# 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 | |

### Results information

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 03 December 2021 |
| First version publication date | 03 December 2021 |

## 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 | Interim |
| Date of interim/final analysis | 18 May 2021 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | 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, and characterized the pharmacokinetics 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: 10 |
| Worldwide total number of subjects | 10 |
| 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) | 0 |
| Children (2-11 years) | 6 |
| Adolescents (12-17 years) | 3 |
| 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 6 investigative sites in the United States from 12 February 2019 to 18 May 2021. The study is ongoing.

### Pre-assignment

Screening details:

Participants with childhood relapsed or refractory acute lymphoblastic leukemia and lymphoblastic lymphoma were enrolled to receive ixazomib 1.6 mg/m^2/day or 2 mg/m^2/day.

### Period 1

| | |
|---|---|
| Period 1 title | Treatment Period: Day 1 to Week 4 |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **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 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 | Doxorubicin |
| Investigational medicinal product code | |
| Other name | Adriamycin |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Doxorubicin solution for infusion.

| | |
|---|---|
| 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 | Intravenous use, Oral use |
| Dosage and administration details:<br>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:<br>PEG-asparaginase solution for injection/infusion. | |
| **Arm title** | Ixazomib 2 mg/m^2 |
| Arm description:<br>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 | Vincristine |
| Investigational medicinal product code | |
| Other name | Oncovin, VCR, LCR |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |
| Dosage and administration details:<br>Vincristine IV push | |
| Investigational medicinal product name | Ixazomib |
| Investigational medicinal product code | |
| Other name | MLN9708 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details:<br>Ixazomib capsules. | |
| 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:<br>PEG-asparaginase solution for injection/infusion. | |
| Investigational medicinal product name | Doxorubicin |
| Investigational medicinal product code | |
| Other name | Adriamycin |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details:<br>Doxorubicin solution for 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.

| **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 | Follow-up Period: Week 5 to Week 104 |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **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 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 | 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 solution for infusion.

| | |
|---|---|
| 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 | 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.

| | |
|---|---|
| Investigational medicinal product name | Doxorubicin |
| Investigational medicinal product code | |
| Other name | Adriamycin |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral 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.

| | |
|---|---|
| **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 | Doxorubicin |
| Investigational medicinal product code | |
| Other name | Adriamycin |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral 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 | 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 solution for 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.

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

## Baseline characteristics

| 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 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 values | Ixazomib 1.6 mg/m^2 | Ixazomib 2 mg/m^2 | Total |
|---|---|---|---|
| Number of subjects | 4 | 6 | 10 |
| Age categorical<br>Units: Subjects | | | |
| Age Continuous<br>Units: years | | | |
| median | 8.7 | 12.1 | |
| full range (min-max) | 4.6 to 15.7 | 6.1 to 20.5 | - |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 3 | 3 | 6 |
| Male | 1 | 3 | 4 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 1 | 1 |
| White | 2 | 5 | 7 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 2 | 0 | 2 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 3 | 5 | 8 |
| Not Hispanic or Latino | 0 | 1 | 1 |
| Unknown or Not Reported | 1 | 0 | 1 |
| Region of Enrollment<br>Units: Subjects | | | |
| United States | 4 | 6 | 10 |

## 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 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 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 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 statistics were reported 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 | 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 statistics were reported 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 statistics were reported 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 statistics were reported 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: 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[5] |
|---|---|

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:

[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 statistics were reported 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: 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[6] |
|---|---|

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:

[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 statistics were reported 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: 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 statistics were reported 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 statistics were reported 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 Maximum Observed Plasma Concentration for Ixazomib at Day 11

| End point title | Tmax: Time to Reach Maximum Observed Plasma Concentration 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 statistics were reported 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 | | | | |
| 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 Plasma Concentration (Cmax) for Ixazomib at Day 11

| End point title | Cmax: Maximum Plasma Concentration (Cmax) 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 statistics were reported 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) | | | | |
| geometric mean (geometric coefficient of variation) | 22.8 (± 169.1) | 73.6 (± 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 statistics were reported 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 (h) | | | | |
| geometric mean (geometric coefficient of variation) | 111 (± 59.8) | 99.4 (± 37.4) | | |

### 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[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 statistics were reported 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 statistics were reported 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 statistics were reported 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 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:

[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 statistics were reported 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: Response (CR and CR+CRp) After Block 1 Chemotherapy

| End point title | Phase 2: Response (CR and CR+CRp) 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 disease.

| 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 statistics were reported 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 | 0[17] | 0[18] | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |

Notes:

[17] - Data is not available for this endpoint as the Phase 2 of the study is ongoing.

[18] - Data is not available for this endpoint as the Phase 2 of the study is ongoing.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 104 weeks

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). 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 | 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 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 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 | Ixazomib 2 mg/m^2 | Ixazomib 1.6 mg/m^2 | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 6 (100.00%) | 3 / 3 (100.00%) | |
| number of deaths (all causes) | 2 | 1 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 3 / 3 (100.00%) | |
| occurrences causally related to treatment / all | 5 / 6 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Generalized edema | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Allergic reaction | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucositis oral | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Catheter related infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 3 (33.33%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hyperglycemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 3 (33.33%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ALT increased | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 1 / 3 (33.33%) | |
| occurrences causally related to treatment / all | 5 / 5 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| AST increased | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 1 / 3 (33.33%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertriglyceridemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoalbuminemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalemia | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophosphatemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Ixazomib 2 mg/m^2 | Ixazomib 1.6 mg/m^2 | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 6 (100.00%) | 3 / 3 (100.00%) | |
| General disorders and administration site conditions | | | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 3 (33.33%) | |
| occurrences (all) | 0 | 1 | |
| Chills | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 3 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 3 (33.33%) | |
| occurrences (all) | 0 | 1 | |
| Pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Oral pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 3 (33.33%) | |
| occurrences (all) | 0 | 1 | |
| Fever | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 3 (33.33%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 3 (33.33%) | |
| occurrences (all) | 1 | 1 | |
| Mucositis oral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 3 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Anorexia | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 3 (33.33%) | |
| occurrences (all) | 2 | 1 | |
| Irritability | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 3 (33.33%) | |
| occurrences (all) | 0 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cardiac disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 3 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Electrocardiogram QT corrected interval prolonged | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 3 (33.33%) | |
| occurrences (all) | 0 | 1 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 3 (0.00%) | |
| occurrences (all) | 2 | 0 | |

| | | | |
|---|---|---|---|
| Blood and lymphatic system disorders | | | |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 3 (33.33%) | |
| occurrences (all) | 1 | 1 | |
| Anemia | | | |
| subjects affected / exposed | 5 / 6 (83.33%) | 3 / 3 (100.00%) | |
| occurrences (all) | 7 | 3 | |
| Blood bicarbonate decreased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 3 (33.33%) | |
| occurrences (all) | 6 | 3 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 3 / 3 (100.00%) | |
| occurrences (all) | 6 | 3 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 5 / 6 (83.33%) | 3 / 3 (100.00%) | |
| occurrences (all) | 6 | 3 | |
| Methemoglobinemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 5 / 6 (83.33%) | 0 / 3 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| White blood cell decreased | | | |
| subjects affected / exposed | 5 / 6 (83.33%) | 3 / 3 (100.00%) | |
| occurrences (all) | 6 | 3 | |
| Thrombus | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Edema face | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 3 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Edema limbs | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eye disorders | | | |
| Eye pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |
| Dyspepsia | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 3 (33.33%) | |
| occurrences (all) | 0 | 1 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Diarrhea | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Constipation | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 3 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Bloating | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pain in groin | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 3 (33.33%) | |
| occurrences (all) | 0 | 1 | |
| Vomiting | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 6 (33.33%) | 2 / 3 (66.67%) | |
| occurrences (all) | 4 | 2 | |
| Nausea | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 1 / 3 (33.33%) | |
| occurrences (all) | 4 | 1 | |
| Increased hunger | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Erythema | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash acneiform | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 3 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Renal and urinary disorders | | | |
| Bladder spasm | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cystitis noninfective | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hematuria | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperuricemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rectal pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Renal colic | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urinary tract pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Endocrine disorders | | | |
| Syndrome of inappropriate antidiuretic hormone secretion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 3 (33.33%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle cramp | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 3 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Back pain | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 3 (33.33%) | |
| occurrences (all) | 2 | 1 | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Adenovirus infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Parainfluenza 1 | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 3 (33.33%) | |
| occurrences (all) | 0 | 1 | |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Herpes simplex reactivation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 3 (33.33%) | |
| occurrences (all) | 0 | 1 | |
| Upper respiratory infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 3 (66.67%) | |
| occurrences (all) | 0 | 2 | |
| Thrush | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| RHINOVIRUS | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 3 (33.33%) | |
| occurrences (all) | 0 | 1 | |
| UTI R/T BK/ADENOVIRUS | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Metabolism and nutrition disorders | | | |
| ALT increased | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 3 / 3 (100.00%) | |
| occurrences (all) | 3 | 4 | |
| Alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 3 / 3 (100.00%) | |
| occurrences (all) | 1 | 4 | |
| AST increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 6 (50.00%) | 2 / 3 (66.67%) | |
| occurrences (all) | 7 | 4 | |
| GGT increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypercalcemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperglycemia | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 3 / 3 (100.00%) | |
| occurrences (all) | 9 | 8 | |
| Hyperkalemia | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 3 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hypoalbuminemia | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 3 / 3 (100.00%) | |
| occurrences (all) | 4 | 4 | |
| Hypertriglyceridemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 3 (33.33%) | |
| occurrences (all) | 0 | 1 | |
| Hyperphosphatemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 3 (33.33%) | |
| occurrences (all) | 0 | 1 | |
| Hypermagnesemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hypernatremia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypocalcemia | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 1 / 3 (33.33%) | |
| occurrences (all) | 6 | 3 | |
| Hypomagnesemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hypokalemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 3 (33.33%) | |
| occurrences (all) | 1 | 4 | |
| Hypoglycemia | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 3 (33.33%) | |
| occurrences (all) | 2 | 2 | |
| Hyponatremia | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 2 / 3 (66.67%) | |
| occurrences (all) | 4 | 5 | |
| Hypophosphatemia | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 1 / 3 (33.33%) | |
| occurrences (all) | 5 | 1 | |
| Weight loss | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 3 (33.33%) | |
| occurrences (all) | 1 | 1 | |
| Weight gain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| INR increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 19 December 2019 | The primary purpose of the amendment 1 was to make following changes:<br>• Dose Modification for Intrathecal Methotrexate/Triple Intrathecal Therapy toxicities: Mercaptopurine dose adjustments made to allow for genotype variations in either TPMT or NUDT15<br>• Dose Modification for Intermediate-Dose Methotrexate toxicities: Added subsection 4.7.7.5 to provide guidance in the event of excess extravasation of fluids into tissues (third spacing)<br>• Clinical and Laboratory Studies: Added neurological exam to be performed prior to each Ixazomib dosing<br>• 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:<br>• Exclusion criteria: updated the list of excluded CYP3A4 agents<br>• Treatment program: under Block 1, 2, and Maintenance Block, revised timing of Leucovorin for Down syndrome Participants to be received at hours 24 and 30 after intrathecal methotrexate (IT MTX) or intrathecal triple therapy (ITT)<br>• 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:<br>• 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<br>• 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. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported