

Population Pharmacokinetic Model Development and Simulation for Recombinant *Erwinia* Asparaginase Produced in *Pseudomonas fluorescens* (JZP-458)

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Abstract

JZP-458 is a recombinant *Erwinia* asparaginase produced using a novel *Pseudomonas fluorescens* expression platform that yields an enzyme expected to lack immunologic cross-reactivity to *Escherichia coli*-derived asparaginases. It is being developed as part of a multiagent chemotherapeutic regimen to treat acute lymphoblastic leukemia or lymphoblastic lymphoma patients who develop *E. coli*-derived asparaginase hypersensitivity. A population pharmacokinetic (PopPK) model was developed for JZP-458 using serum asparaginase activity (SAA) data from a phase I, single-dose study (JZP458-101) in healthy adults. Effects of intrinsic covariates (body weight, body surface area, age, sex, and race) on JZP-458 PK were evaluated. The model included SAA data from 24 healthy adult participants from the phase I study who received JZP-458: intramuscular (IM) data at 12.5 mg/m² (N = 6) and 25 mg/m² (N = 6), and intravenous (IV) data at 25 mg/m² (N = 6) and 37.5 mg/m² (N = 6). Model simulations of adult and pediatric SAA profiles were performed to explore the likelihood of achieving a therapeutic target nadir SAA (NSAA) level ≥ 0.1 IU/mL based on different administration strategies. PopPK modeling and simulation suggest JZP-458 is expected to achieve 72-hour NSAA levels ≥ 0.1 IU/mL in 100% of adult or pediatric populations receiving IM administration at 25 mg/m², and in 80.9% of adult and 94.5% of pediatric populations receiving IV administration at 37.5 mg/m² on a Monday/Wednesday/Friday (M/W/F) dosing schedule. Based on these results, the recommended starting dose for the phase 2/3 pivotal study is 25 mg/m² IM or 37.5 mg/m² IV on a M/W/F dosing schedule in pediatric and adult patients.

Keywords

asparaginase, asparaginase hypersensitivity, healthy adult participants, JZP-458, population PK, recombinant *Erwinia* asparaginase, serum asparaginase activity

L-asparaginase is an important component of acute lymphoblastic leukemia (ALL) therapy that is used in pediatric and adult ALL regimens. It hydrolyzes the amino acid asparagine, which is essential for the growth of leukemic cells, thereby depleting plasma asparagine levels and selectively killing leukemic lymphoblasts.^{1,2} The reliance of leukemic cells on external asparagine provides the rationale for asparaginase treatment. Serum asparaginase activity (SAA) is commonly used as a measure of treatment efficacy and reduction of systemic asparagine; its levels serve as a surrogate marker for asparagine depletion. In clinical practice, nadir SAA (NSAA) levels ≥ 0.1 IU/mL have been used in various studies and treatment protocols and

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are an accepted threshold to demonstrate adequate asparagine depletion, which correlates with clinical efficacy.³ Throughout the long clinical use of asparaginase in the treatment of ALL, SAA has been used to characterize the pharmacokinetic (PK) profiles of asparaginases and has been the basis of PK assessment in clinical studies.

For short half-life asparaginases, the administration schedule is an important variable requiring dosing every 48 to 72 hours, a schedule that in clinical practice translates to a dosing schedule of Monday/Wednesday/Friday (M/W/F) for 2 weeks, for a total of 6 doses for each course. Clinical practice guidelines also recommend checking SAA levels after dosing to make any necessary adjustments to maintain NSAA levels ≥ 0.1 IU/mL throughout the treatment duration. If the 48- or 72-hour postdose level is below the lower limit of quantification, this may indicate a need for higher or more frequent dosing. The route of administration of asparaginases is also an important component. In clinical practice, both the intramuscular (IM) and intravenous (IV) routes are used routinely depending on the treating oncologist's preference and/or institutional guidelines.⁴

Due to their bacterial origin, L-asparaginases are immunogenic and can induce hypersensitivity reactions with high antibody titers that may limit their therapeutic effect. Modifications to L-asparaginases, such as PEGylation, can also be immunogenic.^{2,5} PEGylated *Escherichia coli*-derived asparaginases are used for first-line treatment of ALL; however, up to 30% of patients develop hypersensitivity reactions. Allergic symptoms range from mild, local injection site reactions to severe anaphylaxis and typically lead to discontinuation of treatment. Without robust mitigation strategies or alternative asparaginase preparations, patients typically face early discontinuation of therapy, which is associated with poor outcomes.^{6,7} Patients may also experience silent inactivation, in which they develop antibodies that inactivate the asparaginase without leading to clinical hypersensitivity.² High-risk and slow early responding standard-risk patients with ALL who do not complete their prescribed asparaginase course have a significantly inferior event-free survival compared with those who received more asparaginase doses or completed their prescribed course.^{8,9}

Alternative asparaginase preparations are necessary for patients who develop hypersensitivity to *E coli*-derived asparaginases so that they may complete their full treatment course. Asparaginase *Erwinia chrysanthemi* (ERW; crisantaspase) is an effective treatment alternative. However, since 2016, there has been a worldwide shortage of ERW due to ongoing manufacturing issues, which have resulted in disruptions in the

ability to make the product available on a consistent basis. This has prevented some patients from receiving all of their planned doses of L-asparaginase, resulting in a critical patient need for a reliable product that can provide patients with hypersensitivity to *E coli* products the opportunity to complete their full course of asparaginase therapy.⁸⁻¹⁰

