158 Model-Informed Development of Recombinant *Erwinia* Asparaginase (JZP458) in Patients With Acute Lymphoblastic Leukemia

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Background

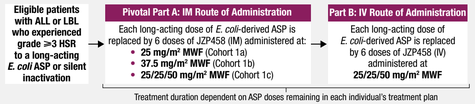
- L-asparaginase is a cornerstone of multi-agent chemotherapeutic regimens for acute lymphoblastic leukemia or lymphoblastic lymphoma (ALL/LBL)[1,2]
- *Erwinia*-derived asparaginase addresses a critical need for patients who cannot complete *Escherichia coli* (*E. coli*)-derived asparaginase therapy due to hypersensitivity reactions (HSRs) and silent inactivation[2]
- Switching to an *Erwinia* asparaginase had been historically challenging due to manufacturing issues with native asparaginase *Erwinia chrysanthemi*, which led to global supply shortages[3]
- Recombinant *Erwinia* asparaginase JZP458 was developed in collaboration with the Children's Oncology Group (COG) to provide a high-quality drug with reliable supply[3]
- The pivotal phase 2/3 AALL1931 COG study (NCT04145531) evaluated the efficacy and safety of JZP458 in patients with ALL/LBL who developed HSRs or silent inactivation to a long-acting *E. coli*-derived asparaginase and led to the approval of JZP458 in the United States and the European Union[4-8]
- Population pharmacokinetic (PPK) modeling was used throughout the program to inform dose selection and support the regulatory approval of JZP458[4,5,9]
  - JZP458 is approved by the United States Food and Drug Administration for intramuscular (IM) administration at 25/25/50 mg/m^2 on Monday/Wednesday/Friday (MWF) or at 25 mg/m^2 every 48 hours[10]
  - The recommended dosage in the European Union is 25 mg/m^2 IM or intravenously (IV) every 48 hours or a MWF schedule as follows[6]:
    - 25/25/50 mg/m^2 IM or IV on MWF; or
    - 25 mg/m^2 IV on M/W and 50 mg/m^2 IM on F

Objectives

- To develop a PPK model for JZP458 including evaluation of clinically relevant covariates on the pharmacokinetics (PK) of JZP458
- To utilize model-based simulations of serum asparaginase activity (SAA)-time profiles to evaluate various dosing regimens, including regimens not tested in the clinical study
- To evaluate the JZP458 exposure-safety relationship

Methods

Figure 1. Overall Study Design and PK Blood Collection



PK Blood Sample Collection Schedule to Determine SAA Levels in Course 1

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6
Part A - IM[a,b]	0 h (pre-dose 1); 2.5 h post-dose 1	48 h post-dose 1 (pre-dose 2)	48 h post-dose 2 (pre-dose 3)	72 h post-dose 3 (pre-dose 4); 2.5 h post-dose 4	48 h post-dose 4 (pre-dose 5)	48 h post-dose 5 (pre-dose 6)
Part B - IV[a,b,c]	0 h (pre-dose 1); 2 h post-dose 1	48 h post-dose 1 (pre-dose 2)	48 h post-dose 2 (pre-dose 3)	72 h post-dose 3 (pre-dose 4); 2 h post-dose 4	48 h post-dose 4 (pre-dose 5)	48 h post-dose 5 (pre-dose 6)

[a]This is a sample schedule for a Monday start; sample collection window: 2.5 h post-dose ± 15 minutes; 48 h ± 2 h; 72 h ± 2 h. [b]Three samples were collected for each of the subsequent courses. [c]An end-of-infusion sample is collected 2 h following the start of infusion.
ALL, acute lymphoblastic leukemia; ASP, asparaginase; *E. coli*, *Escherichia coli*; h, hour; HSR, hypersensitivity reaction; IM, intramuscular; IV, intravenous; LBL, lymphoblastic lymphoma; m, meter; mg, milligram; MWF, Monday/Wednesday/Friday; PK, pharmacokinetic; SAA, serum asparaginase activity.

- AALL1931 enrolled 3 IM cohorts and 1 IV cohort with JZP458 administered on a MWF **(Figure 1)** schedule[7]
- Efficacy was assessed by measuring SAA at defined points and calculating the proportion of patients maintaining the target nadir SAA (NSAA) of ⩾0.1 IU/mL at the last 72-hour (primary endpoint) or 48-hour (key secondary endpoint) time point during course 1
  - NSAA was utilized as the surrogate efficacy endpoint; NSAA of ⩾0.1 IU/mL is the commonly accepted threshold for asparagine depletion
- A PPK model was developed using the phase 1 healthy volunteer study and SAA data from AALL1931 (including all cohorts) using nonlinear mixed-effects modeling software to characterize the PK of IM and IV JZP458
- Both 1- and 2-compartment models were tested; effects of covariates were assessed and quantified
- Model-based simulations of SAA-time profiles using the National Health and Nutrition Examination Survey (NHANES) database were performed to evaluate various dosing regimens
  - In total, 200 simulations were conducted using the final model in 2000 NHANES subjects
- Exposure-safety analyses were conducted for 5 asparaginase-related adverse events of special interest: hepatotoxicity, pancreatitis, hypertriglyceridemia, thrombosis, and HSRs
- Subgroup analysis was performed by age, race, and body surface area (BSA) using the IM 25/25/50 mg/m^2 MWF and IV 25 mg/m^2 every 48-hour regimens

