Clinical trial results:
A TACL Phase 1/2 Study of PO Ixazomib in Combination with Chemotherapy for Childhood Relapsed or Refractory Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma

Summary

EudraCT number	2019-001947-28
Trial protocol	Outside EU/EEA
Global end of trial date	03 December 2023

Results information

Result version number	v2 (current)
This version publication date	19 June 2024
First version publication date	03 December 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	T2017-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03817320
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, MA, United States, 60015
Public contact	Study Director, Takeda, trialdisclosures@takeda.com
Scientific contact	Study Director, Takeda, trialdisclosures@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001410-PIP02-17
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 December 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D), define and describe toxicities, characterize the pharmacokinetics, and determine the efficacy of orally (PO) administered ixazomib in conjunction with block 1 re-induction chemotherapy in children with relapsed/refractory acute lymphoblastic leukaemia (ALL) or lymphoblastic lymphoma (LLy).

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 February 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 20
Worldwide total number of subjects	20
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	2
Children (2-11 years)	11
Adolescents (12-17 years)	6
Adults (18-64 years)	1
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at investigative sites in the United States from 12 February 2019 to 03 December 2023.

Pre-assignment

Screening details:

Participants with childhood relapsed/refractory acute lymphoblastic leukemia & lymphoblastic lymphoma were enrolled to receive ixazomib 1.6 mg/m^2/day or 2 mg/m^2/day in Phase 1 & those who received 2 mg/m^2/day(RP2D) in Phase 1 continued to Phase 2 to receive ixazomib 2 mg/m^2/day along with the newly enrolled participants in Phase 2 of the study.

Period 1

Period 1 title	Phase 1
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Ixazomib 1.6 mg/m^2

Arm description:

Ixazomib at dose level 1, 1.6 mg/m^2/day, for participants 1 year of age or older (Strata A), and 0.05 milligrams per kilograms per day (mg/kg/day), for infants less than 1 year of age (Strata B), orally, once on Days 1, 4, 8 and 11 of each 28-day cycle, given in combination with VXLD backbone chemotherapy (vincristine, dexamethasone, asparaginase, and doxorubicin), up to 4 weeks. Participants were followed for safety up to 100 weeks after last dose.

Arm type	Experimental
Investigational medicinal product name	Ixazomib
Investigational medicinal product code	
Other name	MLN9708
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ixazomib capsules.

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	Oncovin, VCR, LCR
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Vincristine IV push

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	Adriamycin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Doxorubicin solution for infusion.

Investigational medicinal product name	PEG-asparaginase
Investigational medicinal product code	
Other name	Oncaspar, Pegaspargase, Polyethylene Glycol Conjugated L-

	asparaginase-H
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intramuscular and intravenous use

Dosage and administration details:

PEG-asparaginase solution for injection/infusion.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	Decadron, Hexadrol, Dexone, Dexameth
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Dexamethasone PO or IV.

Arm title	Ixazomib 2 mg/m^2

Arm description:

Ixazomib at dose level 2, 2 mg/m^2/day, for participants 1 year of age or older (Strata A), and 0.07 mg/kg/day, for infants less than 1 year of age (Strata B), orally, once on Days 1, 4, 8 and 11 of each 28-day cycle, given in combination with VXLD backbone chemotherapy (vincristine, dexamethasone, asparaginase, and doxorubicin), up to 4 weeks. Participants were followed for safety up to 100 weeks after last dose.

Arm type	Experimental
Investigational medicinal product name	Ixazomib
Investigational medicinal product code	
Other name	MLN9708
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ixazomib capsules.

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	Oncovin, VCR, LCR
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Vincristine IV push

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	Decadron, Hexadrol, Dexone, Dexameth
Pharmaceutical forms	Solution for injection
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

Dexamethasone PO or IV.

Investigational medicinal product name	PEG-asparaginase
Investigational medicinal product code	
Other name	Oncaspar, Pegaspargase, Polyethylene Glycol Conjugated L-asparaginase-H
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intramuscular and intravenous use

Dosage and administration details:

PEG-asparaginase solution for injection/infusion.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	Adriamycin
Pharmaceutical forms	Solution for infusion

Routes of administration	Intravenous use

Dosage and administration details:

Doxorubicin solution for infusion.

Number of subjects in period 1	Ixazomib 1.6 mg/m^2	Ixazomib 2 mg/m^2
Started	4	6
Completed	4	6

Period 2

Period 2 title	Phase 2
Is this the baseline period?	Yes[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Ixazomib 2 mg/m^2

Arm description:

Ixazomib at dose level 2, 2 mg/m^2/day, for participants 1 year of age or older (Strata A), and 0.07 mg/kg/day, for infants less than 1 year of age (Strata B), orally, once on Days 1, 4, 8 and 11 of each 28-day cycle, given in combination with VXLD backbone chemotherapy (vincristine, dexamethasone, asparaginase, and doxorubicin), up to 4 weeks. Participants were followed for safety up to 100 weeks after last dose.

Arm type	Experimental
Investigational medicinal product name	Ixazomib
Investigational medicinal product code	
Other name	MLN9708
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ixazomib capsules.

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	Oncovin, VCR, LCR
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Vincristine solution for infusion.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	Adriamycin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Doxorubicin solution for infusion.