In an effort to overcome this limitation, another alternative asparaginase is currently being investigated. JZP-458 is a recombinant *Erwinia* asparaginase derived from a novel *Pseudomonas fluorescens* expression platform to produce an enzyme that is expected to have no immunologic cross-reactivity to *E coli*-derived asparaginases.¹¹ It is being developed as a component of a multiagent chemotherapeutic regimen to treat patients with ALL or lymphoblastic lymphoma (LBL) who develop hypersensitivity to *E coli*-derived asparaginases. As the intent-to-treat population is more prevalent among children, and first-in-human studies are not usually conducted in pediatric cancer patients, the phase 1 study for JZP-458 was conducted in healthy adult participants. In a randomized, single-center, open-label, phase 1 study (JZP458-101) in healthy adult participants, JZP-458 was administered to 24 healthy adult participants and maintained SAA levels ≥ 0.1 IU/mL for up to 72 hours after dosing at the highest doses tested for each route of administration (ie, 25 mg/m² IM and 37.5 mg/m² IV), with no unanticipated adverse events (AEs), no serious AEs, and no grade 3 or higher AEs.¹²

Detailed PK parameters for JZP-458 using non-compartmental analysis (NCA) have been reported separately.¹² However, due to limitations with NCA predictions and in the absence of observed data for JZP-458 in the pediatric patient population, one goal of the current population PK (PopPK) modeling and simulation was to develop a PopPK model using adult SAA data and then use the covariates in the model to extrapolate to pediatric patients based on allometric principles and perform simulations to inform the starting dose and dosing regimen selection in pediatric patients. PopPK analysis was also used to evaluate the effect of intrinsic and extrinsic factors affecting the PK of JZP-458 and to evaluate the effect of body size on PK to determine the appropriate dosing approach (eg, body size-based or fixed dosing). The dose and dosing schedule proposed in this analysis was the starting dose for the phase 2/3 pivotal study; there is a dose-finding phase built into the phase 2/3 study for dose confirmation before dose expansion.

PopPK models have been frequently used to characterize the PK of asparaginases, assess SAA levels, determine inter- and intraindividual variability, detect covariate effects on asparaginase exposure, and provide

simulated SAA profiles under different conditions.^{13–16} In addition, predicting pediatric exposures from adult data based on PopPK model covariates such as clearance (CL) correlation with body size is a standard approach routinely used in drug development.^{17–20} There has been growing regulatory support for the use of PK modeling to inform pediatric dose selection using adult PK data.²¹

Methods

Institutional Review Board

A phase 1, randomized, single-center, open-label study (JZP458-101) was conducted in the United States between November 19, 2018, and May 20, 2019. This study was approved by the IntegReview Institutional Review Board in Austin, Texas, and conducted at QPS Miami Research Associates (Miami Clinical Research) in Miami, Florida, in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All healthy volunteers provided written informed consent before enrollment.

Study Design, Study Population, and PK Sampling

The JZP-458 PopPK analysis was based on data collected from a phase 1, randomized, single-center, open-label study in healthy adult participants, in which 24 participants received JZP-458 and 6 participants received ERW.¹² For the PopPK model development, only data from participants administered JZP-458 (N = 24) were used.

JZP-458 was dosed at 2 dose levels for each route of administration, at 12.5 and 25 mg/m² for IM (N = 6 each), and 25 and 37.5 mg/m² for IV (N = 6 each). The site of injection for IM administration was either the dorsogluteal region or deltoid muscle. The total volume injected was dependent on the participant's body surface area (BSA); however, the volume of JZP-458 at a single injection site was limited to 2 mL.¹²

Eligible healthy participants included men and non-pregnant, nonlactating women between the ages of 18 and 55 years with a normal body mass index (ie, 19.0–30.0 kg/m²) who were in good general health as determined by the investigator at screening and day –1 and were able to understand and comply with study-specific requirements. Key exclusion criteria included a history or presence of any illness, physical finding, or laboratory examination or electrocardiogram finding that, in the opinion of Jazz Pharmaceuticals and/or the investigator, might confound the results or conduct of the study or pose a risk to the healthy participant, including any condition that might interfere with the distribution, metabolism, or excretion of drugs.

Serial blood samples were collected from all participants at prespecified time points up to 96 hours after dosing. For IM dosing, samples were taken before dos-

ing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, and 96 hours after dosing. For IV dosing, samples were taken before dosing and at 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, and 96 hours after the start of the 2-hour infusion.

Population PK Modeling

A PopPK model was developed for JZP-458 using intensive SAA data from a single-dose, phase 1 study using nonlinear mixed effects modeling (NONMEM) (version 7.3) to describe the PK of JZP-458 after IM and IV administration. SAA was the basis of the PK assessment in this study. PK samples were analyzed for SAA levels using a validated enzyme activity assay in human serum. The assay was validated across the calibration range from 0.025 IU/mL (lower limit of quantitation) to 0.15 IU/mL (upper limit of quantitation), with dilution linearity established for sample dilutions of up to 467.72-fold. Intra-assay precision (% coefficient of variation) ranged from 87.5% to 100%; accuracy (% relative error [RE]) was 100%. Inter-assay precision (% coefficient of variation) ranged from 6.11% to 12.39%; accuracy (% RE) ranged from –9.40% to –4.24%. SAA 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, which correlates with clinical efficacy. This threshold was used to evaluate model-based simulations.

A total of 331 quantifiable SAA data points from 24 healthy adult participants who received JZP-458 were included in the development of the PopPK model: 12.5 mg/m² IM (N = 6), 25 mg/m² IM (N = 6), 25 mg/m² IV (N = 6), and 37.5 mg/m² IV (N = 6). Data from both routes of administration were used in the development of the PopPK model and were fit simultaneously to (1) increase the sample size for model development and covariate analysis, (2) identify a base model to characterize the absorption rate–limited elimination of SAA after IM administration, and (3) estimate the bioavailability after IM administration relative to IV administration.

