SUPPLEMENTARY TABLE 1 Demographic and clinical characteristics by pediatric and young adult age subgroups in the local MTX assay (non-HPLC) population (*N* = 163)

	Local assay (non-HPLC) population (*N* = 163)			
	Infant ≥28 days to <2 years (*N* = 4)	**Children** ≥2 to <12 years (*N* = 64)	**Adolescent** ≥12 to <15 years (*N* = 39)	**Young adult** ≥15 to <25 years (*N* = 56)
Demographic characteristics				
Age, years (range)	0 (0–0.5)	8 (2–11)	13 (12–14)	17 (15–22)
Female sex, n (%)	*(n = 3)*	*(n = 50)*	*(n = 30)*	*(n = 46)*
	1 (33.3)	17 (34.0)	17 (56.7)	18 (39.1)
	(n = 4)	*(n = 63)*	*(n = 39)*	*(n = 55)*
Weight, kg (range)	6.8	29.0	52.9	67.0
	(3.5–8.3)	(12.5–71.2)	(25.0–82.0)	(38.0–157.0)
BSA, m^2 (range)	*(n = 4)*	*(n = 63)*	*(n = 39)*	*(n = 54)*
	0.4 (0.3–0.4)	1.0 (0.6–1.8)	1.6 (1.0–1.9)	1.8 (1.4–2.9)
Tumor type, n (%)	*(n = 4)*	*(n = 64)*	*(n = 39)*	*(n = 56)*
ALL	2 (50.0)	29 (45.3)	13 (33.3)	12 (21.4)
NHL	0	10 (15.6)	7 (18.0)	12 (21.4)
Osteosarcoma	0	20 (31.3)	18 (46.2)	24 (42.9)
Other	2 (50.0)	1 (1.6)	0	5 (8.9)
PCNSL	0	1 (1.6)	0	0
Unknown	0	3 (4.7)	1 (2.6)	3 (5.4)
Clinical characteristics				

MTX dose, g/m^2 (range)	*(n = 4)*	*(n = 64)*	*(n = 39)*	*(n = 56)*
	3.3 (0.01–4.0)	5.0 (1.0–17.0)	8.0 (0.3–18.0)	5.5 (0.01–20.0)
	(n = 4)	*(n = 62)*	*(n = 38)*	*(n = 53)*
First glucarpidase dose, U/kg (range)	50.3	50.0	48.8	38.6
	(50.0–52.6)	(31.3–100.0)	(25.5–56.6)	(12.7–54.7)
Number of glucarpidase doses, n (%)	*(n = 4)*	*(n = 64)*	*(n = 39)*	*(n = 56)*
1	4 (100.0)	44 (68.8)	28 (71.8)	45 (80.4)
2	0	19 (29.7)	11 (28.2)	10 (17.9)
3	0	1 (1.6)	0	1 (1.8)
Time between MTX and first glucarpidase dose, days (range)	*(n = 4)*	*(n = 64)*	*(n = 39)*	*(n = 56)*
	3 (2–4)	3 (2–8)	3 (1–9)	3 (1–8)
Baseline (pre-glucarpidase) local MTX concentration, µmol/L (range)	*(n = 4)*	*(n = 63)*	*(n = 39)*	*(n = 54)*
	44.8	39.0	28.9	20.3
	(1.6–120.4)	(0.2–1606.0)	(0.5–1728.0)	(0.3–4500.0)
Normalized baseline (pre-glucarpidase) calculated creatinine clearance, mL/min/1.73m^2 (range)	*(n = 4)*	*(n = 61)*	*(n = 39)*	*(n = 53)*
	194.2	79.0	41.8	52.2
	(117.8–202.1)	(19.1–302.9)	(12.8–135.5)	(20.8–115.0)
<15 mL/min/1.73m^2, n (%)	0	0	1 (2.6)	0
≥15–<30 mL/min/1.73m^2, n (%)	0	5 (7.8)	9 (23.1)	6 (10.7)
≥30–<60 mL/min/1.73m^2, n (%)	0	17 (26.6)	16 (41.0)	28 (50.0)
≥60 mL/min/1.73m^2, n (%)	4 (100.0)	39 (60.9)	13 (33.3)	19 (33.9)
Hepatic impairment, n (%)	*(n = 4)*	*(n = 64)*	*(n = 39)*	*(n = 56)*
Bilirubin >3 × ULN	0	10 (15.6)	4 (10.3)	3 (5.4)

Data are median (range) unless otherwise stated.

