A Phase 1/2 Open-label Study to Investigate the Safety, Efficacy, and Pharmacokinetics of Administration of Subcutaneous Blinatumomab for the Treatment of Adults with Relapsed or Refractory B cell Precursor Acute Lymphoblastic Leukemia (R/R B-ALL)

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This study has been transitioned to CTIS with ID 2023-506136-32-00 check the CTIS register for the current data. Primary:Dose Escalation• Evaluate the safety and tolerability of subcutaneous (SC) blinatumomab for treatment of Relapsed or Refractory…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON56021

Source
ToetsingOnline

Brief title
20180257

Condition

- Other condition
- Leukaemias

Synonym

Acute lymphocytic leukaemia; Blood Cancer

Health condition

recidiverende of refractaire B-cel precursor acute lymfoblastische leukemie (R/R B-ALL)

Research involving
Human

Sponsors and support

Primary sponsor: Amgen
Source(s) of monetary or material Support: Amgen

Intervention

Keyword: Blinatumomab, Phase 1/2 Study, Relapsed or refractory B-precursor ALL (R/R B-ALL), Subcutaneous

Outcome measures

Primary outcome

Dose Escalation

• Dose limiting toxicities (DLTs), treatment-emergent adverse events

(TEAE), serious TEAE, treatment-related TEAE, and adverse events.

Dose Expansion and Phase 2 (Ph-IIR and Ph-IIM cohorts)

• CR/CRh within the first 2 cycles for Ph2a and Ph-IIR cohorts (R/R B-ALL)

and CR with MRD < 0.01% within the first 2 cycles for Ph-IIM cohort (MRD

B-ALL).

Phase 2 Ph-IIC (SC1 and SC2 Cohorts)

• Blinatumomab PK parameters following SC administration including, but not

limited to Cmax, average concentration (Cavg), tmax, and AUC

Secondary outcome

Dose Escalation

• Blinatumomab PK parameters following SC administration including, but not limited to, minimum concentration over the dosing interval (Cmin), maximum concentration (Cmax), time to maximum concentration (Tmax), area under the concentration-time curve (AUC)

• Anti-blinatumomab antibody formation

• Complete remission / complete remission with partial hematological recovery (CR/CRh) within the first 2 cycles

Dose Expansion and Phase 2 (Ph-IIR and Ph-IIM cohorts)

• Blinatumomab PK parameters following SC administration including, but not limited to Cmin, Cmax, Tmax, and AUC

• Anti-blinatumomab antibody formation

• RFS in subjects who achieve response (CR/CRh within the first 2 cycles for Ph2a and Ph-IIR cohorts and CR with MRD<0.01% within the first 2 cycles for Ph-IIM cohort) is defined as the time from the first achievement of this response until date of the first relapse including extramedullary relapse, or death due to any cause, whichever occurs first

• Overall survival is calculated from the time of the start of first dose of SC blinatumomab until death due to any cause

• Duration of complete response is defined as the time from the first onset of response (CR/CRh within the first 2 cycles for Ph2a and Ph-IIR

cohorts and CR with MRD <0.01% within the first 2 cycles for Ph-IIM cohort) until the relapse including extramedullary relapse.

• TEAEs, serious TEAEs, treatment related TEAEs, and adverse events

• Summary scores at each assessment and change from baseline as assessed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ C30)

Phase 2 Ph-IIC (SC1 and SC2 Cohorts)

• Complete remission/complete remission with partial hematological recovery (CR/CRh) within the first 2 cycles

• Anti blinatumomab antibody formation

• RFS in subjects who achieve response (CR/CRh within the first 2 cycles) is defined as the time from the first achievement of this response until date of the first relapse including extramedullary relapse, or death due to any cause, whichever occurs first

• OS is calculated from the time of the start of first dose of SC blinatumomab until death due to any cause

• Duration of complete response is defined as the time from the first onset of response (CR/CRh within the first 2 cycles) until relapse including extramedullary relapse

• TEAEs, serious TEAEs, treatment related TEAEs, and adverse events

• Summary scores at each assessment and change from baseline as assessed by the European Organization for Research and Treatment of Cancer (EORTC)

Quality of Life Questionnaire (QLQ C30)

Study description

Background summary

Acute lymphoblastic leukemia (ALL) is a malignant disease of lymphoid progenitor cells in the bone marrow (BM) or sites of lymphatic system. Immature lymphoblasts proliferate in the BM and may infiltrate other organs. As a consequence, the normal hematopoiesis in the BM is suppressed. Acute lymphoblastic leukemia is a rare malignant disease with an overall incidence of 1.1/100,000 per year. Acute lymphoblastic leukemia has a bimodal distribution with an early peak at 4 to 5 years of age (incidence of 4.5/100,000 per year) followed by a second gradual increase at 50 years (incidence of 2/100,000 per year). It represents 80% of acute childhood leukemia and 20% of acute leukemia cases in adults (Howlader et al, 2012; Jabbour et al, 2005; Larson 2005; Pui and Evans 1998).