This analysis was conducted in a series of steps:

- (1) Modeling data sets with SAA levels were assembled from source and derived data sets for graphical exploration and individual model fitting.
- (2) Model fits for IM and IV routes individually and simultaneously were explored.
- (3) The base model was selected in consideration of the numerical results, that is, objective function value (OFV) and graphical evaluation including goodness-of-fit (GOF) diagnostics for the testing of a variety of random effects and residual error models. GOF diagnostics were used for model

evaluation with no additional model qualification conducted.

- (4) All models were fitted using first-order conditional estimation with interaction for optimization, and random effects assumed a log-normal distribution.
- (5) For the covariate model, a statistical significance level of 0.05 (drop in OFV of >3.84) was used to screen covariates.
- (6) Where covariates were highly correlated, the most useful covariate that was statistically significant was selected by the analysts.

The effect of intrinsic covariates (body weight, BSA, age, sex, and race) was evaluated to identify the covariates likely to contribute to the variability of JZP-458 PK. Extrinsic covariates were not evaluated in this healthy adult population.

Model-based Simulations

The model was used to simulate adult and pediatric SAA profiles (1000 participants/population) to explore the likelihood of achieving a therapeutic target NSAA level ≥ 0.1 IU/mL based on different doses, schedules, and routes of administration. Simulations were performed with a virtual population created from the Centers for Disease Control and Prevention National Health and Nutrition Examination Survey (NHANES) database. Subjects in the NHANES database snapshot were categorized into pediatric (between 2 and 17 years of age) and adult (≥ 18 years of age) subjects based on age. The simulation population ranged from 2 to 85 years of age with a weight range of 8.9 kg to 174.6 kg (median 62.7 kg). A virtual population was created by selecting a random sample (resampling with replacement) of 2000 subjects (1000 pediatric and 1000 adult), with subject-specific body size metrics (body weight, height, and body mass index) from the NHANES database to be used as covariates for simulation. Simulations for IM administrations at 12.5 and 25 mg/m² and IV administrations at 25 and 37.5 mg/m² were performed.

Results

Participant Demographics

Baseline demographics included a mean \pm standard deviation (SD) age of 38.3 ± 8.6 years, weight of 78.3 ± 9.6 kg, and BSA of 1.9 ± 0.1 m² (Table 1).

Base Model

The modeling data set consisted of intensive SAA data collected from 24 healthy adult participants through 96 hours. Semilogarithmic plots of the SAA versus time data for both routes did not reveal multiexponential behavior in the distribution and elimination phases. One-compartment models were fit to the SAA data and

Table 1. Baseline Demographics for Patients Receiving JZP-458 in the JZP-458 Phase 1 Study

Characteristic	JZP-458 Patients ^a (N = 24)
Age, mean \pm SD, y	38.3 \pm 8.6
Male, n (%)	17 (71)
Weight, mean \pm SD, kg	78.3 \pm 9.6
BSA, mean \pm SD, m ²	1.9 \pm 0.1
Ethnicity, n (%) ^b	
Hispanic/Latino	23 (96)
Not Hispanic/Latino	1 (4)
Race, n (%)	
White	20 (83)
Black/African American	4 (17)

BSA, body surface area; SD, standard deviation.

^a Patients who received JZP-458 in the phase 1 JZP-458 study.

^b Ethnicity was self-reported; healthy participants could identify as more than 1 ethnicity.

evaluated given that no reasonable peripheral compartment starting estimates could be selected.

Some underprediction of SAA was noted for the IM route, notably in the initial phase of the profile, so a sequential mixed order absorption function was used to estimate both zero- and first-order absorption rate constant parameters. Bioavailability of JZP-458 from the IM route of administration was also estimated in relation to the IV route of administration.

Covariate Analysis and Final Covariate Population PK Model Selection

An exploratory graphical analysis was performed using a scatterplot matrix with a loess smooth to examine potential relationships between the base model parameter estimates and patient demographics (Figure S1). The plots suggested JZP-458 CL was positively correlated with body size metrics (Figure 1). Effects of 5 intrinsic covariates (age, sex, body weight, BSA, and race) were screened within NONMEM for potential effect on JZP-458 CL and volume of distribution (V_d).

Only body weight and BSA were identified as statistically significant covariates for JZP-458 CL, leading to statistically significant drops in the OFV at a 0.05 significance level. Body weight and BSA each accounted for 2.8% and 3.4% variability, respectively, in JZP-458 CL. Body weight was selected over BSA for inclusion in the model due to the established allometric scaling of CL on the basis of body weight. Covariates that typically correlated with body size, such as age and sex, were not included in the final model because they displayed no trends after including weight in the model. Race and ethnicity could not be evaluated due to the small participant numbers in each of these subgroups in the study. Effects of extrinsic factors were not evaluated in this healthy adult population.

