1498

Efficacy and Safety of Recombinant *Erwinia* Asparaginase (JZP458) in Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma (LBL): Complete Follow-Up of the Children's Oncology Group AALL1931 Study

Luke Maese,[1,*] Mignon L. Loh,[2] Mi Rim Choi,[3] Tong Lin,[3] Etsuko Aoki,[3] Shirali Agarwal,[3] Vijayalakshmi Chandrasekaran,[4] Yali Liang,[4] Suzette Girgis,[4] Cuiping Chen,[3] Robert Iannone,[4] Lewis B. Silverman,[5] Elizabeth A. Raetz,[6] Rachel E. Rau[2]

[1]University of Utah, Primary Children's Hospital, Salt Lake City, UT, USA; [2]Ben Towne Center for Childhood Cancer Research, Seattle Children's Hospital, University of Washington, Seattle, WA, USA; [3]Jazz Pharmaceuticals, Palo Alto, CA, USA; [4]Jazz Pharmaceuticals, Philadelphia, PA, USA; [5]Dana-Farber Cancer Institute, Boston, MA, USA; [6]New York University Langone Medical Center, New York, NY, USA

*Presenting author.

Background

- L-asparaginase (ASP) is an important component of multi-agent treatment regimens for pediatric and adult patients with ALL/LBL[1,2]
  - However, antibody-mediated hypersensitivity reactions (HSRs) occur in up to 30% of patients receiving *Escherichia coli (E. coli)*-derived ASP, often leading to treatment delay or discontinuation, which is associated with inferior clinical outcomes[3-5]
- JZP458, a recombinant *Erwinia chrysanthemi* ASP derived from a novel *Pseudomonas fluorescens* expression platform, was evaluated in study AALL1931 (ClinicalTrials.gov ID: NCT04145531), a two-part, open-label, phase 2/3 trial conducted in collaboration with the Children's Oncology Group
  - The study investigated the efficacy, safety, and pharmacokinetics (PK) of intramuscular (IM) JZP458 in patients with ALL or LBL who were hypersensitive to *E. coli*-derived ASP; the study also explored the efficacy, safety, and PK of intravenous (IV) JZP458
- Based on interim results from part A of AALL1931,[2] JZP458 (Rylaze®) was approved by the US Food and Drug Administration for IM administration at 25/25/50 mg/m^2 on Monday/Wednesday/Friday (MWF) or at 25 mg/m^2 every 48 hours as a component of a multi-agent chemotherapeutic regimen for the treatment of ALL or LBL in adult and pediatric patients (1 month or older) who have developed hypersensitivity to *E. coli*-derived ASP[6]
  - JZP458 (recombinant crisantaspase; Enrylaze) was also recently approved by the European Medicines Agency for the treatment of ALL and LBL in adult and pediatric patients (1 month and older) who developed hypersensitivity or silent inactivation to *E. coli*-derived ASP for IM and IV administration MWF or every 48 hours[7]
  - Observed data and population pharmacokinetic (popPK) modeling and simulations were used throughout AALL1931 to inform dosing decisions

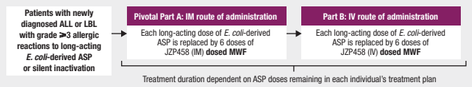
Objectives

- To report the efficacy, safety, and immunogenicity of IM and IV JZP458 at the completion of AALL1931, in addition to the development of a popPK model to determine the appropriate dosing for IM and IV JZP458

Methods

- Eligible patients with ALL/LBL who developed hypersensitivity (grade ⩾3 allergic reaction or silent inactivation) to *E. coli*-derived ASP received JZP458 as part of their multi-agent treatment plan (**Figure 1**)

