Amsterdam, 26 March 2026
EMADOC-1700519818-3071647
Committee for Medicinal Products for Human Use (CHMP)

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

Besponsa

Inotuzumab ozogamicin

Procedure no: EMA/PAM/0000319860

Note

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

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Abbreviation	Term
ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
allo	allogeneic
amended mR3	dexamethasone dose reduced by 50% in mR3
ASP	asparaginase
AST	aspartate aminotransferase
BCP	B-cell precursor
BLA	Biologics license application
BLQ	below limit of quantification
CD	cluster of differentiation
CI	confidence interval
CHMP	committee for medicinal products for human use
CNS	central nervous system
CR	complete remission/response
CRi	complete remission with incomplete hematologic recovery
CRp	complete remission with incomplete platelet recovery
CSR	clinical study report
CTC	Common Terminology Criteria
CTCAE	common terminology criteria for adverse events
DL	dose level
DLT	dose limiting toxicity
DMH	dimethylhydrazide
DoR	duration of response
EC	European Commission
ECG	electrocardiogram
EFS	event free survival
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
FU	follow-up
G	grade
GGT	gamma-glutamyl transferase
GvHD	graft versus host disease
HR	hazard ratio
HSCT	hematopoietic stem cell transplant
IC50	half-maximal inhibitory concentration
InO	Inotuzumab Ozogamicin
IPD	important protocol deviations
IT	intrathecal
IV	intravenous
LLN	lower limit of normal
LPLV	last patient last visit
LPLD	last patient last dose
MAH	marketing-authorisation holder
MOF	multiple organ failure
mR3	a modified collaborative UKALL trial for relapsed and refractory ALL; InO replaces mitoxantrone; includes dexamethasone 20 mg/m2 on Days 1-5 and 15-19 during induction
MRD	minimal residual disease
MTD	maximum tolerated dose
NE	non-estimable
ORR	overall response rate
OS	overall survival
PD	pharmacodynamic(s)
PIP	Pediatric Investigation Plan
PK	pharmacokinetic(s)

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

Steps taken for the assessment	
Description	**Date**
CHMP Rapporteur AR	2 March 2026
CHMP comments	n/a
Updated CHMP Rapporteur AR	n/a
CHMP outcome	26 March 2026

1. Introduction

On 16 December 2025, the MAH submitted the CSR for a paediatric study for Besponsa within 6 months of LPLV to report the follow-up paediatric data in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

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

2. Scientific discussion

2.1. Information on the development program

Study ITCC-059 is a completed multi-cohort study. The CSR is being submitted in accordance with Article 46 of the Paediatric Regulation (European Commission [EC] No 1901/2006). The MAH is submitting the CSR under Article 46 within 6 months of LPLV to report the follow-up paediatric data.

Study completion (LPLV) date was on 20 June 2025. LPLD + 3 months safety follow up/PCD was on 12 September 2022.

This study is part of an approved EU PIP (PIP Study 1-EMEA-001429-PIP01-13-M08; Table 1).

The PCD CSR was submitted to support the labelling for paediatric patients with CD22-positive relapsed/refractory Acute Lymphoblastic Leukaemia. Update of sections 4.2, 4.6, 4.8, 5.1 and 5.2 of the SmPC in order to update paediatric information based on final results from studies ITCC-059 (WI203581) and INO-Ped-ALL-1 (WI235086) was submitted in July 2023 (Variation - EMEA/H/C/004119/II/0026) with a CHMP Opinion received on 14 December 2023.

Extension of indication to include treatment of paediatric patients 1 year and older with relapsed or refractory CD22-positive B-cell precursor ALL for Besponsa, based on final results from studies ITCC-059 (WI203581) and INO-Ped-ALL-1 (WI235086) was submitted to EMA (EMA/VR/0000257310) in March 2025 (final opinion in March 2026). 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.

