Inotuzumab ozogamicin for Acute Lymphoblastic Leukemia

Estado	Tipo de Participantes	Rangos de Edad
Fin Reclutamiento	Sujetos incapaces de otorgar consentimiento	Menores de 18 , Adolescentes (12-17 años) , Niños (2-11 años) , Lactantes y preescolar (28 días - 23 meses) , Recién nacidos (0-27 días)
Género	**Fases**	**Participantes esperados**
Ambos	Fase I , Fase II	16
Resultados	**Bajo nivel intervención**	**Enfermedad rara**
Sin resultados	No	Si
Cobertura geográfica	**Ámbitos del ensayo**	**Terapia avanzada**
Sin determinar	seguridad, eficacia, dosis	NO

Información

Identificador

2023-504694-20-00 (CTIS)

Cod. Protocolo

No aportado

Transicionado 2016-000227-71

Área terapéutica

Enfermedades [C] - Hematología [C15]|

Enfermedad investigada

pediatric CD22-positive relapsed/refractory Acute Lymphoblastic Leukemia

Título Científico

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

Justificación

No aportado

Objetivo Principal

STRATUM 1 Stratum 1A: To establish the MTD or the RP2D of single agent InO when administered in children with CD22-positive relapsed/refractory BCP-ALL (completed). Note that: o if the MTD is not reached at the highest tested dose, no further dose-escalation will be performed. o to establish the RP2D for further study in the Phase 2 cohort, additional modelling will be performed regarding cumulative toxicity (as described in Section 9) Phase 2 Cohort: To establish the preliminary clinical activity (efficacy) activity with respect to ORR of single agent InO when administered in children with CD22-positive relapsed/refractory BCP-ALL. (completed) Stratum 1B (and 1B-ASP): To determine the RP2D of InO in children with CD22-positive relapsed/refractory BCP-ALL in combination with a modified UKALL-R3 based re-induction regimen. (completed)
STRATUM 2 (EXPLORATORY) To explore the safety and tolerability of InO as a single agent in children with relapsed/refractory other CD22 positive B-cell malignancies. (completed) STRATUM 3 To establish the preliminary clinical activity (efficacy) with respect to ORR of single agent InO when administered in children with CD22-positive VHR 1st relapse BCP-ALL, excluding patients transplanted in 1st CR. (enrolment completed)
STRATUM 4
To establish the clinical activity (efficacy) with respect to ORR of single agent InO in pediatric patients with R/R CD22+ BCP ALL (including VHR 1st relapse BCP-ALL, 2nd relapse, relapse after HSCT and refractory disease).

Variables de Evaluación Primaria

Stratum 1A : Dose-limiting toxicities (DLTs) during the first cycle of therapy.
Phase 2 cohort: ORR, defined as the percentage of patients with CR, CRi, CRp, measured as best response during InO treatment (see Appendix 2 for definitions).
Stratum 1B and 1B-ASP: Dose-limiting toxicities (DLTs) during the first cycle of InO when added to a modified UKALL-R3 re-induction chemotherapy regimen without or with ASP.
Stratum 2 Safety and tolerability: 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.
Stratum 2 Safety and tolerability: Occurrence of toxic death; i.e., death attributable to InO therapy.
Stratum 2 Safety and tolerability: Occurrence of hepatic VOD/SOS during or after therapy with InO.
Stratum 2 Safety and tolerability: Laboratory abnormalities as characterized by type, frequency, severity and timing.
Stratum 2 Safety and tolerability: 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 relapsed or refractory leukemia or lymphoma, accounting for competing events.
Stratum 3: ORR, defined as the percentage of patients with CR, CRi, CRp, measured as best response of InO treatment (see Appendix 2 for definitions) as a single agent in CD22-positive VHR 1st relapse BCP ALL patients.
Str4: ORR, defined as % of pts with CR, CRi, CRp, measured after course 1 of InO treatment as a single agent in patients with 2nd or greater CD22+ BCP-ALL relapse,1st VHR CD22+ BCP-ALL relapse, any relapse of BCP-ALL post allogeneic HSCT, and refractory disease, defined as newly diagnosed pts who are induction failures after at least 2 previous regimens without attainment of remission, or pts with refractory 1st relapse after 1 previous reinduction regimen without attainment of remission

Momentos temporales de evaluación primaria

No aportado

Objetivo Secundario

Stratum 1A and Phase 2 Cohort (BCP- ALL patients): 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 allogeneic hematopoietic stem cell transplant (allo-HSCT) or CAR-T cells therapy. (completed)
Stratum 1A and Phase 2 Cohort (BCP- ALL patients): To determine the overall hematological response rate in these patients: - after cycle 1 (completed) - as well as the overall best response (Stratum 1A only; this is the primary objective for Phase 2 cohort). (completed)
Stratum 1A and Phase 2 Cohort (BCP- ALL patients): To determine minimal residual disease (MRD) levels in responding patients, including the percentage of patients with a complete MRD response (see Appendix 2.1) - after cycle 1 (completed) - as well as the best ORR. (completed)
Stratum 1A and Phase 2 Cohort (BCP- ALL patients): To describe the durability of response and long-term follow-up, including the number of patients that undergo HSCT or CAR-T cells therapy after treatment with InO as consolidation, the cumulative incidence of non-response or relapse, the cumulative incidence of non-relapse mortality, the event-free survival (EFS) and overall survival (OS). (ongoing)
Stratum 1A and Phase 2 Cohort (BCP- ALL patients): To determine the serum pharmacokinetic parameters of unconjugated calicheamicin and InO in the pediatric population. (completed)
Stratum 1A and Phase 2 Cohort (BCP- ALL patients): To assess the relationship between CD22 receptor density, white blood cell count (WBC) at start of treatment, CD22 saturation kinetics, cytogenetics, and in-vitro calicheamicin resistance to clinical response to InO. (completed)
Stratum 1A and Phase 2 Cohort (BCP- ALL patients): To assess for the persistence of B-Cell aplasia and hypogammaglobulinemia in responding patients following treatment with InO. (completed)
Stratum 1A and Phase 2 Cohort (BCP- ALL patients): To assess the number of patients developing anti-drug antibodies (ADAs; immunogenicity). (NOT applicable for patients enrolled after amendment 4, completed)
Stratum 1B and Stratum 1B-ASP (BCP ALL patients): To determine the safety and tolerability of InO in combination with a modified UKALL-R3 re- induction chemotherapy regimen (1 or 2 cycles), and the cumulative toxicities in patients receiving multiple InO-based cycles, as well as after subsequent allogeneic HSCT. (completed, follow-up ongoing)
Stratum 1B and Stratum 1B-ASP (BCP ALL patients): To determine the overall hematological response rate in these patients: - after cycle 1 (completed) - as well as the overall best response (completed)
Stratum 1B and Stratum 1B-ASP (BCP ALL patients): To determine MRD levels in responding patients, including the percentage of patients with a complete MRD response (see appendix 2.1 for definition): - after cycle 1 (completed) - as well as the best ORR. (completed)
Stratum 1B and Stratum 1B-ASP (BCP ALL patients): To describe the durability of response and long-term follow-up, including the number of patients that undergo HSCT or CAR-T cells therapy after study treatment as consolidation, the cumulative incidence of non-response or relapse, the cumulative incidence of non-relapse mortality, the EFS and OS. (ongoing)
Stratum 1B and Stratum 1B-ASP (BCP ALL patients): To determine the serum pharmacokinetic parameters of unconjugated calicheamicin and InO when added to a modified reinduction UKALL-R3 chemotherapy regimen without (stratum 1B), then with ASP (stratum 1B-ASP). (ongoing)
Stratum 1B and Stratum 1B-ASP (BCP ALL patients): To assess the relationship between CD22 expression and clinical response to InO (completed)
Stratum 1B and Stratum 1B-ASP (BCP ALL patients): To assess the number of patients developing CD22-negative relapse (ongoing)
Stratum 2 (Other B-cell malignancies): To determine the response rate in these patients: - after cycle 1 (completed)- as well as the overall best response. (completed)
Stratum 2 (Other B-cell malignancies): To describe the durability of response and long-term follow-up, including the number of patients that undergo stem-cell transplant after treatment with InO, the cumulative incidence of non-response or relapse, the cumulative incidence of non-relapse mortality, the EFS and OS. (ongoing)
Stratum 2 (Other B-cell malignancies): To determine the serum pharmacokinetic parameters of unconjugated calicheamicin and InO in the pediatric population. (completed)
Stratum 2 (Other B-cell malignancies): To assess for the persistence of B-Cell aplasia and hypogammaglobulinemia in responding patients following treatment with InO. To assess the number of patients developing ADAs (NOT valid for patients enrolled after Amendment 4). (completed)
Stratum 3 (VHR) (ongoing): 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 allogeneic hematopoietic stem cell transplant (allo-HSCT) or CAR-T cells therapy.
Stratum 3 (VHR) (ongoing): To determine the overall hematological response rate in these patients after cycle 1
Stratum 3 (VHR) (ongoing): To determine minimal residual disease (MRD) levels in responding patients, including the percentage of patients with a complete MRD response (see Appendix 2.1) - after cycle 1 - as well as the best ORR.
Stratum 3 (VHR) (ongoing) : To describe the durability of response and long-term follow-up, including the number of patients that undergo HSCT or CAR-T cells therapy after treatment with InO as consolidation, the cumulative incidence of non-response or relapse, the cumulative incidence of non-relapse mortality, the EFS and overall survival (OS).
Stratum 3 (VHR) (ongoing) : To assess the relationship between CD22 receptor density, white blood cell count (WBC) at start of treatment, cytogenetics, and in-vitro calicheamicin resistance to clinical response to InO.
Stratum 3 (VHR) (ongoing): To assess the persistence of B-Cell aplasia and MRD negativity in responding patients following the treatment with InO and the implications for CAR-T cells therapy.
Stratum 4: 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 (maximum 2 cycles); as well as after subsequent allogeneic hematopoietic stem cell transplant (allo-HSCT) or CAR-T cells therapy.
Stratum 4: To determine the overall hematological response rate in these patients after cycle 1.
Stratum 4: To determine minimal residual disease (MRD) levels, assessed at a local laboratory, in responding patients, including the percentage of patients with a complete MRD response after cycle 1 as well as the best ORR.
Stratum 4: To describe the durability of response, including the number of patients that undergo allo-SCT or CART-therapy after treatment with InO, the cumulative incidence of non-response or relapse, the cumulative incidence of non-relapse mortality, EFS and OS.
Stratum 4: To assess the relationship between clinical response to InO and CD22 expression levels determined at the local laboratory.
Stratum 4: To investigate determinants of resistance to InO such as DNA nucleotidylexotransferase (DNTT) expression levels, BCL-2 expression levels as well as other potential determinants of resistance through whole genome sequencing at enrollment, and at the time of relapse after InO when applicable.
Stratum 4: To characterize lymphocyte subsets after InO treatment, including persistence of B-Cell aplasia and hypogammaglobulinemia in responding patients following treatment with InO.

