14 December 2023
EMA/3833/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

BESPONSA

International non-proprietary name: Inotuzumab ozogamicin

Procedure No. EMEA/H/C/004119/II/0026

Note

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

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Steps taken for the assessment	
Description	**Date**
Start of procedure	17 Jul 2023
CHMP Rapporteur Assessment Report	14 Aug 2023
PRAC Rapporteur Assessment Report	16 Aug 2023
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC endorsed relevant sections of the assessment report	31 Aug 2023
CHMP members comments	04 Sep 2023
Updated CHMP Rapporteur Assessment Report	06 Sep 2023
Request for supplementary information (RSI)	14 Sep 2023
Submission of MAH responses	09 Oct 2023
Re-start of procedure	16 Oct 2023
CHMP Rapporteur Assessment Report	13 Nov 2023
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	06 Dec 2023
Opinion	14 Dec 2023

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 14 June 2023 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2, 4.6, 4.8, 5.1 and 5.2 of the SmPC in order to update paediatric information based on final results from studies ITCC-059 (WI203581) and INO-Ped-ALL-1 (WI235086). Study WI203581 is a Phase 1/2, multicenter, European, multi-cohort, open-label study in pediatric patients (≥1 and <18 years of age) with R/R CD22-positive Acute Lymphoblastic Leukemia (ALL); and study WI235086 is an open-label, multi-center Phase 1 study to assess safety and tolerability of InO in Japanese pediatric patients with R/R CD22-positive ALL. The Package Leaflet is updated accordingly. The RMP version 2.0 has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

With the current variation, the MAH proposes paediatric updates to the Besponsa SmPC, sections 4.2, 4.8, 5.1 and 5.2. These changes are supported by an updated discussion of the results of Study ITCC-059, which was previously submitted (March 17, 2023) and discussed within procedure EMEA/H/C/004119/P46/004. Further, the MAH presents data from Study INO-Ped-ALL-1, which is a Phase 1 study to assess safety and tolerability of InO in Japanese paediatric patients. Specifically, PK data from 6 paediatric patients included in study INO-Ped-ALL-1 is used to support SmPC updates on PK. An updated RMP has also been submitted.

The objectives of Study ITCC-059 were to identify the recommended dose of InO 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 (Phase 2), and to evaluate PK and PD in this patient population. As monotherapy data only are proposed for inclusion in the SmPC, only the monotherapy portions of the study are considered in this variation assessment report.

In the dose-finding portion of Study ITCC-059, the RP2D of InO as monotherapy in paediatric patients was 1.8 mg/m2 in Cycle 1. This is the same dose as recommended for adult patients in Cycle 1. The exposure in paediatric patients was slightly higher than in adults given the same dose, based on the population PK (popPK) analysis.

In the dose-finding portion of the study, including 20 evaluable subjects, the ORR after InO monotherapy (both dose levels combined) was 80% (95% CI: 59.0-91.7). In the Phase 2 portion of the study, including 28 subjects, the ORR after InO monotherapy (1.8 mg/m2 in the first cycle) was 78.6% (95% CI: 59.0-91.7).

DoR was 8.0 months (95% CI: 3.9-13.9) and 7.6 months (95% CI: 3.3-NE) in Phase 1 and Phase 2, respectively.

In 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. In the Phase 2 Cohort, 18 (64.3%) participants had post InO allogeneic HSCT transplants. Seventeen 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.

The MAH suggests describing the ORR and DoR results in section 5.1 of the SmPC, which is largely accepted. The efficacy information should include how many subjects had subsequent HSCT, as this is relevant for the data on duration of response.

The safety database from Study ITCC-059 consists of 25 (Phase I) + 28 (Phase II), i.e. 53 paediatric patients treated with InO monotherapy. The subjects were acceptably evenly distributed over the paediatric age range, with 12 subjects < 6 years, 20 subjects 6 to < 12 years and 21 subjects 12 to <18 years old.

The median number of cycles administered was two (2) for InO monotherapy.

The safety profile for InO in paediatric patients was generally manageable. In monotherapy, the most frequently reported TEAEs were pyrexia, vomiting, anaemia and decreased platelet count. Thus, as previously reported in adults, TEAEs were most commonly reported within SOCs Blood and lymphatic disorders, Gastrointestinal disorders and hepatobiliary disorders. Dose-limiting toxicity as evaluated in Cycle 1 of the dose-finding portion of the study included ALT increased, decreased platelet count, and decreased neutrophil count.

An increased risk for veno-occlusive disease (VOD), above the risk of standard chemotherapy, has been observed in adult patients treated with InO. This risk is most marked in patients who undergo subsequent HSCT, and in particular patients who receive a conditioning regimen containing two alkylating agents. In the pivotal registration study in adults, VOD was reported in 14% of the patients. In 3% of the patients, the event was not associated with HSCT. In the paediatric Study ITCC-059, VODs were reported in 8/53 patients (15.1%) after InO monotherapy. Thus, the VOD rate in this study was in the same range as that previously reported in adults. Five of the 8 VOD events occurred after HSCT. As in adults, VOD was more commonly reported in paediatric subjects with hepatic dysfunction (5 events) than in subjects with normal hepatic function (3 events). This was even more evident in patients undergoing subsequent HSCT (1 event in a subject with normal hepatic function and 4 events in subjects with hepatic impairment). Risk factors for VOD are well described in the SmPC. The MAH proposes to describe the paediatric VOD rate in the SmPC which is adequate.

As the paediatric indication investigated in Study ITCC-059 is the same as that approved in adults, the paediatric safety data is described in section 4.8 of the SmPC, in line with the Q&A document *Revision 1 - Frequently asked questions on SmPC paediatric information (europa.eu)*.

Given the limited paediatric efficacy and safety data available, the proposed standard text in section 4.2, i.e.: "Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made" is considered adequate.

The variation is recommended for approval.

The benefit/risk of InO in the approved indication remains unchanged.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2, 4.6, 4.8, 5.1 and 5.2 of the SmPC in order to update paediatric information based on final results from studies ITCC-059 (WI203581) and INO-Ped-ALL-1 (WI235086). Study WI203581 is a Phase 1/2, multicenter, European, multi-cohort, open-label study in pediatric patients (≥1 and <18 years of age) with R/R CD22-positive Acute Lymphoblastic Leukemia (ALL); and study WI235086 is an open-label, multi-center Phase 1 study to assess safety and tolerability of InO in Japanese pediatric patients with R/R CD22-positive ALL. The Package Leaflet is updated accordingly. The MAH took also the opportunity to update the ATC code in section 5.1 and to implement some editorial changes in the PI. The RMP version 2.2 has also been submitted.

is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion Besponsa- EMEA/H/C/004119/II/0026 and Besponsa-EMEA/H/C/004119/P46/004

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Inotuzumab ozogamicin (InO, 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)

On March 17th, the MAH submitted the Clinical Study Report (CSR) for study ITCC-059 for inotuzumab ozogamicin (InO), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, to fulfil the requirement to report paediatric data within 6 months of primary completion date (PCD). This CSR was discussed within procedure EMEA/H/C/004119/P46/004. No amendments to the SmPC or RMP were then proposed.

With the current variation application, the MAH submitted an updated discussion of the results of Study ITCC-059 to add additional safety information that were not available at the time of the previous Article 46 submission. Further, the MAH presents data from Study INO-Ped-ALL-1, which is a Phase 1 study to assess safety and tolerability of InO in Japanese paediatric patients. Specifically, PK data from 6 paediatric patients included in study INO-Ped-ALL-1 is used to support product information updates on PK.

With the current variation, the MAH proposes paediatric updates to the SmPC sections 4.2, 4.8, 5.1 and 5.2, supported by the safety, efficacy, and immunogenicity data from single agent cohorts and population PK results from Study ITCC-059 and Study INO-Ped-ALL-1.

A Clinical Overview and Clinical Summaries have been provided discussing the paediatric data supporting the proposed SmPC updates.

Further, the MAH submitted the final CSR for a non-interventional post-authorisation safety study (PASS) of InO to characterise complications post-hematopoietic stem cell transplantation (HSCT) following InO Treatment in adult and pediatric patients with B-cell precursor ALL. This was included in the EU RMP, under Part III. Pharmacovigilance Plan, Additional Pharmacovigilance Activities (EU Post Authorization Study (PAS) register number - EUPAS23056). This non-interventional study was designated as a post-authorization safety study (PASS) and was a commitment to post-marketing requirement (PMR 3259-1) by the FDA.

An updated RMP has also been submitted.

The proposed SmPC updates are outlined in Section 10 below and in the appended, annotated Product information.

6. Clinical Pharmacology aspects

The design and PK data from Study ITCC-059 (WI203581) which was a Phase 1/2, multicenter, European, multi-cohort, open-label study in paediatric patients (≥1 and <18 years of age) with R/R CD22-positive ALL have been previously described in EMEA/H/C/004119/P46/004 and have been included in the popPK analysis, see below. The data is also summarised in Table 2 for the 1.8 mg/m2 dose.

Study INO-Ped-ALL-1 (WI235086): A Phase I Study of Inotuzumab Ozogamicin as a Single Agent for Paediatric Patients in Japan with Relapsed/Refractory CD22-Positive Acute Lymphoblastic Leukemia

This was a Phase 1, non-randomized, open-label, multi-center study to with a primary objective of evaluating the safety and tolerability of InO in Japanese patients aged 1-17 with R/R CD22-positive ALL. Evaluation of PK and preliminary efficacy were secondary objectives.

A total of seven patients were enrolled (thereof one screen failure). Data is available for 6 patients. The six included patients were aged 2-17 years, weighed 9.3 to 53 kg, had a BSA of 0.47 to 1.53 m^2, and 50% of patients were female.

Three dose levels were defined in the protocol; however, all patients were given the same dosing regimen, which is also identical with the adult regimen. At cycle 1, the InO dose was 1.8 mg/m2 and was fractionated D1, 8 and 15: 0.8, 0.5 and 0.5 mg/m2. For the second cycle, the dose was 1 mg/m2 fractionated in 3x 0.5 mg/m2, unless patients did not achieve CR/CRi, in which case the same dose regimen as the first cycle was given. Of 6 subjects in the per protocol set, 5 subjects achieved CR or Cri and were dosed accordingly.

Blood samples for PK and ADA were to be collected from all participants for analysis according to the protocol specified schedules. Bioanalysis of InO (substance code PF-05208773) and the cytotoxic moiety N-acetyl-gamma calicheamicin dimethylhydrazide using LC/MS-MS was conducted at PPD using previously validated methods (B1939001 and A9016002, respectively). For InO, it is an indirect analytical method using N-acetyl-epsilon-calicheamicin after several sample workup steps as a surrogate for inotuzumab ozogamicin.

The within study validations showed performance within pre-set criteria, samples were measured within established long-term stability and ISR was performed for InO, where 20/21 samples were within 30%.

For antidrug antibodies (ADA), the previously validated and assessed method B1937005 was used, including a population specific cutpoint for ALL.

Assessor's comment:

The validations of both methods were found acceptable at the time of the initial MAA. Within study validation showed adequate performance of the methods.

According to the ICH M10 bioanalysis guideline, 20% and not 30% is to be applied for ISR for LC-MS/MS based methods. Two additional samples did not fall within 20%, however it is still more than 2/3 of samples that passed ISR. As this study does not formally require an ISR, the issue is not pursued.

A summary of InO serum concentrations by visit and time for the PK analysis set (n=6) is provided in Table 12. The data has also been included in the popPK analysis. Mean peak serum InO concentrations were observed at the end of infusion (1-hour post-dose) with a peak mean concentration of 330 ng/mL

by Cycle 1 Day 1. There was no clear trend for trough serum InO concentrations increasing after cycle 1. Overall, the InO serum exposures in paediatric patients with ALL were similar to those previously reported in adult patients with ALL (Table 23).

Serum concentrations for N-acetyl-gamma calicheamicin DMH were < LLOQ for all tested samples.

Table 1. Summary of InO Serum Concentrations (ng/mL) in PK Analysis Set: Study WI235086

Visit	Dose on Day 1 (mg/m^2)	Nominal Time Post-dose	n	Mean (%CV)
Cycle 1 Day 1	0.8	0H	5	- (-)
		1H	5	330 (24)
		6H	5	106 (32)
Cycle 1 Day 4	0.8	72H	5	8.53 (44)
Cycle 1 Day 8	0.8	0H	6	3.87 (70)
		1H	6	219 (36)
Cycle 1 Day 15	0.8	0H	6	20.6 (88)
		1H	6	183 (36)
Cycle 2 Day 1	0.5	0H	4	29.8 (80)
		1H	3	201 (36)
	0.8	0H	1	- (-)
		1H	1	- (-)
Cycle 3 Day 1	0.5	0H	2	- (-)
	0.8	0H	1	- (-)
Cycle 4 Day 1	0.5	0H	1	- (-)

Summary statistics have been calculated by setting concentration values below the LLOQ to zero.
The LLOQ was 1.00 ng/mL.

Amongst InO single agent treated participants, none had ADA positive results.

A summary of InO serum concentrations by visit and time following 1.8 mg/m^2/cycle in adult and paediatric patients with B-cell ALL is provided in Table 23. InO serum concentrations in paediatric patients with ALL administered as 1.8 mg/m^2/cycle dosing regimen were generally comparable to those in adult patients with ALL administered as the same dosing regimen.

Table 2. Comparison of Serum Concentrations (ng/mL) of InO Following the 1.8 mg/m^2/Cycle: Studies B1931022, WI235086 and WI203581

Visit	Nominal Time Post-dose	B1931022 in Adults Overall (N = 162)		WI235086 in Paediatrics Japan (N= 6)		WI203581 Phase 2 in Paediatrics Europe (N = 28)	
		n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
Cycle 1 Day 1	0H	160	2.22 (754)	5	- (-)	25	1.9 (500)
	1H	128	211 (110)	5	330 (24)	-	- (-)
	2H	145	160 (52)	-	- (-)	24	173 (61)
	4H	145	104 (57)	-	- (-)	26	124 (62)
Cycle 1 Day 4	72H	84	10.6 (124)	5	8.53 (44)	-	- (-)
Cycle 1 Day 8	0H	151	6.84 (276)	6	3.87 (70)	25	11.0 (197)
	1H	126	194 (117)	6	219 (36)	-	- (-)
Cycle 1 Day 15	0H	147	21.3 (168)	6	20.6 (88)	25	28.7 (92)
	1H	117	170 (46)	6	183 (36)	-	- (-)
Cycle 2 Day 1	0H	122	32.0 (147)	4	29.8 (80)	-	- (-)
	1H	107	224 (53)	3	201 (36)	-	- (-)
	2H	113	250 (41)	-	- (-)	14	301 (33)
Cycle 2 Day 8	0H	115	61.9 (77)	-	- (-)	14	77.5 (47)

Table 2. Comparison of Serum Concentrations (ng/mL) of InO Following the 1.8 mg/m²/Cycle: Studies B1931022, WI235086 and WI203581

Visit	Nominal Time Post-dose	B1931022 in Adults Overall (N = 162)		WI235086 in Paediatrics Japan (N= 6)		WI203581 Phase 2 in Paediatrics Europe (N = 28)	
		n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)

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Only concentration data collected at the same time points in at least 2 studies are shown.
Summary statistics have been calculated by setting concentration values below the LLOQ to zero.
The LLOQ was 1.00 ng/mL.

Pop PK analysis

A pop PK analysis (PMAR-EQDD-B193e-DP4-1490) was conducted using NONMEM to characterize the PK of InO in paediatric patients with R/R ALL and to compare InO PK between adult and paediatric patients with R/R ALL.

The current popPK analysis was conducted based on pooled data (N = 824, previously n = 765 adults) adding 2 studies in paediatric patients with relapsed or refractory ALL (n = 59) from Japan (n = 6) and global (n = 53) to characterize the pharmacokinetics (PK) of inotuzumab ozogamicin in paediatric patients with relapsed or refractory ALL. Of the 8978 observations, 3397 (37.8%) observations were < LLOQ, with the majority of the data < LLOQ originating from the NHL studies, and the M3 method was used. In paediatric patients, 0.8% were < LLOQ. The model developed previously for adults with NHL or ALL re-estimated on the updated dataset (including paediatric data) was used as base model and was found of adequate structure (2-compartment popPK model with both linear and time-dependent clearance) to characterize InO PK in paediatric patients.

In the previous analysis in adults, significant covariates included baseline body surface area (BBSA) on linear clearance (CL1), clearance associated with time-dependent clearance (CL2), and volume of distribution in central compartment (V1); disease and/or bioanalytical assay method (PTST) on CL1 and decay coefficient associated with time-dependent clearance (kdes); inotuzumab ozogamicin administered with rituximab (RITX) on CL1; and baseline percent of blasts in peripheral blood (BLSTPB) on kdes. No other significant covariates were identified.

Table 3: Base model parameters

Parameter	Value	RSE(%)	Shrinkage(%)[a]	95% CI[b]
CL_1 (θ_1) [L/hr]	0.113	4.18	-	(0.104- 0.123)
V_1 (θ_2) [L]	6.55	1.98	-	(6.29- 6.80)
CL_2 (θ_3) [L/hr]	0.386	6.00	-	(0.341- 0.432)
k_{des} (θ_4) [/hr]	0.0384	14.0	-	(0.0279- 0.0490)
Q (θ_5) [L/hr]	0.0447	9.46	-	(0.0364- 0.0530)
V_2 (θ_6) [L]	4.50	23.0	-	(2.47- 6.52)
Proportional error for NHL (θ_7)	0.449	5.64	18.1	(0.399- 0.499)
Proportional error for ALL (θ_8)	0.587	5.03	-	(0.529- 0.645)
ALL effect on CL_1 (θ_9)	-0.755	-1.81	-	(-0.781- -0.728)
ALL effect on k_{des} (θ_{10})	-0.866	-2.12	-	(-0.902- -0.830)
BBSA effect on CL_1 (θ_{11})	1.44	8.21	-	(1.21- 1.67)

Parameter	Value	RSE(%)	Shrinkage(%)[a]	95% CI[b]
RITX effect on CL_1 (θ_{12})	0.147	34.7	-	(0.0470- 0.248)
BBSA effect on CL_2 (θ_{13})	1.10	15.0	-	(0.775- 1.42)
BBSA effect on V_1 (θ_{14})	0.649	2.84	-	(0.613- 0.685)
BLSTPB effect on k_{des} (θ_{15})	-0.0430	-21.5	-	(-0.0611- -0.0248)
	Value	**CV(%)**		**95% CI**
$\omega^2_{CL_1}$	0.161	40.1	19.6	(0.0952- 0.226)
$\omega_{CL_1}\omega_{V_1}$	0.142	-	-	(0.0960- 0.189)
$\omega^2_{V_1}$	0.169	41.1	16.1	(0.128- 0.209)
$\omega_{CL_1}\omega_{CL_2}$	0.198	-	-	(0.125- 0.270)
$\omega_{V_1}\omega_{CL_2}$	0.203	-	-	(0.149- 0.257)
$\omega^2_{CL_2}$	0.456	67.6	23.3	(0.202- 0.711)
$\omega^2_{k_{des}}$	0.310	55.7	51.8	(0.145- 0.476)
OFV_{IMP}	1452.772	-	-	-

Item 15, repository artifact ID FI-39712772.
Abbreviations: ALL=acute lymphoblastic leukemia; BBSA=baseline body surface area; CI=confidence interval; BLSTPB=baseline percent of blasts in the peripheral blood; CL_1=linear clearance; CL_2=clearance associated with time-dependent clearance; CV=coefficient of variation; hr=hours; k_{des}=decay coefficient associated with time-dependent clearance; NHL=non-Hodgkin's lymphoma; OFV_{IMP}=objective function value by Monte Carlo importance sampling estimation method; PK=pharmacokinetics; Q=intercompartment clearance; RITX=inotuzumab ozogamicin administered with rituximab; RSE=relative standard error; V_1=volume of distribution in central compartment; V_2=volume of distribution in peripehral compartment.
a. ε-shrinkage: combined ε-shrinkage of NHL and ALL
b. Calculated as the final estimate $\pm$ 1.96 $\times$ standard error of the estimate.

In this analysis, covariates were added to the base model (Table 3) sequentially in a stepwise addition manner. The model resulting from the forward selection algorithm was subjected to a backward elimination algorithm using likelihood ratio tests (based on ΔOFV) to assess the significance of the covariate parameters in the model when excluded one at a time.

There were no strong correlations identified based on the visual inspection of the base model ETAs versus covariate plots, except for one identified trend which kdes tended to be higher in paediatric patients with ALL compared to adult patients with NHL or ALL. As a result, Patient Type (1=NHL adults, 2=ALL adults, 3=ALL paediatrics) was identified as a potential covariate for further investigation by the forward and backward selection algorithm and was included in the final model (Table 4).

Table 4: Parameter estimates for the final population PK model

Parameter	Final Run (OFV_{IMP}:1436.591) Estimate	%RSE	Shrinkage (%)[a]	SIR Run Statistics Mean	%RSE	Median	Lower 2.5%	Upper 97.5%
CL_1 (θ_1) [L/hr]	0.114	4.25	-	0.114	2.77	0.114	0.108	0.120
V_1 (θ_2) [L]	6.54	1.95	-	6.54	1.66	6.53	6.32	6.76
CL_2 (θ_3) [L/hr]	0.384	5.68	-	0.386	3.90	0.386	0.356	0.415
k_{des} (θ_4) [/hr]	0.0382	13.7	-	0.0386	10.5	0.0386	0.0309	0.0469
Q (θ_5) [L/hr]	0.0454	9.30	-	0.0457	6.15	0.0457	0.0404	0.0513
V_2 (θ_6) [L]	4.51	22.5	-	4.57	9.43	4.56	3.86	5.44
ALL effect on CL_1 (θ_9)	-0.759	1.77	-	-0.758	1.76	-0.758	-0.784	-0.731
ALL adults effect on k_{des} (θ_{10})	-0.877	1.91	-	-0.877	1.48	-0.878	-0.902	-0.847
BBSA effect on CL_1 (θ_{11})	1.40	8.66	-	1.40	6.59	1.39	1.22	1.58
RITX effect on CL_1 (θ_{12})	0.149	34.6	-	0.148	32.1	0.147	0.0634	0.250
BBSA effect on CL_2 (θ_{13})	0.920	19.2	-	0.933	16.0	0.936	0.648	1.22
BBSA effect on V_1 (θ_{14})	0.652	2.93	-	0.655	2.58	0.655	0.620	0.684
BLSTPB effect on k_{des} (θ_{15})	-0.0449	20.7	-	-0.0442	15.7	-0.0446	-0.0577	-0.0314
ALL pediatrics effect on k_{des} (θ_{16})	-0.795	5.00	-	-0.794	3.94	-0.796	-0.847	-0.729
Proportional error for NHL (θ_7)	0.450	5.62	18.2	0.450	1.81	0.450	0.436	0.466
Proportional error for ALL (θ_8)	0.587	5.07	-	0.587	1.54	0.587	0.570	0.604
$\omega^2_{CL_1}$ (%CV)	0.161 (40.1)	21.0	20.2	0.161	12.7	0.159	0.125	0.206
$\omega_{CL_1}\omega_{V_1}$	0.140	16.3	-	0.139	10.1	0.139	0.114	0.169
$\omega^2_{V_1}$ (%CV)	0.167 (40.9)	11.8	16.1	0.166	7.46	0.166	0.143	0.191
$\omega_{CL_1}\omega_{CL_2}$	0.197	19.8	-	0.195	11.7	0.194	0.150	0.245
$\omega_{V_1}\omega_{CL_2}$	0.206	13.8	-	0.206	8.98	0.206	0.172	0.246
$\omega^2_{CL_2}$ (%CV)	0.452 (67.2)	26.8	23.2	0.475	13.8	0.471	0.373	0.608

Parameter	Final Run (OFV_{IMP}:1436.591) Estimate	%RSE	Shrinkage (%)[a]	SIR Run Statistics Mean	%RSE	Median	Lower 2.5%	Upper 97.5%
$\omega^2_{k_{des}}$ (%CV)	0.308 (55.5)	27.2	52.0	0.310	15.9	0.311	0.222	0.415

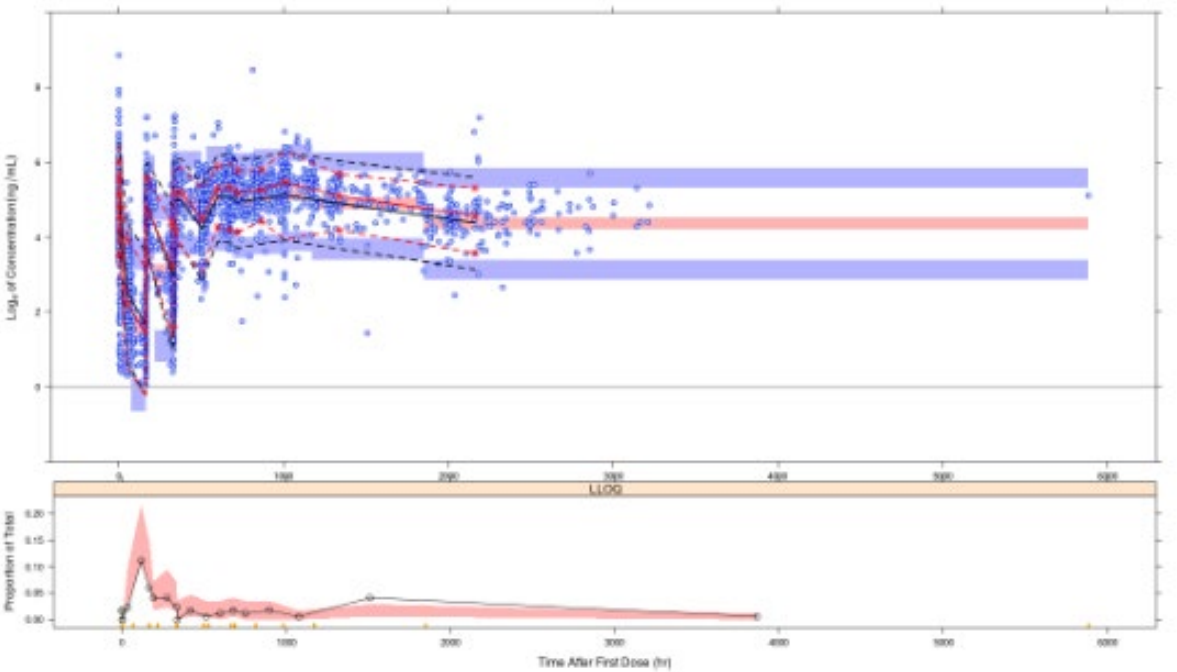
Item 24, repository artifact ID FI-38762788. Lines 1–2 substituted.
Abbreviations: ALL=acute lymphoblastic leukemia; BBSA=baseline body surface area; CI=confidence interval; BLSTPB=baseline percent of blasts in the peripheral blood; CL_1=linear clearance; CL_2=clearance associated with time-dependent clearance; CV=coefficient of variation; hr=hours; k_{des}=decay coefficient associated with time-dependent clearance; NHL=non-Hodgkin's lymphoma; OFV_{IMP}=objective function value by Monte Carlo importance sampling estimation method; PK=pharmacokinetics; Q=intercompartment clearance; RITX=inotuzumab ozogamicin administered with rituximab; RSE=relative standard error; V_1=volume of distribution in central compartment; V_2=volume of distribution in peripehral compartment.
a. ε-shrinkage: combined ε-shrinkage of NHL and ALL.

The model predicted the population and individual concentrations well and the majority of CWRES and IWRES were evenly distributed across the x-axis of both concentration and time, indicating no major deviation or trend over the entire concentrations and observation time in the population.

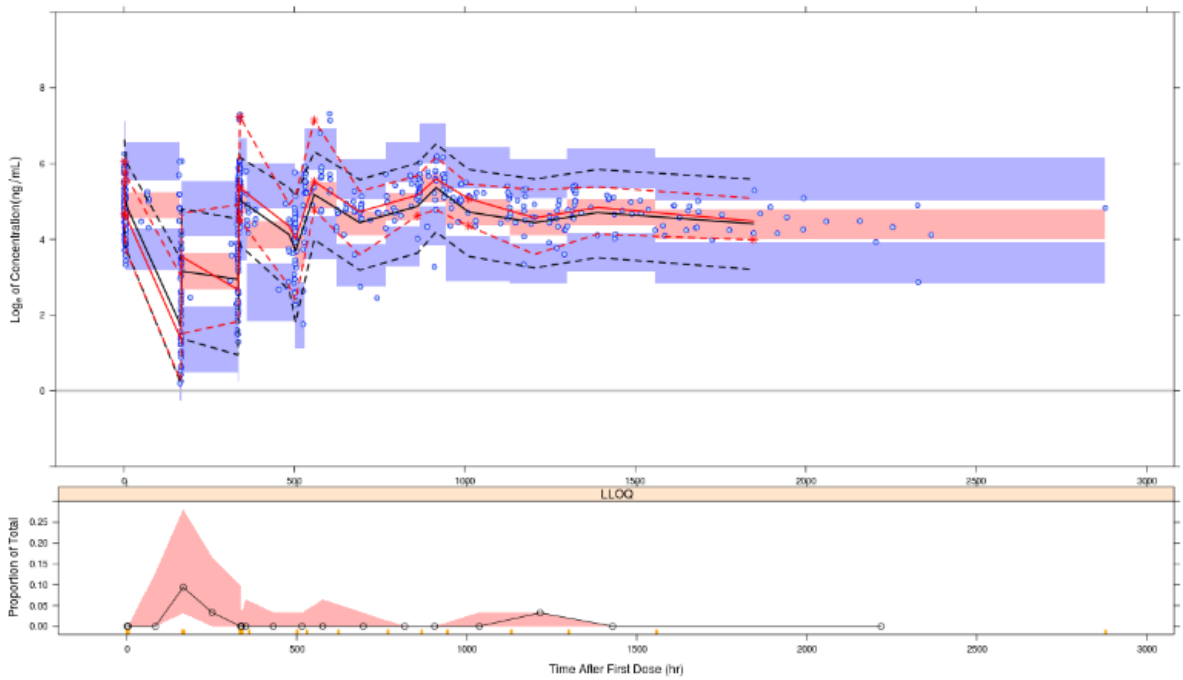
VPC plots based on the actual sampling time of observed data after first dose for all patients with ALL, and paediatric patients with ALL are shown in Figure 1 top and bottom, respectively.

There were no trends in ETA vs categorical or continuous covariates, as shown for age, bodyweight and baseline body surface area (Figure 2).

Adults and paediatric patients with ALL



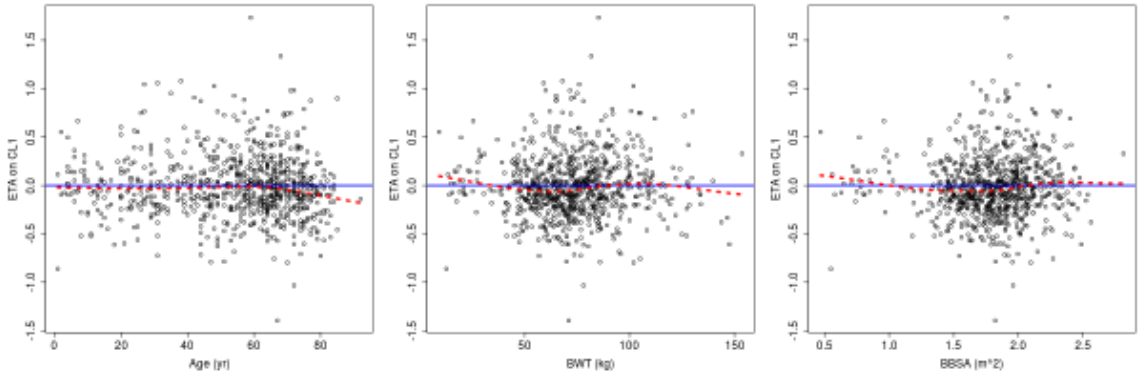
Paediatric patients with ALL



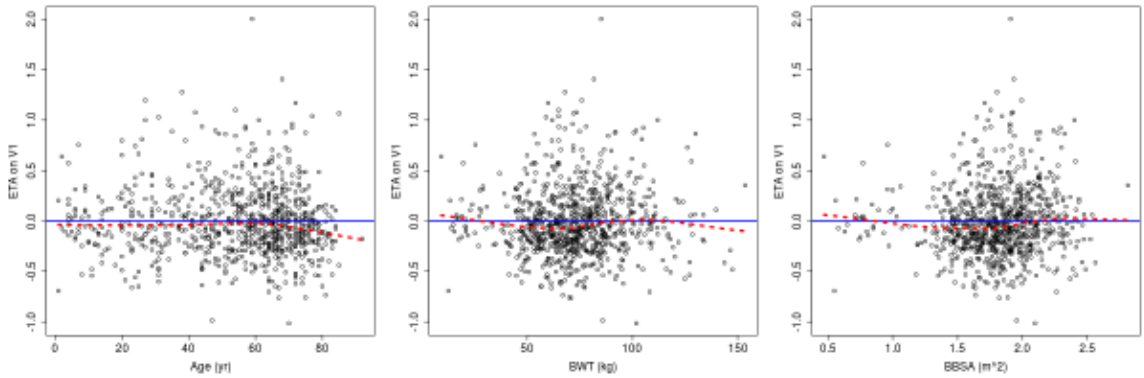
Item 34, repository artifact ID FI-38962889.
Abbreviations: LLOQ=lower limit of quantification; hr= hours.
Upper panel: Plots are based on the actual sampling time of observed data, and represent prediction- and variability-corrected simulations. Blue circles represent the observed data and the red lines represent the median (solid line), 5th percentile (dashed line), and 95th percentile (dashed line) of the observed data. Gray line represents the LLOQ value of 1.0 ng/mL. The 95% confidence intervals for simulated median and each percentile are shown by light pink and light blue shaded areas, respectively. Lower panel: Black circles and solid line represents the fraction of observed data < LLOQ and the light pink shaded areas represent the 95% confidence intervals for fraction of simulated data < LLOQ.

Figure 1: Visual predictive check for the final model in adult and paediatric patients with ALL(top: adult and paediatric; bottom: paediatric)

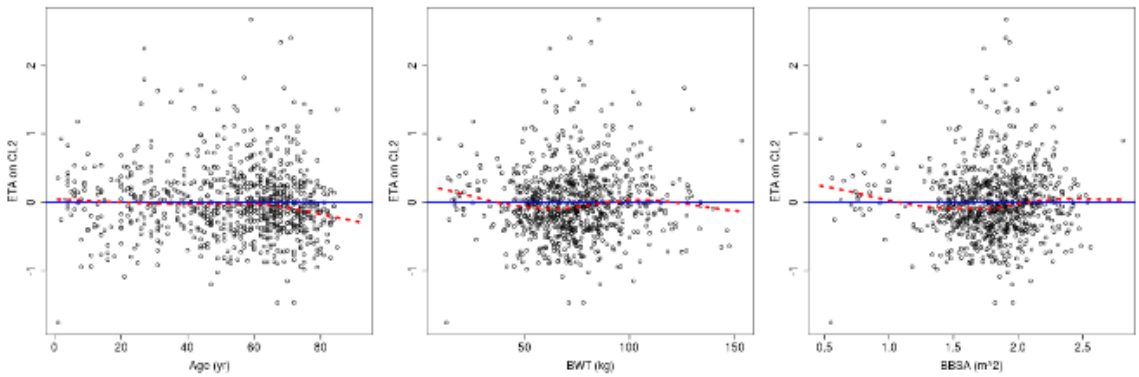
ETA on CL1



ETA on V1



ETA on CL2



ETA on kdes

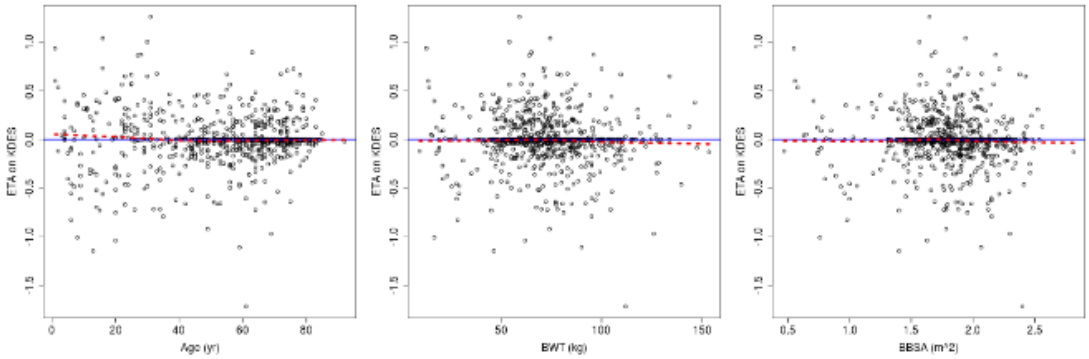


Figure 2: Final model ETA vs selected baseline continuous covariates

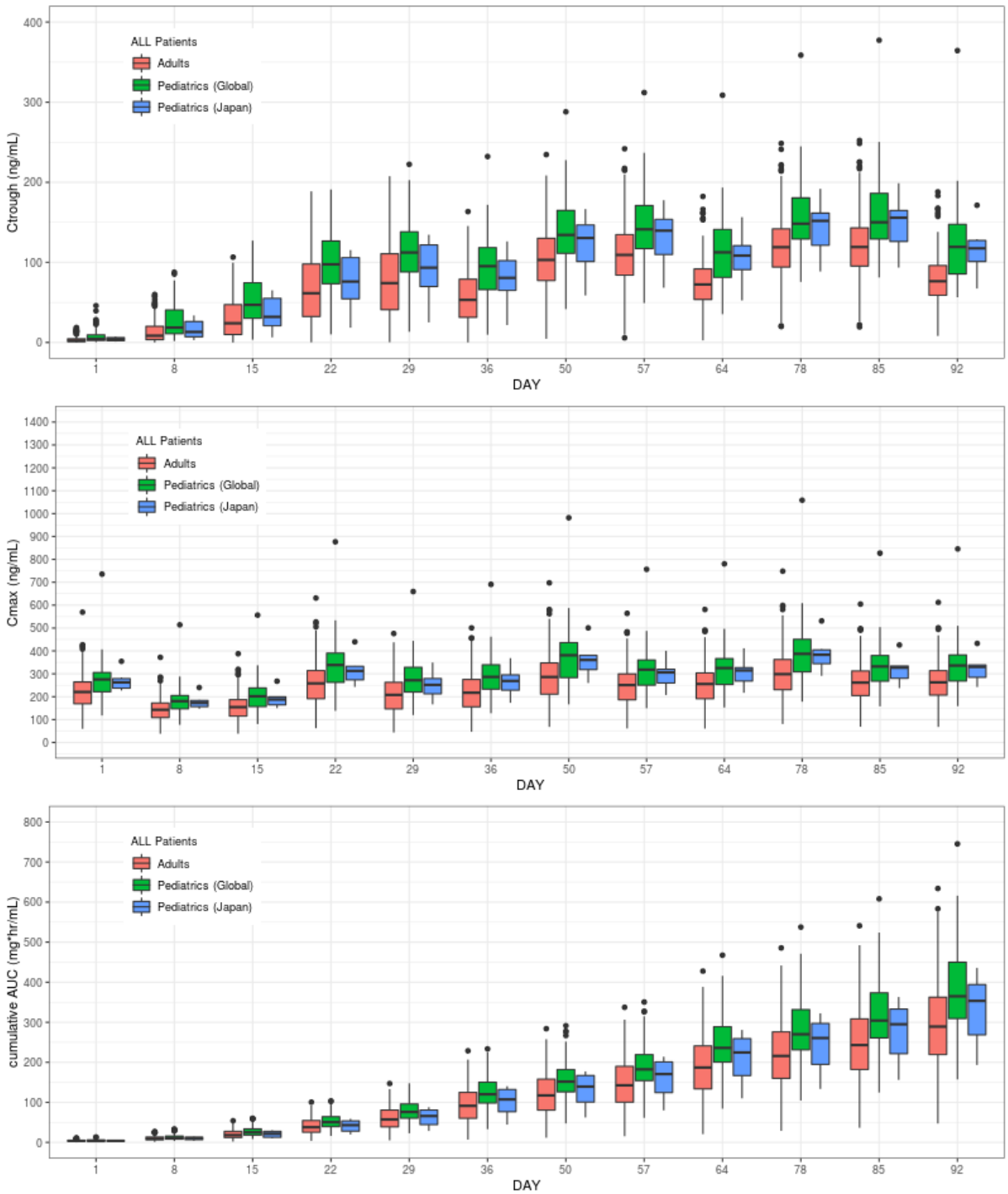
InO Cmax, Ctrough, cumulative AUC and β half-life were simulated for adult and paediatric patients with ALL using the post-hoc estimates (accounting for covariate effects) from the final model. Fixed dosing regimen of 1.8 mg/m2/cycle of inotuzumab ozogamicin, administered at fractionated doses of 0.8 mg/m2 on Day 1 and 0.5 mg/m2 on Days 8 and 15 for the first 21 days and then every 28 days were simulated for 4 continuous cycles. Table 5 shows the median (range) and mean (SD) of simulated inotuzumab ozogamicin exposures and β half-life for the patients with ALL included in the popPK analysis. Figure 3 shows boxplots of the simulated inotuzumab ozogamicin exposures for the patients with ALL included in the popPK analysis. The median exposures of inotuzumab ozogamicin in paediatric patients with ALL seemed to be slightly higher than those in adult patients with ALL. However, boxplots of the range of simulated inotuzumab ozogamicin exposures for the patients with ALL showed the simulated inotuzumab ozogamicin exposures including Ctrough between adult and paediatric patients with ALL generally overlapped (Figure 3).

Table 5: Simulated PK parameters in ALL patients

Parameter	Cycle	Day	Dose (kg/m^2)	ALL Pediatrics (Global)		ALL Pediatrics (Japan)		ALL Adult	
				Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)
C_{max} (ng/mL)	1	1	0.8	275.24 (117.99-735.61)	272.41 (89.65)	262.38 (227.03-354.57)	269.90 (46.87)	220.45 (59.44-569.27)	222.19 (76.77)
	1	8	0.5	180.56 (77.07-514.11)	183.25 (64.49)	172.66 (146.97-240.04)	178.47 (33.49)	142.81 (37.89-372.14)	144.90 (51.41)
	1	15	0.5	201.67 (80.55-556.35)	204.03 (74.92)	187.90 (149.78-267.69)	192.16 (42.05)	154.21 (38.41-387.60)	155.78 (58.19)
	2	22	0.8	338.36 (138.30-876.73)	335.19 (115.84)	312.38 (242.71-439.65)	317.88 (69.29)	258.13 (62.44-631.04)	258.87 (96.05)
	2	29	0.5	271.85 (119.61-659.41)	275.57 (93.00)	251.31 (166.65-349.23)	251.20 (63.94)	207.66 (43.61-475.84)	210.34 (83.44)
	2	36	0.5	286.43 (128.01-690.80)	289.77 (95.91)	268.80 (173.54-368.50)	266.37 (67.48)	217.21 (46.54-500.44)	220.19 (86.08)
	3	50	0.8	380.96 (166.36-981.77)	377.03 (127.93)	360.56 (259.83-500.67)	362.25 (81.72)	286.23 (67.76-697.47)	284.94 (105.26)
	3	57	0.5	318.02 (149.60-756.44)	316.53 (97.83)	305.79 (207.35-400.57)	298.04 (66.56)	250.80 (61.23-563.93)	247.02 (86.07)
	3	64	0.5	324.99 (153.02-780.43)	323.78 (99.98)	314.95 (217.11-411.51)	307.00 (66.87)	255.38 (60.58-581.01)	251.45 (86.84)
	4	78	0.8	387.32 (178.22-1058.25)	398.24 (133.99)	383.21 (290.73-530.86)	388.51 (81.70)	298.44 (80.55-748.40)	301.75 (106.60)
	4	85	0.5	332.02 (158.00-827.09)	333.66 (102.77)	327.07 (237.37-425.86)	319.80 (65.17)	261.34 (68.53-604.64)	260.69 (85.84)
	4	92	0.5	336.00 (158.92-845.69)	337.37 (105.01)	330.29 (242.25-432.70)	324.39 (65.78)	262.47 (67.99-612.05)	261.63 (86.48)
C_{trough} (ng/mL)	1	1	0.8	4.54 (0.44-45.92)	8.14 (9.97)	4.26 (1.12-7.35)	4.21 (2.57)	2.43 (0.04-18.71)	3.57 (3.71)
	1	8	0.5	18.58 (1.79-87.85)	27.96 (23.81)	13.16 (2.97-33.75)	16.44 (12.78)	8.46 (0.05-60.01)	13.60 (13.30)
	1	15	0.5	46.93 (3.54-127.11)	53.04 (32.75)	32.02 (6.47-65.15)	35.94 (23.55)	24.01 (0.09-106.51)	30.82 (24.42)
	2	22	0.8	97.55 (10.12-190.95)	99.27 (44.43)	76.02 (18.56-115.42)	74.89 (37.88)	61.56 (0.27-188.72)	67.82 (41.43)
	2	29	0.5	112.34 (13.37-222.35)	113.44 (45.88)	93.45 (25.15-134.52)	89.98 (41.42)	74.15 (0.39-207.62)	77.58 (43.25)
	2	36	0.5	95.34 (9.67-232.19)	94.65 (40.72)	80.72 (21.83-126.20)	79.78 (36.52)	53.14 (0.19-163.49)	56.41 (31.89)
	3	50	0.8	134.26 (41.71-288.02)	140.22 (44.26)	130.46 (58.68-166.63)	121.63 (39.93)	103.03 (4.61-234.57)	104.43 (40.30)
	3	57	0.5	141.24 (49.21-312.02)	147.46 (45.68)	139.62 (68.40-177.58)	130.58 (39.84)	109.32 (5.86-241.82)	108.83 (40.58)
	3	64	0.5	112.56 (35.36-308.71)	115.87 (44.55)	108.53 (52.55-156.43)	106.03 (35.04)	72.33 (2.64-182.35)	73.22 (30.87)
	4	78	0.8	148.28 (75.76-358.70)	157.37 (47.23)	151.89 (88.66-191.94)	143.40 (37.27)	118.93 (19.96-248.57)	118.11 (38.67)
	4	85	0.5	150.08 (81.16-377.31)	161.06 (49.31)	155.81 (93.53-198.79)	147.99 (37.56)	119.19 (19.38-252.21)	119.02 (39.24)
	4	92	0.5	119.31 (56.49-364.42)	124.32 (49.53)	117.62 (67.37-171.31)	116.71 (34.63)	76.53 (8.19-188.07)	78.24 (30.48)
cAUC (x10^3 ng.hr/mL)	1	1	0.8	3.64 (1.15-13.45)	4.73 (2.86)	3.84 (1.38-5.16)	3.63 (1.37)	3.90 (0.41-11.07)	4.20 (2.05)
	1	8	0.5	11.42 (3.43-33.34)	13.64 (7.90)	10.86 (4.10-14.40)	9.90 (4.18)	9.31 (1.31-27.21)	10.48 (5.56)
	1	15	0.5	25.19 (8.44-60.17)	27.82 (14.43)	21.49 (9.94-30.34)	20.44 (8.92)	18.20 (2.11-54.04)	20.74 (11.08)
	2	22	0.8	50.52 (16.31-103.59)	53.39 (23.33)	43.28 (19.59-58.94)	40.86 (16.47)	37.99 (3.80-100.45)	40.96 (20.31)
	2	29	0.5	75.96 (22.84-147.66)	79.37 (32.16)	65.84 (28.70-88.09)	61.97 (24.31)	57.26 (5.22-147.09)	60.93 (29.52)

Parameter	Cycle	Day	Dose (kg/m^2)	ALL Pediatrics (Global)		ALL Pediatrics (Japan)		ALL Adult	
				Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)
	2	36	0.5	120.09 (33.13-233.57)	126.11 (47.96)	107.35 (44.51-140.31)	101.06 (38.86)	91.39 (7.12-228.76)	94.77 (45.04)
	3	50	0.8	151.60 (47.33-291.30)	159.38 (56.62)	139.21 (62.36-177.26)	130.34 (46.57)	117.52 (11.69-284.03)	121.85 (54.21)
	3	57	0.5	182.46 (61.20-350.47)	191.84 (65.01)	170.54 (80.00-213.85)	159.16 (54.07)	142.64 (15.49-337.36)	147.99 (62.84)
	3	64	0.5	235.95 (84.29-467.48)	247.91 (80.55)	224.58 (110.06-280.89)	209.75 (67.55)	186.95 (20.80-427.69)	190.28 (77.27)
	4	78	0.8	270.01 (104.62-537.57)	284.43 (89.36)	260.58 (133.63-322.49)	243.18 (74.71)	215.71 (28.96-485.70)	220.06 (86.14)
	4	85	0.5	304.15 (124.54-608.15)	319.48 (98.04)	295.07 (156.13-362.98)	275.32 (81.70)	243.06 (36.37-541.07)	248.25 (94.47)
	4	92	0.5	364.88 (157.44-745.45)	379.21 (114.61)	353.25 (193.07-436.02)	330.60 (94.51)	289.10 (47.21-634.03)	293.08 (108.54)
Beta Half-life (hr)	1	1	0.8	123.40 (82.34-1103.75)	178.34 (151.20)	114.79 (89.60-231.64)	134.98 (52.54)	92.68 (70.61-205.07)	99.98 (24.15)
	1	8	0.5	222.08 (88.81-1448.73)	291.04 (210.79)	190.26 (102.87-529.04)	242.69 (155.66)	122.71 (71.27-350.77)	142.03 (56.13)
	1	15	0.5	305.66 (98.16-1467.22)	358.50 (210.93)	310.31 (122.76-640.04)	329.09 (180.09)	168.62 (72.18-398.80)	183.43 (71.03)
	2	22	0.8	365.89 (111.09-1467.97)	393.91 (201.06)	402.70 (149.70-655.63)	385.44 (174.00)	213.89 (73.48-407.06)	214.42 (70.85)
	2	29	0.5	385.25 (127.89-1468.00)	412.84 (193.28)	427.19 (181.88-657.40)	417.77 (166.16)	242.30 (75.32-408.29)	236.02 (65.46)
	2	36	0.5	402.75 (170.54-1468.00)	428.95 (185.37)	440.14 (246.05-657.62)	444.79 (147.38)	265.46 (81.68-411.68)	259.72 (54.92)
	3	50	0.8	403.90 (193.52-1468.00)	432.18 (183.58)	441.34 (270.94-657.62)	450.79 (140.24)	267.66 (86.89-411.99)	265.58 (51.43)
	3	57	0.5	404.13 (215.36-1468.00)	434.03 (182.46)	441.76 (289.35-657.63)	454.60 (135.28)	269.87 (93.83-412.08)	269.27 (48.89)
	3	64	0.5	404.18 (250.98-1468.00)	435.81 (181.24)	441.96 (310.40-657.63)	458.54 (130.03)	274.58 (112.56-412.11)	273.18 (45.54)
	4	78	0.8	404.18 (252.34-1468.00)	436.24 (180.92)	441.97 (315.73-657.63)	459.48 (128.78)	274.63 (122.87-412.11)	274.22 (44.39)
	4	85	0.5	404.19 (252.34-1468.00)	436.53 (180.70)	441.98 (319.05-657.63)	460.06 (128.02)	275.34 (128.46-412.11)	274.95 (43.47)
	4	92	0.5	404.19 (252.34-1468.00)	436.84 (180.45)	441.98 (322.35-657.63)	460.62 (127.29)	275.80 (139.87-412.11)	275.88 (42.16)

Item 35, repository artifact ID FI-38613162. Lines 1–2 substituted.
Abbreviations: ALL=acute lymphoblastic leukemia; cAUC=cumulative area under the concentration-time curve; C_{max}=maximum concentration; C_{trough}=trough concentration; hr=hours; SD=standard deviation.



Box plot provides median and 25%/75% quartiles with whiskers to the last point within 1.5 times the interquartile range. Black dots are individuals beyond the whiskers on the box plot.

Figure 3. Simulated PK Parameters in Patients with R/R ALL by Patient Type

Assessor's comment:

A pooled PopPK analysis was performed including both adult and paediatric PK data. Including adult data is considered reasonable given the limited paediatric PK data.

According to VPCs, the final model gave acceptable description of the observed data, despite a slight trend of underprediction of the median concentrations over time in paediatric patients. The ETA vs covariate plots indicates that there were no relevant trends seen for the most important covariates related to age and body size. Age was not tested as a continuous covariate but only grouping all paediatric patients in a patient type. This is not a generally preferred approach, however, considering that baseline BSA is a significant covariate, and the lack of trend in the ETA of the different parameters vs age and bodyweight, this is acceptable.

The MAH proposes to update SmPC section 5.2 with the following text based on the popPK modelling:

Based on population pharmacokinetic analysis in 824 patients, patient age group (paediatric [≥ 1 and < 18 years of age] vs adult) is not considered to have a significant effect on inotuzumab ozogamicin disposition over the treatment duration.

The MAH´s conclusion that the exposure is similar in adults is however not fully agreed, as the boxed plots show higher median exposure in all PK parameters for paediatric patients compared to adult ALL patients, indicating that the dose may be slightly too high in paediatric patients. The clinical relevance of this higher exposure is unknown. The relative difference in exposure between adults and children should be described in the SmPC instead of the currently proposed text. The SmPC text should be revised to provide information on the exposure (**SmPC comment**), for example:

At the adult recommended dose, the exposure in paediatric patients with ALL (aged ≥ 1 and < 18 years) was [xx%] higher than in adults. The clinical relevance of the increased exposure is unknown.

An exposure/response model has been provided but is not detailed here as no SmPC claims are based on it and no new indication is sought.

7. Clinical Efficacy aspects

7.1. Methods – analysis of data submitted

7.1.1. Study design Study ITCC-059

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 Study ITCC-059.

The objectives of the 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.

Table 6. Overall study design (Study ITCC-059)

Cohort	Treatment	Description
Stratum 1A	Single agent InO	Phase 1 dose-finding part aimed to determine the MTD or the RP2D of single agent InO using a Rolling-6 design
Phase 2	Single agent InO	To assess the preliminary activity, ORR of single agent InO using an exact single-stage design
Stratum 1B (and Stratum 1B-ASP)[a]	InO + UKALL-R3 (+/- PEG-ASP)	To determine the RP2D of InO in combination with a modified version of UKALL-R3 re-induction chemotherapy using a Rolling-6 design

a. No enrollment of Stratum 1B-ASP occurred; thus analysis is not included in this report.

The study protocol includes two other disease strata, ie, Stratum 2 for other CD22 positive B-cell malignancies and Stratum 3 for VHR first relapse CD22-positive BCP-ALL patients; no data are included in the Summary of Clinical efficacy submitted with the current variation, as these cohorts were not included in the PIP (the VHR cohort was added as an amendment and continues to enrol patients).

Assessor's comment:

As Besponsa is currently approved as monotherapy only in the EU, the MAH proposes to update the SmPC with data from Stratum 1A (Phase 1 and 2). Therefore, data from stratum 1B (combination therapy) will not be presented in this assessment report.

Efficacy data from both Stratum 1A and Stratum 1B have been previously presented in the assessment report for procedure EMEA/H/C/004119/P46/004.

7.1.2. 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.

7.1.3. Objective(s), outcomes and endpoints

The primary objective of the Phase 1 dose-escalation portion of the study was to identify a RP2D of InO administered IV either as monotherapy (Stratum 1A) or in combination with chemotherapy (Stratum 1B).

The Phase 2 portion of the study further evaluated the efficacy, safety and tolerability of the selected InO dose as single agent, and evaluated PK and PD in this patient population.

The primary endpoint in Phase 2 was overall response rate, ORR, defined as the percentage of patients with CR/CRi/CRp, measured as best response during InO treatment.

The efficacy objectives and outcomes are further described in Table 7 below.

Table 7. Study Efficacy Objectives and Endpoints

Objective	Endpoints	Presentation of Results
Primary		
Phase 2 Cohort		
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 this SCE
Secondary		
Stratum 1A and Phase 2 Cohort		
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 30 Sep 2022 (Stratum 1A) and 07 October 2022 (Phase 2 Cohort)
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.	

Objective	Endpoints	Presentation of Results
To assess for the persistence of B-Cell aplasia and hypogammaglobulinemia in responding patients following treatment with InO	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	These endpoints are not required per PIP, thus the results are not included in this SCE.

7.1.4. Statistical Methods

Primary Estimand in Stratum 1A: The safety of single agent InO MTD or RP2D measured by DLT rate estimated based on data from DLT-evaluable participants during the first course of therapy in Stratum 1A. The estimand has the following attributes:

- Population: CD22+R/R BCP-ALL pediatric participants, as defined by the inclusion and exclusion criteria to reflect the targeted population of the treatment, who received at least one dose of InO and either experience DLT(s) during the first course of therapy or did not experience DLT during the first course of therapy and received at least 2 out of 3 doses of the prescribed dose (67%) of the InO during that course.
- Variable: Occurrence of DLTs. DLTs are defined in Appendix 1.
- Population-level summary measure: DLT rate defined as the number of DLT- evaluable paticipants with DLTs during first course of therapy divided by the number of DLT-evaluable participants.

Primary Estimand in Phase 2: The treatment effect of single agent InO on ORR as assessed by investigator. The estimand has the following attributes:

- Population: CD22+R/R BCP-ALL pediatric participants, as defined by the inclusion and exclusion criteria to reflect the targeted population of the treatment, who received at least 1 dose of study intervention and have completed a baseline disease assessment and at least one post-baseline disease assessment.
- Variable: Objective response defined as CR, CRi and CRp based on investigator's assessment during InO treatment.
- Intercurrent event(s): The intercurrent event is start of subsequent anti-cancer therapy and discontinuation from InO treatment. While on treatment strategy will be applied and data collected after the start of the intercurrent event will be excluded.
- Population-level summary measure: ORR defined as the proportion of participants in the analysis population with an objective response and 2-sided 90% and 95% CI for ORR.

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 (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.

7.2. Results

7.2.1. Study subjects

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).

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).

Demographic and baseline characteristics

Demographic characteristics are shown in Table 8.

Table 8. Demographic Characteristics - Full Analysis Set

	Stratum 1A (N=25) n (%)	**Phase 2 (N=28) n (%)**
Age (Years)		
1 to <2	1 (4.0)	1 (3.6)
2 to <6	1 (4.0)	9 (32.1)
6 to <12	12 (48.0)	8 (28.6)
12 to <18	11 (44.0)	10 (35.7)
Median (min, max)	11.00 (1, 16)	7.50 (1, 17)
Mean (SD)	10.48 (3.98)	8.50 (4.67)
Gender, n (%)		

	Stratum 1A (N=25) n (%)	Phase 2 (N=28) n (%)
Male	17 (68.0)	19 (67.9)
Female	8 (32.0)	9 (32.1)
BSA (m^2)		
n	25	28
Median (min, max)	1.22 (1, 2)	0.99 (1, 2)
Mean (SD)	1.25 (0.42)	1.11 (0.42)

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).

In Stratum 1A, 12 (48%) participants had received at least 1 prior allogeneic HSCT; 2 (8.0%) participants had received prior CAR T-cell therapy.

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). See Table 8.

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).

In the Phase 2 Cohort, 14 (50.0%) participants had received at least 1 prior allogeneic HSCT; 3 (10.7%) participants had received prior CAR T-cell therapy.

7.2.2. Participant flow

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

Stratum 1A (Phase 1 dose-finding part of the monotherapy):

- In Stratum 1A, a total of 25 participants were treated: 12 received InO 1.4 mg/m^2/cycle (DL1) and 13 received InO 1.8 mg/m^2/cycle (DL2).
- As of the data cut-off date, 6 (24.0%) participants completed the treatment phase and the required follow-up (FU). Eighteen (72.0%) participants discontinued due to death. One (4.0%) participant was lost to FU.

Phase 2 Cohort (monotherapy):

- In Phase 2 Cohort, 28 participants were to receive InO 1.8 mg/m^2/cycle (1 participant with unintended lower dose level at 1.4 mg/m^2/cycle).
- As of the data cut-off date, one (3.6%) participant completed the 3-year FU. Eight (28.6%) participants remained ongoing in the long-term FU phase of the study. Seventeen (60.7%) participants discontinued due to death. Two (7.1%) participants were lost to FU.

7.2.3. Efficacy results

In the Phase 2 Cohort, the primary objective was met demonstrating CR/CRi/CRp rate significantly greater than the 30% null hypothesis rate (30% was chosen based on clinical expert opinion and recent studies in similar populations) with 1-sided p-value <0.0001. 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). See Table 9.

Since the Full Analysis Set is equal to the Response Evaluable Analysis Set, the same results were obtained in both sets.

Table 9. Best Overall Response, and Response at the end of Cycle 1

	Stratum 1A – Phase 1			Stratum 1A - Phase 2
	1.4 mg/m² (N=12) n (%)	**1.8 mg/m² (N=13) n (%)**	**Total (N=25) n (%)**	**1.8 mg/m² (N=28) n (%)**
BEST RESPONSE				
Complete remission (CR)	9 (75.0)	11 (84.6)	20 (80.0)	18 (64.3)
Complete Response withInsufficientPlatelet recovery (CRp)	0	0	0	1 (3.6)
Complete Response without recoveryOfCounts (CRi)	0	0	0	3 (10.7)
Partial Response (PR)	1 (8.3)	0	1 (4.0)	3 (10.7)
Non-responseOr Stable Disease (SD)	1 (8.3)	1 (7.7)	2 (8.0)	1 (3.6)
Progressive disease (PD)	1 (8.3)	0	1 (4.0)	2 (7.1)
Induction Death (ID)	0	0	0	0
Missing	0	1 (7.7)	1 (4.0)	0
Objective Response (CR+CRp+CRi)	9 (75.0)	11 (84.6)	20 (80.0)	22 (78.6)
95% ExactCI [1]	(42.8, 94.5)	(54.6, 98.1)	(59.3, 93.2)	(59.0, 91.7)
90% ExactCI [1]	(47.3, 92.8)	(59.0, 97.2)	(62.5, 91.8)	(62.0, 90.2)
CYCLE 1				
Complete remission (CR)	6 (50.0)	7 (53.8)	13 (52.0)	12 (42.9)
Complete Response withInsufficientPlatelet recovery (CRp)	2 (16.7)	0	2 (8.0)	1 (3.6)
Complete Response without recoveryOfCounts (CRi)	1 (8.3)	4 (30.8)	5 (20.0)	9 (32.1)
Partial Response (PR)	1 (8.3)	0	1 (4.0)	3 (10.7)
Non-responseOr Stable Disease (SD)	1 (8.3)	1 (7.7)	2 (8.0)	1 (3.6)
Progressive disease (PD)	1 (8.3)	0	1 (4.0)	2 (7.1)
Induction Death (ID)	0	0	0	0
Missing	0	1 (7.7)	1 (4.0)	0
Objective Response (CR+CRp+CRi)	9 (75.0)	11 (84.6)	20 (80.0)	22 (78.6)
95% ExactCI [1]	(42.8, 94.5)	(54.6, 98.1)	(59.3, 93.2)	(59.0, 91.7)
90% ExactCI [1]	(47.3, 92.8)	(59.0, 97.2)	(62.5, 91.8)	(62.0, 90.2)

[1] CI Calculated using the exact (Clopper-Pearson) method based on binomial distribution.
(Data cutoff date - Stratum 1A: 30SEP2022 Phase2: 07OCT2022 and Stratum 1B: 21OCT2022)

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 dose level (DL) 1 and 84.6% (95% CI: 54.6-98.1) in DL2 (Table 94).

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.

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).

Table 10. Duration of Response - Full Analysis Set

DOR (Months)	Stratum 1A 1.4 mg/m² (N=12)	Stratum 1A 1.8 mg/m² (N=13)	Stratum 1A Total (N=25)	Phase 2 1.8 mg/m² (N=28)
Participants who achieved CR/CRi/CRp, n (%)	9 (75.0)	11 (84.6)	20 (80.0)	22 (78.6)
Participants with an Event, n (%)	8 (88.9)	6 (54.5)	14 (70.0)	14 (63.6)
Relapse, n (%)	5 (55.6)	6 (54.5)	11 (55.0)	8 (36.4)
Death, n (%)	3 (33.3)	0 (0.0)	3 (15.0)	6 (27.3)
Second malignancies, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

DOR (Months)	Stratum 1A 1.4 mg/m² (N=12)	Stratum 1A 1.8 mg/m² (N=13)	Stratum 1A Total (N=25)	Phase 2 1.8 mg/m² (N=28)
Participants Censored[a], n (%)	1 (11.1)	5 (45.5)	6 (30.0)	8 (36.4)
Ongoing without an event, n (%)	1 (11.1)	4 (36.4)	5 (25.0)	6 (27.3)
Lost to follow-up, n (%)	0 (0.0)	1 (9.1)	1 (5.0)	2 (9.1)
DOR (Months) (95% CI)				
75th Percentile	8.3 (5.0, NE)	NE (13.7, NE)	NE (8.0, NE)	NE (8.5, NE)
Median	6.9 (1.1, 8.4)	13.9 (3.9, NE)	8.0 (3.9, 13.9)	7.6 (3.3, NE)
25th Percentile	2.5 (1.1, 6.9)	6.6 (1.4, 13.9)	3.9 (1.1, 6.9)	3.3 (0.8, 6.6)

Abbreviation: 'NE' = Non Estimable.
a. Participants without an event are censored at the last evaluation date.
Note: One month is assumed to have 30.4375 days.
Note: The percentiles and DOR calculation are based on the Kaplan-Meier Estimate.
Note: The median times and quartiles with associated 2-sided 95% confidence intervals (CIs) based on the Brookmeyer-Crowley log(-log) transformation method.
Note: DOR at the specific time point will be provided together with the associated 2-sided 95% CI based on Greenwood's formula using a log(-log) transformation.
(Data cutoff date - Stratum 1A: 30SEP2022 Phase2: 07OCT2022 and Stratum 1B: 21OCT2022).

7.2.4. 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. Seventeen 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.

7.3. Discussion of Clinical Efficacy aspects

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 1 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.

The results of the primary efficacy evaluation were already submitted within procedure EMEA/H/C/004119/P46/004, however, no SmPC claims were then made. With the current variation, the MAH has suggested updates of the SmPC based on the data from the monotherapy stratum of the study, as Besponsa is currently approved in adults for monotherapy use only. Therefore, only the monotherapy data (Stratum 1A) are discussed in the current assessment report.

In the Phase 1 portion of Study ITCC-059, the RP2D of InO as monotherapy in paediatric patients was 1.8 mg/m^2 during Cycle 1, based on a slightly higher ORR than at the lower dose level, and an acceptable safety profile (see below).

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 in paediatric patients is presented under Clinical Pharmacology aspects above.

In the Phase 1 portion of the study, including 20 subjects, the ORR after InO monotherapy (both dose levels combined) was 80% (95% CI: 59.0-91.7). The ORR was slightly higher for the 1.8 mg/m^2 dose (84.6%, 95% CI: 54.6-98.1) than for the 1.4 mg/m^2 dose level (75.0%, 95% CI: 42.8-94.5).

In the Phase 2 portion of the study, including 28 subjects, the ORR after InO monotherapy (1.8 mg/m^2 in the first cycle) was 78.6% (95% CI: 59.0-91.7).

DoR was 8.0 months (95% CI: 3.9-13.9) and 7.6 months (95% CI: 3.3-NE) in Phase 1 and Phase 2, respectively.

The MAH suggests describing the ORR and DoR results in section 5.1 of the SmPC, which is accepted.

Given the limited paediatric efficacy data yet available, the proposed standard text in section 4.2, i.e.: "*Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made*" is considered adequate.

8. Clinical Safety aspects

8.1. Methods – analysis of data submitted

The basis for the proposed paediatric safety updates in the SmPC is the data from the monotherapy stratum (Stratum 1A) of Study ITCC-059. The study design is described under Clinical Efficacy above.

AEs described in the following sections were all TEAEs if not specifically identified. The AE causality was assessed by the investigator and/or the sponsor.

8.2. Results

Subject demographics, baseline characteristics and disposition are described under Clinical Efficacy above.

8.2.1. Exposure

A maximum of 6 cycles of InO could be given in this study for all patients, with a higher dose given on Day 1 of Cycle 1. For patients proceeding to HSCT, the recommended duration of InO was 2 cycles, up to a maximum of 3 cycles for patients who were not yet MRD negative after 2 cycles of InO. For the

Stratum 1A and Phase 2 cohorts, a cycle of therapy was defined as 3 doses of InO administered weekly on Days 1, 8 and 15. All cycles lasted 28 days (except Cycle 1 may be as short as 22 days), with delays allowed up to 42 days to allow recovery from toxicity.

Stratum 1A:

25 participants were dosed; 14 (56.0%) participants started >1 cycle. 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%).

8.2.2. Dose-limiting toxicity

DLT was evaluated in Cycle 1 only. The results are summarised in Table 11. In stratum 1A, the RP2D for InO was determined to be 1.8 mg/m^2 during Cycle 1.

Table 11. 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

8.2.3. Adverse events (AEs)

A summary of the number of treatment-emergent Adverse events (TEAEs) is provided in Table 127.

A summary the number of TEAEs that were considered *related to treatment* is provided in Table 13.

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

The most frequently reported treatment-related TEAEs were vomiting, nausea, decreased neutrophil count decreased white-blood cell count, anaemia, fatigue, decreased platelet count and increased AST.

Table 12. 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 13. 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.

8.2.4. Deaths

A summary of deaths during the study is provided in Table 149.

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.

For 17 patients, the cause of death was described as Other, which included e.g. sepsis and transplant-related events.

Table 14. 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)

8.2.5. Serious adverse events (SAEs)

Stratum 1A – Phase 1

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%]).

8.2.6. 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.

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

All cases of veno-occlusive disease (VOD) or sinusoidal obstruction syndrome (SOS) are summarized as "VOD" in this report.

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 Grade 3 VOD (59 days after the last dose of InO), which was ongoing at the time of death.
- In DL2, 1 participant developed Grade 4 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 Grade 4 VOD:
    - Onset 17 days after HSCT; 1 ongoing at death;
    - Onset 4 days after HSCT; resolved.
- 3 participants reported Grade 3 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 Grade 2 VOD with onset 10 days after HSCT; resolved.

Table 15. Summary of Participants with VOD/SOS - 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)**
Number of participants with HSCT	3 (25.0)	5 (38.5)	8 (32.0)	18 (64.3)
Number of participants with reported VOD/SOS	1 (8.3)	1 (7.7)	2 (8.0)	6 (21.4)
Number of above VOD/SOS participants with prior transplant	0 (0.0)	0 (0.0)	0 (0.0)	3 (10.7)
Number of above VOD/SOS participants without prior transplant	1 (8.3)	1 (7.7)	2 (8.0)	3 (10.7)
Number of above VOD/SOS participants with pre-study transplant but no post-study transplant	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)
Number of above VOD/SOS participants with post-study transplant but no pre-study transplant	0 (0.0)	0 (0.0)	0 (0.0)	3 (10.7)
Number of above VOD/SOS participants with pre-study transplant and post-study transplant	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.1)
Number (%) of VOD/SOS participants with Post-study HSCT	0 (0.0)	0 (0.0)	0 (0.0)	5 (27.8)
95% CI for post-HSCT VOD rate	[0.00, 70.76]	[0.00, 52.18]	[0.00, 36.94]	[9.69, 53.48]

Among the treated participants, VOD was reported in 4 of 30 (13.3%) participants aged 2-<12 years and 4 of 21 (19.0%) participants aged 12-<18 years. Among the participants who proceeded to post study HSCT, VOD was reported in 3 of 14 (21.4%) participants aged 2-<12 years and 2 of 11 (18.2%) participants aged 12-<18 years. VOD was not reported by participants aged 1-<2 years during InO treatment or after post-study HSCT.

Among the treated participants, VOD was reported in 3 of 27 (11.1%) participants with normal hepatic function and 5 of 26 (19.2%) participants with mild hepatic dysfunction. Among the participants who proceeded to post study HSCT, VOD was reported in 1 of 13 (7.7%) participants with normal hepatic function and 4 of 13 (30.8%) participants with mild hepatic dysfunction.

8.2.8. Other adverse events of special interest

In Stratum 1A, all (100%) participants had AESIs.

- 23 (92.0%) participants had Myelosuppression/Cytopenia. The most frequently reported TEAESIs (by PT) were decreased platelet count (n = 15 [60.0%]), anaemia (n = 12 [48.0%]) and decreased neutrophil count (n = 11 [44.0%]).
- 13 (52.0%) participants had Haemorrhage. The most frequently reported TEAESIs (by PT) were mouth haemorrhage (n = 5 [20.0%]), epistaxis and haematoma (n = 4 [16.0%] each).
- 12 (48.0%) participants had Infections. The most frequently reported TEAESIs (by PT) were device related infection, rhinitis, sepsis and skin infection (n = 2 [8.0%] each).

- 11 (44.0%) participants had Infusion Related Reactions. The most frequently reported TEAESIs (by PT) were pyrexia (n = 7 [28.0%]) and hyperhidrosis (n = 3 [12.0%]).
- 8 (32.0%) participants had Hepatotoxicity. The most frequently reported TEAESIs (by PT) were increased GGT (n = 5 [20.0%]), increased ALT/AST and VOD (n = 3 [12.0%] each).
- 7 (28.0%) participants had Inflammatory Gastrointestinal Events. The most frequently reported TEAESI (by PT) was oral pain (n = 3 [12.0%]).
- 4 (16.0%) participants had Neurotoxicity. The most frequently reported TEAESI (by PT) was muscular weakness (n = 3 [12.0%]).
- 2 (8.0%) participants had QT Prolongation: 1 had ECG QT prolonged and 1 had seizure.
- 1 (4.0%) participant had Interstitial Lung Disease Event (PT: lung infiltration; Investigator Term: non-specific pulmonary infiltrate).
- 1 (4.0%) participant had Tumor Lysis Syndrome.
- 1 (4.0%) participant had fibroma. The identified event was benign and was not considered second primary malignancy.

In the Phase 2 Cohort, all (100.0%) participants had AESIs.

- 20 (71.4%) participants had Myelosuppression/Cytopenia. The most frequently reported TEAESIs (by PT) were decreased platelet count, anaemia (n = 12 [42.9%] each) and decreased neutrophil count and decreased WBC count (n = 10 [35.7%] each).
- 12 (42.9%) participants had Infusion Related Reactions. The most frequently reported TEAESI (by PT) was pyrexia (n = 10 [35.7%]).
- 12 (42.9%) participants had Hepatotoxicity. The most frequently reported TEAESIs (by PT) were VOD (n = 7 [25.0%]), increased AST (n = 6 [21.4%]) and increased ALT (n = 5 [17.9%]).
- 11 (39.3%) participants had Infections. The most frequently reported TEAESIs (by PT) were rhinitis and sepsis (n = 2 [7.1%] each).
- 9 (32.1%) participants had Haemorrhage. The most frequently reported TEAESI (by PT) was haematoma (n = 4 [14.3%]).
- 5 (17.9%) participants had Tumor Lysis Syndrome.
- 4 (14.3%) participants had Inflammatory Gastrointestinal Events. The most frequently reported TEAESI (by PT) was stomatitis (n = 3 [10.7%]).
- 1 (3.6%) participant had Interstitial Lung Disease Event (PT: lung infiltration; Investigator Term: left lower lobe infiltrate).
- 1 (3.6%) participant had Pancreatitis (increased amylase).
- 1 (3.6%) participant had neoplasm progression. The identified event was not considered second primary malignancy and was related to the disease under study.

8.2.9. Clinical chemistry

One participant in the Phase 2 part of the study met the laboratory criteria for potential Hy's Law: concurrent ALT/AST ≥3 × ULN and total bilirubin ≥ 2 × ULN and ALP ≤ 2 × ULN or missing. None of

these abnormalities were reported as AEs. This subject experienced a Grade 3 VOD on the same day of these laboratory abnormalities (shortly after the only dose of InO). The VOD resolved in a few days, and the laboratory abnormalities returned to normal. The concurrent abnormal LFTs may have been attributed to the VOD. Thus, this case was not a confirmed Hy's Law case.

8.2.10. 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.

8.2.11. Intrinsic factors

TEAEs were analysed by intrinsic factors including age, gender, baseline hepatic function, baseline renal function, and baseline CD22 expression in leukemic blasts; and extrinsic factors including prior HSCT and other baseline diagnosis (prior line of ALL therapy). Due to the small sample size, Study ITCC-059 was not powered for formal analyses of factor effects. Based on the available data, the overall AEs do not appear to be substantially affected by these intrinsic or extrinsic factors.

8.3. Discussion of Clinical Safety aspects

The safety database from Study ITCC-059 consists of 25 (Phase I) + 28 (Phase II), i.e. 53 paediatric patients treated with InO monotherapy (Stratum 1A).

The subjects in Stratum 1A were acceptably evenly distributed over the paediatric age range, with 12 subjects < 6 years, 20 subjects 6 to < 12 years and 21 subjects 12 to <18 years old.

The median number of cycles administered was two (2) for InO monotherapy.

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.

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.

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 two patients, the cause of death was described as Toxicity, however, the MAH suggests the toxicity was not due to InO in either case: One case of cardiac arrest was suggested due to cumulative neurotoxicity and one case of bilateral pneumonitis started after follow-up ALL therapy. The latter case was considered at least possibly related to InO by the Investigator. The pattern of deaths in the study do not give raise to immediate concern.

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 undergo 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%) after InO monotherapy. Thus, despite lack of some risk factors such as higher age, the VOD rate in this study was in the same range as that reported in adults. The rate reported in paediatric subjects without subsequent HSCT was about twice as high (3/53; 5.7%) as that reported in adults without subsequent HSCT (3%). However, the small number of events precludes definite conclusions on the rate. About half of the paediatric subjects had mild hepatic dysfunction. As in adults, VOD was more commonly reported in paediatric subjects with hepatic dysfunction (5 events) than in subjects with normal hepatic function (3 events). This was even more evident in patients undergoing subsequent HSCT (1 event in a subject with normal hepatic function and 4 events in subjects with hepatic impairment). Risk factors for VOD are well described in the SmPC.

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.

Conclusion

Overall, it is agreed that the review of the data from Study ITCC-059 did not identify any new ADRs in paediatric patients, as the evaluated events are consistent with the ones already identified in the adult patients. As in adults, VOD was commonly reported in paediatric subjects (in about 15% of subjects after InO monotherapy), and the risk is increased in subjects undergoing HSCT and/or who have some degree of hepatic impairment.

SmPC update

According to the EMA document 'EMA/551202/2010 Frequently asked Questions on SmPC paediatric information', safety data should be described in section 5.1 in case it has been collected in a paediatric development for an indication neither approved in children nor in adults. However, as the paediatric indication investigated in Study ITCC-059 is the same as that approved in adults, it considered more appropriate to describe the paediatric safety data in section 4.8. Accordingly, the MAH has updated Section 4.8 of the SmPC with paediatric immunogenicity and safety data, which is agreed.

9. Risk management plan

The MAH submitted an updated RMP version 2.2 The (main) proposed RMP changes were the following:

Summary of significant changes in this RMP:

RMP Part/Module	Major Changes RMP version 2.2
PART I Product(s) Overview	Aligned to the current SmPC and updated to report that product is not subject to additional monitoring in the EU.
PART II Safety Specification	
PART II.Module SI Epidemiology of the Indication(s) and Target Population(s)	Updated with new references.
PART II.Module SII Non-Clinical Part of the Safety Specification	Minor editing to align with EMA GVP Module V, Rev 2.0.1 Template
PART II.Module SIII Clinical Trial Exposure	Inclusion of data from study ITCC-059 (WI203581) and study B1931030 "A Phase 4, Open-Label, Randomized Study of Two Inotuzumab Ozogamicin Dose Levels in Adult Patients with Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia Eligible for Hematopoietic Stem Cell Transplantation and who have Risk Factor(s) for Veno-Occlusive Disease".
PART II.Module SIV Populations Not Studied in Clinical Trials	Minor editing to align with EMA GVP Module V, Rev 2.0.1 Template.
PART II.Module SV Post-Authorisation Experience	Post-Authorisation Exposure updated to the new DLP.
PART II.Module SVI Additional EU Requirements for the Safety Specification	No change.
PART II.Module SVII Identified and Potential Risks	Risks characterisation updated to the new DLP.
PART II.Module SVIII Summary of the Safety Concerns	No change.
PART III Pharmacovigilance Plan (including post-authorisation safety studies)	
III.1 III.2 III.3	Updated to include information on the follow-up questionnaire for hepatic events. Updated to include the PASSs B1931030. The PASSs B1931030 have been included as ongoing studies.
Error! Reference source not found.PART V Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)	

RMP Part/Module	Major Changes RMP version 2.2
V.1 V.2 V.3	No change. No change. Updated to include the PASSs B1931030 as additional pharmacovigilance activities for the important identified risk "Grade ≥3 and/or serious Hepatotoxicity, including all VOD/SOS".
PART VI Summary of the Risk Management Plan	Updated to reflect all relevant changes described above.
Annex 2 Annex 3 Annex 4 Annex 6 Annex 7 Annex 8	Updated to include the PASSs B1931030. Updated to include the protocols for PASSs B1931028 and B1931030. Updated to include the Hepatic Events DCA. No change. Updated. Updated.

Clinical trial exposure

The MAH presented data for the following studies:

a. ITCC-059 (WI203581); this study involved paediatric participants with R/R CD22-positive BCP-ALL and was ongoing at the DLP of this RMP, the estimated LSLV is 11 April 2025. The interim CSR was issued on 14 February 2023, with 2 amendments after the DLP of this RMP, on 21 February 2023 and on 03 April 2023. This study and results from the CSR and from the safety database are presented in Annex 7.

b. B1931030; this study involved adult participants with R/R B-cell ALL eligible for HSCT and who have risk factor(s) for VOD. The study was ongoing at the DLP of this RMP and is presented in Annex 2.

a. Clinical trial exposure data for Study ITCC-059

Table 16. Inotuzumab Ozogamicin Exposure by Special Population - Full Analysis Set - Protocol ITCC-059 (B193-WI203581)

Cohort Special Population	Participants	Person-Time (Months)[a]
Stratum 1A + Phase2 (N= 53)		
Renal impairment [b]		
No impairment	45	51.45
Mild	7	10.87
Moderate	1	1.58
Severe	0	0
Unknown/Missing data [c]	0	0
Hepatic impairment[d]		
No impairment	27	34.07
Mild	26	29.83
Moderate	0	0

Table 16. Inotuzumab Ozogamicin Exposure by Special Population - Full Analysis Set - Protocol ITCC-059 (B193-WI203581)

Cohort Special Population	Participants	Person-Time (Months)[a]
Severe	0	0
Unknown/Missing data	0	0
Total	53	63.90
Stratum 1B (combo) (N=30)		
Renal impairment[b]		
No impairment	24	29.24
Mild	5	4.14
Moderate	1	0.59
Severe	0	0
Unknown/Missing data[c]	0	0
Hepatic impairment[d]		
No impairment	20	22.64
Mild	10	11.33
Moderate	0	0
Severe	0	0
Unknown/Missing data[c]	0	0
Total	30	33.97

a. Person-Time represents the cumulative number of months of exposure of the participants represented in the adjacent participants column (last dose of Inotuzumab Ozogamicin- first dose of Inotuzumab Ozogamicin+ 1)/ 30.4375. Duration includes the time in which a participant temporarily withdrew from the study but re-started at a later date. One month is defined as 30.4375 days. Person time is based on first total daily dose received and includes time spent at lower doses. Exposure is based on overall person-time exposure to Inotuzumab Ozogamicin using this definition.

b. Renal impairment: normal [creatinine clearance (CCL) >=90mL/min], mild (60 mL/min =< CCL <90 mL/min), moderate (30 mL/min=< CCL <60 mL/min), and severe (CCL <30 mL/min). CCL was calculated by Cockcroft-Gault formula at participant baseline.

c. Unknown/Missing data: Unknown or missing data to calculate baseline impairment.

d. Hepatic impairment categories determined by National Cancer Institute (NCI) scale at patient participant baseline. Normal hepatic function: total bilirubin and AST =< upper limit of normal (ULN); mild impairment: total bilirubin =<ULN and AST >ULN or total bilirubin >1.0 - 1.5 x ULN and AST any level; moderate impairment: total bilirubin >1.5 - 3.0 x ULN and AST any level; severe impairment: total bilirubin >3 x ULN and AST any level.

Table 17. Total Number of Participants Exposed to Inotuzumab Ozogamicin in Clinical Trials - Full Analysis Set - Protocol ITCC-059 (B193-WI203581)

Cohorts	Participants
Stratum 1A + Phase2	53
Stratum 1B (combo)	30
Total participants	**83**

Summary of results (presented in Annex 7):

Study ITCC-059 was a Phase 1/2 multicenter, international, single-arm, multi-cohort, open-label study conducted in 53 paediatric participants ≥1 and <18 years of age with relapsed or refractory CD22-positive B-cell precursor ALL to identify a recommended Phase 2 Dose (Phase 1) of inotuzumab ozogamicin administered intravenously (IV) either as monotherapy (Stratum 1A) or in combination with chemotherapy (Stratum 1B) and to further evaluate the efficacy, safety, and tolerability of the selected inotuzumab ozogamicin dose as a monotherapy agent (Phase 2). The study also evaluated the pharmacokinetics and pharmacodynamics of inotuzumab ozogamicin as monotherapy.

Data from MAH's Safety Database:

Cumulatively through 15 February 2023, 88 cases (2.3% of the total dataset) including 90 SAEs originating from the study ITCC-059 were identified. These cases involved 56 unique paediatric participants, since multiple cases were reported for the same participants.

There were 18 female and 38 male participants; age ranged from 17 months to 18 years.

The most frequently reported (≥3) AEs were: Febrile neutropenia (16), Venoocclusive liver disease (10), Sepsis (8), Pyrexia (6), Neoplasm progression (4), and Venoocclusive disease (3). The clinical outcome of the reported 90 SAEs were resolved (69), resolved with sequelae (2), not resolved (7), and fatal (12).

Out of these 88 cases, in 44 cases, the reported 44 SAEs were assessed related to the administration of inotuzumab ozogamicin by the investigator and/or the Company.

These 44 SAEs were: Febrile neutropenia (13), Venoocclusive liver disease (10), Venoocclusive disease (3), Neutrophil count decreased (2), Acute kidney injury, Atrial fibrillation, Blood bilirubin increased, Haemorrhage intracranial, Malaise, Multiple organ dysfunction syndrome, Pain, Platelet count decreased, Pneumonia, Pneumonia fungal, Pyrexia, Renal failure, Sepsis, Sinusitis, Sinus tachycardia, and Varicella zoster virus infection (1 each).

PRAC Rapporteur comment: Venooclusive liver disease / sinusoidal obstruction syndrome in the context of the current treatment remains an issue of concern warranting further follow-up.

b. Clinical trial exposure data for Study B1931030

This Phase 4 study is a PMR that was requested by the US FDA and is designed to evaluate the safety and efficacy of 2 inotuzumab ozogamicin dose levels in adults with relapsed or refractory B-cell ALL who are eligible for HSCT and who are at higher risk for developing VOD post-HSCT.

Primary Objective: To evaluate the rates of VOD and hematologic remission (CR/CRi) for 2 inotuzumab ozogamicin dose levels in adult patients with relapsed or refractory B-cell ALL who are eligible for HSCT and who are at higher risk for developing VOD post-HSCT.

Secondary Objective: Safety and efficacy of 2 inotuzumab ozogamicin dose levels.

Table 18. Inotuzumab Ozogamicin Exposure by Special Population - Full Analysis Set (Protocol B1931030)

Cohort Special Population	Participants (n)	Person-Time (Months)[a]
Renal impairment [b]		
1.2 mg/m²/cycle (N=64)		
Normal	53	108.3
Mild	9	13.47
Moderate	2	1.71
Severe	0	0
Unknown/Missing data[c]	0	0
Total	64	123.4
1.8 mg/m²/cycle (N=38)		
Normal	29	45.80
Mild	8	17.31
Moderate	1	1.91
Severe	0	0
Unknown/Missing data	0	0
Total	38	65.02
Hepatic impairment[d]		
1.2 mg/m²/cycle (N=64)		
Normal	45	89.49
Mild	19	33.94
Moderate	0	0
Severe	0	0
Unknown/Missing data	0	0
Total	64	123.4
1.8 mg/m²/cycle (N=38)		
Normal	27	50.79
Mild	11	14.23
Moderate	0	0
Severe	0	0
Unknown/Missing data	0	0
Total	38	65.02

a. Person-Time represents the cumulative number of months of exposure of the participants represented in the adjacent participants column (last dose of Inotuzumab Ozogamicin- first dose of Inotuzumab Ozogamicin+ 1)/ 30.4375. Duration includes the time in which a participant temporarily withdrew from the study but re-started at a later date. One month is defined as 30.4375 days. Exposure is based on overall person-time exposure to Inotuzumab Ozogamicin using this definition.
b. Renal impairment: normal [creatinine clearance (CCL) ≥90mL/min], mild (60 mL/min ≤ CCL <90 mL/min), moderate (30 mL/min ≤ CCL <60 mL/min), and severe (CCL <30 mL/min). CCL was calculated at baseline using the Cockcroft-Gault formula.
c. Unknown/Missing data: Unknown or missing data to calculate baseline impairment.
d. Hepatic impairment categories are determined by the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) scale at participant baseline. Normal hepatic function: total bilirubin and AST≤ upper limit of normal (ULN); mild impairment: total bilirubin ≤ULN and AST >ULN or total bilirubin >1.0 - 1.5 x ULN and AST any level; moderate impairment: total bilirubin >1.5 - 3.0 x ULN and AST any level; severe impairment: total bilirubin >3 x ULN and AST any level.

Table 19. Total Number of Participants Exposed to Inotuzumab Ozogamicin in Clinical Trials - Full Analysis Set (Protocol B1931030)

Cohorts	Participants
1.2 mg/m²/cycle	64
1.8 mg/m²/cycle	38
Total participants	**102**

Post-Authorisation Experience

Cumulatively through 15 February 2023, it is estimated that 9120 patients worldwide were exposed to inotuzumab ozogamicin commercially since the product was first approved. The sales of 62,151 standard units have been divided by AVDOS 8.5 vials to obtain North America and IDM countries patient exposure of 7312 patients, out of which 1709 patients are from EU.

PART II. Module SVII Identified and Potential Risks

Risks characterisation were updated to the new DLP

PART II. Module SVIII Summary of the Safety Concerns

Summary of Safety Concerns	
Important identified risks	Grade ≥3 and/or serious hepatotoxicity, including all VOD/SOS Myelosuppression/cytopenia
Important potential risks	Interstitial lung disease Inflammatory gastrointestinal events Pancreatitis Second primary malignancy Reproductive and developmental toxicity (post exposure during pregnancy and while breast feeding) Neurotoxicity Nephrotoxicity
Missing information	Use in patients with moderate or severe hepatic impairment Use in patients with severe renal impairment Use in Hispanic and Black patients

SOS=sinusoidal obstruction syndrome; VOD=venoocclusive disease

There are no new safety concerns. This is endorsed.

PART III Pharmacovigilance Plan

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires for safety concerns:**

To obtain structured follow-up information for the important identified risk Grade ≥3 and/or serious hepatotoxicity, including all VOD/SOS, a Hepatic Events DCA containing specific questions for hepatic events was created. It was attached in Annex 4.

- **Other forms of routine pharmacovigilance activities for safety concerns**:

None.

III.2. Additional Pharmacovigilance Activities

Table 20. Additional Pharmacovigilance Activities

PASS – Study Number	Study Title	Rationale and Study Objectives	Study Design	Study Populations	Milestones
B1931030	A Phase 4, Open- Label, Randomized Study of Two Inotuzumab Ozogamicin Dose Levels in Adult Patients with Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia Eligible for Hematopoietic Stem Cell Transplantation and Who Have Risk Factors for Veno-Occlusive Disease	This Phase 4 study is a PMR that was requested by the US FDA and is designed to evaluate the safety and efficacy of 2 inotuzumab ozogamicin dose levels in adults with relapsed or refractory B-cell ALL who are eligible for HSCT and who are at higher risk for developing VOD post-HSCT. Primary objective: To evaluate the rates of VOD and hematologic remission (CR/CRi) for 2	The study will be conducted in 2 phases: a run-in phase and a randomised phase. Run-in phase: a total of up to 22 patients will be enrolled to receive the starting dose of 1.2 mg/m^2/cycle (dose level 2). A Simon Two Stage optimal design will be used. If acceptable efficacy (CR/CRi and MRD negativity) is observed in the run-in phase, the study will	This open-label study will evaluate 2 inotuzumab ozogamicin dose levels in adults with relapsed or refractory B-cell ALL who are eligible for HSCT and who are at higher risk for developing VOD post-HSCT after inotuzumab ozogamicin treatment. High risk is defined as patients with prior HSCT,	• Study Start Date: 01 July 2019. • Study Primary Completion Date: 21 September 2022. • Estimated Study Completion Date: 13 September 2023.

Table 20. Additional Pharmacovigilance Activities

PASS – Study Number	Study Title	Rationale and Study Objectives	Study Design	Study Populations	Milestones
		inotuzumab ozogamicin dose levels in adult patients with relapsed or refractory B-cell ALL who are eligible for HSCT and who are at higher risk for developing VOD post-HSCT. Secondary objective: Safety and efficacy of 2 inotuzumab ozogamicin dose levels.	enter the randomised phase. Randomised phase: if acceptable efficacy is observed in the run-in phase, the study will enter the randomised phase. A total of approximately 80 patients will be randomised (1:1) to 1 of 2 dose levels of inotuzumab ozogamicin (40 patients per dose level).	ongoing or prior liver disease, older patients (≥55 years), or later salvage line (Salvage ≥2).	

The PASS B1931030 has been included as ongoing study.

V.3. Summary of Risk Minimisation Measures

Table 21. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Grade ☐3 and/or serious hepatotoxicity, including all VOD/SOS	Routine risk minimisation measures: SmPC Sections 4.2, 4.3, 4.4, and 4.8. PL Sections 2, 3 and 4. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: DCA for hepatic events. Additional pharmacovigilance activities: • Study B1931030[a] (Estimated Study Completion Date: 13 September 2023). This PASS is conducted in adults with R/R B-cell ALL who are eligible for HSCT and who are at higher risk for developing VOD post-HSCT after inotuzumab ozogamicin treatment.
Myelosuppression/ cytopenia	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 4.8. PL Sections 2, and 4. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Important Potential Risks		
Interstitial lung disease	Routine risk minimisation measures: None. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Inflammatory gastrointestinal events	Routine risk minimisation measures: None. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Pancreatitis	Routine risk minimisation measures: None. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Second primary malignancy	Routine risk minimisation measures: None. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Reproductive and developmental toxicity (post exposure during pregnancy and while breast feeding)	Routine risk minimisation measures: SmPC Sections 4.6, and 5.3. PL Sections 2. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Neurotoxicity	Routine risk minimisation measures: None. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Nephrotoxicity	Routine risk minimisation measures: None. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Missing Information		
Use in patients with moderate or severe hepatic Impairment	Routine risk minimisation measures: SmPC Sections 4.2, and 5.2. PL Section 2. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Use in patients with severe renal impairment	Routine risk minimisation measures: SmPC Sections 4.2, and 5.2.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None.	Additional pharmacovigilance activities: None.
Use in Hispanic and Black patients	Routine risk minimisation measures: SmPC Section 5.2. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

a. This study is a PMR that was requested by the US FDA. Please refer to Section III.2 and Section III.3.1 for further details.

The Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities was updated to include the PASS B1931030 as additional pharmacovigilance activity for the important identified risk " Grade ≥3 and/or serious Hepatotoxicity, including all VOD/SOS.

9.1. Overall conclusion on the RMP

☒The changes to the RMP are acceptable.

10. Changes to the Product Information

As a result of this variation, section(s) 4.2, 4.8, 5.1 and 5.2 of the SmPC are being updated to reflect the results of Study ITCC-059 and Study INO-Ped-ALL-1. In addition, some editorial changes are proposed in several sections of the SmPC and PL.

Please refer to Attachment 1, which includes all proposed changes to the Product Information.

All the proposed changes are accepted.

11. Request for supplementary information

11.1. Other concerns

Clinical aspects

1. The proposed paediatric updates of the SmPC are largely accepted but given that the investigated paediatric indication is the same as that approved in adults, the safety information should be moved from section 5.1 to section 4.8. Further, some additional amendments are proposed. See annotated SmPC.

12. Assessment of the responses to the request for supplementary information

12.1. Other concerns

Clinical aspects

Question 1
The proposed paediatric updates of the SmPC are largely accepted but given that the investigated paediatric indication is the same as that approved in adults, the safety information should be moved from section 5.1 to section 4.8. Further, some additional amendments are proposed. See annotated SmPC.

Regarding the proposed text in section 5.2

Paediatric population

Based on population pharmacokinetic analysis in 824 patients, patient age group (paediatric [≥ 1 and < 18 years of age] vs adult) is not considered to have a clinically meaningful effect on inotuzumab ozogamicin disposition over the treatment duration.

Rapp Comment:

This should be revised to reflect the increased exposure in paediatric patients, for example:

At the adult recommended dose, the exposure in paediatric patients with ALL (aged ≥ 1 and < 18 years) was [xx%] higher than in adults. The clinical relevance of the increased exposure is unknown.

Summary of the MAH's response
Although Patient Type was identified as a statistically significant covariate on decay coefficient associated with time-dependent clearance (kdes), it is not considered to have a clinically meaningful effect on InO disposition.

The current population pharmacokinetic (PK) analysis (Module 5.3.3.5, PMAR-EQDD-B193e-DP4-1490) for characterization of inotuzumab ozogamicin (InO) PK in paediatric patients with relapsed/refractory acute lymphoblastic leukemia (ALL) showed best fit with a final model that incorporated the effect of Patient Type (paediatric patients with ALL, adult patients with ALL, and adult patients with non-Hodgkin's lymphoma [NHL]) on decay coefficient associated with time-dependent clearance (kdes). The inter-individual variability (IIV) for kdes in the final model remained similar to that of the base model (55.5% versus 55.7%), indicating that the Patient Type did not substantially contribute to the IIV of kdes even though it was a statistically significant covariate of the parameter.

In the final model, the kdes was estimated to be 79.5% (95% CI: 72.9%-84.7%) lower in paediatric patients with ALL and 87.7% (95% CI: 84.7%-90.2%) lower in adult patients with ALL than that in adult patients with NHL, respectively. However, it is important to mention that time-dependent clearance (CLt [i.e., CL2·e[-kdes·Time]]) is one of the components of the total InO CL estimate (i.e., total CL=CL1+CLt) and its contribution changes over time. Thus, the actual impact of any covariate on kdes does not translate into a similar magnitude of change in elimination rate. The estimated 79.5% (ALL paediatrics) and 87.7% (ALL adults) decrease in kdes with BLSTPB =4% leads to variations in the

time that CLt is reduced to 50%, which ranges from 89 (ALL paediatrics) to 147 hours (ALL adults), respectively. For paediatric and adult patients with ALL, the contribution of CLt to total CL becomes negligible after 5 half-lives, or by 2.6 and 4.4 weeks, respectively. Given the estimated change from the typical value of kdes for both paediatric and adult patients, and considering that CL2 is not the only CL component, the Patient Type (paediatric patients with ALL versus adult patients with ALL) is not considered to have a clinically meaningful effect on InO disposition over the treatment duration.

While median exposures in all PK parameters appear to be higher for in paediatric patients compared to adult ALL patients, the simulated InO serum exposures generally overlapped between adult and paediatric patients with ALL (Module 2.7.2, Summary of Clinical Pharmacology Studies, Figure 1).

The recommended Phase 2 dose (RP2D) identified in pediatric studies (ITCC-059 and INO-Ped-ALL-1) is the same as the approved dosing regimen in adults (1.8 mg/m2/cycle).

In summary, the MAH considers the following text "Based on population pharmacokinetic analysis in 824 patients, patient age group (paediatric [≥ 1 and < 18 years of age] vs adult) is not considered to have a clinically meaningful effect on inotuzumab ozogamicin disposition over the treatment duration." adequately describes the InO PK for paediatric patients with ALL.

Assessment of the MAH's response

The applicant has accepted the comments in all section except section 5.2. Further, information on number of subjects who received subsequent HSCT was only added to section 4.8 (as a risk factor for VTE) but not to section 5.1, as requested. As this information is considered relevant for the interpretation of Duration of Response data, it should be included also in section 5.1.

Regarding the text in 5.2:

As noted previously, age was not tested as a continuous covariate but only grouping all paediatric patients referred to as a "patient type" (adults vs non-adults). This is not a generally preferred approach, however, considering that baseline BSA is a significant covariate, and the lack of trend in the ETA plots for age and bodyweight, this is acceptable.

While it is agreed that the simulated InO exposures are overlapping, the medians for all parameters (Ctrough, Cmax, cumulative AUC) are still higher in paediatric patients than adults, which should be reflected in the SmPC. This could be an effect of BSA in the model.

Finally, the essence of pharmacokinetics is that the same dose (even when adjusted by BSA) does not necessarily result in the same systemic exposure. The comment is thus reiterated, the text in section 5.2 should read:

At the adult recommended dose, the exposure in paediatric patients with ALL (aged ≥ 1 and < 18 years) was [xx%] higher than in adults. The clinical relevance of the increased exposure is unknown.

Conclusion: Issue not resolved. See outstanding comments in the Annotated SmPC.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Additional issue.

With the response, an amended CSR for Study ITCC-059 has been submitted.

MAH's comment:

Pfizer recently found an error identified in W1203581 (Study ITCC-059) Clinical Study report (CSR) submitted to EMA as part of this Type II variation.

In the Phase 2 Cohort, the 1-sided p-value of overall response rate (ORR), defined as the percentage of patients with complete remission (CR) / complete remission with incomplete hematologic recovery (CRi) / complete remission with incomplete platelet recovery (CRp), as primary efficacy endpoint, was mistakenly calculated using the 50% null hypothesis rate, instead of 30% null hypothesis rate as defined in the study protocol and the statistical analysis plan. In CSR v3.0 (03-Apr-2023), most changes were due to the new data transfer in February 2023 resulting in table and figure updates. In addition, a few programming errors were identified after CSR v2.0 approved on 21-Feb-2023 and were corrected in this amendment as well. Full summary of changes is enclosed within this submission.

Pfizer considers that there is no impact on the conclusion for this study or the positive benefit/risk profile of Besponsa in pediatric patients with R/R ALL.

Amended CSR for Study ITCC-059 along with the document providing the summary of changes is enclosed along with the response to the RSI.

Assessor's comment:

The updated analysis led to the following amendment in the CSR:

"In the Phase 2 Cohort (Table 8), the primary objective was met demonstrating CR/CRi/CRp rate significantly greater than the 30% null hypothesis rate with 1-sided p-value ***<0.0001*** ~~of 0.0019.~~"

It is agreed that this does not change the overall conclusion of the study. Section 7.2.3 of this AR has been updated accordingly.

Furthermore, the company has provided their view on the comments on the Product Information as circulated during second phase of the procedure by the Rapporteur:

- SmPC comment Section 5.1:

Information on subsequent HSCT was added in section 4.8. However, as this information is relevant also for the data on duration of response, the information should be given also here.

MAH response:

Accepted. The Applicant has updated Section 5.1 to include the information on number of subjects that proceeded to subsequent HSCT, in alignment with Section 4.8.

Assessment:

Issue resolved.

SmPC comment Section 5.2:

The MAH´s argumentation is not agreed. The text should reflect the increased mean exposure in paediatric patients, for example: "At the adult recommended dose, the exposure in paediatric patients with ALL (aged ≥ 1 and < 18 years) was [xx%] higher than in adults. The clinical relevance of the increased exposure is unknown."

MAH response:

The MAH accepts and has proposed changes accordingly.

Please see the calculations and source below:

Calculations:

270.01 x10^3 vs 215.71 x10^3 ng.hr/mL

(270.01-215.71)/215.71=25%

Source:

PMAR-EQDD-B193e-DP4-1490 Table 9 Day 78 (C4D1) cAUC from ITCC-059 vs adult

Assessment:

The updated text is agreed.

Issue resolved.