# Recombinant Erwinia Asparaginase (JZP458) in Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma (ALL/LBL): Post Hoc Analysis of Adverse Events of Interest From AALL1931

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## **Background**

- L-asparaginase (ASP) is an important component of multi-agent treatment regimens for pediatric and adult patients with ALL/LBL1,2
- However, antibody-mediated hypersensitivity reactions occur in up to 30% of patients receiving *Escherichia coli (E. coli)*-derived ASP, often leading to treatment discontinuation, which is associated with inferior clinical outcomes<sup>3-5</sup>
- The pivotal Children's Oncology Group Study AALL1931 (NCT04145531) evaluated JZP458, a recombinant *Erwinia* ASP, in patients with ALL/LBL who developed hypersensitivity/silent inactivation to *E. coli*-derived ASPs, leading to the approval of JZP458 in the US (Rylaze®) and the European Union (Enrylaze®)
- In the US, JZP458 is approved for intramuscular (IM) administration at 25 mg/m<sup>2</sup> on Mondays/Wednesday and 50 mg/m<sup>2</sup> on Friday, or at 25 mg/m<sup>2</sup> every 48 hours<sup>6</sup>
- In the European Union, JZP458 is approved for IM or intravenous (IV) administration Monday/Wednesday/Friday (MWF) or every 48 hours<sup>7</sup>
- The primary efficacy and safety results of AALL1931 have been reported<sup>8</sup>

 To report on adverse events (AEs) of interest (AEIs; comprising allergic reactions, [including infusion reactions], pancreatitis, thrombosis, hepatotoxicity) and nausea/vomiting, and to summarize post hoc descriptive analyses of AEIs by timing and known risk factors (e.g., age and ethnicity)

### Methods

Figure 1. Study Design

Eligible patients with ALL or LBL who experienced grade ≥3 HSR to a long-acting <i>E. coli</i> ASP or silent inactivation	

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Pivotal Part A: IM route of administration	Part B: IV route of administration
Each long-acting dose of E. coli-derived ASP is replaced by 6 doses of JZP458 (IM) administered at: IM 25 mg/m² MWF (Cohort 1a) IM 37.5 mg/m² MWF (Cohort 1b)	Each long-acting dose of E. coli-derived ASP is replaced by 6 doses of JZP458 (IV) administered at IV 25/25/50 mg/m² MWF

/50 mg/m² MWF IM 25/25/50 mg/m<sup>2</sup> MWF

Treatment duration depending on ASP doses remaining in each individual's treatment plan

Primary objectives: Safety and efficacy of IM JZP458				
Efficacy	Proportion of patients with the last 72-hour (72 hours after the Friday dose) NSAA level ≥0.1 IU/mL during course 1			
Safety	Occurence of TEAEs			

Key secondary objective: Efficacy of IM JZP458 at a different time point Proportion of patients with the last 48-hour (48 hours after the Monday or

Wednesday dose) NSAA level ≥0.1 IU/mL during course 1 Exploratory objectives: Efficacy and safety of IV JZP458

Proportions of patients with the last 48/72-hour NSAA level ≥0.1 and **≥0.4 IU/mL** during course 1

Occurence of TEAEs

 $ALL, acute \ lymphoblastic \ leukemia; ASP, as paraginase; \textit{E. coli, Escherichia coli, HSR}, \ hypersensitivity \ reactions;$ IM, intramuscular; IV, intravenous; IU, International Unit; LBL, lymphoblastic lymphoma; mL, milliliter; MWF, Monday/Wednesday/Friday; NSAA, nadir serum ASP activity; TEAE, treatment-emergent adverse event.

