol amendments and revisions. Written Informed Consent were obtained for all subjects before performance of any protocol specified procedures or interventions. Consents were amended, as needed, for protocol amendments. Applicant approved significant changes to site-specific sample consent documents.

The FDA's Assessment:

FDA confirms the Applicant's statement of compliance with Good Clinical Practice. See also Section 4.1.

Data Quality and Integrity

Data:
The sponsor conducts clinical trials according to GCP and ICH guidelines and conducts a GCP audit program. Study centers are being monitored by the Applicant and CRO, (b) (4) Centers are contacted at regular intervals and a Visit Log is being maintained. Monitors are responsible for reviewing adherence to the protocol; compliance with GCP; and the completeness, accuracy, and consistency of the data. Case report form data are captured via data entry by study center personnel in a sponsor database system. Data quality checks are applied using electronic verification methods. An audit trail to support data query resolution and any modification to the data is being maintained.

The Applicant's Position:
JZP458-201 study supporting this application is being conducted according to GCP and ICH guidelines with Applicant oversight to ensure the safety of subjects and the integrity and interpretability of the study and study data.

The FDA's Assessment:

The FDA agrees that with the corrected datasets submitted in SDN 35, the submitted data are sufficient for review of this marketing application.

Financial Disclosure

Data:
Financial disclosure information was collected from all investigators participating in JZP458-201

study and information is provided in Appendix 14.2

The Applicant's Position:

The Applicant has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). Each listed clinical investigator was required to disclose if they had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b). Applicant has appropriate procedures to ensure none of the investigator's with disclosable financial interest impacts the integrity and interpretability of the study results for JZP458-201.

The FDA's Assessment:

The FDA agrees that financial disclosure forms were submitted with this application. See Appendix 14.2.

Patient Disposition

Data:

Patient disposition as of the Initial IA, is presented below in Applicant Table 18. Most participants (66 of 86 [76.7%] overall) are continuing to receive JZP-458 treatment in the study. Overall, a total of 5 of 86 participants (5.8%) have discontinued JZP-458 treatment (3 of 86 [3.5%] due to AE, 1 of 86 [1.2%] due to physician decision, and 1 of 86 [1.2%] withdrawn by a parent or guardian due to participant withdrawal).

Applicant Table 18: Patient Disposition (All Screened patients, DCO October 14 2020)

Number(%) of Subjects	**IM 25 mg/m^2 MWF**	**IM 37.5 mg/m^2 MWF (N=53)**	**Total MWF (N=86)**
Patients Screened, n			90
Patient who Screen Failed, n			4
Reason for Screen Failure			
Inclusion/Exclusion Criteria not Met			1
Withdrawal of Consent			2
Death			0
Lost to Follow-up			0
Other			1
Patients in the Enrolled Analysis Set, n	33	53	86
Patients Received at least one dose of JZP-458 treatment,	33 (100)	53 (100)	86 (100)
Patients Ongoing JZP-458 Treatment, n(%)	22 (66.7)	44 (83.0)	66 (76.7)
Patients Completed All Planned JZP-458 Treatment, n(%)	8 (24.2)	7 (13.2)	15 (17.4)

Patients Discontinued JZP-458 Treatment, n(%)	3 (9.1)	2 (3.8)	5 (5.8)
Reason for Discontinuing JZP-458 treatment			
Adverse Event, n(%)	1 (3.0)	2 (3.8)	3 (3.5)
Death, n(%)	0	0	0
Lost To Follow-up, n(%)	0	0	0
Physician Decision, n(%)	1 (3.0)	0	1 (1.2)
Pregnancy, n(%)	0	0	0
Progressive Disease, n(%)	0	0	0
Protocol Deviation, n(%)	0	0	0
Recurrent Disease, n(%)	0	0	0
Study Terminated By Sponsor, n(%)	0	0	0
Trial Site Terminated by Sponsor, n(%)	0	0	0
Withdrawal by Parent or Guardian, n(%)	1 (3.0)	0	1 (1.2)
Withdrawal by Patient, n(%)	0	0	0
Other, n(%)	0	0	0
Patients Ongoing Study, n(%)	26 (78.8)	47 (88.7)	73 (84.9)
Patients Completed Study, n(%)	4 (12.1)	5 (9.4)	9 (10.5)
Patients Discontinued Study, n(%)	3 (9.1)	1 (1.9)	4 (4.7)
Reason for Discontinuing Study			
Adverse Event, n(%)	1 (3.0)	1 (1.9)	2 (2.3)
Death, n(%)	0	0	0
Lost To Follow-up, n(%)	0	0	0
Physician Decision, n(%)	1 (3.0)	0	1 (1.2)
Pregnancy, n(%)	0	0	0
Progressive Disease, n(%)	0	0	0
Protocol Deviation, n(%)	0	0	0
Recurrent Disease, n(%)	0	0	0
Study Terminated By Sponsor, n(%)	0	0	0
Trial Site Terminated by Sponsor, n(%)	0	0	0
Withdrawal by Parent or Guardian, n(%)	1 (3.0)	0	1 (1.2)
Withdrawal by Patient, n(%)	0	0	0
Other, n(%)	0	0	0

Source: Initial IA TFL Table 9.1.2

The Applicant's Position:

Treatment for ALL/LBL can last up to 3 years and the vast majority of the participants (76.7%) in the JZP458-201 are continuing to receive JZP-458 as part of their treatment for ALL/LBL. There were very few participants that had discontinued treatment as of the DCO October 14 2020 and the reasons for discontinuation, including 3 of the 5 participants that discontinued as a result of adverse events, were common for patients with ALL/LBL receiving multi-agent chemotherapeutic therapy.

The FDA's Assessment:

The FDA agrees with the patient disposition for Cohorts 1a and 1b described in Applicant Table 18 with the cutoff date of October 2020. The updated patient disposition table is below (FDA Table 19).

FDA Table 19. JZP458-201: Patient Disposition

	Cohort 1A 25 mg/m^2 (N = 33)	Cohort 1B 37.5 mg/m^2 (N = 53)	Cohort 1C 25(MW)/50(F) mg/m^2 (N =17)	All (N = 108)
Patients Screened, n				108
Patients with Screen Failure, n				5
Reason for Screen Failure				
Inclusion/Exclusion Criteria Not Met				1
Withdrawal of Consent				3
Other				1
Patients in the Enrolled Analysis Set, n	33	53	16	103
Patients who received at least one dose of JZP-458 treatment, n (%)	33 (100)	53 (100)	16 (94)	102 (99)
Patients who completed JZP-458 treatment, n (%)	18 (55)	16 (30)	1 (6)	35 (34)
Patients with ongoing JZP-458 treatment, n (%)	10 (30)	32 (60)	13 (76)	55 (53)
Patients who discontinued JZP-458 treatment, n (%)	5 (15)	5 (9)	3 (18)	13 (13)
Reason for discontinuing JZP-458 treatment				
Adverse event, n (%)	3 (9)	3 (6)	1 (6)	7 (7)
Physician decision, n (%)	1 (3)	2 (4)	1 (6)	4 (4)
Withdrawal by parent/guardian, n (%)	1 (3)	0	0	1 (1)
Other, n (%)	0	0	1 (6)	1 (1)
Patients who completed study, n (%)	13 (39)	11 (21)	1 (6)	25 (24)
Patients continuing study, n (%)	15 (45)	38 (72)	15 (88)	68 (66)
Patients who discontinued study, n (%)	5 (15)	4 (8)	1 (6)	10 (10)
Reason for discontinuing study				
Adverse event, n (%)	2 (6)	1 (2)	0	3 (3)
Death, n (%)	1 (3)	1 (2)	0	2 (2)
Physician decision, n (%)	1 (3)	2 (4)	1 (6)	4 (4)
Withdrawal by parent/guardian, n (%)	1 (3)	0	0	1 (1)

Source: Reviewer's analysis, ADSL dataset

Protocol Violations/Deviations

Data:

In study 201, a major protocol deviation (or important protocol deviation) is defined as a subset of protocol deviations that may significantly impact the completeness, accuracy, and or reliability of key study data, or that may significantly affect a subject's rights, safety, or well-being. Examples of major protocol deviations may include, but are not limited to, failure to obtain informed consent, enrollment of subjects that do not meet the inclusion/exclusion criteria or a drug dispensing or dosing errors. Major protocol deviations may result in data that are not deemed evaluable for the per protocol analysis and/or may require that patients are discontinued from the study. A minor protocol deviation is defined as any change, divergence, or departure from the study design or procedures defined in the protocol. Examples of minor protocol deviations include, but are not limited to, a protocol visit date outside of a visit window, an isolated case of a missed or incomplete study procedure (e.g. lab test) or an isolated incident of a missed or incomplete study evaluation (e.g. examination). Minor protocol deviations would not generally preclude patient data from the per protocol analysis population.

A summary of the Major Protocol Deviations identified as of Initial IA are provide in Applicant Table 20. Overall, 17 of 86 (19.8%) of participants had 1 or more major protocol deviations. Overall, the most frequently reported major protocol deviations were laboratory deviations (for instance, some labs not performed on Course 1 Day 1) and study procedures (blood samples for the primary and key secondary endpoints drawn out of window).

Applicant Table 20: Major Protocol Deviations (Safety Analysis Set as of October 14 2020)

	IM 25 mg/m^2 MWF (N = 33) n (%)	**IM 37.5 mg/m^2 MWF (N = 53)** n (%)	**Total (N = 86) n (%)**
Participants with major protocol deviations	7 (21.2)	10 (18.9)	17 (19.8)
Major deviation term			
Laboratory deviation	5 (15.2)	9 (17.0)	14 (16.3)
Study procedures deviation	2 (6.1)	2 (3.8)	4 (4.7)

Abbreviations: IM = intramuscular
Percentages were calculated with the number of participants in the Safety Analysis Set as a denominator.
Source: Initial IA TFL Table 9.1.3.1
All protocol deviations are provided in IA Listing 10.2.2.1.

The Applicant's Position:

As of the DCO October 14 2020, major protocol deviations did not have an impact on the safety of patients and the study integrity evaluations. No protocol deviations related to inclusion and

exclusion criteria were recorded either by site personnel or Applicant monitors. Appropriate action was taken to ensure the safety of patients and the integrity and interpretability of the study results.

The FDA's Assessment:

The FDA agrees that at the time of the October 2020 cutoff, in Cohort 1A (25 mg/m^2 MWF), seven patients had major protocol deviations. Five patients had eight laboratory deviations; two patients had study procedure deviations. In Cohort 1B, 10 patients had major protocol deviations. Nine patients had ten laboratory deviations. Two patients had four study procedure deviations.

With the Day 60 update, ten patients in Cohort 1A were reported to have a major protocol deviation, 14 patients in 1B were reported to have a major protocol deviation, and 4 patients in 1C were reported to have a major protocol deviation.

Demographic Characteristics

Data:

In JZP458-201, as of the DCO October 14 2020, majority of participants were white (62 of 86 [72.1%]) with a median age of 9.0 years (range: 1 to 24 years). Of the 86 participants, 25 (29.1%) were < 6 years of age, 31 (36.0%) were 6 to < 12 years of age, 19 (22.1%) were 12 to < 18 years of age, and 11 (12.8%) were ≥ 18 years of age. A higher percentage of male (50 of 86 [58.1%]) participants than female (36 of 86 [41.9%]) participants were enrolled. A summary of the demographic characteristics as of DCO October 14 2020 are provide in Applicant Table 21.

Applicant Table 21: JZP458-201 Demographic and baseline characteristic (Safety Analysis Set, DCO October 14 2020)

	IM 25 mg/m^2 MWF (N = 33)	**IM 37.5 mg/m^2 MWF (N = 53)**	**Total (N = 86)**
Sex (n [%])			
Female	16 (48.5)	20 (37.7)	36 (41.9)
Male	17 (51.5)	33 (62.3)	50 (58.1)
Declined to state	0	0	0
Ethnicity (n [%])			
Hispanic or Latino	13 (39.4)	16 (30.2)	29 (33.7)
Not Hispanic or Latino	18 (54.5)	35 (66.0)	53 (61.6)
Declined to state	2 (6.1)	2 (3.8)	4 (4.7)

	IM 25 mg/m^2 MWF (N = 33)	IM 37.5 mg/m^2 MWF (N = 53)	Total (N = 86)
Race (n [%])			
American Indian or Alaska Native	0	0	0
Asian	1 (3.0)	4 (7.5)	5 (5.8)
Black or African American	3 (9.1)	7 (13.2)	10 (11.6)
Native Hawaiian or other Pacific Islander	0	0	0
White	24 (72.7)	38 (71.7)	62 (72.1)
Declined to state	0	0	0
Multiple	1 (3.0)	0	1 (1.2)
Not reported	4 (12.1)	4 (7.5)	8 (9.3)
Age at enrollment (years)			
n	33	53	86
Mean	11.5 (7.11)	9.1 (5.21)	10.0 (6.08)
Median	11.0	8.0	9.0
Minimum, Maximum	1, 24	1, 20	1, 24
Age subgrouping (n [%])			
< 6 years	9 (27.3)	16 (30.2)	25 (29.1)
6 years to <12 years	9 (27.3)	22 (41.5)	31 (36.0)
12 years to < 18 years	7 (21.2)	12 (22.6)	19 (22.1)
>18 years	8 (24.2)	3 (5.7)	11 (12.8)
< 1 year	0	0	0
1 year to <6 years	9 (27.3)	16 (30.2)	25 (29.1)
6 years to <12 years	9 (27.3)	22 (41.5)	31 (36.0)
12 years to < 17 years	6 (18.2)	8 (15.1)	14 (16.3)
>17 years	9 (27.3)	7 (13.2)	16 (18.6)
Body surface area (m^2) (n [%])			
n	33	53	86
Mean	1.283 (0.540)	1.124 (0.430)	1.185 (0.479)
Median	1.280	0.990	1.165
Minimum, Maximum	0.44, 2.53	0.56, 2.05	0.44, 2.53

	IM 25 mg/m^2 MWF (N = 33)	IM 37.5 mg/m^2 MWF (N = 53)	Total (N = 86)
Body surface area (n [%])			
0 < BSA ≤ 1	12 (36.4)	27 (50.9)	39 (45.3)
1 < BSA ≤ 2	19 (57.6)	24 (45.3)	43 (50.0)
2< BSA	2 (6.1)	2 (3.8)	4 (4.7)
Primary disease (n [%])			
ALL	0	0	0
B-ALL	27 (81.8)	37 (69.8)	64 (74.4)
T-ALL	4 (12.1)	9 (17.0)	13 (15.1)
LBL	0	0	0
B-LBL	0	0	0
T-LBL	2 (6.1)	7 (13.2)	9 (10.5)
Time since primary disease diagnosis to Study Day 1 (n [%])			
0-3 months	28 (84.8)	38 (71.7)	66 (76.7)
4-6 months	5 (15.2)	13 (24.5)	18 (20.9)
7-9 months	0	2 (3.8)	2 (2.3)
10-12 months	0	0	0
> 12 months	0	0	0
Prior asparaginase treatment (n [%])			
Oncaspar	33 (100)	53 (100)	86 (100)
Calaspagase Pegol-mknl (Asparlas)	0	0	0
Erwinia Chrysantemi L-asparaginase	0	0	0
Other	0	0	0
Time since last asparaginase received to Study Day 1 (days)			
n	33	53	86
Mean	16.8 (20.90)	29.4 (36.78)	24.5 (32.09)
Median	9.0	12.0	10.5
Minimum, Maximum	2, 116	2, 148	2, 148

	IM 25 mg/m^2 MWF (N = 33)	IM 37.5 mg/m^2 MWF (N = 53)	Total (N = 86)
Eligibility Criteria (n [%])			
Grade 2 allergic reaction to an *E. coli*-derived asparaginase	0	0	0
Grade ≥ 3 allergic reaction to an *E. coli*-derived asparaginase	27 (81.8)	48 (90.6)	75 (87.2)
Silent inactivation	3 (9.1)	3 (5.7)	6 (7.0)
Allergic reaction with inactivation	3 (9.1)	2 (3.8)	5 (5.8)

Abbreviations: ALL = acute lymphoblastic leukemia; B-ALL = B-cell acute lymphoblastic leukemia; B-LBL = B-cell lymphoblastic lymphoma; BSA = body surface area; IM = intramuscular; LBL = lymphoblastic lymphoma; T-ALL = T-cell acute lymphoblastic leukemia; T-cell lymphoblastic lymphoma; T-LBL = T-cell lymphoblastic lymphoma
Percentages were calculated with the number of participants in the Safety Analysis Set as a denominator.
Time Since Diagnosis in months is calculated by taking the integer of '[(Study Day 1 - Date of Diagnosis + 1)/365.25]*12'.
A baseline value is defined as the latest non-missing value obtained prior to or at the start date and/or time of the first dose of JZP-458 (Study Day 1).
Study Day 1 is defined as the date of the first dose of JZP-458.
Source: Initial IA TFL Table 9.1.4.1

The Applicant's Position:

All enrolled participants as of the Initial IA met all of the eligibility criteria. Additional patient data from 25/25/50 mg/m^2 Cohort 1c as of DCO January 11 2021 will be submitted to BLA in Update Report, as outlined in Section 7.2.

The FDA's Assessment:

The FDA agrees with the demographic information in Applicant Table 21 with the following exceptions and additions, as shown in FDA Table 22:

FDA Table 22. JZP458-201 Demographic and Disease Characteristics.

	Cohort 1A 25 mg/m^2 (N = 33)	Cohort 1B 37.5 mg/m^2 (N = 53)	Cohort 1C 25(MW)/50(F) mg/m^2 (N = 17)	All (N = 103)
Sex (N, %)				
Female	16 (49%)	20 (38%)	8 (47%)	44 (43%)
Male	17 (51%)	33 (62%)	9 (53%)	59 (57%)
Declined to state	0	0	0	0

FDA Table 22. JZP458-201 Demographic and Disease Characteristics.				
	Cohort 1A 25 mg/m^2 (N = 33)	**Cohort 1B 37.5 mg/m^2 (N = 53)**	**Cohort 1C 25(MW)/50(F) mg/m^2 (N = 17)**	**All (N = 103)**
Ethnicity (N, %)				
Hispanic or Latino	13 (39%)	16 (30%)	7 (41%)	36 (35%)
Not Hispanic or Latino	18 (55%)	35 (66%)	10 (59%)	63 (61%)
Declined to state	2 (6%)	2 (4%)	0	4 (4%)
Race (N, %)				
American Indian or Alaska Native	0	0	1 (6%)	1 (1%)
Asian	1 (3%)	4 (8%)	0	5 (5%)
Black or African American	3 (9%)	7 (13%)	2 (17%)	12 (12%)
White	24 (73%)	38 (72%)	13 (76%)	75 (73%)
Multiple	1 (3%)	0	0	1 (1%)
Not reported	4 (12%)	4 (8%)	1 (4%)	9 (9%)
Declined to state	0	0	0	0
Age at enrollment (years)				
Mean (std dev)	11.5 (7.1)	9.1 (5.2)	10.2 (4.9)	10 (5.9)
Median	11 (1, 24)	8 (1, 20)	11 (3, 19)	10 (1, 24)
Age Group (N, %)				
0 Days to 28 Days	0 (0%)	0 (0%)	0 (0%)	0 (0%)
1 Month to <2 Years	1 (3%)	1 (2%)	0 (0%)	2 (2%)
2 Years to <12 Years	17 (52%)	37 (70%)	9 (53%)	63 (61%)
12 Years to <17 Years	6 (18%)	8 (15%)	6 (35%)	20 (19%)
≥ 17 Years	9 (27%)	7 (13%)	2 (12%)	18 (17%)
Body surface area (m^2)				
Mean (std dev)	1.28 (0.54)	1.12 (0.43)	1.32 (0.54)	1.21 (0.49)
Median (Min, Max)	1.28 (0.44, 2.53)	0.99 (0.56, 2.05)	1.255 (0.57, 2.21)	1.19 (0.44, 2.53)
BSA by group (N, %)				
0 < BSA ≤ 1	12 (36%)	27 (51%)	5 (31%)	44 (43%)
1 < BSA ≤ 2	19 (58%)	24 (45%)	8 (50%)	51 (50%)
2 < BSA	2 (6%)	2 (4%)	3 (3%)	7 (7%)
Primary Disease				
B-ALL	27 (82%)	37 (70%)	15 (88%)	79 (77%)
T-ALL	4 (12%)	9 (17%)	0	13 (13%)
T-LBL	2 (6%)	7 (13%)	2 (12%)	11 (11%)
Time since primary disease diagnosis to Study Day 1 (N, %)				
0-3 Months	28 (8%)	38 (72%)	14 (82%)	80 (78%)
4-6 Months	5 (15%)	13 (25%)	2 (12%)	20 (19%)
7-9 Months	0	2 (4%)	0	2 (2%)
Did not receive Study Drug	0	0	1 (6%)	1 (1%)
Prior asparaginase treatment (N, %)				
Oncaspar	33 (100%)	53 (100%)	17 (100%)	103 (100%)

FDA Table 22. JZP458-201 Demographic and Disease Characteristics.				
	Cohort 1A 25 mg/m^2 (N = 33)	**Cohort 1B 37.5 mg/m^2 (N = 53)**	**Cohort 1C 25(MW)/50(F) mg/m^2 (N = 17)**	**All (N = 103)**
Time since last asparaginase received to Study Day 1 (days)				
Mean (std dev)	16.8 (20.9)	29.4 (36.8)	20.2 (28.0)	23.9 (31.4)
Median (Minimum, Maximum)	9 (2, 116)	12 (2, 148)	8 (2, 112)	10 (2, 148)
Eligibility criteria (N, %)				
Grade ≥ 3 allergic reaction to an *E. coli*-derived asparaginase	27 (82%)	48 (91%)	15 (88%)	90 (87%)
Silent Inactivation	3 (9%)	3 (6%)	0	6 (6%)
Allergic reaction with inactivation	3 (9%)	2 (4%)	2 (12%)	7 (7%)
Backbone chemotherapy regimen (N, %)				
Children's Oncology Group (COG)	*26 (79%)*	*49 (92%)*	*15 (88%)*	*90 (87%)*
AALL0232	0	1 (2%)	0	1 (1%)
AALL0434	2 (6%)	6 (11%)	2 (12%)	10 (10%)
AALL1131	5 (15%)	10 (19%)	3 (18%)	18 (17%)
AALL1231	3 (9%)	5 (9%)	1 (6%)	9 (9%)
AALL1231, AALL0434	0	2 (4%)	0	2 (2%)
AALL1731	9 (27%)	10 19%)	4 (23%)	23 (22%)
AALL1732	10 (30%)	15 (28%)	5 (29%)	30 (29%)
CHLA Protocol	*2 (6%)*	*1 (2%)*	*1 (6%)*	*4 (4%)*
CHLA B-ALL standard risk	0	1 (2%)	0	1 (1%)
CHLA high risk	1 (3%)	0	0	1 (1%)
CHLA T-ALL	1 (3%)	0	1 (6%)	2 (2%)
Other Protocol	*2 (6%)*	*3 (6%)*	*1 (6%)*	*6 (6%)*
DFCI 16-001	2 (6%)	1 (2%)	0	3 (3%)
Standard of Care	0	0	1 (6%)	1 (1%)
St. Jude Protocol	0	2 (4%)	0	2 (2%)
Source: Reviewer's Analysis, ADSL and suppCM datasets.				

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

As detailed in Applicant Table 20, Overall, primary disease status was reported as B-cell ALL for 64 of 86 participants (74.4%), T cell ALL for 13 of 86 participants (15.1%), and T-cell LBL for 9 of 86 (10.5%) participants. Overall, the time since the primary diagnosis, relative to Study Day 1, ranged from 0 to 3 months for the majority of participants (66 of 86 [76.7%]). Prior asparaginase treatment for all participants was pegaspargase [Oncaspar] (86 of 86 [100%]) and the average time since the last asparaginase treatment, relative to Study Day 1, was 24.5 days (range 2 to 148 days).

The Applicant's Position:

All enrolled participants met all of the eligibility criteria.

The FDA's Assessment:

The FDA agrees that the majority of patients enrolled on JZP458-201 had a diagnosis of B-ALL, with the remaining patients having a diagnosis of T-ALL or T-LBL, and all had received prior therapy with pegaspargase. All met eligibility criteria to enroll on JZP458-201. The fact that patients had documented hypersensitivity only to pegaspargase would not preclude an indication for hypersensitivity to other E. coli-derived pegylated asparaginases.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

As per the protocol, study measurements are focused on Course 1. A course is defined as 6 doses of JZP-458 given on a MWF schedule. In this trial, patients have received a median of 3 courses of JZP-458; however, there could be patients receiving courses in the range of 6 to 7 and the frequency and timing of the courses is based on the each patient's treatment protocol for ALL/LBL. As of the Initial IA, 33 participants had been enrolled in 25 mg/m^2 and 53 participants had been enrolled at 37.5mg/m^2. Most participants (26/33 participants [78.8%] at 25mg/m^2 and 47/53 participants [88.7%] at 37.5mg/m^2) were ongoing in the study as of the initial IA. As of the initial IA at 25mg/m^2 (N = 33), the median (range) duration of time on study (defined as duration from first dose to completion date or data cut-off date for participants ongoing in the study) was 19.1 (1.4 to 32.3) weeks. At 37.5mg/m (N = 53), the median (range) duration of time of study was 6.6 (1.9 to 14.1) weeks. The duration of time on study is summarized categorically in Applicant Table 23.

Applicant Table 23: Study JZP458-201 – Duration of Time on Study in Cohorts 1a (IM 25 mg/m^2 MWF) and 1b (IM 37.5 mg/m^2 MWF) (DCO October 14 2020)

Duration of Time on Study	IM 25 mg/m^2 MWF N	IM 37.5 mg/m^2 MWF N
< 2 weeks	1	3
2 weeks to < 4 weeks	0	6
4 weeks to < 6 weeks	2	15
6 weeks to < 8 weeks	1	6
8 weeks to < 10 weeks	1	10
10 weeks to < 12 weeks	1	9
≥ 12 weeks	27	4

Abbreviations: IM = intramuscular; MWF = Monday, Wednesday, Friday.
Percentages were calculated with the number of patients in the Safety Analysis Set as a denominator.
Duration of time on study in weeks is calculated as [[date of study completion or the data cutoff date - date of first dose date]+1]/7].
Source: posthoc TFL table 9.1.8 DCO October 14 2020

As of Initial IA, at 25mg/m^2, the median (range) number of treatment courses received was 3 (1 to 14) courses. At 37.5mg/m^2, the median (range) number of treatment courses received was 2 (1 to 6) courses. The number of treatment courses received is summarized categorically in Applicant Table 24.

Applicant Table 24: Study JZP458-201 – Number of Treatment Courses Received in Cohorts 1a (IM 25 mg/m^2 MWF) and 1b (IM 37.5 mg/m^2 MWF) (DCO: October 14 2020)

Maximum Number of Courses Received	IM 25 mg/m^2 MWF N	IM 37.5 mg/m^2 MWF N
1	7	25
2	9	20
3	7	5
4	3	2
5	3	0
6	2	1
14	2	0

Abbreviations: IM = intramuscular; MWF = Monday, Wednesday, Friday
Percentages were calculated with the number of patients in the Safety Analysis Set as a denominator.
Duration of time on study in weeks is calculated as [[date of study completion or the data cutoff date - date of first dose date]+1]/7].
Source: posthoc TFL table 9.1.8 DCO October 14 2020

Overall, the majority of participants are white (62 of 86 [72.1%]) with a median (range) age of 9.0 years (1 to 24 years). Of the 86 participants, 25 (29.1%) were < 6 years of age, 31 (36.0%) were 6 to < 12 years of age, 19 (22.1%) were 12 to < 18 years of age, and 11 (12.8%) were ≥ 18 years of age. A higher percentage of male (50 of 86 [58.1%]) participants than female (36 of 86 [41.9%]) participants were enrolled. Overall, primary disease status was reported as B-ALL for 64 of 86 participants (74.4%), T-ALL for 13 of 86 participants (15.1%), and T-LBL for 9 of 86 (10.5%) participants (Initial Analysis Table 9.1.4.1).

The Applicant's Position:
JZP458 and concomitant medications were administered by the clinical site staff and therefore, compliance with JZP-458 protocol administration procedures was 100%. Actual exposure to JZP-458 is reflected in the data.

The FDA's Assessment:

The FDA agrees with the data in Applicant Tables 23 and 24 as of the cutoff date of October 2020. The analysis of age and age groups is in FDA Table above. The updated duration of time on study and courses received are in FDA Tables below.

FDA Table 25. Duration on Study (weeks)					
		Cohort 1A 25 mg/m^2 N = 33	**Cohort 1B 37.5 mg/m^2 (N = 53)**	**Cohort 1C 25(MW)/50(F) mg/m^2 (N = 16)**	**All (N = 102)**
Weeks on Study	Mean (SD)	23.45 (10.62)	13.18 (8.16)	2.78 (1.49)	14.87 (10.91)
	Median (Min, Max)	27.86 (0.14, 38.43)	15.43 (1.43, 27.14)	1.86 (1.71, 5.43)	15.86 (0.14, 38.43)
Source: Reviewer's analysis, ADSL					

FDA Table 26. JZP458-201: Courses completed (one course = 6 doses)					
		Cohort 1A 25 mg/m^2 (N = 33)	**Cohort 1B 37.5 mg/m^2 (N = 53)**	**Cohort 1C 25(MW)/50(F) mg/m^2 (N = 16)**	**All (N = 102)**
Courses of JZP-458 completed (n)	Mean (SD)	4.55 (3.01)	3.04 (1.94)	1.31 (0.48)	3.25 (2.45)
	Median (Min, Max)	4 (1, 14)	3 (1, 12)	1 (1, 2)	5 (1, 14)
Source: Reviewer's analysis, EX datafile					

An assessment of the use of drugs to prevent allergic reactions could not be performed, since adcm.xpt did not include a flag for drugs used for prophylaxis, and the text in the variable CMINDC was not sufficiently standardized to allow selection of such drugs specifically for use with the investigational product.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

See Section 6.1

The Applicant's Position:

The Efficacy of JZP-458 is demonstrated by the totality of data, which includes observed nadir serum asparaginase activity (NSAA) data at the protocol-specified time points, population pharmacokinetic (PPK) modeling and simulation results, asparagine depletion data, asparaginase enzyme content data, available immunogenicity data, adverse events (AEs), and clinical laboratory results. The totality of the available data from ongoing JZP458-201 study planned for inclusion in the BLA and Update Report submissions support review of the preferred dose and regimen for JZP-458: 25/25/50 mg/m^2 administered IM on MWF. This dose and schedule provide a positive benefit: risk profile for JZP-458, with sustained SAA levels ≥ 0.1 IU/mL to provide meaningful benefit to patients who require a non-*E.coli* asparaginase alternative. This is a population with significant unmet medical need.

The FDA's Assessment:
See Section 6 for the independent analysis of the primary endpoint.

Efficacy Results – Secondary and other relevant endpoints

Data:
See Section 6.1.

The Applicant's Position:
In line with the assessment of the primary efficacy endpoint, the applicant considers that the totality of efficacy data from Study JZP458-201 as discussed under Section 6.1 demonstrates that JZP 458 is effective as a component of a multi-agent chemotherapeutic regimen for the treatment of pediatric and adult patients with ALL or LBL who have developed hypersensitivity to *E. coli* derived L-asparaginase (including clinical hypersensitivity and silent inactivation) at a dose of 25/25/50mg/m^2 MWF.

The FDA's Assessment:
See Section 6 for the independent analysis of the secondary endpoints.

Efficacy Results – Subpopulations

Data:
There is no data available at this time.

The Applicant's Position:
No sub-population analyses were conducted.

The FDA's Assessment:
See Section 6 for the independent analyses regarding intrinsic and extrinsic factors.

Efficacy Results – Exploratory and COA (PRO) endpoints

Data:
The exploratory endpoints of the JZP458-201 study include:

- To determine the efficacy of intravenous (IV) RC-P administration as measured by the response, defined as the last 48-hour NSAA ≥ 0.1 IU/mL and the last 72-hour NSAA ≥ 0.1 IU/mL during the first course
- To assess the safety and tolerability of IV RC-P in patients with ALL/LBL who are hypersensitive to E. coli-derived asparaginases
- To characterize the PK of IV RC-P using a population PK approach
- To assess the immunogenicity of IV RC-P following repeat administration of RC-P

This part of the study (Part B) had not been opened to enrollment as of the DCO October 14 2020 and there are no data to report at this time.

The Applicant's Position:
Applicant continues to develop JZP-458 for IV administration under the IND 129622. At least 6 patients will be enrolled in the IV portion of the study (Part B) and the Applicant will engage with FDA during the review of this BLA to provide updates on these results.

The FDA's Assessment:
The FDA agrees that no patient-reported outcomes were submitted. See Section 6 for independent analyses of the additional endpoints.

Additional Analyses Conducted on the Individual Trial

Data:
A population PK (PPK) modeling and simulation was performed based on observed JZP-458-201 trial data outside of the trial objectives to inform the label and regulatory decisions. The details of this analysis is provided in Section 6.2 Summary of Clinical Pharmacology Assessment within this document and within Modules 2.5 and 5 of the BLA.

The Applicant's Position:
The PPK modeling and simulation analyses conducted with observed JZP458-201 provide support and additional confirmation for the proposed indication and dose regimen.

The FDA's Assessment:
See Section 6 for the independent Population PK modeling.