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

Table 1. Paediatric investigation plan for inotuzumab ozogamicin

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

2.2. Information on the pharmaceutical formulation used in the study

Besponsa is marketed as a 1 mg powder for concentrate for solution for infusion.

2.3. Clinical aspects

2.3.1. Introduction

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

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

Approvals of InO for treatment for adults with R/R ALL have been granted in the US (BLA761040 on 17 August 2017, EU (EMEA/H/C/4119 on 29 June 2017), Switzerland (10 July 2017), and Japan (19 January 2018) (specific indications vary according to country/region) based on the favorable benefit/risk demonstrated in Study B1931022.

The approved indication in the EU is:

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

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

The safety and efficacy of Besponsa in children aged 0 to < 18 years have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2. but no recommendation on a posology can be made.

With the current submission, in accordance with Art 46 of Regulation (EC) No. 1901/2006, as amended, the MAH submitted a CSR including all data collected from the cut-off date for the primary CSR up to the Last Subject Last Visit for the 3 year follow-up period for:

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

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

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

As described in Section 2.1 above, no updates to the SmPC are proposed within the current procedure. The SmPC is being updated in the context of an ongoing variation procedure for an extension of indication to include treatment of paediatric patients 1 year and older with relapsed or refractory CD22-positive B-cell precursor ALL (EMA/VR/0000257310, opinion March 2026).

2.3.2. Clinical study ITCC-059

Description

Table 2- Study objectives and endpoints

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

Table 3- Study objectives and endpoints (cont.)

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

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

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

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

Methods

Study participants

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

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

Treatments

Stratum 1A:

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

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

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

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

Stratum 1B: 30 participants were treated with combination therapy of InO plus vincristine and dexamethasone.

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

- Initially, 4 participants received InO at a starting dose of 1.1 mg/m2/cycle, combined with the UKALL-R3 modified regimen (referred to as mR3 in tables: IV vincristine 1.5 mg/m2 on Days 3, 10, 17 and 24; oral dexamethasone 20 mg/m2/day on Days 1-5 and 15-19, divided in 2 daily doses, and IT methotrexate prophylaxis on Days 1 and 8).
- Due to 2 out of 4 participants at this 1.1 mg/m2/cycle dose level experiencing DLTs, the dose of InO was de-escalated to 0.8 mg/m2/cycle as required by the protocol while awaiting approval of Protocol Amendment 4. During this delay, 6 participants were treated with 0.8 mg/m2/cycle + mR3; 1 participant randomized to 0.8 mg/m2/cycle dose level was mis-dosed by site at 1.8 mg/m2/cycle (reported as an IPD), thus the participant was counted in 1.8 mg/m2/cycle group in tables. The actual dose of this participant received was 1.3 mg/m2 in total (0.8 mg/m2 on C1D1 and 0.5 mg/m2 on C1D8; C1D15 dose was not given as the error was recognized).
- After Study ITCC-059 LPLV CSR, Appendix 16.1.1, Protocol Amendment 4 was approved, the dose of InO was re-escalated to 1.1 mg/m2 during Cycle 1; 6 participants received InO combined with a reduced dose of dexamethasone at 10 mg/m2/day (referred to as amended mR3 in tables). Next, 3 participants received nO 1.4 mg/m2/cycle + amended mR3. Finally, 10 participants received InO 1.8 mg/m2/cycle + amended mR3. A total of 19 participants were treated with the reduced dose of dexamethasone.

- A total of 12 (40.0%) participants completed the treatment phase and the required FU. 16 (53.3%) participants discontinued due to death. 1 (3.3%) participant was lost to FU, and 1 (3.3%) participant discontinued due to other reason.

Objective(s)

See Table 3.

Outcomes/endpoints

See Table 3.

Sample size

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

Randomisation and blinding (masking)

N/A

Pharmacokinetics

Serum samples were collected for InO and unconjugated calicheamicin.

A specific and sensitive bioanalytical method using LC-MS/MS method was developed and validated to measure InO and unconjugated calicheamicin.