ALL, acute lymphoblastic leukemia; BSA, body surface area; HPLC, high-performance liquid chromatography; MTX, methotrexate; NHL, non-Hodgkin lymphoma; ULN, upper limit of normal.

SUPPLEMENTARY TABLE 2 Analysis of reduction in MTX concentration to ≤1 µmol/L by local MTX assay

	Local MTX assay population (*N* = 241) Reduction in MTX concentration to ≤1 µmol/L[a]	
	***n*/N1 (%)**	**[95% CI][b]**
Age group		
Infant (≥28 days to <2 years)	3/5 (60.0)	[23.1, 88.2]
Children (≥2 to <12 years)	37/80 (46.3)	[35.8, 57.2]
Adolescent (≥12 to <15 years)	26/58 (44.8)	[32.7, 57.5]
Young adult (≥15 to <25 years)	54/98 (55.1)	[45.2, 64.6]

[a]Post 24 hours after glucarpidase for studies 001 and 003; ≥2 days after glucarpidase dose for studies 002 and 006;

[b]Newcombe and Altman method.

CI, confidence interval; MTX, methotrexate; N1, number of patients in each subgroup, used as the denominator.

SUPPLEMENTARY TABLE 3 Summary of pharmacokinetic parameters by age group

	Central HPLC population			
	Infant ≥28 days to <2 years (*N* = 1)	**Children** ≥2 to <12 years (*N* = 16)	**Adolescent** ≥12 to <15 years (*N* = 24)	**Young adult** ≥15 to <25 years (*N* = 45)
MTX[a] by central HPLC				
AUC_{0-2} (µmol·h/L)	–	43.2 (42.6)	30.6 (44.1)	14.9 (18.0)
C_2 (µmol/L)	–	2.5 (3.3)	1.5 (1.6)	1.0 (1.2)
C_{max} (µmol/L)	–	3.3 (3.9)	1.7 (1.7)	1.4 (2.1)
T_{max} (h)	–	1.0 (0.9)	0.8 (0.7)	0.7 (0.6)
C_0 (µmol/L)	–	306.3 (301.4)	179.0 (224.8)	95.4 (109.3)
C_{first} (µmol/L)	–	3.0 (3.6)	1.4 (1.2)	1.3 (2.0)
T_{first} (h)	–	0.24 (0.02)	0.27 (0.06)	0.37 (0.41)
DAMPA by central HPLC				
AUC_{0-2} (µmol·h/L)	6.8 (–)	411.1 (511.4)	239.2 (372.9)	92.1 (138.3)
C_2 (µmol/L)	2.1 (–)	207.3 (267.0)	114.0 (179.4)	42.4 (68.1)
C_{max} (µmol/L)	6.2 (–)	248.8 (295.2)	133.0 (196.1)	65.3 (95.6)
T_{max} (h)	0.3 (–)	0.3 (0.2)	1.7 (5.1)	0.9 (3.7)
C_0 (µmol/L)	0.0 (–)	3.5 (9.1)	0.1 (0.4)	0.2 (0.9)
C_{first} (µmol/L)	6.2 (–)	247.8 (294.0)	118.1 (170.4)	64.8 (95.2)
T_{first} (h)	0.25 (–)	0.24 (0.02)	1.45 (5.17)	0.86 (3.71)
AUC_{last} (µmol·h/L)	43.2 (–)	4621.4 (8154.7)	1951.6 (3430.7)	563.2 (1254.3)
C_{last} (µmol/L)	0.6 (–)	29.5 (58.4)	7.9 (15.3)	11.4 (32.8)
T_{last} (h)	29.0 (–)	33.8 (30.2)	46.6 (39.4)	32.3 (34.6)

$t_{1/2}$ (h)	–	9.8 (5.6)	10.0 (4.6)	10.4 (9.6)
AUC_{inf} (µmol·h/L)	–	4692.7 (8869.2)	2811.8 (4070.6)	976.2 (1622.9)

Data are mean (standard deviation)

[a]Pharmacokinetic analyses for the period 0–2 hours.

AUC, area under the concentration-time curve; C, concentration; DAMPA, 2,4-diamino-N10-methylpteroic acid; HPLC, high-performance liquid chromatography; MTX, methotrexate; T, time; –, not reported.

SUPPLEMENTARY TABLE 4 Adverse events with a fatal outcome

Main safety population
Infant ≥28 days to <2 years
Hemophagocytic lymphohistiocytosis (*n* = 1)
Children ≥2 to <12 years
Bone marrow toxicity (*n* = 1)
Death (*n* = 2)
Mucosal inflammation (*n* = 1)
Multi-organ failure (*n* = 1)
Infection (*n* = 1)
Pulmonary toxicity (*n* = 1)
Skin toxicity (*n* = 1)
Circulatory collapse (*n* = 1)
Adolescent ≥12 to <15 years
Multi-organ failure (*n* = 1)
Toxic shock syndrome (*n* = 1)
Young adult ≥15 to <25 years
Anemia (*n* = 1)
Leukopenia (*n* = 1)
Thrombocytopenia (*n* = 1)
Death (*n* = 1)
Hepatic failure (*n* = 1)
Graft versus host disease (*n* = 1)
Infection (*n* = 2)
Sepsis (*n* = 1)
Malignant neoplasm progression (*n* = 1)
Encephalitis (*n* = 1)
Neurological decompensation (*n* = 1)
Pulmonary edema (*n* = 1)
Respiratory disorder (*n* = 1)

Adverse events with a fatal outcome are listed in the table; a patient could have experienced more than 1 adverse event with a fatal outcome

SUPPLEMENTARY TABLE 5 Laboratory abnormalities that worsened from baseline by at least 2 CTCAE grades by age group

	Main safety population[a]			
	Infant ≥28 days to <2 years	**Children ≥2 to <12 years**	**Adolescent ≥12 to <15 years**	**Young adult ≥15 to <25 years**
Highest value post-baseline worsened by ≥2 grades, *n* (%)				
Sodium (mEq/L)	0 (0)	0 (0)	1 (1.7)	1 (1.1)
Potassium (mEq/L)	0 (0)	5 (6.5)	4 (6.8)	7 (7.6)
AST (U/L)	1 (25.0)	7 (10.6)	8 (14.3)	7 (7.7)
ALT (U/L)	2 (50.0)	8 (11.0)	10 (17.2)	10 (11.4)
Bilirubin (mg/dL)	0 (0)	7 (9.9)	7 (12.5)	5 (5.9)
Lowest value post-baseline worsened by ≥2 grades, *n* (%)				
Sodium (mEq/L)	1 (20.0)	6 (7.9)	7 (12.1)	6 (6.5)
Potassium (mEq/L)	2 (40.0)	27 (35.1)	16 (27.1)	21 (22.8)
Bicarbonate (mEq/L)	1 (25.0)	3 (5.4)	3 (6.7)	2 (2.6)
Hemoglobin (g/dL)	3 (60.0)	31 (41.9)	19 (34.5)	17 (18.5)
Leukocytes ($\times 10^3$/µL)	3 (60.0)	39 (53.4)	21 (36.8)	37 (40.7)
Neutrophils ($\times 10^3$/µL)	N/A	3 (25.0)	3 (27.3)	8 (57.1)
Platelets ($\times 10^3$/µL)	5 (100.0)	25 (34.2)	13 (23.6)	28 (30.1)

Data are the number of patients (%) among those who had both baseline and ≥1 post-baseline assessment within 30 days of the last glucarpidase dose, who had worsening of at least 2 CTCAE grades for the specified assessment.

[a]Only includes patients who have evidence of follow-up post-glucarpidase.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; N/A, not available.