22 June 2023
EMA/3836/2024
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

BESPONSA

Inotuzumab ozogamicin

Procedure no: EMEA/H/C/004119/P46/004

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Abbreviations

ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
amended mR3	dexamethasone dose reduced by 50% in mR3
ASP	asparaginase
AST	aspartate aminotransferase
BCP	B-cell precursor
BLA	Biologics license application
BLQ	below limit of quantification
BSA	body surface area
CD	cluster of differentiation
CI	confidence interval
CR	complete remission/response
CRi	complete remission with incomplete hematologic recovery
CRp	complete remission with incomplete platelet recovery
CSR	clinical study report
CTC	Common Terminology Criteria
DL	dose level
DLT	dose limiting toxicity
DMH	dimethylhydrazide
DoR	duration of response
EC	European Commission
ECG	electrocardiogram
EFS	event free survival
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
FU	follow-up
G	grade
GGT	gamma-glutamyl transferase
GvHD	graft versus host disease
HR	hazard ratio
HSCT	hematopoietic stem cell transplant
InO	Inotuzumab Ozogamicin
IT	intrathecal
IV	intravenous
LSLD	last subject last dosed
MAH	marketing-authorisation holder
MOF	multiple organ failure
mR3	a modified collaborative UKALL trial for relapsed and refractory ALL; InO replaces mitoxantrone; includes dexamethasone 20 mg/m^2 on Days 1-5 and 15-19 during induction
MRD	minimal residual disease
NE	non-estimable
ORR	overall response rate
OS	overall survival
PD	pharmacodynamic(s)

PIP	Pediatric Investigation Plan
PK	pharmacokinetic(s)
PT	preferred term
RP2D	recommended phase 2 dose
RQ-PCR	real-time quantitative polymerase chain reaction
R/R	relapsed/refractory
PCD	primary completion date
PD	pharmacodynamic
PFS	progression fee survival
PIP	Paediatric Investigational Plan
PK	pharmacokinetics
PT	preferred term
SoC	system organ class
TEAE	treatment-emergent adverse event
TEAESI	treatment-emergent adverse event of special interest
TESAE	treatment-emergent serious adverse event
TR	treatment-related
UKALL-R3	a historical clinical trial for relapsed and refractory ALL
VOD	veno-occlusive disease

1. Introduction

On March 17th, the MAH submitted the CSR for a paediatric study for inotuzumab ozogamicin (InO), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

No updates of the product information or the RMP are proposed within the current procedure.

A variation is planned to be submitted in Q3 2023, to update the SmPC with safety information from the study (see further information below).

Steps taken for the assessment	
Description	**Actual Date**
Start of procedure	24 April 2023
CHMP Rapporteur Assessment Report	22 May 2023
CHMP adoption of conclusions:	22 June 2023

2. Scientific discussion

2.1. Information on the development program

Study ITCC-059 is an ongoing multi-cohort study. The MAH is currently submitting the Clinical study report (CSR) under Article 46, to fulfil the requirement to report paediatric data within 6 months of primary completion date (PCD).

Study ITCC-059 is part of the PIP for inotuzumab ozogamicin (Study 1; see Table 1). The MAH considers that this PIP measure is completed with the current submission of the interim ITCC-059 CSR dated 21 Feb 2023.

The last subject last dose (LSLV) for Study ITCC-059 is estimated to be 11 April 2025. The MAH, however, would like to clarify that is an estimate that may be subjected to re-evaluation.

There will be a CSR amendment for the final stratum 1B to add additional safety information that are not available at the time of this Article 46 submission due to monitoring/COVID site restrictions. The amended CSR will support an update to the paediatric section of the SmPC for patients with CD22-positive relapsed/refractory Acute Lymphoblastic Leukaemia (ALL). A variation is therefore planned to be submitted in Q3 2023, to update the SmPC with the updated safety information from the study.

Thus, no updates of the product information or the RMP are proposed within the current PAM/PAC procedure.

Table 1. Paediatric investigation plan for inotuzumab ozogamicin

Area	Number of measures	Description
Quality-related studies	0	Not applicable.
Non-clinical studies	0	Not applicable.
Clinical studies	2	Study 1: Open-label, multiple dose, two-strata trial to establish the optimal biological dose of inotuzumab ozogamicin used as single agent and to determine the recommended dose of inotuzumab ozogamicin as add-on to modified regimen from trial UKALL-R3 in children from 1 to less than 18 years of age with CD22-positive relapsed/refractory acute lymphoblastic leukaemia.
		Study 2: Open-label, randomised superiority trial to evaluate safety and efficacy of inotuzumab ozogamicin as add-on to modified regimen from trial UKALL-R3 over standard UKALL-R3 regimen in patients from 1 to less than 18 years of age (and adults) with early first relapse of CD22 positive B cell precursor acute lymphoblastic leukaemia.
Extrapolation, modelling and simulation studies	0	Not applicable.
Other studies	0	Not applicable.
Other measures	0	Not applicable.

2.2. Information on the pharmaceutical formulation used in the study

Besponsa is marketed as a 1 mg powder for concentrate for solution for infusion. The batches used in Study ITCC-059 are shown in Table 2.

Table 2. Study intervention administered

Study Intervention Description	CSP number	Packaging Batch Number
PF-05208773 (CMC-544) (InO) 1 mg/vial lyophilized powder	CSP14770	15-007774
PF-05208773 (CMC-544) (InO) 1 mg/vial lyophilized powder	CSP18432	17-004170
PF-05208773 (CMC-544) (InO) 1 mg/vial powder for concentrate for solution for infusion.	CSP20195	17-004397
PF-05208773 (CMC-544) (InO) 1 mg/vial lyophilized powder	CSP18796	18-003795
PF-05208773 (CMC-544) (InO) 1 mg/vial lyophilized powder	CSP22555	19-002862
PF-05208773 (CMC-544) (InO) 1 mg/vial powder for concentrate for solution for infusion	CSP24034(1) CSP24034(2)	21-LU-00494

Assessor's comment: The MAH did not discuss comparability of the batches used in the study with marketed batches. This is accepted, as the study is not pivotal for a paediatric indication or dose recommendation.

2.3. Clinical aspects

2.3.1. Introduction

Inotuzumab ozogamicin (BESPONSA) is an ADC, with CD22-directed humanized immunoglobulin type G, subtype 4 antibody covalently linked to N-Ac-γ-calichaemicin dimethylhydrazide, a potent cytotoxic antitumor antibiotic, approved for adult patients with R/R BCP-ALL.

InO causes cell death by inducing double-strand DNA breaks.2,3 CD22 is a B-cell adhesion molecule that is expressed on both normal cells of the mature B-lymphocyte lineage and on the malignant cells of the majority of B-cell cancers. It is highly expressed in more than 90% cases of childhood BCP-ALL.