Variables de Evaluación Secundaria

Stratum 1A Safety and tolerability: 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. Stratum 1A Safety and tolerability: Occurrence of toxic death; i.e., death attributable to InO therapy. Stratum 1A Safety and tolerability: Occurrence of hepatic veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS) during or after therapy with InO. Stratum 1A Safety and tolerability: Laboratory abnormalities as characterized by type, frequency, severity and timing. Stratum 1A Safety and tolerability: 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 relapsed or refractory leukemia or lymphoma, accounting for competing events. Stratum 1A Measures of anti-leukemic activity: ORR, defined as CR, CRi, or CRp both after cycle 1 as well as the best response over multiple cycles of InO therapy (see Appendix 2 for definitions). Stratum 1A Measures of anti-leukemic activity: MRD levels, including the percentage of patients who become MRD-negative (complete MRD response defined as an MRD-level < 1x10-4), after cycle 1, as well as the overall best response (MRD-negativity) over multiple cycles. Stratum 1A Measures of anti-leukemic activity: Duration of response, defined as the time between achieving response (CR, CRi or CRp) after starting study treatment and documented relapse or death. Stratum 1A Measures of anti-leukemic activity: Number and percentage of patients being transplanted and those receiving CAR T-cell therapy after treatment with InO. Stratum 1A Measures of anti-leukemic activity: 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. Stratum 1A Measures of anti-leukemic activity: Overall survival, defined as time to death following start of study treatment. Stratum 1A Measures of anti-leukemic activity: 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. Stratum 1A: Serum pharmacokinetic parameters of InO and unconjugated calicheamicin. Stratum 1A Pharmacodynamics parameters: Relationship between response (ORR) and CD22 expression levels and WBC. Stratum 1A Pharmacodynamics parameters: Relationship between response (ORR) and CD22 saturation kinetics. Stratum 1A Pharmacodynamics parameters: Relationship between response (ORR) and calicheamicin sensitivity. Stratum 1A Pharmacodynamics parameters: Clonal evolution (CD22-negativity) and relation to loss of response. Stratum 1A Other endpoints: The percentage of patients responding to InO (ORR) without adequate recovery of CD19-positive B-cells (below lower limit of normal (LLN) for age) or immunoglobulins (below LLN for age). Following 4 weeks, 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 cells therapy. Stratum 1A Other endpoints: Percentage of patients who exhibit anti-drug antibodies (ADA) (NOT valid for patients enrolled after Amendment 4). Phase 2 cohort Safety: 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. Phase 2 cohort Safety: Occurrence of toxic death; i.e., death attributable to InO therapy. Phase 2 cohort Safety: Occurrence of VOD/SOS during or after therapy with InO. Phase 2 cohort Safety: Laboratory abnormalities as characterized by type, frequency, severity and timing. Phase 2 cohort Safety: 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 relapsed or refractory leukemia or lymphoma, accounting for competing events. Phase 2 cohort Other measures of anti-leukemic activity: ORR after cycle 1. Phase 2 cohort Other measures of anti-leukemic activity: Minimal residual disease levels, including the percentage of patients who become MRD-negative (complete MRD response defined as an MRD-level < 1x10-4), after cycle 1, as well as the best response (MRD-negativity) over multiple cycles. Phase 2 cohort Other measures of anti-leukemic activity: Duration of response, defined as the time between achieving response (CR, CRi or CRp) after starting study treatment and documented relapse or death. Phase 2 cohort Other measures of anti-leukemic activity: Number and percentage of patients being transplanted and those receiving CAR T-cell therapy after treatment with InO. Phase 2 cohort Other measures of anti-leukemic activity: 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. Phase 2 cohort Other measures of anti-leukemic activity: Survival, defined as time to death following start of study treatment. Phase 2 cohort Other measures of anti-leukemic activity: 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. Phase 2 cohort Serum pharmacokinetic parameters of InO and unconjugated calicheamicin. Phase 2 cohort Pharmacodynamics parameters: Relationship between response (ORR) and CD22 expression levels and WBC. Phase 2 cohort Pharmacodynamics parameters: Relationship between response (ORR) and CD22 saturation kinetics. Phase 2 cohort Pharmacodynamics parameters: Relationship between response (ORR) and calicheamicin sensitivity. Phase 2 cohort Pharmacodynamics parameters: Clonal evolution (CD22-negativity) and relation to loss of response. Phase 2 cohort Other endpoints: 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 weeks, 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 cells therapy. Percentage of patients who exhibit ADA (NOT valid for patients enrolled after Amendment 4). Stratum 1B and 1B-ASP Safety: AEs (secondary endpoints have same definitions as for Stratum 1A) Stratum 1B and 1B-ASP Safety: Occurrence of toxic death; i.e., death attributable to InO therapy. Stratum 1B and 1B-ASP Safety: Occurrence of hepatic VOD/SOS during or after therapy with InO. Stratum 1B and 1B-ASP Safety: Laboratory abnormalities Stratum 1B and 1B-ASP Safety: Cumulative incidence of non-relapse mortality Stratum 1B and 1B-ASP Other measures of anti-leukemic activity: ORR Stratum 1B and 1B-ASP Other measures of anti-leukemic activity: MRD levels Stratum 1B and 1B-ASP Other measures of anti-leukemic activity: Duration of response Stratum 1B and 1B-ASP Other measures of anti-leukemic activity: Number and percentage of patients being transplanted and those receiving CAR T-cell therapy after treatment with InO. Stratum 1B and 1B-ASP Other measures of anti-leukemic activity: EFS Stratum 1B and 1B-ASP Other measures of anti-leukemic activity: Overall survival Stratum 1B and 1B-ASP Other measures of anti-leukemic activity: Cumulative incidence of non-response or relapse Stratum 1B and 1B-ASP Serum pharmacokinetic parameters of InO and unconjugated calicheamicin during treatment combined with modified UKALL-R3 re-induction regimen both with and without pegylated asparaginase. Stratum 1B and 1B-ASP Pharmacodynamics parameters Relationship between response (ORR) and CD22 expression levels Stratum 1B and 1B-ASP Pharmacodynamics parameters Clonal evolution (CD22-negativity) and relation to loss of response. Stratum 2 Measures of anti-tumor activity: Overall remission rate (CR and PR) both after cycle 1 as well as overall best response in patients receiving multiple cycles of InO therapy (see Appendix 2 for