8.1.2. JZP458-101

A Phase 1 Study to Assess the Safety, Tolerability, and Pharmacokinetics of RC-P in Healthy Adult Subjects

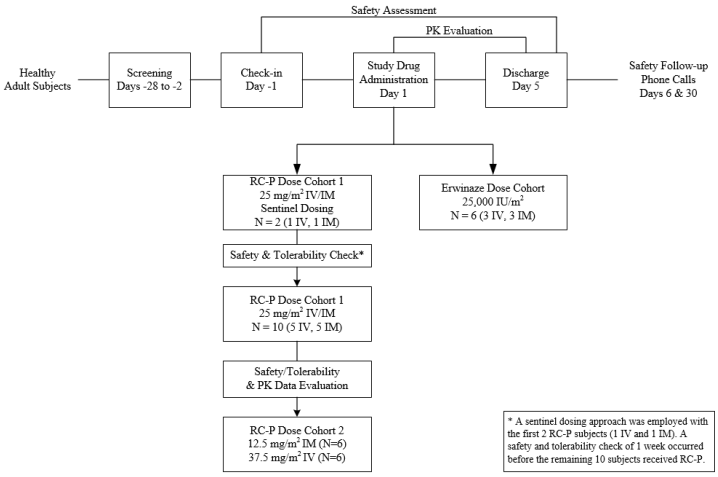
INVESTIGATIONAL PLAN

Trial Design

The Applicant's Description:
Study JZP458-101 was a randomized, single-center, open-label Phase 1 study conducted to evaluate the safety, tolerability, and PK of a single dose of JZP-458 via either a 2-hour IV infusion or IM administration in healthy adult subjects. An Erwinaze dosing arm was also included to allow comparisons to JZP-458 treatment. This study was conducted in

order to establish an appropriate dose for the pivotal study JZP458-201. The study was conducted at a single investigative site. A total of 30 subjects were treated in the study. The protocol defined an initial dose cohort of JZP-458 (12 subjects) and Erwinaze (6 subjects); a second JZP-458 dose cohort was permitted (12 subjects) based on the safety, tolerability, and PK evaluation from the initial dose cohort. For dose cohort 1 subjects, 25 mg/m^2 JZP-458 was administered as a single IV infusion or a single IM injection. Following safety, tolerability, and PK assessments from JZP-458 dose cohort 1, a second cohort treated an additional 12 healthy subjects in RC-P Dose Cohort 2, which received 12.5 mg/m2 IM or 37.5 mg/m2 IV. The Erwinaze cohort received a standard dose of 25,000 IU/m^2, which was administered via both IV and IM routes. Within each initial cohort dosing arms, subjects were randomized to IV or IM administration in a 1:1 ratio. This randomization schema was equivalent to randomizing all 18 initial-cohort study subjects to IV RC-P, IM RC P, IV Erwinaze, and IM Erwinaze in a 2:2:1:1 ratio, while ensuring that the first 2 randomized subjects received IV RC P and IM RC-P following the sentinel dosing approach.

Applicant Figure 8: JZP458-101 Study Schema



Abbreviations: IM = intramuscular; IU = International Units; IV = intravenous; PK = pharmacokinetics;
RC-P = Recombinant Crisantaspase *Pseudomonas fluorescens/JZP-458*

The safety, tolerability, and PK data for each subject in RC-P Dose Cohort 1 were evaluated by the investigator and the sponsor to determine the need to enroll subjects in another cohort. A JZP-458 Dose cohort 2 was enrolled based on the data from JZP-458 Dose cohort 1. The dose levels for JZP-458 dose cohort 2 were 12.5 mg/m^2 IM (N = 6) and 37.5 mg/m^2 IV (N = 6), which did not exceed the protocol-stipulated option of up to a 2-fold increase in the dose for JZP-458 dose cohort 1. Subjects were administered study drug on Day 1 and were to underwent daily assessments in accordance with the

protocol-specified schedule of assessments and procedures. Serial blood samples for PK analysis were to be collected from all subjects at pre-specified timepoints up to 96 hours postdose. The protocol-specified study duration for individual subjects was up to 58 days, depending on day of screening and final follow-up contact. Screening procedures to determine eligibility were to occur within 28 days prior to the dose of study drug. Following Screening, eligible subjects checked in at the study center on Day 1 (baseline); after completion of Day 1 assessments, eligible subjects were admitted to the phase 1 inpatient unit. Subjects remained in the phase 1 unit until discharged on Day 5 (6 days in total). Subjects were to receive an initial Safety Follow-up phone call on Day 6 and a final Safety Follow-up phone call on Day 30.

The FDA's Assessment:
The FDA agrees with the study description and trial design above.

Study Endpoints

The Applicant's Description:
Both safety and PK were evaluated in this study. The primary endpoint of the study was an assessment of safety and tolerability of RC-P by IV or IM dosing route for each cohort. The secondary endpoint of the study was the PK of RC-P by IV or IM dosing route for each cohort, and were assessed based on the calculation of PK parameters from SAA.

Safety

- Treatment-emergent adverse events (TEAEs) for the Safety Analysis Set summarized by study drug (JZP-458 or Erwinaze), dose level (cohort), and route of administration (IV or IM).
- Serious TEAEs, TEAEs leading to discontinuation, CTCAE Grade 3 or above TEAEs, TEAEs related to study drug, and deaths (if any).

Pharmacokinetics

- PK based on SAA for IV and IM of JZP-458.
- PK parameters, including but not limited to AUC, C_{max}, T_{max}, C_{48h}, C_{72h}, $t_{1/2}$, CL, V_{ss}

The FDA's Assessment:
The FDA agrees that these were the safety and PK endpoints for JZP458-101.

Statistical Analysis Plan and Amendments

The Applicant's Description:
The study was conducted according to the Statistical Analysis Plan – Protocol JZP458-101 (Amendment 1.0), Version 1, dated 22 April 2019. No formal statistical testing was performed for the PK and PD analyses.

The FDA's Assessment:
The FDA agrees that no formal statistical testing was performed for the PK and PD analyses.

Protocol Amendments

The Applicant's Description:

The original protocol dated October 12 2018 was amended once (Amendment 1) prior to dosing the first subject.

Applicant Table 27: Study JZP458-101 Protocol Amendments

Number*	Reasons for Amendment
Amendment 1.0 November 20 2018	Specific study stopping rules were updated so that the study would be terminated if, at any time during the 5-day inpatient treatment period, a subject developed a CTCAE ≥ Grade 3 event. Duration of the study for individual subjects was extended from 34 days to 58 days. A Safety Follow-up phone call on Day 30 was added.

*date of internal approval

The FDA's Assessment:
The FDA agrees that there was one protocol amendment for JZP458-101.

RESULTS

For Sections that are not relevant to the protocol, state "Not relevant". Do not delete sections.

Compliance with Good Clinical Practices

The Applicant's Position:

Study JZP458-101 was conducted in compliance with ICH Good Clinical Practice Regulations and ethical principles from the Declaration of Helsinki. The original protocol and protocol amendments were approved by an independent IRB/Ethics Committee associated with each study center. Signed informed consent was obtained from all participants prior to enrollment in the study.

The FDA's Assessment:
This is acceptable.

Data Quality and Integrity

The Applicant's Position:

JZP458-101 study supporting this application was conducted according to GCP and ICH guidelines with Sponsor oversight to ensure the safety of subjects and the integrity and interpretability of the study and study data.

The FDA's Assessment:
The FDA agrees that the submitted data are sufficient for review.

Financial Disclosure

Data:

No investigators participating in Study JZP458-101 disclosed financial interests at this time.

The Applicant's Position:

Financial disclosure information was collected from all investigators participating in JZP458-101 study.

The FDA's Assessment:

The FDA agrees that the financial disclosure information is acceptable.

Patient Disposition

Data:

Subject disposition is summarized in the Applicant Table 28 below. In total, 30 subjects were enrolled and randomized in the study. Of the 30 subjects enrolled, all 30 (100%) completed the study, including receiving 1 dose of study drug and the initial assessments (through Day 5); 30 of 30 subjects completed the final scheduled safety follow-up phone call on Day 30.

Applicant Table 28: Subject Disposition (Randomized Analysis Set JZP458-101)

Category	RC-P, IV 25 mg/m^2 (N=6)	RC-P, IV 37.5 mg/m^2 (N=6)	RC-P, IM 12.5 mg/m^2 (N=6)	RC-P, IM 25 mg/m^2 (N=6)	ERW, IV 25,000 IU/m^2 (N=3)	ERW, IM 25,000 IU/m^2 (N=3)
Subjects Randomized, n	6	6	6	6	3	3
Subjects Treated, n (%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	3 (100%)	3 (100%)
Completed Study, n (%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	3 (100%)	3 (100%)

Abbreviations: IM = intramuscular; IV = intravenous; N = number of subjects in Randomized Analysis Set; RC-P = Recombinant Crisantaspase *Pseudomonas/ JZP-458.* Percentages are based on N. Source JZP458-101 CSR Table 14.1.1

The Applicant's Position:

No subjects discontinued the study prematurely. All subjects were enrolled at the single investigative site.

The FDA's Assessment:
The FDA agrees with the data in Applicant's Table.

Protocol Violations/Deviations

Data:
JZP458-101, Protocol deviations listed in JZP458-101 CSR (listing 16.2.2.1). There were 5 protocol deviations recorded for the study occurring in 5 different subjects. Two of the 5 deviations concerned blood samples drawn a few minutes out of window (3 minutes out of window) or processed and stored out of window (7 minutes out of window). One of the deviations concerned a urine pregnancy test being performed erroneously for a male subject. The remaining 2 protocol deviations were due to mislabeling of the tubes for some of the pharmacodynamics samples data time points. The site staff was re-trained on lab procedures and these specific samples were not analyzed.

The Applicant's Position:
No protocol deviations related to inclusion and exclusion criteria were recorded either by site personnel or by Applicant's monitors. Protocol deviations were minor and had no impact to the integrity of the study results.

The FDA's Assessment:
Five minor protocol deviations were reported. The FDA agrees with the Applicant's position.

Demographic Characteristics

Data:
The mean ± SD values for demography characteristics includes age of 38.4 (± 8.30) years, weight of 77.04 (± 9.998) kg, and body surface area (BSA) of 1.91 (± 0.150) m^2. In addition, 63.3% were male, 96.7% were Hispanic or Latino ethnicity, and 83.3% were White with 16.7% Black/African American.

The Applicant's Position:
No differences in demographics to assess the PK and safety profile were observed in the groups studied in JZP458-101 study.

The FDA's Assessment:
The FDA agrees with this demographic assessment of the patients enrolled in JZP458-101.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:
Not applicable.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:
Not applicable.

The Applicant's Position:
Not applicable as this is a Phase 1 study in Healthy adult subjects.

The FDA's Assessment:
All patients received one dose of assigned investigational drug product. There were fourteen concomitant medications reported, with the most common being ondansetron, acetaminophen, ibuprofen, and famotidine.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:
JZP458-101 was a randomized, single-center, open-label study to evaluate the safety, tolerability, and pharmacokinetics (PK) of a single dose of JZP-458 in healthy adult participants via either IV infusion or an IM administration.

An Erwinaze dosing arm was also included.

The Applicant's Position:
In this study, there were no efficacy endpoints.

The FDA's Assessment:
The FDA agrees that there were no efficacy endpoints; see section 6 for PK/PD analyses and section 8.3 for safety analyses.

Efficacy Results – Secondary and other relevant endpoints

Data:
Not applicable.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

Efficacy Results – Subpopulations

Data:
Not applicable.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

Efficacy Results – Exploratory and COA (PRO) endpoints

Data:
Not applicable.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

Additional Analyses Conducted on the Individual Trial

Data:
Not applicable.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

8.2. Integrated Review of Effectiveness

The FDA's Assessment:

The indication proposed by the Applicant for JZP-458 was "as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia and lymphoblastic lymphoma in adult and pediatric patients who have developed hypersensitivity or silent inactivation to *E. coli*-derived asparaginase." The results of Study JZP458-201 were submitted to support the indication. The primary objective of JZP458-201 was to determine the proportion of patients with a 72-hour NSAA level ≥ 0.1 IU/mL during the first course of IM JZP-458.

Obtaining and maintaining the PD endpoint nadir serum asparaginase activity (NSAA) has been used as the basis for approval of asparaginase products (see section 2.2). The pharmacokinetics data from study JZP458-201 were considered credible. See Section 6 for the details of the clinical pharmacology assessment used to establish the efficacy of JZP-458.

The Clinical Pharmacology Reviewers concluded that JZP-458 dosages of either a) 25 mg/m^2 IM q 48 hours or b) 25 mg/m^2 IM on Monday and Wednesday and 50 mg/m^2 IM on Friday would provide NSAA consistent with levels required for efficacy.

There were insufficient data submitted to allow for meaningful conclusions regarding efficacy in patients identified as having silent inactivation.

8.3. Review of Safety

THE APPLICANT'S POSITION

8.3.1 Safety Review Approach

The Applicant's Position:

The safety information that is summarized in this BLA consists of data from 1 Phase 1 completed study (JZP458-101) and 1 pivotal Phase 2/3 ongoing clinical study (JZP458-201), as described in Applicant Table 13. The safety information supporting BLA 761179 is being submitted in several packages: CRFs (Early Submission package), Safety Summary and Clinical Overview (Initial BLA package), and Update Report (pending agreement in pre-submission meeting).

Safety was first analyzed in study JZP458-101, in 24 healthy adult subjects, the results of which did not reveal any unanticipated, serious, or severe AEs in any dose cohort.

Safety analysis is being further conducted in JZP458-201 in patients of any age with ALL/LBL who are hypersensitive to *E.coli*-derived asparaginases (allergic reaction or silent inactivation). In this study patients are being treated with intramuscular JZP458 with either 25 mg/m^2 (cohort 1a), 37.5 mg /m^2 (cohort 1b), or 25/25/50 mg/m^2 (cohort 1c) on a MWF dosing regimen.

The initial analysis of the JZP458-201 safety analysis set includes 86 patients who received at least 1 dose of JZP-458 intramuscularly: cohort 1a (N=33) received 25 mg/m^2 MWF and cohort 1b (N=53) received 37.5 mg/m^2 MWF. The safety profile of JZP-458 is assessed by the nature and frequency of TEAEs, SAEs, AE leading to study drug discontinuation, AEs leading to a recommendation of overall study dose modification, vital sign measurements and clinical laboratory assessments, and AEs of special interest (AESIs). The AESIs include study-drug related allergic reaction (including hypersensitivity and anaphylactic reaction), pancreatitis and thrombosis.

The safety analysis in JZP458-201 represents a relevant core population for the indication being sought and is representative of the expected safety profile. The safety data in this application

support the use of JZP458 in patients with ALL/LBL who are hypersensitive to *E.coli*-derived asparaginases.

8.3.2 Review of the Safety Database

Overall Exposure
Data:
The ongoing phase 2/3 study is an open-label, multicenter, dose confirmation, and PK study of JZP-458 in patients (of any age) with ALL/LBL who are hypersensitive to *E. coli*-derived asparaginases (allergic reaction or silent inactivation). This study is designed to assess the tolerability and efficacy of JZP-458, as measured by serum asparaginase activity with additional supportive analyses for asparagine depletion and anti-drug antibody (ADA) levels. Six doses of JZP 458 are substituted for each dose of a long-acting *E. coli*-derived asparaginase. Two consecutive weeks of treatment with JZP-458 is defined as one course. Multiple courses could be administered as per participant's treatment plan. This study consists of 2 parts: Part A to determine the dose of JZP-458 for IM administration and to confirm safety and efficacy; and Part B to define the optimal dose and schedule of IV JZP-458. **Error! Reference source not found.** below lists and categorizes the number of subjects exposed to JZP-458 as of 08-March-2021 in part A of study 201 and in study 101.

Applicant Table 29: Overall Number of Subjects Exposed to JZP458 (As of March 8, 2021)

Study	Dose	Diagnosis	Subjects Exposed	Planned Duration	Range of Exposure
Subjects with Cancer					
JZP458-201	25mg/m^2, MWF	ALL/LBL	33	Total 6 doses (TIW x 2)	
	37.5 mg/m^2, MWF	ALL/LBL	84	Total 6 doses (TIW x2)	
	25/25/50mg/m^2, MWF	ALL/LBL	52	Total 6 doses (TIW x2)	
Subjects without Cancer					
JZP458-101	25mg/m^2	Healthy Adult Volunteers	6 (IM) 6 (IV)		
	37.5 mg/m^2	Healthy Adult Volunteers	6 (IV)		
	12.mg/m^2	Healthy volunteers	6		

*As of March 8, 2021

A total of 86 patients received at least one dose of JZP-458 at the time of the initial IA, details of the Safety Analysis Set are provided in **Error! Reference source not found.**

Applicant Table 30: JZP458-201 Study Drug Administration (Safety Analysis Set, DCO October 14 2020)

	IM 25 mg/m^2 MWF (N = 33)	IM 37.5 mg/m^2 MWF (N = 53)	Total (N = 86)
Number of Planned JZP-458 Courses			
n	33	53	86
Mean	5.3 (2.65)	4.0 (1.71)	4.5 (2.19)
Median	5.0	4.0	5.0
Minimum, Maximum	1, 14	1, 7	1, 14
Number of Planned JZP-458 Courses, (n [%])			
1 courses	2 (6.1)	8 (15.1)	10 (11.6)
2 courses	0	2 (3.8)	2 (2.3)
3 courses	3 (9.1)	7 (13.2)	10 (11.6)
4 courses	5 (15.2)	12 (22.6)	17 (19.8)
5 courses	12 (36.4)	12 (22.6)	24 (27.9)
6 courses	8 (24.2)	11 (20.8)	19 (22.1)
7 courses	0	1 (1.9)	1 (1.2)
8 courses	1 (3.0)	0	1 (1.2)
14 courses	2 (6.1)	0	2 (2.3)
Number of Actual JZP-458 Courses Completed[a]			
n	11	9	20
Mean	3.7 (3.95)	0.9 (0.33)	2.5 (3.22)
Median	3.0	1.0	1.0
Minimum, Maximum	0, 14	0, 1	0, 14
Number of Actual JZP-458 Courses Completed[a], (n [%])			
1 courses	2 (6.1)	8 (15.1)	10 (11.6)
3 courses	2 (6.1)	0	2 (2.3)
4 courses	2 (6.1)	0	2 (2.3)
5 courses	1 (3.0)	0	1 (1.2)
6 courses	1 (3.0)	0	1 (1.2)
14 courses	1 (3.0)	0	1 (1.2)
Percent of Planned Courses Completed[a]			
n	7	6	13

	IM 25 mg/m^2 MWF (N = 33)	IM 37.5 mg/m^2 MWF (N = 53)	Total (N = 86)
Mean (SD)	59.53 (50.783)	83.33 (40.825)	70.52 (46.222)
Median	100.00	100.00	100.00
Minimum, Maximum	0.0, 100.0	0.0, 100.0	0.0, 100.0
Percent of Planned Doses Completed[a]			
n	7	6	13
Mean (SD)	66.67 (41.935)	97.22 (6.818)	80.77 (33.909)
Median	100.00	100.00	100.00
Minimum, Maximum	16.7, 100.0	83.3, 100.0	16.7, 100.0
Total Volume Administered (mL)			
n	33	53	86
Mean (SD)	31.348 (30.451)	21.317 (13.789)	25.166 (22.124)
Median	23.400	16.800	18.300
Minimum, Maximum	2.00, 158.10	6.60, 61.50	2.00, 158.10
Average Volume per Dose Administered (mL)			
n	33	53	86
Mean (SD)	1.629 (0.680)	2.095 (0.795)	1.916 (0.783)
Median	1.730	1.810	1.800
Minimum, Maximum	0.60, 3.14	1.10, 3.85	0.60, 3.85

DCO 14 October 2021
Abbreviations: IM = intramuscular
a-The "Completed" status includes data for participants who have completed all treatments or who discontinued at the time of the data cut off of October 14 2020; it does not reflect the data for those participants who were ongoing at the time of the data cut off. Percentages were calculated with the number of participants in the Safety Analysis Set as a denominator. The percent of planned doses and courses is only presented for participants who are no longer active on the study either due to completing the study or early discontinuation from the study. There were 6 planned doses per course. A participant was considered to have completed a course if all 6 doses for that course were administered. The number of actual courses completed is only presented for participants who reached the end of treatment.
Source: Initial IA TFL Table 9.1.7

Exposure in JZP458-201 as of the data cutoff date for initial IA showed that the median duration of time on study was 19.1 (Range 1.4-14.1) weeks for cohort 1a and 6.6 (range 1.9-14.1) weeks

for cohort 1b. The mean number of treatment courses received was 3 (range: 1-14) in Cohort 1a and 1 (range: 1-6) in cohort 1b (25 and 37.5 mg/m^2 respectively). Exposure related data and information from Cohort 1c (25/25/50 mg/m^2 safety Data) will be provided in the BLA. Final TFLs for the 25/25/50 mg/m^2 safety data set once available are intended to support the positive benefit: risk profile for the use of JZP-458 in all patients.

The Applicant's Position:
A comprehensive review of the safety database was conducted with the analysis populations described in section **Error! Reference source not found.**.

As shown in **Error! Reference source not found.Error! Reference source not found.** and **Error! Reference source not found.**, the Applicant has studied exposure of JZP-458 at several total dose levels in subjects of diverse demographics (Applicant Table 21). The overall exposure to JZP-458 is adequate to support characterization of the JZP-458 safety profile and determine the benefit risk ratio for patients.

Relevant characteristics of the safety population:
Data:
Demographic and baseline characteristic of JZP458-201 summarized by dose as of the DCO October 14 2020 are provided in Applicant Table 21. Treatment cohorts had similar characteristics and no analysis related to differences was deemed necessary.

The Applicant's Position:
In JZP458-201, the demography of study subjects encompasses the range of population of ALL/LBL treated with asparaginase containing multi-agent chemotherapy. By design, all patients in the JZP458-201 trial have been previously exposed to an asparaginase product, and demonstrated either hypersensitivity and/or silent inactivation. The safety analysis data set is therefore considered appropriate to support the intended use of JZP-458.

The median age of patients (based on the initial IA dataset) in JZP458-201 study was 9 years (range 1-24): 11 years (range 1-24) for cohort 1a and 8 years (range 1-20) for cohort 1b (25 and 37.5 mg/m^2 respectively). The proportion of patients who are 18 years or older was 12.8%. The percentage of male patients was 58.1%. The majority of patients (87.2%) fulfilled the eligibility criteria by having Grade 3 or higher allergic reaction without inactivation of *E.coli*-derived asparaginase. The remaining patients had silent inactivation (7.0%) or allergic reaction with inactivation to *E.coli*-derived asparaginase (5.8%).

The complete demographic information from the JZP458-201 clinical trial once available is intended to support a complete assessment of the positive benefit: risk profile for the use of JZP-458 in all patients for the proposed indication of 25/25/50 mg/m^2.

Adequacy of the safety database:

Data:

In the study JZP458-101, 24 healthy adult subjects received a single dose of JZP-458 at dose or 12.5 mg/m^2 (intramuscularly), 25 mg/m^2 (intramuscularly or intravenously), or 37.5mg/m^2 (intravenously).
In the JZP458-201 study, at the point of initial BLA submission, 86 patients were included in the safety database for assessment (as of the data cut of date October 14 2020) and safety analyses will continue throughout the end of the trial as specified in the protocol.

The initial BLA safety analyses based on the JZP458-201 study was comprised of 33 patients at the 25 mg/m^2 dose MWF for a total dose of 150 mg/m^2 per each course and 53 patients at the 37.5 mg/m^2 dose MWF for a total dose of 225 mg/m^2 per each course. The ongoing IM portion of the study includes patients at 25/25/50 mg/m^2 dosing regimen MFW for a total dose of 200 mg/m^2 per each course. At the time of the Update Report, there will be approximately 101 patients in the safety database for which data will be reported. Final TFLs for the 25/25/50 mg/m^2 safety data set once available is intended to the positive benefit: risk profile for the use of JZP-458 in all patients.

The Applicant's Position:

The safety profile of asparaginases has been well established over several decades in the ALL/LBL populations who received asparaginase-containing multi-agent chemotherapy. As agreed with FDA the safety database at considered dosing regimens for JZP-458 had a minimum of 51 patients. With a sample size of 51, the probability of identifying adverse events (AEs) related to asparaginase with an incidence as low as 3% is 79%. The applicant proposed point estimate bounds for the safety endpoint of AESIs (allergic reactions, pancreatitis, and thrombosis). The FDA agreed that a sample size of 50 would be sufficient to exclude a clinically meaningful increase in those toxicities.

8.3.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

There is no available data at this time regarding data integrity issues or submission quality.

The Applicant's Position:

There are no concerns anticipated in the quality and integrity of the submitted datasets and individual case narratives. These deliverables are considered in line with the relevant guidance's and CFR passages and will support a complete and thorough review of safety. Any concerns related to site documentation due to Covid-19 restrictions have been documented in the JZP-458 Clinical Covid-19 memo and the JZP-458-201 Covid-19 CSR appendix. Data in CRFs and AE databases have been checked for consistently before submission.

Categorization of Adverse Event
Data:
There is no available data at this time on Adverse Event categorization.

The Applicant's Position:
The reported adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) to classify events under the primary system organ class (SOC) and preferred term (PT). The severity of adverse events was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. AESIs were identified using the criteria specified in the statistical analysis plan (See SAP v1.4, Appendix 2).

Safety was assessed and recorded in line with section 6.5 of JZP458-101 protocol and section 6.7 of JZP458-201 protocol. This information includes (but it not limited to) surveillance and recording of all reported and observed AEs (including serious adverse events [SAEs]), listings of concomitant medications, physical examinations, and laboratory test results. Safety monitoring is ongoing for the IM portion of the study. Final TFLs for the safety data set once available is intended to support the positive benefit: risk profile for the use of JZP-458 in all patients.

Categorization of all AEs reported during the development program was appropriate for a complete safety data evaluation.

Routine Clinical Tests
Data:
All protocol-required laboratory assessments were conducted in accordance with the laboratory manual and the Schedule of Assessments outlined in Applicant Table 14 .

The Blood samples are collected for serum asparaginase activity (SAA) level determination, other PK/Pharmacodynamics (PD), immunogenicity, and laboratory evaluations as defined in JZP458-201 Protocol 2.

The Applicant's Position:
Laboratory results were graded using NCI-CTCAE (version 5), when applicable. Frequency and selection of clinical assessments are adequate for expected toxicities associated with JZP-458

8.3.4 Safety Results

Deaths
Data:
No deaths were reported for the JZP458-101 phase 1 study in healthy volunteers.

Safety results continue to be monitored for the ongoing IM portion of the study. There have been 3 Grade 5 adverse events reported. A full description of these Grade 5 AEs can be found

in the **JZP-458 Pre-BLA Meeting Package**. Safety results from 24 subjects in the JZP458-101 study as well as 33 patients at the 25 mg/m^2 dose MWF, 53 patients at the 37.5 mg/m^2 dose MWF and 16 patients at the 25/25/50 mg/m^2 dosing regimen MWF for the JZP458-201 study will be made available.

Safety Data for 25/25/50 mg/m^2: Final TFLs for the 25/25/50 mg/m^2 safety data set once available is intended to support the positive benefit: risk profile for the use of JZP-458 in all patients. As of January 11, 2021, there were no deaths reported for patients at 25/25/50 mg/m^2 (N=16).

The Applicant's Position:
The JZP458-201 trial has not reported deaths attributed to JZP-458 in the initial BLA (based on the Initial IA DCO October 14, 2020). The study population is immunocompromised and receiving multi-agent/modal antineoplastic treatment, and there is a risk of mortality in this population. A review of detailed information for the participants that have been reported as deceased during the trial did not reveal safety risks that change the positive benefit-risk assessment of JZP-458.

Deaths reported after the Initial IA DCO (known at the time of this document) are discussed below under Serious Adverse Events and in the **JZP-458 Pre-BLA Meeting Package**. A listing of all Deaths will be provided in the final study CSR and BLA.

Serious Adverse Events
Data:
There were no SAEs reported in the JZP458-101 study. The summary of SAEs for JZP458-201 is presented below **Error! Reference source not found.**.

Applicant Table 31: Summary of JZP458-201 Serious Treatment-emergent Adverse Events

System Organ Class **Preferred Term, n (%)**	**IM 25 mg/m^2 MWF (N = 33)**	**IM 37.5 mg/m^2 MWF (N = 53)**	**Total (N = 86)**
Number of participants with at least 1 SAE	15 (45.5)	12 (22.6)	27 (31.4)
Blood and lymphatic system disorders	8 (24.2)	6 (11.3)	14 (16.3)
Febrile neutropenia	7 (21.2)	6 (11.3)	13 (15.1)
Methaemoglobinemia	1 (3.0)	0	1 (1.2)
Cardiac disorders	0	1 (1.9)	1 (1.2)
Sinus tachycardia	0	1 (1.9)	1 (1.2)
Gastrointestinal disorders	3 (9.1)	4 (7.5)	7 (8.1)
Stomatitis	3 (9.1)	1 (1.9)	4 (4.7)
Pancreatitis acute	0	2 (3.8)	2 (2.3)

System Organ Class **Preferred Term, n (%)**	**IM 25 mg/m^2 MWF (N = 33)**	**IM 37.5 mg/m^2 MWF (N = 53)**	**Total (N = 86)**
Abdominal pain	0	1 (1.9)	1 (1.2)
Vomiting	0	1 (1.9)	1 (1.2)
General disorders and administration site conditions	3 (9.1)	2 (3.8)	5 (5.8)
Pyrexia	3 (9.1)	0	3 (3.5)
Chills	0	1 (1.9)	1 (1.2)
Non-cardiac chest pain	0	1 (1.9)	1 (1.2)
Pain	0	1 (1.9)	2 (2.3)
Immune system disorders	1 (3.0)	1 (1.9)	2 (2.3)
Drug hypersensitivity	1 (3.0)	1 (1.9)	2 (2.3)
Infections and infestations	1 (3.0)	2 (3.8)	3 (3.5)
Sepsis	1 (3.0)	1 (1.9)	2 (2.3)
Anal abscess	0	1 (1.9)	1 (1.2)
Metabolism and nutrition disorders	2 (6.1)	1 (1.9)	3 (3.5)
Dehydration	2 (6.1)	1 (1.9)	3 (3.5)
Musculoskeletal and connective tissue disorders	1 (3.0)	1 (1.9)	2 (2.3)
Bone pain	0	1 (1.9)	1 (1.2)
Osteonecrosis	1 (3.0)	0	1 (1.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1 (1.9)	1 (1.2)
Histiocytic sarcoma	0	1 (1.9)	1 (1.2)
Nervous system disorders	3 (9.1)	1 (1.9)	1 (1.2)
Cerebrospinal fluid leakage	1 (3.0)	0	1 (1.2)
Headache	0	1 (1.9)	1 (1.2)
Leukoencephalopathy	1 (3.0)	0	1 (1.2)
Presyncope	1 (3.0)	0	1 (1.2)

System Organ Class Preferred Term, n (%)	IM 25 mg/m^2 MWF (N = 33)	IM 37.5 mg/m^2 MWF (N = 53)	Total (N = 86)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IM = intramuscular; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SOC = System Organ Class; TEAE = treatment-emergent adverse event

Percentages were calculated with the number of participants in the Safety Analysis Set as a denominator.

Adverse events were coded to SOC and PT using MedDRA 22.1. The severity of AEs was recorded using CTCAE 5.0.

SOC and PT were sorted alphabetically and decreasing order of total frequency, respectively.

A TEAE was defined as any event with onset date on or after the first dose of study treatment through the end of the study or any ongoing event that worsens in severity after the date of the first dose of study treatment through the end of the study.

Severity: Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe or medically significant but not immediately life-threatening; Grade 4 = Life-threatening consequences; Grade 5 = Death related to AE. Participants reporting an AE more than once within a SOC/PT are counted only once for that SOC/PT.

Source: Initial IT TFL Table 9.3.1.3

In JZP458-201 (as of the initial IA), overall, 31.4% of patients experienced at least 1 SAE during the study. The most frequently (ie, those occurring in at least 3 of 86 participants [3.5%]) reported SAEs included Febrile neutropenia (13 of 86 participants [15.1%]), Stomatitis (4 of 86 participants [4.7%]), and Pyrexia and Dehydration (3 of 86 participants [3.5%] each). All of the SAEs were considered not related to study drug, except for the events of Febrile neutropenia, Pancreatitis acute, and Drug hypersensitivity (2 of 86 participants [2.3%] each); and Chills, Pain, and Headache (1 of 86 participants [1.2%] each).

Safety Data from 25/25/50 mg/m^2:

Final TFLs for the 25/25/50 mg/m^2 safety data from N=16 patients (as of DCO January 11, 2021) will be included in the update report, and is intended to support the positive benefit: risk profile for the use of JZP-458 in all patients.

The Applicant's Position:

The SAEs listed (**Error! Reference source not found.**) are consistent with the known adverse event profile of asparaginase-containing chemotherapy in patients with ALL/LBL and overall safety profiles were similar between cohorts. The incidence of each event is within the expected range in the population being studied.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

As per JZP458-101 and JZP458-201 protocols, patients who experience an AE may discontinue

study drug at the recommendation of the physician. However, there is no option for dose interruption or reduction within the study.
There were no dropouts or discontinuations due to adverse effects reported for JZP458-101.

In JZP458-201, as of the Initial IA, overall 3 of 86 participants (3.5%) experienced a TEAE that lead to discontinuation of study drug. Events that led to discontinuation of study drug included drug hypersensitivity (1 of 86 participants [3.0%] in the IM 25 mg/m^2 MWF cohort) and acute pancreatitis (2 of 86 participants [3.8%] in the IM 37 mg/m^2 MWF cohort). All events leading to study drug discontinuation were considered related to study treatment.
Source Initial IA Table 9.3.1.9 and Table 9.3.1.10

The Applicant's Position:
Within the JZP458-201 study, discontinuations due to adverse events are consistent with the profile of asparaginase-containing chemotherapy in patients with ALL/LBL.

Dose Interruption/Reduction Due to Adverse Effects

Data:
There is no available data at this time for Dose Interruption/Reduction Due to Adverse Effects.

The Applicant's Position:
There were no dose interruptions or reductions in either study (JZP458-101 or JZP458-201).

Significant Adverse Events

Data:
There were no Grade 3 or higher adverse events reported in JZP458-101. In JZP458-201, overall, 56 out of 86 (65.1%) of patients experienced at least one Grade 3 or higher TEAE. The most common Grade 3 or higher TEAE (>10 %) included Anemia (24.4%), Febrile neutropenia (16.3%), Neutrophil count decreased (32.6%), Platelet count decreased (22.1%), White blood cell count decreased (17.4%), and Lymphocyte count decreased (15.1%).

