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Efficacy, Safety, and Population Pharmacokinetic Modeling of Intravenous Recombinant *Erwinia* Asparaginase (JZP458) in Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma: Results from Study AALL1931

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Background

- L-asparaginase is an important component in multiagent treatment regimens for acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in pediatric and adult patients[1,2]
- Antibody-mediated hypersensitivity reaction (HSR) to both native and pegylated forms of *Escherichia coli* (*E. coli*)–derived asparaginase is a common issue associated with treatment discontinuation, occurring in up to 30% of patients[3-5]
- JZP458 is a recombinant *Erwinia* asparaginase derived from a novel *Pseudomonas fluorescens* expression platform to produce a reliable supply of asparaginase with minimal immunologic cross-reactivity to *E. coli*–derived asparaginases
- Based on interim results from Part A of AALL1931, a phase 2/3, 2-part, open-label, multicenter study conducted in collaboration with the Children's Oncology Group, JZP458 (Rylaze®; asparaginase erwinia chrysanthemi (recombinant)-rywn) was approved by the US Food and Drug Administration in June 2021 for intramuscular (IM) administration under the accelerated Real Time Oncology Review (RTOR) program for the treatment of ALL/LBL in patients ≥1 month of age with previous hypersensitivity to *E. coli*–derived asparaginase[6]
  - Results showed that the IM JZP458 dosing regimen of 25 mg/m^2 Monday/Wednesday (MW) and 50 mg/m^2 Friday (F) achieved therapeutic serum asparaginase activity (SAA) levels ≥0.1 IU/mL in ≥90% of patients at both 48 and 72 hours[7]
  - Population pharmacokinetic (PopPK) modeling and simulations were used throughout AALL1931 to inform dosing decisions

Objective

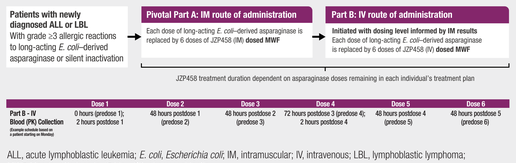
- To report the results from Part B (intravenous [IV] administration) of AALL1931, with the exploratory objectives of characterizing the efficacy, safety, and pharmacokinetics (PK) of IV JZP458, in addition to the development of a PopPK model to determine the appropriate dosing for IV administration as well as for a mixed IV/IM schedule of JZP458

Methods

Study Design and Treatments

- This phase 2/3 study (ClinicalTrials.gov Identifier: NCT04145531) had 2 parts: A and B (**Figure 1**)

Figure 1. Overall Study Design



ALL, acute lymphoblastic leukemia; *E. coli, Escherichia coli*; IM, intramuscular; IV, intravenous; LBL, lymphoblastic lymphoma; MWF, Monday/Wednesday/Friday; PK, pharmacokinetic.

- Based on the results from Part A of the study, Part B evaluated the dosing regimen JZP458 25/25/50 mg/m^2 MWF administered IV over 2 hours for 2 consecutive weeks (6 doses = 1 course) to replace each dose of long-acting *E. coli*–derived asparaginase remaining in the patient's original treatment plan

Exploratory Study Endpoints

- Efficacy was evaluated as the proportion of participants with the last 72-hour nadir SAA (NSAA) level ≥0.1 IU/mL (to evaluate SAA coverage from Friday to Monday) and the proportion of participants with the last 48-hour NSAA level ≥0.1 IU/mL during the first course of IV JZP458 administration
- Safety and tolerability were assessed by the occurrence of treatment-emergent adverse events (AEs), which were graded by severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5

PopPK Modeling and Simulation

- Characterization of the PK profile of IV JZP458 based on SAA was performed using a PopPK approach
  - A PopPK model was developed using nonlinear mixed-effects modeling (NONMEM; version 7.3) with 3,544 SAA data points from all available time points, across all available treatment courses, from 249 participants who received IM or IV JZP458 in the phase 1 or phase 2/3 studies of JZP458[7,8]
  - Model-based simulations of SAA profiles using 2,000 virtual subjects predict the proportions of subjects achieving a therapeutic NSAA level ≥0.1 IU/mL at 72 and 48 hours postdose following different dosing regimens