Statistical Methods

See Table 3.

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

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

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

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

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

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

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

Results

Participant flow

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

The Full Analysis Set included all enrolled participants who received at least 1 dose of study

therapy and was used for the efficacy analysis and the safety analysis (Stratum 1A: 25 participants, Phase 2 Cohort: 28, Stratum 1B: 30).

The PK Analysis Set for Stratum 1B includes all 30 participants in the Full Analysis Set who provided at least 1 PK sample of interest.

Pharmacokinetics

After a single dose (C1D1), InO mean maximum serum concentration in Stratum 1B was 141.6 ng/mL in 0.8 mg/m2 + mR3 group, 242.0 ng/mL in 1.1 mg/m2 + mR3 group, 203.2 ng/mL in 1.1 mg/m2 + amended mR3 group, 248.0 ng/mL in 1.4 mg/m2 + amended mR3 group, and 288.9 ng/mL in 1.8 mg/m2 + amended mR3 group, respectively. After multiple doses, mean maximum serum concentration was 433.5 ng/mL in 0.8 mg/m2 + mR3 group, 287.5 ng/mL in 1.1 mg/m2 + mR3 group, 197.8 ng/mL in 1.1 mg/m2 + amended mR3 group, 265.0 ng/mL in 1.4 mg/m2 + amended mR3 group, and 363.7 ng/mL in 1.8 mg/m2 + amended mR3 group, respectively, at C2D15.

Baseline data

Demographic and baseline characteristics are presented in Study ITCC-059 PCD CSR and discussed in other procedures (EMEA/H/C/004119/P46/004, EMA/VR/0000257310 (opinion March 2026)). No new information is being provided with this Critical Expert Overview.

Efficacy results

Primary Endpoint

Results for ORR and MRD are provided in Study ITCC-059 PCD CSR, Sections 5.1.1-4 and discussed in other procedures (EMEA/H/C/004119/P46/004, EMA/VR/0000257310 (opinion march 2026)). There were no updates after the study PCD data-cutoff.

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

Secondary endpoints (selected)

DoR

Stratum 1A:

Of the 20 participants who achieved CR/CRi/CRp in Stratum 1A, 14 (70.0%) participants had subsequent events, of which 12 events were relapse and 2 were death. The median DoR was 8.0 months (95% CI: 3.9-13.9) for Stratum 1A, with 6.9 months (95% CI: 1.1-8.4) in DL1 and 13.9 months (95% CI: 3.9-NE) in DL2.

Phase 2 Cohort:

Of the 22 participants who achieved CR/CRi/CRp in the Phase 2 Cohort, 14 (63.6%) participants had subsequent events, of which 8 events were relapse and 6 were death. The median DoR was 7.6 months (95% CI: 3.3-NE).

Stratum 1B:

Of the 24 participants who achieved CR/CRi/CRp in Stratum 1B, 14 (58.3%) participants had subsequent events, of which 9 events were relapse and 5 were death. The median DoR was 8.4 months (95% CI: 5.0-NE).

Secondary Efficacy Endpoint: HSCT and CAR T-cell Therapy Rate

Stratum 1A:

All 8 participants who received HSCT post InO treatment in Stratum 1A had allogeneic transplants. 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). The conditioning therapy used was always myeloablative.

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

Phase 2 Cohort:

All 18 participants who received HSCT post InO treatment in the Phase 2 Cohort had allogeneic transplants. 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; 17 of 18 participants peripheral blood (10). The conditioning therapy used was always myeloablative. A total of 10 (35.7%) participants in the Phase 2 Cohort underwent at least 1 CAR T-cell therapy given after end of study therapy or after last dose of InO.

Stratum 1B:

All 19 participants who received HSCT post InO treatment in Stratum 1B, had allogeneic transplants (18 myeloablative). Among these participants, 12 had transplants within 2 months after the last dose of InO; 3 participants had more than 1 FU HSCT; 13 had related donors; 18 of 19 participants were in CR/CRi/CRp at the time of HSCT. The stem cell source was bone marrow (11), peripheral blood (6) and cord blood (2).