Significant Adverse Events reported at the time of the initial IA are listed in **Error! Reference source not found.**

Applicant Table 32: Summary of Grade 3 or 4 Treatment-emergent Adverse Events Occurring in at Least 5% of Participants Overall (Safety Analysis Set as of October 14 2020)

System Organ Class Preferred Term Severity Grade, n (%)	IM 25 mg/m^2 MWF (N = 33)	IM 37.5 mg/m^2 MWF (N = 53)	Total (N = 86)
Number of participants with at least 1 Grade 3 or Grade 4 TEAE	22 (66.7)	34 (64.2)	56 (65.1)
Grade 3	10 (30.3)	22 (41.5)	32 (37.2)
Grade 4	12 (36.4)	12 (22.6)	24 (27.9)
Blood and lymphatic system disorders	17 (51.5)	17 (32.1)	34 (39.5)
Grade 3	16 (48.5)	16 (30.2)	32 (37.2)
Grade 4	1 (3.0)	1 (1.9)	2 (2.3)
Anemia[a]	9 (27.3)	12 (22.6)	21 (24.4)
Febrile neutropenia[a]	8 (24.2)	6 (11.3)	14 (16.3)
Gastrointestinal disorders[a]	4 (12.1)	6 (11.3)	10 (11.6)
Stomatitis[a]	3 (9.1)	2 (3.8)	5 (5.8)
Investigations	18 (54.5)	24 (45.3)	42 (48.8)
Grade 3	5 (15.2)	11 (20.8)	16 (18.6)
Grade 4	13 (39.4)	13 (24.5)	26 (30.2)
Neutrophil count decreased	13 (39.4)	15 (28.3)	28 (32.6)
Grade 3	2 (6.1)	3 (5.7)	5 (5.8)
Grade 4	11 (33.3)	12 (22.6)	23 (26.7)
Platelet count decreased	9 (27.3)	10 (18.9)	19 (22.1)
Grade 3	3 (9.1)	5 (9.4)	8 (9.3)
Grade 4	6 (18.2)	5 (9.4)	11 (12.8)
White blood cell count decreased	8 (24.2)	7 (13.2)	15 (17.4)
Grade 3	1 (3.0)	2 (3.8)	3 (3.5)
Grade 4	7 (21.2)	5 (9.4)	12 (14.0)
Lymphocyte count decreased	6 (18.2)	7 (13.2)	13 (15.1)
Grade 3	3 (9.1)	5 (9.4)	8 (9.3)
Grade 4	3 (9.1)	2 (3.8)	5 (5.8)
Alanine aminotransferase increased	3 (9.1)	3 (5.7)	6 (7.0)
Grade 3	3 (9.1)	2 (3.8)	5 (5.8)
Grade 4	0	1 (1.9)	1 (1.2)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IM = intramuscular; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event

a Only grade 3 TEAEs were reported; no grade 4 TEAEs were reported.

System Organ Class Preferred Term Severity Grade, n (%)	IM 25 mg/m^2 MWF (N = 33)	IM 37.5 mg/m^2 MWF (N = 53)	 Total (N = 86)

Percentages were calculated with the number of participants in the Safety Analysis Set as a denominator.
Adverse events were coded to SOC and PT using MedDRA 22.1. The severity of AEs was recorded using CTCAE 5.0.
SOC and PT were sorted alphabetically and decreasing order of total frequency, respectively.
A TEAE was defined as any event with onset date on or after the first dose of study treatment through the end of the study or any ongoing event that worsens in severity after the date of the first dose of study treatment through the end of the study.
Severity: Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe or medically significant but not immediately life-threatening; Grade 4 = Life-threatening consequences; Grade 5 = Death related to AE.
Participants reporting an AE more than once within a SOC/PT are counted only once for that SOC/PT at the maximum severity.
Source: Initial IA TFLTable 9.3.1.6

The Applicant's Position:

The Significant Adverse Events listed in **Error! Reference source not found.** are consistent with the known adverse events profile of patients who received multi-agent chemotherapy for ALL/LBL. Significant Adverse Events continue to be recorded for the study.

Final tabulated adverse events for the 25/25/50 mg/m^2 dosing regimen which will be included in the update report as detailed in section 7.2 are is intended to support the positive benefit: risk profile for the use of JZP-458 in all patients.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

In JZP458-101, the majority of subjects experienced at least 1 TEAE with most related to study treatment. Most of these subjects experienced Grade 1 TEAEs. Grade 2 events of nausea and vomiting were experienced by no more than a single subject in each of the dosing cohorts. No subjects experienced allergic reactions, pancreatitis, hyperglycemia, elevated transaminases, and clinical coagulation abnormalities. TEAEs and ADRs for JZP458-201 are summarized in below in **Error! Reference source not found.** and **Error! Reference source not found.**

Applicant Table 33: Summary of TEAE Occurring in > 10% of Participants by System Organ Class and Preferred Term (Study JZP458 201 Safety Analysis Set DCO October 14 2020)

Preferred Term, n (%)	IM 25 mg/m^2 MWF (N = 33)	IM 37.5 mg/m^2 MWF (N = 53)	Total (N = 86)
Number of Patients With at Least 1 TEAE	32 (97.0)	51 (96.2)	83 (96.5)
Anaemia	11 (33.3)	21 (39.6)	32 (37.2)
Neutrophil count decreased	14 (42.4)	16 (30.2)	30 (34.9)
Platelet count decreased	11 (33.3)	14 (26.4)	25 (29.1)
Vomiting	9 (27.3)	15 (28.3)	24 (27.9)
Fatigue	6 (18.2)	14 (26.4)	20 (23.3)
Nausea	5 (15.2)	15 (28.3)	20 (23.3)
White blood cell count decreased	11 (33.3)	9 (17.0)	20 (23.3)
Pyrexia	7 (21.2)	11 (20.8)	18 (20.9)
Decreased appetite	3 (9.1)	12 (22.6)	15 (17.4)
Febrile neutropenia	8 (24.2)	7 (13.2)	15 (17.4)
Lymphocyte count decreased	7 (21.2)	8 (15.1)	15 (17.4)
Stomatitis	6 (18.2)	9 (17.0)	15 (17.4)
Abdominal pain	3 (9.1)	9 (17.0)	12 (14.0)
Alanine aminotransferase increased	3 (9.1)	9 (17.0)	12 (14.0)
Back pain	5 (15.2)	7 (13.2)	12 (14.0)
Headache	8 (24.2)	4 (7.5)	12 (14.0)
Pain in extremity	6 (18.2)	6 (11.3)	12 (14.0)
Sinus tachycardia	3 (9.1)	7 (13.2)	10 (11.6)
Aspartate aminotransferase increased	3 (9.1)	6 (11.3)	9 (10.5)
Cough	4 (12.1)	5 (9.4)	9 (10.5)
Diarrhoea	2 (6.1)	7 (13.2)	9 (10.5)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IM = intramuscular; MedDRA = Medical Dictionary for Regulatory Activities; MWF = Monday, Wednesday, Friday; PT = Preferred Term; SOC = System Organ Class; TEAE = treatment-emergent adverse event

Percentages were calculated with the number of participants in the Safety Analysis Set as a denominator.

Adverse events were coded to SOC and PT using MedDRA 22.1. The severity of AEs was recorded using CTCAE 5.0.

SOC and PT were sorted alphabetically and decreasing order of total frequency, respectively.

A TEAE was defined as any event with onset date on or after the first dose of study treatment through the end of the study or any ongoing event that worsens in severity after the date of the first dose of study treatment through the end of the study.
Participants reporting an AE more than once within a SOC/PT are counted only once for that SOC/PT.
Source: Interim IA TFLTable 9

Applicant Table 34: Adverse Reactions (≥ 5% (after rounding) in total study population for the study JZP458-201 (DCO October 14 2020)

Preferred term	**Total study population(N=86: 25 mg/m^2 M/W/F [N=33] and 37.5 mg/m^2 M/W/F [N=53])**	
	All Grades	**Grades 3-4**
Neutrophil count decreased	16 (18.6%)	15 (17.4%)
Anemia	13 (15.1%)	6 (7.0%)
Nausea	13 (15.1%)	0
Vomiting	12 (14.0%)	0
Platelet count decreased	9 (10.5%)	7 (8.1%)
White blood cell count decreased	9 (10.5%)	7 (8.1%)
Alanine aminotransferase increased	8 (9.3%)	3 (3.5%)
Aspartate aminotransferase increased	7 (8.1%)	1 (1.2%)
Fatigue	7 (8.1%)	0
Lymphocyte count decreased	7 (8.1%)	6 (7.0%)
Abdominal pain	5 (5.8%)	1 (1.2%)
Decreased appetite	5 (5.8%)	1 (1.2%)
Pain in extremity	5 (5.8%)	0
Pyrexia	5 (5.8%)	1 (1.2%)
Drug hypersensitivity	4 (4.7%)	1 (1.2%)
Febrile neutropenia	4 (4.7%)	3 (3.5%)
Hypoalbuminemia	4 (4.7%)	0

Source: Initial IA TFL

In JZP458-201, the most frequently observed TEAEs included Anemia (37.2%), Neutrophil count decreased (34.9%), and Platelet count decreased (29.1%). The observed TEAEs are consistent with the toxicity profile of asparaginase-containing chemotherapy in patients with ALL/LBL.
A multidisciplinary applicant team performed a comprehensive review of all TEAEs and Adverse Events of Special Interest to identify those that could be categorized as ADRs. The TEAEs from Study JZP458-201 were reviewed using the safety analysis set for the determination of whether

they represent ADRs. ADRs are events that have been assessed as being at least possibly causally related to JZP-458 by the investigator or the applicant. These ADRs are considered class effect of asparaginase and/or biologically plausible and observed in at least 5% (after rounding) of total participants in cohort1a and cohort 1b (25 and 37.5 mg/m^2 respectively). The most common ADRs included Neutrophil count decreased (18.6%), Anemia (15.1%), Nausea (15.1%), Vomiting (14.0%), Platelet count decreased (10.5%), and White blood cell count decreased (10.5%). These ADRs are consistent with the known safety profile of asparaginase and asparaginase-containing chemotherapeutic regimens in patients with ALL/LBL. The list of adverse reactions determined by the applicant in **Error! Reference source not found.**, represents the safety profile of JZP-458.

25/25/50 mg/m^2 Safety Data: Updated final categorized safety rates for the 25/25/50 mg/m^2 dosing regimen will be included in the update report as detailed in section 7.2.

The Applicant's Position:
The safety profile observed for JZP458-101 was consistent with other asparaginase products. There were no unanticipated AEs reported. The Treatment Emergent Adverse Events and Adverse Reactions reported in the JZP458-201 trial are aligned with the safety profile of asparaginase and IM products.

Laboratory Findings
Data:
Results of clinical laboratory evaluations were classified based on CTCAE v5.0 toxicity grade. Summary Post hoc lab shift tables are presented in initial IA (TFL T9.3.2.4, T9.3.2.5 and T9.3.2.6).

The Applicant's Position:
As of Initial IA, no safety signals from the laboratory parameters were detected. Abnormal laboratory results considered clinically significant by the investigators during the study were reported as AEs and are therefore included in the safety tables. Commonly reported laboratory findings were hematologic in nature, consistent with the study population in a trial receiving combination chemotherapeutic agents.

Vital Signs
Data:
In study JZP458-201, vital sign evaluations include blood pressure, heart rate, respiratory rate, and temperature. Results are presented in initial TFL Table T9.3.3.

The Applicant's Position:
Physical examinations assessed as clinically significant by the investigators were reported as AEs. As of the IA, mean and median vital sign values did not reveal meaningful changes from baseline or differences in weight, blood pressure (including diastolic and systolic values), heart

rate or body temperature.

Electrocardiograms (ECGs)/QT
Data:
Not applicable

The Applicant's Position:
JZP-458 is an enzyme, and is not expected to have an effect on the QT interval. FDA advice (14 September 2018) indicated that it was not necessary to conduct a formal assessment of JZP-458 for QTc prolongation.

Immunogenicity
Data:
Immunogenicity of JZP-458 is being evaluated in the ongoing Phase 2/3 Study JZP458-201 in ALL/LBL patients who have developed hypersensitivity to *E. coli* derived asparaginase. In Study JZP458-201, immunogenicity samples are being collected from all participants (IM and IV participants) prior to the first dose in each course, prior to dose 6 in Course 1, and at the End of Study visit (30 days [±3] after last dose in the last course). Additional samples to test for ADAs may be obtained if a participant experiences an allergic reaction. If it is determined that a participant has subtherapeutic NSAA levels (< 0.1 IU/mL), a test for ADA may be performed if there is a blood sample available. In addition, for participants who exhibit positive ADA from samples obtained prior to the end of study, efforts are being made to collect follow-up ADA samples up to approximately 6 months after a participant's last dose of their last course of JZP-458. For these ADA positive participants, their follow-up ADA samples will be the last sample obtained. All immunogenicity samples are being assessed using validated methods.

In an initial IA of the ongoing Study JZP458-201 34.9% of participants (30/86) were confirmed ADA+ and 3.5% of participants (3/86) were positive for neutralizing antibodies. The range of ADA titer among these 30 participants was 6-3697 (excluding <minimum required dilution). As of the Initial IA, only limited ADA data are available during subsequent courses. ADA was evaluated as a covariate for the PK of JZP-458 within the population PK analysis, and it was not a significant covariate. However, we did observe two patients with lower SAA levels (<0.1 IU/mL) who had positive ADA.

Of the 30 participants who were ADA+, only 1 participant had a hypersensitivity reaction (<=Grade 2 Drug hypersensitivity) and was discontinued (after the data cut-off date of October 14, 2020) due to progression of T-LBL.

The maximum ADA titer for this patient was 153. The most commonly occurring treatment-related TEAEs in participants with at least 1 ADA positive result included Neutrophil count decreased, Nausea, Vomiting, Abdominal pain (including Abdominal pain upper), and Pain in

extremity. No treatment-related TEAE occurring in participants with ADA positive results led to a dose change or a discontinuation of study drug.

ADA samples will collected until the end of the study. Further assessments of ADA results including patients in cohort 1c (25/25/50 mg/m^2) will be provided once available and are intended to support the positive benefit: risk profile for the use of JZP-458 in all patients.

The Applicant's Position:
Based on the initial immunogenicity risk assessment for JZP-458 described above, no additional risks are expected for JZP-458 compared with other asparaginases. Confirmation of current conclusions regarding the immunogenicity of JZP-458 will be finalized at the end of the study.

8.3.5 Analysis of Submission-Specific Safety Issues
8.2.5.1 [AE of special interest]

Data:
In JZP458-101, there were no AESIs reported.

The following AEs are identified as AESIs based on the known class effects and mechanism of action and have been monitored carefully per the protocol.

Based on the initial IA data cut including 25 mg/m^2 and 37.5 mg/m^2:

Allergic reaction including hypersensitivity and anaphylactic reaction: Overall, allergic reactions, inclusive of hypersensitivity and anaphylactic reaction, have occurred in 21 of 86 subjects (24.4%), of which 6 subjects (7.0%) had at least 1 event that was considered related to study drug. The most frequently (ie, those occurring in at least 3 of 86 subjects [3.5%]) reported events related to allergic reactions included Rash maculo-papular (8.1%), Drug hypersensitivity and Rash (4.7% each), and Allergic transfusion reaction (3.5%). Study drug-related allergic reactions included Drug hypersensitivity in 4 subjects (3 subjects had Grade 1 or 2 events and 1 subject had a Grade 3 event), Infusion-related reaction (Grade 2) in 1 participant, and Rash maculopapular (Grade 1) in 1 participant. All allergic reactions in these 6 participants were resolved. The participant who developed Grade 3 Drug hypersensitivity discontinued JZP-458 due to the event.

Pancreatitis: As of the data cut-off date of October 14 2020 for the initial IA, 2 of 86 subjects (3.8%) have experienced an event of ≥ Grade 3 pancreatitis that were considered related to the study drug and led to discontinuation of study drug. Both subjects who developed pancreatitis were in cohort 1b.

Pancreatitis occurring after the cut-off date is described in the subsequent submission made during the BLA review.
*Preliminary review (on February 19 2021) of 1a, 1b, and 1c (*25, 37.5 and 25/25/50 mg/m^2*):*
In addition to the data summarized above from the Initial IA DCO, Jazz has conducted a preliminary review (on February 19 2021) of the clinical database for reports of pancreatitis in JZP458-201. Amongst the 161 participants currently enrolled, including 44 participants from Cohort 1c, there are 7 reported events of pancreatitis across all cohorts. Five reports occurred in participants enrolled in Cohort 1b and 2 reports in participants enrolled in Cohort 1c. Six of the 7 reports were considered to be serious, and 1 was non-serious. Two participants who experienced serious pancreatitis in 1b subsequently died (1 participant developed sepsis and the other developed aspiration pneumonia associated with esophageotracheal fistula). The detail of these deaths are described in the **JZP-458 Pre-BLA Meeting Package**. Details regarding deaths reported in the Initial IA DCO can be found in the Deaths Section above.
The overall rate of pancreatitis is in range of expectations for asparaginases.

Thrombosis: No subjects experienced thrombosis as of the data cutoff date for initial IA.

The Applicant's Position:
In JZP458-201, overall, the incidence of AESIs has been within the expected range. Applicant believes that the AESI profile is aligned with the established asparaginase safety profile.

Final TFLs for the 25/25/50 mg/m^2 safety data set once available is intended to support the positive benefit: risk profile for the use of JZP-458 in all patients.

8.3.7 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability
Data:
There is no available data at this time.

The Applicant's Position:
There were no patient reported outcomes planned or assessed in the JZP458-201 study. The Applicant is not seeking to include PRO data in proposed labeling.

8.3.6 Safety Analyses by Demographic Subgroups
Data:
There is no available data at this time on the safety analyses of demographic subgroups

The Applicant's Position:
There were no safety analysis by demographic subgroups conducted within the clinical trials for JZP-458.

8.3.8 Specific Safety Studies/Clinical Trials
Data:
There is no available data at this time related to specific safety studies available

The Applicant's Position:
There were no specific studies conducted within the clinical trials for JZP-458

8.3.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development
Data:
A case of histiocytic sarcoma was reported in study JZP458-201. However, this was considered by the Investigator as being associated with the underlying ALL, skin papilloma and combination therapy and not assessed as being related to JZP-458.

The Applicant's Position:
Patients with underlying hematologic malignancies are at risk of developing secondary malignancies due to their exposure to multiple chemotherapeutic agents as well as their underlying immune impairment. No cases of secondary malignancies related to JZP-458 have been reported in the study at this time. Safety monitoring is ongoing for the IM portion of the study. Final TFLs for the safety data set once available is intended to support the positive benefit: risk profile for the use of JZP-458 in all patients.

Human Reproduction and Pregnancy
Data:
There is no available data at this time on Human Reproduction and Pregnancy for JZP-458. Pregnant women were excluded from the JZP458-101 and JZP458-201 studies.

The Applicant's Position:
There are no available human data at this time on JZP-458 use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. JZP-458 can cause fetal harm based upon findings from animal studies as described above in section 5.5.4.

Pregnancy testing in females of reproductive potential is recommended prior to starting treatment with JZP-458. Female subjects of child bearing potential treated with JZP458 should be advised of the potential risk to the fetus. Use of asparaginase as part of multi-agent chemotherapy treatment regimen in pregnancy should be based on benefit risk assessment for each individual patient.

Pediatrics and Assessment of Effects on Growth
Data:
There is no available study data at this time on Pediatrics and Assessment of Effects on Growth. Based on adverse event reporting (ref summary of all AE event) no reports on growth impairment have been reported in this ongoing JZP458-201 study.

The Applicant's Position:
There were no specific studies conducted within the clinical trials for JZP-458 and this is not a

known adverse effect of asparaginases.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

There is no available study data at this time on Overdose, Drug Abuse Potential, Withdrawal, and Rebound for JZP-458. There were no reports of overdose in JZP-458 studies. No reports of drug abuse with JZP-458 have occurred. No withdrawal or rebound effects have been observed in JZP-458 clinical studies to date.

The Applicant's Position:

Potential for drug abuse or dependence is not expected for an asparagine specific enzyme. No withdrawal or rebound effects are expected with an asparagine specific enzyme.

8.3.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

There is no available post-marketing data at this time for JZP-458

The Applicant's Position:

JZP-458 is not marketed in any country

Expectations on Safety in the Postmarket Setting

Data:

There is no available post-marketing data at this time for JZP-458

The Applicant's Position:

Toxicities have been monitored in Study JZP458-201 in alignment with the protocol and clinic procedures. Toxicities monitoring is ongoing for the IM portion of the study. Potential safety concerns beyond risks conveyed in proposed labeling are not expected. Routine pharmacovigilance activities will monitor unexpected AEs.

8.3.11 Integrated Assessment of Safety

Data:

The JZP-458 BLA is supported by two clinical studies, JZP458-101 in healthy subjects and JZP458-201 in patients. A statistical integrated assessment of safety across these two studies was not performed

The Applicant's Position:

A statistical integrated assessment of safety across the two clinical studies, JZP458-101 in healthy subjects and JZP458-201 in patients would not provide additional supportive information related to the safety of patients.

THE FDA'S POSITION

8.3.1. Safety Review Approach

The FDA reviewed the safety data for the subjects in trial JZP458-101 and for the 102 patients in trial JZP458-201, all of whom were treated with JZP-458. The following cohorts were utilized for the safety review:

- Cohort 1a: 33 patients treated with 25 mg/m^2 JZP-458 on Monday, Wednesday, Friday x 6 doses per course.
- Cohort 1b: 58 patients treated with 37.5 mg/m^2 JZP-458 on Monday, Wednesday, Friday x 6 doses per course.
- Cohort 1c: 16 patients treated with 25 mg/m^2 JZP-458 on Monday and Wednesday and 50 mg/m^2 JZP-458 on Friday x 6 doses per course.

All analyses were performed using the JZP458-201 datasets (SDN 35, 36, and 39).

8.3.2. Review of the Safety Database

Overall Exposure

There were 102 patients with ALL and LBL exposed to JZP-458 (FDA Table 35).

FDA Table 35 Exposure of JZP-458 in the Safety Database.

JZP-458 Exposure	Cohort 1A (25 mg/m^2 MWF)	Cohort 1B (37.5 mg/m^2 MWF)	Cohort 1C (25-25-50 mg/m^2 MWF)	Total
Number of Patients	N = 33	N = 53	N = 16	N = 102
Median (Range) Number of Courses	4 (1-14)	3 (1-12)	1 (1-2)	3 (1-14)
% of Patients Receiving > 4 Courses	48% (16)	23% (12)	0%	27% (28)

Source: Reviewer's analysis, ADSL and EX datasets.

Relevant characteristics of the safety population
See FDA Table in Section 8.1 for the relevant demographic and disease characteristics of the safety population.

Adequacy of the Safety Database
The safety database was assessed for adequacy with the following conclusions:

- There was a sufficient number of total patients treated with JZP-458 to assess for rare adverse reactions.
- There was an insufficient number of patients treated with the 25/25/50 mg/m^2 dosing regimen to assess for differences in the safety profile of that regimen.
- There were sufficient patients to evaluate differences by sex.
- There were no data on adult patients over the age of 65 years to assess safety signals in that population.

8.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The number of JZP-458 courses recording in adex.xpt are apparently complete only for patients who completed their prescribed course. This is not noted in the Reviewer's Guide or the Define File.

Categorization of Adverse Events

Adverse events were reported down to the verbatim term. The adverse events were coded using MedDRA 22.1 for study JZP458-201. Where indicated in the tables or text, some adverse events are presented as grouped terms (FDA Table 36). Treatment-emergent adverse events (TEAEs) included events that began after the start of JZP-458 administration.

FDA Table 36. Grouped Terms used in Safety Analyses

Grouped Term	Basis for Grouping
Abdominal pain	HLT Gastrointestinal and abdominal pains (excl oral and throat)
Acute kidney injury	PT Acute kidney injury, Blood creatinine increased, Blood urea increased
Bacterial infection	HLGT Bacterial infectious disorders
Diarrhoea	HLT Colitis (excl infective), Diarrhoea (excl infective)
Drug Hypersensitivity	Verbatim Term Custom Drug Hypersensitivity – Allergic drug reaction to RC-P; Allergic drug reaction RC-P; Allergic reaction to drug – hives; Allergic reaction to drug RC-P – urticaria and chills; Allergic reaction to Erwinia; Allergic reaction to RC-P; Allergic reaction – abdominal, back and leg pain, angioedema of eyelids and lips – drug reaction; Allergic reaction: hives, itching, abdominal pain – suspected drug reaction confirmed; Allergic study drug reaction urticarial rash hives and facial flushing; Dermatitis on both hands; Eczema; hives (allergic drug RC-P reaction); Infusion related-reaction;

	Itchiness (allergic drug reaction RC-P, Lip swelling; Maculo-papular rash; Maculopapular rash on face; Maculopapular rash on forehead; Maculopapular rash on hands; Palmar rash; Periorbital edema; Preorbital edema; Rash – maculopapular; Rash – right thigh/abdomen; Rash – trunk; Rash acneform; Rash acneiform; Rash B/L lower extremities; Rash maculopapular; Rash maculo-papular; Rash maculo-papular (chest); Rash maculopapular (diffuse); Rash maculo-papular (pruritus); Rash maculo-papular (scrotal); Rash on arms; Rash on face; Rash – maculopapular; Skin rash; Skin rash on right thigh; Urticaria
Fatigue	HLT Asthenic conditions
Fungal infection	HLGT Fungal infectious disorders
Haemorrhage	SMQ Haemorrhage terms (excl laboratory terms) (SMQ)
Hypersensitivity	Verbatim Term Custom Hypersensitivity – Allergic reaction due to blood transfusion, allergic reaction to amphotericin and cefepime, allergic reaction to ketamine, allergic reaction to pentamidine, allergic reaction to platelet transfusion (suspected due to lip swelling), allergic reaction to PRBC transfusion (suspected due to urticaria), allergic reaction to transfusion, allergic rhinitis, anaphylaxis related to transfusion, rash around Port-A-Cath, Rash maculopapular (diaper rash), Redman syndrome (related to Vancomycin)
Infection	HLGT Infections - pathogen unspecified
Injection site reaction	HLT Injection site reactions
Liver function test abnormal	HLT Liver function analyses
Musculoskeletal pain	HLT Muscle pains, HLT Musculoskeletal and connective tissue pain and discomfort; PT Arthralgia
Nausea	HLT Nausea and vomiting symptoms
Neuropathy peripheral	HLGT Peripheral neuropathies
Pancreatitis	PT Acute pancreatitis, Pancreatitis, Amylase increased
Tachycardia	PT Tachycardia, Sinus tachycardia
Thrombosis	SMQ Embolic and thrombotic events (SMQ)
Viral infection	HLGT Viral infectious disorders

Adverse events of special interest (AESIs) included the following: pancreatitis, drug hypersensitivity, thrombosis, and hepatotoxicity. The FDA's search criteria as provided in Section 8.3.5. At the Type A EOP1 meeting on 6/21/2019, the Applicant described benchmarks of 16% for hypersensitivity, 4% for pancreatitis and 3% for thrombosis, and they proposed to

target excluding 25% for hypersensitivity, 10% for pancreatitis and 10% for thrombosis in order to show no clinically meaningful increase in toxicity. FDA indicated those benchmarks were acceptable for the analysis of safety.

Routine Clinical Tests

Chemistry, hematology, and coagulation studies were performed for each patient at the start of each course of JZP-458. These included:

- Chemistry
  - Albumin
  - Alkaline Phosphatase
  - Alanine Aminotransferase
  - Amylase
  - Aspartate Aminotransferase
  - Bilirubin
  - Direct Bilirubin
  - Calcium
  - Cholesterol
  - Chloride
  - Creatinine
  - Glucose
  - Potassium
  - Lipase
  - Phosphate
  - Sodium
  - Triglycerides
- Hematology/Coagulation
  - Antithrombin III Activity
  - Antithrombin III Antigen
  - Activated Partial Thromboplastin Time
  - Basophils
  - Eosinophils
  - Fibrinogen
  - Hematocrit
  - Hemoglobin
  - Lymphocytes
  - Monocytes
  - Neutrophils
  - Platelets

- Prothrombin Time
- White Blood Cells (Leukocytes)

Of these, the following abnormal laboratory values were collected as AEs in the Investigations System Organ Category (SOC) and were converted into Grouped Terms as above:

- Activated partial thromboplastin time prolonged
- Alanine aminotransferase increased
- Amylase increased
- Antithrombin III increased
- Aspartate aminotransferase increased
- Bilirubin conjugated increased
- Blood alkaline phosphatase increased
- Blood alkaline phosphatase decreased
- Blood bilirubin increased
- Blood cholesterol increased
- Blood creatinine increased
- Eosinophil count increased
- Hematocrit decreased
- Hemoglobin decreased
- Lymphocyte count decreased
- Lymphocyte count increased
- Monocyte count decreased
- Monocyte count increased
- Neutrophil count decreased
- Platelet count decreased
- Protein total decreased
- Prothrombin time prolonged
- Transaminases increased
- White blood cell count decreased

8.3.4. Safety Results

Deaths

There were three deaths reported on study JZP458-201.

FDA Table 37. Study JZP458-201 - Deaths

Patient ID	Dosing cohort of JZP-458	Study Day of Death	Applicant Adjudication of Death	FDA Adjudication of Death
(b) (6)	1A (25 mg/m^2 MWF)	Study Day 157	Sepsis	AR – infection
	1B (37.5 mg/m^2 MWF)	Study Day 33	Pneumonia	AR – infection
*	1B (37.5 mg/m^2 MWF)	Study Day 18	Multiple organ dysfunction syndrome	AR – infection

*Patient death was reported after the cutoff data date. This patient is not included in other tables of demographic characteristics, disease characteristics, or adverse events.
Source: *Reviewer's analysis, narratives, Summary of Clinical Safety (SCS)*

Patient (b) (6): This was a 23-year-old patient with B-ALL, who experienced grade 3 allergic reaction with inactivation to pegasparaginase 37 days prior to initiation of study treatment. He was enrolled in cohort 1A. The patient received Course 3, Dose 6 of JZP-458 on Study Day 146; each study drug dose was reported to have been administered in 2 injections to the anterior thighs of both legs. On study day 148, the patient experienced grade 4 ARDS, followed by grade 4 acidosis, cardiac failure, hypotension, and respiratory failure on study day 149. On study day 150, right thigh wound culture and blood culture were positive for ESBL *E coli*. On study day 151, the right thigh wound was classified as grade 4 necrotizing fasciitis. Emergency debridement was performed. During the debridement, the patient experienced PEA arrest and received 5 minutes of ACLS prior to ROSC. On study day 152, the patient underwent additional debridement of the right lower extremity. The patient died on study day 157.

Clinical TL Review Comment: A concern was raised by the observation of tissue infection in the extremities were JZP-458 was injected. The exact location of the injections was not documented, and the site identified no protocol deviations with regard to handling the investigational product. The Applicant reported that Batch records indicated to manufacturing issues and no other patients who received product from the same batch had an E. coli infection (Response to Information Request received 5/21/2021). Thus, the conclusion was that the infection may have been related to the injection procedure rather than to the investigational product.

Patient (b) (6): This was an 11-year-old female patient with B-ALL, who experienced grade 3 allergic reaction to pegasparaginase 3 days prior to study day 1. The patient was enrolled in cohort 1B. The patient received Course 1, Dose 5 on study day 10. On study day 12, the patient experienced grade 3 pancreatitis. The patient also was diagnosed with febrile neutropenia. The patient discontinued study participation on day 13. On day 14, pancreatitis was resolving, and by day 23, pancreatitis was considered to be resolved. On study day 28, the patient was admitted to the ICU with tachypnea, increased work of breathing, and fever. A chest CT on study day 28 showed fistulae between the esophagus, distal trachea, and left main stem bronchus, thought to be due to radiation therapy for previous Ewing sarcoma treatment. Esophageal stent was placed on study day 31, and the patient remained unresponsive following

the procedure. On study day 34, the patient experienced a grade 5 SAE of aspiration pneumonia.

Clinical Reviewer's Comment: AESI of pancreatitis resolved prior to fatal event.

Patient (b) (6): This was an 18-year-old male patient with ALL who received four doses of Course 1 of JZP-458, on cohort 1B. On study day 8, the patient was hospitalized with grade 4 pancreatitis and grade 4 hyperglycemia. On study day 12, both events were reported as resolving. On study day 13, the patient developed *Klebsiella pneumoniae* bacteremia and sepsis, in addition to a pulmonary embolism in the right lower lobe. The participant died on study day 18.

Clinical Reviewer's Comment: AESI of pancreatitis and AE of hyperglycemia contributed to fatal adverse event.

Serious Adverse Events

In JZP458-201, all of the serious adverse events received a CTCAE grade of 3-5. The most common serious adverse event (SAE) was febrile neutropenia, which occurred relatively equally in cohort 1A (21%) and cohort 1B (23%) (FDA Table 38). Of note, infection was more common in cohort 1B (17%) than in cohort 1A (6%).

FDA Table 38. Grade 3-5 Serious Adverse Events (SAEs) by Preferred Term* with occurrence of >5% in JZP458-201.

Preferred Term*	Cohort 1A 25 mg/m^2 (N = 33)	Cohort 1B 37.5 mg/m^2 (N = 53)	Cohort 1C 25(MW)/50(F) mg/m^2 (N = 16)
	N (%)	N (%)	N (%)
Febrile neutropenia	7 (21)	12 (23)	0
Dehydration	3 (9)	3 (6)	1 (6)
Pyrexia	3 (9)	4 (8)	0
Stomatitis	3 (9)	1 (2)	1 (6)
Diarrhoea	2 (6)	1 (2)	0
Drug hypersensitivity	2 (6)	3 (6)	0
Infection	2 (6)	9 (17)	0
Nausea	2 (6)	4 (8)	0
Viral infection	2 (6)	1 (2)	0
Dysarthria	0	0	1 (6)
Gastritis	0	0	1 (6)
Muscular weakness	0	0	1 (6)

Neurotoxicity	0	0	1 (6)
Pancreatitis	0	3 (6)	1 (6)

Source: Reviewer's analysis, MAED (ADSL, ADAEGT)
**Includes grouped terms*

Dropouts and/or Discontinuations Due to Adverse Effects

Seven patients discontinued JZP-458 treatment due to adverse events, three patients in cohort 1A (9%), three patients in cohort 1B (6%), and one patient in cohort 1C (6%) (FDA Table 39). Six patients discontinued JZP-458 because of AESI, either drug hypersensitivity or pancreatitis.

FDA Table 39. Reason for JZP-458 treatment discontinuation in JZP458-201.

Patient	Cohort	Reason for discontinuation	AESI (yes/no)
(b) (6)	1A	Drug hypersensitivity	Yes
	1A	Drug hypersensitivity	Yes
	1B	Pancreatitis	Yes
	1C	Pancreatitis	Yes
	1B	Pancreatitis	Yes
	1A	Infection	No
	1B	Pancreatitis	Yes

Significant Adverse Events

See Section 8.3.5 for a discussion of adverse events of special interest.

Treatment Emergent Adverse Events and Adverse Reactions

Treatment emergent adverse events (TEAEs) in patients enrolled in JZP458-201 are listed by System Organ Class (SOC) in FDA Table 40. Most TEAEs by SOC are as expected for patients receiving multi-agent chemotherapy.

FDA Table 40. All Grade TEAEs by System Organ Class (SOC), with occurrence of at least 10%.