definitions). Stratum 2 Measures of anti-tumor activity: Duration of response, defined as the time between achieving response (CR and PR) after starting study treatment and documented relapse or death. Stratum 2 Measures of anti-tumor activity: Number and percentage of patients being transplanted and those receiving CAR T-cell therapy after treatment with InO. Stratum 2 Measures of anti-tumor activity: EFS, defined as the time between start of study treatment and first event including failure to achieve CR/PR (calculated as an event on day 0), relapse, death of any cause and second malignancies. Stratum 2 Measures of anti-tumor activity: Overall survival, defined as time to death following start of study treatment. Stratum 2 Measures of anti-tumor activity: 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. Stratum 2 Serum pharmacokinetic parameters of InO and unconjugated calicheamicin. Stratum 2 Other endpoints: 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 weeks, 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 cells therapy. Stratum 2 Other endpoints: Percentage of patients who exhibit ADA (NOT valid for patients enrolled after Amendment 4). Stratum 3 Safety: 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. Stratum 3 Safety: Occurrence of any induction death and/or toxic death attributable to InO therapy. Stratum 3 Safety: Occurrence of VOD/SOS during or after therapy with InO. Stratum 3 Safety: Laboratory abnormalities as characterized by type, frequency, severity and timing. Stratum 3 Safety: 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 relapsed or refractory leukemia or lymphoma, accounting for competing events. Stratum 3 Other measures of anti-leukemic activity: ORR after cycle 1 Stratum 3 Other measures of anti-leukemic activity: Minimal residual disease levels, including the percentage of patients who become MRD-negative (complete MRD response defined as an MRD-level < 1x10-4) after cycle 1, as well as the best response (MRD-negativity) over multiple cycles. Stratum 3 Other measures of anti-leukemic activity: Duration of response, defined as the time between achieving response (CR, CRi or CRp) after starting study treatment and documented relapse or death. Stratum 3 Other measures of anti-leukemic activity: Number and percentage of patients being transplanted and those receiving CAR T-cell therapy after treatment with InO. Stratum 3 Other measures of anti-leukemic activity: 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. Stratum 3 Other measures of anti-leukemic activity: Survival, defined as time to death following start of study treatment. Stratum 3 Other measures of anti-leukemic activity: 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. Stratum 3 Other measures of anti-leukemic activity: To study the interval between InO re-induction and CAR-T cells therapy based on MRD negativity and B cell aplasia after InO re-induction. Stratum 3 Pharmacodynamics parameters Relationship between response (ORR) and CD22 expression levels and WBC. Stratum 3 Pharmacodynamics parameters Relationship between response (ORR) and calicheamicin sensitivity. Stratum 3 Pharmacodynamics parameters Clonal evolution (CD22-negativity) and relation to loss of response. Stratum 3 Other endpoints The percentage of patients responding to InO (ORR) without adequate recovery of CD19-positive B-cells and CD4+/CD8+ T-cells(below LLN for age) or immunoglobulins (below LLN for age) following 4,6,8 and 10 weeks, 3, 6 and 12 months after treatment with InO, excluding patients who have been transplanted from the date of HSCT or CAR T-cell infusion. Stratum 4 Safety and tolerability: 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 courses of therapy. Stratum 4 Safety and tolerability: Occurrence of toxic death; i.e., death attributable to InO therapy. Stratum 4 Safety and tolerability: Occurrence of VOD/SOS during or after therapy with InO Stratum 4 Safety and tolerability: Laboratory abnormalities as characterized by type, frequency, severity and timing. Stratum 4 Safety and tolerability: 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 relapsed or refractory leukemia or lymphoma, accounting for competing events. Stratum 4 Other measures of anti-leukemic activity: ORR after cycle 1. Stratum 4 Other measures of anti-leukemic activity: Minimal residual disease levels, including the percentage of patients who become MRD-negative (complete MRD response defined as an MRD-level < 1x10-4) after cycle 1, as well as the best response (MRD-negativity) over multiple cycles. Stratum 4 Other measures of anti-leukemic activity: Duration of response, defined as the time between achieving response (CR, CRi or CRp) after starting study treatment and documented relapse or death. Stratum 4 Other measures of anti-leukemic activity: Number and percentage of patients being transplanted and those receiving CAR T-cell therapy

after treatment with InO. Stratum 4 Other measures of anti-leukemic activity: 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. Stratum 4 Other measures of anti-leukemic activity: Survival, defined as time to death following start of study treatment. Stratum 4 Other measures of anti-leukemic activity: 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. Stratum 4 Other measures of anti-leukemic activity: To study the interval between InO re-induction and CAR-T cells therapy based on MRD negativity and B cell aplasia after InO re-induction. Stratum 4 Pharmacodynamics parameters: Relationship between response (ORR) and CD22 expression levels and WBC. Stratum 4 Pharmacodynamics parameters: Clonal evolution (CD22-negativity) and relation to loss of response. Stratum 4 Pharmacodynamics parameters: Screening through whole genome sequencing of genomic determinants of response/resistance to InO, assessing the relationship between response (ORR and MRD negativity) and DNTT expression levels, cytogenetics, as well as other emerging mechanisms of resistance. Stratum 4 Other endpoints: The percentage of patients responding to InO (ORR) without adequate recovery of CD19-positive B-cells and CD4+/CD8+ T-cells(below LLN for age) or immunoglobulins (below LLN for age) following 4,6,8 and 10 weeks, 3, 6 and 12 months after treatment with InO, excluding patients who have been transplanted from the date of HSCT or CAR T-cell infusion.