- This two-part, open-label, phase 2/3 study evaluated IM and IV administration of
- Each dose of long-acting E. coli-derived ASP was replaced by 1 course (6 doses) of JZP458 administered over 2 weeks
- This post hoc descriptive analysis assessed rates of AEIs, and results were stratified by known risk factors (age and ethnicity); timing of AEIs and grade ≥2 nausea/vomiting (a common treatment-related AE [TRAE] in the trial) were summarized by dosage
- The timing of AEIs and nausea/vomiting were described by the median (range) number of doses on or before the first event and the number (frequency) of events after the 25 mg/m<sup>2</sup> doses and after the 50 mg/m<sup>2</sup> doses (before the next dose)

### Results

	Table 1. Demographic and Baseline Characteristics								
		IV JZP458							
Characteristics	25 mg/m² MWF n=33	37.5 mg/m² MWF n=83	25/25/50 mg/m² MWF n=51	IM Total N=167	25/25/50 mg/m² MWF N=61				
Age									
Median (range), years <6 years, n (%) 6 to <12 years, n (%) 12 to <18 years, n (%) ≥18 years, n (%)	11 (1-24) 9 (27) 9 (27) 7 (21) 8 (24)	8 (1-20) 24 (29) 34 (41) 20 (24) 5 (6)	12 (3-25) 11 (22) 14 (28) 18 (35) 8 (16)	10 (1-25) 44 (26) 57 (34) 45 (27) 21 (13)	10 (1-24) 20 (33) 14 (23) 17 (28) 10 (16)				
Sex, n (%)									
Male Female	17 (52) 16 (48)	55 (66) 28 (34)	31 (61) 20 (39)	103 (62) 64 (38)	36 (59) 25 (41)				
BMI <sup>a</sup>	19.9	17.9	18.4	18.4	19.6				
Median (range), kg/m <sup>2</sup>		(13.7-30.7) <sup>b</sup>							
<25 kg/m², n (%) 25 to <30 kg/m², n (%) ≥30 kg/m², n (%)	26 (79) 4 (12) 3 (9)	74 (89) 6 (7) 2 (2)	41 (80) 2 (4) 8 (16)	141 (84) 12 (7) 13 (8)	51 (84) 4 (7) 6 (10)				
Median (range) BSA, m²	1.28 (0.44-2.53)	1.01 (0.56-2.26) <sup>b</sup>	1.29 (0.54-2.43)	1.18 (0.44-2.53) <sup>c</sup>	1.18 (0.52-2.42				
Race, <sup>d</sup> n (%) White Black or African American Asian	24 (73) 3 (9) 1 (3)	58 (70) 11 (13) 5 (6)	33 (65) 8 (16) 1 (2)	115 (69) 22 (13) 7 (4)	43 (70) 2 (3) 3 (5)				
American Indian or Alaska native	0	0	3 (6)	3 (2)	2 (3)				
Multiple Not reported	1 (3) 4 (12)	0 9 (11)	0 6 (12)	1 (1) 19 (11)	1 (2) 10 (16)				
Ethnicity, <sup>d</sup> n (%) Hispanic or Latino Not Hispanic or Latino Declined to state	13 (39) 18 (55) 2 (6)	23 (28) 56 (67) 4 (5)	17 (33) 32 (63) 2 (4)	53 (32) 106 (63) 8 (5)	21 (34) 34 (56) 6 (10)				
Primary Disease, n (%) ALL B-ALL	27 (82)	60 (72)	37 (73)	124 (74)	51 (84)				
T-ALL LBL B-LBL	4 (12) 0	13 (16)	9 (18)	26 (16)	7 (11)				

<sup>a</sup>Only patients with data available. <sup>b</sup>Based on 82 patients. <sup>c</sup>Based on 166 patients. <sup>d</sup>Self-reported. ALL, acute lymphoblastic leukemia; B-ALL, B-cell acute lymphoblastic leukemia; B-LBL, B-cell lymphoblastic lymphoma; BMI, body mass index; BSA, body surface area; IM, intramuscular; IV, intravenous; LBL, lymphoblastic lymphoma; riday: T-ALL T-cell acute lymphoblastic leukemia: T-LBL T-cell lymphoblastic lym