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 (predose 1); 2.5 h postdose 1	48 h postdose 1 (predose 2)	48 h postdose 2 (predose 3)	72 h postdose 3 (predose 4); 2.5 h postdose 4	48 h postdose 4 (predose 5)	48 h postdose 5 (predose 6)
	Dose 1	**Dose 2**	**Dose 3**	**Dose 4**	**Dose 5**	**Dose 6**
Part B - IV[b,c]	0 h (predose 1); 2 h postdose 1	48 h postdose 1 (predose 2)	48 h postdose 2 (predose 3)	72 h postdose 3 (predose 4); 2 h postdose 4	48 h postdose 4 (predose 5)	48 h postdose 5 (predose 6)

[a]This is a sample schedule for a Monday start; sample collection window: 2.5 hours postdose ±15 minutes; 48 hours ±2 hours; 72 hours ±2 hours.
[b]Three samples were collected for each of the subsequent courses. [c]An end-of-infusion sample is collected 2 hours following the start of infusion.

ALL, acute lymphoblastic leukemia; ASP, asparaginase; *E. coli, Escherichia coli*; h, hour(s); IM, intramuscular; IV, intravenous; LBL, lymphoblastic lymphoma; MWF, Monday/Wednesday/Friday; PK, pharmacokinetics; SAA, serum asparaginase activity.

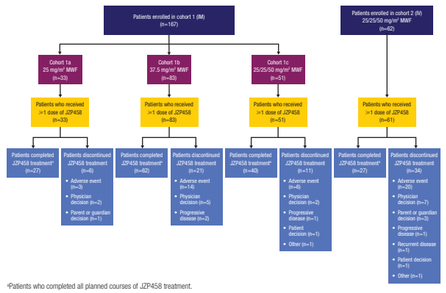
- The study enrolled three IM cohorts (1a [25 mg/m^2 MWF], 1b [37.5 mg/m^2 MWF]), and 1c [25/25/50 mg/m^2 MWF]), and one IV cohort (25/25/50 mg/m^2 MWF)
- The treatment duration was dependent on ASP doses remaining in each individual's treatment plan. Follow-up duration was at least 30 days post the last administration of JZP458 for each patient
- Efficacy was assessed by measuring serum ASP activity (SAA) at defined points and calculating the proportion of patients maintaining therapeutic nadir serum ASP activity (NSAA) ⩾0.1 IU/mL at the last 72-hour (primary endpoint) or 48-hour (key secondary endpoint) time point during course 1
- A popPK model was developed based on SAA from AALL1931 to characterize the PK of both IM and IV JZP458; model-based simulations of SAA profiles for a virtual population using 2000 subjects were performed to predict the proportions of patients achieving a therapeutic NSAA level ⩾0.1 IU/mL at 72 and 48 hours postdose with different dosing regimens
- Presence of antidrug antibody (ADA) and neutralizing antibody (NAb) to JZP458 was evaluated at prespecified time points during the study using a validated electro-chemiluminescence immunosorbent assay and a validated enzymatic activity assay, respectively

Results

Patients

- At the final database lock on November 22, 2022, a total of 167 patients received IM JZP458 (1a, n=33; 1b, n=83; 1c, n=51) and 61 patients received IV JZP458 (**Figure 2**)

Figure 2. Patient Disposition by Cohort



[a]Patients who completed all planned courses of JZP458 treatment.
IM, intramuscular; IV, intravenous; MWF, Monday/Wednesday/Friday.

- The median (range) of JZP458 courses completed was 5 (0-14), 4 (0-15), 5 (1-10), and 3 (0-15) for the IM cohorts 1a, 1b, 1c, and the IV cohort, respectively
- Patient demographics and baseline characteristics are shown in **Table 1**