Momentos temporales de evaluación secundaria

No aportado

Criterios de Inclusión

Age (for all patients) Patients must be 1 and < 18 years of age at the time of enrollment. Additional criteria for limited to Stratum 1A and 1B only: 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. Stratum 4: Patients must have either: 2nd or greater CD22 positive BCP-ALL relapse; 1st VHR CD22 positive BCP-ALL relapse defined as isolated bone marrow or combined relapse occurring less than 18 months from initial diagnosis and/or with cytogenetic-high risk characteristics, including KTM2A/AF4, E2A/TCF3-PBX1 t(1;19), E2A/TCF3-HLF t(17;19), hypodiploidy (less than 40 chromosomes), TP53 mutation and/or deletion. Acceptable laboratory techniques to confirm these cytogenetic abnormalities include chromosome banding analysis (CBA), fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR), and/or Next Generation Sequencing (based on local laboratory results); Any relapse of BCP-ALL post HSCT; 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 must be CD22 surface antigen positive (in either bone marrow or peripheral blood) by institutional standards as determined by the local immunophenotyping laboratory. For 1st VHR BCP-ALL relapse evidence of prior fusion gene abnormalities is acceptable as they tend to be stable during the course of the disease. Laboratory techniques acceptable to test the presence of the cytogenetic-high risk characteristics are chromosome banding analysis (CBA), FISH, PCR and/or Next Generation Sequencing (inclusion is based on local laboratory results). Stratum 1A, Phase 2 and Stratum 1B/1B-ASP: 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) by institutional standards as determined by the local immunophenotyping laboratory. The first 6

patients (Stratum 1A only) must have M3 marrow status (25% blasts by morphology). Stratum 2: Diagnosis Patients must have second or greater relapsed or refractory CD22-positive B-cell malignancy including but not limited to diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL), Burkitt lymphoma, Burkitt leukemia or B-cell precursor lymphoblastic lymphoma: There must be histologic verification of disease at original diagnosis or subsequent relapse. Patient must have evaluable or measurable disease documented by radiographic criteria or bone marrow disease present at study entry. The malignant cells need to be CD22 surface antigen positive (in either biopsy material, the bone marrow or peripheral blood) by institutional standards as determined by the local immunophenotyping laboratory. Stratum 3: Diagnosis; Patients must have: First BM or combined relapse of CD22+ VHR BCP-ALL defined as any relapse <18 months from initial diagnosis and/or cytogenetic-high risk characteristics: KTM2A/AF4, E2A/TCF3-PBX1 t(1;19) or E2A/TCF3-HLF t(17;19), hypodiploidy (less than 40 chromosomes), TP53 mutation and/or deletion, as also shown in Table 2 (excluding patients who received a HSCT in 1st CR). 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) by institutional standards as determined by the local immunophenotyping laboratory. Evidence of prior fusion gene abnormalities is acceptable as they tend to be stable during the course of the disease. Laboratory techniques acceptable to test the presence of the above mentioned cytogenetic-high risk characteristics are chromosome banding analysis (CBA), FISH, PCR and/or Next Generation Sequencing (inclusion is based on local laboratory results). For all patients Performance Level and Life Expectancy Karnofsky > 60% for patients > 16 years of age and Lansky > 60% for patients 16 years of age. (See Appendix I for Performance Scales). Patient must have a life expectancy of at least 6 weeks. For all patients 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 per the CTCAE 4.03 prior to entering this study, with the exception of the authorized laboratory abnormalities as defined in the inclusion/exclusion criteria. a. Chemotherapy: At least 7 days must have elapsed 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 enrollment onto this study. b. Radiotherapy: At least 28 days must have elapsed since any prior radiation therapy. c. 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. d. 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®). e. 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). f. 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. g. 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. h. Prior calicheamicin exposure: Patient has not received prior treatment with a calicheamicin-conjugated antibody (e.g. gemtuzumab ozogamicin). For all patients Renal and Hepatic Function Patients 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 GFR 70mL/min/1.73 m2 estimated based on serum creatinine and/or cystatin C levels (e.g. Bedside Schwartz formula). AST and ALT must be 5 x institutional ULN. (stratum 3 & 4) Patients total total bilirubin must be 1.5 x institutional ULN unless the patient has documented Gilbert syndrome, in which case the AST and ALT must be 5 x ULN. (stratum 3 & 4) For all patients Cardiac Function Patient must have a shortening fraction 30% by echocardiogram or an ejection fraction > 50% by MUGA. For all patients Reproductive Function Female patients of childbearing potential must have a negative urine or serum pregnancy test confirmed 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. Highly effective methods of contraception include (but not exclusively) the following contraceptive methods:

combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation progestogen-only hormonal contraception associated with inhibition of ovulation intrauterine device (IUD) intrauterine hormone-releasing system (IUS) sexual abstinence.

Criterios de Exclusión

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 VOD/SOS per the modified Seattle criteria are excluded, as specified in Appendix 3, or prior liver-failure [defined as severe acute liver injury with encephalopathy and impaired synthetic function (INR of 1.5)].
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. The patient may not have: A requirement for vasopressors; Positive blood culture within 48 hours of study enrollment; Fever above 38.2 degrees Celsius within 48 hours of study enrollment with clinical signs of infection. Fever that is determined to be due to tumor burden is allowed if patients have documented negative blood cultures for at least 48 hours prior to enrollment and no concurrent signs or symptoms of active infection or hemodynamic instability. A positive fungal culture within 30 days of study enrollment. Active fungal, viral, bacterial, or protozoal infection requiring IV or oral treatment. Chronic prophylaxis therapy to prevent infections is allowed.
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.
Allergic reaction Patients with prior Grade 3/4 allergic reaction to a monoclonal antibody are excluded.
Concurrent disease Patients will be excluded if they have significant concurrent disease, illness, psychiatric disorder or social issue that would compromise patient safety or compliance with protocol therapy, interfere with consent, study participation, follow up, or interpretation of study results. 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, stratum 3 and stratum 4.
Additional exclusion criteria for Stratum 1B Patients with grade 3-4 peripheral neuropathy (as defined in the Delphi consensus of acute toxic effects for childhood ALL by Schmiegelow et al.12). Patients with prior history of thrombosis during steroid and/or asparaginase are eligible provided they use adequate anti-coagulant prophylaxis, according to institutional guidelines. Patients in whom prior experience suggests that a timely delivery of therapy is unlikely or associated with an undue risk because of intolerance.
Additional exclusion criteria for Stratum 1B-ASP cohort only Patients with any history of PEG-asparaginase intolerance due to allergic reactions or silent inactivation during prior treatment. Patients with any history of prior asparaginase-associated acute pancreatitis (any grade as defined in the Delphi consensus12. Patients who are excluded from Stratum 1B-ASP may potentially be enrolled in Stratum 1B expansion cohort.
Additional exclusion criteria for Stratum 3 (VHR cohort) only Patients who are transplanted in CR1 (such patients are eligible for the phase 1B cohort).

Calendario

(Última actualización: 12/12/2025)

Autorización	Inicio de Ensayo	Inclusión Primer Paciente	Interrumpido	Reiniciado
11/10/2017	09/04/2018	05/04/2018	No aportado	No aportado

Fin de reclutamiento	Fin prematuro (España)	Fin prematuro (Global)	Fin del ensayo en España	Fin del ensayo global
13/02/2025	No aportado	No aportado	No aportado	No aportado

Promotor

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Tipo de promotor: No comercial

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Centros

Activo (06/04/2018)

Hospital de Sant Joan de Déu

Esplugues de Llobregat

BARCELONA

Oncología Pediátrica

No iniciado (--/--/----)

Hospital Infantil Universitario Nino Jesus

Madrid

MADRID

Oncology

Activo (04/03/2018)

HOSPITAL UNIVERSITARI I POLITÈCNIC LA FE

Valencia

VALENCIA

Oncología Pediátrica

No iniciado (--/--/----)

Hospital Universitari Vall D Hebron

Barcelona

BARCELONA

Pediatric Hematology and HSCT

Activo (28/03/2018)

Hospital Universitari Vall d'Hebron

Barcelona

BARCELONA

Oncología Pediátrica

No iniciado (--/--/----)

Hospital Universitario Y Politecnico La Fe

Valencia

VALENCIA

Paediatric Transplant

No iniciado (--/--/----)