A total of 12 (40.0%) participants in Stratum 1B underwent at least 1 CAR T-cell therapy given after end of study therapy or after last dose of InO.

Secondary Efficacy Endpoint: EFS

Stratum 1A:

In Stratum 1A, 19 (76.0%) participants had events (ie, induction failure, relapse, death, or second malignancies) after InO treatments (6 [24.0%] participants were censored), of which 4 were induction failure, 12 were relapse, and 3 were death[2]. 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, 29.8% (95% CI: 13.3-48.3) at Month 12, and 21.3% (95% CI: 7.8-39.1) at Month 24.

Phase 2 Cohort:

In the Phase 2 Cohort, 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, 35.7% (95% CI: 18.9-53.0) at Month 12, and 32.1% (95% CI: 16.1-49.3) at Month 24.

Stratum 1B:

In Stratum 1B, 20 (66.7%) participants had events after InO combination treatments (10 [33.3%] participants were censored), of which 6 were induction failure, 9 were relapse, and 5 were death. The median EFS was 6.8 months (95% CI: 4.9-33.9). Estimated EFS rate was 59.5% (95% CI: 39.8-74.6) at Month 6, 38.2% (95% CI: 20.9-55.3) at Month 12, and 34.4% (95% CI: 17.9-51.6) at Month 24.

Secondary Efficacy Endpoint: OS

In Stratum 1A:

- 18 (72.0%) participants died (7 [28.0%] participants were censored). The median OS was 10.3 months (95% CI: 4.8-26.2). Estimated OS rate was 62.9% (95% CI: 40.7-78.7) at Month 6, 41.9% (95% CI: 22.4-60.3) at Month 12, and 33.5% (95% CI: 16.0-52.1) at Month 24.

In the Phase 2 Cohort:

- 17 (60.7%) participants died (11 [39.3%] participants were censored). The median OS was 14.8 months (95% CI: 5.5-NE). Estimated OS rate was 64.3% (95% CI: 43.8-78.9) at Month 6, 53.6% (95% CI: 33.8-69.8) at Month 12, and 42.9% (95% CI: 24.6-60.0) at Month 24.

In Stratum 1B:

- 16 (53.3%) participants died (14 [46.7%] participants were censored). The median OS was 24.4 months (95% CI: 8.3-NE). Estimated OS rate was 76.7% (95% CI: 57.2-88.1) at Month 6, 59.2% (95% CI: 39.5-74.5) at Month 12, and 52.3% (95% CI: 33.0-68.4) at Month 24.

A summary of follow-up for OS is provided in Study ITCC-059 LPLV CSR, with an estimated median follow-up of 40.9 months (95% CI: 38.2-41.7) for Stratum 1A, 38.1 months (95% CI: 36.8-39.1) for the Phase 2 Cohort, and 37.7 months (95% CI: 37.3-38.5) for Stratum 1B.

Safety results

Exposure

Exposure to InO is provided in Study ITCC-059 PCD CSR, Section 4.6.1 and is discussed in previous procedures (EMEA/H/C/004119/P46/004, EMA/VR/0000257310 (final opinion March 2026)).

Dose-limiting toxicity

DLT was evaluated in Cycle 1 only and discussed further in previous procedures (EMEA/H/C/004119/P46/004, EMA/VR/0000257310 (final opinion March 2026)). No new information has been provided.