Table 1. Demographic and Baseline Characteristics

	IM 25 mg/m² MWF (n=33)	IM 37.5 mg/m² MWF (n=83)	IM 25/25/50 mg/m² MWF (n=51)	IM Total (n=167)	IV 25/25/50 mg/m² MWF (n=61)
Median (range) age, years	11 (1-24)	8 (1-20)	12 (3-25)	10 (1-25)	10 (1-24)
Sex, n (%)					
Female	16 (48)	28 (34)	20 (39)	64 (38)	25 (41)
Male	17 (52)	55 (66)	31 (61)	103 (62)	36 (59)
Ethnicity[a], n (%)					
Hispanic or Latino	13 (39)	23 (28)	17 (33)	53 (32)	21 (34)
Not Hispanic or Latino	18 (55)	56 (67)	32 (63)	106 (63)	34 (56)
Declined to state	2 (6)	4 (5)	2 (4)	8 (5)	6 (10)
Race[a], n (%)					
American Indian or Alaska native	0	0	3 (6)	3 (2)	2 (3)
Asian	1 (3)	5 (6)	1 (2)	7 (4)	3 (5)
Black or African American	3 (9)	11 (13)	8 (16)	22 (13)	2 (3)
White	24 (73)	58 (70)	33 (65)	115 (69)	43 (70)
Multiple	1 (3)	0	0	1 (1)	1 (2)
Not reported	4 (12)	9 (11)	6 (12)	19 (11)	10 (16)
Median (range) BMI, kg/m²	19.9 (13.4-42.6)	17.9 (13.7-30.7)[b]	18.4 (13.8-42.0)	18.4 (13.4-42.6)[c]	19.6 (13.2-43.8)
Median (range) BSA, m²	1.28 (0.44-2.53)	1.01 (0.56-2.26)[b]	1.29 (0.54-2.43)	1.18 (0.44-2.53)[c]	1.18 (0.52-2.42)
Primary disease, n (%)					
ALL					
B-ALL	27 (82)	60 (72)	37 (73)	124 (74)	51 (84)
T-ALL	4 (12)	13 (16)	9 (18)	26 (16)	7 (11)
LBL					
B-LBL	0	0	1 (2)	1 (1)	2 (3)
T-LBL	2 (6)	10 (12)	4 (8)	16 (10)	1 (2)
Eligibility criteria met, n (%)					
Grade ⩾3 allergic reaction to an *E. coli*-derived ASP[d]	27 (82)	75 (90)	44 (86)	146 (87)	44 (72)
Silent inactivation[d]	3 (9)	3 (4)	1 (2)	7 (4)	8 (13)
Allergic reaction with inactivation	3 (9)	5 (6)	6 (12)	14 (8)	9 (15)

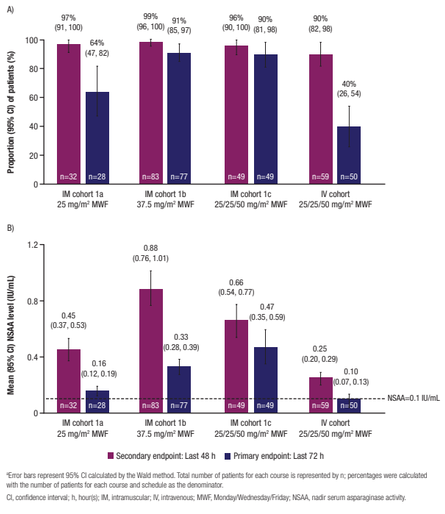
[a]Self-reported; [b]Based on 82 patients; [c]Based on 166 patients; [d]Prior long-acting *E. coli*-derived ASP treatment was pegaspargase for all patients apart from one who received another type of *E. coli*-derived ASP; [e]Silent inactivation was defined as NSAA <0.5 IU/mL within 1 hour to 1 day, or <0.3 IU/mL within 7 days, or <0.1 IU/mL within 14 days of completing a long-acting *E. coli*-derived ASP infusion without clinical signs/symptoms of hypersensitivity or allergy.