Sant Joan De Deu Barcelona Hospital

Esplugues De Llobregat

BARCELONA

Pediatric Cancer Center Barcelona

Medicamentos

BESPONSA 1 mg powder for concentrate for solution for infusion

SOLUTION FOR INFUSION

INTRAVENOUS USE

Código ATC: L01XC26 - INOTUZUMAB OZOGAMICINA

Principios Activos: N/A

Huérfano **Experimental**

Sin resultados

Inotuzumab ozogamicin for Acute Lymphoblastic Leukemia

State	Type of participants	Age Ranges
End of recruitment	Incapable subjects of giving consent	Less than 18 , Teens (12-17 years) , Children (2-11 years) , Infants and preschool (28 days - 23 months) , Newborn infants (0-27 days)
Gender	**Phases**	**Expected Participants**
Both	Phase I , Phase II	16
Results	**Low level of intervention**	**Rare disease**
No results	No	Yes
Geographic coverage	**Areas of the study**	**Advanced therapy**
Undetermined	safety, effectiveness, dose	NO

Information

Identifier
2023-504694-20-00 (CTIS)

Protocol Code
No aportado

Transitioned 2016-000227-71

Therapeutic area
Diseases [C] - Hemic and Lymphatic Diseases [C15]|

Investigated Disease
pediatric CD22-positive relapsed/refractory Acute Lymphoblastic Leukemia

Scientific Title
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

Rationale

Not provided

Main Objective

STRATUM 1 Stratum 1A: To establish the MTD or the RP2D of single agent InO when administered in children with CD22-positive relapsed/refractory BCP-ALL (completed). Note that: o if the MTD is not reached at the highest tested dose, no further dose-escalation will be performed. o to establish the RP2D for further study in the Phase 2 cohort, additional modelling will be performed regarding cumulative toxicity (as described in Section 9) Phase 2 Cohort: To establish the preliminary clinical activity (efficacy) activity with respect to ORR of single agent InO when administered in children with CD22-positive relapsed/refractory BCP-ALL. (completed) Stratum 1B (and 1B-ASP): To determine the RP2D of InO in children with CD22-positive relapsed/refractory BCP-ALL in combination with a modified UKALL-R3 based re-induction regimen. (completed)
STRATUM 2 (EXPLORATORY) To explore the safety and tolerability of InO as a single agent in children with relapsed/refractory other CD22 positive B-cell malignancies. (completed) STRATUM 3 To establish the preliminary clinical activity (efficacy) with respect to ORR of single agent InO when administered in children with CD22-positive VHR 1st relapse BCP-ALL, excluding patients transplanted in 1st CR. (enrolment completed)
STRATUM 4
To establish the clinical activity (efficacy) with respect to ORR of single agent InO in pediatric patients with R/R CD22+ BCP ALL (including VHR 1st relapse BCP-ALL, 2nd relapse, relapse after HSCT and refractory disease).

Primary Endpoints

Stratum 1A : Dose-limiting toxicities (DLTs) during the first cycle of therapy.
Phase 2 cohort: ORR, defined as the percentage of patients with CR, CRi, CRp, measured as best response during InO treatment (see Appendix 2 for definitions).
Stratum 1B and 1B-ASP: Dose-limiting toxicities (DLTs) during the first cycle of InO when added to a modified UKALL-R3 re-induction chemotherapy regimen without or with ASP.
Stratum 2 Safety and tolerability: 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.
Stratum 2 Safety and tolerability: Occurrence of toxic death; i.e., death attributable to InO therapy.
Stratum 2 Safety and tolerability: Occurrence of hepatic VOD/SOS during or after therapy with InO.
Stratum 2 Safety and tolerability: Laboratory abnormalities as characterized by type, frequency, severity and timing.
Stratum 2 Safety and tolerability: 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 relapsed or refractory leukemia or lymphoma, accounting for competing events.
Stratum 3: ORR, defined as the percentage of patients with CR, CRi, CRp, measured as best response of InO treatment (see Appendix 2 for definitions) as a single agent in CD22-positive VHR 1st relapse BCP ALL patients.
Str4: ORR, defined as % of pts with CR, CRi, CRp, measured after course 1 of InO treatment as a single agent in patients with 2nd or greater CD22+ BCP-ALL relapse,1st VHR CD22+ BCP-ALL relapse, any relapse of BCP-ALL post allogeneic HSCT, and refractory disease, defined as newly diagnosed pts who are induction failures after at least 2 previous regimens without attainment of remission, or pts with refractory 1st relapse after 1 previous reinduction regimen without attainment of remission

Temporary moments of secondary assessment

Not provided

Secondary Objective

Stratum 1A and Phase 2 Cohort (BCP- ALL patients): 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 allogeneic hematopoietic stem cell transplant (allo-HSCT) or CAR-T cells therapy. (completed)
Stratum 1A and Phase 2 Cohort (BCP- ALL patients): To determine the overall hematological response rate in these patients: - after cycle 1 (completed) - as well as the overall best response (Stratum 1A only; this is the primary objective for Phase 2 cohort). (completed)
Stratum 1A and Phase 2 Cohort (BCP- ALL patients): To determine minimal residual disease (MRD) levels in responding patients, including the percentage of patients with a complete MRD response (see Appendix 2.1) - after cycle 1 (completed) - as well as the best ORR. (completed)
Stratum 1A and Phase 2 Cohort (BCP- ALL patients): To describe the durability of response and long-term follow-up, including the number of patients that undergo HSCT or CAR-T cells therapy after treatment with InO as consolidation, the cumulative incidence of non-response or relapse, the cumulative incidence of non-relapse mortality, the event-free survival (EFS) and overall survival (OS). (ongoing)
Stratum 1A and Phase 2 Cohort (BCP- ALL patients): To determine the serum pharmacokinetic parameters of unconjugated calicheamicin and InO in the pediatric population. (completed)
Stratum 1A and Phase 2 Cohort (BCP- ALL patients): To assess the relationship between CD22 receptor density, white blood cell count (WBC) at start of treatment, CD22 saturation kinetics, cytogenetics, and in-vitro calicheamicin resistance to clinical response to InO. (completed)
Stratum 1A and Phase 2 Cohort (BCP- ALL patients): To assess for the persistence of B-Cell aplasia and hypogammaglobulinemia in responding patients following treatment with InO. (completed)
Stratum 1A and Phase 2 Cohort (BCP- ALL patients): To assess the number of patients developing anti-drug antibodies (ADAs; immunogenicity). (NOT applicable for patients enrolled after amendment 4, completed)
Stratum 1B and Stratum 1B-ASP (BCP ALL patients): To determine the safety and tolerability of InO in combination with a modified UKALL-R3 re- induction chemotherapy regimen (1 or 2 cycles), and the cumulative toxicities in patients receiving multiple InO-based cycles, as well as after subsequent allogeneic HSCT. (completed, follow-up ongoing)
Stratum 1B and Stratum 1B-ASP (BCP ALL patients): To determine the overall hematological response rate in these patients: - after cycle 1 (completed) - as well as the overall best response (completed)
Stratum 1B and Stratum 1B-ASP (BCP ALL patients): To determine MRD levels in responding patients, including the percentage of patients with a complete MRD response (see appendix 2.1 for definition): - after cycle 1 (completed) - as well as the best ORR. (completed)
Stratum 1B and Stratum 1B-ASP (BCP ALL patients): To describe the durability of response and long-term follow-up, including the number of patients that undergo HSCT or CAR-T cells therapy after study treatment as consolidation, the cumulative incidence of non-response or relapse, the cumulative incidence of non-relapse mortality, the EFS and OS. (ongoing)
Stratum 1B and Stratum 1B-ASP (BCP ALL patients): To determine the serum pharmacokinetic parameters of unconjugated calicheamicin and InO when added to a modified reinduction UKALL-R3 chemotherapy regimen without (stratum 1B), then with ASP (stratum 1B-ASP). (ongoing)
Stratum 1B and Stratum 1B-ASP (BCP ALL patients): To assess the relationship between CD22 expression and clinical response to InO (completed)
Stratum 1B and Stratum 1B-ASP (BCP ALL patients): To assess the number of patients developing CD22-negative relapse (ongoing)
Stratum 2 (Other B-cell malignancies): To determine the response rate in these patients: - after cycle 1 (completed)- as well as the overall best response. (completed)
Stratum 2 (Other B-cell malignancies): To describe the durability of response and long-term follow-up, including the number of patients that undergo stem-cell transplant after treatment with InO, the cumulative incidence of non-response or relapse, the cumulative incidence of non-relapse mortality, the EFS and OS. (ongoing)
Stratum 2 (Other B-cell malignancies): To determine the serum pharmacokinetic parameters of unconjugated calicheamicin and InO in the pediatric population. (completed)
Stratum 2 (Other B-cell malignancies): To assess for the persistence of B-Cell aplasia and hypogammaglobulinemia in responding patients following treatment with InO. To assess the number of patients developing ADAs (NOT valid for patients enrolled after Amendment 4). (completed)
Stratum 3 (VHR) (ongoing): 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 allogeneic hematopoietic stem cell transplant (allo-HSCT) or CAR-T cells therapy.
Stratum 3 (VHR) (ongoing): To determine the overall hematological response rate in these patients after cycle 1
Stratum 3 (VHR) (ongoing): To determine minimal residual disease (MRD) levels in responding patients, including the percentage of patients with a complete MRD response (see Appendix 2.1) - after cycle 1 - as well as the best ORR.
Stratum 3 (VHR) (ongoing) : To describe the durability of response and long-term follow-up, including the number of patients that undergo HSCT or CAR-T cells therapy after treatment with InO as consolidation, the cumulative incidence of non-response or relapse, the cumulative incidence of non-relapse mortality, the EFS and overall survival (OS).
Stratum 3 (VHR) (ongoing) : To assess the relationship between CD22 receptor density, white blood cell count (WBC) at start of treatment, cytogenetics, and in-vitro calicheamicin resistance to clinical response to InO.
Stratum 3 (VHR) (ongoing): To assess the persistence of B-Cell aplasia and MRD negativity in responding patients following the treatment with InO and the implications for CAR-T cells therapy.
Stratum 4: 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 (maximum 2 cycles); as well as after subsequent allogeneic hematopoietic stem cell transplant (allo-HSCT) or CAR-T cells therapy.
Stratum 4: To determine the overall hematological response rate in these patients after cycle 1.
Stratum 4: To determine minimal residual disease (MRD) levels, assessed at a local laboratory, in responding patients, including the percentage of patients with a complete MRD response after cycle 1 as well as the best ORR.
Stratum 4: To describe the durability of response, including the number of patients that undergo allo-SCT or CART-therapy after treatment with InO, the cumulative incidence of non-response or relapse, the cumulative incidence of non-relapse mortality, EFS and OS.
Stratum 4: To assess the relationship between clinical response to InO and CD22 expression levels determined at the local laboratory.
Stratum 4: To investigate determinants of resistance to InO such as DNA nucleotidylexotransferase (DNTT) expression levels, BCL-2 expression levels as well as other potential determinants of resistance through whole genome sequencing at enrollment, and at the time of relapse after InO when applicable.
Stratum 4: To characterize lymphocyte subsets after InO treatment, including persistence of B-Cell aplasia and hypogammaglobulinemia in responding patients following treatment with InO.

Secondary Endpoints

Stratum 1A Safety and tolerability: 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. Stratum 1A Safety and tolerability: Occurrence of toxic death; i.e., death attributable to InO therapy. Stratum 1A Safety and tolerability: Occurrence of hepatic veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS) during or after therapy with InO. Stratum 1A Safety and tolerability: Laboratory abnormalities as characterized by type, frequency, severity and timing. Stratum 1A Safety and tolerability: 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 relapsed or refractory leukemia or lymphoma, accounting for competing events. Stratum 1A Measures of anti-leukemic activity: ORR, defined as CR, CRi, or CRp both after cycle 1 as well as the best response over multiple cycles of InO therapy (see Appendix 2 for definitions). Stratum 1A Measures of anti-leukemic activity: MRD levels, including the percentage of patients who become MRD-negative (complete MRD response defined as an MRD-level < 1x10-4), after cycle 1, as well as the overall best response (MRD-negativity) over multiple cycles. Stratum 1A Measures of anti-leukemic activity: Duration of response, defined as the time between achieving response (CR, CRi or CRp) after starting study treatment and documented relapse or death. Stratum 1A Measures of anti-leukemic activity: Number and percentage of patients being transplanted and those receiving CAR T-cell therapy after treatment with InO. Stratum 1A Measures of anti-leukemic activity: 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. Stratum 1A Measures of anti-leukemic activity: Overall survival, defined as time to death following start of study treatment. Stratum 1A Measures of anti-leukemic activity: 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. Stratum 1A: Serum pharmacokinetic parameters of InO and unconjugated calicheamicin. Stratum 1A Pharmacodynamics parameters: Relationship between response (ORR) and CD22 expression levels and WBC. Stratum 1A Pharmacodynamics parameters: Relationship between response (ORR) and CD22 saturation kinetics. Stratum 1A Pharmacodynamics parameters: Relationship between response (ORR) and calicheamicin sensitivity. Stratum 1A Pharmacodynamics parameters: Clonal evolution (CD22-negativity) and relation to loss of response. Stratum 1A Other endpoints: The percentage of patients responding to InO (ORR) without adequate recovery of CD19-positive B-cells (below lower limit of normal (LLN) for age) or immunoglobulins (below LLN for age). Following 4 weeks, 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 cells therapy. Stratum 1A Other endpoints: Percentage of patients who exhibit anti-drug antibodies (ADA) (NOT valid for patients enrolled after Amendment 4). Phase 2 cohort Safety: 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. Phase 2 cohort Safety: Occurrence of toxic death; i.e., death attributable to InO therapy. Phase 2 cohort Safety: Occurrence of VOD/SOS during or after therapy with InO. Phase 2 cohort Safety: Laboratory abnormalities as characterized by type, frequency, severity and timing. Phase 2 cohort Safety: 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 relapsed or refractory leukemia or lymphoma, accounting for competing events. Phase 2 cohort Other measures of anti-leukemic activity: ORR after cycle 1. Phase 2 cohort Other measures of anti-leukemic activity: Minimal residual disease levels, including the percentage of patients who become MRD-negative (complete MRD response defined as an MRD-level < 1x10-4), after cycle 1, as well as the best response (MRD-negativity) over multiple cycles. Phase 2 cohort Other measures of anti-leukemic activity: Duration of response, defined as the time between achieving response (CR, CRi or CRp) after starting study treatment and documented relapse or death. Phase 2 cohort Other measures of anti-leukemic activity: Number and percentage of patients being transplanted and those receiving CAR T-cell therapy after treatment with InO. Phase 2 cohort Other measures of anti-leukemic activity: 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. Phase 2 cohort Other measures of anti-leukemic activity: Survival, defined as time to death following start of study treatment. Phase 2 cohort Other measures of anti-leukemic activity: 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. Phase 2 cohort Serum pharmacokinetic parameters of InO and unconjugated calicheamicin. Phase 2 cohort Pharmacodynamics parameters: Relationship between response (ORR) and CD22 expression levels and WBC. Phase 2 cohort Pharmacodynamics parameters: Relationship between response (ORR) and CD22 saturation kinetics. Phase 2 cohort Pharmacodynamics parameters: Relationship between response (ORR) and calicheamicin sensitivity. Phase 2 cohort Pharmacodynamics parameters: Clonal evolution (CD22-negativity) and relation to loss of response. Phase 2 cohort Other endpoints: 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 weeks, 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 cells therapy. Percentage of patients who exhibit ADA (NOT valid for patients enrolled after Amendment 4). Stratum 1B and 1B-ASP Safety: AEs (secondary endpoints have same definitions as for Stratum 1A) Stratum 1B and 1B-ASP Safety: Occurrence of toxic death; i.e., death attributable to InO therapy. Stratum 1B and 1B-ASP Safety: Occurrence of hepatic VOD/SOS during or after therapy with InO. Stratum 1B and 1B-ASP Safety: Laboratory abnormalities Stratum 1B and 1B-ASP Safety: Cumulative incidence of non-relapse mortality Stratum 1B and 1B-ASP Other measures of anti-leukemic activity: ORR Stratum 1B and 1B-ASP Other measures of anti-leukemic activity: MRD levels Stratum 1B and 1B-ASP Other measures of anti-leukemic activity: Duration of response Stratum 1B and 1B-ASP Other measures of anti-leukemic activity: Number and percentage of patients being transplanted and those receiving CAR T-cell therapy after treatment with InO. Stratum 1B and 1B-ASP Other measures of anti-leukemic activity: EFS Stratum 1B and 1B-ASP Other measures of anti-leukemic activity: Overall survival Stratum 1B and 1B-ASP Other measures of anti-leukemic activity: Cumulative incidence of non-response or relapse Stratum 1B and 1B-ASP Serum pharmacokinetic parameters of InO and unconjugated calicheamicin during treatment combined with modified UKALL-R3 re-induction regimen both with and without pegylated asparaginase. Stratum 1B and 1B-ASP Pharmacodynamics parameters Relationship between response (ORR) and CD22 expression levels Stratum 1B and 1B-ASP Pharmacodynamics parameters Clonal evolution (CD22-negativity) and relation to loss of response. Stratum 2 Measures of anti-tumor activity: Overall remission rate (CR and PR) both after cycle 1 as well as overall best response in patients receiving multiple cycles of InO therapy (see Appendix 2 for