Investigational medicinal product name	PEG-asparaginase
Investigational medicinal product code	
Other name	Oncaspar, Pegaspargase, Polyethylene Glycol Conjugated L-asparaginase-H
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intramuscular and intravenous use

Dosage and administration details:

PEG-asparaginase solution for injection/infusion.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	Decadron, Hexadrol, Dexone, Dexameth
Pharmaceutical forms	Solution for injection
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

Dexamethasone PO or IV.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 does not include all subjects enrolled in the study thus, it is not the baseline period.

Number of subjects in period 2	Ixazomib 2 mg/m^2
Started	20
Completed	18
Not completed	2
Reason Not Specified	2

Baseline characteristics

Reporting groups	
Reporting group title	Ixazomib 2 mg/m^2
Reporting group description:	
Ixazomib at dose level 2, 2 mg/m^2/day, for participants 1 year of age or older (Strata A), and 0.07 mg/kg/day, for infants less than 1 year of age (Strata B), orally, once on Days 1, 4, 8 and 11 of each 28-day cycle, given in combination with VXLD backbone chemotherapy (vincristine, dexamethasone, asparaginase, and doxorubicin), up to 4 weeks. Participants were followed for safety up to 100 weeks after last dose.	

Reporting group values	Ixazomib 2 mg/m^2	Total	
Number of subjects	20	20	
Age Categorical Units: Subjects			
Age continuous Units: years			
median	8.2		
full range (min-max)	1.5 to 20.5	-	
Gender categorical Units: Subjects			
Male	11	11	
Female	9	9	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic/Latino	13	13	
Not Hispanic/Latino	7	7	
Unknown	0	0	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	2	2	
White	11	11	
More than one race	0	0	
Unknown or Not Reported	6	6	
Region of Enrollment Units: Subjects			
United States	20	20	

End points

End points reporting groups

Reporting group title	Ixazomib 1.6 mg/m^2

Reporting group description:

Ixazomib at dose level 1, 1.6 mg/m^2/day, for participants 1 year of age or older (Strata A), and 0.05 milligrams per kilograms per day (mg/kg/day), for infants less than 1 year of age (Strata B), orally, once on Days 1, 4, 8 and 11 of each 28-day cycle, given in combination with VXLD backbone chemotherapy (vincristine, dexamethasone, asparaginase, and doxorubicin), up to 4 weeks. Participants were followed for safety up to 100 weeks after last dose.

Reporting group title	Ixazomib 2 mg/m^2

Reporting group description:

Ixazomib at dose level 2, 2 mg/m^2/day, for participants 1 year of age or older (Strata A), and 0.07 mg/kg/day, for infants less than 1 year of age (Strata B), orally, once on Days 1, 4, 8 and 11 of each 28-day cycle, given in combination with VXLD backbone chemotherapy (vincristine, dexamethasone, asparaginase, and doxorubicin), up to 4 weeks. Participants were followed for safety up to 100 weeks after last dose.

Reporting group title	Ixazomib 2 mg/m^2

Reporting group description:

Ixazomib at dose level 2, 2 mg/m^2/day, for participants 1 year of age or older (Strata A), and 0.07 mg/kg/day, for infants less than 1 year of age (Strata B), orally, once on Days 1, 4, 8 and 11 of each 28-day cycle, given in combination with VXLD backbone chemotherapy (vincristine, dexamethasone, asparaginase, and doxorubicin), up to 4 weeks. Participants were followed for safety up to 100 weeks after last dose.

Primary: Number of Participants With Dose Limiting Toxicity (DLT) During Block (Cycle) 1 of Chemotherapy

End point title	Number of Participants With Dose Limiting Toxicity (DLT) During Block (Cycle) 1 of Chemotherapy [1]

End point description:

DLT:defined as per National Cancer Institute Common Toxicity Criteria(NCI CTC)version 5.0 as follows:1)Any Grade 4/3 non-hematologic toxicity that occurs after first dose of ixazomib and results in omission of subsequent block of chemotherapy or delay of beginning of subsequent block of chemotherapy for>7 days,with exception of fever or infection.2)Hematologic toxicities:Failure to recover a peripheral absolute neutrophil count(ANC)≥500/µL and platelet(PLT)>20,000/µL,PLT infusion independent, due to documented bone marrow hypoplasia(cellularity<10-20%)within 49 days of beginning of systemic chemotherapy without evidence of active disease or infection by bone marrow aspiration. Participants from evaluable response set who were evaluable for safety. Evaluable response set: all participants enrolled and received all or part of protocol therapy, are under follow-up for a sufficient period to evaluate disease at end of one treatment cycle or meet definition of progressive

End point type	Primary

End point timeframe:

Up to Cycle 1 (28 days)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Ixazomib 1.6 mg/m^2	Ixazomib 2 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	2		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Ixazomib at Day 1

End point title	Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Ixazomib at Day 1[2]

End point description:

Evaluable response set included all participants enrolled and who received all or part of protocol therapy and are under follow-up for a sufficient period to evaluate the disease at the end of the one treatment cycle or meet the definition of progressive disease.