SOC	Cohort 1A 25 mg/m^2 (N = 33)	Cohort 1B 37.5 mg/m^2 (N = 53)	Cohort 1C 25(MW)/50(F) mg/m^2 (N = 16)
	N (%)	N (%)	N (%)
Gastrointestinal disorders	23 (70)	42 (79)	7 (44)
Investigations	23 (70)	39 (74)	4 (25)
General disorders and administration site conditions	21 (64)	34 (64)	3 (19)
Blood and lymphatic system disorders	19 (58)	35 (66)	4 (25)

FDA Table 40. All Grade TEAEs by System Organ Class (SOC), with occurrence of at least 10%.

SOC	Cohort 1A 25 mg/m^2 (N = 33)	Cohort 1B 37.5 mg/m^2 (N = 53)	Cohort 1C 25(MW)/50(F) mg/m^2 (N = 16)
	N (%)	N (%)	N (%)
Metabolism and nutrition disorders	18 (55)	25 (47)	7 (44)
Nervous system disorders	16 (48)	17 (32)	5 (31)
Infections and infestations	15 (45)	21 (40)	0
Musculoskeletal and connective tissue disorders	15 (45)	25 (47)	4 (25)
Skin and subcutaneous tissue disorders	13 (39)	24 (45)	3 (19)
Psychiatric disorders	12 (36)	21 (40)	3 (19)
Respiratory, thoracic and mediastinal disorders	12 (36)	22 (42)	3 (19)
Injury, poisoning and procedural complications	9 (27)	10 (19)	1 (6)
Cardiac disorders	8 (24)	14 (26)	1 (6)
Vascular disorders	7 (21)	4 (8)	3 (19)
Eye disorders	6 (18)	6 (11)	1 (6)
Renal and urinary disorders	3 (9)	9 (17)	0
Ear and labyrinth disorders	2 (6)	2 (4)	0
Immune system disorders	2 (6)	8 (15)	0
Reproductive system and breast disorders	2 (6)	5 (9)	0
Endocrine disorders	0	1 (2)	0
Hepatobiliary disorders	0	0	1 (6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	3 (6)	0

Source: Reviewer's analysis, MAED (ADSL, ADAEGT)

TEAEs were then analyzed using the grouped terms in FDA Table 36 above. Similarly, the most common all-grade adverse reactions (ARs) included nausea, hematologic toxicities, musculoskeletal pain, fatigue, infection, headache, and fever. Adverse events of special interest (AESI) included drug hypersensitivity, pancreatitis, and thrombosis, and will be discussed in section 8.3.5.

FDA Table 41. All Grade TEAEs by PT*, with occurrence of at least 10%.			
Preferred Term*	**Cohort 1A 25 mg/m^2 (N = 33)**	**Cohort 1B 37.5 mg/m^2 (N = 53)**	**Cohort 1C 25(MW)/50(F) mg/m^2 (N = 16)**
	N (%)	**N (%)**	**N (%)**
Nausea	15 (46)	25 (47)	2 (13)
Neutrophil count decreased	14 (42)	20 (38)	3 (19)
Anaemia	13 (39)	29 (55)	4 (25)
Musculoskeletal pain	13 (39)	21 (39)	2 (13)
Platelet count decreased	13 (39)	21 (39)	2 (13)
Fatigue	12 (36)	19 (36)	0
White blood cell count decreased	12 (36)	13 (25)	2 (13)
Infection	10 (30)	17 (32)	0
Headache	10 (30)	8 (15)	1 (6)
Pyrexia	9 (27)	22 (42)	0
Drug hypersensitivity	8 (24)	17 (32)	1 (6)
Liver function test abnormal	8 (24)	16 (30)	3 (19)
Febrile neutropenia	8 (24)	13 (25)	0
Lymphocyte count decreased	8 (24)	11 (21)	3 (19)
Decreased appetite	7 (21)	18 (34)	2 (13)
Stomatitis	7 (21)	12 (23)	2 (13)
Haemorrhage	7 (21)	9 (17)	0
Hyperglycaemia	7 (21)	3 (6)	1 (6)
Abdominal pain	6 (18)	15 (28)	2 (13)
Tachycardia	6 (18)	13 (25)	1 (6)
Diarrhoea	6 (18)	9 (17)	1 (6)
Constipation	5 (18)	9 (17)	0
Dehydration	5 (18)	8 (15)	1 (6)
Neuropathy peripheral	5 (18)	6 (11)	2 (13)
Cough	5 (18)	6 (11)	1 (6)
Insomnia	5 (18)	6 (11)	1 (6)
Rhinorrhoea	4 (12)	6 (11)	1 (6)
Hypoalbuminaemia	4 (12)	6 (11)	0
Pain	4 (12)	5 (9)	0
Viral infection	4 (12)	4 (8)	0
Flushing	4 (12)	2 (4)	1 (6)
Alopecia	4 (12)	2 (4)	0
Gastrooesophageal reflux disease	4 (12)	0	1 (6)
Hypokalaemia	3 (9)	8 (15)	2 (13)
Hypocalcaemia	3 (9)	6 (11)	2 (13)
Injection site reaction	3 (9)	3 (6)	3 (19)
Anxiety	2 (6)	8 (15)	2 (13)
Oropharyngeal pain	2 (6)	7 (13)	1 (6)
Pruritus	2 (6)	6 (11)	0
Hypersensitivity	1 (3)	10 (19)	0

FDA Table 41. All Grade TEAEs by PT*, with occurrence of at least 10%.			
Preferred Term*	**Cohort 1A 25 mg/m^2 (N = 33)**	**Cohort 1B 37.5 mg/m^2 (N = 53)**	**Cohort 1C 25(MW)/50(F) mg/m^2 (N = 16)**
	N (%)	**N (%)**	**N (%)**
Weight decreased	1 (3)	8 (15)	1 (6)
Hypertension	1 (3)	3 (6)	2 (13)
Pancreatitis	0	4 (8)	2 (13)
Gastritis	0	2 (4)	2 (13)
Source: Reviewer's analysis, MAED (ADSL, ADAEGT) **Includes grouped terms*			

Grade 3-5 TEAEs that were most common in the 25 mg/m^2 cohort (1A) included hematologic toxicities, febrile neutropenia, infection, abnormal liver function tests, mucositis, and other GI toxicities.

FDA Table 42. Grade 3-5 TEAEs by PT*, with occurrence of at least 5%.			
Preferred Term*	**Cohort 1A 25 mg/m^2 (N = 33)**	**Cohort 1B 37.5 mg/m^2 (N = 53)**	**Cohort 1C 25(MW)/50(F) mg/m^2 (N = 16)**
	N (%)	**N (%)**	**N (%)**
Neutrophil count decreased	13 (39)	20 (38)	3 (19)
Anaemia	12 (36)	20 (38)	2 (13)
Platelet count decreased	10 (30)	17 (32)	0
White blood cell count decreased	9 (27)	12 (23)	1 (6)
Febrile neutropenia	8 (24)	13 (25)	0
Lymphocyte count decreased	7 (21)	10 (19)	2 (13)
Infection	5 (15)	9 (17)	0
Liver function test abnormal	4 (12)	8 (15)	0
Stomatitis	3 (9)	4 (8)	0
Dehydration	3 (9)	3 (6)	0
Nausea	3 (9)	3 (6)	0
Pyrexia	2 (6)	4 (8)	0
Decreased appetite	2 (6)	2 (4)	0
Musculoskeletal pain	2 (6)	2 (4)	0
Viral infection	2 (6)	1 (2)	0
Diarrhoea	2 (6)	0	0
Drug hypersensitivity	2 (6)	0	0
Bacterial infection	1 (3)	3	0
Hypokalaemia	1 (3)	1 (2)	1 (6)
Pancreatitis	0	3 (6)	1 (6)
Anxiety	0	0	1 (6)
Gastritis	0	0	1 (6)
Neurotoxicity	0	0	1 (6)
Source: Reviewer's analysis, MAED (ADSL, ADAEGT) **Includes grouped terms*			

FDA Table 43 shows the analysis for TEAEs assessed by the investigator as related to JZP458-201.

FDA Table 43. Related TEAEs by Preferred Term* in >5% of Patients on Study JZP458-201.

PT*	Cohort 1A 25 mg/m^2 (N = 33)	Cohort 1B 37.5 mg/m^2 (N = 53)	Cohort 1C 25(MW)/50(F) mg/m^2 (N = 16)
	N (%)	N (%)	N (%)
Nausea	9 (27)	16 (30)	1 (6)
Neutrophil count decreased	6 (18)	11 (21)	3 (19)
Fatigue	4 (12)	9 (17)	0
Hyperglycaemia	3 (9)	1 (2)	1 (6)
Hypoalbuminaemia	3 (9)	4 (8)	0
Injection site reaction	3 (9)	2 (4)	3 (19)
Liver function test abnormal	3 (9)	10 (19)	2 (13)
Decreased appetite	2 (6)	7 (13)	1 (6)
Drug hypersensitivity	2 (6)	4 (8)	0
Flushing	2 (6)	0	1 (6)
Hypertriglyceridaemia	2 (6)	1 (2)	0
Lymphocyte count decreased	2 (6)	7 (13)	2
Muscle spasms	2 (6)	0	0
Pain	2 (6)	2 (4)	0
Abdominal pain	1 (3)	5 (10)	1 (6)
Anaemia	1 (3)	13 (25)	2 (13)
Febrile neutropenia	1 (3)	5 (10)	0
Headache	1 (3)	3 (6)	0
Musculoskeletal pain	1 (3)	6 (11)	0
Platelet count decreased	1 (3)	10 (19)	1 (6)
Pyrexia	1 (3)	8 (15)	0
White blood cell count decreased	1 (3)	8 (15)	2 (13)
Activated partial thromboplastin time prolonged	0	3 (6)	0
Acute kidney injury	0	3 (6)	0
Anxiety	0	2 (4)	1 (6)
Diarrhoea	0	4 (8)	0
Gastrooesophageal reflux disease	0	0	1 (6)
Hypertension	0	0	1 (6)
Hypokalaemia	0	3	0

FDA Table 43. Related TEAEs by Preferred Term* in >5% of Patients on Study JZP458-201.			
PT*	**Cohort 1A 25 mg/m^2 (N = 33)**	**Cohort 1B 37.5 mg/m^2 (N = 53)**	**Cohort 1C 25(MW)/50(F) mg/m^2 (N = 16)**
	N (%)	**N (%)**	**N (%)**
Hypophosphataemia	0	0	1 (6)
Insomnia	0	0	1 (6)
Muscle tightness	0	0	1 (6)
Pancreatitis	0	4 (8)	2 (13)
Procedural anxiety	0	0	1 (6)
Weight decreased	0	4 (8)	1 (6)
Source: Reviewer's analysis, MAED (ADSL, ADAEGT) **Includes grouped terms*			

Clinical Reviewer's Comment: Because JZP-458 is administered as part of multi-agent chemotherapy, assessment of "related" versus "unrelated" is challenging. It is expected that most patients will have hematologic toxicities, GI toxicities, and increased risk of infection (including febrile neutropenia). See Section 8.3.5 for analysis of asparaginase-related AESIs and other known toxicities of asparaginase class products.

Laboratory Findings

As JZP-458 is used as part of a multi-agent chemotherapy regimen for patients with ALL or LBL, cytopenias occur in nearly 100% of patients. Other laboratory abnormalities are listed below. There are very few grade 3-4 laboratory abnormalities in the 25 mg/m^2 JZP-458 dosing regimen.

FDA Table 44. Selected Laboratory Abnormalities (Nonhematologic) by Maximum Grade in JZP458-201.

Laboratory Analyte	**Cohort 1A 25 mg/m^2 N = 33**		**Cohort 1B 37.5 mg/m^2 N = 53**		**Cohort 1C 25(MW)/50(F) mg/m^2 N = 16**	
	Grades 1-4 n/N (%)	**Grades 3-4 n/N (%)**	**Grades 1-4 n/N (%)**	**Grades 3-4 n/N (%)**	**Grades 1-4 n/N (%)**	**Grades 3-4 n/N (%)**
Alanine Aminotransferase (U/L) Increased	24/33 (73)	2/33 (6)	30/53 (57)	6/53 (11)	9/16 (56)	1/16 (6)
Aspartate Aminotransferase (U/L) Increased	18/33 (55)	1/33 (3.0)	24/53 (45)	2/53 (3.8)	5/16 (31)	1/16 (6)
Glucose (mmol/L) Increased	13/33 (39)	0	12/53 (23)	0/53 (0.0)	3/16 (19)	0
Glucose (mmol/L) Decreased	4/33 (12)	0	3/53 (6)	1/53 (1.9)	0	0

FDA Table 44. Selected Laboratory Abnormalities (Nonhematologic) by Maximum Grade in JZP458-201.

Laboratory Analyte	Cohort 1A 25 mg/m² N = 33		Cohort 1B 37.5 mg/m² N = 53		Cohort 1C 25(MW)/50(F) mg/m² N = 16	
	Grades 1-4 n/N (%)	Grades 3-4 n/N (%)	Grades 1-4 n/N (%)	Grades 3-4 n/N (%)	Grades 1-4 n/N (%)	Grades 3-4 n/N (%)
Triglyceride (mmol/L) Increased	11/33 (33)	0	8/53 (15)	0	0	0
Albumin (g/L) Decreased	9/33 (27)	0	14/53 (26)	2/53 (3.8)	3/16 (19)	0
Cholesterol (mmol/L) Increased	9/33 (27)	0	11/53 (21)	0	0	0
Bilirubin, total (umol/L) Increased	8/33 (24)	0	16/53 (30)	1/53 (1.9)	3/16 (19)	0
Sodium (mmol/L) Decreased	7/33 (21)	0	10/53 (19)	0	1/16 (6)	0
Creatinine (umol/L) Increased	5/33 (15)	0	6/53 (11)		1/16 (6)	0
Bilirubin, direct (umol/L) Increased	5/33 (15)	0	8/53 (15)	0	2/16 (13)	0)
Potassium (mmol/L) Decreased	4/33 (12)	0	10/53 (19)	0	2/16 (13)	1/16 (6)
Fibrinogen (umol/L) Decreased	2/32 (6)	0	4/52 (8)	1/52 (1.9)	2/15 (13)	0
Activated Partial Thromboplastin Time (sec) Increased	1/33 (3.0)	0	11/51 (22)	1/51 (2.0)	0	0

N = evaluable patients; n = number of patients with laboratory abnormality
Source: ADSL (Subject-Level Analysis Dataset) - 2021-05-26, ADLB (Laboratory Test Results Analysis Dataset) - 2021-06-11. Variables used: USUBJID, TRT01A, SAFFL, PARAM, ABLFL, AVAL, LBSTNRLO, LBSTNRHI, SAFFL, TRTEDT, ADT, TRTSDT, ADY, ATOXGR

Vital Signs

Vital signs were submitted for the following timepoints: screening and prior to each dose of JZP-458. There were no vital signs submitted from timepoints during JZP-458 injection to assess for evidence of drug hypersensitivity.

QT/Electrocardiograms (ECGs)

Not applicable, as JZP-458 is a biologic.

Immunogenicity

OBP determined that the assays to evaluate immunogenicity were not valid (see Section 4.2).

8.3.5. Analysis of Submission-Specific Safety Issues

AESI: Drug Hypersensitivity

The incidence of drug hypersensitivity was based on the grouped term "Drug Hypersensitivity" in FDA Table 36 above. Results are shown in FDA Table 45. In the overall population, the incidence of drug hypersensitivity reactions was 25%, and the events were severe in 2%. Some patients had multiple reactions. The types of hypersensitivity reactions included rash (16%), urticaria alone (5%), allergic reaction (4%), periorbital oedema (3%), and infusion-related reaction (2%). The median time from the first dose of JZP-458 to the onset of the first hypersensitivity event was 27 days (range 1-171 days), and the median time from the first dose to the first onset of rash was 33.5 days (ange 1-127 days).

FDA Table 45. Drug Hypersensitivity in Study JZP458-201.

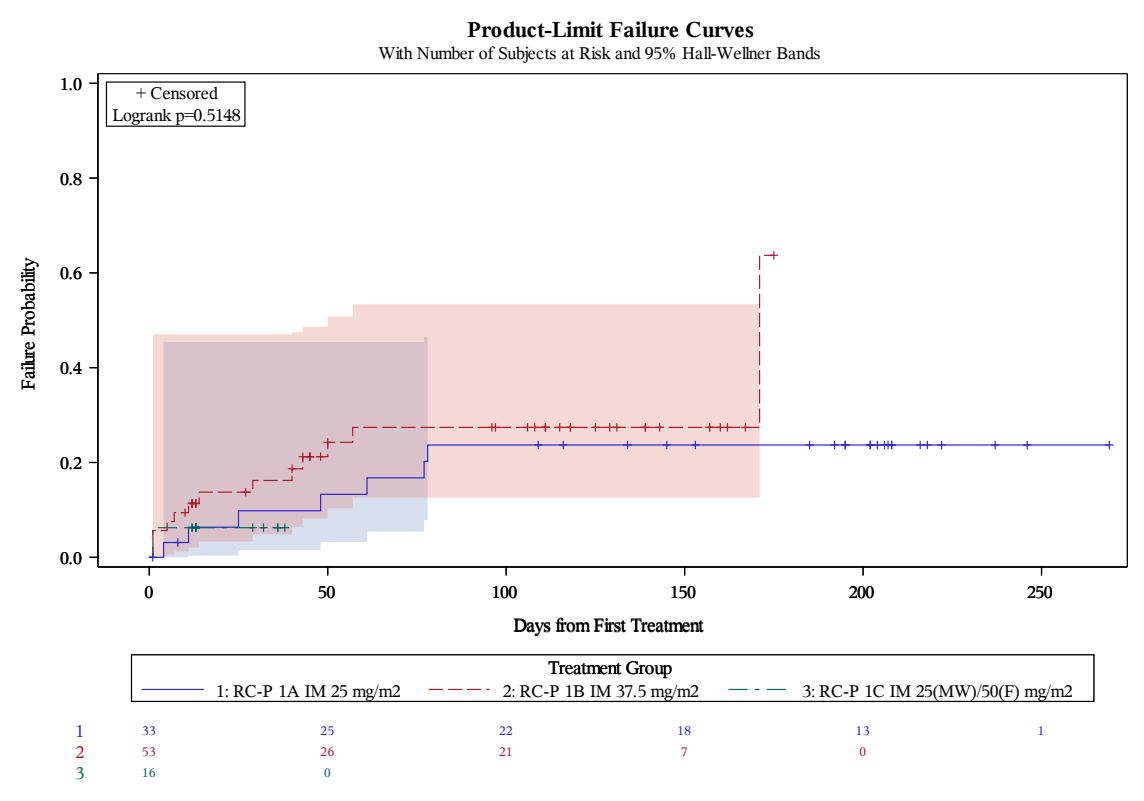
	Cohort 1A 25 mg/m^2 N = 33		Cohort 1B 37.5 mg/m^2 N = 53		Cohort 1C 25(MW)/50(F) mg/m^2 N = 16	
	All grade N (%)	Grade 3-5 N (%)	All grade N (%)	Grade 3-5 N (%)	All grade N (%)	Grade 3-5 N (%)
Drug Hypersensitivity	8 (24)	2 (6)	17 (32)	0	1 (6)	0

Source: Reviewer's analysis (ADSL, ADAEGT)

In addition, time to event (TTE) analysis was performed for all-grade drug hypersensitivity, based on the grouped term "Drug Hypersensitivity." This is shown in FDA Figure 9.

FDA Figure 9. Drug Hypersensitivity: Time to Event Analysis in Study JZP458-201

"Failure probability" on the y-axis indicates that likelihood of patients in a cohort developing drug hypersensitivity. The x-axis is days from first treatment throughout treatment and into follow-up.



Clinical Reviewer's Comment: In JZP458-201, there was increased hypersensitivity in Cohort 1B (37.5 mg/m² MWF dosing) compared to Cohort 1A. We note limited number of patients in Cohort 1C and limited data on the Cohort 1C patients, which make it difficult to assess the risk of hypersensitivity in this treatment regimen (25/25/50 mg/m² MWF).

Clinical TL Review Comment: The 24% incidence of hypersensitivity has a wide CI that does not exclude the unacceptable rate of 25%. It should be noted, however, that the search criteria for this analysis differed from used for the reported benchmark, so it is not clear that the incidence is unacceptably high. A larger sample size would be needed to accomplish that. Additionally, although the protocol did not mandate use of prophylaxis, some patients did receive antihistamines and/or steroids, but the variable CMINDC was not sufficiently standardized to allow for an assessment of the impact of prophylaxis on the incidence of hypersensitivity.

AESI: Pancreatitis

The incidence of pancreatitis was based on pancreatitis-associated laboratory values (amylase and lipase), and the grouped term pancreatitis, which includes the PT "acute pancreatitis," "pancreatitis," and "amylase increased." Patients with grade 1 increases in amylase or lipase at baseline at excluded. FDA Table 46 shows this analysis.

FDA Table 46. Pancreatitis in Study JZP458-201.

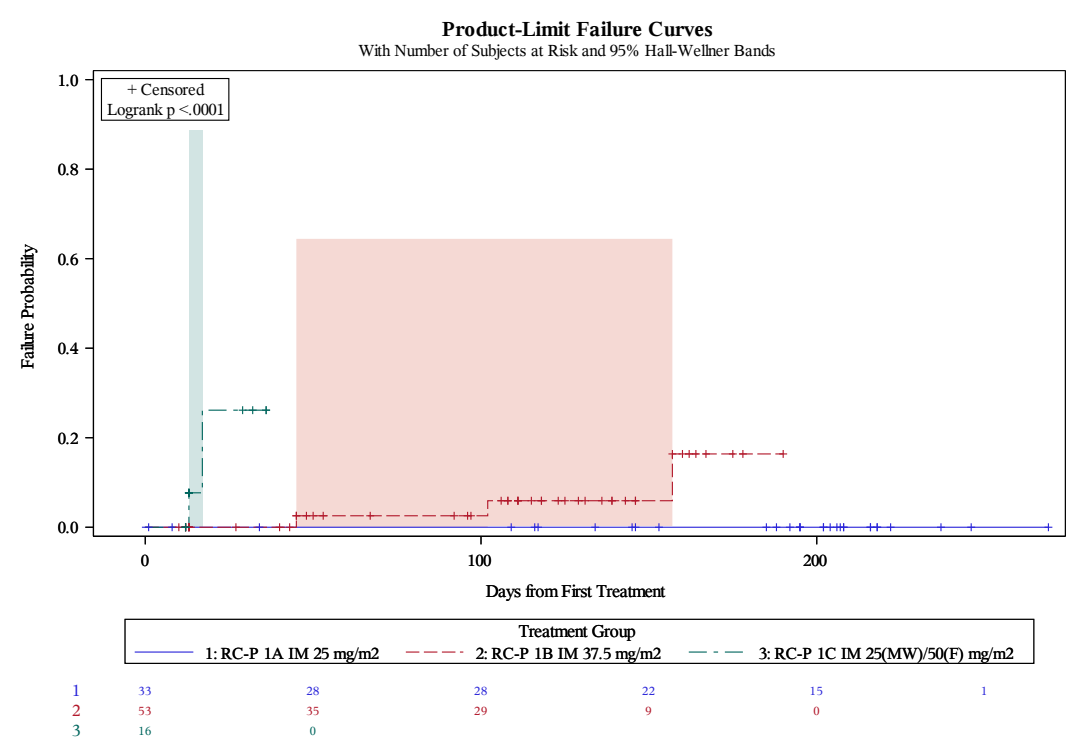
	Cohort 1A 25 mg/m^2 N = 33		**Cohort 1B 37.5 mg/m^2 N = 53**		**Cohort 1C 25(MW)/50(F) mg/m^2 N = 16**	
	All grade N (%)	**Grade 3+ N (%)**	**All grade N (%)**	**Grade 3+ N (%)**	**All grade N (%)**	**Grade 3+ N (%)**
Pancreatitis (grouped term)	0	0	4 (8)	3 (6)	2 (13)	1 (6)
Laboratory abnormality						
Amylase	1 (3)	0	3 (6)	2 (4)	0	0
Lipase	2 (6)	0	3 (6)	1 (2)	0	0
Total	**3 (9)**	**0**	**9 (17)***	**5 (9)***	**2 (13)**	**1 (6)**

*Patient had both elevated amylase and elevated lipase.
Source: Reviewer's analysis (ADSL, ADAEGT, ADLB)

In addition, time to event (TTE) analysis was performed for all-grade pancreatitis, based on the grouped term "Pancreatitis." This is shown in FDA Figure 10.

FDA Figure 10. Pancreatitis: Time to Event Analysis in Study JZP458-201.

"Failure probability" on the y-axis indicates that likelihood of patients in a cohort developing pancreatitis. The x-axis is days from first treatment throughout treatment and into follow-up.



Clinical Reviewer's Comment: We note low incidence of pancreatitis in Cohort 1A (25 mg/m^2), with increased rates in Cohort 1B (37.5 mg/m^2). There are insufficient patient numbers and number of courses in Cohort 1C (25/25/50 mg/m^2 MWF) to ascertain if the early rates of pancreatitis observed in FDA Figure 10 will be significant.

Clinical TL Review Comment: The 95% CI for pancreatitis (2% - 24%) does not exclude the prespecified clinically meaningful incidence for Cohort 1A. Again, however, the case ascertainment differed from that for the benchmark.

AESI: Thrombosis

The incidence of thrombosis was based on the grouped term "Thrombosis" in FDA Table 36 above. Results are shown in FDA Table 47.

FDA Table 47. Thrombosis in Study JZP458-201.

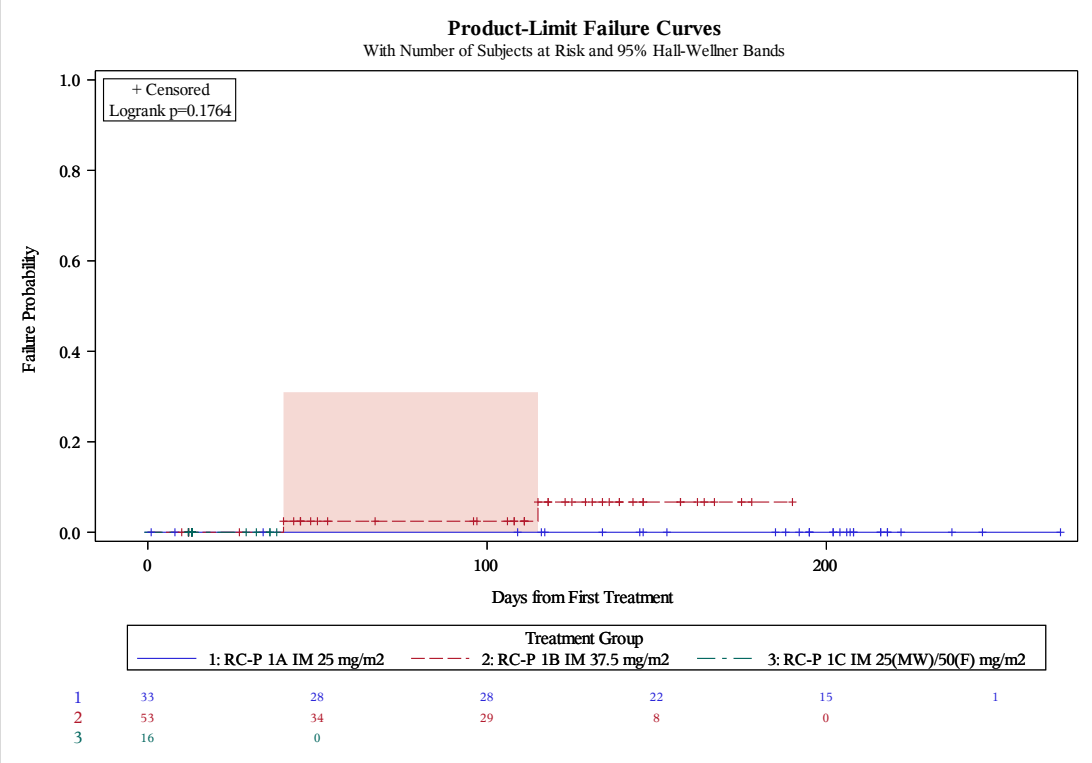
	Cohort 1A 25 mg/m² N = 33		Cohort 1B 37.5 mg/m² N = 53		Cohort 1C 25(MW)/50(F) mg/m² N = 16	
	All grade N (%)	Grade 3-5 N (%)	All grade N (%)	Grade 3-5 N (%)	All grade N (%)	Grade 3-5 N (%)
Thrombosis	0	0	2 (4)	1(2)	0	0

Source: Reviewer's analysis (ADSL, ADAEGT)

In addition, time to event (TTE) analysis was performed for all-grade drug hypersensitivity, based on the grouped term "Thrombosis." This is shown in FDA Figure 11.

FDA Figure 11. Thrombosis: Time to Event Analysis in Study JZP458-201.

"Failure probability" on the y-axis indicates that likelihood of patients in a cohort developing all-grade thrombosis. The x-axis is days from first treatment throughout treatment and into follow-up.



Clinical Reviewer's Comment: There is no signal of excess adverse events related to thrombosis in JZP458-201.

Clinical TL Review Comment: The 95% CI for thrombosis (0% - 11%) does not exclude the prespecified clinically meaningful incidence for Cohort 1A. This may be due to the small number of patients. When assessed in all 86 patients in Cohorts 1A and !B, the 95% CI (0.3% - 8.2% does, in fact, exclude the prespecified 10% incidence.

Hepatotoxicity

While hepatotoxicity is not an asparaginase class product AESI, it is a common toxicity of asparaginase class products, as well as other components of multi-agent chemotherapy regimens used for ALL/LBL. The incidence of hepatotoxicity was based on laboratory values associated with liver toxicity and the grouped term "Liver function test abnormal," which includes the HLT "Liver function analyses." Patients with grade 1 increases in amylase or lipase at baseline at excluded. FDA Table 48 shows this analysis.

FDA Table 48. Hepatotoxicity in Study JZP458-201.

	Cohort 1A 25 mg/m^2 N = 33		**Cohort 1B 37.5 mg/m^2 N = 53**		**Cohort 1C 25(MW)/50(F) mg/m^2 N = 16**	
	All grade N (%)	**Grade 3+ N (%)**	**All grade N (%)**	**Grade 3+ N (%)**	**All grade N (%)**	**Grade 3+ N (%)**
Liver function test abnormal (grouped term)	8 (24)	4 (12)	16 (31)	8 (15)	3 (19)	0
Laboratory abnormality						
Alanine Aminotransferase	24 (73)	2 (6)	30 (57)	6 (11)	9 (56)	1 (6)
Aspartate Aminotransferase	18 (55)	1 (3)	24 (45)	2 (4)	5 (31)	1 (6)
Bilirubin, total	8 (24)	0	16 (30)	1 (2)	3 (19)	0
Bilirubin, direct	5 (15)	0	8 (15)	0	2 (13)	0)
Source: Reviewer's analysis (ADSL, ADAEGT, ADLB)						

Clinical Reviewer's Comment: There is no signal of increased grade 3-4 hepatotoxicity by dose in patients treated with JZP-458.

8.3.6. Safety Analyses by Subgroups

Drug-Demographic Interactions

TEAEs by Sex

For the proposed dosing regimen of 25 mg/m^2 (Cohort 1A), TEAEs with a risk difference (RD) of >10% between female and male patients are shown in FDA Table 49. Female patients were more likely to have anemia, headache, and hemorrhage compared to male patients in JZP458-201. Male patients were more likely to have peripheral neuropathy, muscular weakness, drug hypersensitivity, and hepatotoxicity. However, female patients were more likely to have grade 3-5 drug hypersensitivity (FDA Table 50).

FDA Table 49. TEAEs by Preferred Term* with a Risk Difference of >10%: Patients by Sex in JZP458-201 (Cohort 1A, 25 mg/m2 MWF)

Preferred Term*	Female (N = 16)	Male (N = 17)	RD
	N (%)	N (%)	(per hundred)
Anaemia	9 (56)	4 (24)	32.721
Headache	7 (44)	3 (18)	26.103
Haemorrhage	5 (31)	2 (12)	19.485
Fatigue	7 (44)	5 (29)	14.338
Viral infection	3 (19)	1 (6)	12.868
Anxiety	2 (13)	0	12.5
Haematocrit decreased	2 (13)	0	12.5
Haemoglobin decreased	2 (13)	0	12.5
Hypertriglyceridaemia	2 (13)	0	12.5
Sinus bradycardia	2 (13)	0	12.5
Drug hypersensitivity	3 (19)	5 (29)	-10.662
Liver function test abnormal	3 (19)	5 (29)	-10.662
Lymphocyte count decreased	3 (19)	5 (29)	-10.662
Alopecia	1 (6)	3 (18)	-11.397
Flushing	1 (6)	3 (18)	-11.397
Gastrooesophageal reflux disease	1 (6)	3 (18)	-11.397
Acute kidney injury	0	2 (12)	-11.765
Bone pain	0	2 (12)	-11.765
Hyperphosphataemia	0	2 (12)	-11.765
Hypotension	0	2 (12)	-11.765
Pain in jaw	0	2 (12)	-11.765
Pruritus	0	2 (12)	-11.765

FDA Table 49. TEAEs by Preferred Term* with a Risk Difference of >10%: Patients by Sex in JZP458-201 (Cohort 1A, 25 mg/m2 MWF)

Preferred Term*	Female (N = 16)	Male (N = 17)	RD
	N (%)	N (%)	(per hundred)
Weight increased	0	2 (12)	-11.765
Hyperglycaemia	2 (13)	5 (29)	-16.912
Constipation	1 (6)	4 (24)	-17.279
Blood fibrinogen decreased	0	3 (18)	-17.647
Hypokalaemia	0	3 (18)	-17.647
Muscular weakness	0	3 (18)	-17.647
Neuropathy peripheral	0	5 (29)	-29.412

Source: Reviewer's analysis, MAED (ADSL, ADAEGT)
**Includes grouped terms*

FDA Table 50. Grade 3-5 TEAEs by Preferred Term* with a Risk Difference of >10%: Patients by Sex in JZP458-201 (Cohort 1A, 25 mg/m2 MWF)

Preferred Term*	Female (N = 16)	Male (N = 17)	RD
	N (%)	N (%)	(per hundred)
Anaemia	9 (56)	3 (18)	38.603
Dehydration	3 (19)	0	18.75
Platelet count decreased	6 (38)	4 (24)	13.971
Liver function test abnormal	3 (19)	1 (6)	12.868
Diarrhoea	2 (13)	0	12.5
Drug hypersensitivity	2 (13)	0	12.5
Pyrexia	2 (13)	0	12.5
Viral infection	2 (13)	0	12.5
Musculoskeletal pain	0	2 (12)	-11.765
White blood cell count decreased	3 (19)	6 (35)	-16.544
Lymphocyte count decreased	2 (13)	5 (29)	-16.912

Source: Reviewer's analysis, MAED (ADSL, ADAEGT)
**Includes grouped terms*

TEAEs by Age

The majority of patients enrolled on JZP458-201 were under the age of 18, and that is true of the patients enrolled in Cohort 1A (25 mg/m^2). Patients from 1 month to < 17 years of age were compared to adult patients. Pediatric patients were more likely to have hematologic toxicities and febrile neutropenia.

