A Phase 1b Open-label Study Investigating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Administration of Blinatumomab in Combination With AMG 404 for the Treatment of Adults With Relapsed or Refractory B Cell Precursor Acute Lymphoblastic Leukemia (ALL)

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Primary :• To evaluate the safety and tolerability of blinatumomab incombination with AMG 404 in adults with R/R B-ALL• To estimate the Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D) of AMG 404 when combined with cIV...

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

Summary

ID

NL-OMON55298

Source
ToetsingOnline

Brief title
20190117 (Blinatumomab + AMG404 combination)

Condition

- Other condition

Synonym
Acute lymphocytic leukaemia; Blood Cancer

Health condition

bloedkanker

Research involving
Human

Sponsors and support

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

Intervention

Keyword: AMG 404, Blinatumomab, Phase 1b Study, Relapsed or refractory B-precursor ALL (R/R B-ALL)

Outcome measures

Primary outcome

• Dose-limiting toxicities (DLT)

• Treatment-emergent adverse events (TEAEs), serious TEAEs, treatment-related

TEAEs and adverse events of interest (EOI).

Secondary outcome

• CR/CRh* within the first 2 cycles and across all cycles,

• CR within the first 2 cycles and across all cycles

• Duration of CR

• Duration of CR/CRh

• Blinatumomab PK parameters

• AMG 404 PK parameters

• Anti-blinatumomab Antibodies

• Anti-AMG 404 antibodies

Study description

Background summary

Acute lymphoblastic leukemia is a malignant disease of lymphatic progenitor cells in the 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

Primary :
• To evaluate the safety and tolerability of blinatumomab incombination with AMG 404 in adults with R/R B-ALL
• To estimate the Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D) of AMG 404 when combined with cIV blinatumomab

Secondary:
• To evaluate the efficacy of blinatumomab and AMG 404 combination therapy in the treatmentof R/R B-ALL
• To characterize PK following blinatumomab and AMG 404 combination therapy
• To evaluate the immunogenicity oblinatumomab and AMG 404 following blinatumomab and AMG 404 combination therapy

Study design

This is a multicenter, non-randomized, open-label, Phase 1b trial of blinatumomab in combination with AMG 404 in adults with relapsed or refractory B-precursor acute lymphoblastic leukemia (R/R B-ALL), evaluating safety, tolerability, pharmacokinetics (PK), and efficacy of blinatumomab and AMG 404 combination therapy. The study will consist of up to a 3-week screening and prephase period, a treatment period, a safety follow-up (SFU) visit 30 (± 7) days after last dose of blinatumomab, and an end of study (EOS) visit 120 ±7 days after the last administration of AMG 404.

Subjects in this study will receive at least 2 and up to 5 cycles of combination therapy with blinatumomab and AMG 404 in combination (Blin + 404).

Cohort 1
Each cycle will be 42 days and includes a 14-day blinatumomab treatment-free interval between Days 29 and 42. Blinatumomab cIV will be given on Day 1 to Day 28. In Cycle 1, blinatumomab will be administered at 9 µg/day on Day 1 to Day 7, then at 28 µg/day on Day 8 to Day 28 for subjects >=45 kg and 5 µg/m2/day, not to exceed 9 µg/day, on Day 1 to Day 7, then 15 µg/m2/day on Day 8 to Day 28 for subjects < 45 kg, not to exceed 28 µg/day.
In Cycle 2 to Cycle 5, blinatumomab will be administered at a dose of 28 µg/day for subjects >=45 kg and 15µg/m2/day for subjects < 45 kg, not to exceed 28 µg/day on Day 1 to Day 28. AMG 404 will be administered intravenously (IV) over approximately 30 minutes starting on Day 11 of Cycle 1 and dosed every 4 weeks (Q4W) thereafter.

For cohort 1c, 2a and 2b, please refer to section 4.1 of the protocol.

The planned doses of AMG 404 in Cohorts 1 and 2a will be 240 and 480 mg, respectively. Other cohorts may be considered to evaluate different dosing schedules of AMG 404 in relation to the blinatumomab infusion (refer to Figure 4-2 of the protocol).
The study will consist of 2 stages, dose exploration and dose expansion.

In the dose exploration stage, subjects will be enrolled in groups of 3 to 6. The Dose Level Review Team (DLRT) will meet after all subjects in a group are DLT evaluable to determine if additional subjects need to be enrolled into the cohort, if it is appropriate to dose escalate or de-escalate, or to stop the study for safety concerns. Maximum of 9 subjects overall may be enrolled at each dose level during dose exploration.