definitions). Stratum 2 Measures of anti-tumor activity: Duration of response, defined as the time between achieving response (CR and PR) after starting study treatment and documented relapse or death. Stratum 2 Measures of anti-tumor activity: Number and percentage of patients being transplanted and those receiving CAR T-cell therapy after treatment with InO. Stratum 2 Measures of anti-tumor activity: EFS, defined as the time between start of study treatment and first event including failure to achieve CR/PR (calculated as an event on day 0), relapse, death of any cause and second malignancies. Stratum 2 Measures of anti-tumor activity: Overall survival, defined as time to death following start of study treatment. Stratum 2 Measures of anti-tumor activity: 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. Stratum 2 Serum pharmacokinetic parameters of InO and unconjugated calicheamicin. Stratum 2 Other endpoints: 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 weeks, 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 cells therapy. Stratum 2 Other endpoints: Percentage of patients who exhibit ADA (NOT valid for patients enrolled after Amendment 4). Stratum 3 Safety: 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. Stratum 3 Safety: Occurrence of any induction death and/or toxic death attributable to InO therapy. Stratum 3 Safety: Occurrence of VOD/SOS during or after therapy with InO. Stratum 3 Safety: Laboratory abnormalities as characterized by type, frequency, severity and timing. Stratum 3 Safety: 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 relapsed or refractory leukemia or lymphoma, accounting for competing events. Stratum 3 Other measures of anti-leukemic activity: ORR after cycle 1 Stratum 3 Other measures of anti-leukemic activity: Minimal residual disease levels, including the percentage of patients who become MRD-negative (complete MRD response defined as an MRD-level < 1x10-4) after cycle 1, as well as the best response (MRD-negativity) over multiple cycles. Stratum 3 Other measures of anti-leukemic activity: Duration of response, defined as the time between achieving response (CR, CRi or CRp) after starting study treatment and documented relapse or death. Stratum 3 Other measures of anti-leukemic activity: Number and percentage of patients being transplanted and those receiving CAR T-cell therapy after treatment with InO. Stratum 3 Other measures of anti-leukemic activity: 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. Stratum 3 Other measures of anti-leukemic activity: Survival, defined as time to death following start of study treatment. Stratum 3 Other measures of anti-leukemic activity: 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. Stratum 3 Other measures of anti-leukemic activity: To study the interval between InO re-induction and CAR-T cells therapy based on MRD negativity and B cell aplasia after InO re-induction. Stratum 3 Pharmacodynamics parameters Relationship between response (ORR) and CD22 expression levels and WBC. Stratum 3 Pharmacodynamics parameters Relationship between response (ORR) and calicheamicin sensitivity. Stratum 3 Pharmacodynamics parameters Clonal evolution (CD22-negativity) and relation to loss of response. Stratum 3 Other endpoints The percentage of patients responding to InO (ORR) without adequate recovery of CD19-positive B-cells and CD4+/CD8+ T-cells(below LLN for age) or immunoglobulins (below LLN for age) following 4,6,8 and 10 weeks, 3, 6 and 12 months after treatment with InO, excluding patients who have been transplanted from the date of HSCT or CAR T-cell infusion. Stratum 4 Safety and tolerability: 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 courses of therapy. Stratum 4 Safety and tolerability: Occurrence of toxic death; i.e., death attributable to InO therapy. Stratum 4 Safety and tolerability: Occurrence of VOD/SOS during or after therapy with InO Stratum 4 Safety and tolerability: Laboratory abnormalities as characterized by type, frequency, severity and timing. Stratum 4 Safety and tolerability: 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 relapsed or refractory leukemia or lymphoma, accounting for competing events. Stratum 4 Other measures of anti-leukemic activity: ORR after cycle 1. Stratum 4 Other measures of anti-leukemic activity: Minimal residual disease levels, including the percentage of patients who become MRD-negative (complete MRD response defined as an MRD-level < 1x10-4) after cycle 1, as well as the best response (MRD-negativity) over multiple cycles. Stratum 4 Other measures of anti-leukemic activity: Duration of response, defined as the time between achieving response (CR, CRi or CRp) after starting study treatment and documented relapse or death. Stratum 4 Other measures of anti-leukemic activity: Number and percentage of patients being transplanted and those receiving CAR T-cell therapy

after treatment with InO. Stratum 4 Other measures of anti-leukemic activity: 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. Stratum 4 Other measures of anti-leukemic activity: Survival, defined as time to death following start of study treatment. Stratum 4 Other measures of anti-leukemic activity: 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. Stratum 4 Other measures of anti-leukemic activity: To study the interval between InO re-induction and CAR-T cells therapy based on MRD negativity and B cell aplasia after InO re-induction. Stratum 4 Pharmacodynamics parameters: Relationship between response (ORR) and CD22 expression levels and WBC. Stratum 4 Pharmacodynamics parameters: Clonal evolution (CD22-negativity) and relation to loss of response. Stratum 4 Pharmacodynamics parameters: Screening through whole genome sequencing of genomic determinants of response/resistance to InO, assessing the relationship between response (ORR and MRD negativity) and DNTT expression levels, cytogenetics, as well as other emerging mechanisms of resistance. Stratum 4 Other endpoints: The percentage of patients responding to InO (ORR) without adequate recovery of CD19-positive B-cells and CD4+/CD8+ T-cells(below LLN for age) or immunoglobulins (below LLN for age) following 4,6,8 and 10 weeks, 3, 6 and 12 months after treatment with InO, excluding patients who have been transplanted from the date of HSCT or CAR T-cell infusion.