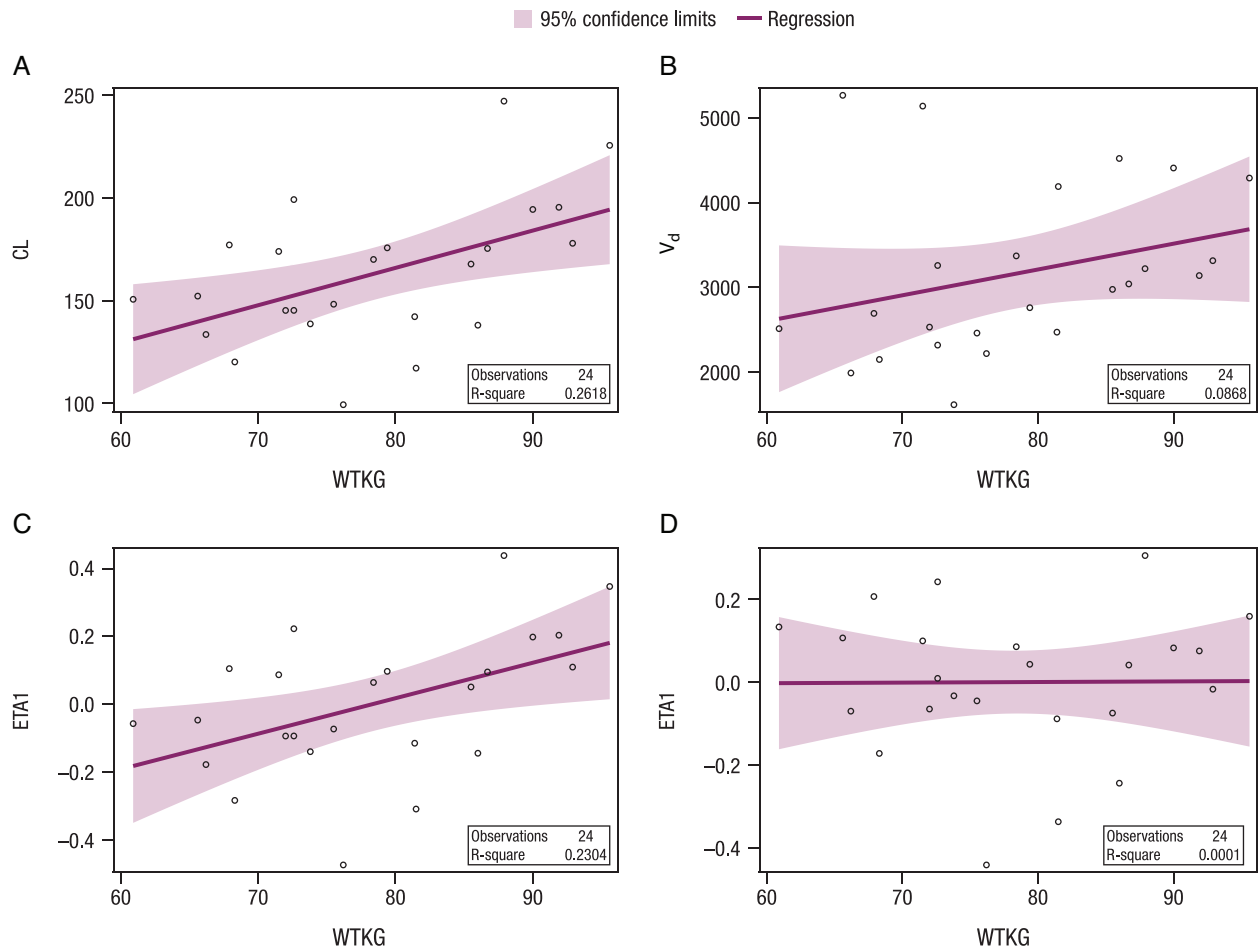


Figure 1. Scatterplots of body weight and (A) clearance, (B) volume of distribution, (C) base model random effect on clearance, and (D) covariate model random effect on clearance. Notes: Panels A, B, and C are the post hoc relationships from the base model fit. Panel D from the covariate model shows that after inclusion of weight on clearance, the random effects on clearance do not show a relationship with each participant's weight. The solid line is the linear regression line, with dots representing paired observations. The band is the confidence limit of the mean regression line. CL, clearance; ETA, interindividual random effect; ETA1 relates to clearance; V_d , volume of distribution; WTKG, weight (kg).

The final covariate model, which describes IM and IV routes simultaneously, was a 1-compartment model with linear elimination and mixed order absorption (IM only), with weight included as a covariate on JZP-458 SAA CL (Table 2). The final model equation for CL was $CL \text{ (mL/h)} = 146 \text{ (mL/h)} \times (\text{weight [kg]/70})^{0.863}$. For a 70-kg adult, the CL, V_d , and half-life for the IV route was estimated at 0.146 L/h, 3.03 L, and 14.4 hours, respectively. For the IM route, CL/F and V/F were estimated at 0.4 L/h and 8.30 L, respectively; first-order absorption rate constant was estimated at 0.0348 h^{-1} and bioavailability at 36.5%. The PK parameters determined from this PopPK analysis were very similar to the numbers determined from the NCA analysis in the phase 1 study.¹²

Model diagnostics showed good fits based on individual- and population-predicted JZP-458 SAA

levels versus the observed JZP-458 SAA values reported in the phase 1 study¹² for both the IM and IV routes of administration (Figures 2 and 3). Examination of the overall GOF of the developed model with the observed versus population-predicted (Figures S2 and S3) and conditional weighted residuals versus time (Figure S4) and predicted population-concentration (Figure S5) demonstrated acceptable fit of the PK model to the observed data.

Model-based Simulations

The final covariate model was used to simulate SAA profiles to explore the likelihood of achieving a therapeutic NSAA $\geq 0.1 \text{ IU/mL}$ based on different doses, schedules, and routes of administration.

A typical M/W/F dosing schedule was simulated for 6 doses per course of treatment, where JZP-458 doses were given at 0, 48, 96, 168, 216, and 264 hours.