The planned dose level for blinatumomab are:
Cohort 1 cycle 1: administer 9 µg/day on Day 1 to Day 7 and 28 µg/day on Day 8 to Day 28 for subjects >=45 kg. Administer 5 µg/m2/day, not to exceed 9 µg/day, on Day 1 to Day 7, then 15 µg/m2/day on Day 8 to Day 28 for subjects < 45 kg, not to exceed 28 µg/day.

For cycle 1 the dose levels for AMG 404 are:
• Cohort 1: 240 mg Q4W starting on Day 11 of Cycle 1
• Cohort 2a: 480 mg Q4W starting on Day 1 of Cycle 1
• Cohort 2b: 240 mg Q4W starting on Day 1 of Cycle 1
• Cohort 1c: 120 mg Q4W starting on Day 11 of Cycle 1
• Cohort 2: 480 mg Q4W starting on Day 11 of Cycle 1
• Cohort 1b: 120 mg Q4W starting on Day 11 of Cycle 1

Refer to section 6.2.1.1. of the protocol.

Intervention

Blinatumomab will be administered as a continuous IV for 28 days per cycle and AMG 404 will be administered intravenously (IV) over approximately 30 minutes starting on Day 1 or 11 of Cycle 1 and dosed every 4 weeks (Q4W) thereafter.

Study burden and risks

Please see section E9 en E9a.

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

• Age >= 18 years at enrollment.
• Subjects with B-precursor ALL, with any of the following:
-Refractory to primary induction or refractory to salvage therapy.
-In untreated first, second or greater relapse or refractory relapse or relapse after salvage therapy
-Relapse at any time after allogeneic HSCT:
o Relapse is defined as achievement of CR (CR1) during upfront therapy then relapse during or after continuation therapy.
o Refractory disease is defined as the absence of CR after standard induction therapy.
o Refractory relapse lack of CR after first salvage therapy
o Second relapse or later relapse defined as relapse after achieving a second CR (CR2) in first or later salvage.
• Greater than or equal to 5% blasts in the BM.
• Eastern Cooperative Oncology Group performance status (ECOG PS) <= 2.
• Negative pregnancy test in women of childbearing potential.

Refer to section 5.1 of the protocol.

Exclusion criteria

• History or presence of clinically relevant CNS pathology such as epilepsy, childhood or adult seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson*s disease, cerebellar disease, organic brain syndrome or psychosis.
• Presence of ALL in the CNS (confirmed by presence of blast cells in CSF) or testes.
• Isolated extramedullary disease.
• Current autoimmune disease or history of autoimmune disease with potential CNS involvement.
• Allogeneic HSCT within 12 weeks before the start of protocol-specified therapy.
• Active acute or chronic graft versus host disease requiring systemic treatment with immunosuppressive medication.
• Cancer chemotherapy (radiotherapy, chemotherapy, antibody therapy, molecular targeted therapy) within 14 days prior to study Day 1 with the exception of intrathecal chemotherapy and/or low dose maintenance therapy (eg vinca alkaloids, mercaptopurine, methotrexate, or hydroxyurea). If subject is eligible for pre phase then all low dose chemotherapy with the exception of intrathecal chemotherapy must be discontinued prior to starting pre phase. Tyrosine kinase inhibitors use in patients with Ph+ ALL is allowed.
• Immunotherapy (eg rituximab, alemtuzumab) within 4 weeks before start of

protocol-specified therapy. Prior treatment (given > 4 weeks prior to protocol therapy) with any CD19-directed therapy (eg, blinatumomab, CD19-directed chimeric antigen receptor T-cell therapy, anti-CD19 antibodies will be allowed).

Refer to section 5.2 of the protocol.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	14-04-2021
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AMG404
Generic name:	AMG404
Product type:	Medicine
Brand name:	Blincyto
Generic name:	Blinatumomab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	06-08-2020

Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-11-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-02-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-04-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-07-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-10-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-10-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-12-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-03-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-04-2022

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-08-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-09-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
EudraCT	EUCTR2019-004304-36-NL
ClinicalTrials.gov	NCT-nummerisnognietbekend.Hetnummervolgt.
CCMO	NL72451.042.20

Study results

Date completed:	20-07-2022
Results posted:	06-09-2023

First publication
06-09-2023