Adverse events

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

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

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

Table 3. Summary of Treatment-Emergent Adverse Events (All Causalities) - Full analysis set

Number (%) of Participants	Stratum 1A (N=25) n (%)	Phase 2 (N=28) n (%)	Stratum 1B (N=30) n (%)	Total (N=83) n (%)
Participants evaluable for adverse events	25	28	30	83
Number of adverse events	348	245	366	959
Participants with adverse events	25 (100.0)	28 (100.0)	30 (100.0)	83 (100.0)
Participants with serious adverse events	16 (64.0)	16 (57.1)	18 (60.0)	50 (60.2)
Participants with non-serious adverse events	25 (100.0)	28 (100.0)	30 (100.0)	83 (100.0)
Participants with Maximum Grade 3 or 4 adverse events	21 (84.0)	23 (82.1)	28 (93.3)	72 (86.7)
Participants with Maximum Grade 5 adverse events	3 (12.0)	3 (10.7)	1 (3.3)	7 (8.4)
Participants permanent discontinuation from treatment	8 (32.0)	4 (14.3)	3 (10.0)	15 (18.1)
Participants leading to study drug interruption/reduction/delay	1 (4.0)	5 (17.9)	17 (56.7)	23 (27.7)

Participants are counted only once in each row.
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 v28.0 coding dictionary applied.

Table 4. Summary of Treatment-Emergent Adverse Events (Treatment Related) – Full analysis set

Number (%) of Participants	Stratum 1A (N=25) n (%)	Phase 2 (N=28) n (%)	Stratum 1B (N=30) n (%)	Total (N=83) n (%)
Participants evaluable for adverse events	25	28	30	83
Number of adverse events	161	109	168	438
Participants with adverse events	21 (84.0)	25 (89.3)	28 (93.3)	74 (89.2)
Participants with serious adverse events	9 (36.0)	9 (32.1)	12 (40.0)	30 (36.1)
Participants with non-serious adverse events	21 (84.0)	25 (89.3)	28 (93.3)	74 (89.2)
Participants with Maximum Grade 3 or 4 adverse events	21 (84.0)	22 (78.6)	25 (83.3)	68 (81.9)
Participants with Maximum Grade 5 adverse events	0	0	0	0
Participants permanent discontinuation from treatment	7 (28.0)	2 (7.1)	2 (6.7)	11 (13.3)
Participants leading to study drug interruption/reduction/delay	0	5 (17.9)	14 (46.7)	19 (22.9)

Participants are counted only once in each row.
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 v28.0 coding dictionary applied.

Deaths

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

There were two deaths due to toxicity in Phase 2:

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

There were no induction deaths in any cohort.

Table 5. Summary of Deaths (Full Analysis Set)

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

	Stratum 1B					
	0.8 mg/m² + mR3 (N=6)	1.1 mg/m² + amended mR3 (N=4)	1.1 mg/m² + mR3 (N=6)	1.4 mg/m² + amended mR3 (N=3)	1.8 mg/m² + amended mR3 (N=11)	Total (N=30)
Deaths	4 (66.7)	3 (75.0)	3 (50.0)	0	6 (54.5)	16 (53.3)
Cause of Death						
Disease Progression	3 (50.0)	2 (50.0)	1 (16.7)	0	5 (45.5)	11 (36.7)
Toxicity	0	0	0	0	0	0
Other	1 (16.7)	1 (25.0)	2 (33.3)	0	1 (9.1)	5 (16.7)
Induction Death	0	0	0	0	0	0
Deaths Within 10 weeks After Last Dose of Study Treatment	1 (16.7)	0	2 (33.3)	0	1 (9.1)	4 (13.3)
Cause of Death						
Disease Progression	1 (16.7)	0	1 (16.7)	0	1 (9.1)	3 (10.0)
Toxicity	0	0	0	0	0	0
Other	0	0	1 (16.7)	0	0	1 (3.3)

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

Cumulative Incidence of Non-Relapse Mortality

2 (8.0%) participants in Stratum 1A, 6 (21.4%) participants in the Phase 2 Cohort, and 5 (16.7%) participants in Stratum 1B had non-relapse death:

On Day 100, the cumulative incidence rate of non-relapse mortality was 4.25% (95% CI: 0.27-18.50) for Stratum 1A, 7.14% (95% CI: 1.19-20.79) for the Phase 2 Cohort, and 3.33% (95% CI: 0.23-14.84) for Stratum 1B.