Temporary moments of secondary assessment

Not provided

Inclusion criteria

Age (for all patients) Patients must be 1 and < 18 years of age at the time of enrollment. Additional criteria for limited to Stratum 1A and 1B only: 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. Stratum 4: Patients must have either: 2nd or greater CD22 positive BCP-ALL relapse; 1st VHR CD22 positive BCP-ALL relapse defined as isolated bone marrow or combined relapse occurring less than 18 months from initial diagnosis and/or with cytogenetic-high risk characteristics, including KTM2A/AF4, E2A/TCF3-PBX1 t(1;19), E2A/TCF3-HLF t(17;19), hypodiploidy (less than 40 chromosomes), TP53 mutation and/or deletion. Acceptable laboratory techniques to confirm these cytogenetic abnormalities include chromosome banding analysis (CBA), fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR), and/or Next Generation Sequencing (based on local laboratory results); Any relapse of BCP-ALL post HSCT; 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 must be CD22 surface antigen positive (in either bone marrow or peripheral blood) by institutional standards as determined by the local immunophenotyping laboratory. For 1st VHR BCP-ALL relapse evidence of prior fusion gene abnormalities is acceptable as they tend to be stable during the course of the disease. Laboratory techniques acceptable to test the presence of the cytogenetic-high risk characteristics are chromosome banding analysis (CBA), FISH, PCR and/or Next Generation Sequencing (inclusion is based on local laboratory results). Stratum 1A, Phase 2 and Stratum 1B/1B-ASP: 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) by institutional standards as determined by the local immunophenotyping laboratory. The first 6

patients (Stratum 1A only) must have M3 marrow status (25% blasts by morphology). Stratum 2: Diagnosis Patients must have second or greater relapsed or refractory CD22-positive B-cell malignancy including but not limited to diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL), Burkitt lymphoma, Burkitt leukemia or B-cell precursor lymphoblastic lymphoma: There must be histologic verification of disease at original diagnosis or subsequent relapse. Patient must have evaluable or measurable disease documented by radiographic criteria or bone marrow disease present at study entry. The malignant cells need to be CD22 surface antigen positive (in either biopsy material, the bone marrow or peripheral blood) by institutional standards as determined by the local immunophenotyping laboratory. Stratum 3: Diagnosis; Patients must have: First BM or combined relapse of CD22+ VHR BCP-ALL defined as any relapse <18 months from initial diagnosis and/or cytogenetic-high risk characteristics: KTM2A/AF4, E2A/TCF3-PBX1 t(1;19) or E2A/TCF3-HLF t(17;19), hypodiploidy (less than 40 chromosomes), TP53 mutation and/or deletion, as also shown in Table 2 (excluding patients who received a HSCT in 1st CR). 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) by institutional standards as determined by the local immunophenotyping laboratory. Evidence of prior fusion gene abnormalities is acceptable as they tend to be stable during the course of the disease. Laboratory techniques acceptable to test the presence of the above mentioned cytogenetic-high risk characteristics are chromosome banding analysis (CBA), FISH, PCR and/or Next Generation Sequencing (inclusion is based on local laboratory results). For all patients Performance Level and Life Expectancy Karnofsky > 60% for patients > 16 years of age and Lansky > 60% for patients 16 years of age. (See Appendix I for Performance Scales). Patient must have a life expectancy of at least 6 weeks. For all patients 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 per the CTCAE 4.03 prior to entering this study, with the exception of the authorized laboratory abnormalities as defined in the inclusion/exclusion criteria. a. Chemotherapy: At least 7 days must have elapsed 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 enrollment onto this study. b. Radiotherapy: At least 28 days must have elapsed since any prior radiation therapy. c. 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. d. 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®). e. 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). f. 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. g. 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. h. Prior calicheamicin exposure: Patient has not received prior treatment with a calicheamicin-conjugated antibody (e.g. gemtuzumab ozogamicin). For all patients Renal and Hepatic Function Patients 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 GFR 70mL/min/1.73 m2 estimated based on serum creatinine and/or cystatin C levels (e.g. Bedside Schwartz formula). AST and ALT must be 5 x institutional ULN. (stratum 3 & 4) Patients total total bilirubin must be 1.5 x institutional ULN unless the patient has documented Gilbert syndrome, in which case the AST and ALT must be 5 x ULN. (stratum 3 & 4) For all patients Cardiac Function Patient must have a shortening fraction 30% by echocardiogram or an ejection fraction > 50% by MUGA. For all patients Reproductive Function Female patients of childbearing potential must have a negative urine or serum pregnancy test confirmed 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. Highly effective methods of contraception include (but not exclusively) the following contraceptive methods:

combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation progestogen-only hormonal contraception associated with inhibition of ovulation intrauterine device (IUD) intrauterine hormone-releasing system (IUS) sexual abstinence.

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 VOD/SOS per the modified Seattle criteria are excluded, as specified in Appendix 3, or prior liver-failure [defined as severe acute liver injury with encephalopathy and impaired synthetic function (INR of 1.5)].
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. The patient may not have: A requirement for vasopressors; Positive blood culture within 48 hours of study enrollment; Fever above 38.2 degrees Celsius within 48 hours of study enrollment with clinical signs of infection. Fever that is determined to be due to tumor burden is allowed if patients have documented negative blood cultures for at least 48 hours prior to enrollment and no concurrent signs or symptoms of active infection or hemodynamic instability. A positive fungal culture within 30 days of study enrollment. Active fungal, viral, bacterial, or protozoal infection requiring IV or oral treatment. Chronic prophylaxis therapy to prevent infections is allowed.
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.
Allergic reaction Patients with prior Grade 3/4 allergic reaction to a monoclonal antibody are excluded.
Concurrent disease Patients will be excluded if they have significant concurrent disease, illness, psychiatric disorder or social issue that would compromise patient safety or compliance with protocol therapy, interfere with consent, study participation, follow up, or interpretation of study results. 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, stratum 3 and stratum 4.
Additional exclusion criteria for Stratum 1B Patients with grade 3-4 peripheral neuropathy (as defined in the Delphi consensus of acute toxic effects for childhood ALL by Schmiegelow et al.12). Patients with prior history of thrombosis during steroid and/or asparaginase are eligible provided they use adequate anti-coagulant prophylaxis, according to institutional guidelines. Patients in whom prior experience suggests that a timely delivery of therapy is unlikely or associated with an undue risk because of intolerance.
Additional exclusion criteria for Stratum 1B-ASP cohort only Patients with any history of PEG-asparaginase intolerance due to allergic reactions or silent inactivation during prior treatment. Patients with any history of prior asparaginase-associated acute pancreatitis (any grade as defined in the Delphi consensus12. Patients who are excluded from Stratum 1B-ASP may potentially be enrolled in Stratum 1B expansion cohort.
Additional exclusion criteria for Stratum 3 (VHR cohort) only Patients who are transplanted in CR1 (such patients are eligible for the phase 1B cohort).

Calendar

(Last Update: 12/12/2025)

Authorization	Start of Trial	First patient inclusion	Halted	Restarted
11/10/2017	09/04/2018	05/04/2018	Not aported	Not aported

End of recruitment	Premature end (Spain)	Premature End (Global)	Trial end (Spain)	Trial end (Global)
13/02/2025	Not aported	Not aported	Not aported	Not aported

Sponsor

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Contact Person

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Monetary support: N/A

Sponsor type: No commercial

Ceim

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Sites

Active (06/04/2018)

Hospital de Sant Joan de Déu

Esplugues de Llobregat

BARCELONA

Oncología Pediátrica

not initialized (--/--/----)

Hospital Infantil Universitario Nino Jesus

Madrid

MADRID

Oncology

Active (04/03/2018)

HOSPITAL UNIVERSITARI I POLITÈCNIC LA FE

Valencia

VALENCIA

Oncología Pediátrica

not initialized (--/--/----)

Hospital Universitari Vall D Hebron

Barcelona

BARCELONA

Pediatric Hematology and HSCT

Active (28/03/2018)

Hospital Universitari Vall d'Hebron

Barcelona

BARCELONA

Oncología Pediátrica

not initialized (--/--/----)

Hospital Universitario Y Politecnico La Fe

Valencia

VALENCIA

Paediatric Transplant

not initialized (--/--/----)

Sant Joan De Deu Barcelona Hospital

Esplugues De Llobregat

BARCELONA

Pediatric Cancer Center Barcelona

Medication

BESPONSA 1 mg powder for concentrate for solution for infusion

SOLUTION FOR INFUSION

INTRAVENOUS USE

ATC code: L01XC26 - INOTUZUMAB OZOGAMICINA

Active Principles: N/A

Orphan Experimental

No results