End point type	Primary

End point timeframe:

Day 1 at multiple time points (up to 72 hours) post-dose for participants weighing <20 kg and ≥20 kg

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Ixazomib 1.6 mg/m^2	Ixazomib 2 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	4		
Units: hours (h)				
median (full range (min-max))	4.50 (1.00 to 8.00)	1.50 (1.00 to 4.00)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Grade 3 or More Treatment Emergent Adverse Events (TEAEs) Graded Using Common Toxicity Criteria for Adverse Event (CTCAE) Criteria Version 5.0 During Block (Cycle) 1 of Chemotherapy

End point title	Number of Participants with Grade 3 or More Treatment Emergent Adverse Events (TEAEs) Graded Using Common Toxicity Criteria for Adverse Event (CTCAE) Criteria Version 5.0 During Block (Cycle) 1 of Chemotherapy [3]

End point description:

TEAEs are defined as any AEs that occurred or worsened during the on-treatment period. TEAEs were graded using National Cancer Institute (NCI) CTCAE Version 5.0. SAEs are generally defined in this Phase 1 study as all Grade 3 and 4 events both unexpected and expected that are possibly, probably, or definitely related to Ixazomib or the chemotherapy backbone, excluding hematologic toxicities unless the event meets the criteria for a DLT. Participants from evaluable response set who were evaluable for safety.

End point type	Primary

End point timeframe:

Up to 104 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Ixazomib 1.6 mg/m^2	Ixazomib 2 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	6		
Units: participants	3	6		

Statistical analyses

No statistical analyses for this end point

Primary: Cmax: Maximum Observed Plasma Concentration for Ixazomib at Day 1

End point title	Cmax: Maximum Observed Plasma Concentration for Ixazomib at Day 1[4]

End point description:

Evaluable response set included all participants enrolled and who received all or part of protocol therapy and are under follow-up for a sufficient period to evaluate the disease at the end of the one treatment cycle or meet the definition of progressive disease.

End point type	Primary

End point timeframe:

Day 1 at multiple time points (up to 72 hours) post-dose for participants weighing <20 kg and ≥20 kg

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Ixazomib 1.6 mg/m^2	Ixazomib 2 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	4		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	10.0 (± 809.5)	28.1 (± 30.5)		

Statistical analyses

No statistical analyses for this end point

Primary: T1/2: Terminal Elimination Half-Life of Ixazomib at Day 1

End point title	T1/2: Terminal Elimination Half-Life of Ixazomib at Day 1[5]

End point description:

Evaluable response set included all participants enrolled and who received all or part of protocol therapy and are under follow-up for a sufficient period to evaluate the disease at the end of the one treatment

cycle or meet the definition of progressive disease. 99999 indicates geometric coefficient of variation was not estimable for one participant.

End point type	Primary

End point timeframe:

Day 1 at multiple time points (up to 72 hours) post-dose for participants weighing <20 kg and ≥20 kg

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Ixazomib 1.6 mg/m^2	Ixazomib 2 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	4		
Units: hours (h)				
geometric mean (geometric coefficient of variation)	67.7 (± 99999)	36.4 (± 41.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Adjusted R^2: Coefficient of Determination for the Terminal Disposition Phase Slope Adjusted for the Number of Data Points Used in the Analysis at Day 1

End point title	Adjusted R^2: Coefficient of Determination for the Terminal Disposition Phase Slope Adjusted for the Number of Data Points Used in the Analysis at Day 1[6]

End point description:

Adjusted Rsq describes the goodness of fit for the terminal phase slope (log concentration vs time, used to then calculate the half-life). Evaluable response set included all participants enrolled and who received all or part of protocol therapy and are under follow-up for a sufficient period to evaluate the disease at the end of the one treatment cycle or meet the definition of progressive disease. 99999 indicates geometric coefficient of variation was not estimable for one participant.

End point type	Primary

End point timeframe:

Day 1 at multiple time points (up to 72 hours) post-dose for participants weighing <20 kg and ≥20 kg

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Ixazomib 1.6 mg/m^2	Ixazomib 2 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	4		
Units: Unitless				
geometric mean (geometric coefficient of variation)	0.587 (± 99999)	0.495 (± 58.5)		

Statistical analyses

No statistical analyses for this end point

Primary: AUC%extrap,obs: Percent of Area Under the Plasma Concentration-time Curve from Dosing Time Infinity due to Extrapolation From the Last Observed Concentration for Ixazomib at Day 1

End point title	AUC%extrap,obs: Percent of Area Under the Plasma Concentration-time Curve from Dosing Time Infinity due to Extrapolation From the Last Observed Concentration for Ixazomib at Day 1[7]

End point description:

Evaluable response set included all participants enrolled and who received all or part of protocol therapy and are under follow-up for a sufficient period to evaluate the disease at the end of the one treatment cycle or meet the definition of progressive disease. 99999 indicates geometric coefficient of variation was not estimable for one participant.

End point type	Primary

End point timeframe:

Day 1 at multiple time points (up to 72 hours) post-dose for participants weighing <20 kg and ≥20 kg

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Ixazomib 1.6 mg/m^2	Ixazomib 2 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	4		
Units: percentage of AUC				
geometric mean (geometric coefficient of variation)	39.7 (± 99999)	26.8 (± 45.7)		

Statistical analyses

No statistical analyses for this end point

Primary: AUC(0-72): Area Under the Plasma Concentration-Time Curve From Time 0 to 72 Hours Postdose for Ixazomib at Day 1

End point title	AUC(0-72): Area Under the Plasma Concentration-Time Curve From Time 0 to 72 Hours Postdose for Ixazomib at Day 1[8]

End point description:

Evaluable response set included all participants enrolled and who received all or part of protocol therapy and are under follow-up for a sufficient period to evaluate the disease at the end of the one treatment cycle or meet the definition of progressive disease.