#### **Patients**

• As of the final database lock, 167 patients received IM JZP458 (1a. n=33: 1b, n=83; 1c, n=51) and 61 patients received IV JZP458 (**Table 1**)

Table 2. Summary of Overall AEs and Any-Grade Treatment-Related AEIs by Age G	roun
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	IM JZP458			IV JZP458						
	<6 Years n=44	6 to <12 Years n=57	12 to <18 Years n=45	≥18 Years n=21	IM Total N=167	<6 Years n=20	6 to <12 Years n=14	12 to <18 Years n=17	≥18 Years n=10	IV Total N=61
Any TEAEs, n (%)	43 (98)	55 (96)	45 (100)	21 (100)	164 (98)	20 (100)	13 (93)	17 (100)	10 (100)	60 (98)
Any TRAEs, n (%)	31 (70)	38 (67)	40 (89)	17 (81)	126 (75)	19 (95)	13 (93)	14 (82)	9 (90)	55 (90)
Grade 3/4 TRAEs, n (%)	20 (45)	30 (53)	28 (62)	10 (48)	88 (53)	14 (70)	9 (64)	10 (59)	5 (50)	38 (62)
Any-grade treatment-re	elated AEIs,	n (%)								
Allergic reactions	7 (16)	6 (11)	3 (7)	2 (10)	18 (11)	4 (20)	4 (29)	6 (35)	2 (20)	16 (26)
Pancreatitis	0	1 (2)	7 (16)	4 (19)	12 (7)	1 (5)	0	2 (12)	0	3 (5)
Thrombosis	0	0	1 (2)	1 (5)	2 (1)	0	0	0	1 (10)	1 (2)
Increased ALT/AST	7 (16)	7 (12)	10 (22)	2 (10)	26 (16)	3 (15)	4 (29)	3 (18)	1 (10)	11 (18)
Increased bilirubin	1 (2)	2 (4)	7 (16)	1 (5)	11 (7)	0	3 (21)	0	0	3 (5)

Note: ALT/AST increased includes the terms ALT increased, AST increased, and transaminase increased. Bilirubin increased includes the terms blood bilirubin increased and conjugated AF adverse events: AFIs adverse events of interest: ALT alanine aminotransferase: AST aspartate aminotransferase: IM intramuscular: IV intravenous: TEAF treatment-emergent adverse events

#### **AEIs by age group**

- There were no apparent increases in rates of TEAEs or TRAEs by age group across dosing cohorts (**Table 2**)
- Rates of any-grade treatment-related allergic reactions, pancreatitis, thrombosis, increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST), and increased bilirubin in the IM cohort were 11%, 7%, 1%, 16%, and 7%, respectively, and 26%, 5%, 2%,
- Subgroup analyses showed no consistent trends in rates of any-grade treatment-related AEIs by age group (Table 2)

#### Table 3. Summary of Any-Grade Treatment-Related AEIs by Ethnicity

Any-grade treatment-related AEIs, n (%) <sup>a</sup>	Hispanic/Latino n=74	Non-Hispanic/Latino n=140
Allergic reactions	9 (12)	22 (16)
Pancreatitis	4 (5)	11 (8)
Thrombosis	1 (1)	2 (1)
Increased ALT/AST	14 (19)	22 (16)
Increased bilirubin	5 (7)	8 (6)

Note: ALT/AST increased includes the terms ALT increased, AST increased, and transaminase increased. Bilirubin increased includes the terms blood bilirubin increased and conjugated

<sup>a</sup>Numbers and frequences of AEIs from the IM and IV cohorts were pooled by ethnicity AEI, adverse events of interest: ALT, alanine aminotransferase: AST, aspartate aminotransferase: IM, intramuscular: IV, intravenous

#### **AEIs by ethnicity**

• Rates of any-grade treatment-related allergic reactions, pancreatitis, thrombosis, increased ALT/AST, and increased bilirubin were similar between Hispanic patients (n=74) and non-Hispanic patients (n=140) (**Table 3**)