Study objective

This study has been transitioned to CTIS with ID 2023-506136-32-00 check the CTIS register for the current data.

Primary:

Dose Escalation
• Evaluate the safety and tolerability of subcutaneous (SC) blinatumomab for treatment of Relapsed or Refractory B cell Precursor Acute Lymphoblastic Leukemia (R/R B-ALL)
• Determine the maximum tolerated dose (MTD) and preliminary recommended phase 2 dose(s) (RP2D) of SC administered blinatumomab

Dose Expansion and Phase 2 (Ph-IIR and Ph-IIM Cohorts)
• Evaluate the efficacy of SC blinatumomab

Phase 2 Ph-IIC (SC1 and SC2 Cohorts)
• Evaluate the PK following SC administration of SC1 and SC2 blinatumomab formulation

Secondary:

Dose Escalation
• Determine pharmacokinetics (PK) following SC blinatumomab

• Evaluate the immunogenicity of SC blinatumomab
• Evaluate the efficacy of SC blinatumomab

Dose Expansion and Phase 2 (Ph-IIR and Ph-IIM Cohorts)
• Determine PK following SC blinatumomab
• Evaluate the immunogenicity of SC blinatumomab
• Evaluate the relapse-free survival (RFS) induced by SC blinatumomab
• Evaluate the effect of SC blinatumomab on overall survival and on the duration of complete response
• Evaluate the safety and tolerability of SC blinatumomab
• Evaluate patient-reported outcomes and quality of life outcomes with SC blinatumomab

Phase 2 Ph-IIC (SC1 and SC2 Cohorts)
• Evaluate the efficacy and immunogenicity, safety and tolerability of SC blinatumomab
• Evaluate the relapse-free survival (RFS) induced by SC blinatumomab
• Evaluate the effect of SC blinatumomab on OS and duration of complete response
• Evaluate patient-reported outcomes and quality of life outcomes with SC blinatumomab

Study design

This is a multicenter, single arm, open-label, phase 1/2 dose escalation and expansion study in adult subjects with R/R B-ALL, evaluating the safety, tolerability, pharmacokinetic (PK), and efficacy of SC blinatumomab as monotherapy. The study includes a dose escalation stage and an expansion stage. The study will evaluate SC administration of blinatumomab as a potentially more convenient mode of administration and explore higher doses in the dose escalation phase of the study and will be conducted at approximately 40 sites. The study will consist of up to a 3-week screening and pre-phase period, a treatment period, a safety follow-up visit 30 (+/- 3) days after last dose of study treatment, and a long-term follow-up period (only for the dose expansion phase) lasting approximately 2 years after the first dose of investigational product (IP) is received.

Dose Escalation: During dose escalation, subject safety to different doses and dosing schedules of SC blinatumomab will be reviewed. Subjects will be enrolled in groups of 3 to 6 subjects. A dose level review team (DLRT) will meet after all subjects in each cohort complete the DLT-evaluation period to determine if additional subjects need to be enrolled into the cohort, if it is appropriate to dose escalate or deescalate, change the dosing schedule, or to stop the study for safety concerns. A maximum of 9 subjects overall may be enrolled at each dose level. Meanwhile, this dose escalation phase has been finalized.

Dose expansion: Up to 60 additional subjects will be enrolled to the recommended phase 2 dose (RP2D) and schedule determined from dose escalation

stage to further assess safety, PK, PD, and efficacy.

Intervention

Subjects in this study will receive at least 2 and up to 5 cycles of SC blinatumomab.
Each cycle will be 34 days and includes 26-day treatment period and an 8-day treatment free interval between day 27 and day 34.