Results

Description of the Final Model

- In total, 4269 SAA data points from 250 participants (phase 1, n=24; AALL1931, n=226) were included in this model
  - This analysis included 3315 quantifiable observations and 954 below-the-limit-of-quantification (BLQ) data points; the M3 method was included in the model to analyze the SAA values that were BLQ
- A 1-compartment model with 2 first-order absorption rate constants (KA1, KA2) was determined to be the best fit, with a flexible change point absorption function for IM and zero-order input for IV
- The model included the effects of disease, BSA, and race (African American) on clearance; and disease and BSA on central volume of distribution, and age on KA1
  - At the base model stage, it was determined that the effect of BSA and disease on clearance, central volume of distribution, and age on KA1 were necessary because the patient data were primarily pediatric, and the healthy volunteers were all adults
- Parameter values for the final model are listed in **Table 1**

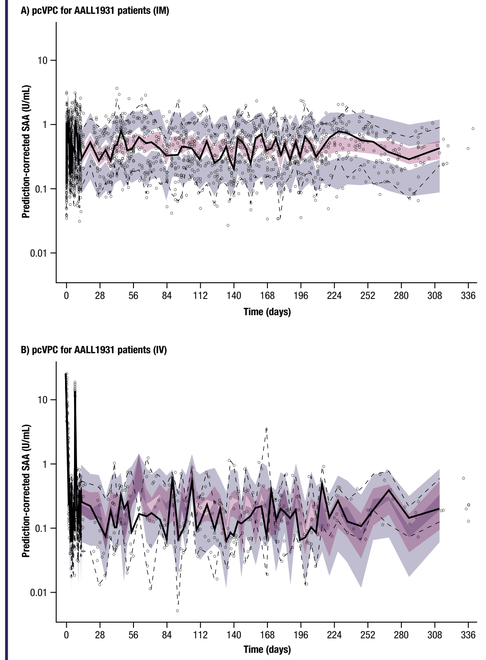
Table 1. JZP458 PK Model Parameter Values for the Final Model

Parameter (units)	Typical Value	SE (CV%)
CL (mL/h)	68.72	1.5
V (mL)	1220	5.6
CP (h)	7.26	44.4
KA1 (1/h)	0.0279	1.7
KA2 (1/h)	0.0555	1.5
F1 (%)	37.7	18.7
Effect of BSA on CL	1.31	5.5
Effect of BSA on V	1.3	5.8
Effect of age on KA1	-0.624	14.7
Effect of disease on CL	1.01	6.9
Effect of disease on V	1160	9.5
Effect of race on CL[a]	-0.282	19.8
Residual error (CV%)	0.528	1.3
Share parameter	22.9	326.6
BSVCL (CV%)	16.1	32.2
BSVV (CV%)	0 FIXED	NE
BSVCP (CV%)	461.5	54.2
BSVKA1 (CV%)	51.7	12.7
BSVKA2 (CV%)	10 FIXED	NE
BSVF1 (CV%)	62.6	11.2

[a]Black or African American.
BSA, body surface area; BSV, between-subject variability; CL, clearance; CP, change point; CV, coefficient of variation; F1, bioavailability; h, hour; KA, absorption rate constant (1 and 2); mL, milliliter; NE, not estimated; PK, pharmacokinetic; SE, standard error; V, central volume of distribution.

- The final PK model visual predictive check for JZP458 by route of administration in AALL1931 demonstrated that the final revised PPK model predicts the observed SAA acceptably **(Figure 2)**

Figure 2. JZP458 Final PK Model Prediction-Corrected Visual Predictive Check (pcVPC) by Route of Administration for the First Cycle A) pcVPC for AALL1931 Patients (IM Cohorts) and B) pcVPC for AALL1931 Patients (IV Cohort)