ALL, acute lymphoblastic leukemia; ASP, asparaginase; B-ALL, B-cell acute lymphoblastic leukemia; B-LBL, B-cell lymphoblastic lymphoma; BMI, body mass index; BSA, body surface area; *E. coli, Escherichia coli*; IM, intramuscular; IV, intravenous; LBL, lymphoblastic lymphoma; MWF, Monday/Wednesday/Friday; NSAA, nadir serum ASP activity; T-ALL, T-cell acute lymphoblastic leukemia; T-LBL, T-cell lymphoblastic lymphoma.

Efficacy

- **Figure 3** shows the summary of primary and key secondary efficacy endpoints as well as mean NSAA levels by cohort

Figure 3. (A) Proportion of Patients Achieving NSAA Levels ⩾0.1 IU/mL in the First Treatment Course[a] (B) Mean NSAA Levels 48 and 72 Hours After Dose During the First Treatment Course by Cohort[a]



[a]Error bars represent 95% CI calculated by the Wald method. Total number of patients for each course is represented by *n*; percentages were calculated with the number of patients for each course and schedule as the denominator.
CI, confidence interval; h, hour(s); IM, intramuscular; IV, intravenous; MWF, Monday/Wednesday/Friday; NSAA, nadir serum asparaginase activity.

PopPK Modeling and Simulations

- PopPK model-based simulations predicted that therapeutic NSAA levels are achieved in the vast majority of patients with multiple IM and IV dosing schedules (**Table 2**)

Table 2. Predicted Proportion (95% CI) of Patients Achieving NSAA ⩾0.1 IU/mL Based on the PopPK Model

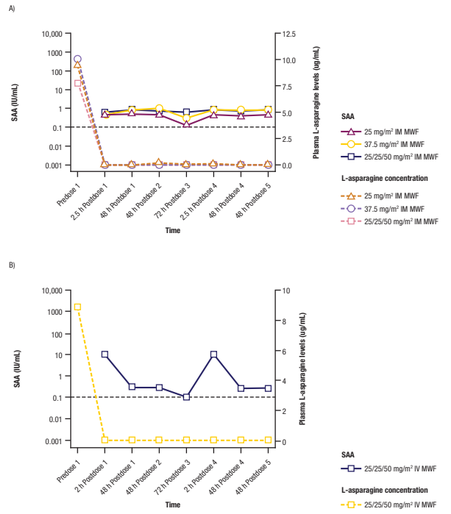
	25/25/50 mg/m² MWF (6 Doses)			25 mg/m² Every 48 h (7 Doses)	
Through Trough	IM	IV	IV/IV/IM	IM	IV
Last 48 h	94.6% (93.6%, 95.6%)	84.0% (82.4%, 85.6%)	89.5% (88.1%, 90.8%)	96.7% (95.9%, 97.4%)	83.4% (81.7%, 85.0%)
Last 72 h	88.5% (87.1%, 89.9%)	38.2% (36.1%, 40.4%)	88.8% (87.4%, 90.1%)	N/A	N/A

CI, confidence interval; h, hour(s); IM, intramuscular; IV, intravenous; MWF, Monday/Wednesday/Friday; N/A, not available; NSAA, nadir serum asparaginase activity; popPK, population pharmacokinetics.

Asparagine Depletion

- Depletion of plasma L-asparagine was observed after JZP458 administration in all dosing cohorts (**Figure 4**)

Figure 4. Asparagine Depletion in the First IM (A) and IV (B) Treatment Course. Mean SAA–Time Profiles and Corresponding Mean Plasma L-Asparagine Levels by Cohort and Dosing Schedule[a,b]



Only showing patients who initiated JZP458 treatment on Mondays; [a]The LLOQ were as follows: SAA = 0.0350 IU/mL; L-asparagine = 0.0250 µg/mL. SAA is graphed on a semi-logarithmic scale while L-asparagine is graphed on a linear scale; [b]For cohort 1a, the sample size for mean SAA levels and plasma asparagine levels ranged from 8-12 patients for all time points. For cohort 1b, the sample size ranged from 15-22 patients for all time points. For cohort 1c, the sample size ranged from 17-19 patients for all time points. For the IV cohort, the sample size ranged from 15-20 patients for all time points.
h, hour(s); IM, intramuscular; IV, intravenous; LLOQ, lower limit of quantitation; MWF, Monday/Wednesday/Friday; SAA, serum asparaginase activity.

