



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) | EMA-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/m²/day or 2 mg/m²/day in Phase 1 & those who received 2 mg/m²/day (RP2D) in Phase 1 continued to Phase 2 to receive ixazomib 2 mg/m²/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/m²/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 VXL 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 VXL 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/m²/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/m² |
| 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/m²/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/m²/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 VXL 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/m²/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 VXL 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/m²/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 VXL 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) $\geq 500/\mu\text{L}$ and platelet (PLT) $> 20,000/\mu\text{L}$, PLT infusion independent, due to documented bone marrow hypoplasia (cellularity $< 10\text{-}20\%$) 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: 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 ^[2] |
|-----------------|--|

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:

[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 | 3 | 6 | | |
| Units: participants | 3 | 6 | | |

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 ^[3] |
|-----------------|--|

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:

[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 | 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: 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 R²: 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 (\pm 169.1) | 73.6 (\pm 75.1) | | |

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 ^[11] |
|-----------------|--|

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:

[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: hours (hr) | | | | |
| geometric mean (geometric coefficient of variation) | 111 (\pm 59.8) | 99.4 (\pm 37.4) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Adjusted R²: 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 ^[12] |
|-----------------|---|

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:

[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: 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 ^[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 post-dose (up to 72 hours for participants weighing <20 kg and up to 264 hours for participants weighing ≥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 | 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 ^[14] |
|-----------------|---|

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:

[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: 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) ^[15] |
|-----------------|--|

End point description:

AE: any untoward medical occurrence in a clinical investigation participant administered a investigational 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 or 6) 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:

[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 | 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: 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: 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

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

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/m²/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/m²/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/m²/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 occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 14 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Cardiac disorders | | | |
| Sinus tachycardia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 5 / 14 (35.71%) 5 | 4 / 6 (66.67%) 5 |
| Hypertension subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 3 / 14 (21.43%) 3 | 2 / 6 (33.33%) 2 |
| Electrocardiogram QT corrected interval prolonged subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 14 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 2 / 14 (14.29%) 2 | 0 / 6 (0.00%) 0 |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 14 (0.00%) 0 | 2 / 6 (33.33%) 2 |
| Blood and lymphatic system disorders | | | |
| Anemia subjects affected / exposed occurrences (all) | 3 / 3 (100.00%) 3 | 10 / 14 (71.43%) 10 | 5 / 6 (83.33%) 7 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 3 | 5 / 14 (35.71%) 5 | 2 / 6 (33.33%) 6 |
| Febrile neutropenia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 14 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 4 / 14 (28.57%) 4 | 1 / 6 (16.67%) 1 |
| Blood bicarbonate decreased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 4 / 14 (28.57%) 4 | 1 / 6 (16.67%) 2 |

| | | | |
|--|----------------------|------------------------|---------------------|
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 12 / 14 (85.71%) 12 | 5 / 6 (83.33%) 5 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 3 / 3 (100.00%) 3 | 9 / 14 (64.29%) 9 | 5 / 6 (83.33%) 6 |
| Platelet count decreased subjects affected / exposed occurrences (all) | 3 / 3 (100.00%) 3 | 9 / 14 (64.29%) 9 | 4 / 6 (66.67%) 6 |
| White blood cell decreased subjects affected / exposed occurrences (all) | 3 / 3 (100.00%) 3 | 11 / 14 (78.57%) 11 | 5 / 6 (83.33%) 6 |
| Edema face subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 14 (7.14%) 1 | 2 / 6 (33.33%) 2 |
| Hypoxia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 14 (7.14%) 1 | 0 / 6 (0.00%) 0 |
| Methemoglobinemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 14 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Thrombus subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 14 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Edema limbs subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 14 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Eye disorders Eye pain subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 14 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Gastrointestinal disorders Diarrhea subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 5 / 14 (35.71%) 5 | 1 / 6 (16.67%) 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 occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 14 (7.14%) 1 | 0 / 6 (0.00%) 0 |
| Lesion on left thumb subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 14 (7.14%) 1 | 0 / 6 (0.00%) 0 |
| Perirectal breakdown subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 14 (7.14%) 1 | 0 / 6 (0.00%) 0 |
| Pressure injury subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 14 (7.14%) 1 | 0 / 6 (0.00%) 0 |
| Skin rash subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 14 (7.14%) 1 | 0 / 6 (0.00%) 0 |
| Bleeding labial skin subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 14 (7.14%) 1 | 0 / 6 (0.00%) 0 |
| Dry skin subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 14 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Rash acneiform subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 14 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Palmar-plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 14 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Erythema subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 14 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Renal and urinary disorders Hematuria subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 14 (7.14%) 1 | 1 / 6 (16.67%) 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 | <p>The primary purpose of the amendment 1 was to make following changes:</p> <ul style="list-style-type: none">• 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 | <p>The primary purpose of the amendment 2 was to make following changes:</p> <ul style="list-style-type: none">• 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 $\geq 20,000/\mu\text{L}$, platelet infusion independent and length of evaluation time to 49 days. |
| 11 May 2021 | <p>The primary purpose of the amendment 3 was to make following changes:</p> <ul style="list-style-type: none">• 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 | <p>The primary purpose of the amendment 4 was to make following changes:</p> <ul style="list-style-type: none">• 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 | <p>The primary purpose of the amendment 5 was to make following changes: •</p> <ul style="list-style-type: none"> 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 | <p>The primary purpose of the amendment 6 was to make following changes: •</p> <ul style="list-style-type: none"> 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 | <p>The primary purpose of the amendment 7 was to make following changes: •</p> <ul style="list-style-type: none"> 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