To date, approvals of InO for treatment for adults with R/R ALL have been granted in the US (on 17 August 2017, the EU (on 29 June 2017), Switzerland (10 July 2017), and Japan (19 January 2018).

The approved indication in the EU is:

BESPONSA is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL). Adult patients with Philadelphia chromosome positive (Ph+) relapsed or refractory B cell precursor ALL should have failed treatment with at least 1 tyrosine kinase inhibitor (TKI)

Currently, the SmPC includes the following information regarding the paediatric population:

The safety and efficacy of BESPONSA in children aged 0 to <18 years have not been established. No data are available.

With the current submission, in accordance with Art 46 of Regulation (EC) No1901/2006, as amended, the MAH submitted an interim report for:

- Study ITCC-059: A Phase I/II Study of Inotuzumab Ozogamicin as a Single Agent and in Combination With Chemotherapy for Paediatric CD22-Positive Relapsed/Refractory Acute Lymphoblastic Leukaemia

Study ITCC-059 (PIP Study 1) is one of the 2 studies that are part of EU PIP (Table 1) to determine the optimal dose of InO as a single agent as well as in combination with a standard combination chemotherapy regimen in paediatric patients with R/R ALL.

Study B1931036 (PIP Study 2) was initially planned to be a Phase 2, randomized open-label superiority trial to evaluate the safety and efficacy of InO (based on the dose determined in PIP Study 1) added to a modified UKALL-R3 regimen in children and adolescents with early first relapse of CD22-positive B cell precursor ALL. Based on the data from Study ITCC-059, PIP Study 2 B1931036 was modified and will evaluate InO monotherapy as induction compared to the UKALL-R3 induction regimen (2:1 randomization) in children and adolescents with high risk first relapse of CD22 positive BCP-ALL.

As described in Section 2.1 above, no updates to the SmPC are proposed within the current procedure. The MAH will submit at type II variation, once an updated CSR for Study ITCC-059 is available (planned in Q3 2023).

2.3.2. Clinical study ITCC-059

Description

Table 3- Study objectives and endpoints

Type	Objective	Endpoints	Presentation of Results
Primary			
Stratum 1A			
Safety	To establish the MTD or the RP2D of single agent InO when administered in children with CD22-positive R/R BCP-ALL	DLTs during the first cycle of therapy	Final data presented in Study ITCC-059 CSR (Report date: 21 Feb 2023)
Phase 2 Cohort			
Efficacy	To establish the efficacy (ORR defined as the rate of patients with CR/CRi/CRp) of single agent InO when administered in children with CD22-positive R/R BCP-ALL	ORR, defined as the percentage of patients with CR/CRi/CRp, measured as best response during InO treatment	Final data presented in Study ITCC-059 CSR (Report date: 21 Feb 2023)
Stratum 1B			
Safety	To determine the RP2D of InO in children with CD22-positive R/R BCP-ALL in combination with a modified UKALL-R3-based re-induction regimen	DLTs during the first cycle of InO when added to a modified UKALL-R3 re-induction chemotherapy regimen without mitoxantrone or ASP	Final data presented in Study ITCC-059 CSR (Report date: 21 Feb 2023)
Secondary			
Stratum 1A and Phase 2 Cohort			
Safety	To determine the safety and tolerability of InO as a single agent during Cycle 1; the cumulative toxicities in patients receiving multiple cycles of InO; as well as after subsequent allo-HSCT or CAR T-cell therapy	• AEs, as characterized by type, frequency, severity (as graded using CTCAE, v4.03), timing, seriousness, and relation to study therapy, during the first and subsequent cycles of therapy • Occurrence of toxic death; ie, death attributable to InO therapy • Occurrence of hepatic VOD/SOS during or after therapy with InO • Laboratory abnormalities as characterized by type, frequency, severity and timing • The cumulative incidence of non-relapse mortality, defined as the cumulative probability of non-relapse mortality, with time calculated between start of study treatment and death due to other causes than R/R leukemia, accounting for competing events	Data presented as of the cutoff date of Study ITCC-059 CSR (Report date: 21 Feb 2023)
Efficacy	To determine the ORR in these patients: - after Cycle 1 - as well as the overall best response (Stratum 1A only; this is the primary objective for the Phase 2 Cohort)	• **For Stratum 1A:** ORR both after Cycle 1 as well as the best response over multiple cycles of InO therapy • **For Phase 2 Cohort:** ORR after cycle 1	Data presented as of the cutoff date of Study ITCC-059 CSR (Report date: 21 Feb 2023)
	To determine MRD levels in responding patients, including the percentage of patients with a complete MRD response - after Cycle 1 - as well as the best overall response	MRD levels, including the percentage of responding patients who become MRD-negative (complete MRD response defined as an MRD-level $<1\times10^{-4}$), after Cycle 1, as well as the overall best response (MRD negativity) over multiple cycles	
	To describe the durability of response and long-term follow-up, including the number of patients that undergo HSCT or CAR T-cell therapy as consolidation after treatment with InO, the cumulative incidence of non-response or relapse, the cumulative incidence of non-relapse mortality, the EFS and OS	• DoR, defined as the time between achieving response (CR/CRi/CRp) after starting study treatment and documented relapse or death • Number and percentage of patients who undergo HSCT and those who receive CAR T-cell therapy after treatment with InO • EFS, defined as the time between start of study treatment and first event including failure to achieve CR/CRi/CRp (calculated as an event on Day 0), relapse, death of any cause and second malignancies • OS, defined as time to death following start of study treatment • The cumulative incidence of non-response or relapse, defined as the cumulative probability of non-response or relapse, with time calculated between start of study treatment and relapse and with non-responders included as an event on Day 0. Non-relapse death is considered a competing event.	
PK	To determine the serum PK parameters of unconjugated calicheamicin and InO in the pediatric population	Serum PK parameters of InO and unconjugated calicheamicin	Data presented as of the cutoff date of Study ITCC-059 CSR (Report date: 21 Feb 2023)

Table 3- Study objectives and endpoints (cont.)