Safety

- A total of 126 (75%) patients in the IM cohort and 55 (90%) in the IV cohort experienced ⩾1 treatment-related adverse event (TRAE). A total of 48 (29%) patients in the IM cohort and 29 (48%) in the IV cohort experienced a serious TRAE
  - Three patients in the IM cohort had a fatal event; all three deaths were considered unrelated to JZP458
- A total of 22 (13%) patients across all IM cohorts (1a, n=2; 1b, n=14; 1c, n=6) and 20 (33%) patients in the IV cohort experienced a TRAE leading to treatment discontinuation. The most common TRAEs leading to treatment discontinuation were drug hypersensitivity (IM cohort, 4%; IV cohort, 15%) and pancreatitis (IM cohort, 6%; IV cohort, 3%)
  - All AEs leading to discontinuation were treatment-related, except one case of necrotizing fasciitis in the IM cohort
- **Table 3** shows TRAEs of interest and other commonly reported nonhematologic TRAEs

Table 3. TRAEs of Interest and Other Commonly Reported (⩾10% in IM Total or IV Cohort) Nonhematologic TRAEs[a]

	IM 25 mg/m² MWF (n=33)		IM 37.5 mg/m² MWF (n=83)		IM 25/25/50 mg/m² MWF (n=51)		IM Total (n=167)		IV 25/25/50 mg/m² MWF (n=61)	
Patients, n (%)[b]	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
TRAEs of interest										
Allergic reactions[c]	2 (6)	2 (6)	11 (13)	6 (7)	5 (10)	2 (4)	18 (11)	10 (6)	16 (26)	11 (18)
Pancreatitis[c]	0	0	6 (7)	6 (7)	6 (12)	4 (8)	12 (7)	10 (6)	3 (5)	2 (3)
Thrombosis[c]	0	0	2 (2)	2 (2)	0	0	2 (1)	2 (1)	1 (2)	0
ALT/AST increased[c]	3 (9)	2 (6)	14 (17)	9 (11)	9 (18)	3 (6)	26 (16)	14 (8)	11 (18)	7 (11)
Blood bilirubin increased[c]	0	0	8 (10)	1 (1)	3 (6)	2 (4)	11 (7)	3 (2)	3 (5)	1 (2)
Hyperammonemia	0	0	3 (4)	2 (2)	0	0	3 (2)	2 (1)	2 (3)	1 (2)
Other commonly reported nonhematologic TRAEs										
Nausea	7 (21)	1 (3)	20 (24)	6 (7)	13 (25)	2 (4)	40 (24)	9 (5)	27 (44)	7 (11)
Vomiting	7 (21)	0	22 (26)	3 (4)	10 (20)	1 (2)	39 (23)	4 (2)	36 (59)	8 (13)
Decreased appetite	3 (9)	1 (3)	12 (14)	3 (4)	9 (18)	1 (2)	24 (14)	5 (3)	5 (8)	0
Fatigue	3 (9)	1 (3)	17 (20)	0	3 (6)	0	23 (14)	1 (1)	8 (13)	0
Abdominal pain	2 (6)	0	9 (11)	2 (2)	6 (12)	0	17 (10)	2 (1)	3 (5)	1 (2)
Febrile neutropenia	2 (6)	2 (6)	11 (13)	11 (13)	4 (8)	4 (8)	17 (10)	17 (10)	3 (5)	3 (5)
Hyperglycemia	3 (9)	1 (3)	5 (6)	2 (2)	7 (14)	3 (6)	15 (9)	6 (4)	7 (11)	6 (10)