FDA Table 51. TEAEs by Preferred Term* with a Risk Difference of >15%: Patients by Age in JZP458-201 (Cohort 1A, 25 mg/m2 MWF)

Preferred Term*	Pediatric (1 month to < 17 years) N = 24		Adult (≥ 17 years) N = 9		RD (per hundred), all grade toxicity
	All Grade	Grade 3-5	All Grade	Grade 3-5	
	N (%)	N (%)	N (%)	N (%)	
White blood cell count decreased	11 (46)	9 (38)	1 (11)	0	34.722
Anaemia	11 (46)	10 (42)	2 (22)	2 (22)	23.611
Cough	5 (21)	0	0	0	20.833
Febrile neutropenia	7 (29)	7 (29)	1 (11)	1 (11)	18.056
Pain	4 (17)	0	0	0	16.667
Viral infection	4 (17)	3 (8)	0	0	16.667
Blood fibrinogen decreased	1 (4)	0	2 (22)	0	-18.056
Hypokalaemia	1 (4)	0	2 (22)	1 (11)	-18.056
Injection site reaction	1 (4)	0	2 (22)	0	-18.056
Paraesthesia	1 (4)	0	2 (22)	0	-18.056
Headache	6 (25)	0	4 (44)	0	-19.444
Infection	6 (25)	3 (13)	4 (44)	2 (22)	-19.444
Tachycardia	3 (13)	0	3 (33)	0	-20.833
Musculoskeletal pain	8 (33)	1 (4)	5 (56)	1 (11)	-22.222
Hypotension	0	0	2 (22)	1 (11)	-22.222
Oropharyngeal pain	0	0	2 (22)	0	-22.222
Pain in jaw	0	0	2 (22)	0	-22.222
Gastrooesophageal reflux disease	1 (4)	0	3 (33)	0	-29.167

Source: Reviewer's analysis, MAED (ADSL, ADAEGT)
**Includes grouped terms*

Clinical Reviewer's Comment: There are small number of adult patients enrolled in this trial.

TEAEs by Race and Ethnicity

Of the 33 patients enrolled in JZP458-201 Cohort 1A (25 mg/m^2 MWF), twenty-four of the patients self-identified as "white," three as "Black or African American," 1 as "Asian," and 1 as "American Indian or Alaska Native." This was an insufficient number of patients to assess for meaningful differences in AEs.

Of the 33 patients enrolled in Cohort 1A, thirteen patients self-identified as Hispanic or Latino, and eighteen as not Hispanic or Latino. Patients who identified as Hispanic or Latino were more

likely to have gastrointestinal reflux, viral infection, hypotension, and hyperglycemia (FDA Table 52).

FDA Table 52. TEAEs by Preferred Term* with a Risk Difference of >10%: Patients by Ethnicity in JZP458-201 (Cohort 1A, 25 mg/m2 MWF)

Preferred Term*	Hispanic or Latino (N = 13)	Not Hispanic or Latino (N = 18)	RD (per hundred)
	N (%)	N (%)	
Gastrooesophageal reflux disease	3 (23)	1 (6)	17.521
Viral infection	3 (23)	1 (6)	17.521
Anxiety	2 (15)	0	15.385
Hypotension	2 (15)	0	15.385
Hyperglycaemia	4 (31)	3 (17)	14.103
Infection	3 (23)	6 (33)	-10.256
Blood cholesterol increased	0	2 (11)	-11.111
Haematocrit decreased	0	2 (11)	-11.111
Hyperphosphataemia	0	2 (11)	-11.111
Mood swings	0	2 (11)	-11.111
Muscular weakness	0	2 (11)	-11.111
Sinus bradycardia	0	2 (11)	-11.111
Vision blurred	0	2 (11)	-11.111
Weight increased	0	2 (11)	-11.111
Nausea	5 (38)	9 (50)	-11.538
Neutrophil count decreased	5 (38)	9 (50)	-11.538
Decreased appetite	2 (15)	5 (28)	-12.393
Drug hypersensitivity	2 (15)	5 (28)	-12.393
Stomatitis	2 (15)	5 (28)	-12.393
Abdominal pain	1 (8)	4 (22)	-14.53
Constipation	1 (8)	4 (22)	-14.53
Dehydration	1 (8)	4 (22)	-14.53
Alopecia	0	3 (17)	-16.667
Irritability	0	3 (17)	-16.667
Oral pain	0	3 (17)	-16.667
Lymphocyte count decreased	2 (15)	3 (17)	-17.949
Platelet count decreased	4 (31)	9 (50)	-19.231
Tachycardia	1 (8)	5 (28)	-20.085
Fatigue	3 (23)	8 (44)	-21.368
Insomnia	0	4 (22)	-22.222
Pain	0	4 (22)	-22.222

FDA Table 52. TEAEs by Preferred Term* with a Risk Difference of >10%: Patients by Ethnicity in JZP458-201 (Cohort 1A, 25 mg/m2 MWF)			
Preferred Term*	**Hispanic or Latino (N = 13)**	**Not Hispanic or Latino (N = 18)**	**RD (per hundred)**
	N (%)	**N (%)**	
Musculoskeletal pain	3 (23)	9 (50)	-26.923
Source: Reviewer's analysis, MAED (ADSL, ADAEGT) **Includes grouped terms*			

Drug-Disease Interactions

The majority of patients enrolled on JZP458-201 had a diagnosis of pre-B cell ALL (B-ALL), with the remaining patients having a diagnosis of T-ALL or T-LBL. There are an insufficient number of patients to assess differences in safety by disease.

Drug-Drug Interactions

There were no additional drug-drug interaction analyses performed. In a subsequent submission, with additional follow-up data, we plan to perform a multivariate analysis of JZP-458 dose versus backbone chemotherapy regimen to assess for differences among chemotherapy regimens.

Dose Dependency for Adverse Events

Dose dependency for AESIs is discussed in Section 8.3.5.

Time Dependency for Adverse Events

Time dependency for AESIs is discussed in Section 8.3.5. There is insufficient duration of treatment especially in Cohort 1c for a meaningful analysis for late effects.

8.3.7. Clinical Outcomes Assessments Informing Tolerability/Safety

Not applicable.

8.3.8. Specific Safety Studies/Clinical Trials (including dose-related safety)

Study JZP458-201

See Section 8.3.5 for a discussion of AEs and AESIs by dose.

Study JZP458-101

The FDA agrees with the overview of data from Study JZP458-101 as described by the Applicant. Table 53 shows FDA's summary tabulation of the all-grade adverse reactions in this study.

FDA Table 53. Study JZP458-101 - Summary of Adverse Events

	JZP-458 IM 12.5 mg/m2 (N = 6)		JZP-458 IM 25 mg/m2 (N = 6)		Erwinaze, IM 25,000 IU/m2 (N = 3)	
Adverse Event	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Nausea	2	33	4	67	2	67
Vomiting	1	17	2	33	0	0
Leukopenia	0	0	1	17	0	0
Gastrooesophageal reflux disease	0	0	1	17	0	0
Headache	0	0	1	17	0	0
Malaise	0	0	1	17	0	0
Oral disorder	0	0	1	17	0	0
Upper respiratory tract infection	0	0	1	17	0	0
Dyspepsia	5	83	0	0	1	33
Pain in extremity	1	17	0	0	0	0

Source: FDA Analysis

Clinical TL Review Comment: The analysis of adverse events in the volunteer population confirms GI events as adverse reactions of JZP-458.

Table 54 shows FDA's summary tabulation of laboratory abnormalities in this study.

FDA Table 54. Study JZP458-101 - Summary of Laboratory Abnormalities

	JZP-458 IM 12.5 mg/m2 (N = 6)		JZP-458 IM 25 mg/m2 (N = 6)		Erwinaze, IM 25,000 IU/m2 (N = 3)	
	Grades 1-4 n/N evaluable (%)	**Grades 3-4 n/N evaluable (%)**	**Grades 1-4 n/N evaluable (%)**	**Grades 3-4 n/N evaluable (%)**	**Grades 1-4 n/N evaluable (%)**	**Grades 3-4 n/N evaluable (%)**
Direct Bilirubin Increased	2/6 (33)	0/6 (0.0)	4/6 (67)	0/6 (0.0)	0/0 (0.0)	0/0 (0.0)
Bilirubin Increased	2/6 (33)	0/6 (0.0)	2/6 (33)	0/6 (0.0)	0/0 (0.0)	0/0 (0.0)

FDA Table 54. Study JZP458-101 - Summary of Laboratory Abnormalities

	JZP-458 IM 12.5 mg/m2 (N = 6)		JZP-458 IM 25 mg/m2 (N = 6)		Erwinaze, IM 25,000 IU/m2 (N = 3)	
	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)
Leukocytes Decreased	0/0 (0.0)	0/0 (0.0)	2/6 (33)	0/6 (0.0)	0/0 (0.0)	0/0 (0.0)
Neutrophils Decreased	0/0 (0.0)	0/0 (0.0)	2/6 (33)	1/6 (17)	0/0 (0.0)	0/0 (0.0)
Activated Partial Thromboplastin Time Increased	2/6 (33)	0/6 (0.0)	1/6 (17)	0/6 (0.0)	2/3 (67)	0/3 (0.0)
Potassium Increased	1/6 (17)	1/6 (17)	1/6 (17)	0/6 (0.0)	1/3 (33)	0/3 (0.0)
Creatinine Increased	0/0 (0.0)	0/0 (0.0)	1/6 (17)	0/6 (0.0)	0/0 (0.0)	0/0 (0.0)
Glucose Increased	0/0 (0.0)	0/0 (0.0)	1/6 (17)	0/6 (0.0)	1/3 (33)	0/3 (0.0)
Triglycerides Increased	3/6 (50)	1/6 (17)	0/0 (0.0)	0/0 (0.0)	2/3 (67)	1/3 (33)
Alanine Aminotransferase Increased	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)	1/3 (33)	0/3 (0.0)
Lipase Increased	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)	1/3 (33)	0/3 (0.0)

Source: FDA Analysis

Clinical TL Review Comment: The analysis of laboratory abnormalities in the volunteer population confirms hepatic events as adverse reactions of JZP-458.

8.3.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

An analysis of the SOC "Neoplasms benign, malignant, and unspecified (including cysts and polyps)" in JZP458-201 revealed three patients in Cohort 1B (6%) with these events, all occurring after enrolment on JZP458-201. The Preferred Terms for these events were "Histiocytic sarcoma" (study day 41), "T-cell lymphoma" (study day 74) and "Skin papilloma" (study day 21)."

Human Reproduction and Pregnancy

There are no identified case reports or studies of patients who became pregnancy while receiving JZP-458, or of children who were born of parents who received JZP-458.

Pediatrics and Assessment of Effects on Growth

The majority of patients who were treated on JZP458-201 were pediatric patients < 17 years of age. See Section 8.3.6 for analysis by age.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

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 safety issues expected to arise in the postmarket setting other than those identified above.

8.3.11. Integrated Assessment of Safety

Base on the analysis of all patients treated on Study JZP458-201 through the data cut-off in the Day-60 update, the major adverse reactions included hypersensitivity reactions (25%), pancreatitis (14%), thrombosis (2%), bleeding (17%), and hepatoxicity (62%). These are of sufficient severity to warrant Warnings in the USPI. Monitoring and modifications of dosing are needed to prevent life-threatening or fatal outcomes.

The recommended dosage of JZP-458 is 25 mg/m^2 every 48 hours. This dosage was determined by PK modeling and simulations, but it was not studied in the pivotal trial. As the JZP-458 dose and schedule are nearest to 25 mg/m^2 MWF, the safety data from Cohort 1A would be useful as a description of the expected safety profile. On the basis of dose-toxicity analyses, there is concern that data from Cohort 1B using a higher dose may overestimate the risks, so those data would not be useful in the USPI. The data from Cohort 1C are not relevant to the recommended dose.

Additionally, for a true estimate of risks, grouped terms were used as described in Section 8.3.3. As there will be no laboratory abnormalities table in the USPI, the grouped terms for pancreatitis and hepatotoxicity included both the reported adverse event in addition to

observed laboratory abnormalities. Lastly, as this is a single-arm trial of a combination therapy, all reported events will be considered adverse reactions of the treatment; clearly unrelated event (e.g., relapse) are excluded.

For Cohort 1A, a fatal adverse reactions (infection) occurred in 1 patient. Serious adverse reactions occurred in 55% of patients; the most frequent serious adverse reactions (in ≥ 5% of patients) were febrile neutropenia, dehydration, pyrexia, stomatitis, diarrhea, drug hypersensitivity, infection, nausea, and viral infection. Permanent discontinuation due to an adverse reaction occurred in 9%; adverse reactions resulting in permanent discontinuation included hypersensitivity (6%) and infection (3%). Table 55 shows the common adverse reactions identified for Cohort 1A.

FDA Table 55. Adverse Reactions (≥ 15% incidence) in Patients Receiving RYLAZE 25 mg/m2 Monday, Wednesday and Friday as a Component of Multi-Agent Chemotherapy in Study JZP458-201

Adverse Reaction	RYLAZE 25 mg/m^2 Dosage [a] N=33	
	All Grades (%)	Grades 3-4 [a] (%)
Abnormal liver test	70	12
Nausea	46	9
Musculoskeletal pain	39	6
Fatigue	36	3
Infection	30	12
Headache	30	0
Pyrexia	27	6
Drug hypersensitivity	24	6
Febrile neutropenia	24	24
Decreased appetite	21	6
Stomatitis	21	9
Bleeding	21	0
Hyperglycemia	21	3
Abdominal pain	18	0
Tachycardia	18	0
Diarrhea	18	6
Constipation	15	0
Dehydration	15	9
Neuropathy peripheral	15	0
Cough	15	0
Insomnia	15	0

Source: FDA Analysis
*Includes grouped terms
[a] Does not include the following fatal adverse reactions: infection (N=1).

Overall, the data suggest that the safety profile of JZP-458 at the recommended dose (25 mg/m^2 every 48 hours) does not differ substantially from that of other asparaginase class products.

SUMMARY AND CONCLUSIONS

8.4. Statistical Issues

The FDA's Assessment:

Not applicable.

8.5. Conclusions and Recommendations

The FDA's Assessment:

The regimen of JZP-458 at a dose of 25 mg/m^2 every 48 hours results in an acceptable NSAA level as an established surrogate marker for efficacy. There are no clinical data at this dose that are concerning for an unexpected or unacceptable safety issue. Approval is recommended.

9 ADVISORY COMMITTEE MEETING AND OTHER EXTERNAL CONSULTATIONS

The FDA's Assessment:

Not applicable.

10 PEDIATRICS

The Applicant's Position:
In April 2020, Sponsor received agreed initial pediatric study plan (iPSP) from FDA and in September 2020, JZP458 was granted Rare Pediatric Disease Designation by the FDA. The data from the JZP458-201 study are adequate to support labeling for pediatric patients.

The FDA's Assessment:

JZP-458 has orphan drug designation and would be exempt from PREA. However, the RACE for Children Act, incorporated as Title V of the FDA Reauthorization Act (FDARA 2017) applies for JZP-458 as it is a targeted agent. As such, a pediatric assessment is required. The agreed iPSP (April 20, 2020) for JZP-458 includes study JZP458-201, parts 1 (IM) and 2 (IV). The Applicant requested a waiver of pediatric studies (Module 1.9.1). The current BLA includes the results to

support safe administration of JZP-458 in pediatric patients by the IM route. For the IV route, additional study is needed to determine the appropriate dose of JZP-458 and to assess for safety, pharmacodynamics, and pharmacokinetics of JZP-458. Due to an on-going drug shortage, consideration of JZP-458 for approval cannot be delayed until completion of the studies of the IV route in children. A postmarketing requirement is recommended for studies to establish dosing by the IV route in children.

The Applicant also requested a Rare Pediatric Disease Priority Review Voucher (RPDPRV) (Cover Letter dated 4/29/2021. This application would not support the request for a RPDPRV, because it was not deemed eligible for priority review.

11 LABELING RECOMMENDATIONS

The table below summarizes high level changes to the proposed United States Prescribing Information (USPI). See the final approved USPI for RYLAZE (asparaginase erwinia chrysanthemi (recombinant)-rwyn)) accompanying the approval letter for more information.

Summary of Significant Labeling Changes		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
1 Indications and Usage	Included patients with silent inactivation.	Silent inactivation deleted from indication because there is no FDA-cleared device for SAA.
2.1 Recommended Dosage	Included a recommended dosage to substitute for a dose of native E. coli-derived asparaginase.	Deleted because there is no native E. coli-derived asparaginase currently marketed.
2.2 Recommended Monitoring and Dosage Modifications for Adverse Reactions	N/A	Add monitoring recommendations for bilirubin, transaminases, glucose, and clinical examinations. Added dosage modifications table.
5 Warnings and Precautions (W&P)	Included W&P for Hypersensitivity Reactions; Pancreatitis, Glucose Intolerance; Thrombosis and Hemorrhage	Updated W&P to remove Glucose Intolerance, split Thrombosis and Hemorrhage into separate W&P, and added a W&P for Hepatoxicity
6 Adverse Reactions	Including safety information from patients who received either the 25 mg/m^2 or 37.5 mg/m^2 on Monday, Wednesday,	Clarified that W&P is for all 102 patients and that the safety population for 6 is based on the 33 patients who received the 25

	and Friday and those who received 25 mg/m^2 on Monday and Wednesday and 50 mg/m2 on Friday.	mg/m^2 Monday, Wednesday, Friday dosage regimen only as it most closely aligns with the recommended dosage.
12.3 Pharmacokinetics	Included population PK modeling for response rates for all 3 study cohorts.	Updated PK parameters based on FDA's independent analysis of all SAA data – pooled from Trials 101 and 201.
14 Clinical Studies	Included results of modeling and simulation to describe efficacy.	Updated the efficacy analysis to include FDA's independent analysis of modeling/simulation based on the 25 mg/m^2 IM dose every 48 hours.

12 RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

The FDA's Assessment:

Not applicable.

13 POSTMARKETING REQUREMENTS AND COMMITMENT

The FDA's Assessment:

The following are the recommended PMRs and PMCs:

PMR #1 Conduct a clinical trial to determine the appropriate dose of JZP-458 by the intravenous route and to assess safety, pharmacokinetics, and pharmacodynamics of JZP-458 administered by the intravenous route in pediatric patients with acute lymphoblastic leukemia or lymphoblastic lymphoma. Include at least 6 patients < 6 years old, 6 patients 6-11 years old and 6 patients 12-17 years old.

PMC #1 Conduct an assessment of the binding and neutralizing anti-drug antibody (ADA) responses in all JZP-458 treated patients from Study JZP458-201 with a validated assay (requested in PMC 2 and 3) capable of sensitively detecting ADA responses in the presence of JZP-458 levels that are expected to be present in the serum at the time of patient sampling. Include information on the level of JZP-458 in each patient's test sample at each sampling point and an assessment of the effects of binding and neutralizing ADA on clinical hypersensitivity reactions in the final report. In addition, assess the effects of binding and neutralizing ADA on JZP-458 exposure (serum asparaginase activity and serum asparaginase content) in the final report.

PMC #2 Develop and validate a binding anti-drug antibody (ADA) assay with sufficient drug tolerance to be able to detect, confirm, and titer anti-RYLAZE binding antibodies in the presence of RYLAZE concentrations in clinical samples at the time of sampling.

PMC #3 Develop and validate a neutralizing ADA (NAb) assay with sufficient drug tolerance to detect neutralizing antibodies against RYLAZE in the presence of expected RYLAZE concentrations in clinical samples at the time of sampling.

PMC #4 Conduct a study examining quantitative recovery of anti-JZP458 antibodies from serum samples pretreated with Melon Gel Spin Plate Kit if immunogenicity data from an assay that uses the Melon Gel Spin Plate kit are used to support the license.

PMC #5 To define and implement bioburden limits for routine reactivation of chromatography resins after extended storage.

PMC #6 To repeat the bacterial retention study (b) (4) Once (b) (4) validated, monitoring (b) (4) will be implemented during routine manufacturing.

PMC #7 To update the container closure integrity test method to include a 20-µm breached positive control.

PMC#8 To update the RP-UHPLC method validation to include impurities spiking study (e.g. pre-peaks and post-peaks are enriched to assess assay performance at different purity/impurity ratios).

14 APPENDICES

14.1. References

The Applicant's References:

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The FDA's References:

[1] Beal, Stuart L. "Ways to fit a PK model with some data below the quantification limit." *Journal of pharmacokinetics and pharmacodynamics* 28.5 (2001): 481-504.

14.2. Financial Disclosure

The Applicant's Position:

In compliance with 21 CFR 54, the Applicant provided FDA Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and a listing of clinical investigators for covered studies: JZP458101 and JZP458-201. The Applicant has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). Each listed clinical investigator was required to disclose if they had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b). No clinical investigators participating in JZP458-101 disclosed any such interests nor were any the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)

The FDA's Assessment:

Covered Clinical Study (Name and/or Number):* JZP458-101 and JZP458-201		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 08 for JZP458-101 and 524 for JZP458-201		
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): 01 for JZP458-201		
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: N/A Significant payments of other sorts: 01 for JZP458-201 Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in study: N/A Sponsor of covered study: Jazz Pharmaceuticals Ireland Limited		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

The Applicant's Position:

One clinical investigator participating in JZP458-201 disclosed financial interest and the Applicant provided Form 3455 with additional details in the initial BLA.

The FDA's Assessment:
See table above.

14.3. Nonclinical Pharmacology/Toxicology

Data:
Not applicable, refer section 5

The Applicant's Position:
Not applicable, refer section 5

The FDA's Assessment:
No additional information.

14.4. OCP Appendices

14.4.1. Bioanalytical Methods

The Office of Clinical Pharmacology review team has assessed the acceptability of the following bioanalytical methods used in clinical studies JZP458-101 and JZP458-201.

For studies JZP458-101 and JZP458-201, serum L-asparaginase enzyme activity (SAA) and serum concentrations of L-asparaginase (SAC) were determined with the following methods. Study JZP458-101 is completed. The Phase 2/3 Study JZP458-201 is an ongoing study and this bioanalytical review covers the data with cut-off of 14 October 2020.

Summaries of method performance of the SAA and SAC methods are provided in Tables 1 and 2, respectively.

1. Method 00350514: An enzymatic assay procedure for the determination of L-asparaginase enzyme activity in human serum - Table 1
2. Method 00350512: Quantification of recombinant crisantaspase (RC-P) in human serum – Table 2

The SAA and SAC assays for studies JZP458-101 and JZP458-201 were conducted at (b) (4) The Office of Study Integrity and Surveillance (OSIS) Conducted remote record review at this site. Per remote record review recommendation dated (b) (4) OSIS identified objectionable condition related to the SAC assay. The firm did not evaluate potential interference of anti-drug antibodies (ADAs) on measurement of RC-P.

The primary efficacy endpoint of the studies is based on SAA, therefore, the bioanalytical review focused on review of the SAA method validation and sample analysis reports. The review concluded that method 00350514 is validated for determination of SAA. All samples were analyzed within the demonstrated stability window for studies JZP458-101 and JZP458-201. However, potential interference of anti-asparaginase antibodies to the SAA assay was not

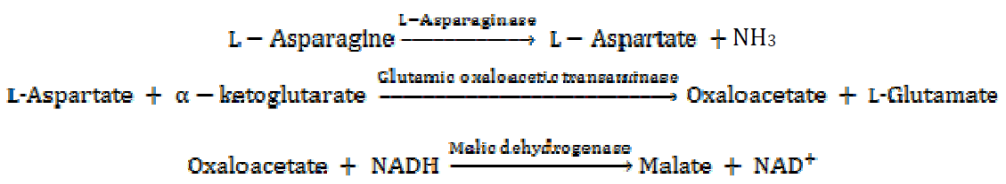
assessed during validation. This should be considered in evaluating changes in SAA values for individual subjects.

Method 00350512 is validated for quantification of recombinant crisantaspase (RC-P) in human serum. However, potential interference of anti-asparaginase antibodies to the SAC assay should be considered in evaluating changes in SAC values.

Method TM.2457 was used for quantification of L-asparagine and L-glutamine in human plasma containing L-asparaginase. The method validation was reported in Report No. 14283.032819, Amendment 2. This method has significant limitations in accurately quantifying depletion of L-asparagine and L-glutamine by L-asparaginase. Subject samples for the JZP458-101 and JZP458-201 trials were collected without an asparaginase enzyme inhibitor at the time point that samples were drawn at the clinical site. During validation, it was demonstrated that a quenching reagent stabilized samples from further depletion of asparagine and glutamine upon storage at the bioanalytical site. However, no measures were taken to prevent potential *ex vivo* conversion during sample collection. In response to IR dated May 11, 2021, the sponsor acknowledges that the current assay requires further development and considers the measurement of L-asparagine and L-glutamine in plasma from patients treated with JZP458 to be an exploratory endpoint. Therefore, the submitted L-asparagine and L-glutamine by L-asparaginase depletion data were not reviewed.

The quantification of L-asparagine and L-glutamine was performed by (b) (4) OSIS declined to inspect this site based on inspection history.

Table 1: Determination of serum L-asparaginase enzyme activity

Bioanalytical method review summary	Validation of method PBA-00350514 was adequate for determination of L-asparaginase enzyme activity in human serum.
Bioanalytical method validation report name, and amendments	Validation of an Enzyme Activity Procedure for the Determination of L-Asparaginase Enzyme Activity (SAA) in Human Serum Report No: 00350514, Amendment 2
Method description	This method involves measurement of L-asparaginase enzyme activity based on the rate of conversion of NADH to NAD+ from the following series of reactions: 

	Absorbance at 340 nm was measured over 30 minutes with a read once per 30 seconds and was detected using a Molecular Devices plate reader. The Vmax (rate in optical density [OD]/min) was determined from a line of best fit through the data between 300 and 1300 seconds (5 and 21.40 minutes). The data for the standards were regressed according to a 5-parameter logistic (5-PL) model.
Materials used for calibration curve & concentration	Reference material, Lot No. M-LAP-P03, was used for preparation of the calibration standards with concentration ranges 25.00 – 150.00 mIU/mL for the validation experiments. Recombinant Crisantaspase (RC-P), Lot No. CMC-M-0002, was used for preparation of the calibration standards with concentration ranges 34.93 to 209.58 mIU/mL for lot bridging experiments and high lipemia selectivity experiment. (b) (4) classifies lipemia based on their SOP. (b) (4) *The lot bridging analysis showed that standards prepared from either the RC-P (Lot No. CMC-M-0002) or reference material (Lot No. M-LAP-P03) are comparable in quantifying quality control samples from each lot. Subsequently, RC-P (Lot No. CMC-M-0002) was used for preparation of calibration standards and quality control samples in studies JZP458-101 and JZP458-201.* (b) (4)
Validated assay range	25.00 – 150.00 mIU/mL (M-LAP-P03); 34.93 to 209.58 mIU/mL (CMC-M-0002)
Material used for QCs & concentration	Reference material, Lot No. M-LAP-P03, was used for preparation of the quality control samples at the following concentrations for validation experiments: Lower limit of quantitation (LLOQ) – 25.00 mIU/mL; low control (LC)– 37.50 mIU/mL; medium control (MC) – 75.00 mIU/mL; high control (HC) – 115.00 mIU/mL; upper limit of quantitation (ULOQ) – 150.00 mIU/mL; dilution control (DC) – 17,580 mIU/mL RC-P, Lot No. CMC-M-0002, was used for preparation of the quality control samples at the following concentrations for lot bridging experiments. LC - 52.39 mIU/mL; MC - 104.79 mIU/mL; HC - 160.68 mIU/mL

	(b) (4)		
Minimum required dilutions (MRDs)	10-fold		
Regression model & weighting	5-PL, $1/y^2$		
Validation parameters	**Method validation summary**		**Acceptability**
Calibration curve performance during accuracy & precision Per BMV, At least 75% and minimum of 6 non-zero calibrators without anchor points and LBA: ±20% bias (±25% at LLOQ), ≤ 20%CV	No of standard calibrators from LLOQ to ULOQ	Seven	Acceptable
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.82 to 1.69	Acceptable
	Cumulative precision (%CV) from LLOQ to ULOQ	1.15 to 2.97	Acceptable
QCs performance during accuracy & precision Per BMV, LBA QCs: ±20% bias (±25% at LLOQ), ≤ 20%CV and ≤ 30% total error (≤ 40% at LLOQ)	Cumulative accuracy (%bias) across all QCs	-9.40 to -2.44	Acceptable
	Inter-batch %CV across all QCs	6.11 to 8.84	Acceptable
	Percent total error (TE) across all QCs	11.29 to 17.57	Acceptable
Selectivity	Unspiked: 100% BLQ At LLOQ (25 mIU/mL): 100% acceptable		Acceptable
Interference & specificity	Interference of anti-asparaginase antibodies to the SAA assay was not assessed		Not acceptable (needs to be considered in evaluating study data)
Hemolysis effect	Hemolysis up to 550 mg Hb/dL did not interfere with the accurate determination of the analyte at 12.50 mIU/mL, but above 550 mg Hb/dL impacted the assay.		Acceptable

Lipemic effect	Levels of lipemia above **medium** may impact accurate determination of the analyte at 25 mIU/mL level. Samples with SAA levels 139.7 mIU/mL or higher can be determined in the presence of high lipemia.	Acceptable
Dilution linearity	Established for up to 467.72-fold (in addition to the MRD)	Acceptable
Bench-top/process stability	18 hours 55 minutes at room temperature	Acceptable
Freeze-Thaw stability	6 cycles stored at -60°C to -80°C	Acceptable
Long-term storage	Ongoing; Up to 183 days at -60°C to -80°C Ongoing; Up to 118 days at -10°C to -30°C	Acceptable
Method performance in study JZP458-101 (test site reference number 00350519, Report: Amendment 3)		
Assay passing rate	• 100% of runs accepted	Acceptable
Standard curve performance	• Calibration curves in 100% of runs accepted • Cumulative accuracy (%RE) range: -2.43 to 1.87 % • Cumulative precision (%CV) range: 1.06 to 3.83%	Acceptable
QC performance	• QCs in 100% of runs accepted • Cumulative accuracy (%RE) range across all QCs: -0.08 to 4.79% • Cumulative precision (%CV) range across all QCs: 6.52 to 8.09%	Acceptable
Method reproducibility	• The results of the incurred sample reanalysis (ISR) run met acceptance criteria with 97.67% (42 of 43 samples tested) quantifying within ± 30% Difference.	Acceptable
Study sample analysis/ stability	*In response to IR dated February 24, 2021, the applicant stated that the SAA samples for study JZP458-101 were stored for up to 16 days at the clinical sites and up to 38 days at the bioanalytical laboratory at -60°C to -85°C prior to analysis. Accordingly, the maximum long-term stability needed to cover sample storage is 54 days. Therefore, the long-term stability assessment for 183 days at -60°C to -80°C covers the storage condition and duration of the study samples.*	
Lipemic and hemolyzed samples	*In response to IR dated February 24, 2021, the applicant stated that no lipemic samples were identified. Five hemolyzed samples with the hemolysis levels < 550 mg Hb/dL were identified.*	
Method performance in study JZP458-201 (test site reference number 00350550, Report: Interim)		
Assay passing rate	• 97.10% (67 out of 69) of runs accepted	Acceptable
Standard curve performance	• Calibration curves in 98.55% (68 out of 69) of runs accepted • Cumulative accuracy (%RE) range: -0.29 to 0.72%	Acceptable

	• Cumulative precision (%CV) range: 1.00 to 4.01%	
QC performance	• QCs in 97.10% (67 out of 69) of runs accepted. QCs did not meet acceptance criteria in Run 24 and QCs were not included in Run 59 • Cumulative accuracy (%RE) range across all QCs: -1.71 to 2.75% • Cumulative precision (%CV) range across all QCs: 4.48 to 8.87%	Acceptable
Method reproducibility	• The results of the ISR run met acceptance criteria with 93.94% (62 of 66 samples tested) quantifying within ± 30% Difference	Acceptable
Study sample analysis/ stability	*In response to IR dated March 15, 2021, the applicant stated that the SAA samples for study JZP458-201 were stored for up to 113 days at the clinical sites, 77 days at central laboratories and 70 days at bioanalytical laboratories at -60°C to -80°C. They also stated that all individual SAA samples were analyzed within 148 days from sample collection date, which includes storage at clinical sites, central labs and at bioanalytical lab. Therefore, the long-term stability assessment for 183 days at -60°C to -80°C covers the storage condition and duration of the study samples.*	
Lipemic and hemolyzed samples	*No hemolyzed samples were reported. Samples with high lipemia were identified in Table 6 of the bioanalytical report and the activity values were reported for reference only and were excluded from PopPK analysis. Upon review of the list in Table 6, we identified one sample from Subject ID* (b) (6) *(72-hour postdose, course 9) with high lipemia that was not excluded from PopPK. This information was communicated to the pharmacometrics reviewer.*	

Table 2: Quantification of RC-P in human serum

Bioanalytical method review summary	Validation of method PBA-00350512 was adequate for quantification of RC-P in human serum.
Bioanalytical method validation report name and amendments	Validation of An Electrochemiluminescent Immunoassay (ECLIA) Procedure for the Quantification of Recombinant Crisantaspase (RC-P) in Human Serum Report No: 00350512, original
Method description	A standard Meso Scale Discovery (MSD) 96-well plate was coated overnight at 2°C to 8°C with a monospecific anti-Erwinaze rabbit IgG antibody that served as a capture antibody. The plates were blocked with assay diluent (1% bovine serum albumin [BSA] in phosphate-buffered saline [PBS]). On the day of the assay, standards, QCs, and blanks were diluted at a MRD of 5-fold in assay diluent. Any RC-P bound to the plate was quantified by incubation with biotinylated anti-Erwinaze rabbit IgG antibody. Streptavidin labeled with ruthenium metal chelate (sulfo-TAG®) was added and bound to the

	biotinylated antibody. The sulfo-tagged labels on the antibody complex emitted light upon electrochemical stimulation of the electrode surfaces on the plate. The intensity of the light emitted was proportional to the concentration of RC-P in the sample. Electrochemiluminescence was detected using an MSD Sector S 600 reader.		
Materials used for calibration curve & concentration	RCP, Lot No. CMC-M-0002, at concentration ranges 1.000 to 128.0 ng/mL		
Validated assay range	1.000 ng/mL to 128.0 ng/mL		
Material used for QCs & concentration	RCP, Lot No. CMC-M-0002, at the following concentrations: LLOQ – 1.000 ng/mL; LC - 3.000 ng/mL; MC - 12.00 ng/mL; HC - 96.00 ng/mL; ULOQ - 128.0 ng/mL; DC – 50,000 ng/mL		
Minimum required dilutions (MRDs)	5-fold		
Regression model & weighting	4-PL, $1/y^2$		
Validation parameters	**Method validation summary**		**Acceptability**
Calibration curve performance during accuracy & precision	No of standard calibrators from LLOQ to ULOQ	Eight	Acceptable
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-0.51 to 1.75	Acceptable
	Cumulative precision (%CV) from LLOQ to ULOQ	0.73 to 2.41	Acceptable
QCs performance during accuracy & precision	Cumulative accuracy (%bias) across all QCs	-7.73 to 9.30	Acceptable
	Inter-batch %CV across all QCs	4.64 to 11.33	Acceptable
	Percent total error (TE) across all QCs	9.12 to 19.50	Acceptable
Selectivity	Unspiked: 100% BLQ At LLOQ: 100% acceptable		Acceptable
Interference & specificity	Interference of anti-asparaginase antibodies to the SAC assay was not assessed		Not acceptable (needs to be considered in evaluating study data)

Hemolysis effect	Hemolysis up to 1100 mg Hb/dL did not interfere with quantification of asparaginase. The experiment was repeated due to suspected sample preparation error.	Acceptable
Lipemic effect	High levels of lipemia did not interfere with quantification of asparaginase. The experiment was repeated due to suspected sample preparation error.	Acceptable
Dilution linearity & hook effect	Established for up to 20,000-fold (in addition to the MRD); no hook effect was observed	Acceptable
Bench-top/process stability	16 hours and 45 minutes at room temperature	Acceptable
Freeze-Thaw stability	6 cycles stored at -60°C to -80°C. The experiment was repeated because lower than expected number of QC replicates at each level (3, instead of 6) were used in the original experiment. The first repeat did not meet acceptance criteria at the LC level. The second repeat met acceptance criteria.	Acceptable
Long-term storage	Ongoing; 369 Days at -60°C to -80°C	Acceptable
Method performance in study JZP458-101 (test site reference number 00350518, Report: Original & Amendment 1)		
Assay passing rate	• 96.6% (28 out of 29) of runs accepted	Acceptable
Standard curve performance (L-asparaginase and Erwinaze)	• Calibration curves in 100% of runs accepted • Cumulative accuracy (%RE) range: -0.88 to 0.58% • Cumulative precision (%CV) range: 0.88 to 2.83%	Acceptable
QC performance (L-asparaginase and Erwinaze)	• QCs in 96.6% (28 out of 29) of runs accepted • Cumulative accuracy (%RE) range across all QCs: -5.28 to -0.67% • Cumulative precision (%CV) range across all QCs: 5.27 to 11.52%	Acceptable
Method reproducibility	• The results of the incurred sample reanalysis (ISR) run met acceptance criteria with 89.83% (53 of 59 samples tested) quantifying within ± 30% Difference.	Acceptable
Study sample analysis/ stability	*In response to IR dated February 24, 2021, the applicant stated that the SAC samples for study JZP458-101 were stored for up to 16 days at the clinical sites and up to 82 days at the bioanalytical laboratory at -60°C to -85°C prior to analysis. Accordingly, the maximum long-term stability needed to cover sample storage is 98 days. Therefore, the long-term stability assessment for 369 days at -60°C to -80°C covers the storage condition and duration of the study samples.*	
Method performance in study JZP458-201 (test site reference number 00350551, Report: Interim)		
Assay passing rate	• 84.6% (55 out of 65) of runs accepted	Acceptable

Standard curve performance	• Calibration curves in 100% of runs accepted • Cumulative accuracy (%RE) range: -2.19 to 2.33 % • Cumulative precision (%CV) range: 2.34 to 11.72%	Acceptable
QC performance	• QCs in 84.6% (55 out of 65) of runs accepted • Cumulative accuracy (%RE) range across all QCs: -11.38 to -2.83% • Cumulative precision (%CV) range across all QCs: 5.92 to 9.59%	Acceptable
Method reproducibility	• The results of the incurred sample reanalysis (ISR) run met acceptance criteria with 96.26% (103 of 107 samples tested) quantifying within ± 30% Difference.	Acceptable
Study sample analysis/ stability	*In response to IR dated March 15, 2021, the applicant stated that the SAC samples for study JZP458-201 were stored for up to 113 days at the clinical sites, 92 days at central laboratories and 194 days at bioanalytical laboratories at -60°C to -80°C. They also stated that all individual SAC samples were analyzed within 221 days from sample collection date, which includes storage at clinical sites, central labs and at bioanalytical lab. Therefore, the long-term stability assessment for 369 days at -60°C to -80°C covers the storage condition and duration of the study samples.*	

(b) (4)

(b) (4)

[redacted]

14.4.3. FDA's Population PK Analysis and SAA Simulation

14.4.3.1. FDA's original population PK analysis using data with cut-off date of 10/14/2020

As discussed above, FDA conducted independent PopPK analysis to correct the over-prediction observed with Applicant's model.

First, to better capture the absorption phase of PK, a PopPK model was developed based on 360 SAA data from 24 healthy subjects with intensive PK sampling schedule in Study 101. The SAA time profiles in healthy subjects were best characterized by a one-compartment model with sequential mixed order absorption and linear elimination, with BSA included as an allometric covariate on CL, with IIV expressed as an exponential term on CL, V, zero-order absorption rate (R1), and first-order absorption rate constant (Ka), and a mixed proportional and additive residual error model. In addition, Black (n=4) subjects tended to have 28.2% lower CL compared to White (n=20) subjects. The parameter estimates of the final PK model in 24 healthy subjects are presented in **Table 67**.

Table 67 Parameter Estimates of the Final PopPK Model in Healthy Subjects from Study 101

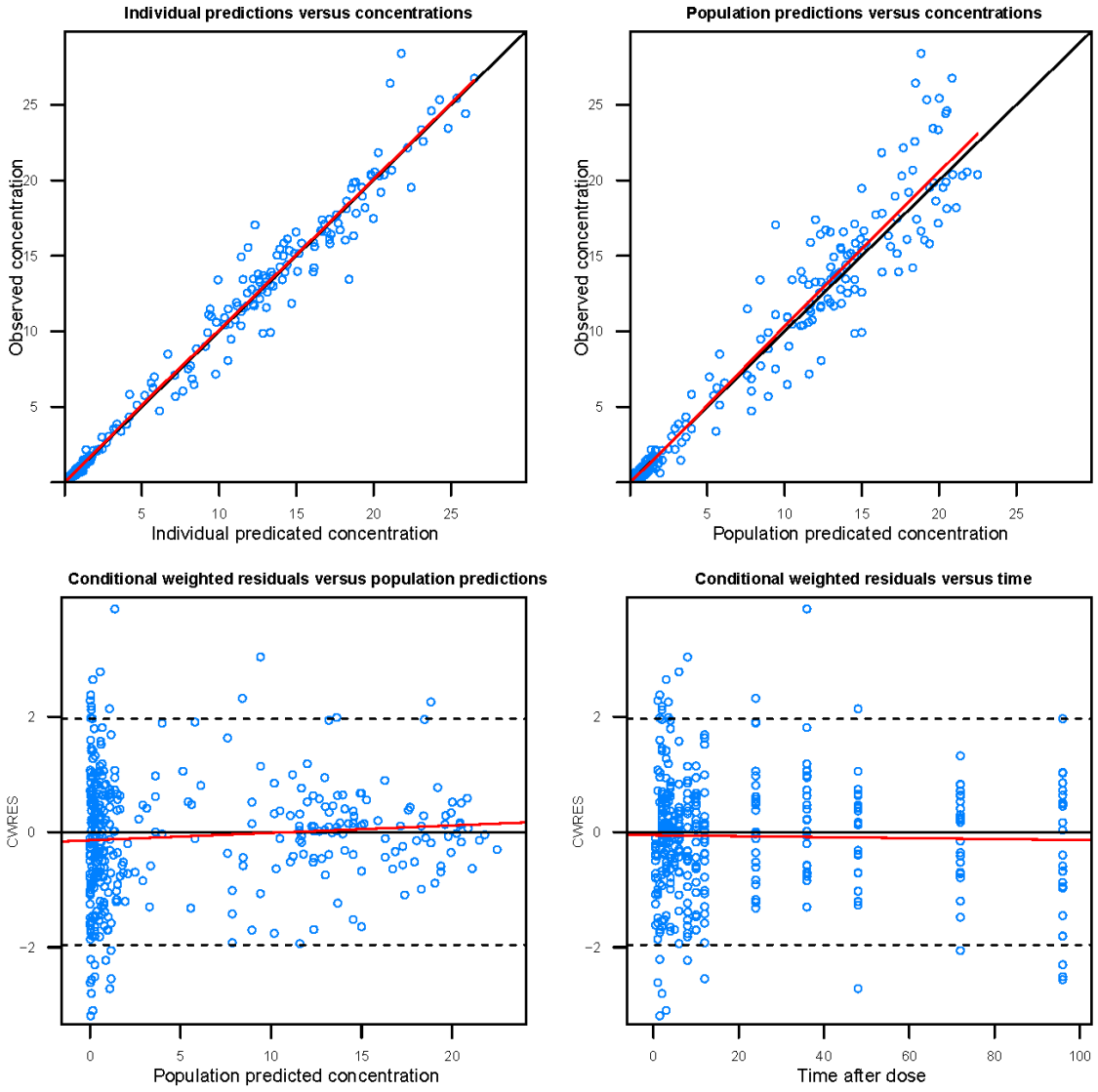
Parameter	Description	Estimate	RSE%
Fixed effect			
CL	Clearance (L/hr)	0.116	4.7%
V	Volume of distribution (L)	2.02	3.6%
R1	Zero-order absorption rate (IU/hr)	2160	7.7%
Ka	First-order absorption rate constant (hr^{-1})	0.0364	1.6%
Fa	Bioavailability	36.5%	11.7%
CL_BSA	Effect of BSA on CL	1.20	2.7%
CL_RACE	% difference in CL between Black vs. White subjects	-28.2%	2.3%
Inter-individual variability (IIV)			
η_{CL}	IIV for CL (CV%)	14.5%	1.0%
η_V	IIV for V (CV%)	17.6%	0.5%

η_{Ka}	IIV for Ka (CV%)	17.9%	0.4%
η_{R1}	IIV for R1 (CV%)	101.5%	1.7%
Corr_η_{CL}_η_{R1}	Correlation between η_{CL} and η_{R1}	-85%	-
Random effect			
ε_{prop}	Standard deviation of proportional random effect	0.152	0.9%
ε_{add}	Standard deviation of additive random effect	0.0104	0.7%

RSE: relative standard error; CV: coefficient of variation.
$\mathrm{CL} = 0.116 \times (\mathrm{BSA}/1.9)^{1.20}$ if White subjects; $\mathrm{CL} = 0.116 \times (\mathrm{BSA}/1.9)^{1.20} \times 0.718$ if Black subjects.
Source: FDA's analysis.

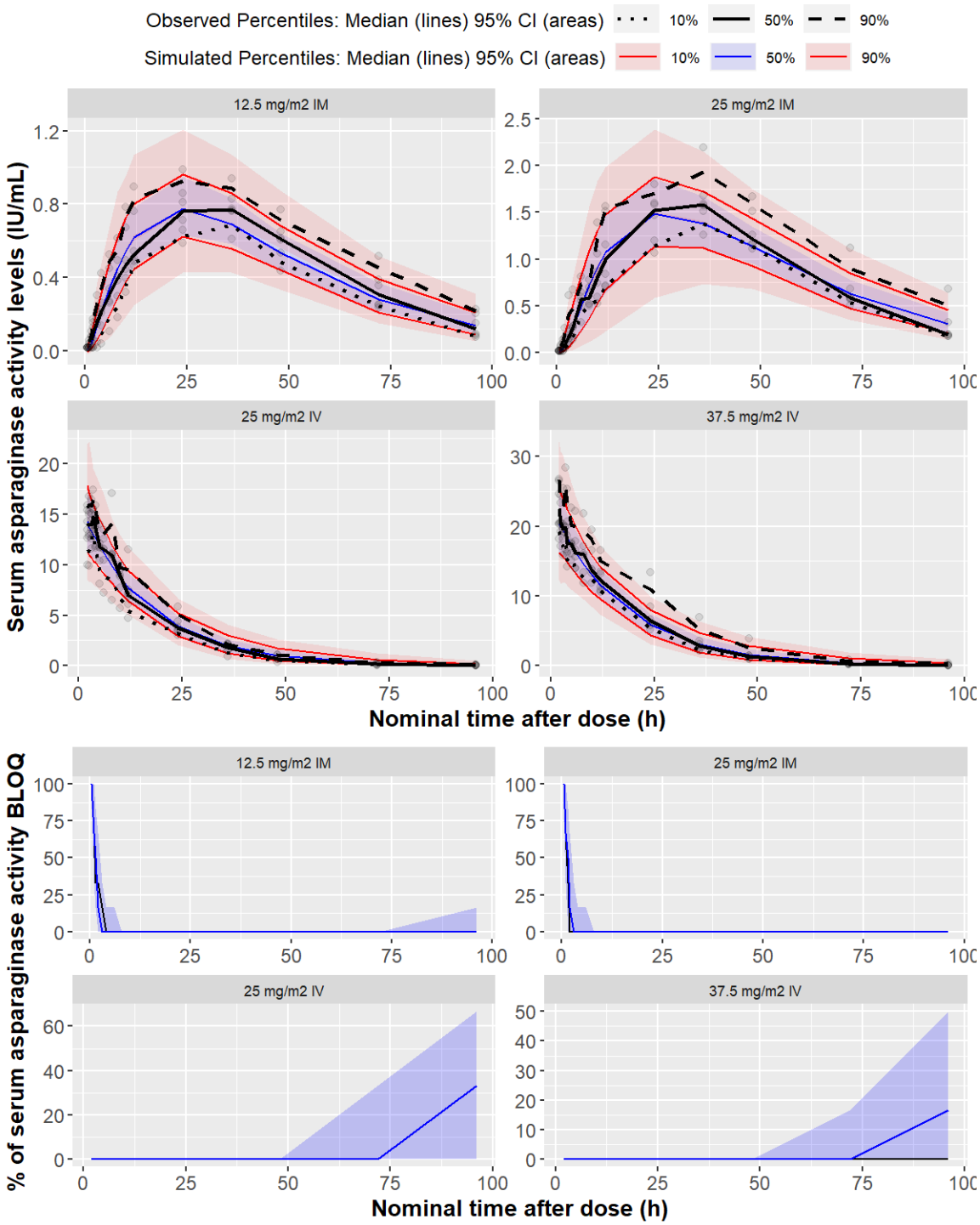
The GOF plots (Figure 15) and VPC plots stratified by dose level (**Figure 16**) show that the FDA's final PopPK model for healthy subjects generally describe the SAA data from Study 101 well.

Figure 15 Goodness-of-fit Plots for the Final PopPK Model in Healthy Subjects from Study 101



Source: FDA's analysis.

Figure 16 Visual Predictive Check for the FDA's Final PopPK Model in Healthy Subjects from Study 101



Source: FDA's analysis.

Then, independent PopPK analysis was conducted based on 895 sparse SAA data from 85 patients (32 from Cohort 1a and 53 from Cohort 1b) in Study 201. Due to the sparse sampling scheme (pre-dose, 2.5, 48 and 72 hours after dosing) in Study 201, R1 and Ka were fixed to the values from final model in healthy subjects (**Table 67**). The SAA time profiles in patients were best described by an one-compartment model with sequential mixed order absorption and linear elimination, with BSA included as an allometric covariate on both CL/F and V/F, with IIV expressed as an exponential term on CL/F, V/F, R1 and Ka, and a mixed proportional and additive residual error model. In addition, Black (n=10) and Asian (n=5) patients tended to have 28.8% lower CL/F compared to White (n=61) subjects. The SAA PK parameter estimates of the final PK model in 85 patients from Cohorts 1a and 1b in Study 201 are presented in **Table 68**.

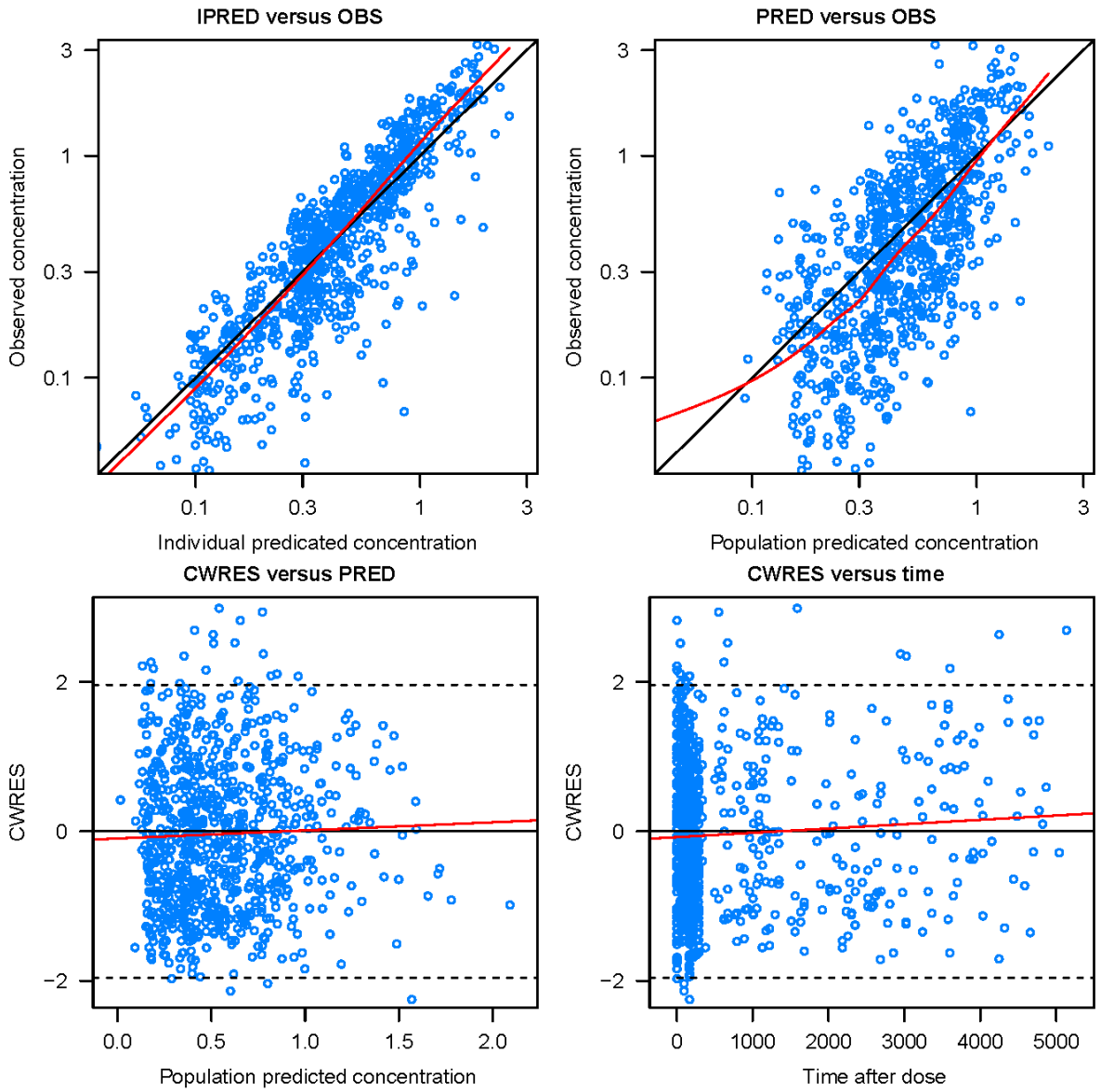
Table 68 Parameter Estimates of the FDA's Final PopPK Model in Patients from Cohorts 1a and 1b in Study 201

Parameter	Description	Estimate	RSE%
Fixed effect			
CL/F	Apparent clearance (L/hr)	0.375	4.4%
V/F	Apparent volume of distribution (L)	1.67	7.7%
R1	Zero-order absorption rate (IU/hr)	2160 (Fix)	-
Ka	First-order absorption rate constant (hr^{-1})	0.0364 (Fix)	-
CL/F _BSA	Effect of BSA on CL/F	1.51	5.5%
V/F _BSA	Effect of BSA on V/F	1.84	9.3%
CL_RACE	% difference in CL/F for Black and Asian subjects vs. other races	-28.8%	20.2%
Inter-individual variability (IIV)			
$\eta_{CL/F}$	IIV for CL/F (CV%)	26.3%	10.5%
$\eta_{V/F}$	IIV for V/F (CV%)	46.5%	20.8%
η_{Ka}	IIV for Ka (CV%)	18.6%	19.1%
η_{R1}	IIV for R1 (CV%)	49.1%	13.4%
Corr_$\eta_{CL/F}$_$\eta_{V/F}$	Correlation between $\eta_{CL/F}$ and $\eta_{V/F}$	62.7%	-
Corr_$\eta_{CL/F}$_η_{Ka}	Correlation between $\eta_{CL/F}$ and η_{Ka}	68.6%	-
Corr_$\eta_{V/F}$_η_{Ka}	Correlation between $\eta_{V/F}$ and η_{Ka}	17.5%	-
Random effect			
ε_{prop}	Standard deviation of proportional random effect	0.438	2.4%
ε_{add}	Standard deviation of additive random effect	0.011	18.1%

RSE: relative standard error; CV: coefficient of variation.
$\mathrm{CL/F} = 0.375 \times (\mathrm{BSA}/1.16)^{1.51} \times 0.712$ if Black and Asian patients; $\mathrm{CL/F} = 0.375 \times (\mathrm{BSA}/1.16)^{1.51}$ if White and other race subjects.
$\mathrm{V/F} = 1.67 \times (\mathrm{BSA}/1.16)^{1.84}$
Source: FDA's analysis.

The GOF plots (Figure 17) show that there was a good agreement between the observed and population predicted or individual predicted SAA levels, with no obvious bias for conditional weighted residuals (CWRES) vs. population predictions or time after first dose.

Figure 17 Goodness-of-fit Plots for the FDA's Final PopPK Model in Patients from Cohorts 1a and 1b in Study 201

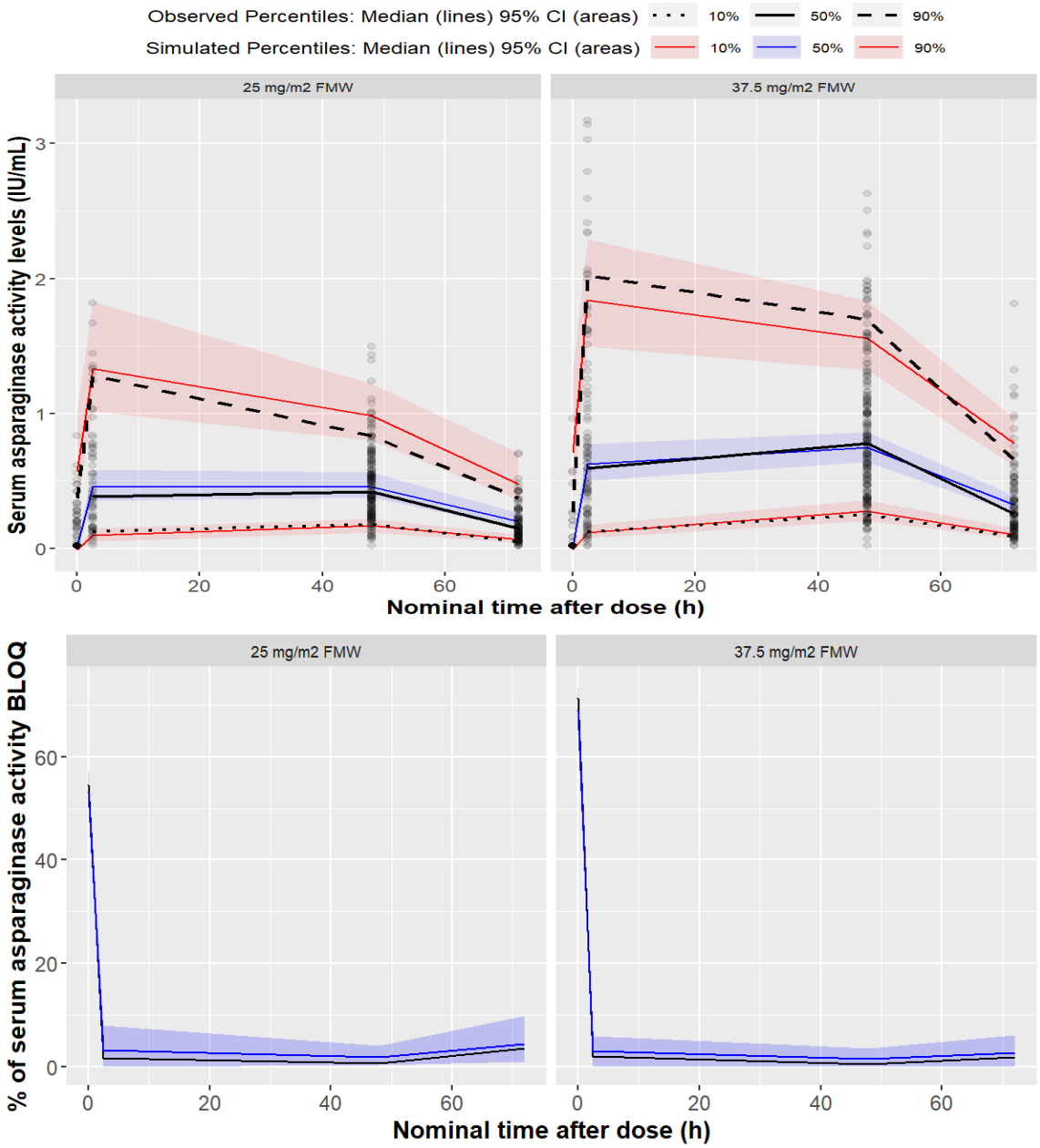


Source: FDA's analysis.

The VPC stratified by dose level is shown in ***Figure 18.*** The upper panels illustrate that the 5th, 50th, and 95th prediction percentiles and the corresponding 95% confidence intervals (CI) of the

simulated SAA time profiles overlaid on the observed 5th, 50th and 95th percentiles of observed SAA above LLOQ. The lower panels in **Figure 18** illustrate that the predicted proportions of SAA data below LLOQ and the corresponding 95% CIs overlaid on the observed proportion of SAA data below LLOQ.

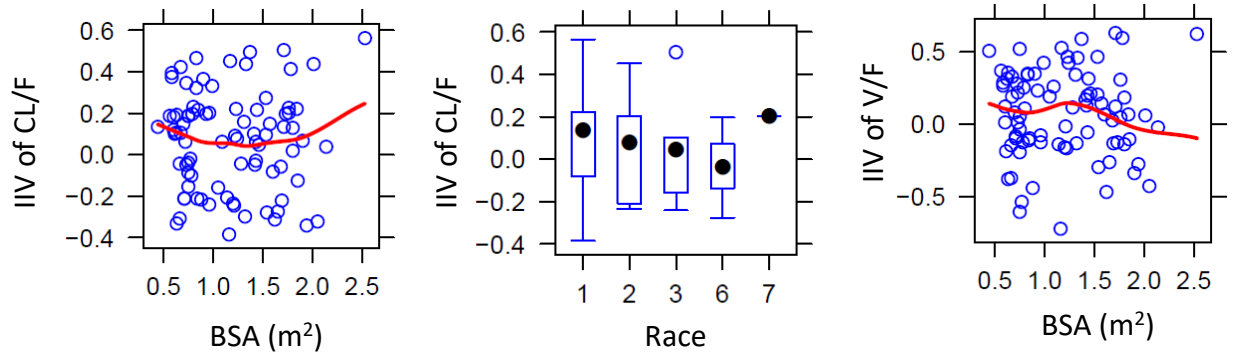
Figure 18 Visual Predictive Check for the FDA's Final PopPK Model in Patients from Cohorts 1a and 1b in Study 201



Source: FDA's analysis.

The unexplained biases in CL/F and V/F when plotted against identified covariates was minimal in the final model (**Figure 19**).

Figure 19 Unexplained Variabilities in Apparent Clearance and Volume of Distribution Plotted Against the Identified Significant Covariates in the FDA's Final PopPK Model.



IIV: Inter-individual variability; CL/F: apparent clearance; V/F: apparent volume of distribution.
Race: 1=White, 2=Black or African American; 3=Asian; 6=Declined to State, 7=Other.
Source: FDA's analysis.

In general, the established final PopPK model based on FDA's independent analysis described well the observed SAA data both above and below LLOQ from 85 patients in Cohorts 1a and 1b of Study 201. The impact of BSA (0.44 to 2.53 m^2) on CL/F and V/F supported the Applicant's proposed BSA-based dosing regimen. Black (n=10) and Asian (n=5) patients had 28.8% lower CL/F compared to White (n=61) patients. See Section 14.4.4 for further discussion on the need of dose adjustment based on race. There were no differences in CL/F between Hispanic (n=28) and Non-Hispanic (n=53) patients. There were no clinically significant differences in PK of JZP-458 SAA based on age (1 to 52 years), weight (9 to 131 kg), or sex after the dose was adjusted by BSA. Therefore, no dosage modification is recommended based on age, weight, sex, or ethnicity.

The final PopPK model was used to generate the individual PK parameters, which are summarized in **Table 69**.

Table 69 Summary of Individual PK parameters based on FDA's Final PopPK Model in Patients from Cohorts 1a and 1b in Study 201

Dose level	Parameter	Dose in Course	Geometric mean (CV%)
12.5 - 50 mg/m^2	CL/F (L/h)	Any dose	0.34 (77.9%)
	V/F (L)		1.58 (98.0%)
	$t_{1/2}$ (h)		8.78 (29.9%)
25, 25, 50 mg/m^2 on Monday, Wednesday, Friday, respectively, for 6 doses per course	C_{max} (IU/mL)	1	3.19 (47.3%)
		6	3.62 (47.2%)
	C_{48h} (IU/mL)	1	0.33 (89.4%)
		6	0.39 (93.4%)
	C_{72h} (IU/mL)	1	0.28 (99.9%)
		6	0.31 (102%)
	$AUC_{0\text{-}48h}$ (IU*h/mL)	1	37.9 (39.1%)
		6	46.5 (41.9%)
	$AUC_{0\text{-}72h}$ (IU*h/mL)	1	87.7 (40.0%)
		6	99.5 (41.3%)
25 mg/m^2 every 48 hours for 7 doses per course	C_{max} (IU/mL)	1	1.80 (40%)
		7	2.24 (42%)
	C_{48h} (IU/mL)	1	0.33 (88%)
		7	0.40 (93%)
	$AUC_{0\text{-}48h}$ (IU*h/mL)	1	37.9 (39.1%)
		7	48.5 (41.4%)

C_{max}: maximum SAA concentration; C_{48h}: concentration 48 hours after the most recent dose at 25 mg/m^2; C_{72h}: concentration 72 hours after the most recent dose at 50 mg/m^2; $AUC_{0\text{-}48h}$: area under time-concentration profile from 0 to 48 hours after the most recent dose at 25 mg/m^2; $AUC_{0\text{-}72h}$: area under time-concentration profile from 0 to 72 hours after the most recent dose at 50 mg/m^2.
Source: FDA's analysis.

14.4.3.1. FDA's simulation for SAA

The FDA's final PopPK model was used to simulate the response rate of achieving a NSAA level ≥ 0.1 IU/mL after the first Friday dose of JZP-458 following fixed dosing schedules (25 and 37.5 mg/m^2 on MWF for 6 doses), and mixed dosing schedules (25/25/50 mg/m^2 on MWF and 50/25/25 mg/m^2 on FMW for 6 doses), and to simulate the response rate of achieving a NSAA level ≥ 0.1 IU/mL after the first dose of JZP-458 following 25 mg/m^2 every 48 hours for 7 doses. Simulations were performed based on the Applicant's simulation dataset, which contains 2000 subjects from NHANES dataset, including 1000 pediatric (2 to 17 years of age) and 1000 adult (18 to 85 years of age) subjects.

A tabular summary of the FDA's simulated proportion of patients achieving NSAA ≥0.1 IU/mL for each dosing schedule is presented in **Table 70**. The FDA's simulated response rates were closer to those observed in three cohorts of Study 201, as compared with the Applicant's simulations (**Table 66**). The FDA's results showed that simulated response rates exceed 90% in general patient population at the Applicant's proposed dosing regimens of 25 mg/m^2 every 48 hours for 7 doses per course and 25/25/50 mg/m^2 on MWF for 6 doses per course, regardless of the starting day of first dose (Monday, Wednesday, or Friday).