Study burden and risks

Please refer to E2 / E9

Contacts

Public
Amgen

Minervum 7061
Breda 4817 ZK
NL
Scientific
Amgen

Minervum 7061
Breda 4817 ZK
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:
• 101 Subject has provided informed consent prior to initiation of any study specific activities/procedures and/or the subject*s legally acceptable representative has provided informed consent prior to any study-specific activities/procedures being initiated when the subject has any kind of condition that, in the opinion of the Investigator, may compromise the ability of the subject to give written informed consent.
• 102 Age >= 18 years at time of informed consent
Disease status: All subjects must fulfill at least 1 of inclusion criteria #103, #104, or #105 for eligibility.
For Ph-IIM cohort (subjects with MRD+ ALL [phase 2]) only: Subjects will be eligible for Ph-IIM if they have B ALL and meet the MRD criteria defined in inclusion criterion #109 below. With the exception of disease status criteria (ie, inclusion criteria #103, #104, #105, #106), Ph-IIM cohort subjects must satisfy all other inclusion criteria to be eligible.
• 103 Subjects with B-precursor ALL with any of the following:
o Either refractory (to primary induction) therapy or refractory to at least 1 salvage therapy OR
o In untreated first, second, third or greater relapse or refractory relapse
* First Relapse is defined as achievement of first CR (CR1) during upfront therapy then relapse during or after continuation therapy
* Primary Refractory disease is defined as the absence of CR after standard induction therapy
* Refractory relapse is defined as lack of CR after salvage treatment
* Second relapse or later relapse is defined as relapse after achieving a second CR (CR2) in first or later salvage
* Refractory to salvage is defined as no attainment of CR after salvage
• 104 Relapsed or Refractory at any time after first salvage therapy.
• 105 Relapse at any time after allogeneic hematopoietic stem cell transplant (HSCT).
• 106 Greater than or equal to 5% blasts in the BM (Exception: Isolated Non-CNS extramedullary disease [EMD]).
• 107 Eastern Cooperative Oncology Group (ECOG) Performance Status <= 2.
• 108 Subjects with relapse or refractory B Cell ALL Ph+ disease and that are intolerant or refractory to prior tyrosine kinase inhibitors (TKIs) are eligible.
• 109 For subjects in the MRD cohorts only (Ph-IIM cohort), BMB must be <5% and >=0.1%. This will replace inclusion criterion #106 for subjects in this cohort
• 111 Subjects enrolled in SC1 and SC2 comparison cohort (Ph-IIC) must provide consent to participate in the additional PK sample collection requirements.
• 112 Subjects with Isolated (< 5% BMB) Non-CNS Extra Medullary Disease (EMD) are eligible in phase 2 cohorts Ph-IIR and Ph-IIM only.

Exclusion criteria

Subjects are excluded from the study if any of the following criteria apply:
Disease Related
• Active ALL in the CNS. Presence of > 5 white blood cells (WBC) per cubic millimeter in cerebrospinal fluid (CSF) with lymphoblasts present (confirmed by CSF analysis) and/or clinical signs of CNS leukemia. If CSF leukemia is present subjects will have to receive intrathecal therapy and have documented negative CSF prior to enrolling.

Other Medical Conditions
• History or presence of clinically relevant CNS pathology or event such as epilepsy, childhood or adult seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson*s disease, cerebellar disease, organic brain syndrome, psychosis or severe (>= grade 3) CNS events including ICANS from prior CD19 CART or other T-cell-engager therapies.

• Current autoimmune disease or history of autoimmune disease with potential CNS involvement.
• Active acute or chronic graft versus host disease requiring systemic treatment with immunosuppressive medication.
• Known hypersensitivity to blinatumomab or to any component of the product formulation.
• Known infection with human immunodeficiency virus (HIV) or chronic infection with hepatitis B virus or hepatitis C virus.
• Symptoms and/or clinical signs and/or radiological and/or sonographic signs that indicate an acute or uncontrolled chronic infection, any other concurrent disease or medical condition that could be exacerbated by the treatment or would seriously complicate compliance with the protocol.

• History of malignancy other than ALL within 3 years prior to start of protocol-specified therapy except for:
o Malignancy treated with curative intent and with no known active disease present for 3 years before enrollment and felt to be at low risk for recurrence by the treating physician.
o Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
o Adequately treated cervical carcinoma in situ without evidence of disease.
o Adequately treated breast ductal carcinoma in situ without evidence of disease.
o Prostatic intraepithelial neoplasia without evidence of prostate cancer.

• Allogeneic HSCT within 12 weeks before the start of protocol-specified therapy
• Cancer chemotherapy within 2 weeks before the start of protocol-specified therapy. With the exception of intrathecal chemotherapy and/or low dose

maintenance therapy for example vinca alkaloids, mercaptopurine, methotrexate, or hydroxyurea (any low dose chemotherapy as stated above must be discontinued before starting pre-phase) or pre-phase chemotherapy and/or dexamethasone as outlined in Section 6.1.2.1 and Section 6.1.2.2, respectively.
• Immunotherapy (eg, rituximab, alemtuzumab) within 4 weeks before start of protocol-specified therapy. Prior failed CD19 directed therapy such as prior blinatumomab or CD19 CAR T cells will be allowed (with demonstrated continued CD19+ expression), if treatment ended > 4 weeks prior to start of protocol therapy and no prior CNS complications.

Prior/Concurrent Clinical Study Experience
• Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study. Other investigational studies are not permitted while participating in this study.

Diagnostic Assessments
• Abnormal screening laboratory values as defined below:
o Total bilirubin >3.0 mg/dL prior to start of treatment (unless due to Gilbert*s or Meulengracht disease)
o Estimated Creatinine clearance < 60 mL/min

Other Exclusions
• Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 96 hours after the last dose of protocol-specified therapy.
• Female subjects of childbearing potential unwilling to use 1 highly effective method of contraception during treatment and for an additional 96 hours after the last dose of protocol-specified therapy. Refer to Section 11.5 for additional contraceptive information.
• Female subjects of childbearing potential with a positive pregnancy test assessed during Screening by a serum pregnancy test and/or urine pregnancy test.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-06-2023
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Blincyto
Generic name:	Blinatumomab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	04-04-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-06-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-08-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	13-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-506136-32-00

Register	ID
EudraCT	EUCTR2019-004780-52-NL
ClinicalTrials.gov	NCT04521231
CCMO	NL80600.056.22