A Phase 1/2 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 701 Monotherapy, or in Combination with Pomalidomide, with and without Dexamethasone in Subjects with Relapsed or Refractory Multiple Myeloma (ParadigMM-1B)

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Phase 1 - AMG 701 dose-exploration as monotherapyPrimary Objectives:• Evaluate the safety and tolerability of AMG 701 in subjects with relapsed/refractory multiple myeloma (RRMM) to determine the maximum tolerated dose (MTD) and/or recommended phase...

Ethical review	Approved WMO
Status	Completed
Health condition type	Haematopoietic neoplasms (excl leukaemias and lymphomas)
Study type	Interventional

Summary

ID

NL-OMON52671

Source
ToetsingOnline

Brief title
20170122

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
plasma cel myeloom, Ziekte van Kahler

Research involving
Human

Sponsors and support

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

Intervention

Keyword: First-in-Human, Multiple Myeloma, Phase 1/2

Outcome measures

Primary outcome

Phase 1 - AMG 701 dose-exploration as monotherapy

Primary Endpoint:

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

treatment-related adverse events

-Clinically-significant changes in vital signs, physical examinations,

electrocardiogram (ECG)s and clinical laboratory tests

Phase 1b - AMG 701 dose-confirmation as monotherapy

Primary Endpoint:

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

treatment-related adverse events, and changes

in vital signs, electrocardiograms (ECGs), and clinical laboratory tests

Phase 1/1b - AMG 701 in combination with pomalidomide, with and without

Dexamethasone (AMG 701-P±d)

Primary Endpoint:

-DLTs, treatment-emergent adverse events, treatment-related adverse events, disease related events

-Clinically-significant changes in vital signs, physical examinations, ECGs, and clinical laboratory tests

For more information, please refer to protocol section 4.

Secondary outcome

Phase 1 - AMG 701 dose-exploration as monotherapy

Secondary Endpoints:

* AMG 701 PK parameters including, but not limited to, maximum concentration (Cmax), time of maximum concentration (Tmax) and area under the concentration-time curve (AUC), and steady state concentration (Css) for extended IV.

* Efficacy parameters:

o Overall response (OR) according to International Myeloma Working Group (IMWG) response criteria, BOR of stringent CR [sCR], complete response [CR], very good partial response [VGPR], or partial response [PR])

Phase 1b - AMG 701 dose-confirmation as monotherapy

Secondary Endpoints:

* OR according to IMWG response criteria (BOR of sCR, CR, VGPR, or PR)

Phase 1/1b - AMG 701 in combination with pomalidomide, with and without

Dexamethasone (AMG 701-P±d)

Secondary Endpoints:

* AMG 701 PK parameters including, but not limited to: Cmax, Tmax, AUC, and Css

for extended IV

For more information, please refer to protocol section 4.

Study description

Background summary

Multiple myeloma is a neoplastic plasma-cell disorder characterized by clonal proliferation of malignant plasma cells in the BM microenvironment, monoclonal protein in the blood or urine and associated organ dysfunction (Palumbo and Anderson, 2011). Multiple myeloma accounts for almost 2% of all cancers and 20% of hematologic malignancies. The disease is slightly more common in males and African Americans (Siegel et al, 2015). Multiple myeloma remains an incurable cancer, although recent improved understanding of pathogenesis of myeloma has led to the development of new treatments and improved survival (Smith and Yong, 2013). The uncontrolled growth of myeloma cells has many consequences, including skeletal destruction, BM failure, increased plasma volume and viscosity, suppression of normal immunoglobulin production, and renal insufficiency (Durie, 2011). Treatment of relapsed and/or refractory multiple myeloma presents a special therapeutic challenge, due to the heterogeneity of disease at relapse and the absence of clear biological based recommendations regarding the choice of salvage therapies at various time points of disease progression. With increasing recognition of the inherent clonal heterogeneity and genomic instability of the plasma cells influencing both inherent and acquired therapeutic resistance, the identification of the optimal choice and sequence of therapies has become critical. Despite advances in the management of multiple myeloma as described, relapse is inevitable in almost all patients. Recurrence of myeloma is typically more aggressive with each relapse, leading to the development of treatment refractory disease, which is associated with a shorter survival (Dimopoulos et al, 2015). More treatment options are still warranted.