Type	Objective	Endpoints	Presentation of Results
PD	To assess the relationship between CD22 density, WBC count at start of treatment, CD22 saturation kinetics, cytogenetics, and in-vitro calicheamicin resistance to clinical response to InO	• Relationship between response (ORR) and CD22 expression levels and WBC • Relationship between response (ORR) and CD22 saturation kinetics • Relationship between response (ORR) and calicheamicin sensitivity • Clonal evolution (CD22-negativity) and relation to loss of response[a]	Data presented as of the cutoff date of Study ITCC-059 CSR (Report date: 21 Feb 2023), except the analyses of clonal evolution (CD22-negativity) and relation to loss of response are not presented
Efficacy	To assess for the persistence of B-Cell aplasia and hypogammaglobulinemia in responding patients following treatment with InO[b]	The percentage of patients responding to InO (ORR) without adequate recovery of CD19-positive B-cells (below LLN for age) or immunoglobulins (below LLN for age) following 4 and 10 weeks, 3, 6 and 12 months after treatment with InO, excluding patients who have been transplanted from the date of HSCT or have received CAR T-cell therapy[b]	Not included in Study ITCC-059 CSR (Report date: 21 Feb 2023)
Immunogenicity	To assess the number of patients developing ADAs	Percentage of patients who exhibit ADA	Data presented as of the cutoff date of Study ITCC-059 CSR (Report date: 21 Feb 2023)
Stratum 1B[a]			
Safety	To determine the safety and tolerability of InO in combination with a modified UKALL-R3 re-induction chemotherapy regimen[a] (1 or 2 cycles); and the cumulative toxicities in patients receiving multiple InO-based cycles, as well as after subsequent allogeneic HSCT	• AEs • Occurrence of toxic death; ie, death attributable to InO therapy • Occurrence of hepatic VOD/SOS during or after therapy with InO • Laboratory abnormalities • Cumulative incidence of non-relapse mortality	Data presented as of the cutoff date of Study ITCC-059 CSR (Report date: 21 Feb 2023)
Efficacy	To determine the ORR in these patients: - after Cycle 1 - as well as the overall best response	ORR	Data presented as of the cutoff date of Study ITCC-059 CSR (Report date: 21 Feb 2023)
	To determine MRD levels in responding patients, including the percentage of patients with a complete MRD response: - after Cycle 1 - as well as the best ORR	MRD levels	
	To describe the durability of response and long-term follow-up, including the number of patients that undergo HSCT or CAR T-cell therapy as consolidation after study treatment, the cumulative incidence of nonresponse or relapse, the cumulative incidence of nonrelapse mortality, the EFS and OS	• Duration of response • Number and percentage of patients who undergo HSCT and those receiving CAR T-cell therapy after treatment with InO • EFS • OS • Cumulative incidence of non-response or relapse	
PK	To determine the serum PK parameters of unconjugated calicheamicin and InO when added to a modified reinduction UKALL-R3 chemotherapy regimen[a]	Serum PK parameters of InO and unconjugated calicheamicin during treatment combined with modified UKALL-R3 re-induction regimen[a] without pegylated ASP	Not included in Study ITCC-059 CSR (Report date: 21 Feb 2023)
PD	To assess the relationship between CD22 expression and clinical response to InO	Relationship between response (ORR) and CD22 expression levels	Data presented as of the cutoff date of Study ITCC-059 CSR (Report date: 21 Feb 2023)
	To assess the number of patients developing CD22-negative relapse[b]	Clonal evolution (CD22-negativity) and relation to loss of response[b]	Not included in Study ITCC-059 CSR (Report date: 21 Feb 2023)

a. Post Protocol Amendment 4, the combination therapy refers to the amended modified UKALL-R3 (50% dose deduction of dexamethasone)
b. These endpoints are not required per PIP, thus the results are not included in this CSR.

Study ITCC-059 is part of an approved EU PIP (EMEA-001429-PIP01-13-M06).

The objectives of this study were to identify the recommended dose of InO administered IV either as monotherapy (Stratum 1A) or in combination with chemotherapy (Stratum 1B) for paediatric patients with R/R CD22-positive ALL, and to estimate the efficacy, safety and tolerability of the selected recommended phase 2 dose (RP2D) of monotherapy InO, and to evaluate PK and PD in this patient population.

Methods

Study participants

Paediatric participants (≥1 and <18 years) with relapsed (2nd or greater relapse or first relapse after transplant)/refractory CD22-positive BCP-ALL were enrolled in this study.

A total of 85 participants were assigned to treatment and 83 participants were treated.

Treatments

Stratum 1A:

Dose escalation: 25 participants were treated; 12 received InO 1.4 mg/m^2/cycle (dose level [DL]1) and 13 received InO 1.8 mg/m^2/cycle (DL2).

Phase 2 Cohort: 28 participants received InO 1.8 mg/m^2/cycle.

A cycle of therapy is defined as 3 doses of InO administered on Days 1, 8 and 15. Cycle 1 lasted 22 days (with possible delays allowed up to 42 days, depending on response and recovery from toxicity); subsequent cycles lasted 28 days, again with possible delays up to 42 days. Following Cycle 1, in patients who had achieved a CR/CRi/CRp, the Day 1 dose of InO was decreased slightly due to no loading dose requirement.

For these single agent InO cohorts, a maximum of 6 cycles of InO was allowed for patients not proceeding to HSCT. For patients proceeding to HSCT, the recommended duration of study treatment was 2 cycles, with a maximum of 3 cycles for any patient who was not MRD-negative after 2 cycles.

Stratum 1B: 30 participants were treated.

A cycle of therapy was defined as 3 doses of InO administered on Days 1, 8 and 15 combined with the UKALL-R3 modified regimen (mR3; dexamethasone and vincristine) with InO replacing mitoxantrone. All cycles lasted 28 days, with delays allowed up to 42 days to allow recovery from toxicity

- InO was given at an initial starting dose of 1.1 mg/m^2/cycle, combined with UKALL- R3 modified regimen 1.5 mg/m^2 on Days 3, 10, 17 and 24; oral dexamethasone 20 mg/m^2/day on Days 1-5 and 15-19, divided in 2 daily doses, and IT methotrexate prophylaxis on Days 1 and 8.
- Due to 2 out of 4 participants at this 1.1 mg/m^2/cycle dose level experienced DLTs, the dose of InO was de-escalated to 0.8 mg/m^2/cycle while awaiting approval of Study ITCC-059 Appendix 16.1.1, Protocol Amendment 4 which supported re-escalation of InO to 1.1 mg/m^2 during C1; 6 participants received InO combined with a reduced dose of dexamethasone at 10 mg/m^2/day (amended mR3). Next, 3 participants received InO 1.4 mg/m^2/cycle + amended mR3. Finally, 10 participants received InO 1.8 mg/m^2/cycle + amended mR3. A total of 19 participants were treated with the reduced dose of dexamethasone.

Objective(s)

See Table 3.

Outcomes/endpoints

See Table 3.

Sample size

A total of 85 participants were assigned to treatment and 83 participants were treated.

Randomisation and blinding (masking)

N/A

Pharmacokinetics

Serum samples were collected for InO and unconjugated calicheamicin.

A specific and sensitive bioanalytical method using LC-MS/MS method was developed and validated at PPD laboratories (Richmond, VA, USA) to measure InO and unconjugated calicheamicin.

Statistical Methods

See Table 3.

The binary endpoints (response rates) will be presented as a proportion with exact 2-sided 95% and 90% confidence intervals.

Categorical variables will be presented as frequencies and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

Time-to-event endpoints (EFS, OS, DOR) will be analyzed using the Kaplan-Meier method or the competing risks method for cumulative incidence functions if time to disease transformation is included as an endpoint. The cumulative incidence and its standard error will be estimated using Gray's method.