### Table 4. Timing and Dose Information of Treatment-Related Any-Grade AEIs and Grade ≥2 Nausea/Vomiting

	IM JZP458 All Dosing Cohorts N=167	IV JZP458 25/25/50 mg/m² MWF N=61
Median (range) number of doses on/before the onset of AEIs		
Allergic reactions <sup>a</sup>	13 (1-64)	6 (1-25)
Pancreatitis	11 (4-30)	18 (12-18)
Thrombosis	9 (4-14)	21 (21-21)
Increased ALT/AST	6 (2-55)	7 (2-30)
Increased bilirubin	11 (1-30)	11 (8-15)
	25/25/50 mg/m² MWF n=51	25/25/50 mg/m² MWF N=61
Number of any-grade allergic reaction events, n	8	20
On/after 25 mg/m <sup>2</sup> , n (%) <sup>b</sup>	3 (38)	9 (45)
On/after 50 mg/m², n (%) <sup>b</sup>	5 (62)	11 (55)
No dose within 7 days of event, n (%) <sup>b</sup>	0	0
Number of patients experiencing grade ≥2 nausea/vomiting, n (%)	11 (22)	37 (61)
Number of grade ≥2 nausea/vomiting events, n	20	81
On/after 25 mg/m <sup>2</sup> , n (%) <sup>b</sup>	8 (40)	36 (44)
On/after 50 mg/m², n (%) <sup>b</sup>	11 (55)	43 (53)
No dose within 7 days of event, n (%) <sup>b</sup>	1 (5)	2 (2)
Described and the state of the		

Percentages may not add up to 100 due to rounding

alncludes anaphylactic reaction, (drug) hypersensitivity, infusion-related reaction, rash, rash erythematous, rash maculopapular, and urticaria. Frequencies were derived based on the number

AEIs, adverse events of interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IM, intramuscular; IV, intravenous; MWF, Monday/Wednesday/Friday.

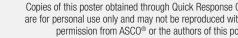
#### Timing of AEIs and nausea/vomiting

- Timing of any-grade AEIs and grade ≥2 nausea/vomiting by route of administration is shown in **Table 4**, including the median number of doses on/before the onset of AEIs
- Consistent with literature reports on native Erwinia ASP,9 treatment-related allergic reactions (including infusion reactions) were observed more frequently in patients receiving IV JZP458 compared with patients receiving IM JZP458 (rates of any-grade treatment-related allergic reactions: 26% [16/61] vs 11% [18/167], respectively)
- Treatment-related allergic reactions occurred after both the 25 mg/m² dose and 50 mg/m² dose, regardless of administration route
- Among patients who developed treatment-related allergic reactions, the events occurred during course 1 in 39% of patients (7/18) receiving IM JZP458, and 62% of patients (10/16) receiving IV JZP458
- Treatment-related grade ≥2 nausea/vomiting occurred in 21% of patients across IM cohorts and 61% of patients in the IV cohort Rates of grade ≥2 nausea/vomiting events were broadly similar following 25 and 50 mg/m² IM or IV dosing

## **Conclusions**

- The safety profile of JZP458 is consistent with other ASPs in patients with ALL/LBL being treated with multi-agent chemotherapy; 8,10,11 rates of treatment-related pancreatitis, thrombosis, and hepatotoxicity were similar for the IM and IV cohorts and in line with the safety profile expected with ASPs in general
- The rates of AEIs were generally similar across age subgroups and between Hispanic and
- Consistent with literature reports on native *Erwinia* ASP,9 treatment-related allergic reactions were more frequent in the IV cohort than in the IM cohort. Rates of nausea and vomiting were also more frequent
- Frequencies of allergic reactions and grade ≥2 nausea/vomiting following the 25 mg/m² and 50 mg/m² doses were broadly similar
- These post hoc analyses were limited by the relatively small number of patients in each subgroup at a certain dose level

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