At Month 12, the cumulative incidence rate of non-relapse mortality was 8.50% (95% CI: 1.36-24.32) for Stratum 1A, 21.43% (95% CI: 8.39-38.39) for the Phase 2 Cohort, and 10.18% (95% CI: 2.48-24.36) for Stratum 1B.

At Month 24, the cumulative incidence rate of non-relapse mortality was 8.50% (95% CI: 1.36-24.32) for Stratum 1A, 21.43% (95% CI: 8.39-38.39) for the Phase 2 Cohort, and 13.68% (95% CI: 4.13-28.91) for Stratum 1B.

Treatment-emergent serious adverse events (TE-SAEs)

In Stratum 1A, 16 (64.0%) participants had TESAEs. The most frequently reported TESAEs (by PT, ≥10%) were febrile neutropenia (n = 4 [16.0%]) and pyrexia (n = 3 [12.0%]).

In the Phase 2 Cohort, 16 (57.1%) participants had TESAEs. The most frequently reported TESAEs (by PT, ≥10%) were VOD[6] (n = 6 [21.4%]) and febrile neutropenia (n = 5 [17.9%]).

In Stratum 1B, 18 (60.0%) participants had TESAEs. The most frequently reported TESAEs (by PT, ≥10%) were febrile neutropenia, VOD (n = 5 [16.7%] each) and sepsis (n = 3 [10.0%]).

Dose Modification and/or Discontinuations Due to Adverse Events

Stratum 1A

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

Phase 2 Cohort

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

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

Stratum 1B

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

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

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

All cases of VOD or SOS are summarized as "VOD" in this report. All VOD events reported in the study were considered probably/possibly related to InO or with multiple causalities.

Stratum 1A:

VOD was reported in 2 (8.0%) participants; neither participant reported an allo HSCT before or after InO; both participants were treated with additional intensive chemotherapy after the last dose of InO.

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

In the Phase 2 Cohort:

VOD was reported in 6 (21.4%) participants, 5 of which occurred after FU allo HSCT. The post-HSCT VOD rate was 5/18 (27.8% [95% CI: 9.69-53.48]).

2 participants reported G4 VOD:

- Onset 17 days after HSCT; ongoing at death;
- Onset 4 days after HSCT; resolved.

3 participants reported G3 VOD:

- Onset 3 days after HSCT; ongoing at death;
- 1 event was not associated with HSCT; onset of VOD occurred 7 days after the first dose of InO; resolved;
- 1 event started 17 days after HSCT; resolved.

1 participant had G2 VOD with onset 10 days after HSCT; resolved.

In Stratum 1B:

VOD was reported in 5 (16.7%) participants, 4 of which occurred post-transplant. The post-HSCT VOD rate was 4/19 (21.1% [95% CI: 6.05-45.57]).

In 1.1 mg/m2 + mR3, 2 participants reported G3 VOD:

- First event: no history of HSCT; onset of VOD 7 days after the second dose of InO; resolved;
- Second event: onset 51 days after HSCT; ongoing at death.

In 1.1 mg/m2 + amended mR3, 1 participant reported G4 VOD with onset 18 days after HSCT; resolved.

In 1.4 mg/m2 + amended mR3, 1 participant had G3 VOD with onset 15 days after HSCT; resolved.

In 1.8 mg/m2 + amended mR3, 1 participant had G3 VOD with onset 10 days after HSCT; resolved.

2.3.3. Discussion on clinical aspects

In order to fulfil the requirement to report paediatric data within 6 months of LPLV to report the follow-up paediatric data, the MAH has submitted the LPLV Clinical study report (CSR) for Study ITCC-059, including all data collected from the cut-off date for the primary CSR up to the Last Subject Last Visit for the 3 year follow-up period for.