Table 2. Population Pharmacokinetic Parameters of JZP-458 Following IV and IM Administration

Parameter	Estimate	BSV%	Lower 95% CI ^a	Upper 95% CI ^a	RSE (%)
CL, mL/h	$146 \times (\text{WT}/70)^{0.863}$	18.88	128.4	163.6	6.15
V _d , mL	3030	32.06	2655	3405	6.32
F	0.365	...	0.3074	0.4226	8.05
t _{1/2} (h) ^b	14.4
k _a (h ⁻¹)	0.0348	...	0.02942	0.04018	7.89
Zero-order absorption (IU/h)	4000	...	1569	6431	31.01
Error model proportional	20.6%	...	NA	NA	NA

BSV, between-subject variability; CI, confidence interval; CL, clearance (for a 70 kg adult: IM, CL/F = 0.4 L/h; IV, CL = 0.146 L/h); F, bioavailability for IM route; IM, intramuscular; IV, intravenous; k_a, first-order absorption rate constant; NA, not available; RSE, root square error; t_{1/2}, half-life; V_d, volume of distribution for the central compartment (IM, V_d/F = 8.30 L; IV, V_d = 3.03 L); WT, weight.

An allometric (power) model was used for the effect of weight on CL. BSV was modeled as exponential.

^a Parametric CIs.

^b t_{1/2} only presented for IV; it was calculated using the question: $t_{1/2} = \ln(2)/ke$, $ke = CL/V_d$. t_{1/2} not calculated for IM due to flip-flop kinetics.

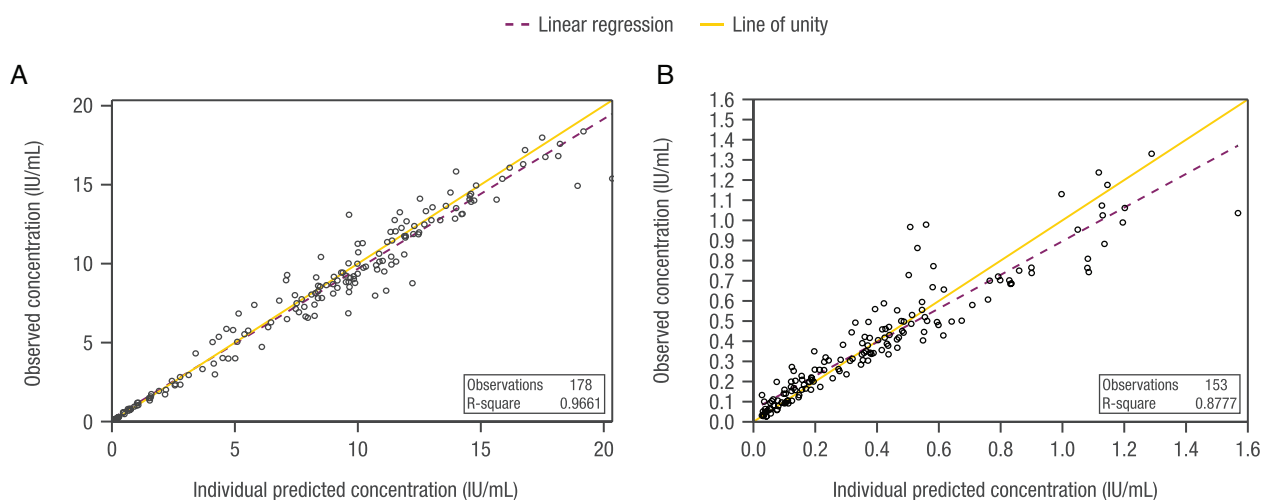


Figure 2. Goodness-of-fit plots demonstrated a robust model fit, providing confidence in model simulations with (A) IV administration and (B) IM administration. IM, intramuscular; IV, intravenous.

A simulated proportion of participants expecting to achieve NSAA levels ≥ 0.1 IU/mL is presented in Table 3 for both adult and pediatric populations (N = 1000 each); simulated JZP-458 median SAA profiles with 90% prediction intervals are presented in Figures 4 and 5. Simulations were also performed using a Friday/Monday/Wednesday dosing schedule with JZP-458 given at 0, 72, 120, 168, 240, and 288 hours; no meaningful differences are evident when comparing the simulated proportion of participants with NSAA levels ≥ 0.1 IU/mL at the last 48 or 72 hours after dosing based on therapy start day.

Discussion

JZP-458 is a recombinant ERW asparaginase produced using a novel *P fluorescens* expression platform that yields an enzyme that is expected to have no immunologic cross reactivity to *E coli*-derived asparaginases. It is being developed as part of a multiagent chemother-

apeutic regimen to treat patients with ALL or LBL who have developed hypersensitivity to *E coli*-derived asparaginases. In a randomized, single-center, open-label, phase 1 study (JZP458-101) in healthy adult participants, JZP-458 was administered to 24 healthy adult participants and maintained SAA levels ≥ 0.1 IU/mL for up to 72 hours after dosing at the highest doses tested for each route of administration (ie, 25 mg/m² IM and 37.5 mg/m² IV) with no unanticipated AEs, no serious AEs, and no grade 3 or higher AEs.¹² Detailed PK parameters for JZP-458 using NCA have been reported separately.¹²

To leverage the SAA data collected in healthy adults, an explicit PK model was developed using a NONMEM approach. This approach was particularly suited for a potential pooled PopPK analysis of subsequent SAA data collected using a sparse sampling design in a largely pediatric patient population. Since there was no observed SAA data for JZP-458 in pediatric patients, the goal of modeling was to extrapolate exposure

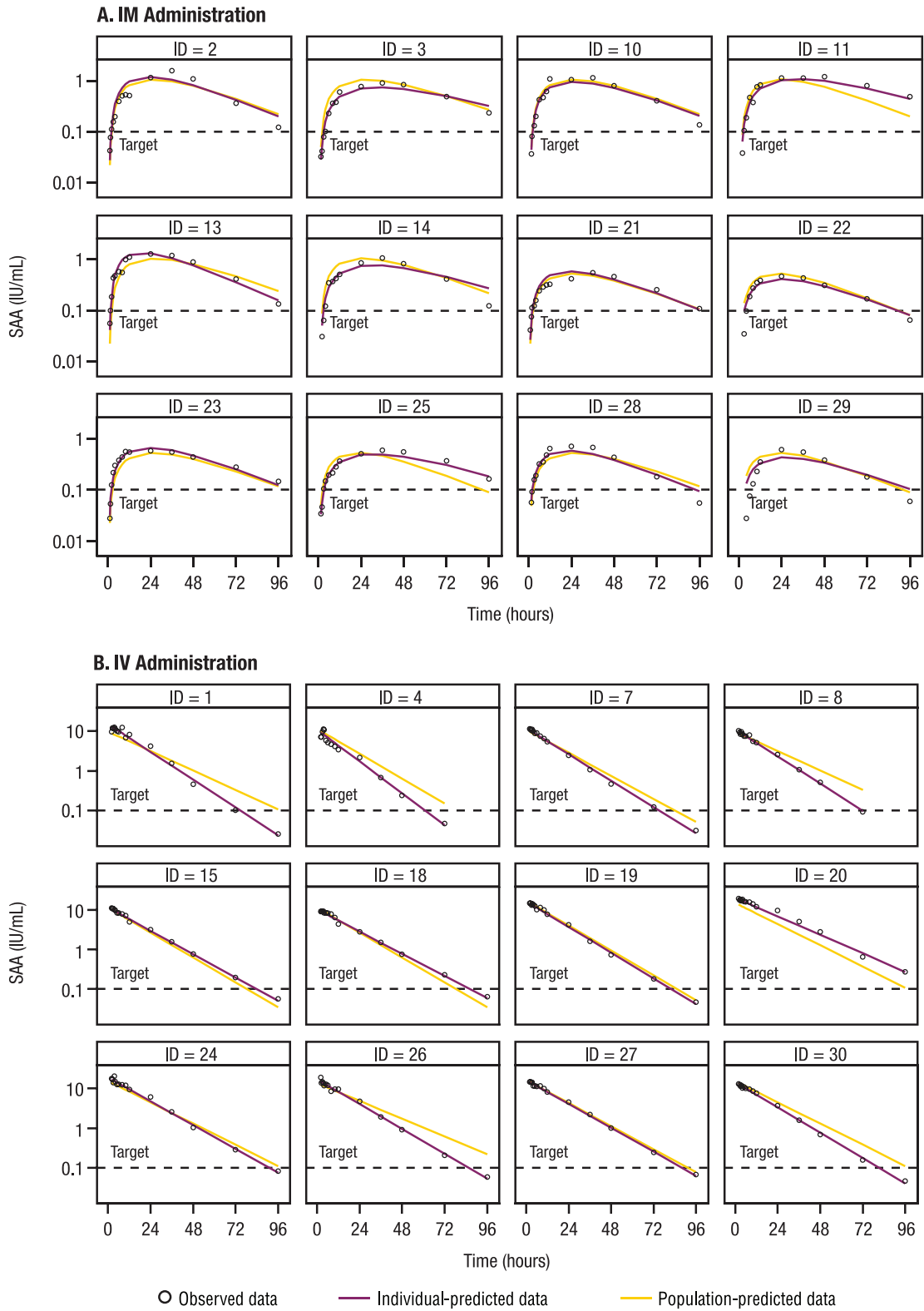


Figure 3. Individual goodness-of-fit semilogarithmic plots. ID, modeling identifier; IM, intramuscular; IV, intravenous; SAA, serum asparaginase activity.

Table 3. Simulation Summary Results: Proportion of Participants Expected to Achieve Target SAA Levels on a M/W/F Dosing Schedule

Dose/Route	Population	Proportion of Participants With SAA ≥ 0.1 IU/mL			Mean SAA (IU/mL)		
		Dose 3 72-Hour	Dose 5 48-Hour	Dose 6 72-Hour	Dose 3 72-Hour	Dose 5 48-Hour	Dose 6 72-Hour
12.5 mg/m ² IM	Adults	99.5	100.0	99.5	0.3	0.5	0.3
	Pediatrics	99.9	100.0	99.9	0.4	0.6	0.5
25 mg/m ² IM	Adults	100.0	100.0	100.0	0.6	1.0	0.6
	Pediatrics	100.0	100.0	100.0	0.9	1.3	0.9
25 mg/m ² IV	Adults	74.5	95.3	74.5	0.4	1.1	0.4
	Pediatrics	91.7	99.2	91.7	1.2	2.1	1.3
37.5 mg/m ² IV	Adults	80.9	97.4	80.9	0.6	1.6	0.6
	Pediatrics	94.5	99.5	94.5	1.8	3.2	2.0

IM, intramuscular; IV, intravenous; M/W/F, Monday/Wednesday/Friday; SAA, serum asparaginase activity.

Proportion represents the number calculated for 1000 simulated healthy participants per population, per route, and per dose level.