Results

Participants

- At the data cutoff (July 19, 2021), 61 participants had received ≥1 dose of IV JZP458; 1 patient was enrolled but never received JZP458
- Patient demographic and baseline characteristics are presented in **Table 1**
- At the time of data cutoff, 39 of the 62 enrolled participants (63%) were receiving ongoing treatment with JZP458, and 1 had completed all planned doses of JZP458 treatment
  - The median (range) number of JZP458 courses received was 1 (1, 10)
- A total of 21 participants (34%) discontinued JZP458 treatment, including 15 participants (24%) due to AEs, 4 (6%) due to physician decision, and 1 each due to recurrent disease and patient withdrawal

Table 1. Demographic and Baseline Characteristics (Safety Analysis Set)

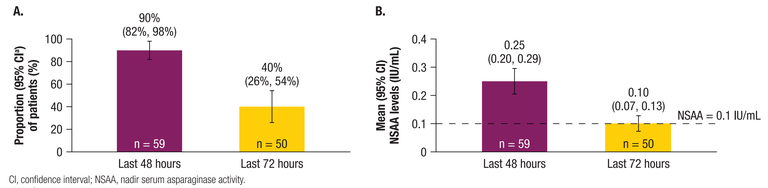
Characteristic	IV JZP458 25/25/50 mg/m^2 MWF (n = 61)
Age, years	
Median (range)	10 (1, 24)
<6, n (%)	20 (33)
6 to <12, n (%)	14 (23)
12 to <18, n (%)	17 (28)
≥18, n (%)	10 (16)
Male, n (%)	36 (59)
Race, n (%)	
White	43 (70)
Asian	3 (5)
Black or African American	2 (3)
American Indian or Alaska Native	2 (3)
Multiple	1 (2)
Not reported	10 (16)
BMI, median (range), kg/m^2	19.6 (13.2, 43.8)
BSA, median (range), m^2	1.2 (0.5, 2.4)
Primary disease, n (%)	
B-ALL	51 (84)
T-ALL	7 (11)
B-LBL	2 (3)
T-LBL	1 (2)
Median (range) days since last asparaginase dose received	13 (2, 138)
Eligibility criteria met, n (%)	
Grade ≥3 allergic reaction to an *E. coli*–derived asparaginase[a]	44 (72)
Silent inactivation[b]	8 (13)
Allergic reaction with inactivation	9 (15)

B-ALL, B-lymphoblastic leukemia; B-LBL, B-lymphoblastic lymphoma; BMI, body mass index; BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events; *E. coli, Escherichia coli*; IV, intravenous; MWF, Monday/Wednesday/Friday; NSAA, nadir serum asparaginase activity; T-ALL, T-lymphoblastic leukemia; T-LBL, T-lymphoblastic lymphoma.
[a]Allergic reactions were graded as per CTCAE version 5.
[b]Silent inactivation was defined as NSAA <0.5 IU/mL within 1 hour to 1 day, or <0.3 IU/mL within 7 days, or <0.1 IU/mL within 14 days of completing a long-acting *E. coli*–derived asparaginase infusion without clinical signs/symptoms of hypersensitivity or allergy.

Efficacy

- At 48 hours after the last dose of IV JZP458 25/25/50 mg/m^2 MWF in Course 1, 53/59 (90%) participants (95% confidence interval [CI]: 82%, 98%) achieved NSAA levels ≥0.1 IU/mL (**Figure 2A**)
- At 72 hours after the last dose of JZP458 in Course 1, 20/50 (40%) participants (95% CI: 26%, 54%) achieved NSAA levels ≥0.1 IU/mL (**Figure 2A**)
- Mean (95% CI) NSAA levels were 0.25 IU/mL (0.20, 0.29) at 48 hours after the last dose of JZP458 and 0.10 IU/mL (0.07, 0.13) at 72 hours after the last dose (**Figure 2B**)

Figure 2. Observed A) Proportion of Participants Achieving NSAA Levels ≥0.1 IU/mL; and B) Mean NSAA Levels in the First Treatment Course



CI, confidence interval; NSAA, nadir serum asparaginase activity.
[a]95% CIs calculated by the Wald method.

Safety

- Fifty-two of the 61 treated participants (85%) experienced treatment-related AEs, and 29 (48%) participants experienced grade 3/4 treatment-related AEs
- Treatment-related AEs of interest and other common treatment-related, nonhematologic AEs are presented in **Table 2**

Table 2. Treatment-related AEs of Interest and Other Commonly Reported (≥5% of Participants) Nonhematologic Treatment-related AEs (Safety Analysis Set)[a]