When applying the Kaplan Meier method, median times and quartiles with associated 2-sided 95% confidence intervals (CIs) based on the Brookmeyer-Crowley linear transformation method will be provided, assuming no ties among observed survival times. If median times will not be reached at the time of the analysis, survival rates at the specific time point will be provided together with the associated 2-sided 95% CI based on Greenwood's formula.

Methods to Manage Missing Data: The baseline value will be defined as the last non-missing value prior to first dose, unless specifically stated otherwise.

Partial dates are handled in the following way: if the month and year are present but day is missing, date is set to 15th of the month. If month is missing, it is set to June. No other imputation of missing data will be performed.

No formal interim analysis was planned for Stratum 1A, phase 2 or Stratum 1B. As this was an open-label study, the SAP specified that the sponsor may conduct unblinded review of the data during the course of study for the purpose of dose confirmation and safety assessment.

Results

Participant flow

A total of 85 participants were enrolled at 22 centers in 11 countries, and 83 participants were treated. The total dose of InO per cycle mentioned hereafter refers to Cycle 1 mainly.

The Full Analysis Set included all enrolled participants who received at least 1 dose of study therapy and was used for the efficacy analysis and the safety analysis (Stratum 1A: 25 participants, Phase 2 Cohort: 28, Stratum 1B: 30).

The Dose Escalation Analysis Set for Stratum 1B (to establish the RP2D for combination therapy) included all enrolled participants who received at least 1 dose of InO in combination with dexamethasone and vincristine and were evaluable for the dose escalation phase (26 participants).

The Response Evaluable Analysis Set (for primary analysis in the Phase 2 Cohort) included all participants who received at least 1 dose of InO and have completed a baseline disease assessment and at least 1 post-baseline disease assessment (28 participants). Therefore, the Response Evaluable Analysis Set is equal to the Full Analysis Set for Phase 2.

The PD Analysis Set included participants who were treated and had at least 1 of the PD parameters available (Stratum 1A: 25 participants, Phase 2 Cohort: 28, Stratum 1B: 30).

The PK Analysis Set includes all Full Analysis Set participants who provided at least 1 PK sample of interest (Stratum 1A: 25 participants, Phase 2 Cohort: 28). This report doesn't include PK results for Stratum 1B, as data are not available yet and will be included in the supplemental CSR.

Pharmacokinetics

After a single dose (C1D1), InO mean maximum serum concentrations in Stratum 1A DL1 (1.4 mg/m2), DL2 (1.8 mg/m2) and the Phase 2 Cohort (1.8 mg/m2) were 157.7 ng/mL, 163.2 ng/mL, and 173.2 ng/mL, respectively. In adults the mean concentration was measured to 161 ng/mL. After multiple doses (C3D1), the mean maximum serum concentrations in Stratum 1A DL1, DL2 and the Phase 2 Cohort were 277.0 ng/mL, 293.0 ng/mL, and 296.4 ng/mL, respectively. At C3D15, the mean pre-dose (trough) concentrations at Stratum 1A DL1, DL2 and the Phase 2 Cohort were 112.5 ng/mL, 135.0 ng/mL and 121.2 ng/mL, respectively. At C1D15 and C2D8 at 0 hours post dose, the exposure for children given 1.8 mg/m2 was 28 88 ng/mL and 88 ng/mL and 29 ng/mL and 77 ng/mL in stratum 1A and Phase 2 respectively. In adults it was measured to 24 ng/mL and 63 ng/mL, respectively. Overall, the Ino exposures in paediatric patients were relatively similar to those previously reported in adult patients.

N-acetyl-gamma calicheamicin DMH concentrations were not summarized since the concentrations for all the tested samples were BLQ.

Baseline data

Stratum 1A:

Of the 25 participants enrolled and treated, 68.0% were male. The median age was 11 years (range: 1 to 16 years) and the median BSA was 1.22 m2 (range: 1-2 m2).

At baseline,

- Median WBC count was 2.30×109/L (range: 0-17×109/L).
- 14 (56.0%) participants had bone marrow blasts ≥50%.
- Median peripheral blood blasts count was 149.5×106/L (range: 0-2950).
- Median mean fluorescence intensity for CD22-positive ALL cells was 2949 (range: 505- 8370).

Phase 2 Cohort:

Of the 28 participants enrolled and treated, 67.9% were male. The median age was 7.5 years (range: 1 to 17 years) and the median BSA was 0.99 m2 (range: 1-2 m2).

At baseline:

- Median WBC count was 2.78×109/L (range: 1-132×109/L).
- 17 (60.7%) participants had bone marrow blasts ≥50%.
- Median peripheral blood blasts count was 170.0×106/L (range: 0-15,140).
- Median mean fluorescence intensity for CD22-positive ALL cells was 2297 (range: 479- 9619).

Stratum 1B:

Of the 30 participants enrolled and treated, 63.3% were male. The median age was 8.5 years (range: 1 to 17 years) and the median BSA was 1.08 m2 (range: 1-2 m2).

At baseline:

- Median WBC count was 3.92×109/L (range: 1-99×109/L).
- 18 (60.0%) participants had bone marrow blasts ≥50%.
- Median peripheral blood blasts count was 211.0×106/L (range: 0-77,211)
- Median mean fluorescence intensity for CD22-positive ALL cells was 1691 (range: 359- 7003)

Efficacy results

Primary endpoint

Best Overall Response in the Phase 2 Cohort (dose confirmation part)

In the Phase 2 Cohort (Table 4), the primary objective was met demonstrating CR/CRi/CRp rate significantly greater than the 30% null hypothesis rate with 1-sided p-value of 0.0019. There were 22 participants who achieved an objective response (CR/CRi/CRp) among the 28 participants in the Response Evaluable Analysis Set (CR: 18, CRp: 1, CRi: 3). The estimated ORR (CR+CRi+CRp) was 78.6% (95% CI: 59.0-91.7).