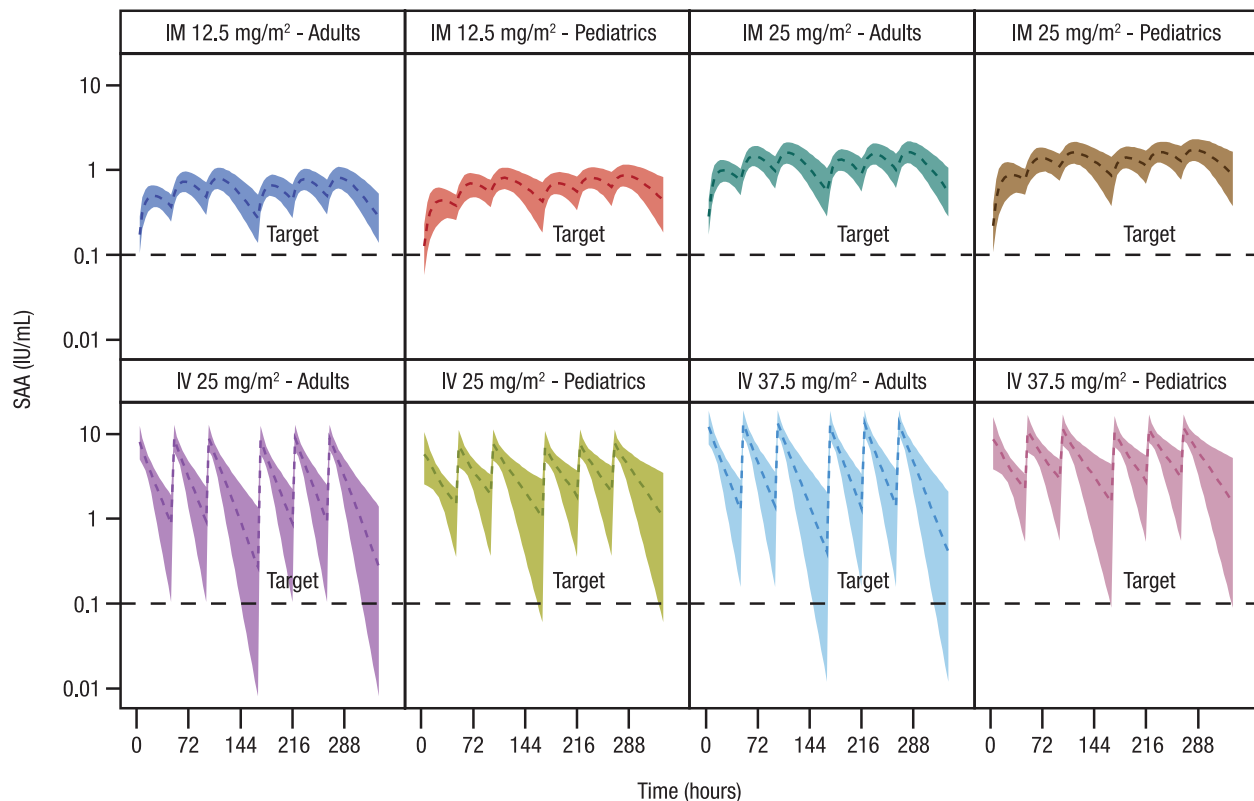


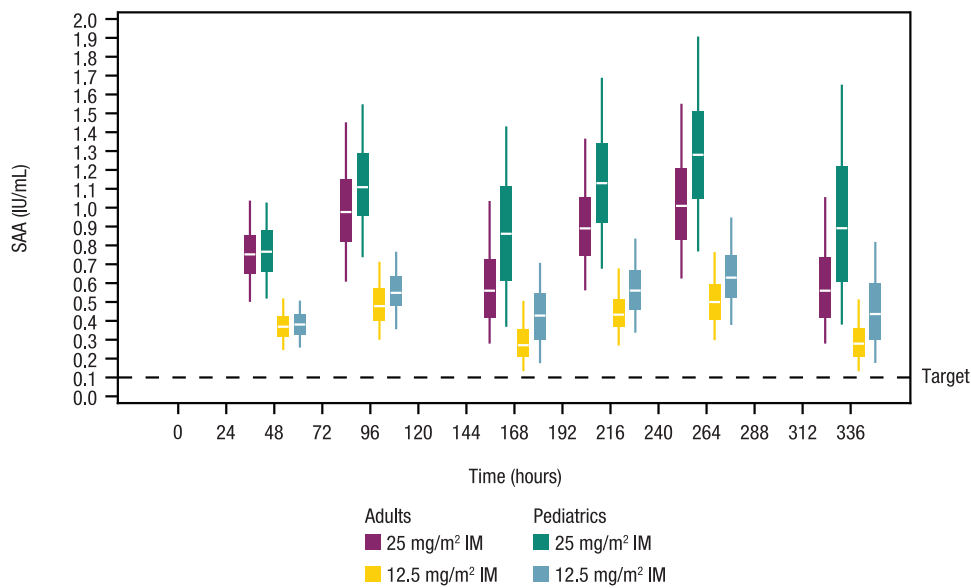
Figure 4. Simulated JZP-458 median SAA levels using a M/W/F dosing schedule. Notes: Center lines are the median value. Bands (90% prediction interval) represent the 5th and 95th percentiles. IM, intramuscular; IV, intravenous; M/W/F, Monday/Wednesday/Friday; SAA, serum asparaginase activity.

to pediatric patients based on allometric principles and perform simulations to inform the starting dose and dosing regimen selection in pediatric patients. PopPK analysis was also used to evaluate the effect of intrinsic and extrinsic factors affecting the PK of JZP-458 and to evaluate the effect of body size on PK to determine the appropriate dosing. The current analysis provides an example of how a PopPK model can be used in

model-based drug development in the treatment of ALL using asparaginases. Knowing the SAA levels to maintain ≥ 0.1 IU/mL throughout the 2-week treatment duration allows the prediction of different doses and dosing schedules, as well as from adult to pediatric populations.