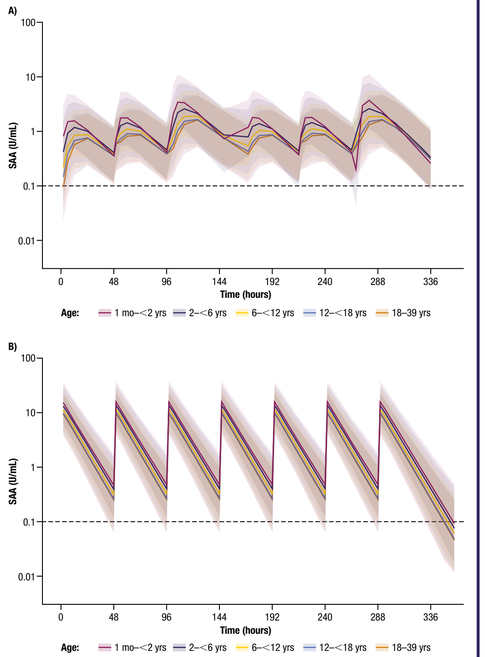


The black open circles represent individual SAA observations. The black solid lines represent the median of the predicted SAA; the dashed lines represent 5th and 95th percentiles of the predicted SAA. The red band represents the 90% confidence interval of the median predicted by the model; the blue bands represent the 5th and 95th percentiles predicted by the model.
IM, intramuscular; IV, intravenous; mL, milliliter; pcVPC, prediction-corrected visual predictive check; PK, pharmacokinetic; SAA, serum asparaginase activity; U, units.

Subgroup Analysis

- Model-based simulations suggested that the SAA-time profiles were similar and largely overlapping across different subgroups regarding age **(Figure 3)**, race (not shown), or BSA (not shown)
- No clinically significant difference is expected in the probability of achieving therapeutic NSAA based on age, race, or BSA following proposed BSA-based dosing regimens

Figure 3. Simulated SAA vs Time by Age for A) IM 25/25/50 mg/m^2 MWF and B) IV 25 mg/m^2 q48h



Bands represent the 2.5th (lower) and 97.5th (upper) percentiles. The dashed line indicates the target trough level of 0.1 IU/mL.
IM, intramuscular; IV, intravenous; mL, milliliter; mo, month; MWF, Monday/Wednesday/Friday; q48h, every 48 hours; SAA, serum asparaginase activity; U, unit; yrs, years.

Model-Based Simulations

- Model-predicted efficacy was consistent with observed data from the trial, and predicted therapeutic NSAA levels are achieved in the vast majority of patients with IM JZP458 at 25 mg/m^2 every 48 hours or 25/25/50 mg/m^2 MWF or IV JZP458 at 25 mg/m^2 every 48 hours, or a mixed regimen of IV/IV/IM 25/25/50 mg/m^2 MWF **(Table 2)**

Table 2. Proportion of Patients Achieving NSAA Levels of ⩾0.1 IU/mL Based on Observed Data and Model Predictions

JZP458 Dosing Regimen	Time Point	Proportion of Patients With NSAA ⩾0.1 IU/mL	
		Observed Data % (95% CI)	Model Prediction % (95% CI)
IM 25/25/50 mg/m^2 MWF[a]	Last 72 h	90 (81, 98)	88 (87, 90)
	Last 48 h	96 (90, 100)	95 (94, 96)
IV 25/25/50 mg/m^2 MWF[b]	Last 72 h	40 (26, 54)	38 (36, 40)
	Last 48 h	90 (82, 98)	84 (82, 86)
IV/IV/IM 25/25/50 mg/m^2 MWF[c]	Last 72 h	N/A	89 (87, 90)
	Last 48 h	N/A	90 (88, 91)
IM 25 mg/m^2 q48h[c]	Last 48 h	N/A	97 (96, 97)
IV 25 mg/m^2 q48h[c]	Last 48 h	N/A	83 (82, 85)

[a]Observed data based on cohort 1c (IM 25/25/50 mg/m^2 MWF, n=51). [b]Observed data based on the IV cohort (n=61). [c]Dosing schedule was not evaluated in AALL1931.
CI, confidence interval; h, hour; IM, intramuscular; IU, international unit; IV, intravenous; mL, milliliter; MWF, Monday/Wednesday/Friday; N/A, not available; NSAA, nadir serum asparaginase activity; q48h, every 48 hours.

Exposure-Safety Analyses

- There were no apparent associations between model-predicted SAA exposure metrics (area under the SAA-time curve from time point 0 to 336 hours post-dose, maximum SAA, SAA concentration at 48 hours post-dose, SAA concentration at 72 hours post-dose) and the incidence of hepatotoxicity, pancreatitis, hypertriglyceridemia, or thrombosis, although the small number of patients with thromboses (IM 1%; IV 2%) prevented any conclusion regarding this adverse event
- Hypersensitivity appeared to be associated with exposure, but the effect is confounded by route of administration (incidence of HSRs with IM, 11%; IV, 26%), consistent with the class of asparaginases

Conclusions

- Observed data and PPK model-based simulations demonstrate that JZP458 achieves therapeutic NSAA levels via multiple IM and IV dosing schedules, including dosing regimens not directly tested in trials, which supported the regulatory approval of these dosing regimens
- Following the proposed BSA-based dosing regimens, subgroup analyses suggested that clinically significant differences are not expected in the probability of achieving a target NSAA level of ⩾0.1 IU/mL based on race, age, or BSA
- Except for HSRs, exposure-safety trends showed no apparent association for hepatotoxicity, pancreatitis, hypertriglyceridemia, or thrombosis
  - This finding is confounded by the route of administration and limited by the small sample size
- The accelerated development and approval of JZP458 showcases an innovative use of a model-based approach to address critical medical needs[4,5]

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