Table 4. Best Overall Response and Response (Phase 2, Response Evaluable analysis set

	Phase 2 (N=28) n (%)
Best Response	
Complete remission (CR)	18 (64.3)
Complete Response with insufficient platelet recovery (CRp)	1 (3.6)
Complete Response without recovery of counts (CRi)	3 (10.7)
Partial Response (PR)	3 (10.7)
Non-response or Stable Disease (SD)	1 (3.6)
Progressive disease (PD)	2 (7.1)
Induction Death (ID)	0
Objective Response (CR+CRp+CRi)	22 (78.6)
95% Exact CI [1]	(59.0, 91.7)
90% Exact CI [1]	(62.0, 90.2)
1 sided p-value	0.0019
Cycle 1	
Complete remission (CR)	12 (42.9)
Complete Response with insufficient platelet recovery (CRp)	1 (3.6)
Complete Response without recovery of counts (CRi)	9 (32.1)
Partial Response (PR)	3 (10.7)
Non-response or Stable Disease (SD)	1 (3.6)
Progressive disease (PD)	2 (7.1)
Induction Death (ID)	0
Objective Response (CR+CRp+CRi)	22 (78.6)
95% Exact CI [1]	(59.0, 91.7)
90% Exact CI [1]	(62.0, 90.2)

[1] CI Calculated using the exact (Clopper-Pearson) method based on binomial distribution.
PFIZER CONFIDENTIAL SDTM Creation: 09NOV2022 (13:49) Source Data: adrs Table Generation: 14DEC2022 (11:42)
(Database snapshot date - Stratum 1A: 30SEP2022 Phase2: 07OCT2022 and Stratum 1B: 21OCT2022) Output File: ./csr_cdisc2/INO_ITCC_059_CSR/adrs_bor_ns002
Table 14.2.1.2 Inotuzumab Ozogamicin is for Pfizer internal use.

Secondary endpoints (selected)

ORR (dose-finding part)

Stratum 1A:

In Stratum 1A, 20 out of 25 participants achieved an objective response (DL1: 9 CR; DL2: 11 CR), for an ORR of 80.0% (95% CI: 59.3-93.2). ORR was 75.0% (95% CI: 42.8-94.5) in DL1 and 84.6% (95% CI: 54.6-98.1) in DL2.

Stratum 1B:

In Stratum 1B, 24 out of 30 participants achieved an objective response, for an ORR of 80.0% (95% CI: 61.4-92.3).

- In 0.8 mg/m2 + mR3, among 6 participants, 3 achieved CR plus 1 achieved CRp, for an RR of 66.7% (95% CI: 22.3-95.7); • In 1.1 mg/m2 + mR3, among 4 participants, 3 achieved CR, for an ORR of 75.0% (95% CI: 19.4-99.4);

- In 1.1 mg/m2 + amended mR3, among 6 participants, 5 achieved CR, for an ORR of 83.3% (95% CI: 35.9-99.6); • In 1.4 mg/m2 + amended mR3, among 3 participants, all achieved CR, for an ORR of 100.0% (95% CI: 29.2-100.0);

- In 1.8 mg/m2 + amended mR3, among 11 participants, 7 achieved CR plus 1 each achieved CRp and CRi, for an ORR of 81.8% (95% CI: 48.2-97.7).

MRD

Stratum 1A:

Of the 20 participants who achieved CR/CRi/CRp, 16/20 (80.0%) participants and 13/20 (65.0%) participants achieved MRD-negativity based on flow cytometry and RQ-PCR, respectively.

At the end of Cycle 1, of the 20 participants who achieved CR/CRi/CRp, 14/20 (70.0%) participants and 11/20 (55.0%) participants achieved MRD-negativity based on flow cytometry and RQ-PCR, respectively.

Phase 2 Cohort:

Of the 22 participants who achieved CR/CRi/CRp, all (100.0%) participants and 19/22 (86.4%) participants achieved MRD-negativity based on flow cytometry and RQ-PCR, respectively.

At the end of Cycle 1, of the 22 participants who achieved CR/CRi/CRp, 18/22 (81.8%) participants and 15/22 (68.2%) participants achieved MRD-negativity based on flow cytometry and RQ-PCR, respectively.

Stratum 1B:

Of the 24 participants who achieved CR/CRi/CRp, 19/24 (79.2%) participants and 17/24 (70.8%) participants achieved MRD-negativity based on flow cytometry and RQ-PCR, respectively.

At the end of Cycle 1, of the 22 participants who achieved CR/CRi/CRp, 15/22 (68.2%) participants and 14/22 (63.6%) participants achieved MRD-negativity based on flow cytometry and RQ-PCR, respectively.

DoR

Stratum 1A:

Of the 20 participants who achieved CR/CRi/CRp, 14 (70.0%) participants had subsequent events, of which 11 events were relapse and 3 were death. The median DoR was 8.0 months (95% CI: 3.9-13.9).

Phase 2 Cohort:

Of the 22 participants who achieved CR/CRi/CRp, 14 (63.6%) participants had subsequent events, of which 8 events were relapse and 6 were death. The median DoR was 7.6 months (95% CI: 3.3-NE).

Stratum 1B:

Of the 24 participants who achieved CR/CRi/CRp, 13 (54.2%) participants had subsequent events, of which 9 events were relapse and 4 were death. The median DoR was 8.4 months (95% CI: 5.0-NE).

Hematologic stem cell transplantation (HSCT) and CAR T-cell Therapy Rate

Stratum 1A:

Eight (32.0%) participants had post InO allogeneic HSCT transplants. All were in CR at the time of HSCT. A total of 4 (16.0%) participants in Stratum 1A underwent at least 1 CAR T-cell therapy given after end of study therapy or after last dose of InO.

Phase 2 Cohort:

Eighteen (64.3%) participants had post InO allogeneic HSCT transplants. Seventeem of 18 participants were in CR/CRi/CRp at the time of HSCT. A total of 9 (32.1%) participants in Phase 2 Cohort underwent at least 1 CAR T-cell therapy given after end of study therapy or after last dose of InO.

Stratum 1B:

Seventeem (56.7%) participants had post InO allogeneic HSCT transplants (16 myeloablative). Sixteen of 17 participants were in CR/CRi/CRp at the time of HSCT. A total of 11 (36.7%) participants in Stratum 1B underwent at least 1 CAR T-cell therapy given after end of study therapy or after last dose of InO.

Safety results

Exposure

Stratum 1A:

25 participants were dosed; 14 (56.0%) participants started >1 cycle (Refer to Table 2 for administration details on InO in subsequent cycles). The median number of cycles initiated was 2 (range: 1-4) cycles. The median total dose of InO received was 2.59 mg/m2 (range: 0.57-5.28 mg/m2), with a median dose intensity of 1.37 mg/m2/cycle (range: 0.57-1.83 mg/m2/cycle). The median relative dose intensity was 100.0% (range: 44.56%-105.13%).

Phase 2 Cohort:

28 participants were dosed; 16 (57.1%) participants started >1 cycle. The median number of cycles initiated was 2 (range: 1-4) cycles. The median total dose of InO received was 3.22 mg/m2 (range: 0.76-6.47 mg/m2), with a median dose intensity of 1.66 mg/m2/cycle (range: 0.76-1.86 mg/m2/cycle). The median relative dose intensity was 100.04% (range: 70.83%- 105.22%).

Stratum 1B:

30 participants were dosed; 14 (46.7%) participants started >1 cycle. The median number of cycles initiated was 1 (range: 1-3) cycle. The median total dose of InO received was 1.84 mg/m2 (range: 0.50-3.82 mg/m2), with a median dose intensity of 1.31 mg/m2/cycle (range: 0.50-1.86 mg/m2/cycle). The median relative dose intensity was 100.16% (range: 94.34%-104.59%).