Participants, n (%)	IV JZP458 25/25/50 mg/m^2 MWF (n = 61)	
	Any grade	Grade 3/4
Treatment-related AEs of interest		
Allergic reaction[b]	14 (23)	9 (15)
Hypersensitivity/drug hypersensitivity	9 (15)	6 (10)
Infusion-related reaction	4 (7)	2 (3)
Anaphylactic reaction	1 (2)	1 (2)
Urticaria	1 (2)	0
Pancreatitis	0	0
Thrombosis	0	0
ALT/AST increased	6 (10)	4 (7)
Blood bilirubin increased	1 (2)	0
Hyperammonemia	1 (2)	1 (2)
Other commonly reported nonhematologic treatment-related AEs		
Vomiting	29 (48)	5 (8)
Nausea	20 (33)	4 (7)

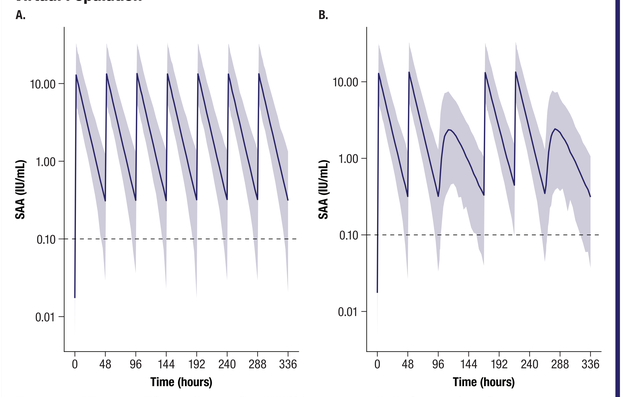
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IV, intravenous; MedDRA, *Medical Dictionary for Regulatory Activities*; MWF, Monday/Wednesday/Friday.
[a]Treatment-related AEs were reported as MedDRA version 22.1 preferred terms.
[b]Some participants reported >1 treatment-related preferred term.

- Treatment-related AEs of any grade led to study discontinuation in 15 participants (25% of treated participants) and included allergic reaction (n = 11; 18% [including 2 patients who discontinued due to grade 2 allergic reaction]), vomiting (n = 2; 3%), nausea (n = 1; 2%), and hyperammonemic encephalopathy (n = 1; 2%)
- There were no fatal AEs

PopPK Modeling and Simulation

- The PK of JZP458 is best characterized by a 1-compartment IVIM combined model with sequential mixed-order IM absorption and linear elimination, with body surface area included as an allometric covariate on JZP458 SAA clearance (CL) and volume of distribution (V), accompanied with race (ie, African American) on JZP458 SAA CL, disease (ALL/LBL) on CL for patients following IM administration, and disease (ALL/LBL) on V
- Preliminary PopPK model–based simulations predicted that NSAA levels ≥0.1 IU/mL are maintained when IV JZP458 is administered at 25 mg/m^2 every 48 hours or when JZP458 is administered IV at 25 mg/m^2 MW and IM at 50 mg/m^2 on F (**Figure 3**)
- Preliminary PopPK model–predicted response rates of NSAA ≥0.1 IU/mL (mean [95% CI]) at the last 48 and 72 hours in the first treatment course were 90.9% (89.5, 92.0) at 48 hours for IV JZP458 25 mg/m^2 every 48 hours, and 92.6% (91.4, 93.7) at 48 hours and 91.3% (90.0, 92.5) at 72 hours for IV/IV/IM JZP458 25/25/50 mg/m^2 MWF

Figure 3. Simulated Median (95% PI) SAA Profiles of A) 25 mg/m^2 IV JZP458 Every 48 Hours; and B) 25/25/50 mg/m^2 IV/IV/IM JZP458 MWF Based on the NHANES Virtual Population



IM, intramuscular; IV, intravenous; MWF, Monday/Wednesday/Friday; NHANES, National Health and Nutrition Examination Survey; PI, prediction interval; SAA, serum asparaginase activity.
Center lines represent the median value; bands (95% PI) represent the 2.5th (lower) and 97.5th (upper) percentiles. The dashed line indicates the target trough level of 0.1 IU/mL.

Conclusions

- IV administration of JZP458 is feasible with a dosing regimen of IV JZP458 25 mg/m^2 every 48 hours or IV/IV/IM JZP458 25/25/50 mg/m^2 on MWF, both of which would maintain NSAA levels ≥0.1 IU/mL in at least 90% of patients based on the study PopPK model
- The safety profile of IV JZP458 was consistent with other asparaginases[3,9,10]
- The proposed regimens would offer dosing flexibility to patients with ALL/LBL, their caregivers, and health care professionals, particularly in many clinical practices where IV administration of asparaginase is preferred

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