Here, a PopPK model was developed for JZP-458 using intensive SAA data that informed the starting dose

A. IM Administration



B. IV Administration

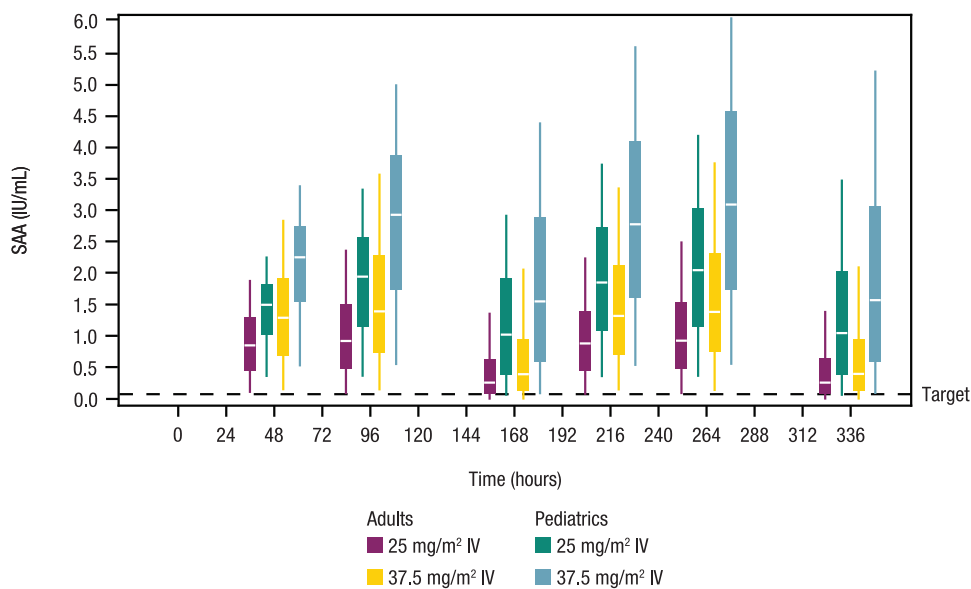


Figure 5. Simulated JZP-458 median SAA levels with 90% prediction intervals using a M/W/F dosing schedule. Note: Box center line represents the median value, and the upper and lower whiskers (90% prediction interval) represent the 95th and 5th percentiles, respectively. IM, intramuscular; IV, intravenous; M/W/F, Monday/Wednesday/Friday; SAA, serum asparaginase activity.

and dosing regimen selection for a pivotal phase 2/3 study in patients with ALL or LBL. The PopPK model was robust, and it allowed simultaneous fitting of data from both IM and IV routes and simultaneous estimation of both inter- and intrasubject variability. Age, sex, body weight, BSA, and race were evaluated as potential covariates on JZP-458 CL and V_d . Only body weight and BSA were identified as statistically significant covariates, and each accounted for 2.8% and 3.4% variability, respectively, in JZP-458 CL.

These data support the traditional approach of body size-based dosing. Body weight was selected over BSA for inclusion in the model because of established allometric scaling of CL on the basis of body weight. The final covariate model demonstrated a good fit to the single-dose healthy adult participant SAA data for both IM and IV routes of administration. Based on the GOF data from healthy adults, the final covariate model was used to extrapolate dosing to pediatric patients, as body weight is a commonly employed

covariate of interest when simulating pediatric PK from adult data.²¹ Simulation results suggested that based on allometric principles and the assumption of time-independent CL, NSAA values may be higher in children compared with adults for both IM and IV routes of administration, and the proportion of participants achieving 72-hour SAA levels ≥ 0.1 IU/mL is expected to be higher in the pediatric population than in the adult population. Based on phase I healthy volunteer data, PopPK modeling and simulation suggested that JZP-458 was predicted to achieve 72-hour NSAA levels ≥ 0.1 IU/mL in 100% of adults or pediatrics based on IM administration at 25 mg/m² and 80.9% in adult or 94.5% in pediatric populations at an IV dose of 37.5 mg/m² on a M/W/F dosing schedule.

Therefore, based on the totality of phase I data and population PopPK modeling and simulations, the recommended starting dose for the phase 2/3 pivotal study is 25 mg/m² for IM and 37.5 mg/m² for IV routes of administration on a M/W/F dosing schedule for 6 doses per course of treatment.

Conclusions

In this study, a PopPK model was developed for using intensive SAA data after IM or IV administration in healthy adult participants. Model-based simulations of SAA profiles after JZP-458 administration were generated to identify the appropriate starting dose and dosing regimen for a pivotal phase 2/3 study, which is expected to largely consist of pediatric patients. Based on the totality of phase I data and PopPK modeling and simulations, the recommended starting dose for the phase 2/3 pivotal study is 25 mg/m² for IM and 37.5 mg/m² for IV routes of administration on a M/W/F dosing schedule.

Acknowledgments

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Conflicts of Interest

T.L., M.R.C., K.Z., and J.A.S. are employees of and hold stock ownership and/or stock options in Jazz Pharmaceuticals. T.D., J.K., and N.S.B. are employees of IQVIA.

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Data Sharing Statement

All relevant data are provided within the manuscript and supporting files.

Author Contributions

T.L.: study design, data analysis/interpretation, and led the drafting/revising of manuscript. T.D. and J.K.: data analysis/interpretation/result deliveries and revising manuscript. N.S.B.: modeling oversight and revising manuscript. M.R.C.: study design, data analysis/interpretation, and drafting/revising manuscript. K.Z. and J.A.S.: study design and drafting/revising manuscript.

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