[a]TRAEs were reported as MedDRA (version 22.1) preferred terms. The severity of TRAEs was recorded using CTCAE 5.0; [b]Some patients had >1 TRAE; [c]Includes the preferred terms drug hypersensitivity, hypersensitivity, anaphylactic reaction, rash maculo-papular, rash erythematous, rash, urticaria, and infusion-related reaction; [d]Includes the preferred terms of pancreatitis and acute pancreatitis; [e]Includes the preferred terms superior sagittal sinus thrombosis, pulmonary embolism, jugular vein thrombosis, and deep vein thrombosis; [f]Includes the preferred terms ALT increased, AST increased; [g]Includes the preferred terms blood bilirubin increased and conjugated bilirubin increased.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; IM, intramuscular; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; MWF, Monday/Wednesday/Friday; TRAE, treatment-related adverse event.

Immunogenicity

- In the IM cohort, 82 (49%) had confirmed ADA toward JZP458. Seventy-five patients developed ADA toward JZP458 following treatment and 55 of them subsequently became ADA negative at least once during the study
  - Among patients receiving IM JZP458, HSRs were experienced by 13% and 8% of ADA positive and ADA negative patients, respectively
- In the IV cohort, 34 (56%) had confirmed ADA toward JZP458. Thirty-three patients developed ADA toward JZP458 following treatment and 18 of them subsequently became ADA negative at least once during the study
  - Among patients receiving IV JZP458, HSRs were experienced by 35% and 15% of ADA positive and ADA negative patients, respectively
- The number of patients who developed NAb was low overall (IM cohort, n=4, 2%; IV cohort, n=2, 3%), and ADA status did not appear to impact the PK of JZP458
- The majority of patients who developed a positive ADA toward JZP458 following administration of JZP458 became ADA negative at least once during the study

Conclusions

- Both observed data and popPK modeling results demonstrate that JZP458 achieves therapeutic NSAA levels via multiple IM and IV dosing schedules providing flexibility to patients and physicians, with IM dosing having more sustained SAA
- Results at the completion of AALL1931 in patients with ALL/LBL and allergic reactions or silent inactivation to *E. coli*-derived ASP show that the safety profile of JZP458 is consistent with other ASP, with no new adverse safety signals[1,8]
- The treatment-related discontinuation rate with IV JZP458 was greater than with IM, primarily due to increased incidence of HSRs/infusion-related reactions; however, the study was not designed nor statistically powered to compare across dosing cohorts or routes of administration
- No specific immunological concerns were identified with JZP458 beyond the known immunogenicity risks associated with other ASP. No specific clinical decisions are recommended based on immunogenicity testing

References: 1. Hijiya N, van der Sluis IM. *Leuk Lymphoma.* 2016;57:748-757. **2.** Maese L, et al. *Blood.* 2023;141:704-712. **3.** Burke MJ, Zalewska-Szewczyk B. *Future Oncol.* 2022;18:1285-1299. **4.** Burke MJ. *Future Oncol.* 2014;10:2615-2627. **5.** Gupta S, et al. *J Clin Oncol.* 2020;38:1897-1905. **6.** RYLAZE™ (asparaginase erwinia chrysanthemi (recombinant)-rywn) [prescribing information]. Jazz Pharmaceuticals Ireland Limited; 2022. **7.** European Medicines Agency. Enrylaze Medicine overview; 2023. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/enrylaze. **8.** Burke MJ, Rheingold SR. *Leuk Lymphoma.* 2017;58:540-551.

Support and Acknowledgments: This study was supported by Jazz Pharmaceuticals. Medical writing support, under the direction of the authors, was provided by Alice Christakou, MSc, and Katie Groschwitz, PhD, of CMC Affinity, a division of IPG Health Medical Communications, with funding from Jazz Pharmaceuticals, in accordance with Good Publication Practice (GPP 2022) guidelines.

Presented at the 65th American Society of Hematology (ASH) Annual Meeting and Exposition
December 9-12, 2023; San Diego, California