BiTE® antibody constructs exert a unique but also uniform mechanism of action

independent from their respective target. Consequently, experiences with other BiTE® antibody constructs are regarded as being relevant for AMG 701.
Most clinical experience exists with a BiTE® antibody construct called blinatumomab (BLINCYTO®, AMG 103; specificity for CD3 and CD19) which has shown that administration of BiTE® antibody constructs by continuous IV (cIV) infusion is feasible and efficacious in subjects with late-stage hematological malignancies (Yuraszeck et al, 2017; Benjamin and Stein, 2016; Nagorsen et al, 2012). Blinatumomab has demonstrated clinical activity in acute lymphoblastic leukemia (ALL). Clinical responses have been seen in both adults and children (Amgen clinical studies 103-206 [NCT01209286], 103-205 [NCT01471782], 103-211 [NCT01466179] and 00103311/TOWER [NCT02013167]) confirming the activity of BiTE® antibody constructs in B-precursor ALL (Kantarjian et al, 2017; Von Stackelberg et al, 2016; Topp et al 2015; Topp et al, 2014). Based on these data, blinatumomab is approved in multiple regions for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL.
Several other BiTE® antibody constructs have entered clinical trials. Specifically, AMG 420, a BCMA-targeting canonical BiTE® antibody construct is currently undergoing investigation in phase 1/2 studies. Targeting the same surface molecule, experience with AMG 420 is relevant for AMG 701. A phase 1 FIH open-label dose-escalation study (1351.1, NCT02514239) evaluating the safety, tolerability, PK, and pharmacodynamics of IV doses of AMG 420/BI 836909 in relapsed / refractory multiple myeloma subjects and has completed enrollment in Europe.

Study objective

Phase 1 - AMG 701 dose-exploration as monotherapy
Primary Objectives:
• Evaluate the safety and tolerability of AMG 701 in subjects with relapsed/refractory multiple myeloma (RRMM) to determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D)

Secondary Objectives:
• Characterize the pharmacokinetics (PK) of AMG 701 when administered by intravenous (IV) infusion
• Estimate anti-myeloma activity of AMG 701

Phase 1b - AMG 701 dose-confirmation as monotherapy
Primary Objectives:
• Establish the safety and tolerability of AMG 701 at the RP2D

Secondary Objectives:
• Estimate anti-myeloma activity of AMG 701

Phase 1/1b - AMG 701 in combination with pomalidomide, with and without Dexamethasone (AMG 701-P±d)
Primary Objectives:

• Evaluate the safety and tolerability of AMG 701 and determine the AMG 701 RP2D in combination with pomalidomide (P), with and without dexamethasone (± d) in subjects with RRMM

Secondary Objectives:
• Characterize the PK of AMG 701 when administered by intra venous (IV) infusion

Please see protocol section 4.1 for the objectives.

Study design

This is a phase 1/2, multicenter, non-randomized, open-label study which will consist of a phase 1 sequential dose-exploration part to evaluate safety and tolerability of AMG 701 monotherapy to identify the RP2D for AMG 701 monotherapy followed by a dose-confirmation part to gather further safety data for AMG 701 monotherapy at the RP2D in adults with RRMM.

All parts of the study will consist of up to a 21-day screening period (combination therapy female subjects of childbearing potential will undergo a 28 day screening period), a treatment period, a safety follow-up visit (SFU) conducted 30 (+ 3) days after the last dose of AMG 701 and a long-term follow-up (LTFU) period that will begin after progression of disease per IMWG criteria, start of new anti myeloma therapy, or withdrawal of consent for disease monitoring.
Subjects will be followed for response evaluation every 28 days (± 3 days) until the earliest of: disease progression per IMWG response criteria, death, or consent withdrawal.

The study therapy consists of the following parts:
• Phase 1:
- dose-exploration
- Additional cohorts for exploration with 7-day extended intravenous infusion (7-day eIV). eIV administration during week 1 of the first cycle 1 will be used to achieve early (within the first week) efficacious AMG 701 exposure levels (figure 2-2 of the protocol).
• Phase 1b AMG 701 monotherapy confirmation parts
• Phase 1/1b AMG 701 in combination with pomalidomide, with and without dexamethasone (AMG 701-P+d)
• Phase 2: dose-expansion part

For more information, please refer to protocol section 5.

Intervention

Infusion of AMG 701, (prolonged) hospitalization, blood samples, tumor biopsy

Study burden and risks

The risks and potential side effects of AMG 701 and the procedures performed in this study are fully described in the Informed Consent Form.
AMG 701 may cause all, some, or none of the side effects listed in the Informed Consent Form. These side effects can be mild but could also be serious, life-threatening or even result in death. The patient may also experience an allergic reaction that has not been seen before. Because this is the first time AMG 701 is being given to humans, it is unknown if the patient will have any side effects. Side effects, listed in in the Informed Consent Form were seen in animals. The meaning of these findings to humans is uncertain.

The patient will have to stop taking any other drugs against your cancer and certain drugs influencing your immune system or your heart at least 14 days before participation in this study. The effects of stopping these drugs as well as any actions to avoid or minimize side effects should be discussed with the study doctor. Disadvantages of participation in the study may be:
* additional time
* additional or longer hospital stays
* additional tests
* instructions to follow
* possible side effects / complications of study related tests or procedures;
* possible adverse effects / discomforts from the study drug

It is uncertain if taking part in this study will be beneficial for the patient. The condition may get better but it could stay the same or even get worse. The information from this study might help in the development of additional treatments for Multiple Myeloma.

Contacts

Public
Amgen

Minervum 7061
Breda 4817ZK
NL
Scientific
Amgen

Minervum 7061
Breda 4817ZK
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 the time of signing the informed consent
• Multiple Myeloma meeting the following criteria:
- Pathologically-documented diagnosis of multiple myeloma that has is relapsed after or is refractory (see section
12.14) as defined by the following:
o Relapsed after >= 3 lines of prior therapy that must include all approved and available therapies deemed eligible by the
investigator, including at a minimum of a proteasome inhibitor (PI), an immunomodulatory drug
(IMiD), and where approved and available, a CD38-directed cytolytic antibody in combination in the same line or separate
lines of treatment OR refractory to PI, IMiD and CD38-directed cytolytic antibody.
o Note: Subjects enrolled in the phase 1b AMG 701 monotherapy dose-confirmation part, Group 2 must be relapsed or
intolerant to BCMA targeting agent.
- Measurable disease, defined by one or more of the following at time of screening:
o a serum M protein > 0.5 g/dl measured by serum protein electrophoresis
o urinary M protein excretion > 200 mg/24 hours
o involved serum free light chain (sFLC) measurement > 10 mg/dl, provided that the sFLC ratio is abnormal (< 0.26 or
> 1.65) as per IMWG response criteria
• ECOG Performance Status of <= 2
• Hematological function without transfusion support as follows:
- absolute neutrophil count (ANC) >= 1.0 x 109/L (without growth factor support)
- platelet count >= 50 x 109/L (without transfusions within 7 days from screening assessment); platelet count between

25 and 50 x 109/L at time of enrollment requires agreement by both the Investigator and Amgen Medical Monitor of
acceptability before enrollment can be approved
- hemoglobin > 8 g/dL
• Renal function as follows:
- calculated or measured creatinine clearance >= 30 mL/min using the Cockcroft-Gault equation or via 24-hour urine
collection with plasma and urine creatinine concentrations
• Hepatic function as follows:
- aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 x upper limit of normal (ULN)

Refer to section 6.1 of the protocol.

Exclusion criteria

• Known extramedullary relapse in the absence of any measurable medullary involvement (exception: this
exclusion criteria only applies to phase 1a (dose escalation) study.)
• Known central nervous system involvement by multiple myeloma
• Previously received an allogeneic stem cell transplant and the occurrence of one or more of the following:
- received the transplant within 6 months prior to study day 1
- received immunosuppressive therapy within the last 3 months prior to study day 1
- any active acute graft versus host disease (GvHD) requiring systemic therapy within the last 4 weeks prior to start of study treatment
- any systemic therapy against GvHD within 4 weeks prior to start of IP treatment
• Autologous stem cell transplantation less than 90 days prior to study day 1
• Recent history of primary plasma cell leukemia (within last 6 months prior to enrollment) or evidence of primary or secondary plasma cell leukemia at the time of screening
• Waldenstrom*s macroglobulinemia
• Prior amyloidosis (patients with multiple myeloma with asymptomatic deposition of amyloid plaques found on biopsy would be eligible if all othercriteria are met)
• Treatment with systemic immune modulators including, but not limited to, nontopical systemic corticosteroids (unless the dose is <= 10 mg/day prednisolone or equivalent), cyclosporine, and tacrolismus within 2 weeks before study day 1
• Last anticancer treatment (*) < 2 weeks prior to study day 1
• Last treatment with a therapeutic antibody less than 4 weeks prior to study day 1
• Radiation therapy to multiple anatomic sites within 28 days prior to study

day 1. Focal radiotherapy within 14 days prior to study day 1.
• Major surgery defined as surgery requiring general anesthesia with endotracheal intubation within 28 days prior to study day 1, unless discussed with and eligibility approved by Amgen medical monitor
• Prior treatment with any drug or construct that targets BCMA on tumor cells (eg, other bispecific antibody constructs,
antibody drug conjugates, or CAR-T cells), other than group 2 where prior treatment with BCMA targeting agent is
required.
• Clinically-not controlled chronic or ongoing bacterial, fungal, viral or other infectious disease requiring treatment at
the time of study day 1 or within the 14 days before study day 1
• Baseline ECG QTc > 470 msec (applying Fridericia correction), defined as the average of individual baseline ECGs
• History of malignancy other than multiple myeloma within the past 3 years with exceptions listed in the protocol
section 6.2.
• Current or known history of autoimmune diseases requiring systemic treatment in past 5 years, excluding
autoimmune thyroid disease, for which treatment should be completed 6 months prior to enrollment.

Refer to section 6.2 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):	12-04-2018
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AMG 701
Generic name:	AMG 701

Ethics review

Approved WMO Date:	02-10-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	01-12-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-02-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	04-06-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-07-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-09-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-09-2018
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	21-11-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-12-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-01-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-02-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-04-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-10-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	05-12-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-02-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	24-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	25-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2017-001997-41-NL
CCMO	NL63108.041.17

Study results

Date completed:	30-06-2023
Results posted:	06-06-2024

Summary results
Trial ended prematurely

First publication
28-03-2024