End point type	Primary

End point timeframe:

Day 1 at multiple time points (up to 72 hours) post-dose for participants weighing <20 kg and ≥20 kg

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Ixazomib 1.6 mg/m^2	Ixazomib 2 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	4		
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	178 (± 125.7)	331 (± 61.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Ixazomib at Day 11

End point title	Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Ixazomib at Day 11[9]

End point description:

Evaluable response set included all participants enrolled and who received all or part of protocol therapy and are under follow-up for a sufficient period to evaluate the disease at the end of the one treatment cycle or meet the definition of progressive disease.

End point type	Primary

End point timeframe:

Day 11 pre-dose and at multiple time points post-dose (up to 72 hours for participants weighing <20 kg and up to 264 hours for participants weighing ≥20 kg)

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Ixazomib 1.6 mg/m^2	Ixazomib 2 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	6		
Units: hours (hr)				
median (full range (min-max))	4.00 (0.50 to 4.00)	3.00 (0.50 to 72.00)		

Statistical analyses

No statistical analyses for this end point

Primary: Cmax: Maximum Observed Plasma Concentration for Ixazomib at Day 11

End point title	Cmax: Maximum Observed Plasma Concentration for Ixazomib at Day 11[10]

End point description:

Evaluable response set included all participants enrolled and who received all or part of protocol therapy and are under follow-up for a sufficient period to evaluate the disease at the end of the one treatment cycle or meet the definition of progressive disease.

End point type	Primary

End point timeframe:

Day 11 pre-dose and at multiple time points post-dose (up to 72 hours for participants weighing <20 kg

and up to 264 hours for participants weighing ≥20 kg)

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Ixazomib 1.6 mg/m^2	Ixazomib 2 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	6		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	22.8 (± 169.1)	73.6 (± 75.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Adjusted R^2: Coefficient of Determination for the Terminal Disposition Phase Slope Adjusted for the Number of Data Points Used in the Analysis at Day 11

End point title	Adjusted R^2: Coefficient of Determination for the Terminal Disposition Phase Slope Adjusted for the Number of Data Points Used in the Analysis at Day 11[11]

End point description:

Adjusted Rsq describes the goodness of fit for the terminal phase slope (log concentration vs time, used to then calculate the half-life). Evaluable response set included all participants enrolled and who received all or part of protocol therapy and are under follow-up for a sufficient period to evaluate the disease at the end of the one treatment cycle or meet the definition of progressive disease.

End point type	Primary

End point timeframe:

Day 11 pre-dose and at multiple time points post-dose (up to 72 hours for participants weighing <20 kg and up to 264 hours for participants weighing ≥20 kg)

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Ixazomib 1.6 mg/m^2	Ixazomib 2 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	5		
Units: Unitless				
geometric mean (geometric coefficient of variation)	0.969 (± 0.5)	0.940 (± 3.8)		

Statistical analyses

No statistical analyses for this end point

Primary: AUC%extrap,obs: Percent of Area Under the Plasma Concentration-time Curve from Dosing Time Infinity due to Extrapolation From the Last Observed

Concentration for Ixazomib at Day 11

End point title	AUC%extrap,obs: Percent of Area Under the Plasma Concentration-time Curve from Dosing Time Infinity due to Extrapolation From the Last Observed Concentration for Ixazomib at Day 11[12]

End point description:

Evaluable response set included all participants enrolled and who received all or part of protocol therapy and are under follow-up for a sufficient period to evaluate the disease at the end of the one treatment cycle or meet the definition of progressive disease.

End point type	Primary

End point timeframe:

Day 11 pre-dose and at multiple time points post-dose (up to 72 hours for participants weighing <20 kg and up to 264 hours for participants weighing ≥20 kg)

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Ixazomib 1.6 mg/m^2	Ixazomib 2 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	5		
Units: percentage of AUC				
geometric mean (geometric coefficient of variation)	14.6 (± 130.5)	12.8 (± 105.6)		

Statistical analyses

No statistical analyses for this end point

Primary: AUC(0-72): Area Under the Plasma Concentration-Time Curve From Time 0 to 72 Hours Postdose for Ixazomib at Day 11

End point title	AUC(0-72): Area Under the Plasma Concentration-Time Curve From Time 0 to 72 Hours Postdose for Ixazomib at Day 11[13]

End point description:

Evaluable response set included all participants enrolled and who received all or part of protocol therapy and are under follow-up for a sufficient period to evaluate the disease at the end of the one treatment cycle or meet the definition of progressive disease.

End point type	Primary

End point timeframe:

Day 11 pre-dose and at multiple time points (up to 72 hours) post-dose for participants weighing <20 kg and ≥20 kg

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Ixazomib 1.6 mg/m^2	Ixazomib 2 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	6		
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	586 (± 58.2)	1650 (± 35.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Treatment Emergent Adverse Events (TEAEs), and Serious Adverse Events (SAEs)

End point title	Percentage of Participants With Treatment Emergent Adverse Events (TEAEs), and Serious Adverse Events (SAEs)[14]

End point description:

AE:any untoward medical occurrence in a clinical investigation participant administered a investigative drug; it does not necessarily have to have a causal relationship with trial drug administration.SAE:any untoward medical occurrence that:1)results in death,2)is life-threatening, 3)requires inpatient hospitalization or prolongation of existing hospitalization,4)results in persistent or significant disability/incapacity,5)leads to a congenital anomaly/birth defect in offspring of participant or6)is a medically important event that satisfies any of following:a)May require intervention to prevent items 1 to 5 above.b)May expose participant to danger, even though event is not immediately life threatening or fatal or does not result in hospitalization. Participants from evaluable response set who were evaluable for safety.

End point type	Primary

End point timeframe:

Up to 104 weeks

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Ixazomib 1.6 mg/m^2	Ixazomib 2 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	6		
Units: percentage of participants				
number (not applicable)				
TEAEs	100	100		
SAEs	100	100		

Statistical analyses

No statistical analyses for this end point

Primary: T1/2: Terminal Elimination Half-Life of Ixazomib at Day 11

End point title	T1/2: Terminal Elimination Half-Life of Ixazomib at Day 11[15]

End point description:

Evaluable response set included all participants enrolled and who received all or part of protocol therapy and are under follow-up for a sufficient period to evaluate the disease at the end of the one treatment cycle or meet the definition of progressive disease.

End point type	Primary

End point timeframe:

Day 11 pre-dose and at multiple time points post-dose (up to 72 hours for participants weighing <20 kg and up to 264 hours for participants weighing ≥20 kg)

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Ixazomib 1.6 mg/m^2	Ixazomib 2 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	5		
Units: hours (hr)				
geometric mean (geometric coefficient of variation)	111 (± 59.8)	99.4 (± 37.4)		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Number of Participants with Complete Remission (CR), Complete Remission, MRD Negative (CR MRD-) and Complete Response with Incomplete Count Recovery (CRi) After Block 1 Chemotherapy

End point title	Phase 2: Number of Participants with Complete Remission (CR), Complete Remission, MRD Negative (CR MRD-) and Complete Response with Incomplete Count Recovery (CRi) After Block 1 Chemotherapy[16]

End point description:

Best response: measured by bone marrow status as percentage of participants with CR: a bone marrow with<5%blasts by morphology;no evidence of circulating blasts or extramedullary disease;recovery of peripheral counts(ANC≥500/µL, PLT≥20,000/µL,platelet infusion independent) or CR MRD-:a bone marrow with<5% blasts by morphology;MRD<0.1%by flow or molecular testing(e.g.PCR);no evidence of circulating blasts or extramedullary disease;recovery of peripheral counts(ANC≥500/µL,PLT≥20,000/µL,platelet infusion independent) or CRi:all CR criteria except for insufficient recovery of ANC (<500/µL), and/or PLT counts (<20,000/µL) are reported. Evaluable response set: all participants enrolled and received all/part of protocol therapy and are under follow-up for a sufficient period to evaluate disease at end of 1 treatment cycle/meet definition of progressive

End point type	Primary

End point timeframe:

Up to Cycle 1 (28 days)

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Ixazomib 2 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: participants				
CR	2			
CR MRD-	6			
CRi	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With CTCAE Toxicities During Block 2 Chemotherapy

End point title	Number of Participants With CTCAE Toxicities During Block 2 Chemotherapy

End point description:

TEAEs are defined as any AEs that occurred or worsened during the on-treatment period. TEAEs were graded using NCI CTCAE Version 5.0. Toxicities included the following system organ classes: blood and lymphatic system, cardiac, gastrointestinal, general, metabolism and nutrition, respiratory, thoracic, and mediastinal, skin and subcutaneous tissue disorders, and psychiatric disorders and infections and infestations. Participants from evaluable response set who were evaluable for safety. Subjects analysed is the number of participants enrolled on dose level 2 (DL2) during Phase 2 portion of the study.

End point type	Secondary

End point timeframe:

Cycle 2 (28 days)

End point values	Ixazomib 2 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: participants	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability Assessed as Percentage of Participants who Found the Taste to be at least Tolerable

End point title	Palatability Assessed as Percentage of Participants who Found the Taste to be at least Tolerable

End point description:

After each dose of ixazomib during block 1, a questionnaire was provided to subject and parent/care giver. If the subject was too young to fill the survey, only parent/care giver was surveyed. In each case, a nurse or research staff recorded the verbal responses to the questions. When facial hedonic scales were utilized, the child or parent/care giver was asked to indicate their preference by circling on the pictorial scale of facial expression. Evaluable response set: all participants enrolled and received all/part of protocol therapy and are under follow-up for a sufficient period to evaluate disease at end of 1 treatment cycle/meet definition of progressive disease.