Dose-limiting toxicity

DLT was evaluated in Cycle 1 only. The results are summarised in Table 5.

Table 5. Summary of Dose Limiting Toxicity (DLT) - Dose Escalation population Set

	Stratum 1A						Stratum 1B				
	1.4 mg/m² Cohort 1 (N = 6)	1.4 mg/m² Cohort 2 (N = 6)	1.4 mg/m² Total (N = 12)	1.8 mg/m² Cohort 1 (N = 5)	1.8 mg/m² Cohort 2 (N = 6)	1.8 mg/m² Total (N = 11)	0.8 mg/m²+mR3 (N = 6)	1.1 mg/m²+mR3 (N = 4)	1.1 mg/m²+amended mR3 (N = 6)	1.4 mg/m²+amended mR3 (N = 3)	1.8 mg/m²+amended mR3 (N = 7)	Total (N = 26)
Dose Limiting Toxicities, DLT	1 (16.7)	0	1 (8.3)	2 (40.0)	1 (16.7)	3 (27.3)	0	2 (50.0)	1 (16.7)	0	1 (14.3)	4 (15.4)
Alanine aminotransferase increased	1 (16.7)	0	1 (8.3)	1 (20.0)	0	1 (9.1)	0	1 (25.0)	1 (16.7)	0	0	2 (7.7)
Neutrophil count decreased	0	0	0	1 (20.0)	0	1 (9.1)	0	0	0	0	1 (14.3)	1 (3.8)
Platelet count decreased	0	0	0	0	1 (16.7)	1 (9.1)	0	0	0	0	0	0
Venoocclusive disease	0	0	0	0	0	0	0	1 (25.0)	0	0	0	1 (3.8)

Note: Table includes DLTs which were confirmed by PI.
N= Number of participants received dose level in Dose Escalation Analysis set
n. =participants reporting more than one DLT within a preferred term are counted only once in that preferred term.
Note: After completed enrollment for DL1 and DL2 for stratum 1A, the dose was de-escalated to DL1 and then re-escalated to DL2, those patients enrolled before de-escalation were included in Cohort 1. and those enrolled after de-escalation were included in Cohort 2

In stratum 1A, the RP2D for InO was determined to be 1.8 mg/m^2 during Cycle 1. In Stratum 1B of the combination therapy, the RP2D for InO combined with the amended mod UKALL-R3 regimen (with reduced dexamethasone of 10 mg/m2/day) was declared at 1.8 mg/m^2 during Cycle 1.

Adverse events

A summary of all treatment-emergent Adverse events (TEAEs) is provided in Table 6.

A summary of TEAEs that were considered *related to treatment* is provided in Table 7.

In monotherapy, the most frequently reported TEAEs were pyrexia, vomiting, anaemia and decreased platelet count.

In combination therapy, the most frequently reported TEAEs were anaemia, decreased platelet count, increased ALT/AST and decreased WBC count.

Table 6. Summary of Treatment-Emergent Adverse Events (All Causalities) - Full analysis set

Number (%) of Participants	Stratum 1A n (%)	Phase 2 n (%)	Stratum 1B n (%)	Total n (%)
Participants evaluable for adverse events	25	28	30	83
Number of adverse events	348	240	363	951
Participants with adverse events	25 (100.0)	28 (100.0)	30 (100.0)	83 (100.0)
Participants with serious adverse events	16 (64.0)	17 (60.7)	18 (60.0)	51 (61.4)
Participants with Maximum Grade 3 or 4 adverse events	21 (84.0)	22 (78.6)	28 (93.3)	71 (85.5)
Participants with Maximum Grade 5 adverse events	3 (12.0)	4 (14.3)	1 (3.3)	8 (9.6)
Participants permanent discontinuation from treatment	8 (32.0)	4 (14.3)	3 (10.0)	15 (18.1)
Participants leading to study drug interruption/reduction/delay	1 (4.0)	5 (17.9)	17 (56.7)	23 (27.7)

Participants are counted only once in each row.
Treatment-emergent adverse events (TEAE) were defined as any event increasing in severity from baseline or within 28 days of the last dose of study treatment.
a. Includes treatment-emergent adverse events leading to delay, reduction and adverse events leading to permanently discontinuation of study treatment.
MedDRA v25.1 coding dictionary applied.

*Table 7. Summary of Treatment-Emergent Adverse Events **(Treatment Related)** – Full analysis set*

Number (%) of Participants	Stratum 1A (N=25) n (%)	Phase 2 (N=28) n (%)	Stratum 1B (N=30) n (%)	Total (N=83) n (%)
Participants evaluable for adverse events	25	28	30	83
Number of adverse events	161	103	167	431
Participants with adverse events	21 (84.0)	25 (89.3)	28 (93.3)	74 (89.2)
Participants with serious adverse events	9 (36.0)	9 (32.1)	12 (40.0)	30 (36.1)
Participants with Maximum Grade 3 or 4 adverse events	21 (84.0)	21 (75.0)	25 (83.3)	67 (80.7)
Participants with Maximum Grade 5 adverse events	0	0	0	0
Participants permanent discontinuation from treatment	7 (28.0)	2 (7.1)	2 (6.7)	11 (13.3)
Participants leading to study drug interruption/reduction/delay	0	5 (17.9)	14 (46.7)	19 (22.9)

Participants are counted only once in each row.
Treatment-emergent adverse events (TEAE) were defined as any event increasing in severity from baseline or within 28 days of the last dose of study treatment.
a. Includes treatment-emergent adverse events leading to delay, reduction and adverse events leading to permanently discontinuation of study treatment.

Deaths

A summary of deaths during the study is provided in Table 8.

There were two deaths due to toxicity in Phase 2:

- one encephalopathy leading to cardiac arrest on Study Day 78, considered not related to InO but attributed to cumulative neuro-toxicity (pre-study prolonged intrathecal chemotherapy)
- one bilateral pneumonitis on Study Day 120, 70 days post-transplant, considered at least possible related to InO as the event started after follow-up ALL treatment.