Table 70 Comparison of Observed and FDA's Simulated Response Rate of Achieving a Therapeutic NSAA Level ≥ 0.1 IU/mL Following Various Dosing Schedules

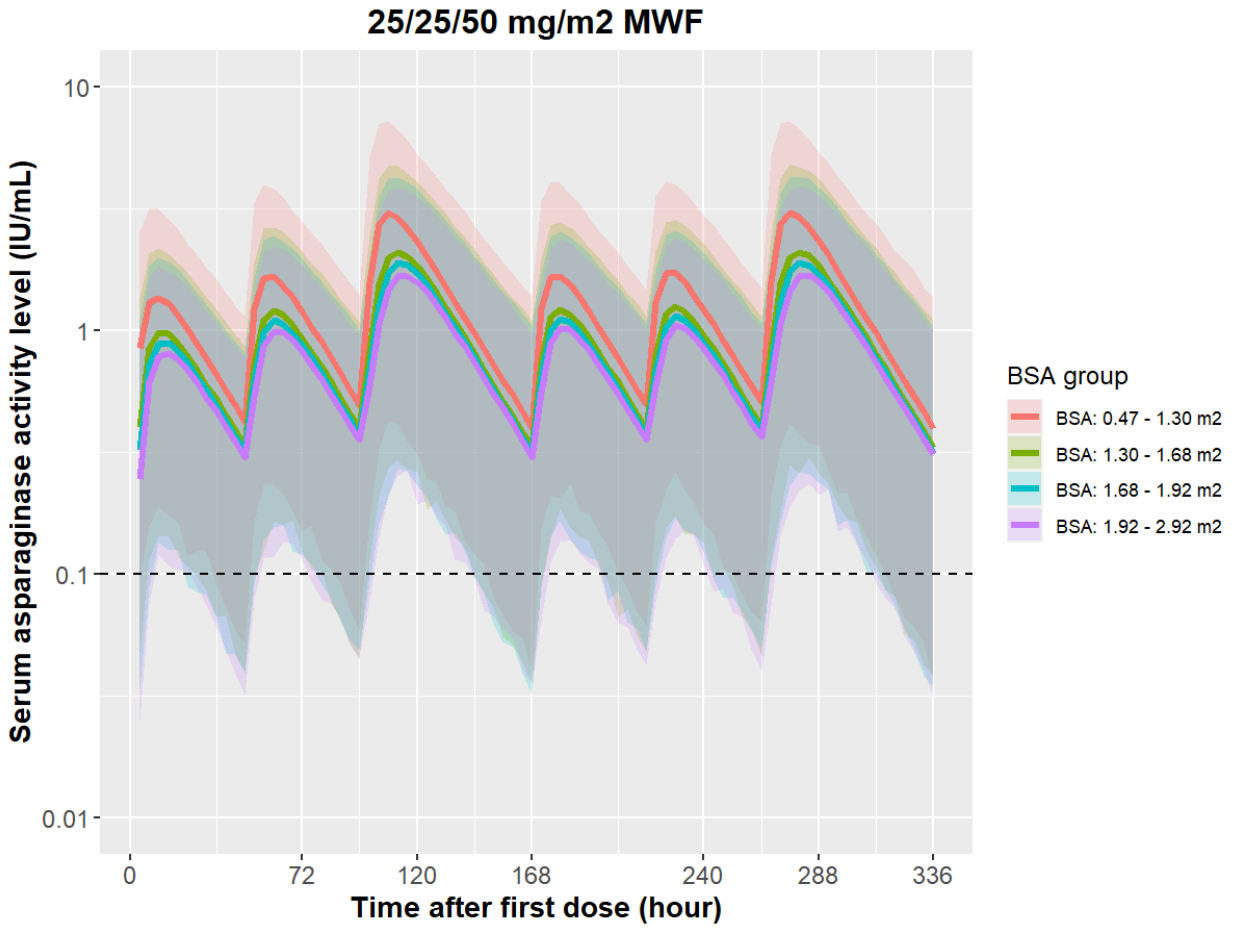
Response rate (NSAA ≥0.1 IU/mL)	25 mg/m^2 MWF x 6	37.5 mg/m^2 MWF x 6	50/25/25 mg/m^2 FMW x 6	25/25/50 mg/m^2 MWF x 6	25 mg/m^2 Q48H X 7
Observation Percentage (n/N)	65.5% (19/29)	80.4% (41/51)	92.3% (12/13)		-
FDA's simulation Mean [95% CI]	67.2% [64.7%, 69.1%]	83.7% [82.1%, 85.4%]	90.6% [89.2%, 91.9%]	91.4% [90.2%, 92.7%]	93.6% [92.6%, 94.6%]

NSAA: Nadir serum asparaginase activity; MWF: Monday/Wednesday/Friday; FMW: Friday/Monday/Wednesday; Q48H: every 48 hours; CI: confidence interval.
Source: FDA's analysis.

Simulation Results by BSA

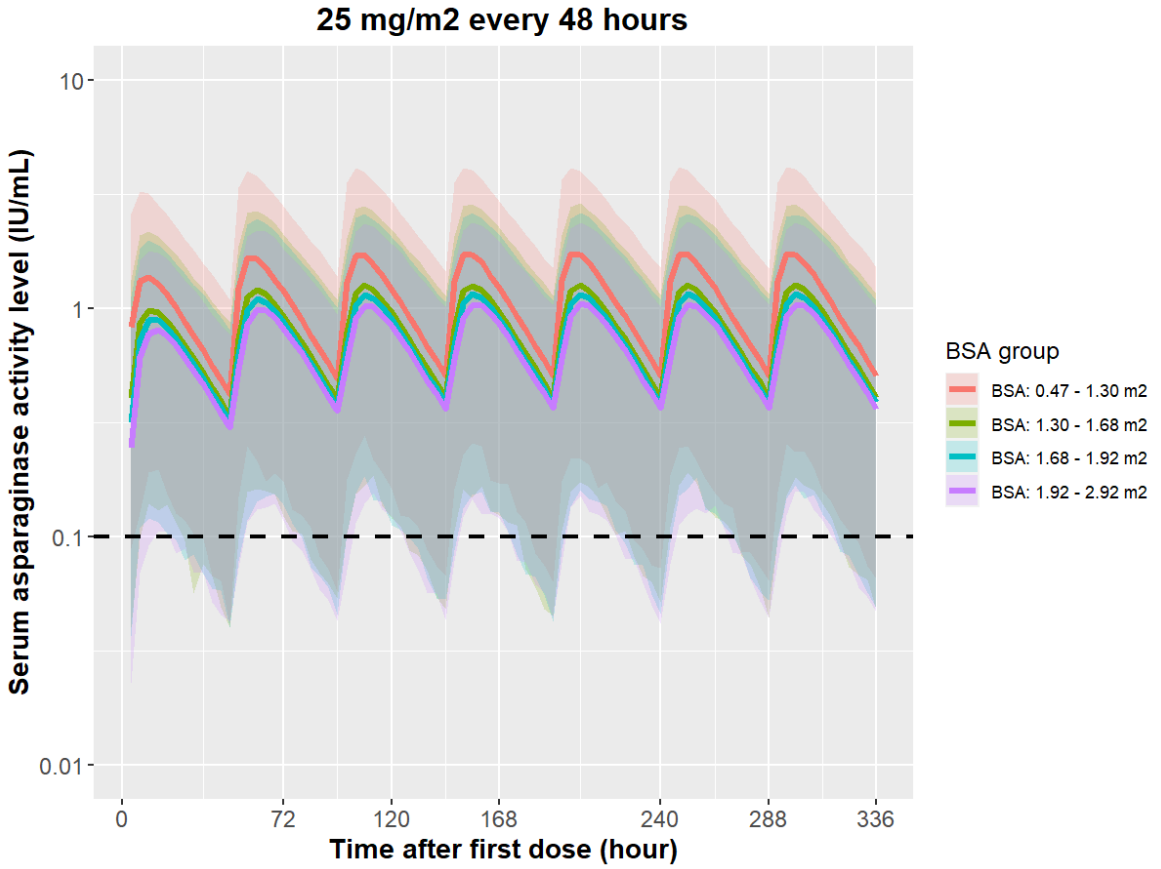
The 2000 subjects in the simulation dataset were divided into four groups with equal number of subjects based on BSA quartiles. The FDA's simulated median and 95% prediction intervals of SAA time profiles were compared across four BSA groups in subjects following 25/25/50 mg/m^2 on Monday/Wednesday/Friday for 6 doses (**Figure 20**) and following 25 mg/m^2 every 48 hours for 7 doses (**Figure 21**). The results showed that the median and 95% prediction intervals of SAA time profiles were largely overlapping across different BSA groups. The simulated response rates of achieving a therapeutic NSAA ≥0.1 IU/mL in four BSA groups all exceed 90% (**Table 71**), which supported the Applicant's proposed BSA-based dosing regimens for JZP-458.

Figure 20 FDA's Simulated Median and 95% Prediction Intervals of SAA Time Profiles in Subjects Following 25/25/50 mg/m2 on Monday/Wednesday/Friday for 6 Doses Stratified by BSA Quartiles



SAA: serum asparaginase activity; MWF: Monday/Wednesday/Friday; BSA: body surface area.
Source: FDA's analysis.

Figure 21 FDA's Simulated Median and 95% Prediction Intervals of SAA Time Profiles in Subjects Following 25mg/m2 Every 48 Hours for 7 Doses Stratified by BSA Quartiles



Source: FDA's analysis.

Table 71 FDA's Simulated Median and 95% Confidence Intervals of Response Rate of Achieving a Therapeutic NSAA in Subjects Following Applicant's Proposed Dosing Regimens Stratified by BSA Quartiles

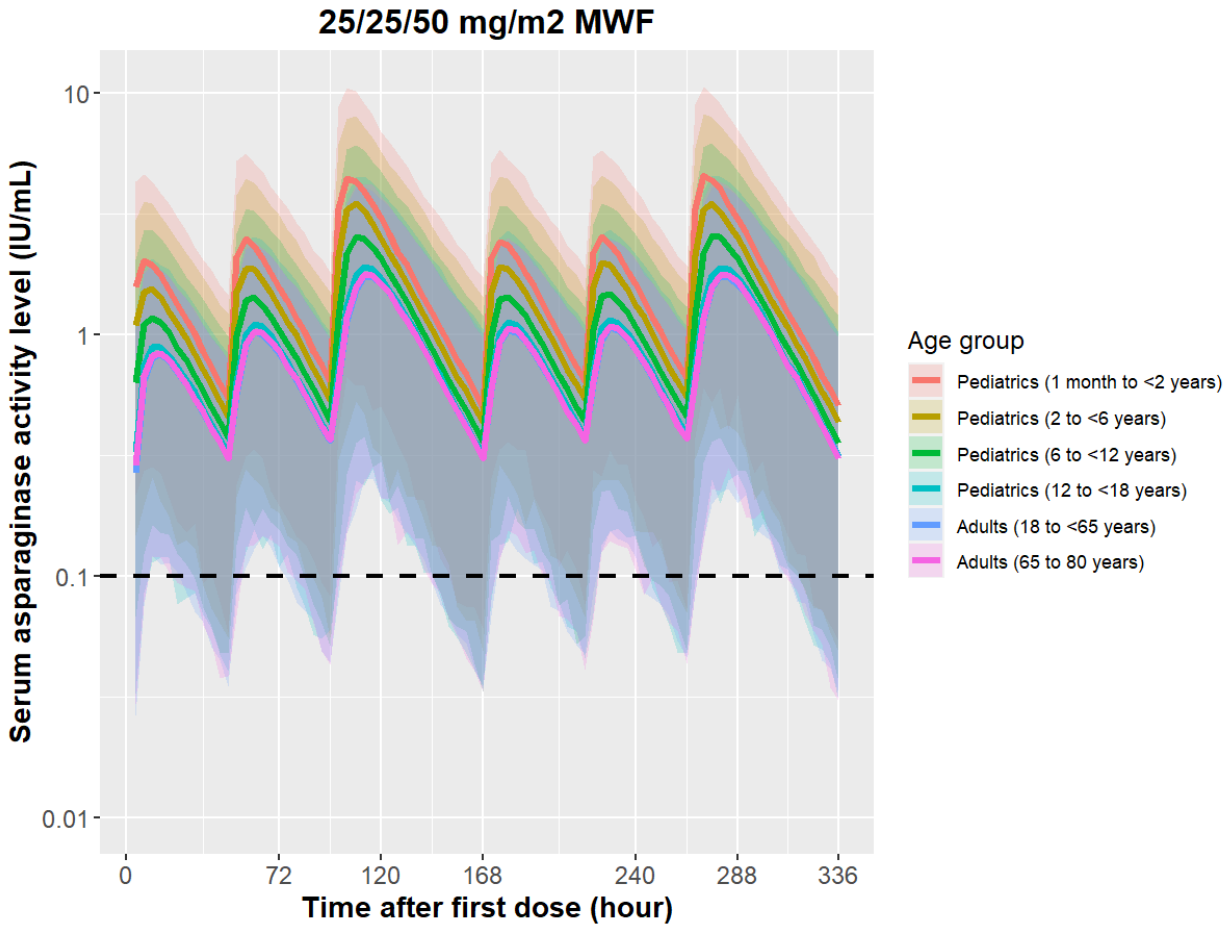
Dosing Regimen	BSA group	Simulated response rate Median [95% CI]
25/25/50 mg/m^2 on Monday/Wednesday/Friday for 6 doses	0.47 - 1.30 m^2	93.3% [90.7%, 95.1%]
	1.30 - 1.68 m^2	91.1% [88.0%, 93.5%]
	1.68 - 1.92 m^2	90.9% [88.3%, 93.7%]
	1.92 - 2.92 m^2	90.3% [88.0%, 92.9%]
25 mg/m^2 every 48 hours for 7 doses	0.47 - 1.30 m^2	95.2% [93.1%, 96.8%]
	1.30 - 1.68 m^2	93.5% [90.9%, 95.7%]
	1.68 - 1.92 m^2	92.9% [90.7%, 94.9%]
	1.92 - 2.92 m^2	92.3% [90.1%, 94.5%]

CI: confidence interval.
Source: FDA's analysis.

Simulation Results by Age

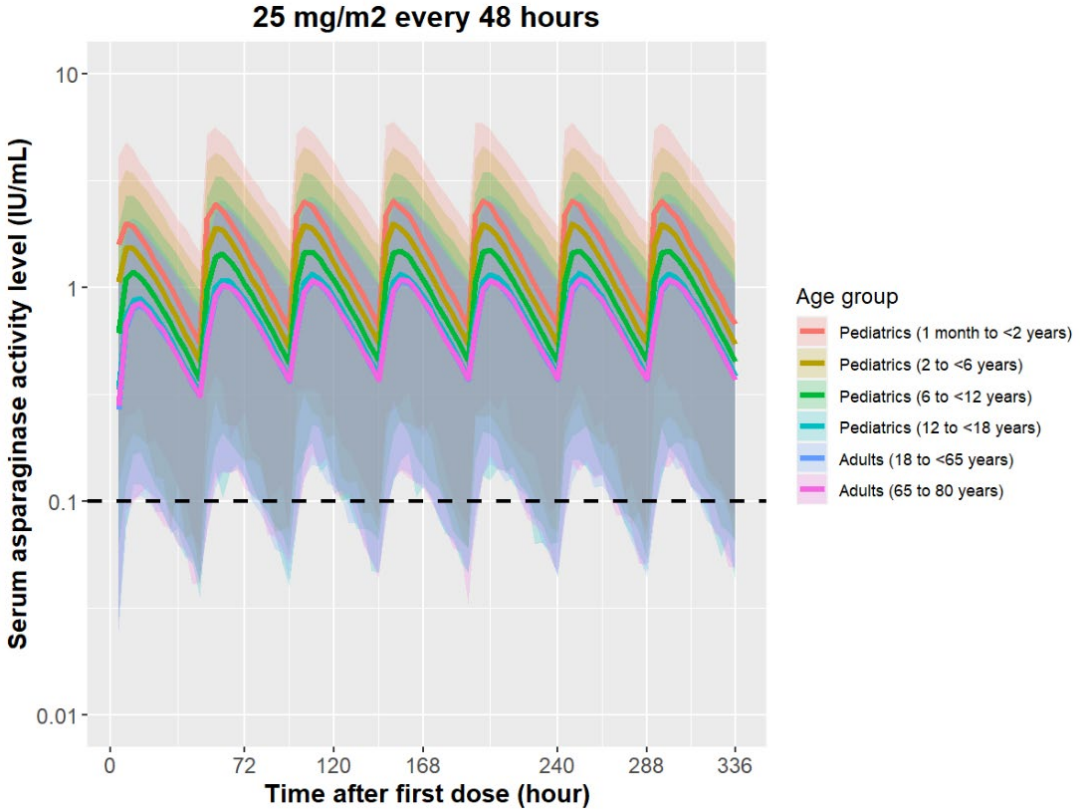
As an enzyme product, JZP-458 is metabolized into small peptides by catabolic pathways in the body. The PK of SAA is not expected to be significantly different in pediatrics less than 1 years of age compared to that in older groups after the effect of body size is accounted for. To support extrapolation of efficacy down to patients 1 month old, FDA conducted additional simulations using the FDA's final PopPK model to predict SAA response across age range from 1 month to 80 years old. The simulation dataset included a virtual population generated by resampling without replacement from the NHANES 2017-March 2020 pre-pandemic database. The final dataset contains 2000 subjects, including 1000 pediatric subjects (155 from 1 month to <2 years of age, 248 from 2 to <6 years of age, 328 from 6 to <12 years of age, and 269 from 12 to <18 years of age) and 1000 adult subjects (739 from 18 to <65 years of age, and 261 from 65 to 80 years of age). The FDA's simulated SAA time profiles were compared across age groups in subjects following 25/25/50 mg/m^2 on MWF for 6 doses (**Figure 22**) and following 25 mg/m^2 Q48 hours for 7 doses (**Figure 23**). The results showed that the median and 95% prediction intervals of SAA time profiles were largely overlapping across different age groups. The simulated response rates of achieving a therapeutic NSAA ≥0.1 IU/mL in six age groups all exceed 90% (**Table 72**), which suggested that no significant difference is expected in probability of achieving a therapeutic NSAA ≥0.1 IU/mL based on age (1 month to 80 years) following the proposed BSA-based dosing regimens.

Figure 22 FDA's Simulated Median and 95% Prediction Intervals of SAA Time Profiles in Subjects Following 25/25/50 mg/m^2 on Monday/Wednesday/Friday for 6 Doses Stratified by Six Age Groups



SAA: serum asparaginase activity; MWF: Monday/Wednesday/Friday.
Source: FDA's analysis.

Figure 23 FDA's Simulated Median and 95% Prediction Intervals of SAA Time Profiles in Subjects Following 25mg/m^2 Every 48 Hours for 7 Doses Stratified by Six Age Groups



Source: FDA's analysis.

Table 72 FDA's Simulated Median and 95% Confidence Intervals of Response Rate of Achieving a Therapeutic NSAA in Subjects Following Applicant's Proposed Dosing Regimens Stratified by Six Age Groups

Dosing Regimen	Age group	Simulated response rate Median [95% CI]
25/25/50 mg/m^2 on Monday/Wednesday/Friday for 6 doses	1 month - <2 years of age	94.8% [91.6%, 98.7%]
	2 - <6 years of age	94.0% [91.1%, 96.8%]
	6 - <12 years of age	93.2% [90.7%, 94.9%]
	12 - <18 years of age	90.8% [88.0%, 93.5%]
	18 - <65 years of age	90.6% [88.5%, 92.6%]
	65 - <80 years of age	90.8% [87.0%, 94.3%]
25 mg/m^2 every 48 hours for 7 doses	1 month - <2 years of age	96.8% [94.2%, 98.7%]
	2 - <6 years of age	96.0% [93.1%, 98.0%]
	6 - <12 years of age	94.5% [91.8%, 96.6%]
	12 - <18 years of age	93.3% [89.6%, 95.5%]
	18 - <65 years of age	92.6% [90.8%, 94.5%]
	65 - <80 years of age	92.5% [89.7%, 95.4%]

CI: confidence interval.
Source: FDA's analysis.

14.4.3.2. FDA's updated population PK model using data with cut-off date of 1/11/2021

Using updated data (cut-off date of 11 Jan 2021) from Study 201, sensitivity analysis was conducted by re-running the FDA's final PopPK model. The updated PopPK dataset included 1342 SAA data both above and below LLOQ from 102 patients (33 from Cohort 1a, 53 from Cohort 1b and 16 from Cohort 1c) in Study 201. The parameter estimates of the updated PopPK model are presented in **Table 73**, which are generally comparable to the FDA's original final PopPK model.

Table 73 Comparison of Parameter Estimates from the Final PopPK Models based on Original and Updated datasets in Patients from Study 201

Parameter	Description	FDA's original model		FDA's updated model	
		Estimate	RSE%	Estimate	RSE%
Fixed effect					
CL/F	Apparent clearance (L/hr)	0.375	4.4%	0.392	4.1%
V/F	Apparent volume of distribution (L)	1.67	7.7%	2.01	6.8%
R1	Zero-order absorption rate (IU/hr)	2160 (Fix)	-	2160 (Fix)	-
Ka	First-order absorption rate constant (hr^{-1})	0.0364 (Fix)	-	0.0364 (Fix)	-
CL/F_BSA	Effect of BSA on CL/F	1.51	5.5%	0.996	4.3%
V/F _BSA	Effect of BSA on V/F	1.84	9.3%	1.33	8.4%
CL/F _RACE	% difference in CL/F for Black and Asian subjects vs. other races	-28.8%	20.2%	-32.9%	14.3%
Inter-individual variability (IIV)					
$\eta_{CL/F}$	IIV for CL/F (CV%)	26.3%	10.5%	40.2%	6.5%
$\eta_{V/F}$	IIV for V/F (CV%)	46.5%	20.8%	69.7%	17.1%
η_{Ka}	IIV for Ka (CV%)	18.6%	19.1%	24%	17.0%
η_{R1}	IIV for R1 (CV%)	49.1%	13.4%	47.2%	9.0%
Corr_$\eta_{CL/F}$ _η_V	Correlation between $\eta_{CL/F}$ and $\eta_{V/F}$	62.7%	-	88.7%	-
Corr_$\eta_{CL/F}$ _η_{Ka}	Correlation between $\eta_{CL/F}$ and η_{Ka}	68.6%	-	69.6%	-
Corr_$\eta_{V/F}$ _η_{Ka}	Correlation between $\eta_{V/F}$ and η_{Ka}	17.5%	-	39.1%	-
Random effect					
ε_{prop}	Standard deviation of proportional random effect	0.438	2.4%	0.524	2.0%
ε_{add}	Standard deviation of additive random effect	0.011	18.1%	0.0128	13.4%

RSE: relative standard error; CV: coefficient of variation.
Original model: $\mathrm{CL/F} = 0.375 \times (\mathrm{BSA}/1.16)^{1.51} \times 0.712$ if Black and Asian patients; $\mathrm{CL/F} = 0.375 \times (\mathrm{BSA}/1.16)^{1.51}$ if White and other race subjects. $\mathrm{V/F} = 1.67 \times (\mathrm{BSA}/1.16)$
Updated model: $\mathrm{CL/F} = 0.392 \times (\mathrm{BSA}/1.21)^{0.996} \times 0.671$ if Black and Asian patients; $\mathrm{CL/F} = 0.392 \times (\mathrm{BSA}/1.21)^{0.996}$ if White and other race subjects. $\mathrm{V/F} = 2.01 \times (\mathrm{BSA}/1.21)^{1.33}$
Source: FDA's analysis.

The updated PopPK model was used to generate individual PK metrics for subsequent exposure-response analysis. The individual PK metrics of 102 patients from Study 201 are summarized in **Table 74**. Average concentration of SAA (C_{mean}) up to the first adverse event was calculated as the cumulative AUC divided by the treatment duration up to the time of the first occurrence of an adverse event. For patients who did not experience an adverse event, SAA C_{mean} was calculated as the cumulative AUC divided by the duration of the treatment period. Durations between two courses without any treatment were not included.

Table 74 Summary of Individual PK Metrics based on FDA's Updated Final PopPK Model in Patients from Cohorts 1a, 1b and 1c in Study 201

Cohort	Dose	Parameter	Geometric mean (CV%)
1a (n = 33)	25 mg/m^2 MWF	C_{max} in Cycle 1 (IU/mL)	2.71 (40.1%)
		$AUC_{0\text{-}336h}$ in Cycle 1 (IU*h/mL)	223.5 (53.0%)
		C_{mean} during treatment (IU /mL)	0.741 (38.8%)
		C_{mean} up to first hypersensitivity event (IU /mL)	0.764 (39.0%)
		C_{mean} up to first hepatotoxicity event (IU /mL)	0.788 (41.1%)
		C_{mean} up to first pancreatitis event (IU /mL)	0.757 (38.1%)
		C_{mean} up to first thrombosis event (IU /mL)	0.757 (38.2%)
1b (n = 53)	37.5 mg/m^2 MWF	C_{max} in Cycle 1 (IU/mL)	4.57 (32.2%)
		$AUC_{0\text{-}336h}$ in Cycle 1 (IU*h/mL)	396.2 (34.2%)
		C_{mean} during treatment (IU /mL)	1.21 (34.7%)
		C_{mean} up to first hypersensitivity event (IU /mL)	1.29 (37.4%)
		C_{mean} up to first hepatotoxicity event (IU /mL)	1.31 (38.7%)
		C_{mean} up to first pancreatitis event (IU /mL)	1.22 (34.7%)
		C_{mean} up to first thrombosis event (IU /mL)	1.22 (34.4%)
1c (n = 16)	25/25/50 mg/m^2 MWF	C_{max} in Cycle 1 (IU/mL)	4.47 (50.9%)
		$AUC_{0\text{-}336h}$ in Cycle 1 (IU*h/mL)	308.8 (48.1%)
		C_{mean} during treatment (IU /mL)	0.465 (48.2%)
		C_{mean} up to first hypersensitivity event (IU /mL)	0.984 (46.3%)
		C_{mean} up to first hepatotoxicity event (IU /mL)	1.02 (56.1%)
		C_{mean} up to first pancreatitis event (IU /mL)	0.951 (46.7%)
		C_{mean} up to first thrombosis event (IU /mL)	0.951 (46.7%)

C_{max}: maximum SAA concentration; C_{mean}: average concentration; AUC: area under SAA time-concentration profile.
Source: FDA's analysis.

14.4.4. Summary of Applicant's Exposure-Response Analysis for Efficacy

The Applicant conducted logistic regression analysis for depletion of L-asparagine and L-glutamine at last sample for Course 1 vs. AUC for 2 weeks (AUC_{336}) during Course 1 in 82 patients from Study 201. The results indicated that there was a statistically significant (p=0.0008) E-R relationship for probability of depletion for L-asparagine.

Figure 24 Plot of Predicted Probability and Observed Proportion of L-asparagine Depletion at Last Sample for Course 1 versus AUC_{336}

(b) (4)

Reviewer's Comments: *Due to the significant limitations in bioanalytical assay Method TM.2457 for accurately quantifying depletion of L-asparagine by L-asparaginase (refer to Section 14.4.1), the E-R relationship for depletion of L-asparagine is not recommended to be included in the labeling.*

14.4.5. Summary of Applicant's Exposure-Response Analysis for Safety

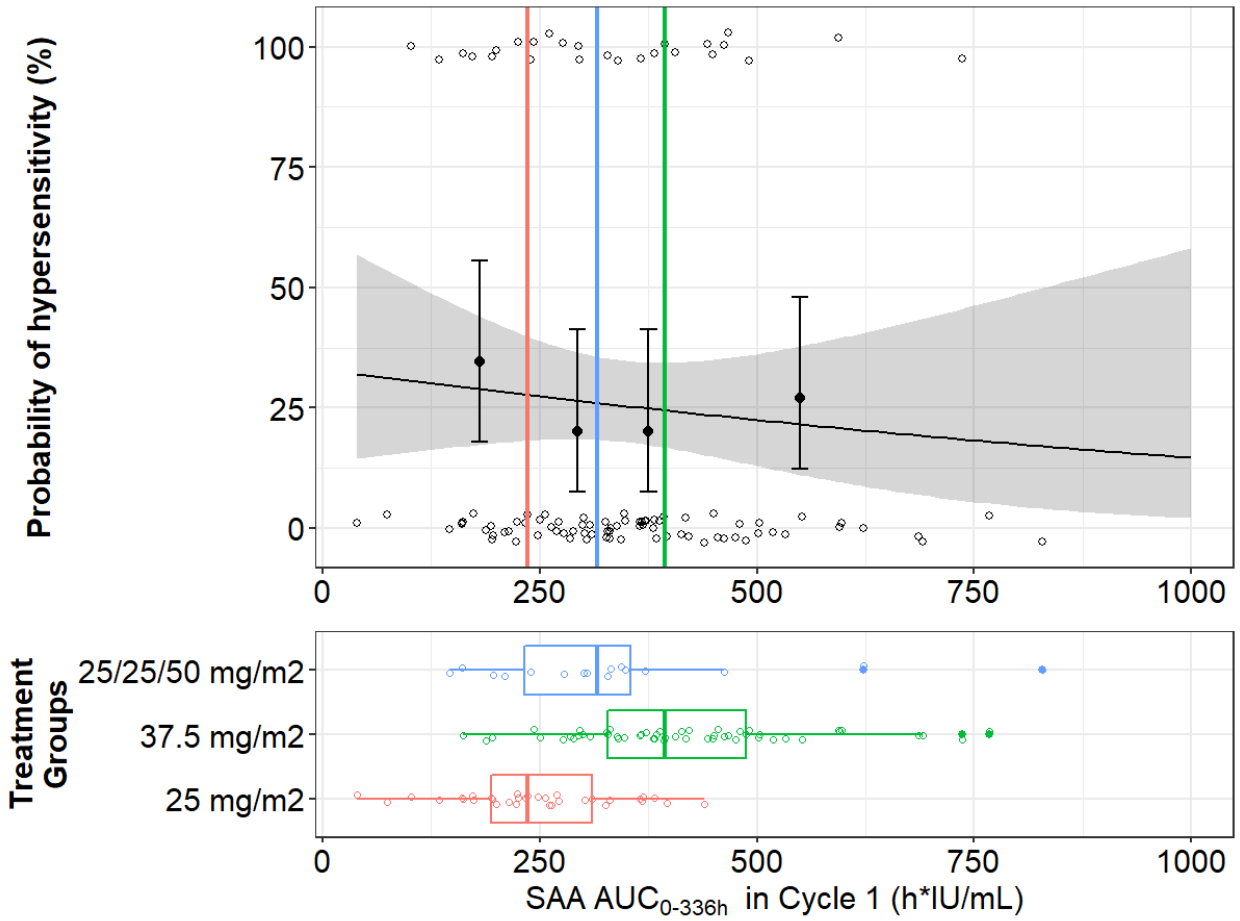
The Applicant conducted logistic regression analysis for hypersensitivity and hepatotoxicity vs. the following SAA PK metrics: C_{max} after the 6th dose ($C_{max,6}$), AUC for 2 weeks (AUC_{336}) , trough SAA following the last 48-hour dosing interval ($C_{48,L}$), and trough SAA following the last 72-hour dosing interval ($C_{72,L}$) during Course 1 or during study in 82 patients from Study 201. The Applicant concluded that there appeared to be no relationship between any of the PK exposure parameters (AUC_{336}, $C_{max,6}$, $C_{48,L}$ and $C_{72,L}$) and the probability of drug-related AEs of hypersensitivity, hepatotoxicity, pancreatitis, thrombosis, and hypertriglyceridemia either during the study or for Course 1.

Reviewer's Comments: *FDA's independent E-R analysis for safety confirmed that there was no apparent E-R relationship between any of the PK exposure parameters (AUC_{0-336h} in Cycle 1, C_{max} in Cycle 1, and C_{mean} during treatment) and probability of hypersensitivity, hepatotoxicity, pancreatitis, and thrombosis. However, there was a trend of E-R indicating earlier onset of hypersensitivity, hepatotoxicity, pancreatitis, and thrombosis with higher SAA average concentration from the first JZP-458 dose up to the occurrence of the first adverse event. See Section 14.4.6 for details.*

14.4.6. FDA's Exposure-Response Analysis for Safety

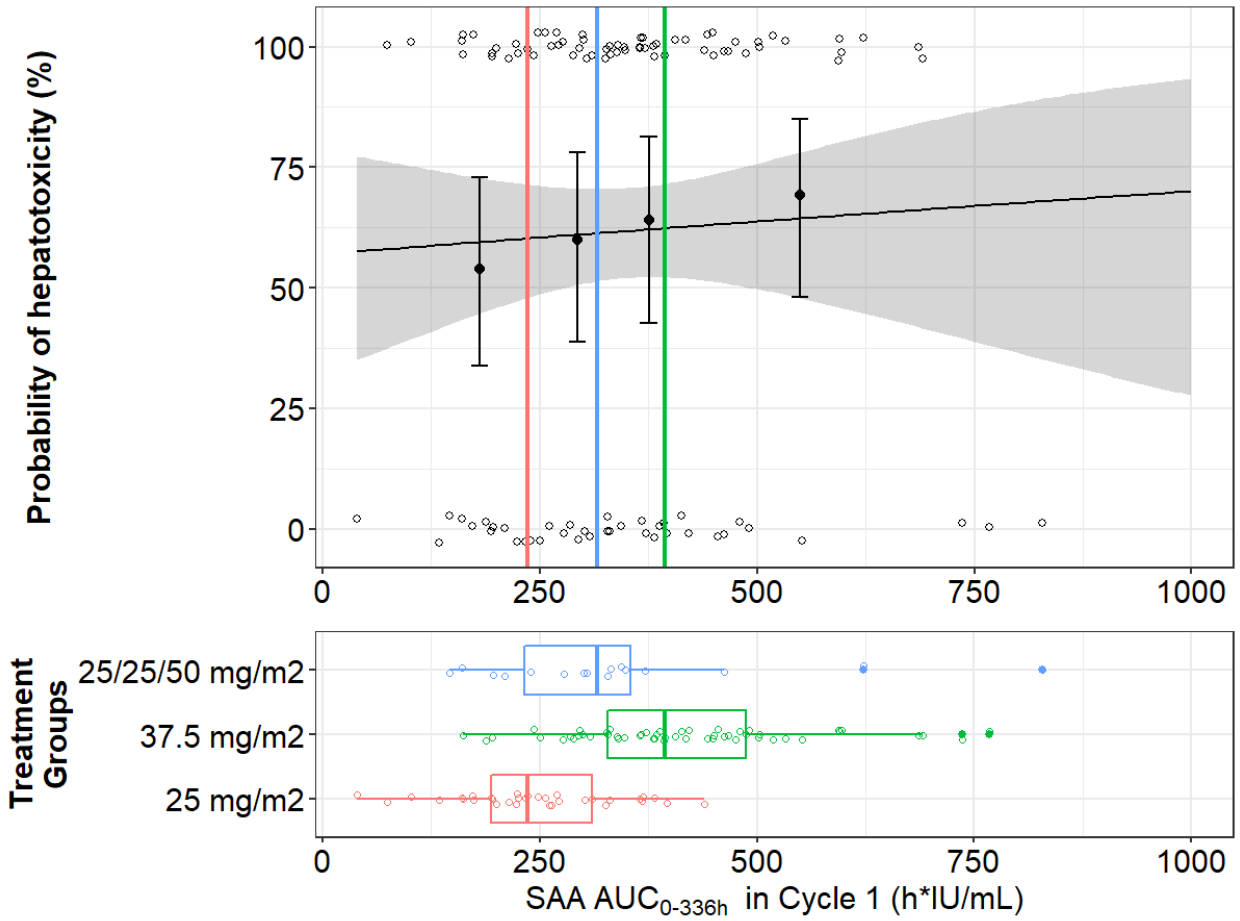
FDA conducted independent E-R analyses for probability and time to first event of hypersensitivity, hepatotoxicity, pancreatitis, and thrombosis in 102 patients from Study 201 using derived SAA PK metrics listed in **Table 74**. FDA confirmed that there was no apparent E-R relationship between any of the PK exposure parameters (AUC_{0-336h} in Cycle 1, C_{max} in Cycle 1, and C_{mean} during treatment) and probability of hypersensitivity, hepatotoxicity, pancreatitis, and thrombosis. As examples, E-R relationships for probability of hypersensitivity, hepatotoxicity, pancreatitis, and thrombosis against AUC_{0-336h} in Cycle 1 are illustrated in **Figure 25**, **Figure 26**, **Figure 27**, and **Figure 28**, respectively. Age, BSA, weight, height, sex, race, ethnicity, disease type, ADA, or NAb was not identified as a statistically significant covariate on the E-R relationships. Although Black and Asian patients tended to have lower CL/F and higher SAA exposure compared to White patients, no significant difference in adverse events was observed across these race groups. Therefore, no dosage modification is recommended based on race.

Figure 25 FDA's Exposure-Response Analysis for Probability of Hypersensitivity Adverse Event versus $AUC_{0\text{-}336\ h}$ in Cycle 1 in Patients from Study 201



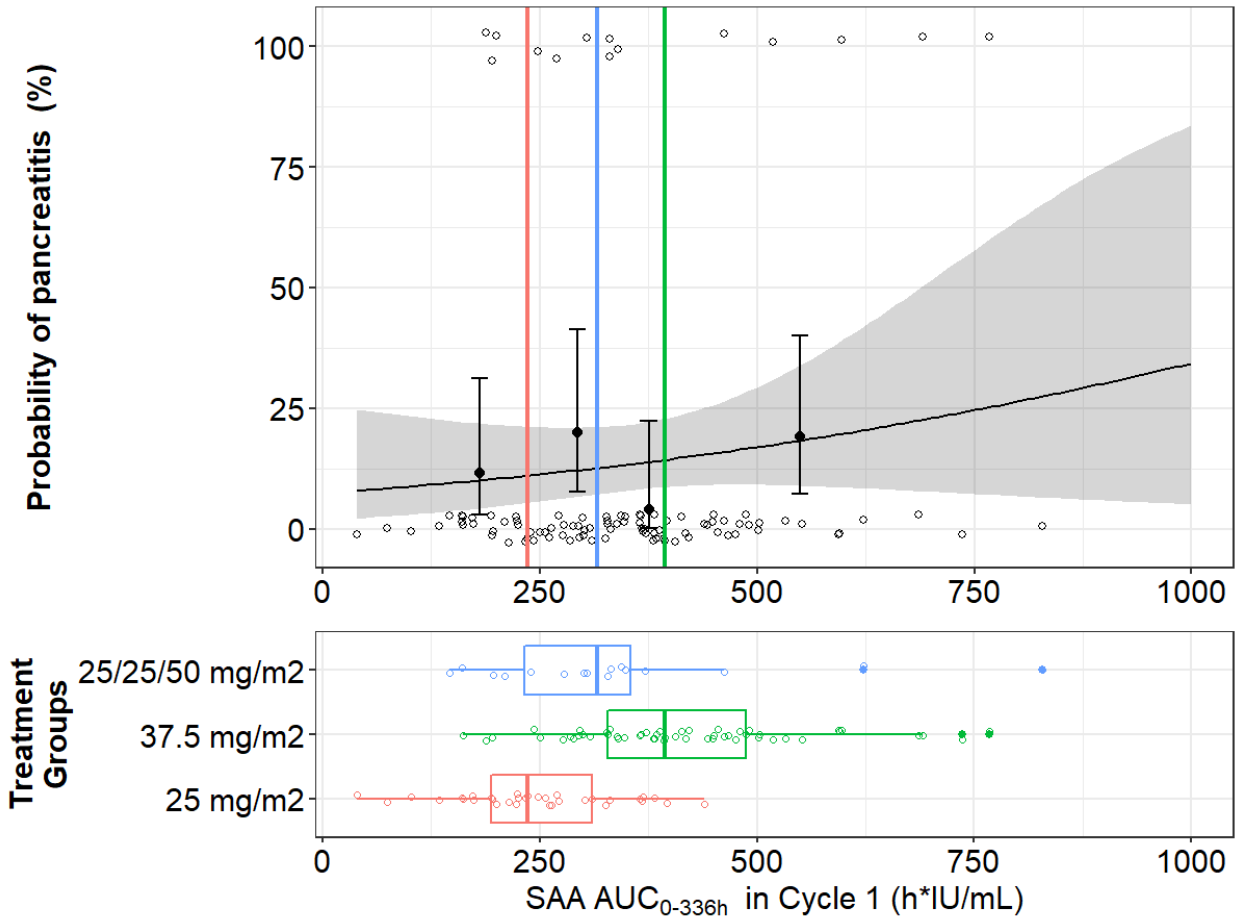
Black open dots: observed hypersensitivity adverse event. Black curve and gray area: mean and 95% confidence interval of the model predicted probability of hypersensitivity adverse event. Black solid dots and bars: mean and 95% confidence interval of observed proportions of hypersensitivity adverse events in four quartiles of SAA $AUC_{0\text{-}336h}$ in Cycle 1. Red open dots and box: SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 25 mg/m^2 MWF. Green open dots and box: SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 37.5 mg/m^2 MWF. Blue open dots and box: SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 25/25/50 mg/m^2 MWF. Red line: median SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 25 mg/m^2 MWF. Green line: median SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 37.5 mg/m^2 MWF. Blue line: median SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 25/25/50 mg/m^2 MWF.
Source: FDA's analysis.

Figure 26 FDA's Exposure-Response Analysis for Probability of Hepatotoxicity Adverse Event versus $AUC_{0\text{-}336\ h}$ in Cycle 1 in Patients from Study 201



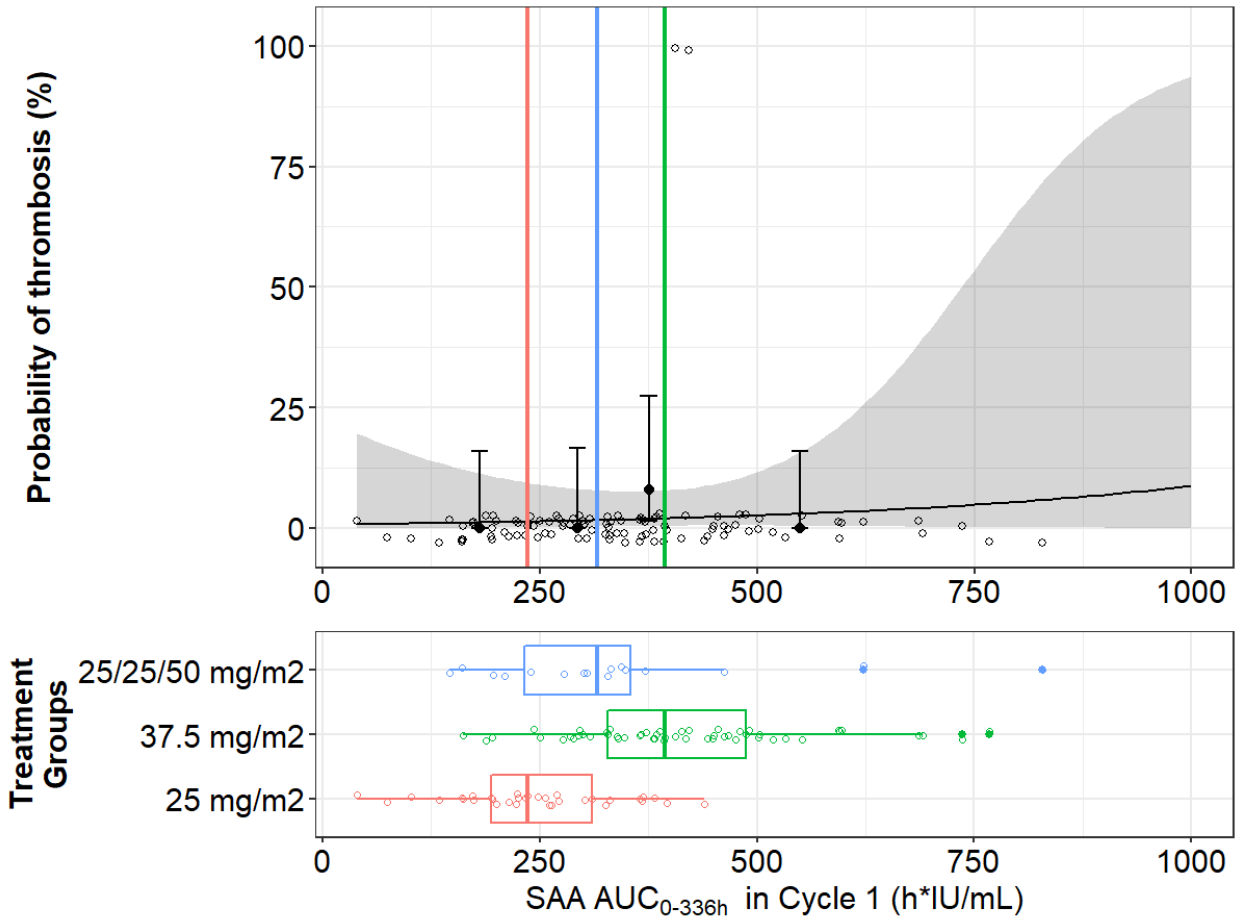
Black open dots: observed hepatotoxicity adverse event. Black curve and gray area: mean and 95% confidence interval of the model predicted probability of hepatotoxicity adverse event. Black solid dots and bars: mean and 95% confidence interval of observed proportions of hepatotoxicity adverse events in four quartiles of SAA $AUC_{0\text{-}336h}$ in Cycle 1. Red open dots and box: SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 25 mg/m^2 MWF. Green open dots and box: SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 37.5 mg/m^2 MWF. Blue open dots and box: SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 25/25/50 mg/m^2 MWF. Red line: median SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 25 mg/m^2 MWF. Green line: median SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 37.5 mg/m^2 MWF. Blue line: median SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 25/25/50 mg/m^2 MWF.
Source: FDA's analysis.

Figure 27 FDA's Exposure-Response Analysis for Probability of Pancreatitis Adverse Event versus $AUC_{0\text{-}336\ h}$ in Cycle 1 in Patients from Study 201



Black open dots: observed pancreatitis adverse event. Black curve and gray area: mean and 95% confidence interval of the model predicted probability of pancreatitis adverse event. Black solid dots and bars: mean and 95% confidence interval of observed proportions of pancreatitis adverse events in four quartiles of SAA $AUC_{0\text{-}336h}$ in Cycle 1. Red open dots and box: SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 25 mg/m^2 MWF. Green open dots and box: SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 37.5 mg/m^2 MWF. Blue open dots and box: SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 25/25/50 mg/m^2 MWF. Red line: median SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 25 mg/m^2 MWF. Green line: median SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 37.5 mg/m^2 MWF. Blue line: median SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 25/25/50 mg/m^2 MWF.
Source: FDA's analysis.

Figure 28 FDA's Exposure-Response Analysis for Probability of Thrombosis Adverse Event versus $AUC_{0\text{-}336\ h}$ in Cycle 1 in Patients from Study 201

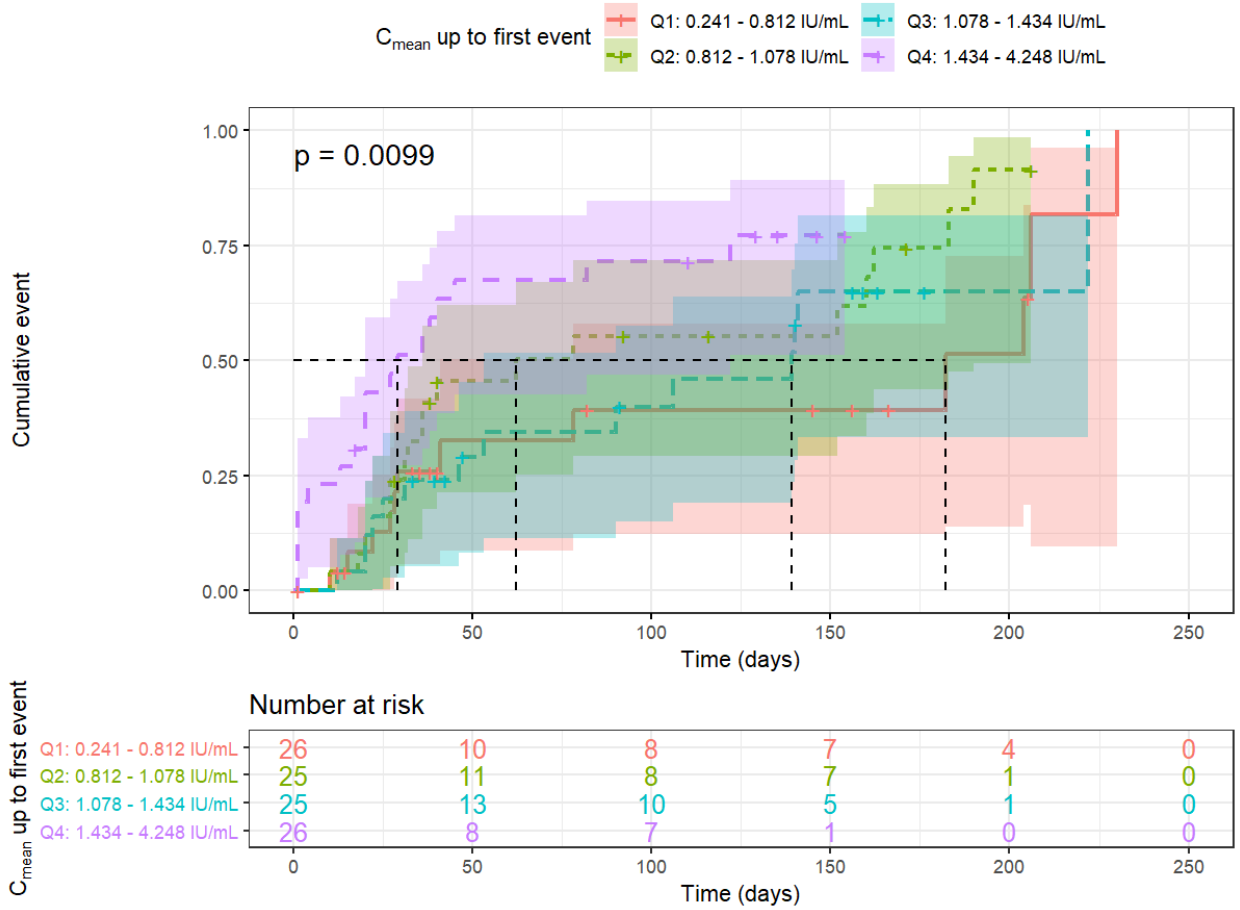


Black open dots: observed thrombosis adverse event. Black curve and gray area: mean and 95% confidence interval of the model predicted probability of thrombosis adverse event. Black solid dots and bars: mean and 95% confidence interval of observed proportions of thrombosis adverse events in four quartiles of SAA $AUC_{0\text{-}336h}$ in Cycle 1. Red open dots and box: SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 25 mg/m^2 MWF. Green open dots and box: SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 37.5 mg/m^2 MWF. Blue open dots and box: SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 25/25/50 mg/m^2 MWF. Red line: median SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 25 mg/m^2 MWF. Green line: median SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 37.5 mg/m^2 MWF. Blue line: median SAA $AUC_{0\text{-}336h}$ in Cycle 1 at 25/25/50 mg/m^2 MWF.
Source: FDA's analysis.

Based on Kaplan-Meier curves of the time to first event stratified by exposure quartiles, there appear to be a trend of E-R towards significantly earlier onset of hepatotoxicity (Figure 29) with higher SAA C_{mean} from the first JZP-458 dose up to the occurrence of the first adverse event. This trend was not observed for hypersensitivity (Figure 30), pancreatitis (Figure 31), or thrombosis (Figure 32). There was no apparent trend in time to first event of any of these four safety endpoints when using other PK metrics like C_{max} in Cycle 1 and $AUC_{0\text{-}336h}$ in Cycle 1. However, it's

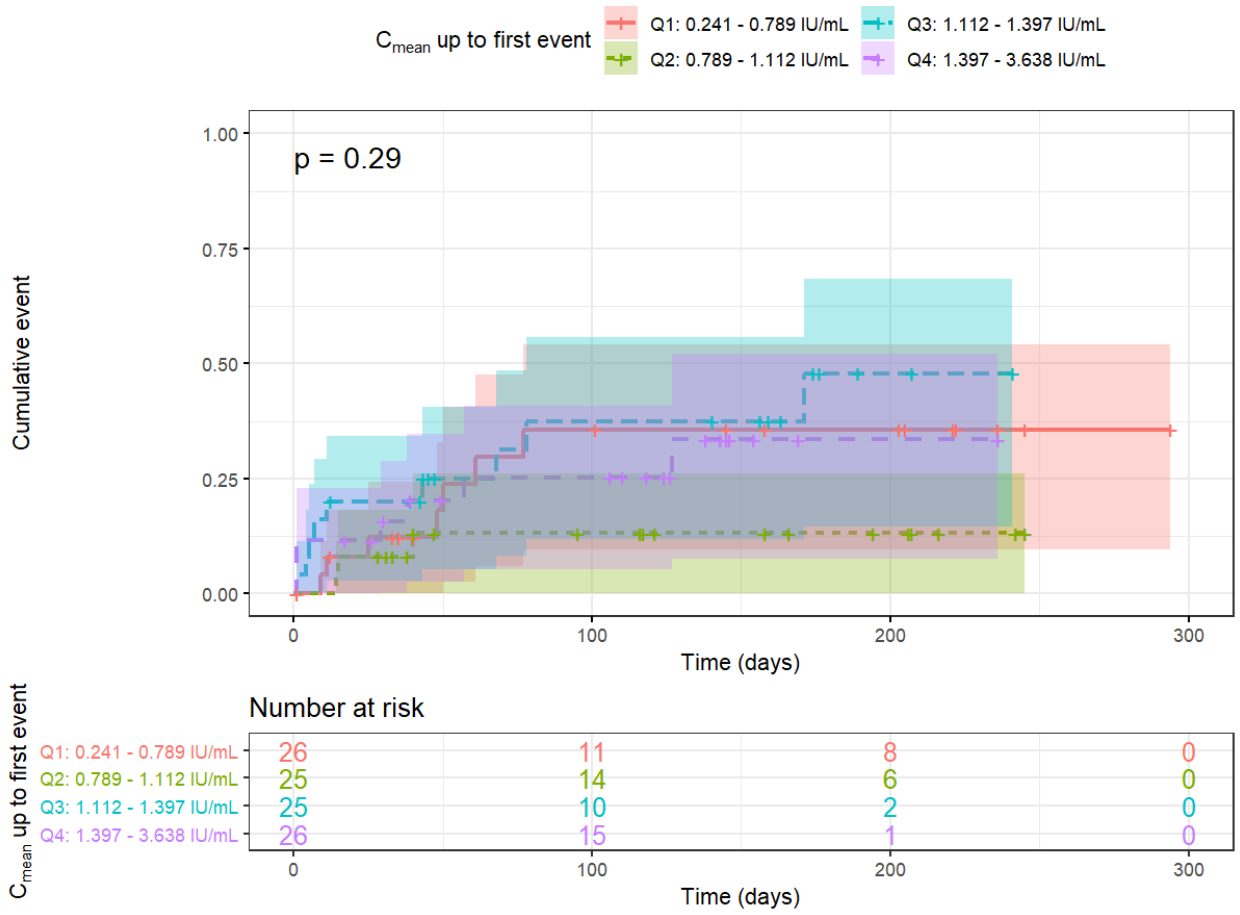
worth noting that the observed E-R relationships were potentially confounded by considerable heterogeneity among patients receiving JZP-458, including but not limited to: varying chemotherapy treatment plans, different points of JZP-458 initiation in the overall treatment regimen, and varying intervals between each course of JZP-458. Given the variability in overall treatment plans among patients treated with JZP-458, the relative contribution of JZP-458 dosage regimen to the observed E-R relationships for safety is not clear.

Figure 29 FDA's Kaplan-Meier Curves of the Time to the First Hepatotoxicity Adverse Event Stratified by the SAA Average Concentration Up to the First Event



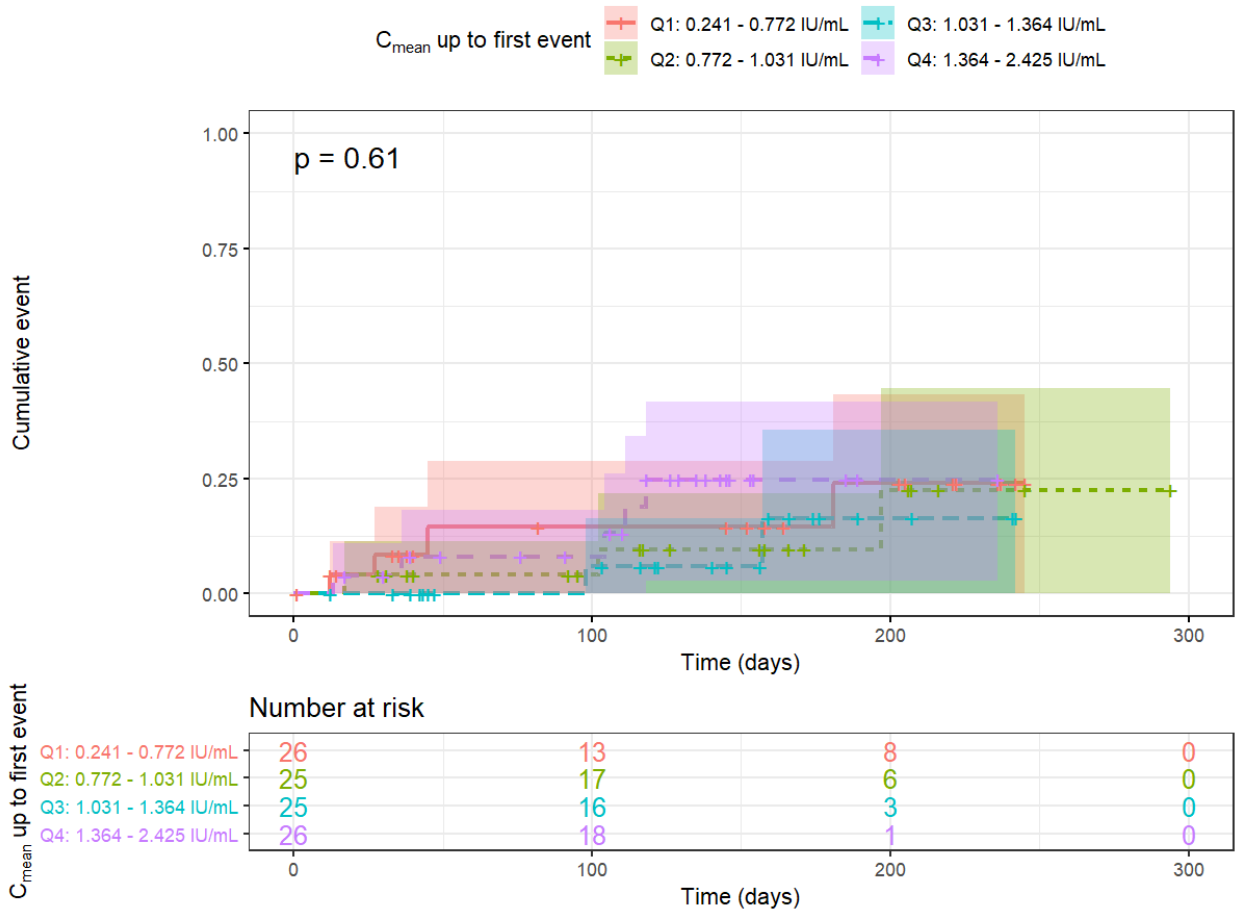
Source: FDA's analysis.

Figure 30 FDA's Kaplan-Meier Curves of the Time to the First Hypersensitivity Adverse Event Stratified by the SAA Average Concentration Up to the First Event



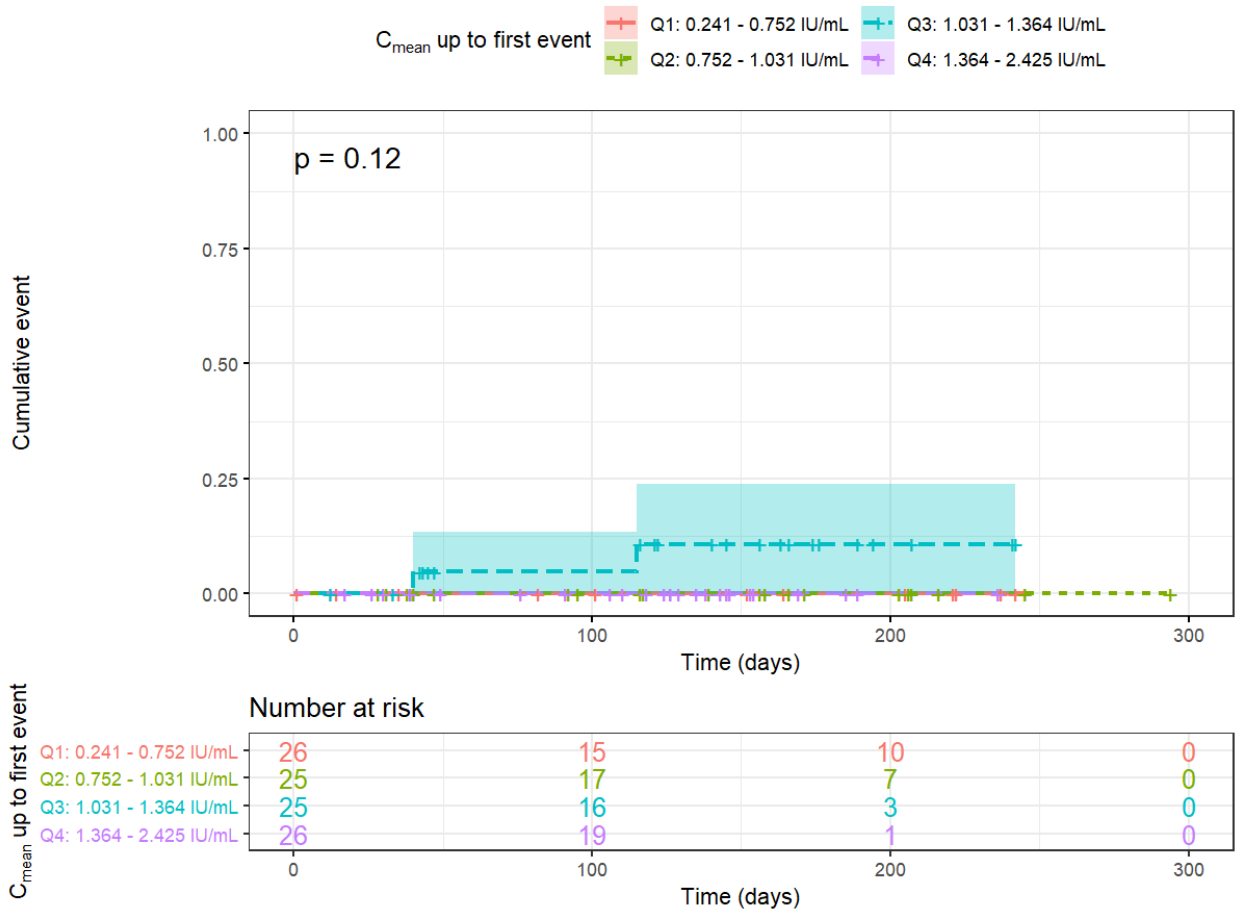
Source: FDA's analysis.

Figure 31 FDA's Kaplan-Meier Curves of the Time to the First Pancreatitis Adverse Event Stratified by the SAA Average Concentration Up to the First Event



Source: FDA's analysis.

Figure 32 FDA's Kaplan-Meier Curves of the Time to the First Thrombosis Adverse Event Stratified by the SAA Average Concentration Up to the First Event



Source: FDA's analysis.

14.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
None.

15 DIVISION DIRECTOR (DHM1)

16 OFFICE DIRECTOR (OR DESIGNATED SIGNATORY AUTHORITY)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

BLA Multidisciplinary Review and Evaluation
BLA 761179
Rylaze (JZP-458)

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Michael Manning, PhD	OOD/DHOT	Sections: 5	**Select one:** ✓ Authored ___ Approved
	Signature: Michael L. Manning -S Digitally signed by Michael L. Manning -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001207192, cn=Michael L. Manning -S Date: 2021.06.17 11:12:14 -04'00'			
Nonclinical Supervisor	Brenda Gehrke, PhD	OOD/DHOT	Sections: 5	**Select one:** ___ Authored ✓ Approved
	Signature: Brenda Gehrke -S Digitally signed by Brenda Gehrke -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Brenda Gehrke -S, 0.9.2342.19200300.100.1.1=0012062023 Date: 2021.06.15 17:18:01 -04'00'			
Nonclinical Deputy Director	Haleh Saber, PhD, MS	OOD/DHOT	Sections: 5	**Select one:** ___ Authored ✓ Approved
	Signature: Haleh Saber -S Digitally signed by Haleh Saber -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Haleh Saber -S, 0.9.2342.19200300.100.1.1=1300212858 Date: 2021.06.15 17:36:09 -04'00'			
Clinical Pharmacology Reviewer	Lauren Price, PharmD	OCP/DCPI	Sections: 6, 14	**Select one:** ✓ Authored ___ Approved
	Signature: Lauren Price -S Digitally signed by Lauren Price -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lauren Price -S, 0.9.2342.19200300.100.1.1=2001978474 Date: 2021.06.16 12:58:20 -04'00'			
Clinical Pharmacology Team Leader	Xiling Jiang, PhD	OCP/DCPI	Sections: 6, 14	**Select one:** ___ Authored ✓ Approved
	Signature: Xiling Jiang -S Digitally signed by Xiling Jiang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiling Jiang -S, 0.9.2342.19200300.100.1.1=2001167656 Date: 2021.06.16 13:07:58 -04'00'			

BLA Multidisciplinary Review and Evaluation
BLA 761179
Rylaze (JZP-458)

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Deputy Director	Olanrewaju Okusanya, PharmD, MS	OCP/DCPI	Sections: 6, 14	**Select one:** ___ Authored ✓ Approved
	Signature: Olanrewaju Okusanya -S Digitally signed by Olanrewaju Okusanya -S Date: 2021.06.16 10:14:24 -04'00'			
Clinical Pharmacology Division Director	Brian Booth, PhD	OCP/DCPI	Sections: 6, 14	**Select one:** ___ Authored ✓ Approved
	Signature: Brian P. Booth -S Digitally signed by Brian P. Booth -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Brian P. Booth -S, 0.9.2342.19200300.100.1.1=1300137436 Date: 2021.06.16 10:24:27 -04'00'			
Pharmacometrics Reviewer	Liang Li, PhD	OCP/DPM	Sections: 6, 14	**Select one:** ✓ Authored ___ Approved
	Signature: Liang Li -S Digitally signed by Liang Li -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Liang Li -S, 0.9.2342.19200300.100.1.1=2001459144 Date: 2021.06.16 12:01:55 -04'00'			
Pharmacometrics Team Leader	Lian Ma, PhD	OCP/DPM	Sections: 6, 14	**Select one:** ___ Authored ✓ Approved
	Signature: Lian Ma -S Digitally signed by Lian Ma -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lian Ma -S, 0.9.2342.19200300.100.1.1=2000825336 Date: 2021.06.16 11:23:52 -04'00'			
OSIS Reviewer	Melkamu Getie Kebtie, PhD	OSIS/DGDSI	Sections: 6, 14	**Select one:** ✓ Authored ___ Approved
	Signature: Melkamu Getie Kebtie -S Digitally signed by Melkamu Getie Kebtie -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0013219608, cn=Melkamu Getie Kebtie -S Date: 2021.06.16 13:16:16 -04'00'			

BLA Multidisciplinary Review and Evaluation
BLA 761179
Rylaze (JZP-458)

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
OSIS Team Leader	Stanley Au, PharmD	OSIS/DGDSI	Sections: 6, 14	**Select one:** ___ Authored ✓ Approved
	Signature: Stanley Au -S Digitally signed by Stanley Au -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stanley Au -S, 0.9.2342.19200300.100.1.1=2000331264 Date: 2021.06.16 12:48:44 -04'00'			
Clinical Reviewer	Cara Rabik, MD, PhD	OOD/DHMI	Sections: 2, 3, 7, 8, 9, 10, 14	**Select one:** ✓ Authored ___ Approved
	Signature: Cara A. Rabik -S Digitally signed by Cara A. Rabik -S Date: 2021.06.15 15:51:37 -04'00'			
Clinical Team Leader	Donna Przepiorka, MD, PhD	OOD/DHMI	Sections: 2, 3, 7, 8, 9, 10, 14	**Select one:** ___ Authored ✓ Approved
	Signature: Donna Przepiorka -S 2021.06.15 10:50:40 -04'00'			
Associate Director for Labeling (ADL)	Elizabeth Everhart, MSN, RN, ACNP	OOD	Sections: 11	**Select one:** ✓ Authored ___ Approved
	Signature: Elizabeth E. Everhart -S Digitally signed by Elizabeth E. Everhart -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000363858, cn=Elizabeth E. Everhart -S Date: 2021.06.16 09:22:03 -04'00'			

BLA Multidisciplinary Review and Evaluation
BLA 761179
Rylaze (JZP-458)

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Cross-Disciplinary Team Leader (CDTL)	Donna Przepiorka, MD, PhD	OOD/DHMI	Sections: 1, 4, 12, 13	**Select one:** ✓ Authored ___ Approved
	Signature: *{See appended electronic signature page}*			
Division Director (Clinical)	R. Angelo de Claro, MD	OOD/DHMI	Sections: All	**Select one:** ___ Authored ✓ Approved
	Signature: *{See appended electronic signature page}*			
Office Director or designee	Marc Theoret, MD	OOD	Sections: All	**Select one:** ___ Authored ✓ Approved
	Signature: *{See appended electronic signature page}*			

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/

DONNA PRZEPIORKA
06/30/2021 11:17:09 AM

ROMEO A DE CLARO
06/30/2021 02:39:16 PM

MARC R THEORET
06/30/2021 04:43:00 PM
My signature indicates that I have considered the FDA assessments and recommendations included in this Review in determining the regulatory action.