26 March 2026
EMADOC-1700519818-3075832
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

Invented name: Besponsa

International non-proprietary name: Inotuzumab ozogamicin

Procedure No. EMA/VR/0000257310

## Note

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

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
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# List of abbreviations

| TERM | DEFINITION |
|---|---|
| ADA | anti-drug antibody |
| ADC | antibody-drug conjugate |
| ADR | adverse drug reaction |
| AE | adverse event |
| ALL | acute lymphoblastic leukemia |
| allo | allogeneic |
| ALT | alanine aminotransferase |
| ASP | asparaginase |
| AST | aspartate aminotransferase |
| BCP | B-cell precursor |
| BL | baseline |
| BLA | Biologics License Application |
| BSA | body surface area |
| CAR T-cell | chimeric antigen receptor T-cell |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | confidence interval |
| CO | clinical overview |
| CR | complete remission |
| CRC | clinical research collaboration |
| CRi | complete remission with incomplete hematologic recovery |
| CRp | complete remission with incomplete platelet recovery |
| CSR | clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DL | dose level |
| DLT | dose limiting toxicity |
| DoR | duration of response |
| ECG | electrocardiogram |
| EFS | event free survival |
| EMA | European Medicines Agency |

| | |
|---|---|
| EU | European Union |
| FDA | US Food and Drug Administration |
| FPFV | first participant first visit |
| FU | follow-up |
| G | grade |
| GGT | gamma-glutamyl transferase |
| HSCT | hematopoietic stem cell transplant |
| InO | inotuzumab ozogamicin |
| LPLV | last participant last visit |
| LLOQ | Lower limit of quantification |
| KOL | key opinion leader |
| MAH | marketing authorization holder |
| MFI | median fluorescence intensity |
| TERM | DEFINITION |
| MHLW | Ministry of Health, Labour and Welfare of Japan |
| MOF | multiple organ failure |
| MRD | minimal residual disease |
| MTD | maximum tolerated dose |
| NE | non-estimable |
| ORR | overall response rate |
| OS | overall survival |
| PCD | primary completion date |
| PD | pharmacodynamic(s) |
| PDCO | Paediatric Committee |
| PEG-ASP | pegylated-asparaginase |
| PIP | pediatric investigation plan |
| PK | pharmacokinetic(s) |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PT | preferred term |
| RMP | risk management plan |
| pvcVPC | variability-corrected visual predictive checks |
| RP2D | recommended phase 2 dose |

| | |
|---|---|
| R/R | relapsed/refractory |
| RQ-PCR | real-time quantitative polymerase chain reaction |
| SCE | summary of clinical efficacy |
| SCS | summary of clinical safety |
| SCP | summary of clinical pharmacology |
| SmPC | Summary of Product Characteristics |
| SOS | sinusoidal obstruction syndrome |
| TEAE | treatment-emergent adverse event |
| TEAESI | treatment-emergent adverse event of special interest |
| TESAE | treatment-emergent serious adverse event |
| TR | treatment-related |
| UKALL-R3 | a historical clinical trial for relapsed and refractory ALL |
| US | United States |
| VOD | veno-occlusive disease (liver) |
| WBC | white blood cell |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 4 March 2025 an application for a variation.

The following variation was requested:

| **Variation(s) requested** | | **Type** |
|---|---|---|
| C.I.6.a | C.I.6.a Addition of a new therapeutic indication or modification of an approved one | Variation type II |

Extension of indication to include treatment of paediatric patients 1 year and older with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia (ALL) for Besponsa, 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 ALL; Study WI235086 is an open-label, Phase 1 study to assess safety and tolerability of InO in Japanese pediatric patients with R/R CD22-positive AL. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

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

## *Information relating to orphan designation*

Besponsa was designated as an orphan medicinal product EU/3/13/1127 on 7 June 2013. Besponsa was designated as an orphan medicinal product in the following indication: treatment of B-cell acute lymphoblastic leukaemia

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision P/0079/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0079/2023 was not yet completed as some measures were deferred.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

### *Protocol assistance*

The MAH did not seek scientific advice and/or protocol assistance from the CHMP.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: n/a

| Timetable | Actual dates |
|---|---|
| Submission date: | 4 March 2025 |
| Start of procedure: | 26 April 2025 |
| CHMP Rapporteur's preliminary assessment report circulated on: | 19 June 2025 |
| PRAC RMP advice and assessment overview adopted by PRAC on: | 10 July 2025 |
| CHMP Rapporteur's updated assessment report circulated on: | 17 July 2025 |
| Request for supplementary information and extension of timetable adopted by the CHMP on: | 24 July 2025 |
| MAH's responses submitted to the CHMP on: | 11 September 2025 |
| CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on: | 14 October 2025 |
| CHMP Rapporteur's updated assessment report on the MAH's responses circulated on: | 6 November 2025 |
| 2nd request for supplementary information and extension of timetable adopted by the CHMP on: | 13 November 2025 |
| MAH's responses submitted to the CHMP on: | 22 January 2026 |
| CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on: | 2 March 2026 |
| CHMP Rapporteur's updated assessment report on the MAH's responses circulated on: | 19 March 2026 |
| CHMP opinion: | 26 March 2026 |
| The CHMP adopted a report on similarity of Besponsa with Tecartus, Kymriah and Blincyto on date | 26 March 2026 |

# 2. Scientific discussion

## *2.1. Introduction*

### 2.1.1. Problem statement

### *Disease or condition*

The initially claimed indication was: "Besponsa is indicated as monotherapy for the treatment of adults and paediatric patients 1 year and older with relapsed or refractory CD22 positive B cell precursor

acute lymphoblastic leukaemia (ALL). Patients with Philadelphia chromosome positive (Ph+) relapsed or refractory B cell precursor ALL(BCP-ALL) should have failed treatment with at least 1 tyrosine kinase inhibitor (TKI)."

The product is already approved for this use in adults; the present extension concerns children and adolescents 1-<18 years of age.

## *Epidemiology*

ALL is the most frequent malignant disease of childhood, with an estimated incidence of 4/100,000 cases per year in children. Approximately 85 percent of cases of paediatric ALL are B cell lineage.

## *Clinical presentation, diagnosis and stage/prognosis*

BCP-ALL is diagnosed through a combination of analyses including morphological assessment of blood and bone marrow, immunophenotyping to identify specific markers that confirm that the cells are B-cell precursors and to determine maturation. In addition, genetic and cytogenetic analyses are performed to detect chromosomal and genetic abnormalities that can help classify the leukaemia and guide treatment decision.

The prognosis is generally better for children than for adults. In the past 2 decades, significant improvement has been made in the treatment of childhood ALL, with current 5-year rates of event free survival (EFS) of 80-90% in the frontline, multi-drug setting. Maintenance therapy of varying duration (range 1.5 to 2.5 years) aims to prevent recurrent ALL. Approximately 20% suffer a relapse. Early relapse (within 6 months after treatment ends) is associated with a poor prognosis while a late relapse (> 6 months after termination of maintenance treatment) is associated with a better prognosis. The incidence of central nervous system (CNS) relapse has decreased to < 10% in the setting of preventive CNS therapy.

The prognosis for those children who experience an early relapse or who are refractory to front-line therapy remains poor. The prognosis for a patient with relapsed ALL depends on the time from diagnosis to relapse, extent of relapse (BM relapse has a worse prognosis than isolated extramedullary relapse), cytogenetics and MRD status. In paediatric ALL, minimal residual disease (MRD) is widely recognized as the most sensitive prognostic factor for relapse regardless of risk classification and MRD status after salvage therapy is incorporated into treatment algorithms that determine whether patients proceed to allogeneic hematopoietic stem cell transplantation (allo-HSCT) or not.

## *Management*

The treatment approach to ALL, whether at the time of primary diagnosis or at relapse, represents one of the most complex and intensive regimens in cancer therapy. Although the specific treatment regimens and selection of drugs, dose schedules and treatment duration differ among various risk groups, the basic treatment principles are similar. For example, the most common treatment regimens consist of multi-agent chemotherapy, and most patients receive vincristine, corticosteroids, asparaginase and an anthracycline. Treatment is subdivided into induction, consolidation with CNS prophylaxis and maintenance phase.

In the management of R/R B-lineage ALL, the goal of treatment is generally to achieve good remission with low MRD, often with the aim of undergoing allo-HSCT. Choice of therapy is dependent on Philadelphia chromosome (Ph) status. For Ph-negative (Ph-) patients, immunotherapy is recommended. Ph+ BCP-ALL is rare in children, accounting for approximately 3-5% of cases. Expression of the BCR:ABL1 tyrosine kinase distinguishes Ph-positive (Ph+) ALL from other types of

ALL as it makes it vulnerable to treatment with a BCR:ABL1 TKI. According to the ESMO guideline (2023), TKI-immunotherapy with or without chemotherapy is recommended for these patients.

Following a first relapse, only about 40% of children can be successfully salvaged with intensive chemotherapy treatment followed by allo-HSCT. Therefore, new therapeutic approaches are urgently needed to overcome chemotherapy resistance and improve outcome.

### 2.1.2. About the product

Inotuzumab ozogamicin (InO, Besponsa) is an antibody-drug conjugate (ADC), with CD22-directed humanised immunoglobulin type G, subtype 4 antibody covalently linked to N-Ac-γ-calichaemicin dimethylhydrazide, a cytotoxic antitumor antibiotic, approved for adult patients with R/R BCP-ALL. InO causes cell death by inducing double-strand DNA breaks. 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 presently approved indication in the EU is for adult use:

*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)*

### 2.1.3. The development programme/compliance with CHMP guidance/scientific advice

On March 17th, 2023, the MAH submitted the Clinical Study Report (CSR) for study ITCC-059 for 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 previous type II variation EMEA/H/C/004119/II/0026, the MAH submitted updated results of Study ITCC-059 with additional safety information that were not available at the time of the previous Article 46 submission. Further, the MAH presented PK data from 6 paediatric patients included in study INO-Ped-ALL-1 that was used to support product information updates on PK. This variation led to updates of the SmPC sections 4.2, 4.8, 5.1 and 5.2.

### 2.1.4. General comments on compliance with GCP

The clinical trial was performed in accordance with GCP as claimed by the MAH.

## *2.2. Non-clinical aspects*

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

### 2.2.1. Ecotoxicity/environmental risk assessment

The company has provided justification for not providing environmental risk assessment studies with this extension of indication considering the provision of CHMP guidance EMEA/CHMP/SWP/444700 entitled, "Guideline on the Environmental fusk Assessment of Medicinal Products for Human Use" published 01 June 2006, which indicates that no environmental risk assessment studies are required if there is no increase in environmental exposure. No increased exposure is expected upon approval of this Type II variation to update paediatric data in the label with ITCC-059 study data. The justification from the company is considered acceptable.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

#### GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

| Protocol No. (Country) | Study Design and Objective | Treatment Groups | No. of participants (by Treatment Group) | Demographics (by Treatment Group) | Duration of Treatment | Study Initiation Date/Completion Date/Status | Link to Study Synopsis |
|---|---|---|---|---|---|---|---|
| **Phase I/II Study** | | | | | | | |
| ITCC-059 (WI203581) (Austria, Czech Republic, Denmark, France, Germany, Ireland, Israel, Italy, Spain, Sweden, Netherlands) | A Phase I/II Study of Inotuzumab Ozogamicin as a Single Agent and in Combination With Chemotherapy for Pediatric CD22-Positive Relapsed/Refractory Acute Lymphoblastic Leukemia<br>• Identify the optimal dose of InO administered IV either as monotherapy or in combination with chemotherapy for pediatric patients with R/R CD22 positive ALL<br>• To estimate the efficacy, safety, and tolerability of the selected RP2D of InO monotherapy, and to evaluate PK and PD in this patient population | Stratum 1A: single agent InO<br><br>Phase 2: single agent InO<br><br>Stratum 1B: InO + UKALL-R3 (+/- PEG-ASP) | Stratum 1A: n = 25<br><br>Phase 2 Cohort: n = 28<br><br>Stratum 1B: n = 30 patients | Stratum 1A: 68% males, median age 11 years<br><br>Phase 2: 67.9% males, median age 7.5 years<br><br>Stratum 1B: 63.3% males, median age 8.5 years | The median number of cycles initiated was 2 cycles, 2 cycles, 1 cycle in Stratum 1A, the Phase 2 Cohort, and Stratum 1B, respectively. | 19 Jan 2017/Not applicable/Ongoing with PCD on 12 Sep 2022 | Module 5.3.5.2 Study ITCC-059 CSR |
| **Phase I Study** | | | | | | | |
| INO-Ped-ALL-1 (WI235086) (Japan) | A Phase I study of Inotuzumab Ozogamicin as a Single Agent for | All patients were enrolled to Dose | n = 6 | 50% males | The medium number of cycles was 2.5. | 18 Oct 2018/18 Sep 2020/Completed | Module 5.3.5.4 Study INO-Ped-ALL-1 CSR |

| Protocol No. (Country) | Study Design and Objective | Treatment Groups | No. of participants (by Treatment Group) | Demographics (by Treatment Group) | Duration of Treatment | Study Initiation Date/Completion Date/Status | Link to Study Synopsis |
|---|---|---|---|---|---|---|---|
| | Pediatric Patients in Japan with Relapsed/Refractory CD22-Positive Acute Lymphoblastic Leukemia<br>• To assess safety and tolerability of InO in pediatric participants in Japan with R/R CD22 positive ALL in order to select the recommended clinical dose<br>• To evaluate the PK profile, overall safety profile, and the efficacy of InO in pediatric participants with R/R CD22 positive ALL | Level 1 (1.8 $mg/m^2$ InO per cycle with a fractionated dose regimen) | | 5 participants were ≥2 to <12 years, 1 participant was ≥12 years. | | | |
| Abbreviations: ALL = acute lymphoblastic leukemia; CD22 = cluster of differentiation-22; InO = Inotuzumab Ozogamicin; IV = intravenous; PEG-ASP = pegylated asparaginase; PCD = primary completion date; PD = pharmacodynamic(s); PK = pharmacokinetic(s); RP2D = recommended phase 2 dose; R/R = relapsed/refractory; UKALL-R3 = a historical clinical trial for relapsed and refractory ALL | | | | | | | |

## 2.3.2. Pharmacokinetics

No new PK data has been provided in the current application. The design and PK data from Study ITCC-059 (WI203581), which was a Phase 1/2, multi-centre, European, multi-cohort, open-label study in paediatric patients (≥1 and <18 years of age) with R/R CD22-positive ALL, have previously been described in EMEA/H/C/004119/P46/004 (https://www.ema.europa.eu/en/documents/variation-report/besponsa-h-c-004119-p46-004-epar-assessment-report_en.pdf ) and EMA/PAM/0000319860. The design and PK data from Study INO-Ped-ALL-1 (WI235086), which was a Phase 1, multi-centre, Japanese, open-label study in paediatric patients (≥1 and <18 years of age) with R/R CD22-positive ALL, have previously been described in EMEA/H/C/004119/II/0026 (https://www.ema.europa.eu/en/documents/variation-report/besponsa-h-c-004119-ii-0026-epar-assessment-report-variation_en.pdf).

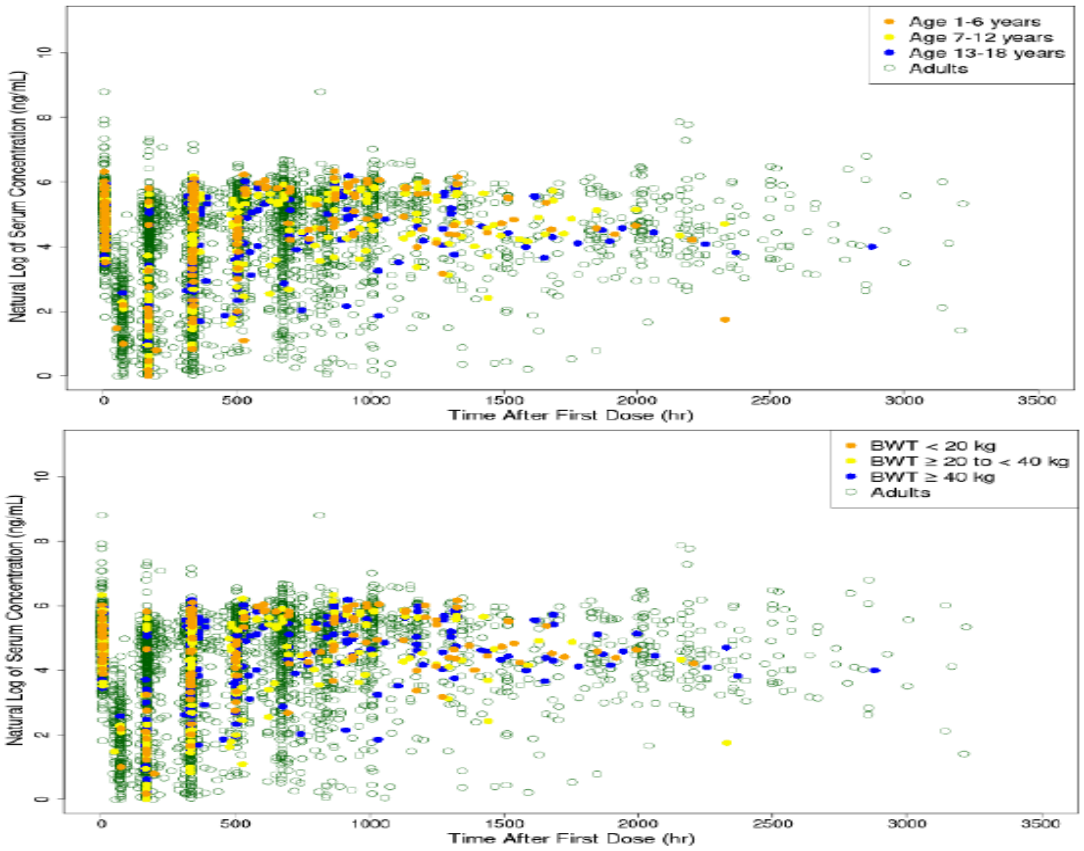
### *2.3.2.1. Population PK analysis*

The population PK analysis was conducted to characterise the PK of inotuzumab ozogamicin (InO) in paediatric patients with R/R CD22-positive ALL and to compare InO PK between adult and paediatric patients with R/R CD22-positive ALL.

**Data**

The dataset for the pooled analysis comprised 4580 serum concentrations from 392 patients treated with InO (59 paediatric patients with R/R CD22-positive ALL from studies WI203581 and WI235086, and 333 adult patients with R/R CD22-positive ALL from studies B1931022, B1931010, and B1931030). Of the 4580 observations, 138 (3.01%) were <LLOQ, and these observations were excluded from the analysis. The observed InO concentration-time profiles using time after first dose (Day 1) in ALL patients by age and body weight, respectively, are shown in Figure 1.

**Figure 1. Inotuzumab ozogamicin concentrations versus time after first dose in patients with relapsed or refractory acute lymphoblastic leukaemia by age and body weight, respectively.**




Among the 59 paediatric patients, the age range was 1 to 17 years, with a median age of 9 years, and the body weight range was 9.30 to 98.0 kg, with a median body weight of 29.1 kg. Among the 234 adult patients with ALL in studies B1931022 and B1931010, the body weight range was 30.9 to 154 kg, with a median body weight of 74.0 kg.

**Model**

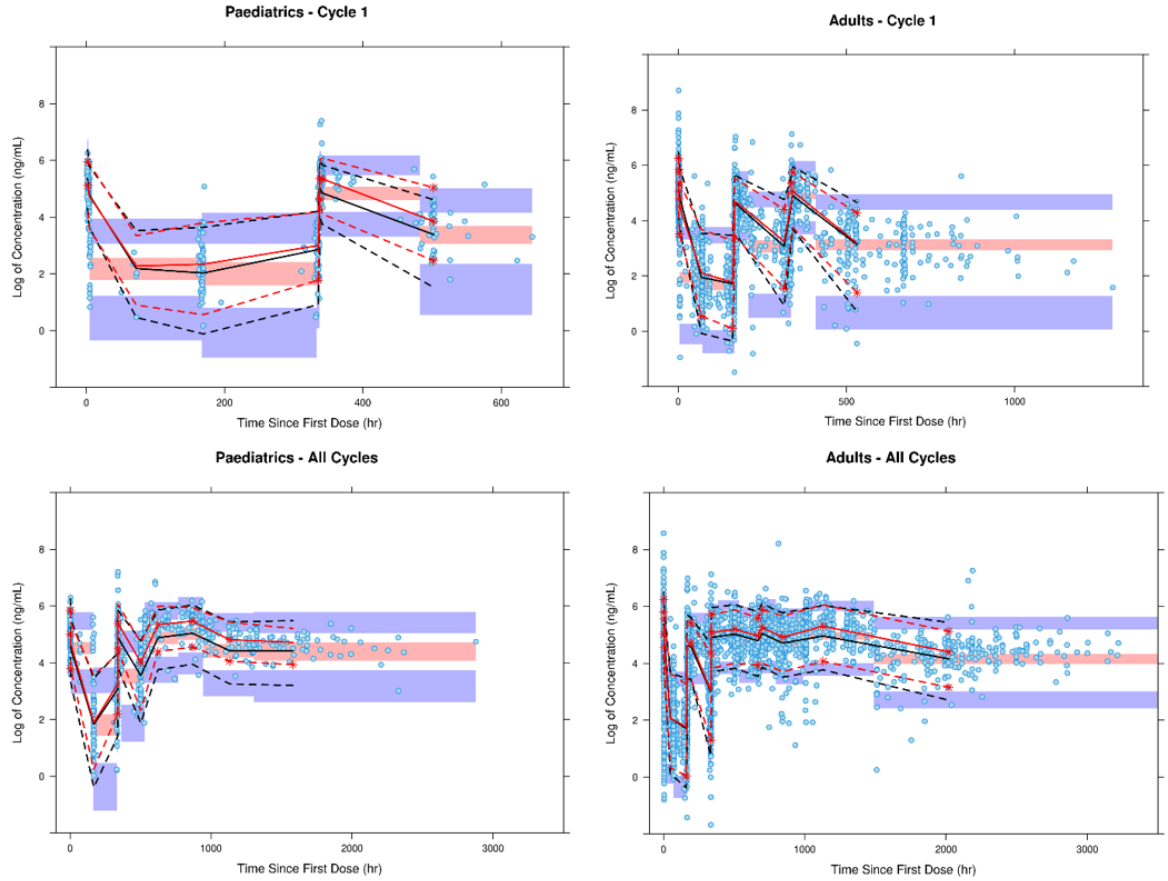
The analysis was conducted in Nonlinear Mixed Effects Modelling (NONMEM) v. 7.5.0, using Stochastic Approximation Expectation-Maximization (SAEM) followed by Importance Sampling (IMP) estimation algorithm. A previous model (PMAR-EQDD-B193e-DP4-1490), developed on data from adults with NHL or ALL, and paediatrics with ALL, was used as base model in this analysis. The base model was a 2-compartment model with both linear and time-dependent clearance. Covariates were added to the base model sequentially in a stepwise addition manner. The final model included the following covariates: baseline body surface area (BBSA) on linear clearance ($CL_1$), clearance associated with time-dependent clearance ($CL_2$), and volume of distribution in central compartment ($V_1$); and baseline percent of blasts in peripheral blood (BLSTPB) on decay coefficient associated with time-dependent clearance ($k_{des}$). Parameter estimates of the final population PK model are presented in Table 1. Prediction- and variability-corrected visual predictive checks (pvcVPC) of the final model stratified on adult and paediatric patients are presented in Figure 2, and pvcVPCs of the final model stratified on paediatric patients and body weight are presented in Figure 3.

**Table 1. Parameter estimates of the final population PK model.**

| | $OFV_{IMP}$: 458.035 | | | SIR Statistics | | | |
|---|---|---|---|---|---|---|---|
| Parameter | Value | RSE(%) | Shrinkage(%)[a] | Mean | RSE(%) | Median | 95% CI |
| $CL_1$ ($\theta_1$) [L/hr] | 0.0397 | 5.38 | - | 0.0396 | 4.68 | 0.0396 | (0.0358 - 0.0433) |
| $V_1$ ($\theta_2$) [L] | 5.59 | 3.10 | - | 5.60 | 2.84 | 5.60 | (5.28 - 5.91) |
| $CL_2$ ($\theta_3$) [L/hr] | 0.632 | 5.75 | - | 0.630 | 4.47 | 0.629 | (0.580 - 0.684) |
| $k_{des}$ ($\theta_4$) [$hr^{-1}$] | 0.00724 | 6.82 | - | 0.00720 | 5.51 | 0.00719 | (0.00647 - 0.00804) |
| Q ($\theta_5$) [L/hr] | 0.300 | 8.93 | - | 0.300 | 5.15 | 0.300 | (0.269 - 0.331) |
| $V_2$ ($\theta_6$) [L] | 11.2 | 9.66 | - | 11.3 | 4.65 | 11.2 | (10.3 - 12.3) |
| Proportional error ($\theta_7$) | 0.515 | 3.24 | 9.49 | 0.516 | 1.21 | 0.517 | (0.503 - 0.528) |
| BBSA effect $CL_1$ ($\theta_8$) | 1.78 | 12.1 | - | 1.81 | 10.8 | 1.81 | (1.44 - 2.20) |
| BBSA effect on $CL_2$ ($\theta_9$) | 1.19 | 13.2 | - | 1.20 | 12.1 | 1.19 | (0.909 - 1.46) |
| BLSTPB effect on $k_{des}$ ($\theta_{10}$) | -0.0353 | -23.7 | - | -0.0350 | 21.4 | -0.0349 | (-0.0503 - -0.0207) |
| BBSA effect on $V_1$ ($\theta_{11}$) | 1.62 | 6.50 | - | 1.62 | 6.52 | 1.61 | (1.42 - 1.83) |
| | Value | CV(%) | | | | | |
| $\omega^2_{CL_1}$ | 0.371 | 60.9 | 24.2 | 0.389 | 21.8 | 0.377 | (0.261 - 0.572) |
| $\omega_{CL_1}\omega_{V_1}$ | 0.192 | - | - | 0.193 | 16.9 | 0.192 | (0.138 - 0.260) |
| $\omega^2_{V_1}$ | 0.213 | 46.1 | 13.9 | 0.213 | 10.2 | 0.212 | (0.172 - 0.256) |
| $\omega_{CL_1}\omega_{CL_2}$ | 0.152 | - | - | 0.149 | 24.8 | 0.148 | (0.0767 - 0.225) |
| $\omega_{V_1}\omega_{CL_2}$ | 0.130 | - | - | 0.129 | 16.1 | 0.129 | (0.0905 - 0.172) |
| $\omega^2_{CL_2}$ | 0.409 | 63.9 | 16.9 | 0.422 | 12.6 | 0.419 | (0.326 - 0.527) |
| $\omega^2_{k_{des}}$ | 0.405 | 63.7 | 28.0 | 0.400 | 16.9 | 0.396 | (0.277 - 0.540) |

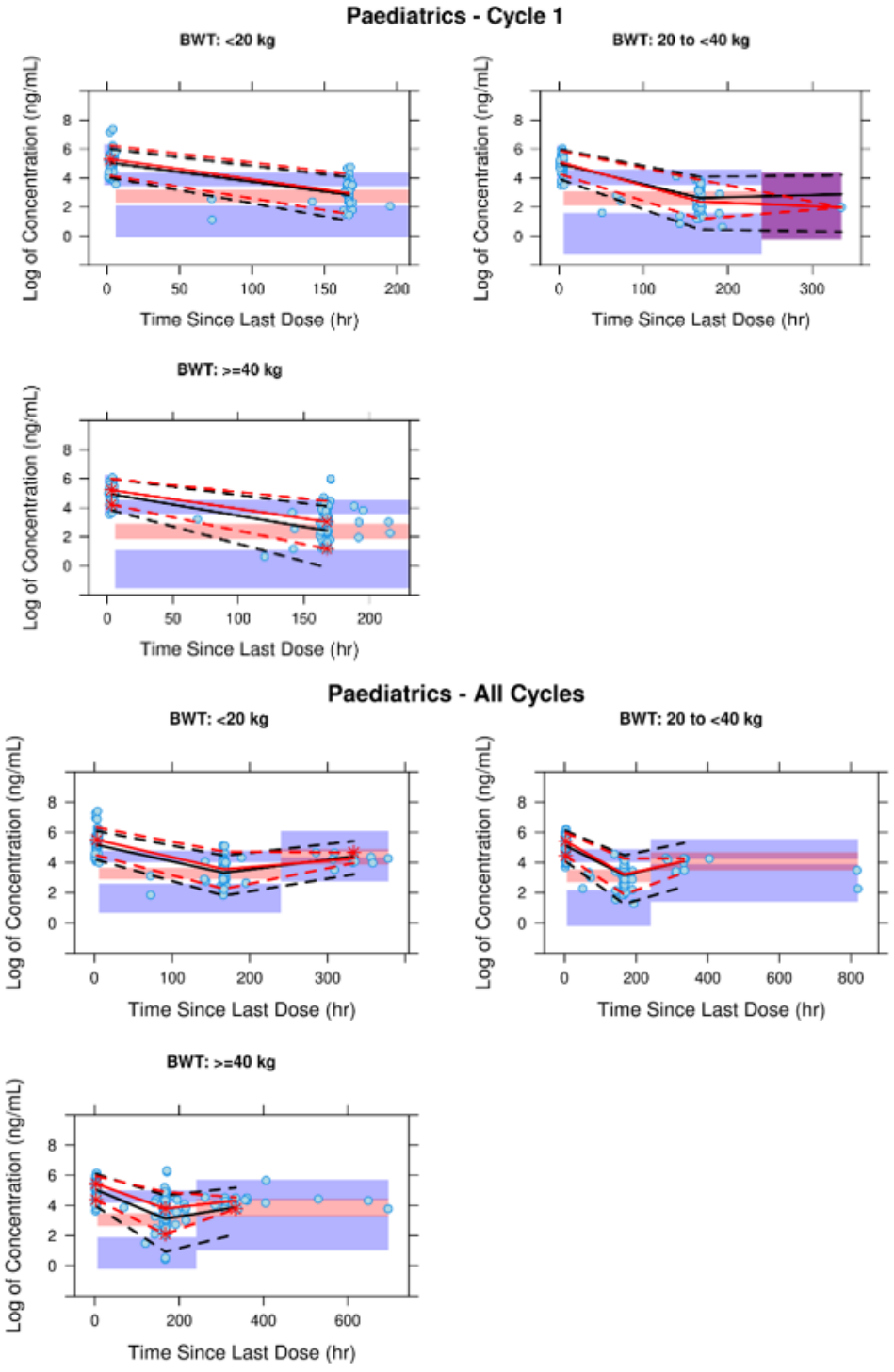
Item 33, repository artifact ID FI-60262650. Lines 1–2 substituted.
Abbreviations: BBSA=baseline body surface area; CI=confidence interval; BLSTPB=baseline percent of blasts in the peripheral blood; $CL_1$=linear clearance; $CL_2$=clearance associated with time-dependent clearance; CV=coefficient of variation; hr=hours; $k_{des}$=decay coefficient associated with time-dependent clearance; $OFV_{IMP}$=objective function value by Monte Carlo importance sampling estimation method; Q=intercompartment clearance; RSE=relative standard error; SIR=sampling-importance resampling; $V_1$=volume of distribution in central compartment; $V_2$=volume of distribution in peripheral compartment.
[a] Values are for $\eta$-shrinkage and $\varepsilon$-shrinkage estimates.

**Figure 2. Prediction- and variability-corrected visual predictive checks for the final population PK model in adult and paediatric patients with relapsed or refractory acute lymphoblastic leukaemia.**




Left-hand panels: paediatric patients; right-hand panels: adult patients; upper panels: Cycle 1; lower panels: all cycles. Blue circles represent the observed data, and the red lines represent the median (solid line), 5$^{th}$ percentile (dashed line), and 95$^{th}$ percentile (dashed line) of the observed data. The black lines represent the median (solid line), 5$^{th}$ percentile (dashed line), and 95$^{th}$ percentile (dashed line) of the simulated data. Shaded areas represent the 90% prediction interval of the simulated median (pink) and percentiles (blue), respectively. The red stars indicate bins where the observed median falls outside the simulated 90% prediction interval.

**Figure 3. Prediction- and variability-corrected visual predictive checks for the final population PK model in paediatric patients with relapsed or refractory acute lymphoblastic leukaemia, stratified on body weight and based on time since last dose.**



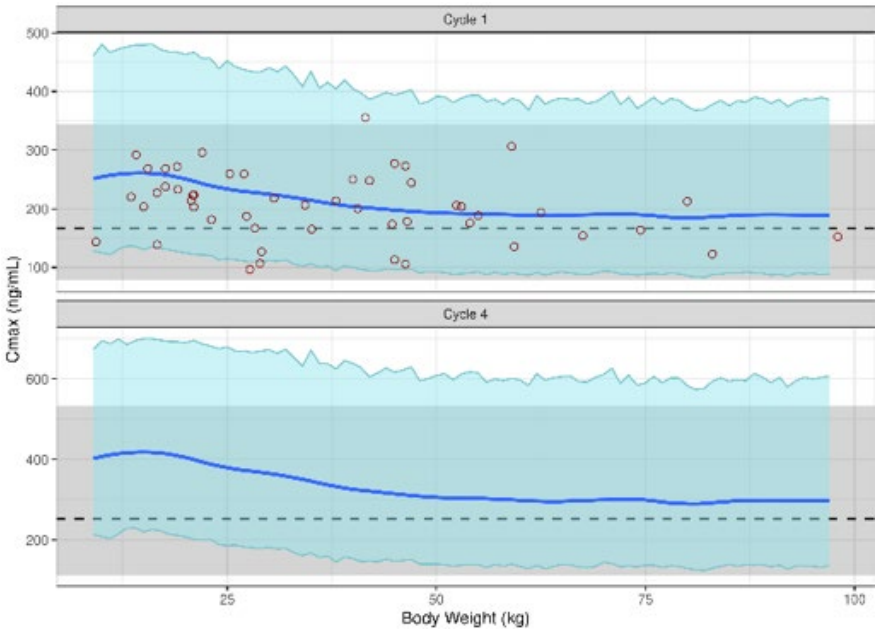

Upper panels: Cycle 1; lower panels: all cycles. Blue circles represent the observed data, and the red lines represent the median (solid line), 5$^{th}$ percentile (dashed line), and 95$^{th}$ percentile (dashed line) of the observed data. The black lines represent the median (solid line), 5$^{th}$ percentile (dashed line), and 95$^{th}$ percentile (dashed line) of the simulated data. Shaded areas represent the 90% prediction interval of the simulated median (pink) and percentiles (blue), respectively. The red stars indicate bins where the observed median falls outside the simulated 90% prediction interval.

**Simulations**

Inotuzumab ozogamicin maximum concentration ($C_{max}$), pre-dose concentration ($C_{min}$), and cumulative AUC during a treatment cycle (cAUC) were simulated for adult and paediatric patients with ALL using the final population PK model. A fixed dosing regimen of 1.8 mg/m$^2$/cycle of InO, administered as fractionated doses of 0.8 mg/m$^2$ on Day 1 and 0.5 mg/m$^2$ on Days 8 and 15 for the first 21 days and then every 28 days, were simulated for 4 continuous cycles. A virtual paediatric population was utilised, with body weights sampled from the observed baseline body weight range maintaining realistic covariate distributions and correlations. Adult simulations were performed using observed covariates from the reference adult population. The paediatric virtual population consisted of 1,780 unique sets of covariates, while the adult population consisted of 333 sets of covariates. For each set of covariates, 300 replicates of individual parameter estimates were sampled from the between subject variabilities, i.e. there were in total 534,000 simulated PK profiles for the paediatric population and 99,900 simulated PK profiles for the adult population.

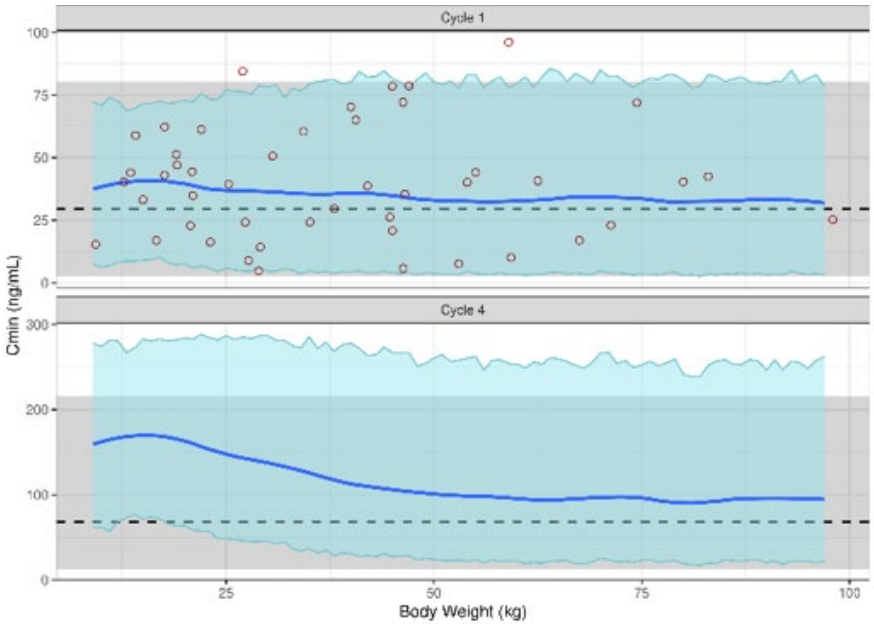
Simulated PK exposure ($C_{max}$, $C_{min}$, and cAUC) in Cycle 1 and Cycle 4 versus baseline body weight are shown in Figure 4 ($C_{max}$), Figure 5 ($C_{min}$), and Figure 6 (cAUC). The adult exposure ranges are presented as reference bands (5$^{th}$ to 95$^{th}$ percentiles with median) and observed paediatric concentrations or individual predictions are overlaid where available. As there was a lack of observed paediatric PK data in Cycle 4, with only one pre-dose concentration recorded, overlays for Cycle 4 are not shown.

**Figure 4. Simulated $C_{max}$ by body weight in paediatric patients (1.8 mg/m²/cycle).**



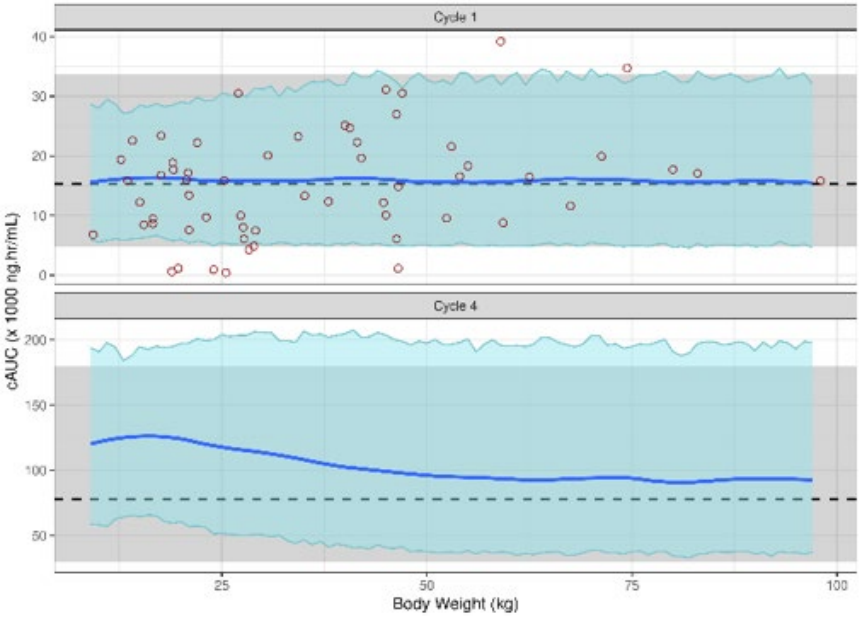

Upper panel: Cycle 1; lower panel: Cycle 4. Abbreviation: $C_{max}$ = maximum concentration (end of infusion). The dashed line and grey shaded areas represent the predicted median and 5$^{th}$ – 95$^{th}$ percentile for adult references. The blue solid line and corresponding shaded regions indicate the predicted median and 5$^{th}$ – 95$^{th}$ percentile for paediatric patients. Red circles depict the individual observed/predicted values for paediatric patients, which are available for Cycle 1 only.

**Figure 5. Simulated $C_{min}$ by body weight in paediatric patients (1.8 mg/m²/cycle).**




Upper panel: Cycle 1; lower panel: Cycle 4. Abbreviation: $C_{min}$ = pre-dose sample taken prior to the next dose. The dashed line and grey shaded areas represent the predicted median and 5th – 95th percentile for adult references. The blue solid line and corresponding shaded regions indicate the predicted median and 5th – 95th percentile for paediatric patients. Red circles depict the individual observed/predicted values for paediatric patients, which are available for Cycle 1 only.

**Figure 6. Simulated cAUC by body weight in paediatric patients (1.8 mg/m²/cycle).**




Upper panel: Cycle 1; lower panel: Cycle 4. Abbreviation: cAUC = cumulative area under the concentration-time curve. The dashed line and grey shaded areas represent the predicted median and 5th – 95th percentile for adult references. The blue solid line and corresponding shaded regions indicate the predicted median and 5th – 95th percentile for paediatric patients. Red circles depict the individual predicted values for paediatric patients, which are available for Cycle 1 only.

## 2.3.3. Pharmacodynamics

### *Mechanism of action*

Inotuzumab ozogamicin is an ADC composed of a CD22-directed monoclonal antibody that is covalently linked to N-acetyl-gamma-calicheamicin dimethylhydrazide. Inotuzumab is a humanised immunoglobulin class G subtype 4 (IgG4) antibody that specifically recognises human CD22. The small molecule, N-acetyl-gamma-calicheamicin, is a cytotoxic product.

N-acetyl-gamma-calicheamicin is covalently attached to the antibody via an acid-cleavable linker. Nonclinical data suggest that the anticancer activity of inotuzumab ozogamicin is due to the binding of the ADC to CD22-expressing tumour cells, followed by internalisation of the ADC-CD22 complex, and the intracellular release of N-acetyl-gamma-calicheamicin dimethylhydrazide via hydrolytic cleavage of the linker. Activation of N-acetyl-gamma-calicheamicin dimethylhydrazide induces double- stranded DNA breaks, subsequently inducing cell cycle arrest and apoptotic cell death.

## 2.3.4. Discussion on clinical pharmacology

No new PK data has been provided in the current application. A new population PK analysis was intended to support comparable exposure in paediatric patients (≥1 and <18 years of age) as in adult patients. Given the limited data in paediatric patients, especially concerning the safety database, ascertaining roughly similar exposure in paediatric patients (across age and body weight) and adult patients is considered pivotal.

Based on observed InO concentrations across time after first dose, paediatric ALL patients appear to have concentrations within the range of those observed in adult ALL patients. However, potential differences in exposure may be concealed by dose interruptions, dosing delays, and/or dose reductions due to safety and tolerability issues.

The population PK model was developed on data from paediatric and adult patients with ALL. The final model was a 2-compartment model with both linear and time-dependent clearance. Potential covariate effects were evaluated on parameters for which a between-subject variability was estimated. Between-subject variabilities were estimated for linear clearance ($CL_1$), clearance associated with time-dependent clearance ($CL_2$), volume of distribution in central compartment ($V_1$), and decay coefficient associated with time-dependent clearance ($k_{des}$). Body surface area (BSA) at baseline was identified as a covariate on $CL_1$, $CL_2$, and $V_1$, with separately estimated effects on these parameters. Given that paediatric patients contribute only 13% of the PK observations included in the analysis, estimated covariate effects are driven mainly by data in adults. As a sensitivity analysis, the MAH investigated alternative models with body weight as covariate on clearance and distribution parameters ($CL_1$, $CL_2$, $k_{des}$, $V_1$, inter-compartmental clearance (Q), and volume of distribution in peripheral compartment ($V_2$)), both with estimated effects and with fixed allometric scaling. The estimates of the structural PK parameters were broadly consistent across models, and diagnostic plots did not indicate any major differences in model fit between the models (not shown).

The pvcVPCs using 'time since first dose' on the x-axis reveals an underprediction of concentrations in later treatment cycles, both for paediatric and adult patients. This may be due to informative drop-out not being handled in the model. Patients who achieved a complete remission (CR), or complete remission with incomplete haematological recovery (CRi), proceeded to haematopoietic stem cell transplant (HSCT) after 2 (maximum 3) treatment cycles. Given that both adult and paediatric data are underpredicted to a similar extent, a comparison of simulated exposures in later treatment cycles is still considered relevant; however, the focus should be on the exposure in Cycle 1. The final model provides an adequate description of data in Cycle 1, both for paediatric and adult patients, and both

when using 'time since first dose' and 'time since last dose' on the x-axis. The pvcVPCs stratified on age (not shown) and body weight, respectively, do not indicate any relevant model misspecification in younger/smaller children compared to older/larger children. The final model is hence considered appropriate for simulation of PK exposure across body weight in paediatric and adult ALL patients.

The MAH has provided simulations of PK exposure ($C_{max}$, $C_{min}$, and cAUC) in Cycle 1 and Cycle 4 versus baseline body weight. Based on the simulations from the final population PK model, the proposed dosing regimen provides a similar cAUC in Cycle 1 for paediatric patients across body weight, compared to that achieved with the recommended dosing regimen in adult patients. Simulations from the alternative models (not shown), with body weight as covariate, indicate that cAUC in Cycle 1 may be increased in paediatric patients with low body weight (<20 kg) compared to older children and adults. However, the individual (post-hoc) predictions of cAUC for the paediatric patients are similar across models, and a lower dose to paediatric patients with low body weight is hence not supported by the data at hand.

Based on the simulations from the final population PK model, the proposed dosing regimen provides a higher Cmax in paediatric patients with low body weight (<35 kg), compared to that achieved with the recommended dosing regimen in adult patients. This finding is also supported by the simulations from the alternative models (not shown). Given that InO is known to prolong the QT interval, the increase of Cmax increases the risk of QT prolongation. Since Besponsa is administered as an IV infusion, Cmax will decrease with an increased time of infusion. To mitigate the risk of QT prolongation, the time of infusion was increased to 1.5 hours in paediatric patients with a body weight <35 kg. Relevant information on PK exposure in the paediatric population and the necessity to increase the time of infusion in paediatric patients weighing <35 kg has been implemented in sections 5.2 and 4.2 of the SmPC, respectively.

Exposure-response analyses have been conducted (not shown) for key efficacy endpoints (CR/CRi/CRp and MRD-negativity) and safety endpoints (neutropenia grade ≥3, thrombocytopenia grade ≥3, elevated ALT grade ≥3, elevated AST grade ≥3, VOD/SOS, and hepatic events) using data from 59 paediatric patients with R/R ALL treated with InO in studies WI203581 and WI235086. Further analyses have also been conducted using data from paediatric and adult patients with R/R ALL treated with InO in studies WI203581, WI235086, B1931022, B1931010, and B1931030. A narrow exposure range, in combination with dose interruptions, dosing delays, and dose reductions following safety and tolerability issues, renders these analyses uninformative. They are hence not further described.

### 2.3.5. Conclusions on clinical pharmacology

Given the limited data in paediatric patients, especially concerning the safety database, evidence of roughly similar PK exposure in paediatric and adult patients with ALL is considered pivotal. The MAH has developed a population PK model deemed appropriate for simulation of PK exposure across body weight in paediatric and adult ALL patients. Overall, simulations from the population PK model support the proposed dosing regimen for paediatric patients; however, an elevated $C_{max}$ is expected in paediatric patients with low body weight (<35 kg). To mitigate the risk of QT prolongation, the recommended time of infusion is increased to 1.5 hours in paediatric patients with a body weight <35 kg (See section 4.2 of the SmPC).

## *2.4. Clinical efficacy*

### 2.4.1. Main study

**ITCC-059 (WI203581)**

**Title of Study:** A Phase I/II Study of Inotuzumab Ozogamicin as a Single Agent and in Combination With Chemotherapy for Pediatric CD22-Positive Relapsed/Refractory Acute Lymphoblastic Leukemia.

This study is part of an approved EU PIP (EMEA-001429-PIP01-13- M06).

## *Methods*

## Study participants

All participants enrolled in the ITCC-059 study were categorized in 3 cohorts. The present application is based on the Stratum 1A and Phase 2 cohorts. The Stratum 1B cohort is not assessed within this procedure.

| 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 | 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 |

## *Key inclusion criteria*

**Age**

- Patients must be ≥ 1 and < 18 years of age at the time of enrolment.
- *Additional criteria for Stratum 1A:* The first 3 BCP-ALL patients on dose level 1 must be aged 6 years to less than 18 years. Then at least 2 additional patients must be enrolled from age 1 year to less than 6 years at the same dose level. After this requirement is met, subsequent dose levels may enroll patients aged 1 year to less than 18 years. In case 2 younger patients are not yet recruited, patients aged 6 years up to less than 18 years may continue to be enrolled at dose level 1 until a maximum of 6 patients are enrolled.

**Diagnosis**

Patients must have either

- First relapse of BCP-ALL post allogeneic HSCT
- Second or greater relapsed or refractory BCP-ALL
- Refractory disease, defined as newly diagnosed patients who are induction failures after at least 2 previous regimens without attainment of remission, or patients with refractory first relapse after 1 previous reinduction regimen without attainment of remission.

**AND** must meet the following criteria:

- Patients must have M2 or M3 marrow status (≥ 5% blasts by morphology)

- The malignant clone needs to be CD22 surface antigen positive (in either the bone marrow or peripheral blood)
- The first 6 patients (Stratum 1A only) must have M3 marrow status (≥ 25% blasts by morphology).

**Performance Level and Life Expectancy**

- Karnofsky > 60% for patients > 16 years of age and Lansky > 60% for patients ≤ 16 years of age.
- Life expectancy of at least 6 weeks.

**Prior Therapy**

Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy defined as resolution of all such non-hematologic toxicities to ≤ Grade 2 prior to entering this study, with the exception of the authorized laboratory abnormalities as defined in the inclusion/exclusion criteria.

- Chemotherapy: At least 7 days must have passed since the completion of cytotoxic therapy, with the exception of hydroxyurea, 6-mercaptopurine and steroids which are permitted up until 48 hours prior to initiating protocol therapy. Patients may have received intrathecal therapy at any time prior to study entry. Patients who relapse while receiving maintenance chemotherapy will not be required to have a waiting period before enrolment onto this study.
- Radiotherapy: At least 28 days must have elapsed since any prior radiation therapy.
- Hematopoietic Stem Cell Transplant: At least 90 days must have elapsed since previous allo-HSCT. Patient must have no evidence of active graft vs. host disease. Patient must not be receiving GVHD prophylaxis or treatment.
- Hematopoietic growth factors: At least 7 days must have elapsed since the completion of therapy with GCSF or other growth factors at the time of enrollment. At least 14 days must have elapsed since the completion of therapy with pegfilgrastim (Neulasta).
- Immunotherapy: At least 42 days must have elapsed after the completion of any type of immunotherapy, e.g. chimeric antigen receptor T cell (CART) therapy. Patients may not have received prior CD22- targeted therapy (immunotoxin or CART therapy).
- Monoclonal antibodies: At least 3 half-lives of the antibody must have elapsed after the last dose of a monoclonal antibody (ie: Rituximab = 66 days, Epratuzumab = 69 days), with the exclusion of blinatumomab. Patients must have been off blinatumomab infusion for at least 14 days and all drug-related toxicity must have resolved to grade 2 or lower as outlined in the inclusion and exclusion criteria.
- Investigational drugs: At least 7 days or 5 drug half-lives (whichever is longer) must have elapsed since prior treatment with any experimental drug (with the exception of monoclonal antibodies) under investigation. No residual toxicities should be observed following previous treatment. An experimental drug is defined as any drug that is not approved and licensed for sale by the FDA for institutions in the United States, by the EMA for institutions in Europe, by Health Canada for institutions in Canada and by The Therapeutic Goods Administration for institutions in Australia.
- Prior calicheamicin exposure: Patient has not received prior treatment with a calicheamicin-conjugated antibody (e.g. gemtuzumab ozogamicin).

**Renal and Hepatic Function**

- Patient's serum creatinine must be ≤ 1.5 x institutional upper limit of normal (ULN) according to age. If the serum creatinine is greater than 1.5 x institutional ULN, the patient must have a radioisotope GFR ≥ 70mL/min/1.73 m2.
- Patient's AST and ALT must be ≤ 2.5 x institutional ULN.
- Patient's total bilirubin must be ≤ 1.5 x institutional ULN unless the patient has documented Gilbert syndrome

**Cardiac Function**

- Patient must have a shortening fraction ≥ 30% by echocardiogram or an ejection fraction > 50% by MUGA.

## *Key exclusion criteria*

**Isolated extramedullary relapse**

- Patients with isolated extramedullary disease are excluded (not applicable to lymphoma patients except for isolated CNS-relapse)

**VOD/SOS**

- Patients with any history of prior or ongoing Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome VOD/SOS per the modified Seattle criteria, or prior liver-failure are excluded

**Infection**

Patients will be excluded if they have a systemic fungal, bacterial, viral or other infection that is exhibiting ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics or other treatment.

**Other anti-cancer therapy**

- Patients will be excluded if there is a plan to administer non-protocol anti-cancer therapy including but not limited to chemotherapy, radiation therapy, or immunotherapy during the study period.
- Patients will be excluded if they have received prior treatment with anti-tumor vaccines.

**Other**

- Children with Down syndrome are excluded from participation in the dose finding parts (stratum 1A and 1B), but not in the single-agent phase 2 cohort.

## Treatments

All patients were intended to receive at least 1 cycle of induction therapy in the absence of progressive disease, dose limiting toxicities (DLT), or investigator/participant preference to withdraw. A cycle of therapy is defined as 3 doses of InO administered on Days 1, 8 and 15 (administered as an IV

infusion). 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 due to no loading dose requirement.

The starting dose of InO for Stratum 1A was 1.4 mg/m$^2$ IV total per cycle, administered as 0.6 mg/m$^2$ on Day 1 and 0.4 mg/m$^2$ on Days 8 and 15. Dose escalation in Stratum 1A followed a Rolling-6 design to establish the single-agent Recommended Phase 2 Dose (RP2D). Patients in the Phase 2 Cohort were treated at this RP2D (a starting dose of 1.8 mg/m$^2$ IV split into 3 doses).

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.

For eligible patients with ALL, all follow-up therapy, including allo-HSCT or CAR T-cell therapy, could be undertaken as per investigator discretion as consolidation of study treatment responses.

## Objectives

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

## Outcomes/endpoints

### Primary objective

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 (Phase 2 cohort).

- Endpoint: ORR, defined as the percentage of patients with CR/CRi/CRp, measured as best response during InO treatment.

### Secondary objectives

- To determine the ORR after cycle 1 (Stratum 1A and Phase 2 cohort, respectively)
- ORR in Stratum 1A
- To determine the safety and tolerability of InO as a single agent during Cycle 1 and the cumulative toxicities in patients receiving multiple cycles of InO

## Sample size

### Stratum 1A

Stratum 1A was planned to include a minimum of 6 evaluable patients. The maximum number of patients was estimated to approximately 36 evaluable patients.

### Phase 2

The statistical design for the phase 2 cohort was a single-stage design, based on the exact binomial distribution. Assuming that an overall response rate (ORR=CR/CRi/CRp) of 30% or less (H0 - null hypothesis) is not promising and an ORR of over 55% (Ha – alternative hypothesis) is expected, a total

of 25 patients evaluable for response would provide 80% power to reject H0 and a significance level of 0.05 (one-sided) when the true ORR is ≤30% (H0).

#### *2.4.1.1. Decision rules*

**Stratum 1A**

A Rolling-6 escalation design was used. Escalation/de-escalation decisions were based on the DLTs that occur during the first course of treatment for patients in Stratum 1A. The starting dose level was dose level 1. Dose level 2 was the minimum dose level considered during the InO monotherapy escalation phase.

The maximum tolerated dose (MTD) was the highest dose level tested at which 0/6 or 1/6 patients experiences DLT during course 1 with at least 2 patients experiencing DLT at the next higher dose. If the highest specified dose level (dose level 3) in this study was reached with 0/6 or 1/6 patients experiencing DLT during course 1 – i.e., the MTD had not been reached – this dose level was referred to as the highest tested dose (HTD), and this dose was taken forward as the recommended phase 2 dose (RP2D), unless modelling for cumulative toxicity (see below) suggests otherwise.

Enrolment during the dose escalation phase was restricted as follows:

a) The first 3 patients enrolled at the starting dose level was age 6 years or older.

b) At least 2 of the next 3 patients at the starting dose levels was < 6 years of age.

c) The first 6 patients enrolled during the escalation phase must have M3 marrow.

If de-escalation occured from the starting dose level, restrictions (a) and (b) above would remain in place for each subsequent dose level until an MTD was established or until the study was halted.

If the dose of InO was escalated above the starting dose level (i.e., 5 evaluable patients are treated with 0 DLT or 6 evaluable patients are treated with at most 1 DLT), restrictions (a) and (b) was relaxed for the remainder of the study.

Note that although the Rolling-6 design allowed escalation after 3 to 5 evaluable patients were treated with no DLTs, up to six patients was to be enrolled if necessary to ensure that if restriction (b) above had been satisfied.

The dose-escalation process to determine the MTD was guided by the safety evaluation during Course 1 in BCP-ALL Stratum 1A patients only. However, at the end of the dose escalation phase, a longitudinal dose-time-toxicity model proposed in Paoletti et al. (2015) was applied to help determine the RP2D by integrating data from all courses. This was applied at the end of the dose escalation phase in Stratum 1A to help evaluate the impact of cumulative toxicities across all courses and more accurately estimate the toxicity probability.

**Phase 2**

Decision rules were determined by the single-stage design in the Phase 2 part of the study. The drug is considered promising if there are ≥12 responders out of 25 response evaluable patients at the end of Phase 2 Part. However, at the time of the final analysis for Phase 2, the decision rule will depend on the exact number of patients in the Phase 2 Part based on the exact test. If the p-value is less than the pre-determined significance level, then the drug will be deemed promising.

## Randomisation

Not applicable as the study is a single-arm study.

## Blinding (masking)

Not applicable as the study is an open label study.

## Statistical methods

No specific statistical hypothesis tests was conducted in Phase I parts of the study.

**Primary Endpoints**

Statistical summaries of primary endpoints was reported for the entire study as appropriate. These included:

1. For Stratum 1A: DLTs during the first course of therapy.
2. For Phase 2 Cohort: Number and percentage of patients who responded to InO (OR defined as CR, CRi, CRp) measured as best response during InO treatment.

Occurrence of DLTs was summarised by dose level based on the dose escalation analysis set for Stratum 1A.

Adverse Events constituting DLTs was listed per dose level.

In Phase 2 Cohort, the primary endpoint was summarised in the **response evaluable analysis** set. Point estimates of ORR was calculated along with corresponding 2-sided 95% and 90% CIs using the exact method. The null hypotheses was tested at 1-sided alpha of 0.05 using an exact binomial test. The corresponding P-value was reported.

In addition, the frequency (number and percentage) of participants with BOR by BICR in the following response categories was summarized: CR, CRi, CRp, PR, SD, PD, ID and not evaluable (NE).

**Secondary Endpoints**

Statistical summaries of secondary endpoints was reported for the entire study as appropriate. The results was presented by phase and stratum, and by dose level within Stratum 1A and Stratum 1B, unless otherwise specified.

*Efficacy*

The analyses was performed in **Full Analysis Set** by phase/stratum and by dose level.

- OR after first course of therapy: the frequency (number and percentage) of participants with BOR by BICR in the following response categories was summarised: CR, CRi, CRp, PR, SD, PD, ID and not evaluable (NE). The frequency (number and percentage) of participants achieving OR (CR, CRi or CRp) will also be summarised, 95% CI for ORR was provided based on exact method.
- OR after the end of study therapy was analysed in the same way as OR after first course of therapy.
- MRD: the number and percentage of participants with specific MRD-levels ($<10^{-2}$, $10^{-3}$, $10^{-4}$ and $10^{-5}$) and of negative MRD ($<10^{-4}$) among participants achieving an OR after course 1 as well as best response during subsequent therapy was summarised. In addition, the number and percentage of participants with MRD negative CR/CRi/CRp will also be summarised in the Full Analysis Set. The 95% CIs will also be provided.
- The number of patients who proceed to HSCT or CAR-T cell therapy after treatment with InO

- DOR: defined as the time between achieving response (CR, CRi or CRp) after starting study treatment and documented relapse or death. Patients without an event at the end of follow-up are censored at the last disease assessment date. The analysis will only include participants with CR/CRi/CRp. DOR was estimated using the Kaplan-Meier method and displayed graphically where appropriate. Patients are not censored at the time of subsequent HSCT.
- EFS: defined as the time between start of study treatment and first event including failure to achieve CR/CRp/CRi (calculated as an event on day 0), relapse, death of any cause and second malignancies. Participants without an event at the end of follow- up was censored at the last disease assessment date. Participants without a post- treatment disease assessment was censored at the first dose date.
- EFS was analysed using the Kaplan-Meier method and displayed graphically where appropriate. Median EFS was presented with 2-sided 95% CI. In addition, the probability of being event-free at 6 months, 12 months, 24 months was presented together with the 95% CIs.
- OS: defined as the time between start of study treatment and death. Patients not known to have died was censored at the last known alive date. OS was analysed using the Kaplan-Meier method and displayed graphically where appropriate. Median OS was presented with 2-sided 95% CI. The survival rate and corresponding 95% CI at clinically meaningful timepoints will also be provided.
- The cumulative incidence of non-response or relapse (CIR) is defined as the cumulative probability of non-response or relapse, with time calculated between start of study treatment and relapse, accounting for competing events, and with non-responders included as an event on day 0. Non-relapse death is considered a competing event. The cumulative incidence and its standard error was estimated using Gray's method.

### *Results*

## Participant flow

| | 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** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| | | | | |
| Disposition phase: End of Treatment | | | | |
| Discontinued | 12 (100.0) | 13 (100.0) | 25 (100.0) | 28 (100.0) |
| Reason for discontinuation | | | | |
| Proceeding to allogeneic HSCT | 3 (25.0) | 2 ( 15.4) | 5 ( 20.0) | 12 ( 42.9) |
| Dose limiting toxicity | 1 ( 8.3) | 3 ( 23.1) | 4 ( 16.0) | 1 ( 3.6) |
| M3 marrow any time after the completion of course 1 of therapy | 2 ( 16.7) | 1 ( 7.7) | 3 ( 12.0) | 2 ( 7.1) |
| Patient is not M1 after the completion of course 2 or later | 2 ( 16.7) | 0 | 2 ( 8.0) | 0 |
| progressive disease as defined in appendix 2 | 0 | 0 | 0 | 1 ( 3.6) |
| Patient/parent withdrawal or refusal | 0 | 0 | 0 | 1 ( 3.6) |

| | | | | |
|---|---|---|---|---|
| Investigator determination | 1 ( 8.3) | 2 ( 15.4) | 3 ( 12.0) | 2 ( 7.1) |
| Death | 0 | 0 | 0 | 1 ( 3.6) |
| Lost to follow-Up | 0 | 0 | 0 | 1 ( 3.6) |
| Other | 3 ( 25.0) | 5 ( 38.5) | 8 ( 32.0) | 7 ( 25.0) |
| Disposition phase: End of Study | | | | |
| Discontinued | 12 (100.0) | 13 (100.0) | 25 (100.0) | 20 ( 71.4) |
| Reason for discontinuation | | | | |
| Patient has completed protocol treatment and the required follow-up period | 1 ( 8.3) | 5 ( 38.5) | 6 ( 24.0) | 1 ( 3.6) |
| Death | 11 (91.7) | 7 (53.8) | 18 (72.0) | 17 (60.7) |
| Lost to follow-Up | 0 | 1 (7.7) | 1 (4.0) | 2 (7.1) |

## Recruitment

This study was initiated on 19 January 2017 and used different data cut-offs for the cohorts: 30 September 2022 for Stratum 1A and 7 October 2022 for Phase 2. A total of 53 participants were enrolled at 22 centres in 11 countries.

## Conduct of the study

Four protocol amendments were done during the study and amendments 2 and 3 are considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Summaries of key amendments are presented below.

**Amendment 3 (issued on 31 August 2019):**

- The platelet count criteria to proceed to subsequent cycles and the hematologic DLT definition were updated based on observations from Stratum 1A.
- PK sampling time-points were optimized according to preliminary paediatric patients PK analysis.

**Amendment 2 (issued on 31 August 2018):**

- Phase 1 study design was amended to allow additional patients to be enrolled in DL1, based on the observed DLTs at DL2, and to better define the RP2D for Stratum 1A.
- The design for the Phase 2 study was modified to a single-stage design rather than a 2-stage design, and the sample size was reduced.
- InO was approved by EMA and FDA for BCP-ALL in adults. Safety information was updated. The number of cycles of InO was limited for patients who were MRD-negative and were to subsequently be transplanted, in line with the SmPC.
- Dose delay guidelines were added for transaminase or total bilirubin elevation during Cycle 1, and at the start of subsequent cycles. DLT definition was modified to include G4 ISR, and to exclude transaminases related to leukemic liver infiltration.

- Inclusion/exclusion criteria were modified to allow patients to be enrolled 90 days after HSCT, and to exclude patients who have already been treated with anti-tumour vaccines.
- For younger children, guidance for infusion of low volume doses was provided, PK sampling time points were reduced, and volume of blood samples collected was modified to comply with EMA blood volume regulations for children.

## Baseline data

**Table 2. Demographic and Baseline Characteristics - Full Analysis Set**

| | Stratum 1A (N=25) n (%) | Phase 2 (N=28) n (%) | Stratum 1B (N=30) n (%) |
|---|---|---|---|
| Age (Years) | | | |
| 1 to <2 | 1 (4.0) | 1 (3.6) | 1 (3.3) |
| 2 to <6 | 1 (4.0) | 9 (32.1) | 4 (13.3) |
| 6 to <12 | 12 (48.0) | 8 (28.6) | 17 (56.7) |
| 12 to <18 | 11 (44.0) | 10 (35.7) | 8 (26.7) |
| Median (min, max) | 11.00 (1, 16) | 7.50 (1, 17) | 8.50 (1, 17) |
| Mean (SD) | 10.48 (3.98) | 8.50 (4.67) | 9.47 (4.34) |
| Gender, n (%) | | | |
| Male | 17 (68.0) | 19 (67.9) | 19 (63.3) |
| Female | 8 (32.0) | 9 (32.1) | 11 (36.7) |
| BSA ($m^2$) | | | |
| N | 25 | 28 | 30 |
| Median (min, max) | 1.22 (1, 2) | 0.99 (1, 2) | 1.08 (1, 2) |
| Mean (SD) | 1.25 (0.42) | 1.11 (0.42) | 1.13 (0.35) |
| Baseline WBC Count($10^9$/L) | | | |
| <100 | 25 (100.0) | 27 (96.4) | 30 (100.0) |
| >=100 | 0 | 1 (3.6) | 0 |
| N | 25 | 28 | 30 |
| Median (min, max) | 2.30 (0, 17) | 2.78 (1, 132) | 3.92 (1, 99) |
| Mean (SD) | 3.06 (3.54) | 10.00 (24.86) | 8.19 (18.17) |
| Lansky Score for age <=16 Years, n (%) | | | |
| n | 25 | 27 | 29 |
| <=60 | 1 (4.0) | 0 | 1 (3.3) |
| 70 | 9 (36.0) | 9 (32.1) | 2 (6.7) |
| 80 | 6 (24.0) | 4 (14.3) | 3 (10.0) |
| 90 | 5 (20.0) | 6 (21.4) | 11 (36.7) |
| 100 | 4 (16.0) | 8 (28.6) | 12 (40.0) |
| Karnofsky score for patients >16 years, n (%) | | | |
| n | 0 | 1 | 2 |
| <=60 | 0 | 0 | 0 |
| 70 | 0 | 1 (3.6) | 0 |
| 80 | 0 | 0 | 1 (3.3) |
| 90 | 0 | 0 | 1 (3.3) |
| 100 | 0 | 0 | 0 |
| Bone marrow blasts, n (%) | | | |
| ≥5- <25 | 3 (12.0) | 6 (21.4) | 7 (23.3) |
| ≥25 - <50 | 6 (24.0) | 5 (17.9) | 5 (16.7) |

| | Stratum 1A (N=25) n (%) | Phase 2 (N=28) n (%) | Stratum 1B (N=30) n (%) |
|---|---|---|---|
| ≥50 | 14 (56.0) | 17 (60.7) | 18 (60.0) |
| Peripheral blood blasts (x$10^6$/L), n (%) | | | |
| 0 | 1 (4.0) | 0 | 3 (10.0) |
| >0 - 1,000 | 15 (60.0) | 20 (71.4) | 14 (46.7) |
| >1,000 - 5,000 | 8 (32.0) | 6 (21.4) | 5 (16.7) |
| >5,000 - 10,000 | 0 | 0 | 1 (3.3) |
| > 10,000 | 0 | 2 (7.1) | 6 (20.0) |
| Not Reported | 1 (4.0) | 0 | 1 (3.3) |
| Median (min, max) | 329.5 (0, 2956) | 181.0 (1, 15433) | 217.0 (0, 77755) |
| Percentage PB CD22+ Blasts | | | |
| n | 24 | 28 | 28 |
| Median (min, max) | 10.95 (0, 70) | 6.50 (0, 84) | 14.55 (0, 93) |
| Mean (SD) | 20.46 (22.67) | 21.38 (25.46) | 23.30 (30.16) |
| ≥0 - <5 | 10 (40.0) | 13 (46.4) | 12 (40.0) |
| ≥5- <25 | 7 (28.0) | 4 (14.3) | 8 (26.7) |
| ≥25 | 7 (28.0) | 11 (39.3) | 8 (26.7) |
| Missing | 1 (4.0) | 0 | 2 (6.7) |
| Baseline PB Abs CD22 Count ($10^6$/L) | | | |
| n | 24 | 28 | 29 |
| Median (min, max) | 149.5 (0, 2950) | 170.0 (0, 15140) | 211.0 (0, 77211) |
| Mean (SD) | 729.6 (939.8) | 1481 (3468) | 5625 (14874) |
| 0 | 1 (4.0) | 1 (3.6) | 3 (10.0) |
| >0 - 1,000 | 15 (60.0) | 19 (67.9) | 14 (46.7) |
| >1,000 - 5,000 | 8 (32.0) | 6 (21.4) | 6 (20.0) |
| >5,000 - 10,000 | 0 | 0 | 1 (3.3) |
| > 10,000 | 0 | 2 (7.1) | 5 (16.7) |
| Missing | 1 (4.0) | 0 | 1 (3.3) |
| CD22+ expression MFI | | | |
| n | 23 | 28 | 28 |
| Median (min, max) | 2949 (505, 8370) | 2297 (479, 9619) | 1691 (359, 7003) |
| Mean (SD) | 309 (1996) | 2687 (2016) | 1943 (1419) |
| Baseline Diagnosis, n (%) | | | |
| first relapse of BCP-ALL post allogeneic HSCT | 7 (28.0) | 6 (21.4) | 1 (3.3) |
| refractory BCP-ALL | 5 (20.0) | 6 (21.4) | 8 (26.7) |
| second or greater relapsed BCP-ALL | 13 (52.0) | 16 (57.1) | 21 (70.0) |

Note: PB blast and CD22+ blast counts are shown from the most recent day prior to dosing where both a CD22 and overall blast count are available.

## Numbers analysed

| Population | Description |
|---|---|
| **Full Analysis Set** | The Full Analysis Set consists of all enrolled patients who received at least one dose of study therapy and was used for the primary analysis and the safety analysis. |

| | |
|---|---|
| **Dose Escalation Analysis Set, Stratum 1A** | The Dose Escalation Analysis Set (evaluable for establishing the maximum tolerated dose) for Stratum 1A includes all enrolled patients who receive at least one dose of study medication and are evaluable for the dose escalation phase. The Dose Escalation Analysis Set was used for establishing the MTD or RP2D in Stratum 1A.<br><br>A patient was considered evaluable for the dose escalation phase (Stratum 1A) if any of the following applies:<br><br>• The patient receives at least one dose of InO and experiences a DLT at any time during the first course of protocol therapy.<br><br>• The patient does not experience DLT during the first course of therapy, and receives at least 2 out of 3 doses of the prescribed dose (67%) of InO during that course.<br><br>A patient was considered not evaluable for the dose escalation phase (Stratum 1A), and was replaced as needed, if:<br><br>• The patient receives ≤1 out of 3 of the prescribed doses of InO during the first course for reasons not related to toxicity or intolerability (e.g. early progressive disease/logistical reasons/noncompliance, etc.), or for reasons possibly related to toxicity or intolerability not fulfilling the definition of a DLT as defined in Section 4.6 of the protocol (e.g. considered related to intrathecal therapy).<br><br>Note that patients who are not evaluable was replaced. |
| **Response Evaluable Analysis Set** | The Response Evaluable Analysis Set includes all subjects who receive at least one dose of InO and have completed a baseline disease assessment and at least one post-baseline disease assessment. The Response Evaluable Analysis Set was used to evaluate the endpoints for the efficacy profile.<br><br>Response evaluable analysis sets will be used for primary analysis in the Phase 2 part. |
| **PD Analysis Set** | The PD Analysis Set includes patients who were treated and had at least one of the pharmacodynamic parameters available. |
| **PK Analysis Set** | The PK Analysis Set includes all FAS patients who provide at least one PK sample of interest. |

**Table 3. Participant *Evaluation Groups (Protocol ITCC-059 (B193-WI203581))***

| | Stratum 1A | | | Phase 2 | | | | Stratum 1B | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1.4 mg/m² (N=12) n (%) | 1.8 mg/m² (N=13) n (%) | Total (N=25) n (%) | 1.8 mg/m² (N=30) n (%) | 0.8 mg/m² + mR3 (N=6) n (%) | 1.1 mg/m² + mR3 (N=4) n (%) | 1.1 mg/m² + amended mR3 (N=6) n (%) | 1.4 mg/m² + amended mR3 (N=3) n (%) | 1.8 mg/m² + amended mR3 (N=11) n (%) | Total (N=30) n (%) |
| Assigned to Treatment | 12 (48.0) | 13 (52.0) | 25 (100.0) | 30 (100.0) | 6 (20.0) | 4 (13.3) | 6 (20.0) | 3 (10.0) | 11 (36.7) | 30 (100.0) |
| Treated | 12 (48.0) | 13 (52.0) | 25 (100.0) | 28 (93.3) | 6 (20.0) | 4 (13.3) | 6 (20.0) | 3 (10.0) | 11 (36.7) | 30 (100.0) |
| Not Treated | 0 | 0 | 0 | 2 (6.7) | 0 | 0 | 0 | 0 | 0 | 0 |
| Full Analysis Set | 12 (48.0) | 13 (52.0) | 25 (100.0) | 28 (93.3) | 6 (20.0) | 4 (13.3) | 6 (20.0) | 3 (10.0) | 11 (36.7) | 30 (100.0) |
| Dose Escalation Analysis Set | 12 (48.0) | 11 (44.0) | 23 (92.0) | NA | 6 (20.0) | 4 (13.3) | 6 (20.0) | 3 (10.0) | 7 (23.3) | 26 (86.7) |
| Response Evaluable Analysis Set | NA | NA | NA | 28 (93.3) | NA | NA | NA | NA | NA | NA |
| PD Analysis Set | 12 (48.0) | 13 (52.0) | 25 (100.0) | 28 (93.3) | 6 (20.0) | 4 (13.3) | 6 (20.0) | 3 (10.0) | 11 (36.7) | 30 (100.0) |
| PK Analysis Set | 12 (48.0) | 13 (52.0) | 25 (100.0) | 28 (93.3) | 0 | 0 | 0 | 0 | 0 | 0 |

No participants received asparaginase during study therapy. mR3 = dexamethasone 20 mg/m2/d split in 2 doses (max dose 40 mg/d) on days 1-5 and days 15-19 + weekly vincristine x4 ; amended mR3 = same as R3 except dexamethasone dose was reduced by 50%. Treated: Participants who received at least 1 dose of Ino.
Full Analysis Set: Participants who received at least 1 dose of Ino.
Response Evaluable Analysis Set: Participants who receive at least one dose of Ino and have completed a baseline disease assessment and at least one post-baseline disease assessment.
PFIZER CONFIDENTIAL SDTM Creation: 22FEB2023 (16:03) Source Data: adsl Table Generation: 09MAR2023 (12:42)
(Data cutoff date - Stratum 1A: 30SEP2022 Phase2: 07OCT2022 and Stratum 1B: 21OCT2022) Output File: ./csr_cdisc2/ITCC_059_CSR2023/adsl_s002

## Outcomes and estimation

### 2.4.1.1.1. ORR in Phase 2 Cohort (primary endpoint)

**Table *4*. Best Overall Response and Response at the end of Cycle 1 - Phase 2**

| | Phase 2 1.8 mg/m² (N=28) n (%) |
|---|---|
| Best Response | |
| Complete remission (CR) | 18 (64.3) |
| Complete Response with insufficient platelet recovery (CRp) | 1 (3.6) |
| Complete Response without recovery of counts (CRi) | 3 (10.7) |
| Partial Response (PR) | 3 (10.7) |
| Non-response or Stable Disease (SD) | 1 (3.6) |
| Progressive disease (PD) | 2 (7.1) |
| Induction Death (ID) | 0 |
| Objective Response (CR+CRp+CRi) | 22 (78.6) |
| 95% Exact CI [1] | (59.0, 91.7) |
| 90% Exact CI [1] | (62.0, 90.2) |
| 1 sided p-value | <.0001 |
| Cycle 1 | |
| Complete remission (CR) | 12 (42.9) |
| Complete Response with insufficient platelet recovery (CRp) | 1 (3.6) |

| | Phase 2<br>1.8 mg/m² (N=28)<br>n (%) |
|---|---|
| Complete Response without recovery of counts (CRi) | 9 (32.1) |
| Partial Response (PR) | 3 (10.7) |
| Non-response or Stable Disease (SD) | 1 (3.6) |
| Progressive disease (PD) | 2 (7.1) |
| Induction Death (ID) | 0 |
| Objective Response (CR+CRp+CRi) | 22 (78.6) |
| 95% Exact CI [1] | (59.0, 91.7) |
| 90% Exact CI [1] | (62.0, 90.2) |

[1] CI Calculated using the exact (Clopper-Pearson) method based on binomial distribution.

#### 2.4.1.1.2. Cycle 1 Response in the Phase 2 Cohort

In the Phase 2 Cohort at the end of Cycle 1, 22 out of 28 participants achieved an objective response (CR: 12, CRp: 1, CRi: 9). The estimated ORR was 78.6% (95% CI: 59.0-91.7).

**Table 5. Best Overall Response and Response at the end of Cycle 1**

| | Stratum 1A | | | Phase 2 | Total |
|---|---|---|---|---|---|
| | 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 (%) | Total (N=53) n (%) |
| Best Response | | | | | |
| Complete remission (CR) | 9 (75.0) | 11 (84.6) | 20 (80.0) | 18 (64.3) | 38 (71.7) |
| Complete Response with insufficient platelet recovery (CRp) | 0 | 0 | 0 | 1 (3.6) | 1 (1.9) |
| Complete Response without recovery of counts (CRi) | 0 | 0 | 0 | 3 (10.7) | 3 (5.7) |
| Partial Response (PR) | 1 (8.3) | 0 | 1 (4.0) | 3 (10.7) | 4 (7.5) |
| Non-response or Stable Disease (SD) | 1 (8.3) | 1 (7.7) | 2 (8.0) | 1 (3.6) | 3 (5.7) |
| Progressive disease (PD) | 1 (8.3) | 0 | 1 (4.0) | 2 (7.1) | 3 (5.7) |
| Induction Death (ID) | 0 | 0 | 0 | 0 | 0 |
| Missing | 0 | 1 (7.7) | 1 (4.0) | 0 | 1 (1.9) |
| Objective Response (CR+CRp+CRi) | 9 (75.0) | 11 (84.6) | 20 (80.0) | 22 (78.6) | 42 (79.2) |

| | | | | | |
|---|---|---|---|---|---|
| 95% Exact CI [1] | (42.8, 94.5) | (54.6, 98.1) | (59.3, 93.2) | (59.0, 91.7) | (65.9, 89.2) |
| 90% Exact CI [1] | (47.3, 92.8) | (59.0, 97.2) | (62.5, 91.8) | (62.0, 90.2) | (68.0, 87.9) |
| Cycle 1 | | | | | |
| Complete remission (CR) | 6 (50.0) | 7 (53.8) | 13 (52.0) | 12 (42.9) | 25 (47.2) |
| Complete Response with insufficient platelet recovery (CRp) | 2 (16.7) | 0 | 2 (8.0) | 1 (3.6) | 3 (5.7) |
| Complete Response without recovery of counts (CRi) | 1 (8.3) | 4 (30.8) | 5 (20.0) | 9 (32.1) | 14 (26.4) |
| Partial Response (PR) | 1 (8.3) | 0 | 1 (4.0) | 3 (10.7) | 4 (7.5) |
| Non-response or Stable Disease (SD) | 1 (8.3) | 1 (7.7) | 2 (8.0) | 1 (3.6) | 3 (5.7) |
| Progressive disease (PD) | 1 (8.3) | 0 | 1 (4.0) | 2 (7.1) | 3 (5.7) |
| Missing | 0 | 1 (7.7) | 1 (4.0) | 0 | 1 (1.9) |
| Objective Response (CR+CRp+CRi) | 9 (75.0) | 11 (84.6) | 20 (80.0) | 22 (78.6) | 42 (79.2) |
| 95% Exact CI [1] | (42.8, 94.5) | (54.6, 98.1) | (59.3, 93.2) | (59.0, 91.7) | (65.9, 89.2) |
| 90% Exact CI [1] | (47.3, 92.8) | (59.0, 97.2) | (62.5, 91.8) | (62.0, 90.2) | (68.0, 87.9) |

[1] CI Calculated using the exact (Clopper-Pearson) method based on binomial distribution.

#### 2.4.1.1.3. ORR in Stratum 1A

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

At the end of Cycle 1, 20 out of 25 participants achieved an objective response (DL1: 6 CR + 2 CRp + 1 CRi; DL2: 7 CR + 4 CRi), for an ORR of 80.0% (95% CI: 59.3-93.2).

#### 2.4.1.1.4. ORR in Monotherapy

A total of 53 participants received InO monotherapy, and 42 out of 53 participants achieved an objective response (CR: 38; CRp: 1; CRi: 3), for an ORR of 79.2% (95% CI: 65.9-89.2).

At the end of Cycle 1, 42 out of 53 participants achieved an objective response (CR: 25; CRp: 3, CRi: 14), for an ORR of 79.2% (95% CI: 65.9-89.2).

#### 2.4.1.1.5. MRD

**Table 6. Summary of Minimal Residual Disease (MRD) Levels**

| | Stratum 1A | | | Phase 2 | Total |
|---|---|---|---|---|---|
| | 1.4 mg/m² (N = 12) | 1.8 mg/m² (N = 13) | Total (N = 25) | 1.8 mg/m² (N = 28) | (N = 53) |
| Participants with CR/CRi/CRp | 9 ( 75.0) | 11 ( 84.6) | 20 ( 80.0) | 22 ( 78.6) | 42 ( 79.2) |

| | | | | | |
|---|---|---|---|---|---|
| MRD Qualitative results based on flow cytometry[a] - n(%) (95% CI) | | | | | |
| Negative | 6 ( 66.7) (29.9, 92.5) | 10 ( 90.9) (58.7, 99.8) | 16 ( 80.0) (56.3, 94.3) | 22 (100.0) (84.6, 100.0) | 38 ( 90.5) (77.4, 97.3) |
| Positive | 3 ( 33.3) | 0 (0.0) | 3 ( 15.0) | 0 (0.0) | 3 ( 7.1) |
| Unknown | 0 (0.0) | 1 ( 9.1) | 1 ( 5.0) | 0 (0.0) | 1 ( 2.4) |
| MRD Qualitative results based on RQ-PCR[b] - n(%) (95% CI) | | | | | |
| Negative | 4 ( 44.4) (13.7, 78.8) | 9 ( 81.8) (48.2, 97.7) | 13 ( 65.0) (40.8, 84.6) | 19 ( 86.4) (65.1, 97.1) | 32 ( 76.2) (60.5, 87.9) |
| Positive | 4 ( 44.4) | 0 (0.0) | 4 ( 20.0) | 3 ( 13.6) | 7 ( 16.7) |
| Unknown | 1 ( 11.1) | 2 ( 18.2) | 3 ( 15.0) | 0 (0.0) | 3 ( 7.1) |
| Cycle 1 | | | | | |
| Participants with CR/CRi/CRp | 9 ( 75.0) | 11 ( 84.6) | 20 ( 80.0) | 22 ( 78.6) | 42 ( 79.2) |
| MRD Qualitative results based on flow cytometry[a] - n(%) (95% CI) | | | | | |
| Negative | 6 ( 66.7) (29.9, 92.5) | 8 ( 72.7) (39.0, 94.0) | 14 ( 70.0) (45.7, 88.1) | 18 ( 81.8) (59.7, 94.8) | 32 ( 76.2) (60.5, 87.9) |
| Positive | 2 ( 22.2) | 1 ( 9.1) | 3 ( 15.0) | 4 ( 18.2) | 7 ( 16.7) |
| Unknown | 1 ( 11.1) | 2 ( 18.2) | 3 ( 15.0) | 0 (0.0) | 3 ( 7.1) |
| MRD Qualitative results based on RQ-PCR[b] - n(%) (95% CI) | | | | | |
| Negative | 3 ( 33.3) (7.5, 70.1) | 8 ( 72.7) (39.0, 94.0) | 11 ( 55.0) (31.5, 76.9) | 15 ( 68.2) (45.1, 86.1) | 26 ( 61.9) (45.6, 76.4) |
| Positive | 4 ( 44.4) | 1 ( 9.1) | 5 ( 25.0) | 7 ( 31.8) | 12 ( 28.6) |
| Unknown | 2 ( 22.2) | 2 ( 18.2) | 4 ( 20.0) | 0 (0.0) | 4 ( 9.5) |

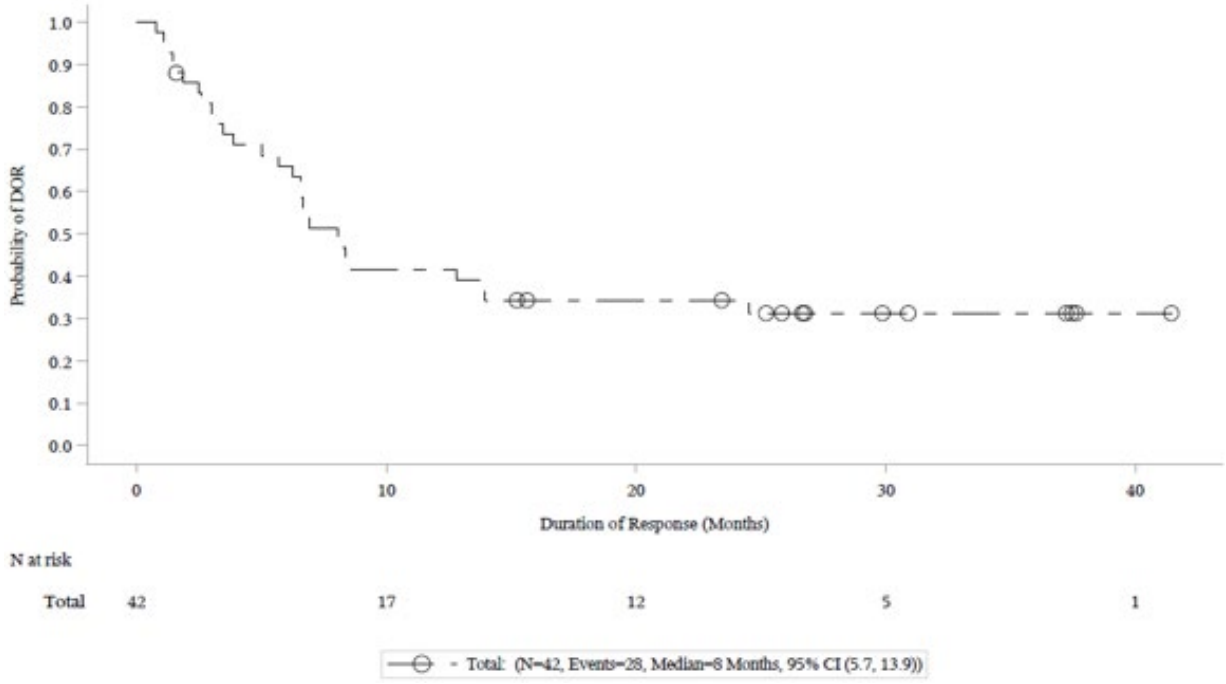
MRD negativity is defined as leukemic blasts < 0.01% by flow cytometry. MRD negativity is defined as leukemic blasts < $1x10^{-4}$ by RQ-PCR. Note:The 95% CI was calculated based on exact method.

#### 2.4.1.1.6. DoR

InO Monotherapy (Stratum 1A and Phase 2 Monotherapy Cohort):

Of the 42 participants who achieved CR/CRi/CRp, 28 (66.7%) participants had subsequent events, of which 19 events were relapse and 9 were death. The median DoR was 8.0 months (95% CI: 5.7-13.9).

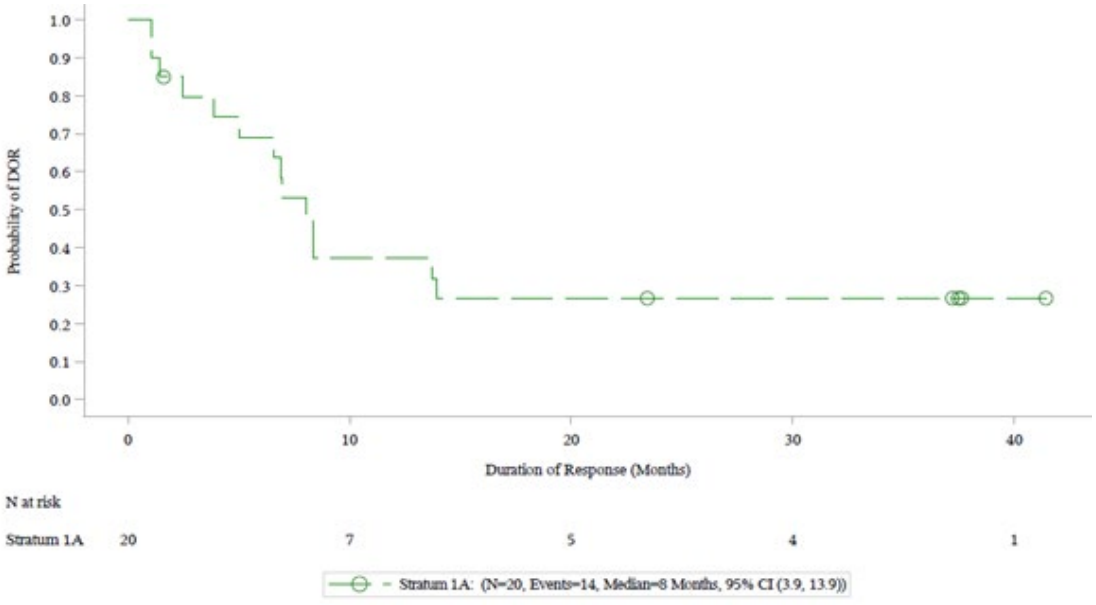
**Figure 7. Kaplan Meier Plot of Duration of Response: InO monotherapy (Stratum 1A and Phase 2 Cohort)**




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).

**Figure 8. Kaplan Meier Plot of Duration of Response: Stratum 1A**




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).

Patients were not censored at the time of subsequent HSCT. For completeness, the MAH has provided additional, DoR analyses. One with censoring for HSCT and one with censoring for HSCT and CAR-T (see below). The median duration of complete response (DoCR defined as the time between achieving complete response after starting study treatment and documented relapse or death is of 10.7 (95% CI: 3.0, NE)

**Figure 9. Kaplan Meier Plot of Duration of Response: Phase 2 Cohort**

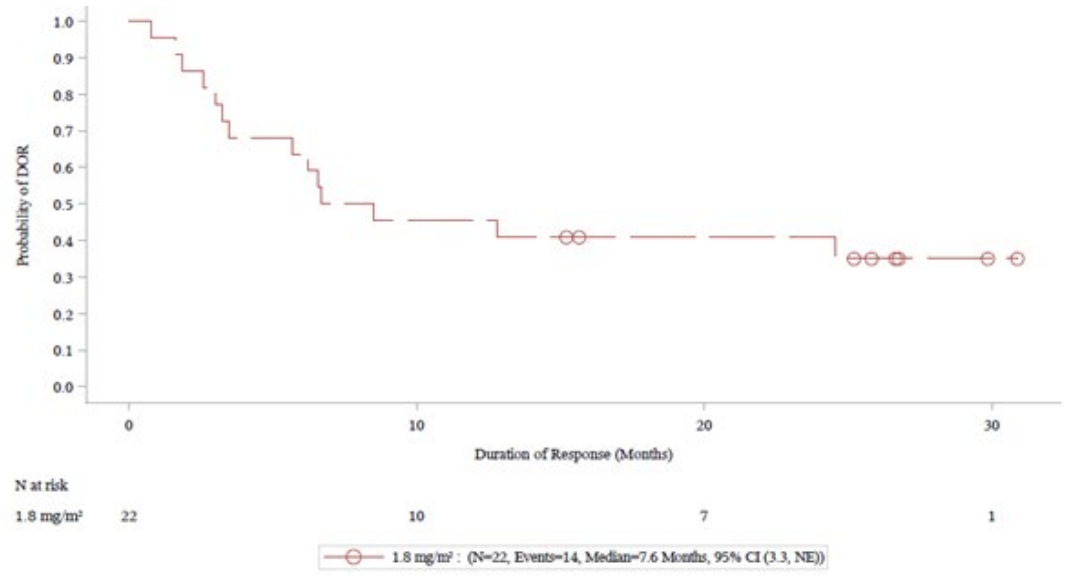



**Figure 10. KM Plot for DoR with Censored Stem Cell Transplant – Full Analysis Set (Protocol ITCC-059, Phase 2 Cohort)**

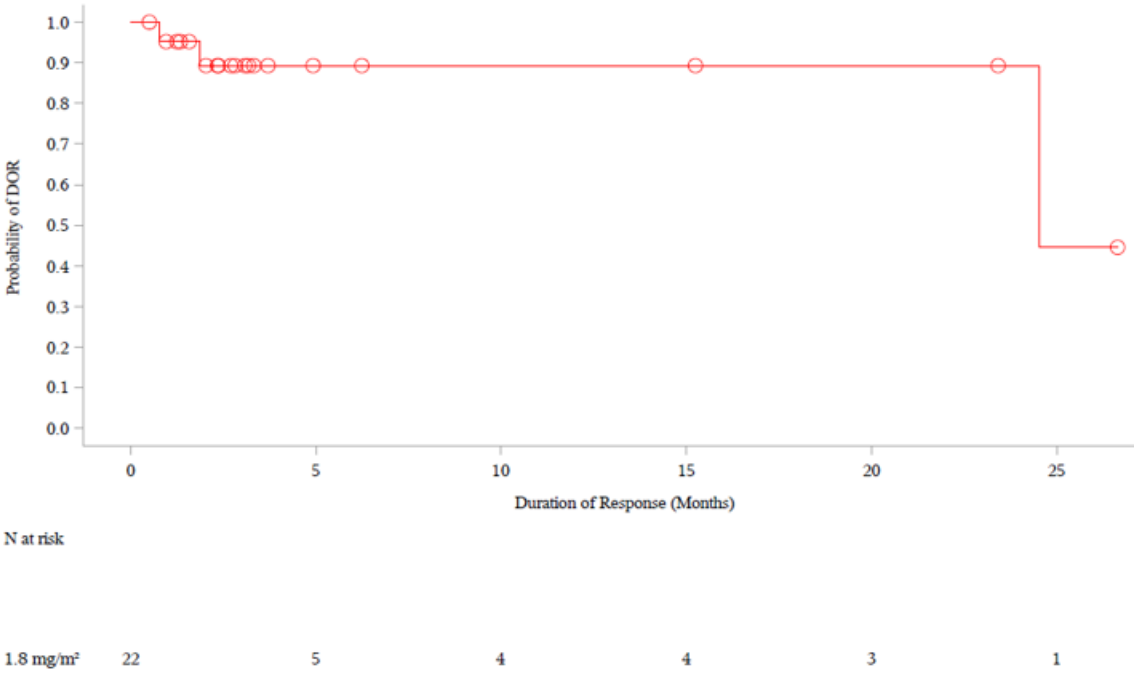
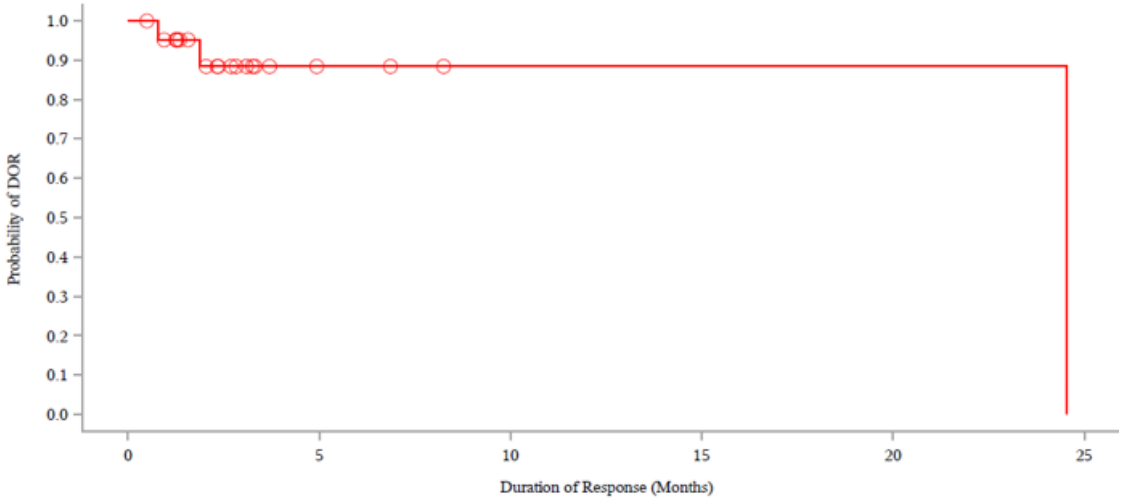


**Figure 11. KM Plot for** *DoR with Censored Stem Cell Transplant and CAR-T – Full Analysis Set (Protocol ITCC-059, Phase 2 Cohort)*




N at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| 1.8 mg/m² | 22 | 3 | 1 | 1 | 1 | 0 |

#### 2.4.1.1.7. HSCT and CAR T-cell Therapy Rate

**Table 7. Summary** of Post-Treatment HSCT

| | 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 received HSCT Post InO treatment, n(%) | 3 ( 25.0) | 5 ( 38.5) | 8 ( 32.0) | 18 ( 64.3) |
| Number of Participants who received HSCT after achieving CR/CRi/CRp, n(%) | 3 ( 25.0) | 5 ( 38.5) | 8 ( 32.0) | 18 ( 64.3) |
| Number of Participants received >1 HSCT, n(%) | 1 ( 8.3) | 1 ( 7.7) | 2 ( 8.0) | 2 ( 7.1) |
| Time of transplant relative to last InO dose | | | | |
| <2 months after last dose of Ino | 2 ( 16.7) | 2 ( 15.4) | 4 ( 16.0) | 11 ( 39.3) |
| >=2 months after last dose of Ino | 1 ( 8.3) | 3 ( 23.1) | 4 ( 16.0) | 7 ( 25.0) |
| Type of transplant | | | | |
| Allogeneic | 3 ( 25.0) | 5 ( 38.5) | 8 ( 32.0) | 18 ( 64.3) |
| Donor relatedness | | | | |
| Related | 1 ( 8.3) | 3 ( 23.1) | 4 ( 16.0) | 10 ( 35.7) |
| Unrelated | 2 ( 16.7) | 2 ( 15.4) | 4 ( 16.0) | 8 ( 28.6) |
| HLA compatibility | | | | |
| 09/10 | 0 | 0 | 0 | 0 |
| 10/10 | 2 ( 16.7) | 2 ( 15.4) | 4 ( 16.0) | 7 ( 25.0) |
| 100% | 0 | 0 | 0 | 0 |
| 12/12 | 0 | 0 | 0 | 1 ( 3.6) |
| 4/6 | 0 | 1 ( 7.7) | 1 ( 4.0) | 0 |
| 5/10 | 1 ( 8.3) | 2 ( 15.4) | 3 ( 12.0) | 5 ( 17.9) |
| 5/10 (haploid) | 0 | 0 | 0 | 0 |
| 5/6 | 0 | 0 | 0 | 0 |
| 50% | 0 | 0 | 0 | 0 |
| 6/10 | 0 | 0 | 0 | 0 |
| 6/8 | 0 | 0 | 0 | 2 ( 7.1) |
| 7/10 | 0 | 0 | 0 | 1 ( 3.6) |
| 7/8 | 0 | 0 | 0 | 0 |
| 9/10 | 0 | 0 | 0 | 1 ( 3.6) |
| Haplo | 0 | 0 | 0 | 0 |
| Stem Cell Source | | | | |
| Bone Marow | 2 ( 16.7) | 2 ( 15.4) | 4 ( 16.0) | 8 ( 28.6) |
| Cordblood | 0 | 1 ( 7.7) | 1 ( 4.0) | 0 |
| Peripheral Blood | 1 ( 8.3) | 2 ( 15.4) | 3 ( 12.0) | 10 ( 35.7) |
| Type of conditioning | | | | |
| Myeloablative | 3 ( 25.0) | 5 ( 38.5) | 8 ( 32.0) | 18 ( 64.3) |
| Non-myeloablative | 0 | 0 | 0 | 0 |

Disease in remission is determined by the disease assessment closest in time to the transplant date. If the disease status is CR/CRi/CRp, then the disease is in remission; otherwise, it is not in remission. Note: Except 'Number of Participants received >1 HSCT', all other summaries are based on the first post InO transplant'.

InO Monotherapy (Stratum 1A and Phase 2 Monotherapy Cohort, n=53):

26 (49.1%) participants received myeloablative allo HSCT after InO (). Among these participants, 15 (28.3%) had transplants within 2 months after the last dose of InO; 4 (7.5%) participants had more than 1 FU HSCT; 14 had related donors; all participants were in CR/CRi/CRp at the time of HSCT. The stem cell source was peripheral blood (13), bone marrow (12), or cord blood (1).

A total of 13 (24.5%) participants underwent at least 1 CAR T-cell infusion after their last dose of InO ().

Stratum 1A (n=25):

8 (32.0%) participants received myeloablative allo HSC T post InO treatment (). Among these participants, 4 had transplants within 2 months after the last dose of InO; 2 had more than 1 FU HSCT; 4 had related donors; all were in CR at the time of HSCT. The stem cell source was bone marrow (4), peripheral blood (3) and cord blood (1).

A total of 4 (16.0%) participants in Stratum 1A underwent at least 1 CAR T-cell infusion given after their last dose of InO.

Phase 2 Cohort (n=28):

In the Phase 2 Cohort (n=28), 18 (64.3%) participants received HSCT post InO treatment. Among these participants, 11 had transplants within 2 months after the last dose of InO; 2 had more than 1 FU HSCT; 10 had related donors; all participants were in CR/CRi/CRp at the time of HSCT. The stem cell source was bone marrow (8) and peripheral blood (10).

A total of 9 (32.1%) participants in the Phase 2 Cohort received at least 1 CAR T-cell infusion given after their last dose of InO.

#### 2.4.1.1.8. EFS

**Table *8*. Summary of Event Free Survival - Monotherapy**

| | Stratum 1A | | | Phase 2 | Total |
|---|---|---|---|---|---|
| | 1.4 mg/m² (N=12) | 1.8 mg/m² (N=13) | Total (N=25) | 1.8 mg/m² (N=28) | Total (N=53) |
| Participants with an Event, n (%) | 11 (91.7) | 8 (61.5) | 19 (76.0) | 20 (71.4) | 39 (73.6) |
| Induction Failure, n (%) | 3 (25.0) | 1 (7.7) | 4 (16.0) | 6 (21.4) | 10 (18.9) |
| Relapse, n (%) | 5 (41.7) | 6 (46.2) | 11 (44.0) | 8 (28.6) | 19 (35.8) |
| Death, n (%) | 3 (25.0) | 1 (7.7) | 4 (16.0) | 6 (21.4) | 10 (18.9) |
| Second malignancies, n (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Participants Censored[a], n (%) | 1 (8.3) | 5 (38.5) | 6 (24.0) | 8 (28.6) | 14 (26.4) |
| Ongoing without an event, n (%) | 1 (8.3) | 4 (30.8) | 5 (20.0) | 6 (21.4) | 11 (20.8) |
| Lost to follow-up, n (%) | 0 (0.0) | 1 (7.7) | 1 (4.0) | 2 (7.1) | 3 (5.7) |
| Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [3] | | | | | |
| Q3 | 8.9 (3.2, NE) | NE (7.6, NE) | 14.6 (7.6, NE) | NE (7.3, NE) | 25.4 (9.0, NE) |
| Median | 4.4 (0.0, 9.0) | 14.2 (2.1, NE) | 7.3 (2.1, 9.1) | 6.7 (2.6, 13.5) | 7.3 (3.3, 9.0) |
| Q1 | 0.9 (0.0, 3.2) | 4.6 (0.0, 7.6) | 2.1 (0.0, 5.7) | 2.0 (0.0, 3.9) | 2.1 (0.0, 3.7) |
| Probability of being event-free, % (95% CI) | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| At month 6 | 41.7 (15.2, 66.5) | 68.4 (35.9, 86.8) | 55.3 (33.8, 72.3) | 53.6 (33.8, 69.8) | 54.3 (39.9, 66.6) |
| At month 12 | 8.3 (0.5, 31.1) | 51.3 (21.9, 74.6) | 29.8 (13.3, 48.3) | 35.7 (18.9, 53.0) | 33.0 (20.7, 45.7) |
| At month 18 | 8.3 (0.5, 31.1) | 34.2 (10.7, 59.8) | 21.3 (7.8, 39.1) | 32.1 (16.1, 49.3) | 27.1 (15.9, 39.6) |
| At month 24 | 8.3 (0.5, 31.1) | 34.2 (10.7, 59.8) | 21.3 (7.8, 39.1) | 32.1 (16.1, 49.3) | 27.1 (15.9, 39.6) |

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 EFS rate 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: EFS Rates 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.

Note: Event-free survival (EFS) is defined as the time period from start of treatment with drug until on-treatment progression, death from any cause, whichever occurs first. Participants without an event are censored at the last evaluation date.

InO Monotherapy (Stratum 1A and Phase 2 Monotherapy Cohort):

In 53 participants who received InO monotherapy, 39 (73.6%) participants had events (ie, induction failure, relapse, death, or second malignancies) after InO treatments (14 [26.4%] participants were censored), of which 10 were induction failure, 19 were relapse, 10 were death, and none were second malignancies. The median EFS was 7.3 months (95% CI: 3.3- 9.0). Estimated EFS rate was 54.3% (95% CI: 39.9-66.6) at Month 6, and 33.0% (95% CI:20.7-45.7) at Month 12.

Stratum 1A:

In Stratum 1A (n=25), 19 (76.0%) participants had events after InO treatments (6 [24.0%] participants were censored), of which 4 were induction failure, 11 were relapse, and 4 were death. The median EFS was 7.3 months (95% CI: 2.1-9.1). Estimated EFS rate was 55.3% (95% CI: 33.8-72.3) at Month 6, and 29.8% (95% CI: 13.3-48.3) at Month 12.

Phase 2 Cohort:

In the Phase 2 Cohort (n=28), 20 (71.4%) participants had events after InO treatments (8 [28.6%] participants were censored), of which 6 were induction failure, 8 were relapse, and 6 were death. The median EFS was 6.7 months (95% CI: 2.6-13.5). Estimated EFS rate was 53.6% (95% CI: 33.8-69.8) at Month 6, and 35.7% (95% CI: 18.9-53.0) at Month 12.

### 2.4.1.1.9. OS

**Table 9. Summary of Overall Survival – Monotherapy (Protocol ITC(159 (B193-WI26581))**

| | 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 (%) | Total (N=53) n (%) |
| Participants with event, n (%) | 11 (91.7) | 7 (53.8) | 18 (72.0) | 17 (60.7) | 35 (66.0) |
| Participants censored, n (%) | 1 (8.3) | 6 (46.2) | 7 (28.0) | 11 (39.3) | 18 (34.0) |
| Reason for censoring, n (%) | | | | | |
| Lost to follow-up [1] | 0 | 1 (7.7) | 1 (4.0) | 2 (7.1) | 3 (5.7) |
| Withdrawal of consent | 0 | 0 | 0 | 0 | 0 |
| Alive | 1 (8.3) | 5 (38.5) | 6 (24.0) | 9 (32.1) | 15 (28.3) |
| Probability of being event-free (95% CI) [2] | | | | | |
| at 6 months | 0.500 (0.208, 0.736) | 0.762 (0.427, 0.917) | 0.629 (0.407, 0.787) | 0.643 (0.438, 0.789) | 0.636 (0.491, 0.751) |
| at 12 months | 0.250 (0.060, 0.505) | 0.592 (0.279, 0.807) | 0.419 (0.224, 0.603) | 0.536 (0.338, 0.698) | 0.482 (0.342, 0.609) |
| Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [3] | | | | | |
| Q1 | 3.5 (1.6, 5.7) | 9.7 (2.1, 26.2) | 3.9 (1.6, 9.1) | 4.0 (1.4, 9.4) | 3.9 (2.3, 6.4) |
| Median | 7.3 (2.7, 12.2) | 38.2 (4.8, NE) | 10.3 (3.9, 26.2) | 14.8 (4.2, NE) | 11.6 (5.7, 26.2) |
| Q3 | 11.5 (5.7, NE) | NE (26.2, NE) | 38.2 (10.8, NE) | NE (23.7, NE) | NE (26.2, NE) |

Abbreviation: 'NE' = Non Estimable.
[1] Includes participants deemed to be lost to follow-up by the Investigator
[2] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[3] Based on the brookmeyer and crowley method.

**Figure 12. Kaplan Meier Plot of OS: InO Monotherapy (Stratum 1A and Phase 2 Cohort)**

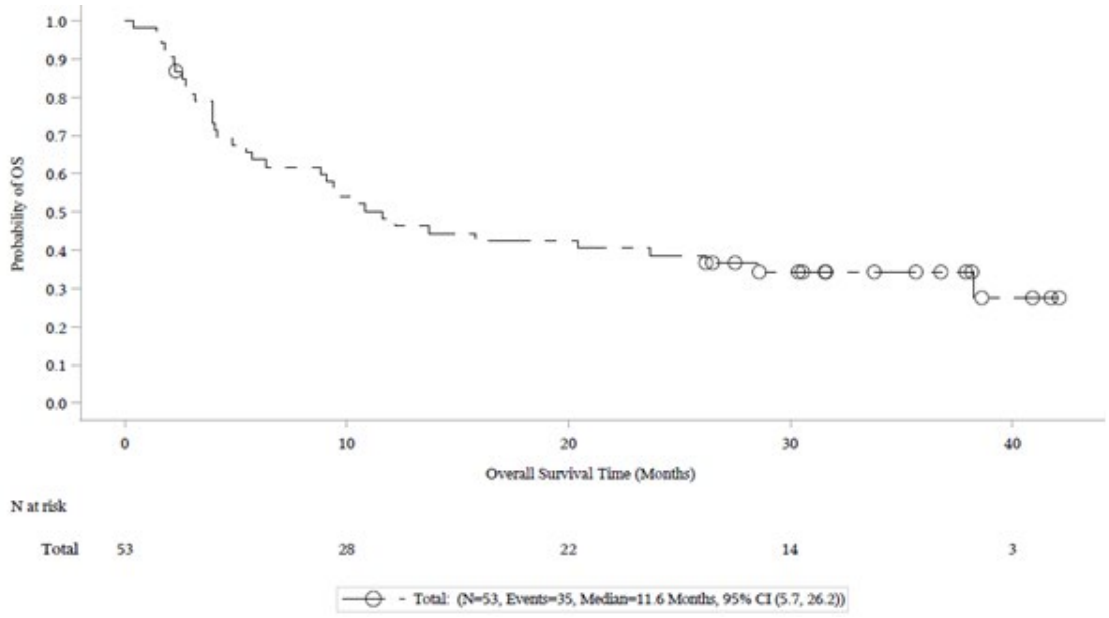


**Figure 13. Kaplan Meier Plot of OS: Stratum 1A**

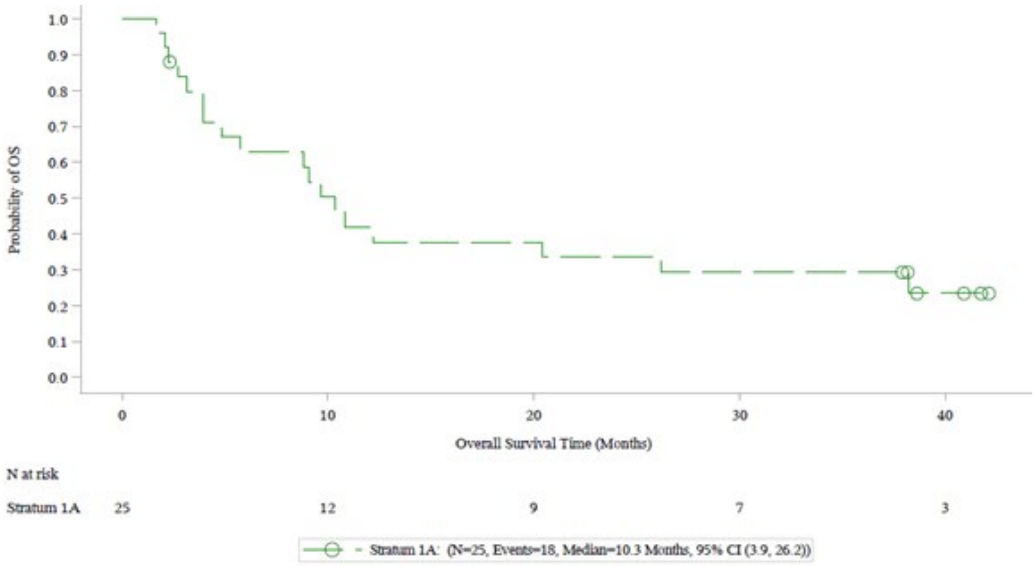
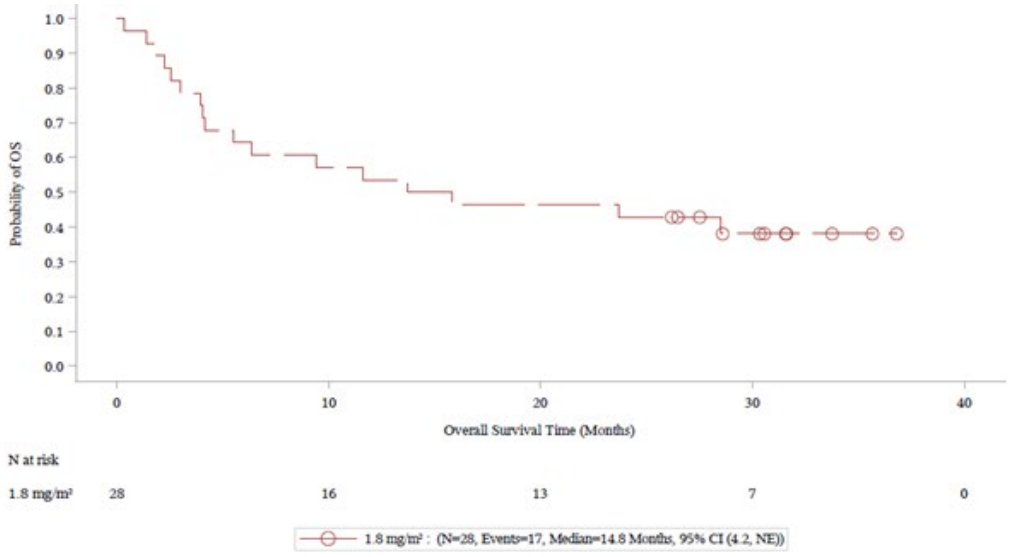



**Figure 14. Kaplan Meier Plot of OS: Phase 2 Cohort**




<u>InO Monotherapy (Stratum 1A and Phase 2 Monotherapy Cohort):</u>

In 53 participants who received InO monotherapy, 35 (66.0%) participants died (18 [34.0%] participants were censored). The median OS was 11.6 months (95% CI: 5.7-26.2). Estimated OS rate was 63.6% (95% CI: 49.1-75.1) at Month 6, and 48.2% (95% CI: 34.2-60.9) at Month 12.

<u>Stratum 1A:</u>

In Stratum 1A (n=25), 18 (72.0%) participants died (7 [28.0%] participants were censored). The median OS was 10.3 months (95% CI: 3.9-26.2). Estimated OS rate was 62.9% (95% CI: 40.7-78.7) at Month 6, and 41.9% (95% CI: 22.4-60.3) at Month 12.

Phase 2 Cohort:

In the Phase 2 Cohort (n=28), 17 (60.7%) participants died (11 [39.3%] participants were censored). The median OS was 14.8 months (95% CI: 4.2-NE). Estimated OS rate was 64.3% (95% CI: 43.8-78.9) at Month 6, and 53.6% (95% CI: 33.8-69.8) at Month 12.

## 2.4.2. Supportive data

In response to the first round MO on use in patients in first relapse that have not undergone HSCT (MO2), the applicant has provided a conference abstract and poster from the European Hematology Association meeting of June 2025 (Brivio et al, EHA-1193)

The use of InO in first relapse BCP-ALL in paediatric patients are investigated in the population of patients with first VHR relapse in the ongoing cohort 3 of the ITCC-059 study. Paediatric patients with first relapse of CD22+ VHR BCP-ALL (defined as any relapse <18 months from initial diagnosis and/or cytogenetic-high risk characteristics) that has not received prior HSCT are eligible for enrolment.

Primary objective was ORR (CR, CRp, Cri) after Cycle 1 (C1).

A Simon 2-staged design was applied to test the null hypothesis (H0) of ORR$\leq$55% and alternative hypothesis (H1) of ORR $\geq$75%. Due to slow recruitment, the protocol was amended to reduce the sample size by modifying the study design. With an increased alfa from 5% to 10% and the use of optimum design, the sample size shrinked from 43 to 31 patients. While awaiting competent authority approval of the amendment, 37 patients were included. Data analysis present below was performed on May 1st 2025.

A total of 37 patients were enrolled between February 2021 and April 2025. Median age was 11 years (range 1-17 years) and 60% were male. VHR genetics were present in 49% of patients, and 51% had very early relapse without high-risk genetics. A median of 3 doses InO per patient (range 2-9) were administered. After C1, 25/37 patients achieved CR/CRp/Cri, resulting in an ORR of 67.6% (95% CI: 50.2-82.0), while 18/25 responding patients achieved MRD negativity (72%; 95% CI 50.6–87.9) as best response. Among 16 responders who underwent consolidation with HSCT post-InO re-induction, 1-year EFS and OS rates were 87.5% (95% CI: 72.7-100.0) and 86.5% (95% CI: 70.7-100.0), respectively.

### *Summary of main study*

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 10. Summary of Efficacy for trial ITCC-059**

| **Title: ITCC-059** | | |
|---|---|---|
| Study identifier | ITCC-059, WI203581 | |
| Design | Phase 1/2, multicenter, European, single-arm, multi-cohort, open-label study in pediatric patients with R/R CD22-positive ALL. | |
| | Duration of main phase: | A maximum of 6 cycles of InO. For patients proceeding to HSCT, 2 cycles were recommended |
| | Duration of Run-in phase: | N/A |
| | Duration of Extension phase: | N/A |

| | | | |
|---|---|---|---|
| Hypothesis | Assuming that an overall response rate (ORR=CR/CRi/CRp) of 30% or less (H0) is not promising and an ORR of over 55% (Ha) is expected, a total of 25 patients evaluable for response will provide 80% power to reject H0 and a significance level of 0.05 (one-sided) when the true ORR is ⩽30% (H0). | | |
| Treatments groups | Stratum 1A | | InO monotherapy. 2-6 cycles, n=25 |
| | Phase 2 | | InO monotherapy. 2-6 cycles, n=28 |
| Endpoints and definitions | Primary endpoint | ORR in Phase 2 cohort | Defined as the rate of patients with CR/CRi/CRp |
| | Secondary endpoint | ORR after cycle 1 | Defined as the rate of patients with CR/CRi/CRp after 1 cycle of therapy |
| | Secondary endpoint | ORR in Stratum 1A | Defined as the rate of patients with CR/CRi/CRp |
| | Secondary endpoint | MRD negativity | The number and percentage of paticipants with specific MRD-levels ($<10^{-2}$, $10^{-3}$, $10^{-4}$ and $10^{-5}$) and of negative MRD ($<10^{-4}$) among participants achieving an OR after course 1 as well as best response during subsequent therapy will be summarized. |
| | Secondary endpoint | DoR | Defined as the time between achieving response (CR, CRi or CRp) after starting study treatment and documented relapse or death. The analysis will only include participants with CR/CRi/CRp |
| | Secondary endpoint | HSCT rate after Ino | The number of patients who proceed to HSC after treatment with InO |
| Database lock | 30 September 2022 for Stratum 1A and 7 October 2022 for Phase 2 | | |

## Results and Analysis

| **Analysis description** | **Primary Analysis** | | |
|---|---|---|---|
| Analysis population and time point description | Other: The Response Evaluable Analysis Set was used to evaluate the endpoints for the efficacy profile. Includes all subjects who received at least one dose of InO and had completed a baseline disease assessment and at least one post-baseline disease assessment. | | |
| Descriptive statistics and estimate variability | Treatment group | **Phase 2 cohort** | **Stratum 1A** |
| | Number of subject | n=28 | n=13 (no. of pts receiving RP2D) |
| | ORR | 22 (78.6) | 11 (84.6%) |
| | 1-sided p-value | <0.001 | N/A |
| | ORR after cycle 1 | 22 (78.6) | 11 (84.6) |
| | MRD (flow cytometry) | 22 (100) | 10 (90.9) |
| | MRD (RQ-PCR) | 19 (86.4%) | 9 (81.8) |
| | DoR (median) | 7.6 months | 8 months |

| | | | |
|---|---|---|---|
| | HSCT rate | 64.3% (n=18) | 38.5% (n=5) |
| Notes | Only the primary endpoint (ORR in Phase 2 cohort) is type 1-error protected. EFS and OS cannot be isolated in a SAT and is therefore not presented here. | | |

## 2.4.3. Discussion on clinical efficacy

### Design and conduct of clinical studies

ITCC-059 was a phase 1/2, multicohort, open-label SAT in paediatric patients (≥1 and <18 years of age) with R/R CD22-positive BCP-ALL. In this variation, data from the Stratum 1A (dose-finding) and Phase 2 cohorts are processed.

A maximum of 6 cycles of InO monotherapy was given for all patients. 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. 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.

The phase 1 part of the study is considered exploratory whereas the phase 2 part is confirmatory. Analyses are performed both in the separate cohorts and combined. In the SmPC section 5.1, results for the patients in the phase 2 cohort are presented in the efficacy table.

Four protocol amendments were introduced during the study. In amendment 2.0 (dated 31 Aug 2018) the design for the Phase 2 study was modified to a single-stage design from the preliminary planned Simon 2-stage design. The assumptions for the preliminary planned design were that an overall response rate (ORR=CR/CRi/CRp) of 30% or less is not promising and an ORR of over 55% is promising. Based on these assumptions, with an alpha of 0.05 and a power of 80% the number of patients required in stage 1 was determined to 15, and the trial would continue if at least 6/15 patients responded. Stage 2 would have required a maximum of 31 additional patients evaluable for response, and the drug would have been considered promising if at least 19/46 patients respond. With amendment 2.0, the sample size changed from 46 planned patients to 25. This is considered acceptable, but it is emphasised that such a decrease in sample size, in a SAT with an already limited no. of patients, is associated with risks such as greater susceptibility to bias, difficulties in interpreting efficacy and limited generalizability. The MAH has clarified that Amendment 2 was introduced before inclusion of the first patient in Phase 2. It is noted that only the primary endpoint (ORR in Phase 2 Cohort) is type I error controlled.

## Baseline characteristics and claimed indication

In Stratum 1A (n=25), the median age was 11 years (range: 1 to 16 years). In the Phase 2 Cohort (n=28), the median age was 7.5 years (range: 1 to 17 years). A total of 2 patients were <2 years of age (of which one was included in Stratum 1A and dose level is not stated).

Of the patients in the Phase 2 cohort, the following baseline diagnosis criteria applied: 21.4% (n=6) had their first relapse of BCP-ALL post allo-HSCT, 21.4% (n=6) had refractory BCP-ALL and 57.1% (n=16) had second or greater relapsed BCP-ALL. No patient had Ph+ disease.

### Efficacy data and additional analyses

The primary endpoint, ORR in Phase 2 cohort, was estimated to 78.6% (22 out of 28 patients achieved CR [n=18], CRp [n=1] or CRi [n=3]).

As a secondary endpoint, Cycle 1 response was determined in the Stratum 1A and Phase 2 Cohort, respectively. At the end of Cycle 1, 22 out of 28 participants (78.6%) in the Phase 2 cohort achieved an objective response (CR: 12, CRp: 1, CRi: 9). Among the patients in Stratum 1A that received the recommended dose, 11 out of 13 (84.6%) had achieved CR at the end of Cycle 1. Thus, the majority of patients that had an objective response, responded during the first cycle.

MRD level was determined by two different methods: flow cytometry and RQ-PCR. The number of MRD negative patients differs somewhat between the two. In the Phase 2 cohort, the percentage of CR/Cri/CRp-responsers with MRD-negativity was 100% (22/22) when determined by flow cytometry and 86.4% (19/22) when determined by RQ-PCR. In Stratum 1A, comparable proportions of MRD-negativity were seen (90.9% by flow cytometry and 81.8% by RQ-PCR).

In the Phase 2 cohort, 64.3% (n=18) of the patients were able to proceed to allo-HSCT due to InO-treatment. In Stratum 1A, 38.5% (n=5) of the patients receiving the recommended dose had allo-HSCT. Information regarding how many subjects had subsequent HSCT has been included in SmPC section 5.1.

The median DoR was 8.0 months. Of the 42 participants who achieved CR/CRi/CRp, 28 (66.7%) participants had subsequent events (19 relapses and 9 deaths). It is noted that 9 of the patients included in the analysis received the lower dose of 1.4 mg/m2/cycle. Among Phase 2-patients, 14 of 22 (63.6%) CR/Cri/CRp patients had subsequent events (8 relapses and 6 deaths). Patients receiving allo-HSCT (5 patients in Stratum 1A and 18 patients in Phase 2 cohort) or CAR-T (4 patients in Stratum 1A and 9 patients in Phase 2 Cohort) after their last dose of InO are included in the DoR analyses. This is agreed since the ability to proceed to HSCT is anticipated as the main benefit of Besponsa treatment.

In Stratum 1A, the median EFS was 14.2 months (95% CI: 2.1-NE). Eight out of 13 (61.5%) patients receiving the recommended dose had events after InO treatments, of which 1 were induction failure, 6 were relapse, and 1 were death. In the Phase 2 Cohort, 20 (71.4%) participants had events after InO treatments, of which 6 were induction failure, 8 were relapse, and 6 were death. The median EFS was 6.7 months (95% CI: 2.6-13.5).

In the Phase 2 and Stratum 1A cohorts (dose level 1.8 mg/m2/cycle), 60.7% (n=17) and 53.8% (n=7) had died at time of the analysis, respectively. A considerable proportion of early deaths were observed. In the Phase 2 cohort, 25% of the patients died within 4 months from start of study treatment.

EFS and OS cannot be isolated in a single arm trial. These measures have been removed from the SmPC section 5.1**.**

In response to the first and second round MO on use in patients at very high risk (VHR) per IntReALL criteria, in first relapse that have not undergone HSCT, the applicant has provided a conference abstract and poster on 37 patients from the ongoing cohort 3 of the ITCC-059 study. At the time of data analysis (01 May 2025), an overall response after C1 of 67.6% (95% CI: 50.2-80.2) was demonstrated, while 18/25 responding patients achieved MRD negativity (72%).

It is not evident that the MAH has demonstrated the relevance and utility of Besponsa after a first relapse in patients not having undergone HSCT. The CSR's provided a SAT of limited size including only first relapse post allo-HSCT or second or greater R/R disease.

The MAH proposes extrapolation of the effect observed in the adult INO-VATE to a corresponding paediatric indication and provides arguments regarding the three risk groups, standard risk (SR), high risk (HR) and very high risk (VHR) to support the proposed wording.

It is noted that this risk stratification score guides the design of the ongoing EU-wide IntReALL study/guidelines, therefore, this is accepted.

Extrapolation of effect to the SR and HR risk groups is, however, not supported. Patients with SR and HR disease achieve clinically relevant responses to chemotherapy. It is noted that, paediatric patients with HR disease are eligible for enrolment in an ongoing RCT evaluating the safety and efficacy of InO as add-on to UK-ALLR3 chemotherapy regimen as compared with standard UKALL-R3 chemotherapy (PIP study 2). This indicates both equipoise for randomisation, as well as the need for the study to determine the utility of InO in the context, not least given the toxicity of this product, including VOD. Considering these factors, a positive B/R cannot be concluded for SR and HR patients based on the limited data available as the basis of the present claim. This has been reflected in the recommended therapeutic indication.

### 2.4.4. Conclusions on the clinical efficacy

Clinically relevant activity of Besponsa was demonstrated in children in advanced stage of difficult-to-treat R/R BCP-ALL, with an ORR rate of 78.6% and high rates of MRD negativity. This is associated with a relevant proportion of patients being able to receive HSCT.

## *2.5. Clinical safety*

### *Introduction*

The key safety data in support of this application derive from the primary analysis of InO monotherapy safety results (Stratum 1A and the Phase 2 Cohort) of the Study ITCC-059 (WI203581), with a data cutoff date of 09 May 2024.

The previously established safety profile of Besponsa in adults include cytopenia, fatigue, pyrexia, abnormal liver function tests and abdominal events (nausea, diarrhoea, vomiting and constipation).

The safety specification according to the latest approved RMP version 2.2, include *`≥Grade 3 and/or serious hepatotoxicity, including all VOD/SOS´* and *`Myelosuppression/cytopenia´* as important identified risks, *`Interstitial lung disease´*, *`Inflammatory gastrointestinal events´*, *`Pancreatitis´*, *`Second primary malignancy´*, *`Reproductive and developmental toxicity (post exposure during pregnancy and while breast feeding)´*, *`Neurotoxicity´*, and *`Nephrotoxicity´* as important potential risks, and *`Use in patients with moderate or severe hepatic impairment´*, *`Use in patients with severe renal impairment´, and `Use in Hispanic and Black patients´* as missing infromation.

*Paediatric population*

In June 2023, based on final results from studies ITCC-059 (WI203581) and INO-Ped-ALL-1 (WI235086), Pfizer submitted a Type II variation EMEA/H/C/004119/II/0026 to include updated paediatric information in the EU SmPC. Study ITCC-059 was also previously submitted and discussed within EU Article 46 procedure, EMEA/H/C/004119/P46/004, and Type II Variation procedure EMEA/H/C/004119/II/0026. The package Leaflet and RMP version 2.2 were updated accordingly as part of this variation, which was approved by CHMP on 14 December 2023.

Another ongoing European pediatric study (PIP Study 2; B1931036) aims to evaluate the efficacy and safety of InO monotherapy as induction compared to the UKALL-R3 induction regimen (2:1

randomization) in children and adolescents with high risk first relapse of CD22 positive BCP-ALL. For Study B1931036, FPFV was on 24 May 2023 and LPLV is targeted for 30 October 2036. A PIP modification 08 has been submitted to EMA/PDCO in Feb 2025 to align with the delay in completion date. Study B1931036 completion date will be delayed due to slow recruitment based on the increasing rarity of the targeted high-risk (HR), first relapse population. Data from this study have been submitted during this ongoing procedure providing further safety aspects,

## *Patient exposure*

Study ITCC-059 included 25 (Phase I) + 28 (Phase II), i.e. 53 paediatric patients treated with InO monotherapy. The subjects were 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 (Table 2).

The InO dose levels are presented in Table 11.

**Table *11*. InO Dose-Levels**

| InO Dose Escalation/De-escalation Schema in mg/m$^2$ IV[a] | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cycle 1 | | | | | Cycle 2-6 | | | | |
| **Day** | **1** | **8** | **15** | **22 ± 2-42 days for all cohorts** | **Total Dose per Cycle** | **1** | **8 ±1 day** | **15 ±1 day** | **28 ± 2-42 days** | **Total Dose per Cycle** |
| Level -2 | 0.4 | 0.2 | 0.2 | | 0.8 | 0.2 | 0.2 | 0.2 | | 0.6 |
| Level -1 | 0.5 | 0.3 | 0.3 | | 1.1 | 0.3 | 0.3 | 0.3 | | 0.9 |
| Level 1 (start)[b] | 0.6 | 0.4 | 0.4 | Disease Evaluation | 1.4 | 0.4 | 0.4 | 0.4 | Disease Evaluation | 1.2 |
| Level 2 (adult dose) | 0.8 | 0.5 | 0.5 | | 1.8 | 0.5 | 0.5 | 0.5 | | 1.5 |
| Level 3 | 1.0 | 0.6 | 0.6 | | 2.2 | 0.6 | 0.6 | 0.6 | | 1.8 |

Dose de-escalation did not go below Level -2.
Note that there was no dose-capping for obese patients/patients with high BSA.
Following Cycle 1, in patients who had achieved a CR/CRi or CRp, the Day 1 dose was decreased slightly due to no loading dose requirement. In patients who had not yet achieved a CR/CRi or CRp after Cycle 1, a loading dose similar to Cycle 2 was given in Cycle 2, but not in subsequent cycles.

*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%).

Exposure to InO is summarized in Table 12.

**Table *12*. Study Treatment Exposure - Monotherapy (Protocol ITCC-059 (B193-WI203581))**

| | Stratum 1A (N=25) n (%) | Phase 2 (N=28) n (%) | Total (N=53) n (%) |
|---|---|---|---|
| Number of Participants Dosed | 25 (100.0) | 28 (100.0) | 53 (100.0) |
| Last Cycle Initiated | 25 (100.0) | 28 (100.0) | 53 (100.0) |
| Cycle 1 | 11 (44.0) | 12 (42.9) | 23 (43.4) |
| Cycle 2 | 10 (40.0) | 10 (35.7) | 20 (37.7) |
| Cycle 3 | 1 (4.0) | 5 (17.9) | 6 (11.3) |
| Cycle 4 | 3 (12.0) | 1 (3.6) | 4 (7.5) |
| Mean | 1.84 | 1.82 | 1.83 |
| SD | 0.98 | 0.86 | 0.91 |
| Median | 2.00 | 2.00 | 2.00 |
| Range | (1.00, 4.00) | (1.00, 4.00) | (1.00, 4.00) |
| Last Cycle Completed | 23 (92.0) | 28 (100.0) | 51 (96.2) |
| Cycle 1 | 10 (40.0) | 13 (46.4) | 23 (43.4) |
| Cycle 2 | 9 (36.0) | 9 (32.1) | 18 (34.0) |
| Cycle 3 | 1 (4.0) | 5 (17.9) | 6 (11.3) |
| Cycle 4 | 3 (12.0) | 1 (3.6) | 4 (7.5) |
| Mean | 1.87 | 1.79 | 1.82 |
| SD | 1.00 | 0.87 | 0.93 |
| Median | 2.00 | 2.00 | 2.00 |
| Range | (1.00, 4.00) | (1.00, 4.00) | (1.00, 4.00) |
| Number of Participants with Dose Reduction | | | |
| Zero(0) Dose Reductions | 25 (100.0) | 27 (96.4) | 52 (98.1) |
| One or More Dose Reductions | 0 | 1 (3.6) | 1 (1.9) |
| Number of Participants with Dose Delay | | | |
| Zero(0) Dose Delays | 23 (92.0) | 21 (75.0) | 44 (83.0) |
| One or More Dose Delays | 2 (8.0) | 7 (25.0) | 9 (17.0) |
| Actual Overall Dose($mg/m^2$) [a] | | | |
| n | 25 | 28 | 53 |
| Mean | 2.55 | 2.92 | 2.75 |
| SD | 1.30 | 1.38 | 1.35 |
| Median | 2.59 | 3.22 | 2.63 |
| Range | (0.57, 5.28) | (0.76, 6.47) | (0.57, 6.47) |
| Actual Dose Intensity($mg/m^2$/cycle) [b] | | | |
| n | 25 | 28 | 53 |
| Mean | 1.41 | 1.61 | 1.52 |
| SD | 0.34 | 0.24 | 0.31 |
| Median | 1.37 | 1.66 | 1.63 |
| Range | (0.57, 1.83) | (0.76, 1.86) | (0.57, 1.86) |
| Relative Dose Intensity(%) [c] | | | |
| n | 25 | 28 | 53 |
| Mean | 98.17 | 98.94 | 98.58 |
| SD | 11.21 | 6.08 | 8.84 |

**Table 12. Study Treatment Exposure - Monotherapy (Protocol ITCC-059 (B193-WI203581))**

| | Stratum 1A (N=25) n (%) | Phase 2 (N=28) n (%) | Total (N=53) n (%) |
|---|---|---|---|
| Median | 100.0 | 100.0 | 100.0 |
| Range | (44.56, 105.13) | (70.83, 105.22) | (44.56, 105.22) |

[a] Actual Overall Dose is defined as the sum of all doses received.
[b] Actual Dose intensity is defined as the total actual exposure divided by the number of cycles received.
[c] Relative dose intensity is defined as the actual dose intensity divided by the planned dose intensity.
(Data cutoff date - Stratum 1A: 30SEP2022 Phase2: 07OCT2022)

## DLT

Cycle 1 DLTs were evaluated in Stratum 1A as the primary endpoint. The RP2D for InO was determined to be 1.8 mg/m$^2$. The results for Stratum 1A InO monotherapy are summarised in Table 13.

**Table 13. Summary of Dose Limiting Toxicity (DLT) - Dose Escalation population Set, Monotherapy (Protocol ITCC-059 (B193-WI203581))**

| | Stratum 1A | | | | | |
|---|---|---|---|---|---|---|
| | 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) |
| Dose Limiting Toxicities, DLT | 1 (16.7) | 0 | 1 (8.3) | 2 (40.0) | 1 (16.7) | 3 (27.3) |
| Alanine aminotransferase increased | 1 (16.7) | 0 | 1 (8.3) | 1 (20.0) | 0 | 1 (9.1) |
| Neutrophil count decreased | 0 | 0 | 0 | 1 (20.0) | 0 | 1 (9.1) |
| Platelet count decreased | 0 | 0 | 0 | 0 | 1 (16.7) | 1 (9.1) |

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

(Data cutoff date - Stratum 1A: 30SEP2022 Phase2: 07OCT2022)

## *Adverse events*

AEs were graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and were coded using the MedDRA version 25.1.

The active safety reporting period was defined as 10 weeks after the last dose of InO or until all drug-related toxicities had resolved, whichever was later. If a patient began a new anticancer therapy, the reporting period for non-serious AEs and SAEs ended at the time the new treatment was started, unless an SAE was considered at least possibly related to InO by the Investigator. All cases of VOD

required reporting as an AE and as an SAE regardless of causality or severity for 1 year after enrolment, even if the event occurs after follow-up therapy.

#### *2.5.1.1. Treatment-Emergent Adverse Events*

**Table 14. Summary of Treatment-Emergent Adverse Events (All Causalities) - Monotherapy (Protocol ITCC-059 (B193-WI203581))**

| Number (%) of Participants | Stratum 1A (N=25) n (%) | Phase 2 (N=28) n (%) | Total (N=53) n (%) |
|---|---|---|---|
| Participants evaluable for adverse events | 25 | 28 | 53 |
| Number of adverse events | 348 | 246 | 594 |
| Participants with adverse events | 25 (100.0) | 28 (100.0) | 53 (100.0) |
| Participants with serious adverse events | 16 (64.0) | 17 (60.7) | 33 (62.3) |
| Participants with Maximum Grade 3 or 4 adverse events | 21 (84.0) | 22 (78.6) | 43 (81.1) |
| Participants with Maximum Grade 5 adverse events | 3 (12.0) | 4 (14.3) | 7 (13.2) |
| Participants permanent discontinuation from treatment | 8 (32.0) | 4 (14.3) | 12 (22.6) |
| Participants leading to study drug interruption/reduction/delay | 1 (4.0) | 5 (17.9) | 6 (11.3) |

Participants are counted only once in each row.
TEAEs are defined as AEs that commence on or after Cycle 1 Day 1 but within 10 weeks of last dose of study drug or one day prior start day of new anticancer therapy, whichever occurs first. All VOD events within 1 year after first dose regardless of causality will be included.
MedDRA v25.1 coding dictionary applied.

(Data cutoff date - Stratum 1A: 30SEP2022 Phase2: 07OCT2022)

**Table 15. Summary of Treatment-Emergent Adverse Events (Treatment Related) - Monotherapy (Protocol ITCC-059 (B193-WI203581))**

| Number (%) of Participants | Stratum 1A (N=25) n (%) | Phase 2 (N=28) n (%) | Total (N=53) n (%) |
|---|---|---|---|
| Participants evaluable for adverse events | 25 | 28 | 53 |
| Number of adverse events | 161 | 111 | 272 |
| Participants with adverse events | 21 (84.0) | 25 (89.3) | 46 (86.8) |
| Participants with serious adverse events | 9 (36.0) | 9 (32.1) | 18 (34.0) |
| Participants with Maximum Grade 3 or 4 adverse events | 21 (84.0) | 22 (78.6) | 43 (81.1) |
| Participants with Maximum Grade 5 adverse events | 0 | 0 | 0 |
| Participants permanent discontinuation from treatment | 7 (28.0) | 2 (7.1) | 9 (17.0) |
| Participants leading to study drug interruption/reduction/delay | 0 | 5 (17.9) | 5 (9.4) |

Participants are counted only once in each row.
TEAEs are defined as AEs that commence on or after Cycle 1 Day 1 but within 10 weeks of last dose of study drug or one day prior start day of new anticancer therapy, whichever occurs first. All VOD events within 1 year after first dose regardless of causality will be included.
MedDRA v25.1 coding dictionary applied.
(Data cutoff date - Stratum 1A: 30SEP2022 Phase2: 07OCT2022)

**Table *16*. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade With a Cutoff ≥10% in any Treatment (All Causalities, Monotherapy) - Monotherapy (Protocol ITCC-059 (B193-WI203581))**

| Number of Participants Evaluable for AEs | Stratum 1A 1.4 mg/m² (N=12) | | | Stratum 1A 1.8 mg/m² (N=13) | | | Phase 2 1.8 mg/m² (N=28) | | | Total (N=53) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Grade 3-4 | Grade 5 | All Grades | Grade 3-4 | Grade 5 | All Grades | Grade 3-4 | Grade 5 | All Grades | Grade 3-4 | Grade 5 | All Grades |
| Number (%) of Participants: by Preferred Term | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| With Any Adverse Event | 9 (75.0) | 2 (16.7) | 12 (100.0) | 12 (92.3) | 1 (7.7) | 13 (100.0) | 22 (78.6) | 4 (14.3) | 28 (100.0) | 43 (81.1) | 7 (13.2) | 53 (100.0) |
| Abdominal pain | 0 | 0 | 3 (25.0) | 1 (7.7) | 0 | 3 (23.1) | 0 | 0 | 2 (7.1) | 1 (1.9) | 0 | 8 (15.1) |
| Abdominal pain upper | 0 | 0 | 1 (8.3) | 0 | 0 | 1 (7.7) | 0 | 0 | 3 (10.7) | 0 | 0 | 5 (9.4) |
| Alanine aminotransferase increased | 2 (16.7) | 0 | 2 (16.7) | 1 (7.7) | 0 | 1 (7.7) | 5 (17.9) | 0 | 7 (25.0) | 8 (15.1) | 0 | 10 (18.9) |
| Anaemia | 5 (41.7) | 0 | 6 (50.0) | 6 (46.2) | 0 | 6 (46.2) | 9 (32.1) | 0 | 12 (42.9) | 20 (37.7) | 0 | 24 (45.3) |
| Aspartate aminotransferase increased | 2 (16.7) | 0 | 2 (16.7) | 1 (7.7) | 0 | 2 (15.4) | 6 (21.4) | 0 | 8 (28.6) | 9 (17.0) | 0 | 12 (22.6) |
| Blood bilirubin increased | 1 (8.3) | 0 | 1 (8.3) | 1 (7.7) | 0 | 1 (7.7) | 2 (7.1) | 0 | 3 (10.7) | 4 (7.5) | 0 | 5 (9.4) |
| Chills | 0 | 0 | 2 (16.7) | 0 | 0 | 2 (15.4) | 0 | 0 | 0 | 0 | 0 | 4 (7.5) |
| Constipation | 0 | 0 | 2 (16.7) | 0 | 0 | 5 (38.5) | 1 (3.6) | 0 | 3 (10.7) | 1 (1.9) | 0 | 10 (18.9) |
| Cough | 0 | 0 | 3 (25.0) | 0 | 0 | 4 (30.8) | 0 | 0 | 2 (7.1) | 0 | 0 | 9 (17.0) |
| Decreased appetite | 1 (8.3) | 0 | 2 (16.7) | 1 (7.7) | 0 | 3 (23.1) | 0 | 0 | 1 (3.6) | 2 (3.8) | 0 | 6 (11.3) |
| Device related infection | 0 | 0 | 0 | 2 (15.4) | 0 | 2 (15.4) | 1 (3.6) | 0 | 1 (3.6) | 3 (5.7) | 0 | 3 (5.7) |
| Diarrhoea | 0 | 0 | 1 (8.3) | 0 | 0 | 4 (30.8) | 0 | 0 | 1 (3.6) | 0 | 0 | 6 (11.3) |
| Disease progression | 1 (8.3) | 1 (8.3) | 2 (16.7) | 1 (7.7) | 0 | 1 (7.7) | 0 | 1 (3.6) | 1 (3.6) | 2 (3.8) | 2 (3.8) | 4 (7.5) |
| Dyspnoea | 1 (8.3) | 0 | 2 (16.7) | 0 | 0 | 2 (15.4) | 0 | 0 | 0 | 1 (1.9) | 0 | 4 (7.5) |
| Epistaxis | 0 | 0 | 2 (16.7) | 0 | 0 | 2 (15.4) | 0 | 0 | 2 (7.1) | 0 | 0 | 6 (11.3) |
| Face oedema | 0 | 0 | 0 | 0 | 0 | 4 (30.8) | 0 | 0 | 0 | 0 | 0 | 4 (7.5) |
| Fatigue | 0 | 0 | 2 (16.7) | 0 | 0 | 4 (30.8) | 0 | 0 | 2 (7.1) | 0 | 0 | 8 (15.1) |
| Febrile neutropenia | 3 (25.0) | 0 | 3 (25.0) | 5 (38.5) | 0 | 5 (38.5) | 7 (25.0) | 0 | 7 (25.0) | 15 (28.3) | 0 | 15 (28.3) |
| Gamma-glutamyltransferase increased | 2 (16.7) | 0 | 2 (16.7) | 3 (23.1) | 0 | 4 (30.8) | 1 (3.6) | 0 | 3 (10.7) | 6 (11.3) | 0 | 9 (17.0) |
| Haematoma | 0 | 0 | 2 (16.7) | 0 | 0 | 2 (15.4) | 1 (3.6) | 0 | 4 (14.3) | 1 (1.9) | 0 | 8 (15.1) |
| Headache | 0 | 0 | 4 (33.3) | 0 | 0 | 2 (15.4) | 0 | 0 | 5 (17.9) | 0 | 0 | 11 (20.8) |
| Hyperhidrosis | 0 | 0 | 1 (8.3) | 0 | 0 | 2 (15.4) | 0 | 0 | 0 | 0 | 0 | 3 (5.7) |
| Hypokalaemia | 1 (8.3) | 0 | 2 (16.7) | 3 (23.1) | 0 | 4 (30.8) | 2 (7.1) | 0 | 3 (10.7) | 6 (11.3) | 0 | 9 (17.0) |
| Hypoxia | 1 (8.3) | 0 | 2 (16.7) | 0 | 1 (7.7) | 1 (7.7) | 0 | 0 | 1 (3.6) | 1 (1.9) | 1 (1.9) | 4 (7.5) |
| Joint range of motion decreased | 0 | 0 | 0 | 0 | 0 | 2 (15.4) | 0 | 0 | 0 | 0 | 0 | 2 (3.8) |
| Lymphocyte count decreased | 2 (16.7) | 0 | 2 (16.7) | 2 (15.4) | 0 | 2 (15.4) | 3 (10.7) | 0 | 3 (10.7) | 7 (13.2) | 0 | 7 (13.2) |

**Table *16*. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade With a Cutoff ≥10% in any Treatment (All Causalities, Monotherapy) - Monotherapy (Protocol ITCC-059 (B193-WI203581))**

| Number of Participants Evaluable for AEs | Stratum 1A 1.4 mg/m² (N=12) | | | Stratum 1A 1.8 mg/m² (N=13) | | | Phase 2 1.8 mg/m² (N=28) | | | Total (N=53) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Grade 3-4 | Grade 5 | All Grades | Grade 3-4 | Grade 5 | All Grades | Grade 3-4 | Grade 5 | All Grades | Grade 3-4 | Grade 5 | All Grades |
| Number (%) of Participants: by Preferred Term | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Mouth haemorrhage | 0 | 0 | 3 (25.0) | 0 | 0 | 2 (15.4) | 0 | 0 | 1 (3.6) | 0 | 0 | 6 (11.3) |
| Muscle spasms | 0 | 0 | 0 | 0 | 0 | 2 (15.4) | 0 | 0 | 0 | 0 | 0 | 2 (3.8) |
| Muscular weakness | 0 | 0 | 1 (8.3) | 0 | 0 | 2 (15.4) | 0 | 0 | 0 | 0 | 0 | 3 (5.7) |
| Nausea | 0 | 0 | 3 (25.0) | 0 | 0 | 5 (38.5) | 0 | 0 | 9 (32.1) | 0 | 0 | 17 (32.1) |
| Neutrophil count decreased | 6 (50.0) | 0 | 6 (50.0) | 5 (38.5) | 0 | 5 (38.5) | 10 (35.7) | 0 | 10 (35.7) | 21 (39.6) | 0 | 21 (39.6) |
| Oedema peripheral | 0 | 0 | 2 (16.7) | 0 | 0 | 3 (23.1) | 0 | 0 | 0 | 0 | 0 | 5 (9.4) |
| Oral pain | 0 | 0 | 3 (25.0) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 (5.7) |
| Pain | 0 | 0 | 1 (8.3) | 0 | 0 | 3 (23.1) | 1 (3.6) | 0 | 4 (14.3) | 1 (1.9) | 0 | 8 (15.1) |
| Pain in extremity | 1 (8.3) | 0 | 5 (41.7) | 0 | 0 | 3 (23.1) | 0 | 0 | 2 (7.1) | 1 (1.9) | 0 | 10 (18.9) |
| Periorbital oedema | 0 | 0 | 3 (25.0) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 (5.7) |
| Platelet count decreased | 7 (58.3) | 0 | 7 (58.3) | 6 (46.2) | 0 | 8 (61.5) | 11 (39.3) | 0 | 12 (42.9) | 24 (45.3) | 0 | 27 (50.9) |
| Pruritus | 0 | 0 | 0 | 0 | 0 | 2 (15.4) | 0 | 0 | 3 (10.7) | 0 | 0 | 5 (9.4) |
| Pyrexia | 0 | 0 | 7 (58.3) | 1 (7.7) | 0 | 6 (46.2) | 1 (3.6) | 0 | 13 (46.4) | 2 (3.8) | 0 | 26 (49.1) |
| Rash | 0 | 0 | 2 (16.7) | 0 | 0 | 0 | 0 | 0 | 2 (7.1) | 0 | 0 | 4 (7.5) |
| Rash maculo-papular | 0 | 0 | 0 | 0 | 0 | 2 (15.4) | 1 (3.6) | 0 | 3 (10.7) | 1 (1.9) | 0 | 5 (9.4) |
| Sinus tachycardia | 0 | 0 | 0 | 1 (7.7) | 0 | 2 (15.4) | 0 | 0 | 1 (3.6) | 1 (1.9) | 0 | 3 (5.7) |
| Skin infection | 0 | 0 | 0 | 2 (15.4) | 0 | 2 (15.4) | 0 | 0 | 1 (3.6) | 2 (3.8) | 0 | 3 (5.7) |
| Stomatitis | 1 (8.3) | 0 | 1 (8.3) | 0 | 0 | 1 (7.7) | 2 (7.1) | 0 | 3 (10.7) | 3 (5.7) | 0 | 5 (9.4) |
| Tumour lysis syndrome | 1 (8.3) | 0 | 1 (8.3) | 0 | 0 | 0 | 5 (17.9) | 0 | 5 (17.9) | 6 (11.3) | 0 | 6 (11.3) |
| Venoocclusive disease | 1 (8.3) | 0 | 1 (8.3) | 0 | 0 | 0 | 3 (10.7) | 0 | 4 (14.3) | 4 (7.5) | 0 | 5 (9.4) |
| Vomiting | 0 | 0 | 5 (41.7) | 0 | 0 | 7 (53.8) | 1 (3.6) | 0 | 12 (42.9) | 1 (1.9) | 0 | 24 (45.3) |
| Weight decreased | 0 | 0 | 0 | 0 | 0 | 2 (15.4) | 0 | 0 | 0 | 0 | 0 | 2 (3.8) |
| Weight increased | 0 | 0 | 0 | 0 | 0 | 2 (15.4) | 1 (3.6) | 0 | 2 (7.1) | 1 (1.9) | 0 | 4 (7.5) |
| White blood cell count decreased | 3 (25.0) | 0 | 3 (25.0) | 4 (30.8) | 0 | 4 (30.8) | 8 (28.6) | 0 | 10 (35.7) | 15 (28.3) | 0 | 17 (32.1) |

MedDRA v25.1 coding dictionary applied. AEs are graded according to CTCAE version 4.03.
(Data cutoff date - Stratum 1A: 30SEP2022 Phase2: 07OCT2022)

#### *2.5.1.2. Treatment-Emergent Serious Adverse Events*

**Table *17*. Summary of Treatment-Emergent SAEs by MedDRA Preferred Term (All Causalities) - Monotherapy (Protocol ITCC-059 (B193-WI203581))**

| Number of Participants Evaluable for AEs | Stratum 1A | | | Phase 2 | Total |
|---|---|---|---|---|---|
| | 1.4 mg/m² (N=12) | 1.8 mg/m² (N=13) | Total (N=25) | 1.8 mg/m² (N=28) | Total (N=53) |
| **Number (%) of Participants: by Preferred Term** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| With Any adverse event | 8 (66.7) | 8 (61.5) | 16 (64.0) | 17 (60.7) | 33 (62.3) |
| Blood bilirubin increased | 0 | 1 (7.7) | 1 (4.0) | 0 | 1 (1.9) |
| Device related infection | 0 | 1 (7.7) | 1 (4.0) | 1 (3.6) | 2 (3.8) |
| Device related sepsis | 0 | 1 (7.7) | 1 (4.0) | 0 | 1 (1.9) |
| Diarrhoea | 0 | 1 (7.7) | 1 (4.0) | 0 | 1 (1.9) |
| Disease progression | 1 (8.3) | 0 | 1 (4.0) | 0 | 1 (1.9) |
| Encephalitis | 1 (8.3) | 0 | 1 (4.0) | 0 | 1 (1.9) |
| Encephalopathy | 0 | 0 | 0 | 1 (3.6) | 1 (1.9) |
| Febrile neutropenia | 2 (16.7) | 2 (15.4) | 4 (16.0) | 5 (17.9) | 9 (17.0) |
| Fracture | 1 (8.3) | 0 | 1 (4.0) | 0 | 1 (1.9) |
| Graft versus host disease in gastrointestinal tract | 0 | 1 (7.7) | 1 (4.0) | 0 | 1 (1.9) |
| Haematuria | 0 | 0 | 0 | 1 (3.6) | 1 (1.9) |
| Haemorrhage intracranial | 0 | 1 (7.7) | 1 (4.0) | 0 | 1 (1.9) |
| Multiple organ dysfunction syndrome | 0 | 0 | 0 | 1 (3.6) | 1 (1.9) |
| Neoplasm progression | 0 | 0 | 0 | 1 (3.6) | 1 (1.9) |
| Neutrophil count decreased | 0 | 1 (7.7) | 1 (4.0) | 0 | 1 (1.9) |
| Pain | 0 | 0 | 0 | 1 (3.6) | 1 (1.9) |
| Pneumonia fungal | 0 | 1 (7.7) | 1 (4.0) | 0 | 1 (1.9) |
| Pyrexia | 3 (25.0) | 0 | 3 (12.0) | 0 | 3 (5.7) |
| Rash maculo-papular | 0 | 0 | 0 | 1 (3.6) | 1 (1.9) |
| Respiratory tract infection | 0 | 1 (7.7) | 1 (4.0) | 0 | 1 (1.9) |
| Sepsis | 1 (8.3) | 1 (7.7) | 2 (8.0) | 2 (7.1) | 4 (7.5) |
| Sinusitis | 1 (8.3) | 0 | 1 (4.0) | 0 | 1 (1.9) |
| Upper respiratory tract infection | 0 | 0 | 0 | 1 (3.6) | 1 (1.9) |
| Venoocclusive disease | 0 | 0 | 0 | 3 (10.7) | 3 (5.7) |
| Venoocclusive liver disease | 1 (8.3) | 1 (7.7) | 2 (8.0) | 3 (10.7) | 5 (9.4) |

MedDRA v25.1 coding dictionary applied.
(Data cutoff date - Stratum 1A: 30SEP2022 Phase2: 07OCT2022)

## *Serious adverse event/deaths/other significant events*

## Deaths

A summary of deaths during the study is provided in Table 18.

**Table *18*. Summary of Deaths - Monotherapy (Protocol ITCC-059 (B193-WI203581))**

| | Stratum 1A | | | Phase 2 | Total |
|---|---|---|---|---|---|
| | 1.4 mg/m² (N=12) | 1.8 mg/m² (N=13) | Total (N=25) | 1.8 mg/m² (N=28) | Total (N=53) |
| Deaths | 11 ( 91.7) | 7 ( 53.8) | 18 ( 72.0) | 17 ( 60.7) | 35 ( 66.0) |
| Cause of Death | | | | | |
| Disease Progression | 7 ( 58.3) | 5 ( 38.5) | 12 ( 48.0) | 8 ( 28.6) | 20 ( 37.7) |
| Toxicity | 0 | 0 | 0 | 2 ( 7.1) | 2 ( 3.8) |
| Other | 4 ( 33.3) | 2 ( 15.4) | 6 ( 24.0) | 7 ( 25.0) | 13 ( 24.5) |
| Induction Death | 0 | 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) | 13 ( 24.5) |
| Cause of Death | | | | | |
| Disease Progression | 2 ( 16.7) | 0 | 2 ( 8.0) | 2 ( 7.1) | 4 ( 7.5) |
| Toxicity | 0 | 0 | 0 | 1 ( 3.6) | 1 ( 1.9) |
| Other | 2 ( 16.7) | 2 ( 15.4) | 4 ( 16.0) | 4 ( 14.3) | 8 ( 15.1) |

The denominator to calculate percentages is N, the number of participants in the Full Analysis Set within each cohort.
Induction death is defined as any patient who died after receiving therapy on this protocol during the first cycle before a final bone-marrow evaluation for response was performed.
(Data cutoff date - Stratum 1A: 30SEP2022 Phase2: 07OCT2022)

## Post HSCT Non-Relapse Mortality

In participants treated with InO monotherapy, 26/53 (49.1%) participants received HSCT post InO treatment and the post HSCT non-relapse mortality rate was 7/26 (26.9%). The post HSCT non-relapse deaths were due to: Sepsis & haemorrhage, Transplant-related sepsis, Haemorrhagic shock, Bilateral pneumonitis, MOF, HSCT related MOF, Progressive pulmonary fibrosis respectively for each case.

## 2.5.2. Treatment Emergent Adverse Events of Special Interest

The following events are considered AESIs: Haemorrhage, Hepatotoxicity, Infections, Inflammatory, gastrointestinal events, Infusion related reactions, Interstitial lung disease events, Myelosuppression/cytopenia, Nephrotoxicity, Neurotoxicity, Pancreatitis, QT prolongation, Secondary primary malignancy, and Tumour lysis syndrome.

**Table *19*. Summary of Treatment-Emergent Adverse Events of Special Interest by Cluster and MedDRA Preferred Term**

| Number of Participants Evaluable for AEs | 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: by AESI Cluster Name and | n (%) | n (%) | n (%) | n (%) |

| Preferred Term | | | | |
|---|---|---|---|---|
| | | | | |
| With any adverse event | 12 (100.0) | 13 (100.0) | 25 (100.0) | 28 (100.0) |
| | | | | |
| Haemorrhage | 5 ( 41.7) | 8 ( 61.5) | 13 ( 52.0) | 9 ( 32.1) |
| Hepatotoxicity | 4 ( 33.3) | 4 ( 30.8) | 8 ( 32.0) | 12 ( 42.9) |
| Infections | 6 ( 50.0) | 6 ( 46.2) | 12 ( 48.0) | 11 ( 39.3) |
| Inflammatory gastrointestinal events | 3 ( 25.0) | 4 ( 30.8) | 7 ( 28.0) | 4 ( 14.3) |
| Infusion related reactions* | 5 ( 41.7) | 6 ( 46.2) | 11 ( 44.0) | 12 ( 42.9) |
| Interstitial lung disease events | 0 | 1 ( 7.7) | 1 ( 4.0) | 1 ( 3.6) |
| Myelosuppression/cytopenia | 10 ( 83.3) | 13 (100.0) | 23 ( 92.0) | 20 ( 71.4) |
| Nephrotoxicity | 0 | 0 | 0 | 0 |
| Neurotoxicity | 1 ( 8.3) | 3 ( 23.1) | 4 ( 16.0) | 0 |
| Pancreatitis | 0 | 0 | 0 | 1 ( 3.6) |
| Qt prolongation | 0 | 2 ( 15.4) | 2 ( 8.0) | 0 |
| Secondary primary malignancy | 0 | 1 ( 7.7) | 1 ( 4.0) | 1 ( 3.6) |
| Tumour lysis syndrome | 1 ( 8.3) | 0 | 1 ( 4.0) | 5 ( 17.9) |

MedDRA v25.1 coding dictionary applied. AEs are graded according to CTCAE version 4.03.
(Data cutoff date - Stratum 1A: 30SEP2022 Phase2: 07OCT2022 and Stratum 1B: 21OCT2022)

***VOD***

All cases of VOD or 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.

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.

**Table *20*. Summary of Participants with VOD/SOS - Monotherapy (Protocol ITCC-059 (B193-WI203581))**

| | Stratum 1A | | | Phase 2 | Total |
|---|---|---|---|---|---|
| | 1.4 mg/m² (N = 12) | 1.8 mg/m² (N = 13) | Total (N = 25) | 1.8 mg/m² (N = 28) | Total (N = 53) |
| a. Number of participants with HSCT | 3 (25.0) | 5 (38.5) | 8 (32.0) | 18 (64.3) | 26 (49.1) |
| b. Number of participants with reported VOD/SOS | 1 (8.3) | 1 (7.7) | 2 (8.0) | 6 (21.4) | 8 (15.1) |
| c. Number of above VOD/SOS participants with prior transplant | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (10.7) | 3 (5.7) |
| d. Number of above VOD/SOS participants without prior transplant | 1 (8.3) | 1 (7.7) | 2 (8.0) | 3 (10.7) | 5 (9.4) |

**Table *20*. Summary of Participants with VOD/SOS - Monotherapy (Protocol ITCC-059 (B193-WI203581))**

| | Stratum 1A | | | Phase 2 | Total |
|---|---|---|---|---|---|
| | 1.4 mg/m² (N = 12) | 1.8 mg/m² (N = 13) | Total (N = 25) | 1.8 mg/m² (N = 28) | Total (N = 53) |
| e. 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) | 1 (1.9) |
| f. 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) | 3 (5.7) |
| g. 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) | 2 (3.8) |
| h. Number (%) of VOD/SOS participants with Post-study HSCT | 0 (0.0) | 0 (0.0) | 0 (0.0) | 5 (27.8) | 5 (19.2) |
| i. 95% CI for post-HSCT VOD rate | [0.00, 70.76] | [0.00, 52.18] | [0.00, 36.94] | [9.69, 53.48] | [6.55, 39.35] |

Note:The 95% CI was calculated based on exact method.

(Data cutoff date - Stratum 1A: 30SEP2022 Phase2: 07OCT2022)

## 2.5.3. Adverse Drug Reactions

The Sponsor determines ADRs following a thorough assessment of available evidence from non-clinical, clinical and post-marketing information. Factors considered in the determination of ADRs may include (but not be limited to) temporal relationship, frequency of occurrence, drug mechanism of action, biological plausibility, dose response, drug class effects, lack of confounding factors, dechallenge and rechallenge information, and an investigator's assessment of relatedness. ADRs in this section may be non-serious or serious. ADR clusters are in upper case and for each cluster, related AE terms (treatment emergent AEs) are combined into a prespecified group of event terms.

ADRs were identified based on whether they were reasonably associated with InO single agent treatment. The most frequently reported ADR clusters (≥20%) are summarized in Table 21.

The most frequently reported serious ADRs (Clustered) (≥10%) in participants who received InO monotherapy (Stratum 1A and Phase 2 Cohort) were listed below:

- INFECTION: 20.8%;
- Febrile neutropenia: 17.0%;
- VOD: 15.1%.

The review of the study data did not identify any new ADRs in paediatric patients, the evaluated events are consistent with the ones already identified in the adult patients.

**Table *21*. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Adverse Reaction (Clustered), and Maximum CTCAE Grade With a Cutoff ≥20% in any Treatment (All Causalities, All Cycles, Grade 3 or higher) - Monotherapy (Protocol ITCC-059 (B193-WI203581))**

| System Organ Class | ADVERSE REACTION | Stratum1A (N=25) All Grades | Stratum1A (N=25) Grade 3 or Higher | Phase2 (N=28) All Grades | Phase2 (N=28) Grade 3 or Higher | Total (N=53) All Grades | Total (N=53) Grade 3 or Higher |
|---|---|---|---|---|---|---|---|
| Blood and lymphatic system disorders | ANAEMIA [b] | 12 (48.0) | 11 (44.0) | 12 (42.9) | 9 (32.1) | 24 (45.3) | 20 (37.7) |
| | Febrile neutropenia | 8 (32.0) | 8 (32.0) | 7 (25.0) | 7 (25.0) | 15 (28.3) | 15 (28.3) |
| | LEUKOPENIA [j] | 7 (28.0) | 7 (28.0) | 10 (35.7) | 8 (28.6) | 17 (32.1) | 15 (28.3) |
| | NEUTROPENIA [l] | 11 (44.0) | 11 (44.0) | 10 (35.7) | 10 (35.7) | 21 (39.6) | 21 (39.6) |
| | THROMBOCYTOPENIA [o] | 15 (60.0) | 13 (52.0) | 12 (42.9) | 11 (39.3) | 27 (50.9) | 24 (45.3) |
| Gastrointestinal disorders | ABDOMINAL PAIN [a] | 8 (32.0) | 1 (4.0) | 5 (17.9) | 0 | 13 (24.5) | 1 (1.9) |
| | Constipation | 7 (28.0) | 0 | 3 (10.7) | 1 (3.6) | 10 (18.9) | 1 (1.9) |
| | Diarrhoea | 5 (20.0) | 0 | 1 (3.6) | 0 | 6 (11.3) | 0 |
| | Nausea | 8 (32.0) | 0 | 9 (32.1) | 0 | 17 (32.1) | 0 |
| | STOMATITIS [n] | 6 (24.0) | 1 (4.0) | 3 (10.7) | 2 (7.1) | 9 (17.0) | 3 (5.7) |
| | Vomiting | 12 (48.0) | 0 | 12 (42.9) | 1 (3.6) | 24 (45.3) | 1 (1.9) |
| General disorders and administration site conditions | FATIGUE [c] | 6 (24.0) | 0 | 3 (10.7) | 0 | 9 (17.0) | 0 |
| | Pyrexia | 13 (52.0) | 1 (4.0) | 13 (46.4) | 1 (3.6) | 26 (49.1) | 2 (3.8) |
| Hepatobiliary disorders | VENOOCCLUSIVE DISEASE [q] | 2 (8.0) | 2 (8.0) | 6 (21.4) | 5 (17.9) | 8 (15.1) | 7 (13.2) |
| Infections and infestations | INFECTION [h] | 11 (44.0) | 8 (32.0) | 9 (32.1) | 3 (10.7) | 20 (37.7) | 11 (20.8) |
| Investigations | Gamma-glutamyltransferase increased | 6 (24.0) | 5 (20.0) | 3 (10.7) | 1 (3.6) | 9 (17.0) | 6 (11.3) |
| | TRANSAMINASE INCREASED [p] | 4 (16.0) | 3 (12.0) | 9 (32.1) | 7 (25.0) | 13 (24.5) | 10 (18.9) |
| Metabolism and nutrition disorders | Decreased appetite | 5 (20.0) | 2 (8.0) | 1 (3.6) | 0 | 6 (11.3) | 2 (3.8) |
| Nervous system disorders | HEADACHE [d] | 6 (24.0) | 0 | 5 (17.9) | 0 | 11 (20.8) | 0 |
| Vascular disorders | HAEMORRHAGE [e] | 10 (40.0) | 0 | 9 (32.1) | 2 (7.1) | 19 (35.8) | 2 (3.8) |

Abbreviation: CTCAE=Common Terminology Criteria for Adverse Events, ADR=Adverse Drug Reaction.
[*]: Singular Event, [++]: Fatal Event and [+]: Serious Singular Event.
TEAEs are defined as AEs that commence on or after Cycle 1 Day 1 but within 10 weeks of last dose of study drug or one day prior start day of new anticancer therapy, whichever occurs first. All VOD events within 1 year after first dose regardless of causality will be included.
Participants are counted only once per treatment in each row. Maximum CTCAE grades are displayed.
The SOC displayed is the SOC associated with the Adverse Reaction.
MedDRA (v25.1) coding dictionary is applied. Adverse events graded according to the NCI CTCAE, version 4.03.
Adverse reactions that are upper case are grouped PT terms.

(Data cutoff date - Stratum 1A: 30SEP2022 Phase2: 07OCT2022

## *Laboratory findings*

### *Haematology*

InO Monotherapy (Stratum 1A and Phase 2 Cohort) in all cycles:

- Anaemia: 24/53 (45.3%) participants had G3 abnormalities, of whom 19 had a shift to G3.
- Decreased lymphocyte count: 16/53 (30.2%) participants had a shift to G3; 22/53 (41.5%) participants had G4 abnormalities, of whom 20 had a shift to G4.
- Decreased neutrophil count: 4/53 (7.5%) participants had a shift to G3; 47/53 (88.7%) participants had G4 abnormalities, of whom 26 had a shift to G4.
- Decreased platelet count: 6/53 (11.3%) participants had a shift to G3; 39/53 (73.6%) participants had G4 abnormalities, of whom 29 had a shift to G4.
- Decreased WBC count: 9/53 (17.0%) participants had a shift to G3; 38/53 (71.7%) participants had G4 abnormalities, of whom 31 had a shift to G4.

***Chemistry***

InO Monotherapy (Stratum 1A and Phase 2 Cohort) in all cycles:

- Increased ALT: 9/53 (17.0%) participants had a shift to G3 abnormalities; 2/53 (3.8%) participant had a shift to G4 abnormalities.
- Increased AST: 11/53 (20.8%) participants had a shift to G3
- Increased blood bilirubin: 3/53 (5.7%) participants had a shift to G3; 2/53 (3.8%) participant had a shift to G4 abnormalities.
- Increased creatinine: 2/53 (3.8%) participants had a shift to G3.
- Increased GGT: 8/33 (24.2%) participants had G3 abnormalities, of whom 6 had a shift to G3; all 33(100%) participants had a shift to G4.
- Hyperkalemia: 1/53 (1.9%) participants had a shift to G3.
- Hypoalbuminemia: 1/53 (1.9%) participant had a shift to G3.
- Hypokalemia: 13/53 (24.5%) participants had G3 abnormalities, of whom 12 had a shift to G3; 1/53(1.9%) participant had a shift to G4.
- Hyponatremia: 1/53 (1.9%) participant had a shift to G3.
- Hypophosphatemia: 2/53 (3.8%) participant had a shift to G3.
- Increased amylase: 1/53 (1.3%) had a shift to G1.

One participant in the Phase 2 part of the study met the laboratory criteria for potential Hy's Law: concurrent ALT/AST $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN and ALP $\leq 2 \times$ ULN or missing. None of these abnormalities were reported as AEs. This subject experienced a Grade 3 VOD on the same day (Study Day 8) of these laboratory abnormalities (ie, 7 days after the only dose of InO). The VOD resolved in 6 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.

## Vital Signs, Physical Findings, and Other Observations Related to Safety

***Electrocardiograms***

- QTcF maximum increase from BL >30 to 60 msec were reported in 5/53 (10.2%) participants who received InO monotherapy (1/24 [4.2%] participant in Stratum 1A, and 4/25 [16.0%] participants in the Phase 2 Cohort, respectively).
- QTcF maximum increase from BL >60 msec were reported in 7/49 (14.3%) participants who received InO monotherapy (3/24 [12.5%] participants in Stratum 1A, and 4/25 [16.0%] participants in the Phase 2 Cohort, respectively). No relevant cardiac AEs were reported.
- QTcF maximum on-treatment absolute value >480 to 500 msec were reported in 4/53 (7.7%) participants who received InO monotherapy (1/25 [4.0%] participant in Stratum 1A, 3/27 [11.1%] participants in the Phase 2 Cohort, respectively).
- QTcF maximum on-treatment absolute value >500 msec were reported in 3/53 (5.8%) participants who received InO monotherapy (1/25 [4.0%] participant in Stratum 1A, and 2/27 [7.4%] participants in the Phase 2 Cohort, respectively). No associated AE was reported.

In Stratum 1A DL2, 1 participant had G1 QT prolonged (probably InO-related) and recovered on the same day; 1 participant had G4 seizure (possibly InO-related) and recovered in 4 days; 1 participant had G3 sinus tachycardia (possibly InO-related) which led to study drug withdrawn. The event was ongoing at death.

### *Safety in special populations*

## *Intrinsic Factors*

For Study ITCC-059 (WI203581), TEAEs of participants who received InO monotherapy were summarized by age, gender, baseline hepatic function, baseline renal function and baseline CD22 expression in leukemic blasts. However, due to the small sample size of participants, the analyses were not powered to compare the safety by intrinsic factors. Therefore, the results are descriptively presented below.

#### *Age*

In the age groups of 2-<12 and 12<18 years, the most frequently reported TEAEs (≥50%) were within the SOCs listed below:

- Investigations (66.7% vs 85.7%), with the most frequent PTs of platelet count decreased, neutrophil count decreased and white blood cell count decreased;
- Blood and Lymphatic System Disorders (63.3% vs 76.2%), with the most frequent PTs of anaemia and febrile neutropenia;
- Gastrointestinal Disorders (63.3% vs 76.2%), with the most frequent PTs of vomiting and nausea;
- General Disorders and Administration Site Conditions (70.0% vs 61.9%), with the most frequent PTs of pyrexia.

Overall, the most frequently reported TESAEs (≥15.0%) in the age groups of 2-<12 and 12 <18 years were within following SOCs:

- Blood and Lymphatic System Disorders (PT of febrile neutropenia) (16.7% vs 19.0%);
- Infections and Infestations (26.7% vs 14.3%), with the most frequent PT being sepsis;
- Hepatobiliary Disorders (PT of VOD) (3.3% vs 19.0%).

#### *Gender*

Overall, the most frequently reported TEAEs (≥50%) in male (n = 36) and female (n = 17) were reported within the SOCs listed below:

- Gastrointestinal Disorders (63.9% vs 82.4%), with the most frequent PTs of vomiting and nausea;
- Investigations (77.8% vs 70.6%), with the most frequent PTs of platelet count decreased, neutrophil count decreased and white blood cell count decreased;
- Blood and Lymphatic System Disorders (66.7% vs 76.5%), with the most frequent PTs of anaemia and febrile neutropenia;
- General Disorders and Administration Site Conditions (69.4% vs 64.7%), with the most frequent PT of pyrexia;
- Metabolism and Nutrition Disorders (38.9% vs 52.9%), with the most frequent PTs of hypokalaemia.

Among the treated participants, VOD was reported in 5 of 36 (13.9%) male participants and 3 of 17 (17.6%) female participants. Among the participants who proceeded to post study HSCT, VOD was reported in 3 of 18 (16.7%) male participants and 2 of 8 (25.0%) female participants.

***Baseline CD22 Expression in Leukemic Blasts***

Median baseline for CD22 expression MFI in leukemic blasts was 2133. Only participants with available baseline CD22 expression in leukemic blasts are discussed below.

Overall, the most frequently reported TEAEs (≥50%) in participants with < median baseline CD22 expression MFI (n = 20) and those with with ≥ median baseline CD22 expression MFI (n = 31) were within the SOCs listed below:

- Investigations (65.0% vs 80.6%), with the most frequent PTs of: platelet count decreased, neutrophil count decreased, white blood cell count decreased and AST increased.
- Blood and Lymphatic System Disorders (60.0% vs 74.2%), with the most frequent PTs of aneamia and febrile neutropenia;
- Gastrointestinal Disorders (65.0% vs 71.0%), with the most frequent PTs of vomiting and nausea;
- General Disorders and Administration Site Conditions (65.0% vs 67.7%), with the most frequent PTs of pyrexia.

Among the treated participants, VOD was reported in 4 of 20 (50.0%) participants with < median baseline
CD22 expression MFI and 3 of 31 (9.7%) participants with ≥ median baseline CD22 expression MFI. Among the participants who proceeded to post study HSCT, VOD was reported in 3 of 10 (30.0%) participants < median baseline CD22 expression MFI and 2 of 16 (12.5%) participants with ≥ median baseline CD22 expression MFI.

***Hepatic Impairment***

Overall, the most frequently reported TEAEs (≥50%) were reported within the SOCs listed below by participants with normal hepatic function (n = 27) vs those with mild hepatic impairment (n = 26):

- Investigations (81.5% vs 69.2%), with the most frequent PTs of platelet count decreased, neutrophil count decreased and white blood cell count decreased;
- Gastrointestinal Disorders (77.8% vs 61.5%), with the most frequent PTs of vomiting and nausea;
- Blood and Lymphatic System Disorders (77.8% vs 61.5%), with the most frequent PTs of anaemia and febrile neutropenia;
- General Disorders and Administration Site Conditions (74.1% vs 61.5%), with the most frequent PTs of pyrexia.

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 function. 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 function.

***Renal Impairment***

Based on limited data from different baseline renal impairment categories, the overall AEs do not appear to be substantially different by renal impairment status.

The most frequently reported TEAEs (≥50%) in participants with normal renal function (n = 45) and those with mild renal impairment (n = 7) were reported within the SOCs listed below:

- Investigations (71.1% vs 100%), with the most frequent PTs of platelet count decreased, neutrophil count decreased, and white blood cell count decreased.
- Blood and Lymphatic System Disorders (66.7% vs 85.7), with the most frequent PTs of anaemia and febrile neutropenia.
- Gastrointestinal Disorders (68.9% vs 71.4%), with the most frequent PTs of vomiting and nausea.
- General Disorders and Administration Site Conditions (66.7% vs 71.4%), with the most frequent PT of pyrexia.

Among the treated participants, VOD was reported in 7 of 45 (15.6%) participants with normal renal function and 1 of 7 (14.3%) participants with mild renal function. Among the participants who proceeded to post study HSCT, VOD was reported in 4 of 20 (20.0%) participants with normal renal function and 1 of 5 (20.0%) participants with mild renal function. No participants with mild renal impairment reported VOD during InO treatment or after post-study HSCT.

## Extrinsic Factors

Data from Study ITCC-059 (WI203581) were examined for the effect of prior HSCT and other baseline diagnosis (prior line of ALL therapies including first relapse of BCP-ALL post allo HSCT, second or greater relapsed BCP-ALL and refractory BCP-ALL). However, due to the small sample size of participants, the study was not powered for formal analyses of factor effects but briefly discussed for transparency.

***Prior Hematopoietic Stem Cell Transplant (HSCT)***

Overall, of the most frequently reported TEAEs (≥50%) were reported within the SOCs listed below by participants with prior HSCT (n = 26) and participants with no prior HSCT (n = 27):

- Investigations (65.5% vs 85.2%), with most frequent PTs of platelet count decreased, neutrophil count decreased and white blood cell count decreased.
- Blood and Lymphatic System Disorders (65.4% vs 74.1%), with the most frequent PTs of anaemia and febrile neutropenia.
- Gastrointestinal Disorders (65.4% vs 74.1%), with the most frequent PTs of vomiting and nausea;
- General Disorders and Administration Site Conditions (84.6% vs 51.9%), with the most frequent PTs of pyrexia;
- Respiratory, Thoracic and Mediastinal Disorders (53.8% vs 25.9%), with the most frequent PT of cough;
- Infections and Infestations (50.0% vs 37.0%), with the most frequent PTs of rhinitis and sepsis;

Among the treated participants, VOD was reported in 3 of 26 (11.5%) participant with prior HSCT and 5 of 27 (18.5%) participants with no prior HSCT. Among the participants who proceeded to post study HSCT, VOD was reported in 2 of 9 (22.2%) participant with prior HSCT and 3 of 17 (17.6%) participants with no prior HSCT.

***Baseline Diagnosis: Prior Line of ALL Therapy***

Overall, the most frequently reported TEAEs (≥50%) were reported within the SOCs listed below in participants of first relapsed post allo HSCT (n = 13), second/greater relapsed (n = 29), and refractory BCP-ALL(n = 11), respectively:

- Investigations (61.5%, 82.8% and 72.7%, respectively), with the most frequent PTs of neutrophil count decreased, platelet count decreased and white blood cell count decreased;
- Blood and Lymphatic System Disorders (69.2%, 69.0% and 72.7%, respectively), with the most frequent PTs of anaemia and febrile neutropenia;
- Gastrointestinal Disorders (69.2%, 69.0% and 72.7%, respectively), with the most frequent PTs of vomiting and nausea;
- General Disorders and Administration Site Conditions (84.6%, 65.5% and 54.5%, respectively), with the most frequent PT of pyrexia;
- Respiratory, Thoracic and Mediastinal Disorders (53.8%, 37.9% and 27.3%, respectively), with the most frequent PTs of cough and epistaxis;
- Skin and Subcutaneous Tissue Disorders (53.8%, 37.9% and 9.1%, respectively), with the most frequent PT of rash in participants with first relapse of post allo HSCT BCP-ALL.

Among the treated participants, VOD was reported in 3 of 29 (10.3%) participants who had second or greater relapsed BCP-ALL and 5 of 11 (45.5%) participants who had refractory BCP-ALL. Among the participants who proceeded to post study HSCT, VOD was reported in 2 of 15 (13.3%) participants who had second or greater relapsed BCP ALL and 3 of 6 (50.0%) participants who had refractory BCP-ALL. No VOD was reported in participants who had first relapse of BCP-ALL post allo HSCT during the InO treatment or after the post-study HSCT (5 participants received HSCT after InO treatment).

## *Safety related to drug-drug interactions and other interactions*

***Drug Interactions***

The discussion of drug interaction is not applicable for Stratum 1A and Phase 2 cohorts in Study ITCC-059 (WI203581) since the single agent of InO was examined.

***Use in Pregnancy and Lactation***

Study ITCC-059 (WI203581)

No pregnancies were reported in female participants or in the partners of male participants in this study. As outlined in the study protocol all female patients of childbearing potential must have a negative serum or urine pregnancy test prior to enrollment; female patients with infants must agree not to breastfeed their infants while on this study; male and female patients of child-bearing potential must agree to use a highly effective method of contraception approved by the investigator during the study, following the CTFG recommendations, and for at least 8 months for females and for at least 5 months for males after the last dose of InO.

## *Discontinuation due to adverse events*

### *Dose Reduction/Interruption/Delay Due to Adverse Events*

In participants who received InO monotherapy, 6 (11.3%) participants had study drug interruption/reduction/delay due to AEs of headache (1), increased ALT (4), increased AST (2) and febrile neutropenia (1), of which, all except the headache were considered to be TR by the investigator.

In Stratum 1A, 1 (8.3%) participant in DL1 had InO interruption due to headache (not TR).

In the Phase 2 Cohort, 5 (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 TR.

### *Permanent Discontinuation From Study Intervention due to Adverse Events*

In participants who received InO monotherapy, 12 (22.6%) permanently discontinued InO due to TEAEs, of which, 9 (17.0%) participants permanently discontinued InO due to TR TEAEs. The all-causality TEAEs associated with permanent discontinuation in ≥2 participants included increased ALT and decreased platelet count.

In Stratum 1A, 8 (32.0%) participants permanently discontinued InO due to TEAEs, of which 7 (28.0%) participants permanently discontinued InO due to TR TEAEs. The all-causality TEAEs associated with permanent discontinuation in ≥2 participants included increased ALT and decreased platelet count.

In the Phase 2 Cohort, 4 (14.3%) participants permanently discontinued InO due to TEAEs of increased ALT/AST, VOD, and multiple organ dysfunction syndrome. The increased ALT/AST and VOD reported in 2 participants were TR.

## *Post marketing experience*

Besponsa received approval in the EU on 29 June 2017 as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B cell precursor ALL. Adult patients with Ph+ relapsed or refractory B cell precursor ALL should have failed treatment with at least 1 TKI.

On 06 March 2024, an extension of indication was approved by FDA to provide for the treatment of R/R CD22-positive B-cell precursor ALL in paediatric patients 1 year and older.

As of 28 June 2024, no new safety information was identified upon review of the cases involving paediatric patients. During the reporting period (29 December 2023 through 28 June 2024), there were 19 cases involving paediatric patients (8.9%, compared to 14.5% in the previous reporting period when InO had not been approved for paediatric use) reported from the post-marking sources:

The use of InO is not approved in paediatric patients except in Japan (since 26 March 2024) and US (since 06 March 2024 for patients ≥1 year old). Therefore, 13 paediatric cases (including 2 from Japan received before 26 March 2024) reported the PT Off label use.

Of these 13 cases, 1 case co-reported myelosuppression, mucosal inflammation, and pyrexia. Outcome of myelosuppression was unknown, while mucosal inflammation and pyrexia resolved. Action taken with InO was unknown. Methotrexate, cytarabine, pegaspargase, dexamethasone, cyclophosphamide, vincristine and prednisone were all listed as co-suspects.

No new safety information was identified upon review of the remaining 12 cases reporting only Off-label use.

Among the 6 paediatric cases received from Japan after 26 March 2024, 3 reported serious veno-occlusive liver disease and the remaining 3 the nonserious events neoplasm progression (2) and platelet count decreased (1). No new safety information was identified upon review of these cases.

During the reporting period, there were 14 clinical trial cases involving paediatric participants from Study B1931036: 9 did not receive InO and were therefore excluded from the analysis; the remaining 5 (all female, aged from 11-17 years old) experienced AEs of bone marrow failure (recovered, unrelated), febrile neutropenia (recovered, related), loss of consciousness (recovered, unrelated), mucosal inflammation (recovered, unrelated), pyrexia (recovered, unrelated), sepsis (fatal, unrelated) (1 each). an 11-year-old female participant experienced the event of febrile neutropenia 10 days after the third InO infusion. Dexamethasone was reported as co-suspect medication. The event resolved 2 days later. The fatal case of sepsis involved the same participant: she experienced fatal sepsis (unrelated) 2 months after the febrile neutropenia episode. No additional InO infusions were administered after the 3 listed above.

## 2.5.4. Discussion on clinical safety

The safety database of Study ITCC-059 consists of 25 (Phase I) + 28 (Phase II), i.e., 53 paediatric patients treated with InO monotherapy. The subjects were 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. Twelve patients in the Phase I cohort received a dose of 1.4 mg/m², while the rest received the Recommended Phase 2 Dose (RP2D) of 1.8 mg/m².

The median number of administered cycles across the entire population (N=53) was 2 for InO monotherapy, the median dose was 2.63 mg/m² (range: 0.57-6.47 mg/m$^2$), and the median relative dose intensity was 100% (range: 44.56–105.22).

Among the 53 participants treated with InO monotherapy, 43 (81.1%) had G3/4 TEAEs; 7 (13.2%) had G5 TEAEs which included disease progression (2), multiple organ dysfunction syndrome (2), sepsis, pneumonia, encephalopathy, and hypoxia (1 each).

The most commonly reported TEAEs (⩾ 20%) were decreased platelet count (n = 27 [50.9%]), pyrexia (n = 26 [49.1%]), anaemia and vomiting (n = 24 [45.3%] each), followed by decreased neutrophil count (n = 21 [39.6%]), nausea (n = 17 [32.1%]), febrile neutropenia (n = 15 [28.3%]) and AST increase (n = 12 [22.6%]). SAEs were reported in 33 (62.3%) participants; the most frequently reported TESAEs (≥10%) were febrile neutropenia (n = 9 [17.0%]) and hepatic veno-occlusive disease (VOD) (n = 8 [15.1%]).

The overall AE profile does not appear to differ substantially depending on age; the frequencies are higher in the older group (12-18 years) for most adverse reactions, with the exception of infections, where a higher frequency was observed in the younger group (2-12 years), i.e., (26.7% vs 14.3%).

A total of 47 patients (56.6%) died during the study, the majority (n=28) due to disease progression. For 17 patients, the cause of death was described as Other, which included e.g. sepsis and transplant-related events. For the remaining 2 patients the cause of death was described as Toxicity, however, the toxicity seemed not due to InO: One case of encephalopathy leading to cardiac arrest and one case of bilateral pneumonitis started after follow-up ALL therapy. The overall pattern of these cases does not immediately raise concern.

Treatment interruption due to TEAE was reported in 6 (11.3%) patients; the most commonly reported treatment-related AEs leading to study drug interruption or dose reduction were increased ALT and increased AST. A total of 11 patients permanently discontinued treatment due to AEs that were considered treatment related: increased ALT (n=4), increased AST (n=2), platelet count decreased

(n=2) and VOD (n=2). Overall, the pattern of dose modifications and treatment discontinuations in the paediatric patients mirrors the known safety profile from adults.

The most commonly reported AESIs (≥ 30%) in the total population (N=53) were Myelosuppression (n = 43 [81.1%]), Infusion-related reactions and infections (n = 23 [43.4%], each), Haemorrhage (n = 22 [41.5%]), and Hepatotoxicity (n = 20 [37.7%]).

VOD was reported in 8 out of 53 patients (15.1%) after InO monotherapy, 5 of which occurred after subsequent HSCT. The post-HSCT VOD rate was 5/26 (19.2% [95% CI: 6.55-39.35]). The incidence rates were comparable with those reported in the adult study. About half of the paediatric patients had mild liver dysfunction, and VOD was more common in those with liver impairment. Risk factors for VOD are well described in the SmPC.

QT Prolongation: In the paediatric study, 14% had an increase in QTcF > 60 msec, of which 6% had QTcF values > 500 msec. QTcF increases were observed in both adults and children, but a higher proportion of pediatric patients had QTcF > 500 msec (6% compared to 0% in adults). Additionally, 1 participant had Grade 1 QT prolongation, 1 participant had Grade 4 seizure and 1 participant had Grade 3 sinus tachycardia, which led to study drug withdrawal. Due to the relatively high incidence and given that QT prolongation is already listed in the 4.8 SmPC ADR table for adults, the causal association is considered at least a reasonable possibility. The applicant was requested and has agreed to list QT prolongation in the 4.8. SmPC ADR table for children. In addition, to mitigate this risk, the MAH has increased the time of infusion to 1.5 hours in paediatric patients with a body weight <35 kg.

ADRs: The type and frequency of ADRs are similar to those reported in the adult population. Relatively higher frequencies are observed for Tumor Lysis Syndrome (TLS), vomiting, fever, and elevated transaminases, while lower frequencies are seen for infections, among others. ADRs are considered adequately described in 4.4. and 4.8 sections of the SmPC.

The safety database, however, is very limited, specifically in smaller children. Moreover, exposure in the latter is unclear. Nevertheless, the data was generally consistent with the known safety profile of InO in adults and no new safety concerns have been identified.

To provide further data the applicant has agreed to submit the final results of the ongoing, randomised B1931036 study at the earliest appropriate regulatory opportunity (REC).

### 2.5.5. Conclusions on clinical safety

The final data review from Study ITCC-059 did not reveal any new safety concerns in paediatric patients. The events observed were consistent with those previously identified in earlier reports and in adult populations. As seen 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 in paediatric patients.

Overall, the identified risks are considered manageable and appropriately communicated in the product information.

### 2.5.6. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.6. Risk management plan*

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.0 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 4.0 with the following content:

## *Safety concerns*

**Table 22. Summary of Safety Concerns**

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

SOS=sinusoidal obstruction syndrome; VOD=venoocclusive disease

## *Pharmacovigilance plan*

None

## *Risk minimisation measures*

**Table 23. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| **Important Identified Risks** | | |
| Grade ³3 and/or serious hepatotoxicity, including all VOD/SOS | Routine risk minimisation measures:<br>SmPC Sections 4.2, 4.3, 4.4, and 4.8.<br>PL Sections 2, 3 and 4.<br><br>Additional risk minimisation measures: None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: DCA for hepatic events.<br><br>Additional pharmacovigilance activities: None. |

**Table 23. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| Myelosuppression/ cytopenia | Routine risk minimisation measures:<br>SmPC Sections 4.2, 4.4, and 4.8.<br>PL Sections 2, and 4.<br>Additional risk minimisation measures: None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.<br>Additional pharmacovigilance activities: None. |
| **Important Potential Risks** | | |
| Interstitial lung disease | Routine risk minimisation measures:<br>None.<br>Additional risk minimisation measures: None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.<br>Additional pharmacovigilance activities: None. |
| Inflammatory gastrointestinal events | Routine risk minimisation measures:<br>None.<br>Additional risk minimisation measures: None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.<br>Additional pharmacovigilance activities: None. |
| Pancreatitis | Routine risk minimisation measures:<br>None.<br>Additional risk minimisation measures: None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.<br>Additional pharmacovigilance activities: None. |
| Second primary malignancy | Routine risk minimisation measures:<br>None.<br>Additional risk minimisation measures: None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.<br>Additional pharmacovigilance activities: None. |
| Reproductive and developmental toxicity (post exposure during pregnancy and while breast feeding) | Routine risk minimisation measures:<br>SmPC Sections 4.6, and 5.3.<br>PL Section 2.<br>Additional risk minimisation measures: None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.<br>Additional pharmacovigilance activities: None. |
| Neurotoxicity | Routine risk minimisation measures:<br>None.<br>Additional risk minimisation measures: None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.<br>Additional pharmacovigilance activities: None. |
| Nephrotoxicity | Routine risk minimisation measures:<br>None.<br>Additional risk minimisation measures: None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.<br>Additional pharmacovigilance activities: None. |
| **Missing Information** | | |

**Table 23. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| Use in patients with moderate or severe hepatic Impairment | Routine risk minimisation measures:<br>SmPC Sections 4.2, and 5.2.<br>PL Section 2.<br>Additional risk minimisation measures: None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.<br>Additional pharmacovigilance activities: None. |
| Use in patients with severe renal impairment | Routine risk minimisation measures:<br>SmPC Sections 4.2, and 5.2.<br>Additional risk minimisation measures: None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.<br>Additional pharmacovigilance activities: None. |
| Use in Hispanic and Black patients | Routine risk minimisation measures:<br>SmPC Section 5.2.<br>Additional risk minimisation measures: None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.<br>Additional pharmacovigilance activities: None. |

## *2.7. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Belgium, Ireland and United Kingdom (Northern Ireland)

### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

There have not been revisions that significantly affect the overall readability and design of the package leaflet.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

Besponsa is indicated as monotherapy for the treatment of paediatric patients 1 year and older with CD22-positive B cell precursor ALL: in first relapse after allo-haematopoietic stem cell transplant (HSCT); after any first relapse in patients with Very High Risk (VHR) disease (see section 5.1); after a second or greater relapse; and in those with refractory disease. Patients with Philadelphia chromosome positive (Ph+) disease should have exhausted relevant BCR-ABL targeting treatment options.

### 3.1.2. Available therapies and unmet medical need

There is an unmet medical need for patients with late-stage R/R B-lineage ALL. The goal of treatment is generally to achieve remission with low MRD, often with the aim of undergoing allo-HSCT. Following a first relapse, only about 40% of children can be successfully salvaged. Prognosis after further relapses is assumed to be yet poorer. Therefore, new therapeutic approaches are urgently needed to overcome chemotherapy resistance and improve outcome.

### 3.1.3. Main clinical studies

The phase I/II study ITCC-059 was an open-label, multi-cohort SAT in paediatric patients (≥1 and <18 years of age) with R/R CD22-positive ALL.

The present application is based on the two InO monotherapy cohorts from the ITCC-059 study: Stratum 1A (exploratory) and Phase 2 (confirmatory). Stratum 1A was a phase 1 dose-finding part that aimed to determine recommended dose of InO monotherapy. The Stratum 1A and Phase 2 cohorts included 25 and 28 patients, respectively. A total of 41 patients received the recommended dose (1.8 mg/m2/cycle) during either phase 1 or phase 2.

The primary endpoint was ORR, defined as the percentage of patients with CR/CRi/CRp, in the Phase 2 cohort. Secondary endpoint were ORR after cycle 1 (Stratum 1A and Phase 2 cohort, respectively), ORR in Stratum 1A, MRD, DoR and HSCT and CAR-T rate.

With respect to hypothesis, the applicant specified that an overall response rate (ORR=CR/CRi/CRp) of 30% or less is not promising and an ORR of over 55% is promising.

## *3.2. Favourable effects*

In the Phase 2 cohort, 22 out of 28 patients achieved CR (CR: 18, CRp: 1, CRi: 3) resulting in an estimated ORR of 78.6% (95% CI [59.0, 91.7]). Fourteen (63.6%) patients had subsequent events (8 relapses and 6 deaths), resulting in a median DoR of 7.6 months (95% CI: 3.3-NE).

In the Phase 2 cohort, all 22 responders achieved remission after the first cycle of therapy. The proportion of patients with complete remission did however increase from 42.9% after cycle 1 to 64.3% over multiple courses of InO therapy.

Among the patients in Stratum 1A that were allocated to the recommended dose, 11 out of 13 (84.6%, 95% CI [54.6, 98.1]) had achieved CR at the end of Cycle 1. This is supportive of the observation that the majority of patients who had an objective response, responded during the first cycle.

MRD reached a relevant outcome with MRD negativity for patients achieving CR/CRi/CRp;  nrate (%) [95% CI] based on flow cytometry scoring 22/22 [100% (95% CI: 84.6, 100.0)] and MRD negativity for patients achieving CR/CRi/CRp; nrate (%) [95% CI] based on RQ-PCR scoring 19/22 [86.4% (65.1, 97.1)]

In the Phase 2 cohort, 64.3% (n=18) of the patients received allo-HSCT post InO-treatment. In Stratum 1A, 38.5% (n=5) of the patients allocated to the recommended dose had allo-HSCT. The possibility of HSCT is understood to be caused by the test treatment.

## *3.3. Uncertainties and limitations about favourable effects*

In the present SAT, a total of 41 patients were allocated to the recommended dose of 1.8 mg/m2/cycle (28 in Phase 2 and 13 in Phase 1). Such a limited number of participants is associated with risks such as greater susceptibility to selection bias and low precision of estimates. Furthermore, only the primary

endpoint was type I error controlled (based on 28 patients) and all other results are primarily descriptive.

There are no patients in the study treated after first relapse unless this occurred after HSCT. Moreover, there are no patients with Ph+ disease which contributed to the revision of the initially claimed indication.

## *3.4. Unfavourable effects*

The adverse effect profile of Besponsa in paediatric patients appears qualitatively similar to that seen in adults. The key safety issues are myelosuppression and hepatic veno-occlusive disease (VOD).

The most important unfavourable effects of Besponsa in paediatric patients include myelosuppression, hepatotoxicity, and infections. Specifically, 71.4% of patients experienced myelosuppression, 42.9% experienced hepatotoxicity, and 39.3% experienced infections.

Overall, 43 (81.1%) participants experienced G3/4 TEAEs and 33 (62.3%) SAEs. The most common (> 30%) adverse reactions in the paediatric study (N=53) were thrombocytopenia (51%), pyrexia (49%), anaemia (45%), vomiting (45%), neutropenia (40%), infection (38%), haemorrhage (36%), leukopenia (32%), and nausea (32%).

The most common ($\geqslant$ 2%) serious adverse reactions in the paediatric study were febrile neutropenia (15%), VOD (1315%), and infection (13%).

A total of 7 (13.2%) participants had G5 TEAEs, which included disease progression (2), multiple organ dysfunction syndrome (2), sepsis, pneumonia, encephalopathy, and hypoxia (1 each).

Given the limited safety database in paediatric patients, evidence of roughly similar PK exposure in paediatric and adult patients with ALL is considered pivotal. The MAH has developed a population PK model deemed appropriate for simulation of PK exposure across body weight in paediatric and adult ALL patients. Overall, simulations from the population PK model support the proposed dosing regimen for paediatric patients; however, an elevated $C_{max}$ is expected in paediatric patients with low body weight (<35 kg). To mitigate the known risk of QT prolongation, the time of infusion has been increased to 1.5 hours in paediatric patients with a body weight <35 kg.

## *3.5. Uncertainties and limitations about unfavourable effects*

The safety database is limited in number. Therefore, frequency estimates are uncertain.

The safety database is very limited (N=12) in children 6 years of age and below.

## *3.6. Effects Table*

**Table 24. Effects Table for besponsa as monotherapy for the treatment of paediatric patients 1 year and older with CD22-positive B cell precursor ALL: in first relapse after allo-haematopoietic stem cell transplant (HSCT); after any first relapse in patients with Very High Risk (VHR) disease; after a second or greater relapse; and in those with refractory disease. Patients with Philadelphia chromosome positive (Ph+) disease should have exhausted relevant BCR-ABL targeting treatment options. (data cut-off: 30 September 2022 for Stratum 1A and 7 October 2022 for Phase 2).**

| Effect | Short description | Unit | Treatment: InO monotherapy | Uncertainties / Strength of evidence |
|---|---|---|---|---|
| ORR in Phase 2 cohort | Defined as the % of patients with CR/CRi/CRp, measured as best response during InO treatment | N (%) [95% CI] | 22 (78.6%) [59.0, 91.7] | Significant<br><br><.0001 (1-sided) |
| ORR after cycle 1 (stratum 1A) | Defined as the % of patients with CR/CRi/CRp, measured as best response after cycle 1 | N (%) [95% CI] | 11 (84.6%) [[54.6, 98.1] | Lacks type 1-error control |
| DoR (Phase 2 cohort) | Defined as the time between achieving response (CR/CRi/CRp) after starting study treatment and documented relapse or death | Months (95% CI) | 7.6 months (95% CI: 3.3-NE) | Lacks type 1-error control |
| MRD negativity for patients achieving CR/CRi/CRp; nrate (%) [95% CI] based on flow cytometry | minimal residual disease | N [%] (95% CI) | 22/22 [100% (95% CI: 84.6, 100.0)] | Lacks type 1-error control |
| MRD negativity for patients achieving CR/CRi/CRp; nrate (%) [95% CI] based on RQ-PCR | minimal residual disease | N [%] (95% CI) | 9/22 [86.4% (65.1, 97.1)] | Lacks type 1-error control |
| HSCT rate (Phase 2 cohort) | Patients who underwent allo-HSCT after treatment with InO | N (%) | 18 (64.3%) | Lacks type 1-error control |
| **Unfavourable Effects (N=53)** | | | | |
| Myelosuppression | All | N (%) | 43 (81%) | |
| Haemorrhage | All | N (%) | 22 (43.4%) | |
| Hepatotoxicity | All | N (%) | 20 (37.7%) | |
| VOD | All | N (%) | 8 (15.1%) | |

Abbreviations: ORR (obejective response rate); CR (complete remission); CRi (complete remission with incomplete hematologic recovery); CRp (complete remission with incomplete platelet recovery); DoR (duration of response); MRD (minimal residual disease); HSCT (haematopoietic stem cell transplantation); VOD (veno-occlusive disease)

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

The submitted single arm trial data include a limited number of patients. Nevertheless, the applicant's success criterion (ORR >55%) was met. Observed data indicate clinically relevant activity of Besponsa for children in advanced stage of difficult-to-treat R/R BCP-ALL, with an ORR rate of 78.6% and high rates of MRD negativity. This is associated with a relevant proportion of patients being able to receive HSCT.

It is not evident that the MAH has demonstrated the relevance and utility of Besponsa after a first relapse in patients not having undergone HSCT. The CSR's provided a SAT of limited size including only first relapse post allo-HSCT or second or greater R/R disease.

The MAH proposes extrapolation of the effect observed in the adult INO-VATE to a corresponding paediatric indication and provides arguments regarding the three risk groups, standard risk (SR), high risk (HR) and very high risk (VHR) to support the proposed wording.

It is noted that this risk stratification score guides the design of the ongoing EU-wide IntreALL study/guidelines, therefore, this is accepted.

Extrapolation of effect to the SR and HR risk groups is, however, not supported. Patients with SR and HR disease achieve clinically relevant responses to chemotherapy. It is noted that, paediatric patients with HR disease are eligible for enrolment in an ongoing RCT evaluating the safety and efficacy of InO as add-on to UK-ALLR3 chemotherapy regimen as compared with standard UKALL-R3 chemotherapy (PIP study 2). This indicates both equipoise for randomisation, as well as the need for the study to determine the utility of InO in the context, not least given the toxicity of this product, including VOD. Considering these factors, a positive B/R cannot be concluded for SR and HR patients based on the limited data available as the basis of the present claim.

VHR patients have very unsatisfying treatment outcomes despite intensive re-induction chemotherapy and HSCT. This subgroup of patients is currently investigated in cohort 3 of the ITCC-059 study. At the time of data analysis (01 May 2025), an overall response after C1 of 67.6% (95% CI: 50.2-80.2) was demonstrated, while 18/25 responding patients achieved MRD negativity (72%). Among 16 responders who underwent consolidation with HSCT post-InO re-induction, 1-year EFS and OS rates were 87.5% (95% CI: 72.7-100.0) and 86.5% (95%CI: 70.7-100.0), respectively. In conclusion, use in patients in first relapse without prior HSCT, who are deemed at VHR is agreed, as Besponsa is deemed a reasonable treatment option based on the totality of available data on use in pediatric ALL. However, the utility and B/R of use in HR and SR patients in that situation has not been shown.

Moreover, the claimed indication includes patients with Ph+ disease. In the absence of a specific efficacy demonstration, the MAH was asked to justify for which, if any, patients with Ph+ disease the efficacy and utility of Besponsa treatment may be inferred. In response to this, the MAH refers to the pivotal study in procedure EMEA/H/C/4119 that concluded the efficacy of Besponsa, including in the Ph+ subpopulation, which represented approx. 20% of the study population. The MAH contends that these results are applicable to the paediatric population, given a biological rationale that Ph+ ALL represents the same disease in both adults and children. The shared underlying genetic abnormality is recognized. It is agreed that this may be considered to suffice for the proposed extrapolation, given the rarity of Ph+ disease in children. The MAH has updated the indication statement accordingly.

Safety data are qualitatively consistent with the known safety profile of InO in adults. No new safety concerns have been identified; however, the safety database is very limited, specifically in smaller children. Given the limited safety database, evidence of roughly similar PK exposure in paediatric and adult patients with ALL is considered pivotal. The MAH has developed a population PK model deemed appropriate for simulation of PK exposure across body weight in paediatric and adult ALL patients. Overall, simulations from the population PK model support the proposed dosing regimen for paediatric patients; however, an elevated $C_{max}$ is expected in paediatric patients with low body weight (<35 kg). To mitigate the known risk of QT prolongation, the time of infusion was increased to 1.5 hours in paediatric patients with a body weight <35 kg.

### 3.7.2. Balance of benefits and risks

The B/R of Besponsa used as monotherapy in paediatric CD22 positive B cell precursor ALL as per the final agreed indication is considered positive.

### 3.7.3. Additional considerations on the benefit-risk balance

N/A

## *3.8. Conclusions*

The overall B/R of Besponsa is positive.

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change(s):

| **Variation(s) accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a Addition of a new therapeutic indication or modification of an approved one | Variation type II | I and IIIB |

Extension of indication to include treatment of paediatric patients 1 year and older with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia (ALL) for Besponsa, 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 paediatric patients (≥1 and <18 years of age) with R/R CD22-positive ALL; Study WI235086 is an open-label, Phase 1 study to assess safety and tolerability of InO in Japanese paediatric patients with R/R CD22-positive AL. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives for Belgium, Ireland and United Kingdom (Northern Ireland) in the Package Leaflet.

## *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.

## *Paediatric data*

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0079/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

## *Similarity with authorised orphan medicinal products*

The CHMP, by consensus, is of the opinion that Besponsa is not similar to Tecartus, Kymriah and Blincyto within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

# 5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

## *Scope*

Please refer to the Recommendations section above.

## *Summary*

Please refer to Scientific Discussion EMA/VR/0000257310