End point type	Secondary

End point timeframe:

Up to Cycle 1 (28 days)

End point values	Ixazomib 2 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percentage of participants				
number (not applicable)	83			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 4.8 years

Adverse event reporting additional description:

At each visit investigator had to document any occurrence of AE and abnormal laboratory findings. Any event reported by participant or by investigator was recorded, irrespective of the relation to study treatment. All-cause mortality: Evaluable response set(n=4,6,20). SAE and non-SAEs: Participants from evaluable response set with data for safety.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	Unknown

Reporting groups

Reporting group title	Phase 1: Ixazomib 1.6 mg/m^2

Reporting group description:

Phase 1: Ixazomib at dose level 1, 1.6 mg/m^2/day, for participants 1 year of age or older (Strata A), and 0.05 mg/kg/day, for infants less than 1 year of age (Strata B), orally, once on Days 1, 4, 8 and 11 of each 28-day cycle, given in combination with VXLD backbone chemotherapy (vincristine, dexamethasone, asparaginase, and doxorubicin), up to 4 weeks. Participants were followed for safety up to 100 weeks after last dose.

Reporting group title	Phase 2: Ixazomib 2 mg/m^2

Reporting group description:

Phase 2: Ixazomib at dose level 2, 2 mg/m^2/day, for participants 1 year of age or older (Strata A), and 0.07 mg/kg/day, for infants less than 1 year of age (Strata B), orally, once on Days 1, 4, 8 and 11 of each 28-day cycle, given in combination with VXLD backbone chemotherapy (vincristine, dexamethasone, asparaginase, and doxorubicin), up to 4 weeks. Participants were followed for safety up to 100 weeks after last dose.

Reporting group title	Phase 1: Ixazomib 2 mg/m^2

Reporting group description:

Phase 1: Ixazomib at dose level 2, 2 mg/m^2/day, for participants 1 year of age or older (Strata A), and 0.07 mg/kg/day, for infants less than 1 year of age (Strata B), orally, once on Days 1, 4, 8 and 11 of each 28-day cycle, given in combination with VXLD backbone chemotherapy (vincristine, dexamethasone, asparaginase, and doxorubicin), up to 4 weeks. Participants were followed for safety up to 100 weeks after last dose.

Serious adverse events	Phase 1: Ixazomib 1.6 mg/m^2	Phase 2: Ixazomib 2 mg/m^2	Phase 1: Ixazomib 2 mg/m^2
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	14 / 14 (100.00%)	6 / 6 (100.00%)
number of deaths (all causes)	1	5	2
number of deaths resulting from adverse events	0	2	0
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	3 / 3 (100.00%)	0 / 14 (0.00%)	4 / 6 (66.67%)
occurrences causally related to treatment / all	3 / 3	0 / 0	5 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalized edema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Mucositis oral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	2 / 6 (33.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 3 (33.33%)	4 / 14 (28.57%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	1 / 1	2 / 4	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Septic Shock			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Catheter related infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 14 (14.29%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypertriglyceridemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycemia			

subjects affected / exposed	1 / 3 (33.33%)	1 / 14 (7.14%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
AST increased			
subjects affected / exposed	1 / 3 (33.33%)	3 / 14 (21.43%)	3 / 6 (50.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ALT increased			
subjects affected / exposed	1 / 3 (33.33%)	2 / 14 (14.29%)	4 / 6 (66.67%)
occurrences causally related to treatment / all	1 / 1	2 / 2	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphatemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 14 (14.29%)	2 / 6 (33.33%)
occurrences causally related to treatment / all	0 / 0	1 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GGT increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 14 (14.29%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypernatremia			

subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatremia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Phase 1: Ixazomib 1.6 mg/m^2	Phase 2: Ixazomib 2 mg/m^2	Phase 1: Ixazomib 2 mg/m^2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	14 / 14 (100.00%)	6 / 6 (100.00%)
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 6 (16.67%)
occurrences (all)	0	1	2
Alopecia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Chills			
subjects affected / exposed	0 / 3 (0.00%)	2 / 14 (14.29%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Dehydration			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Fatigue			

subjects affected / exposed	1 / 3 (33.33%)	4 / 14 (28.57%)	0 / 6 (0.00%)
occurrences (all)	1	4	0
Fever			
subjects affected / exposed	1 / 3 (33.33%)	7 / 14 (50.00%)	0 / 6 (0.00%)
occurrences (all)	1	7	0
Oral pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Generalized edema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 3 (33.33%)	1 / 14 (7.14%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Mucositis oral			
subjects affected / exposed	0 / 3 (0.00%)	2 / 14 (14.29%)	2 / 6 (33.33%)
occurrences (all)	0	2	2
Psychiatric disorders			
Anorexia			
subjects affected / exposed	1 / 3 (33.33%)	4 / 14 (28.57%)	2 / 6 (33.33%)
occurrences (all)	1	4	2
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	2 / 14 (14.29%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Irritability			
subjects affected / exposed	1 / 3 (33.33%)	2 / 14 (14.29%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Injury, poisoning and procedural complications			

Infusion related reaction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	5 / 14 (35.71%)	4 / 6 (66.67%)
occurrences (all)	0	5	5
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	3 / 14 (21.43%)	2 / 6 (33.33%)
occurrences (all)	0	3	2
Electrocardiogram QT corrected interval prolonged			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 3 (33.33%)	2 / 14 (14.29%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	3 / 3 (100.00%)	10 / 14 (71.43%)	5 / 6 (83.33%)
occurrences (all)	3	10	7
Blood bilirubin increased			
subjects affected / exposed	1 / 3 (33.33%)	5 / 14 (35.71%)	2 / 6 (33.33%)
occurrences (all)	3	5	6
Febrile neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 3 (33.33%)	4 / 14 (28.57%)	1 / 6 (16.67%)
occurrences (all)	1	4	1
Blood bicarbonate decreased			
subjects affected / exposed	0 / 3 (0.00%)	4 / 14 (28.57%)	1 / 6 (16.67%)
occurrences (all)	0	4	2