Table 8. Summary of Deaths (Full Analysis Set)

	Stratum 1A			Phase 2
	1.4 mg/m² (N=12)	1.8 mg/m² (N=13)	Total (N=25)	1.8 mg/m² (N=28)
Deaths	11 (91.7)	7 (53.8)	18 (72.0)	17 (60.7)
Cause of Death				
Disease Progression	7 (58.3)	5 (38.5)	12 (48.0)	8 (28.6)
Toxicity	0	0	0	2 (7.1)
Other	4 (33.3)	2 (15.4)	6 (24.0)	7 (25.0)
Induction Death	0	0	0	0
Deaths Within 10 weeks After Last Dose of Study Treatment	4 (33.3)	2 (15.4)	6 (24.0)	7 (25.0)
Cause of Death				
Disease Progression	2 (16.7)	0	2 (8.0)	2 (7.1)
Toxicity	0	0	0	1 (3.6)
Other	2 (16.7)	2 (15.4)	4 (16.0)	4 (14.3)

	Stratum 1B					
	0.8 mg/m² + mR3 (N=6)	1.1 mg/m² + amended mR3 (N=4)	1.1 mg/m² + mR3 (N=6)	1.4 mg/m² + amended mR3 (N=3)	1.8 mg/m² + amended mR3 (N=11)	Total (N=30)
Deaths	4 (66.7)	3 (75.0)	2 (33.3)	0	3 (27.3)	12 (40.0)
Cause of Death						
Disease Progression	3 (50.0)	2 (50.0)	1 (16.7)	0	2 (18.2)	8 (26.7)
Toxicity	0	0	0	0	0	0
Other	1 (16.7)	1 (25.0)	1 (16.7)	0	1 (9.1)	4 (13.3)
Induction Death	0	0	0	0	0	0
Deaths Within 10 weeks After Last Dose of Study Treatment	1 (16.7)	0	2 (33.3)	0	1 (9.1)	4 (13.3)
Cause of Death						
Disease Progression	1 (16.7)	0	1 (16.7)	0	1 (9.1)	3 (10.0)
Toxicity	0	0	0	0	0	0
Other	0	0	1 (16.7)	0	0	1 (3.3)

The denominator to calculate percentages is N, the number of participants in the Full Analysis Set within each cohort. Induction death is defined as any patient who died after receiving therapy on this protocol during the first cycle before a final bone-marrow evaluation for response was performed.

Treatment-emergent serious adverse events (TE-SAEs)

Stratum 1A

In Stratum 1A, 16 (64.0%) participants had TE-SAEs. Nine (36.0%) participants had treatment-related TE-SAEs.

The TE-SAE SOC with the highest proportion of participants was Infections and Infestations (n = 7 [28.0%]).

The most frequently reported TE-SAEs (by PT, ≥10%) were febrile neutropenia (n = 4 [16.0%]) and pyrexia (n = 3 [12.0%]).

Phase 2 cohort

In the Phase 2 Cohort, 17 (60.7%) participants had TESAEs. Nine (32.1%) participants had treatment-related TE-SAEs.

The TE-SAE SOCs with the highest proportion of participants were Blood and Lymphatic System Disorders (n = 5 [17.9%]) and Infections and Infestations (n = 4 [14.3%]).

The most frequently reported TE-SAEs (by PT, ≥10%) were veno-occlusive disease (VOD; n = 6 [21.4%]) and febrile neutropenia (n = 5 [17.9%]).

Stratum 1B:

In Stratum 1B, 18 (60.0%) participants had TESAEs. Twelve (40.0%) participants had treatment-related TE-SAEs.

The TE-SAE SOCs with the highest proportion of participants were Infections and Infestations (n = 7 [23.3%]) and Blood and Lymphatic System Disorders (n = 5 [16.7%])

The most frequently reported TE-SAEs (by PT, ≥10%) were febrile neutropenia, VOD (n = 5 [16.7%] each) and sepsis (n = 3 [10.0%]).

Immunogenicity

In InO single agent treated participants, 1 (2.0%) participant in Stratum 1A was positive for ADA at pre-dose. No participant had treatment-induced or treatment-boosted ADA.

Dose Modification and/or Discontinuations Due to Adverse Events

Stratum 1A

One (8.3%) participant in DL1 had InO interruption due to headache (not treatment-related). Eight (32.0%) participants permanently discontinued InO due to TEAEs, of which 7 (28.0%) participants permanently discontinued InO due to treatment-related TEAEs. The all-causality TEAEs associated with permanent discontinuation in ≥2 participants included increased ALT and decreased platelet count

Phase 2 Cohort

Five (17.9%) participants had study drug interruption/reduction/delay due to AEs of increased ALT (4), increased AST (2) and febrile neutropenia (1), all of which were considered by the investigator to be treatment-related.

Four (14.3%) participants permanently discontinued InO due to TEAEs of increased ALT/AST, VOD, disease progression and multiple organ dysfunction syndrome. The increased ALT/AST and VOD reported in 2 participants were treatment-related.

Stratum 1B

Seventeen (56.7%) participants had study drug interruption/reduction/delay due to AEs. The most frequent reasons for dose modifications were: increased ALT (n = 10 [33.3%]) and increased AST (n = 6 [20.0%]). A total of 14 (46.7%) participants had study drug interruption/reduction/delay due to treatment-related AEs. The most frequent reasons for dose modifications were: increased ALT (n = 9 [30.0%]) and increased AST (n = 5 [16.7%]).

Three (10.0%) participants permanently discontinued InO due to the following TEAEs: increased ALT/AST, VOD, and disease progression. The increased ALT/AST and VOD reported in 2 participants were treatment-related.

Adverse events of special interest – veno-occlusive disease (VOD)

All VOD events reported in Study ITCC-059 were considered probably/possibly related to InO or with multiple causalities.

Stratum 1A:

VOD was reported in 2 (8.0%) participants; neither participant reported an allo HSCT before or after InO.

- In DL1, 1 participant developed G3 VOD (59 days after the last dose of InO, which was ongoing at the time of death.
- In DL2, 1 participant developed G4 VOD 44 days after the last dose of InO, which was ongoing at the time of death.

Phase 2 Cohort:

VOD was reported in 6 (21.4%) participants, 5 of which occurred after follow-up allo HSCT. The post-HSCT VOD rate was 5/18 (27.8% [95% CI: 47.8176-100.0]).

- 2 participants reported G4 VOD:
    - Onset 17 days after HSCT; 1 ongoing at death;
    - Onset 4 days after HSCT; resolved.
- 3 participants reported G3 VOD:
    - Onset 3 days after HSCT; ongoing at death;
    - 1 event was not associated with HSCT; onset of VOD occurred 7 days after the 1st dose of InO; resolved;
    - 1 event started 17 days after HSCT; resolved.
- 1 participant had G2 VOD with onset 10 days after HSCT; resolved.

Stratum 1B:

VOD was reported in 5 (16.7%) participants, 4 of which occurred post-transplant. The post-HSCT VOD rate was 4/17 (23.5% [95% CI: 39.7635-100.0]).

- In 1.1 mg/m^2 + mR3, 2 participants reported G3 VOD:
    - First event: no history of HSCT; onset of VOD 7 days after the 2nd dose of InO; resolved;
    - Second event: onset 51 days after HSCT; ongoing at death.
- In 1.1 mg/m^2 + amended mR3, 1 participant reported G4 VOD with onset 18 days after HSCT; resolved.
- In 1.4 mg/m^2 + amended mR3, 1 participant had G3 VOD with onset 15 days after HSCT; resolved.
- In 1.8 mg/m^2 + amended mR3, 1 participant had G3 VOD with onset 10 days after HSCT; resolved.

2.3.3. Discussion on clinical aspects

In order to fulfil the requirement to report paediatric data within 6 months of primary completion date (PCD), the MAH has submitted a preliminary Clinical study report (CSR) for Study ITCC-059.

Study ITCC-059 is an ongoing Phase I/II study. It is the first of two clinical studies included in the paediatric investigation plan (PIP) for inotuzumab ozogamicin (InO). The primary evaluation of the study has been finalised and includes the following:

- The primary objective of the Phase I portion of the study was to determine the recommended Phase 2 dose (RP2D) for InO as monotherapy (Stratum 1A) or in combination with chemotherapy (modified UKALL-R3-based re-induction regimen; Stratum 1B) in paediatric patients with R/R CD22-positive ALL.
- The primary objective of the Phase 2 portion of the study was to determine efficacy (ORR) for InO monotherapy at the RP2D in paediatric patients with R/R CD22-positive ALL.

Secondary endpoints included safety evaluations. The MAH, however, informs that the safety evaluation has not yet been finalised and an updated CSR is expected later this year. Therefore, the MAH does not propose any updates of the paediatric safety information in the SmPC at present time but is planning to submit a type II variation when the updated CSR is available. The assessment of any paediatric safety claims from the MAH will therefore have to await the Type II variation submission.

Recommended Phase 2 dose

In the Phase I portion of the study, the RP2D of InO as monotherapy as well as in combination with chemotherapy in paediatric patients was 1.8 mg/m^2 during Cycle 1.

This is the same dose as recommended for adult patients, in the approved SmPC: "For the first cycle, the recommended total dose of BESPONSA for all patients is 1.8 mg/m^2 per cycle, given as 3 divided doses on Days 1 (0.8 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m2)."

InO exposure was similar between paediatric patients in stratum 1A and adult patients with R/R ALL.

Efficacy

In the Phase II portion of the study, the ORR after InO monotherapy was 78.6% (95% CI: 59.0-91.7). The MAH makes no efficacy claims based on the current submission, and efficacy claims are not expected with the submission of the final safety report, later this year.

Safety profile

The safety database consists of 25 (Phase I) + 28 (Phase II), i.e. 53 paediatric patients treated with InO monotherapy and 30 patients treated with InO in combination with chemotherapy.

The median number of cycles administered was two (2) for InO monotherapy and one (1) for InO + chemotherapy.

The MAH suggests that the safety profile for InO in paediatric patients was acceptable and generally manageable. In monotherapy, the most frequently reported TEAEs were pyrexia, vomiting, anaemia and decreased platelet count. In combination therapy, the most frequently reported TEAEs were anaemia, decreased platelet count, increased ALT/AST and decreased WBC count.

Thus, as previously reported in adults, TEAEs were most commonly reported within SOCs Blood and lymphatic disorders, Gastrointestinal disorders and hepatobiliary disorders. Haemorrhage, likely secondary to thrombocytopenia, and infections appeared to be less severe and slightly less commonly

reported in the paediatric patients compared with what was observed in the pivotal registration study in adults. However, as further described below, the safety data from the study are still preliminary.

Deaths

A total of 47 patients (56.6%) died during the study, the majority (n=28) due to disease progression. For 17 patients, the cause of death was described as Other, which included e.g. sepsis and transplant-related events. For the remaining 2 patients the cause of death was described as Toxicity, however, the MAH suggests the toxicity was not due to InO: One case of cardiac arrest was suggested due to cumulative neurotoxicity and one case of bilateral pneumonitis started after follow-up ALL therapy. The pattern of deaths in the study do not give raise to immediate concern. However, as mentioned above, the safety data from the study are still preliminary.

Veno-occlusive disease (VOD)

An increased risk for VOD/sinusoidal obstruction syndrome (SOS), above the risk of standard chemotherapy, has been observed in adult patients treated with InO. This risk is most marked in patients who undergoes subsequent HSCT, and in particular patients who receive a conditioning regimen containing two alkylating agents. The risk is also increased in patients ≥65 years of age and patients with a serum bilirubin ≥ ULN prior to HSCT. In the pivotal registration study in adults, VOD/SOS was reported in 14% of the patients. In 3% of the patients, the event was not associated with HSCT.

In study ITCC-059, VODs were reported in 8/53 patients (15.1%) in Stratum 1A, after InO monotherapy. Three of these events (5.7%) were not associated with HSCT. In stratum 1B, after InO + chemo, VOD was reported in 5/30 patients (16.7%). One of these (3.3%) was not associated with HSCT. All 13 cases of VOD were of severity Grade 3 or Grade 4, and all were SAEs.

Thus, the VOD rate in this study was in the same range as that reported in adults. However, in the registration study in adults, patients with considerably increased risk for VOD (up to 50%), such as conditioning regimens including one or two alkylating agents or high age, were included. Therefore, the rate of VOD in paediatric patients, without some of these risk factors, appears high. Again, however, it is noted that the safety data from the study are still preliminary.

With the submission of the final study results, the MAH should provide a thorough discussion of the observed VOD cases in this study, and whether data might indicate a higher rate of such events in paediatric patients, e.g. due to differences in the presence of risk factors in the adult and paediatric populations.

Dose-limiting toxicity, dose modifications and treatment discontinuations

Dose-limiting toxicity as evaluated in Cycle 1 of the dose-finding portions of the study included ALT increased, decreased platelet count, decreased neutrophil count, and veno-occlusive liver disease (VOD; the latter in combination with chemotherapy).

The most commonly reported treatment-related AEs leading to study drug interruption or dose reduction were increased ALT and increased AST. Other events included blood bilirubin increased, neutrophil count decreased, Escherichia infection, oropharyngeal pain, pain in extremity, urticaria and febrile neutropenia.

A total of 11 patients permanently discontinued treatment due to AEs that were considered treatment related. The AEs leading to permanent discontinuation in ≥2 patients were increased ALT (n=4), increased AST (n=2), platelet count decreased (n=2) and VOD (n=2).

The pattern of dose modifications and treatment discontinuations in the paediatric patients, thus, mirrors the known safety profile from adults.

3. Overall conclusion and recommendation

☒ **Fulfilled:**

No further action required, however further data are expected in the context of a variation prior to any conclusion on product information amendments. The MAH intends to submit a variation application by Q3 2023. In the variation application the following issue should be addressed:

1. The VOD rate in Study ITCC-059 was in the same range as that reported in adults. However, in the registration study in adults, patients with considerably increased risk for VOD (up to 50%), such as conditioning regimens including one or two alkylating agents or high age, were included. With the submission of the final study results, the MAH should provide a thorough discussion of the observed VOD cases in Study ITCC-059, and whether data might indicate a higher rate of such events in paediatric patients, e.g. due to differences in the presence of risk factors in the adult and paediatric populations.