Study ITCC-059 is a Phase I/II study, and part of the paediatric investigation plan (PIP) for inotuzumab ozogamicin (InO). Study completion (LPLV) date was on 20 June 2025. LPLD + 3 months safety follow up (Primary Completion Date - PCD) was on 12 September 2022.

The final efficacy and safety data were previously submitted in the PDC CSR dated 21 February 2023, which was initially assessed in the context of the P46 procedure (EMEA/H/C/004119/P46/004). An updated version of the PDC CSR, dated 26 September 2023, was subsequently submitted to support the extension of the indication to include the treatment of paediatric patients aged 1 year and older with relapsed or refractory CD22-positive B-cell precursor ALL, and is currently under assessment in procedure EMA/VR/0000257310 (receiving an opinion in March 2026).

The efficacy and safety results presented in the LPLV CSR, reflecting the longer follow-up period, are consistent with the previously reported findings in the above-mentioned procedures and with the established safety profile of InO in line with those reported in the PDC CSRs.

To summarize, no updates on the primary efficacy endpoints ORR and MRD have been reported after the study PCD data-cutoff. Updated results for the secondary endpoints have been presented and are consistent with those previously reported, including DoR and OS:

- Median DoR was 8.0 months (95% CI: 3.9-13.9) in Stratum 1A, 7.6 months (95% CI: 3.3-NE) in the Phase 2 Cohort, and 8.4 months (95% CI: 5.0-NE) in Stratum 1B, which is consistent with the PDC data (DCO 12 Sep 2022), where median DOR was 8.0 months (95% CI: 5.7-13.9), 8.0 months (95% CI: 3.9-13.9), and 7.6 months (95% CI: 3.3-NE), respectively.

- Median OS was 10.3 months (95% CI: 4.8-26.2) in Stratum 1A, 14.8 months (95% CI: 5.5-NE) in the Phase 2 Cohort, and 24.4 months (95% CI: 8.3-NE) in Stratum 1B, which is also consistent with the PDC data (DCO 12 Sep 2022), where median OS was 10.3 months (95% CI: 3.9-26.2), 14.8 months (95% CI: 4.2-NE), and 13.7 months (95% CI: 8.3-NE), respectively.

The safety data are consistent with the results previously reviewed under procedure EMA/VR/0000257310 (final opinion in March 2026). In monotherapy, the most frequently reported TEAEs were pyrexia, vomiting, anaemia and decreased platelet count. In combination therapy, the most frequently reported TEAEs were anaemia, decreased platelet count, increased ALT/AST and decreased WBC count. No additional SAEs or AESIs of interest (i.e., VOD) have been reported.

Most patients (n=31/41) died due to disease progression. Non-relapse mortality was reported in 2 participants (8.0%) in Stratum 1A, 6 participants (21.4%) in the Phase 2 Cohort, and 5 participants (16.7%) in Stratum 1B, and included cases of sepsis and transplant-related events. At Month 24, the cumulative incidence rate of non-relapse mortality was 8.50% (95% CI: 1.36-24.32) for Stratum 1A, 21.43% (95% CI: 8.39-38.39) for the Phase 2 Cohort, and 13.68% (95% CI: 4.13-28.91) for Stratum 1B.

Two toxicity-related deaths were reported; however, neither was considered related to InO. These comprised one case of encephalopathy leading to cardiac arrest and one case of bilateral pneumonitis that occurred after subsequent ALL therapy during follow-up. No additional mortality data were reported in the LPLV CSR.

Overall, the safety profile of InO in paediatric patients is considered acceptable and generally manageable. It is noted that SmPC sections 4.1, 4.2, 4.8, 5.1, and 6.6 will be revised to reflect the extension of the indication to include the treatment of paediatric patients aged 1 year and older with relapsed or refractory CD22-positive B-cell precursor ALL (EMA/VR/0000257310, final opinion in March 2026). No further updates to the product information or the RMP are proposed within the current PAM/PAC procedure.

3. Overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required.

Annex. Line listing of all the studies included in the development program

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