Lymphocyte count decreased			
subjects affected / exposed	0 / 3 (0.00%)	12 / 14 (85.71%)	5 / 6 (83.33%)
occurrences (all)	0	12	5
Neutrophil count decreased			
subjects affected / exposed	3 / 3 (100.00%)	9 / 14 (64.29%)	5 / 6 (83.33%)
occurrences (all)	3	9	6
Platelet count decreased			
subjects affected / exposed	3 / 3 (100.00%)	9 / 14 (64.29%)	4 / 6 (66.67%)
occurrences (all)	3	9	6
White blood cell decreased			
subjects affected / exposed	3 / 3 (100.00%)	11 / 14 (78.57%)	5 / 6 (83.33%)
occurrences (all)	3	11	6
Edema face			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Hypoxia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Methemoglobinemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Thrombus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Edema limbs			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	0 / 3 (0.00%)	5 / 14 (35.71%)	1 / 6 (16.67%)
occurrences (all)	0	5	1
Abdominal distension			

subjects affected / exposed	1 / 3 (33.33%)	2 / 14 (14.29%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	5 / 14 (35.71%)	1 / 6 (16.67%)
occurrences (all)	0	5	1
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	3 / 14 (21.43%)	2 / 6 (33.33%)
occurrences (all)	0	3	3
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 14 (14.29%)	3 / 6 (50.00%)
occurrences (all)	0	2	3
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	8 / 14 (57.14%)	3 / 6 (50.00%)
occurrences (all)	1	8	4
Pain in groin			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	2 / 3 (66.67%)	10 / 14 (71.43%)	2 / 6 (33.33%)
occurrences (all)	2	10	4
Increased hunger			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Bloating			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 3 (0.00%)	2 / 14 (14.29%)	2 / 6 (33.33%)
occurrences (all)	0	2	2
Cool/mottled skin			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

Erythematous facial rash			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Lesion on left thumb			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Perirectal breakdown			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pressure injury			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Skin rash			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Bleeding labial skin			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Rash acneiform			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Hyperuricemia			

subjects affected / exposed	0 / 3 (0.00%)	3 / 14 (21.43%)	1 / 6 (16.67%)
occurrences (all)	0	3	1
Proteinuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Rectal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Urinary tract pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Bladder spasm			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Cystitis noninfective			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dysuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Renal colic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Endocrine disorders			
Syndrome of inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 3 (33.33%)	1 / 14 (7.14%)	2 / 6 (33.33%)
occurrences (all)	1	1	2
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	3 / 14 (21.43%)	2 / 6 (33.33%)
occurrences (all)	0	3	2
Arthralgia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Muscle cramp			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Edema face			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Enterocolitis infectious			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Herpes simplex reactivation			
subjects affected / exposed	1 / 3 (33.33%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Parainfluenza 1			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Sepsis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Upper respiratory infection			
subjects affected / exposed	2 / 3 (66.67%)	0 / 14 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Parvovirus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Decreased respiration, intermittent			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Increased respiration, intermittent			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Positive MRSA			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

RHINOVIRUS			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Thrush			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
UTI R/T BK/ADENOVIRUS			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Febrile neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 14 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Fever			
subjects affected / exposed	0 / 3 (0.00%)	7 / 14 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	7	0
Adenovirus infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
ALT increased			
subjects affected / exposed	3 / 3 (100.00%)	6 / 14 (42.86%)	2 / 6 (33.33%)
occurrences (all)	4	6	3
Hypoalbuminemia			
subjects affected / exposed	3 / 3 (100.00%)	9 / 14 (64.29%)	4 / 6 (66.67%)
occurrences (all)	4	9	4
GGT increased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 14 (21.43%)	1 / 6 (16.67%)
occurrences (all)	0	3	1
Hypercalcemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Hyperkalemia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 14 (21.43%)	2 / 6 (33.33%)
occurrences (all)	0	3	2
Hypermagnesemia			

subjects affected / exposed	0 / 3 (0.00%)	5 / 14 (35.71%)	1 / 6 (16.67%)
occurrences (all)	0	5	2
Hypernatremia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 14 (21.43%)	1 / 6 (16.67%)
occurrences (all)	0	3	1
Hyperphosphatemia			
subjects affected / exposed	1 / 3 (33.33%)	8 / 14 (57.14%)	0 / 6 (0.00%)
occurrences (all)	1	8	0
Hypertriglyceridemia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 14 (14.29%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Hypocalcemia			
subjects affected / exposed	1 / 3 (33.33%)	10 / 14 (71.43%)	3 / 6 (50.00%)
occurrences (all)	3	10	6
Hypoglycemia			
subjects affected / exposed	1 / 3 (33.33%)	4 / 14 (28.57%)	2 / 6 (33.33%)
occurrences (all)	2	4	2
Hypokalemia			
subjects affected / exposed	1 / 3 (33.33%)	7 / 14 (50.00%)	1 / 6 (16.67%)
occurrences (all)	4	7	1
Hypomagnesemia			
subjects affected / exposed	0 / 3 (0.00%)	5 / 14 (35.71%)	1 / 6 (16.67%)
occurrences (all)	0	5	2
Hyponatremia			
subjects affected / exposed	2 / 3 (66.67%)	13 / 14 (92.86%)	4 / 6 (66.67%)
occurrences (all)	5	13	4
Hypophosphatemia			
subjects affected / exposed	1 / 3 (33.33%)	8 / 14 (57.14%)	3 / 6 (50.00%)
occurrences (all)	1	8	5
INR increased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 14 (21.43%)	1 / 6 (16.67%)
occurrences (all)	0	3	1
Alkaline phosphatase increased			
subjects affected / exposed	3 / 3 (100.00%)	4 / 14 (28.57%)	1 / 6 (16.67%)
occurrences (all)	4	4	1
Hyperglycemia			

subjects affected / exposed	3 / 3 (100.00%)	9 / 14 (64.29%)	3 / 6 (50.00%)
occurrences (all)	8	9	9
AST increased			
subjects affected / exposed	2 / 3 (66.67%)	7 / 14 (50.00%)	3 / 6 (50.00%)
occurrences (all)	4	7	7
Weight loss			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Weight gain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2019	The primary purpose of the amendment 1 was to make following changes: • Dose Modification for Intrathecal (IT) Methotrexate (MTX) /Triple Intrathecal Therapy toxicities: Mercaptopurine dose adjustments made to allow for genotype variations in either TPMT or NUDT15. • Dose Modification for Intermediate-Dose Methotrexate toxicities: Added a subsection to provide guidance in the event of excess extravasation of fluids into tissues (third spacing). • Clinical and Laboratory Studies: Added neurological exam to be performed prior to each Ixazomib dosing. • Bone Marrow Response Criteria for participants with leukemia: Amended response definitions to replace CRp category with CRi and divide the CR category to include CR MRD-.
16 September 2020	The primary purpose of the amendment 2 was to make following changes: • Exclusion criteria: updated the list of excluded CYP3A4 agents. • Treatment program: under Block 1, 2, and Maintenance Block, revised timing of Leucovorin for Down syndrome (DS) participants to be received at hours 24 and 30 after IT MTX or ITT. • Dose Limiting Toxicity: changed platelet criteria for hematological toxicity definition to platelet ≥20,000/µL, platelet infusion independent and length of evaluation time to 49 days.
11 May 2021	The primary purpose of the amendment 3 was to make following changes: • Inclusion criteria: clarify the definition of what chemotherapy regimens and drugs and dosages (i.e. maintenance therapy drugs) are allowed prior to enrollment and what length of washout is required for the drugs and biologics. • Treatment program: added clarification to allow for flexibility in the timing of chemotherapy administration, including the timing of Day 29 IT therapy, allowing for up to 72 hours flexibility for scheduling or other issues.
23 January 2022	The primary purpose of the amendment 4 was to make following changes: • Chemotherapy Backbone: Added clarification that DS and infants (<1 year of age) would enroll to Phase 2 at Dose Level 1. Their data would only be descriptive and not included in DLT and response evaluation. Added clarification regarding leucovorin treatment for DS participants. • Treatment program: Added change crisantapase (Erwinase®) or asparaginase Erwinia chrysanthemi (recombinant)-rywn (Rylaze®) may be substituted for allergy to Pegaspargase. • Ixazomib: Added clarification that administration of ixazomib capsules should be rounded to the nearest 0.2mg.

26 October 2022	The primary purpose of the amendment 5 was to make following changes: • Inclusion criteria: Revised eligibility criteria to read "Participants must be <22 years of age at time of enrollment." Revised eligibility criteria for prior therapeutic attempts for B-cell ALL/LLy participants from failed two or more prior attempts to failed one or more prior attempts. • Exclusion Criteria: Revised exclusion criteria to include allergy or intolerance to Calaspargase. • Treatment program: Added Calaspargase to treatment schedule for Block 1 and Block 2. Added footnote that regarding the administration of either pegaspargase or calaspargase according to current approved labeling based on age and regional availability. Added dosage administration for calaspargase to be only administered once per cycle and on Day 2 for Block 1 and Day 9 or 10 for Block 2. Updated language regarding substituting crisantapase (Erwinase®) asparaginase or Erwinia chrysanthemi (recombinant)-rywn (Rylaze®) for Pegaspargase or Calaspargase. • Correlative Studies: Added clarification regarding leftover samples banked for future therapeutic advances in childhood leukemia and lymphoma (TACL) biology studies.
20 July 2023	The primary purpose of the amendment 6 was to make following changes: • Statistical Considerations: Revised definition of a participants evaluable for response to include those who die as a result of a DLT and that such participants will be considered a non-responder. Also added that participants who are not considered evaluable for response will be replaced. •Added clarification that the occurrence of a toxic death will be defined as a death occurring anytime during protocol therapy or until 30 days following the last dose of study therapy. • Response Criteria: Added new Non-responder (NR) response criteria.
07 September 2023	The primary purpose of the amendment 7 was to make following changes: • Ixazomib: Updated Toxicity/Adverse Events to reflect recent updates in the Ixazomib Investigator's Brochure edition 15.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported