A Phase III, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of Single Agent Belantamab Mafodotin Compared to Pomalidomide plus Low-dose Dexamethasone (pom/dex) in Participants with Relapsed/Refractory Multiple Myeloma (RRMM) (DREAMM 3)

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This study has been transitioned to CTIS with ID 2023-508962-14-00 check the CTIS register for the current data. Primary objective:To compare the efficacy with belantamab mafodotin vs pomalidomide plus low dose dexamethasone (pom/dex) in...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Plasma cell neoplasms
Study type	Interventional

Summary

ID

NL-OMON52689

Source
ToetsingOnline

Brief title
GSK207495 (DREAMM 3)

Condition

- Plasma cell neoplasms

Synonym
Kahler's disease, Multiple Myeloma

Research involving
Human

Sponsors and support

Primary sponsor: GlaxoSmithKline Research & Development Ltd
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: Belantamab Mafodotin, Efficacy, Multiple Myeloma, Safety

Outcome measures

Primary outcome

PFS, defined as the time from the date of randomization until the earliest date

of documented disease progression (according to IMWG Response

Criteria) or death due to any cause

Secondary outcome

- OS, defined as the time from randomization until death due to any cause

- ORR, defined as the percentage of participants with a confirmed PR or better

per IMWG

- Clinical benefit rate (CBR), defined as the percentage of participants with a

confirmed minimal response (MR) or better per IMWG

- DoR, defined as the time from first documented evidence of PR or better until

PD per IMWG or death due to any cause among participants who achieve confirmed

PR or better

- TTR, defined as the time between the date of randomization and the first

documented evidence of response (PR or better) among participants who achieve

confirmed PR or better

- TTP, defined as the time from the date of randomization until the earliest

date of documented PD (per IMWG Response Criteria) or death

due to PD

- Incidence of adverse events (AEs) and changes in laboratory parameters

- Ocular findings on ophthalmic exam

- Plasma concentrations of belantamab mafodotin, total mAb, and cysmcMMAF

- Incidence and titers of ADAs against belantamab mafodotin

- Symptomatic adverse effects as measured by the PRO-CTCAE and OSDI

- Health-related QOL as measured by EORTC QLQ-C30, EORTC IL52* and EORTC

QLQMY20*.

- MRD negativity rate, defined as; the percentage of participants who are MRD

negative by NGS method

Study description

Background summary

Multiple myeloma (MM) is an incurable malignancy which accounts for 1% of all cancers and for 10% of all hematologic malignancies. A variety of drugs and combination treatments have been evaluated and found effective in treating MM. However, despite those treatment options, most, if not all, MM patients will ultimately develop resistance to existing therapies supporting the urgent need for new treatments.

Immunomodulatory agents (IMiDS), such as lenalidomide and pomalidomide, are an important cornerstone of treatment for relapsed/refractory MM (RRMM). Pomalidomide administered with low-dose dexamethasone (pom/dex) is approved in the US, European Union (EU) and a number of other countries worldwide for patients with RRMM who have received at least two prior therapies including lenalidomide and bortezomib and
have demonstrated disease progression on, or within 60 days of completion of, the last therapy. Pom/dex has been widely adopted globally as a treatment regimen for patients with advanced RRMM and is recommended in treatment guidelines.

Belantamab mafodotin (GSK2857916) is a humanized (IgG1) immuno-conjugate which binds to BCMA, a target widely expressed on malignant plasma cells in MM. The parent anti-BCMA antibody is conjugated to the small molecule microtubule inhibitor monomethyl auristatin-F (MMAF), which is released inside the malignant cell after binding and internalization of the antibody.
Single agent belantamab mafodotin has demonstrated to have a strong single-agent activity with a well-defined manageable safety profile in heavily pre-treated participants with RRMM (Q3W schedule via intravenous (IV) administration), based on final data from in the First-Time-in-Human (FTIH) study BMA117159 (DREAMM-1) in participants who were refractory to at least one line of therapy and primary analysis data from in the ongoing Phase II study 205678 (DREAMM 2) in participants who have failed at least 3 prior lines of anti-myeloma therapy, including an anti-CD38 antibody, and who are refractory to an IMiD and a proteasome inhibitor.

The efficacy and safety results from BMA117159 and primary analysis data from study 205678 indicate that belantamab mafodotin is an effective single agent treatment option for patients with RRMM, with a novel mechanism of action (MOA). In binding to BCMA on malignant plasma cells, belantamab mafodotin initiates cell killing via a multimodal-mechanism, including delivering MMAF to BCMA-expressing MM cells, inducing apoptosis, enhancing antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis, and inducing immunogenic cell death. Further evaluation of single agent belantamab mafodotin is warranted in a randomized Phase III study against pom/dex, an established standard of care in RRMM.

Study objective

This study has been transitioned to CTIS with ID 2023-508962-14-00 check the CTIS register for the current data.

Primary objective:
To compare the efficacy with belantamab mafodotin vs pomalidomide plus low dose dexamethasone (pom/dex) in participants with relapsed/refractory multiple myeloma (RRMM)

Secondary objectives:
- To compare the overall survival with belantamab mafodotin vs Pom/Dex in participants with RRMM
- To compare other markers of efficacy of belantamab mafodotin vs pom/dex in participants with RRMM
- To evaluate the safety and tolerability of belantamab mafodotin vs pom/dex in participants with RRMM
- To evaluate the pharmacokinetic profile of belantamab mafodotin
- To assess anti-drug antibodies (ADAs) against belantamab mafodotin
- To evaluate the tolerability of belantamab mafodotin vs pom/dex based on self-reported symptomatic adverse effects

- To evaluate and compare changes in symptoms and health-related quality of life (HRQOL) of belantamab mafodotin to pom/dex
- To assess Minimal Residual Disease (MRD) in participants who achieve >=VGPR or better for belantamab mafodotin vs pom/dex

Study design

This study is a Phase III, open-label, randomized, multicenter study evaluating the efficacy and safety of single agent belantamab mafodotin compared to pom/dex in participants with RRMM.

The study will include a screening period, study treatment period, and follow-up.

During screening participants will be evaluated for study eligibility per protocol as defined in the Inclusion and Exclusion criteria. Eligible participants must have been previously treated with at least two prior lines of therapy, including at least 2 consecutive cycles of both lenalidomide and a proteasome inhibitor (PI), (given separately or in combination) and must have documented progression (a) on, or (b) within 60 days of completion of the last therapy.

Following screening, participants will be centrally randomized in a 2:1 ratio to either Arm 1 (single agent belantamab mafodotin) or Arm 2 (pom/dex), as described in Intervention Groups and Duration. No cross-over will be allowed during the study, until the final OS analysis.

The study assessments will be performed during Screening, prior to the first dose of Cycle 1, and during each cycle of treatment.

Participants who received at least one dose of belantamab mafodotin and who develop Keratopathy Visual Acuity (KVA) Grade 2 or above treatment-related corneal toxicities will be randomised into the ocular sub study. Participants will be randomized until up to 60 evaluable participants are achieved

Upon permanent discontinuation of study treatment, participants will enter the follow-up phase: PFS follow-up for participants who discontinue study treatment but have not yet progressed and OS follow-up for participants with progressive disease (including those who were previously in PFS follow-up and have subsequently progressed). Participants are to follow the assessments as specified in the SoA.

Intervention

The study intervention consists of Belantamab Mafodotin administered intravenously on Day 1 of a 21-day cycle (arm 1) or Pomalidomide administered

orally on Days 1 to 21 of each 28-day cycle together with dexamethasone administered orally once weekly (arm 2).

Study burden and risks

The study population has a high unmet medical need as patients failing multiple lines of prior treatments do not have many therapeutic options left, and if response can be achieved with currently available drugs, it is usually of short duration.
For pom/dex, based on available data, approximately a third of patients responded and the median PFS was 4.0 months.
Belantamab mafodotin has demonstrated strong single-agent activity in two clinical studies conducted in heavily pre-treated participants with RRMM (Q3W schedule via IV administration). Based on the available data for the FTIH study BMA117159, as of the efficacy cut-off of 31 August 2018, participants receiving belantamab mafodotin had a median PFS of 12.0 in a heavily pre-treated population. In 205678/ DREAMM 2 both dose levels evaluated have a positive benefit/risk profile. Based on this profile, it is reasonable to hypothesize that the use of belantamab mafodotin as a single agent will provide an improved benefit compared to the combination regimen of pom/dex in this patient population.

Taking into account the measures to minimize risks to participants in this study, the potential risks identified in association with belantamab mafodotin are justified by the anticipated benefits that may be afforded to participants with RRMM.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Capable of giving signed informed consent as described in Protocol Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in the protocol.
2. Participants must be 18 or older, at the time of signing the ICF.
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (Protocol Appendix 9).
4. Histologically or cytologically confirmed diagnosis of multiple myeloma (MM) as defined according to International Myeloma Working Group (IMWG), and:
a. Has undergone autologous stem cell transplant (SCT), or is considered transplant ineligible, and
b. Has received at least 2 prior lines of anti-myeloma treatments, including at least 2 consecutive cycles of both lenalidomide and a proteasome inhibitor (given separately or in combination), and i) Must have documented disease progression on, or within 60 days of, completion of the last treatment OR (ii) Must be non-responsive while on last treatment, where non-responsive is defined as not achieving at least Minimal Response (MR) after 2 complete treatment cycles. In such cases lack of achieving of at least MR must be determined no earlier than at least 4 weeks after the last treatment.
5. Has measurable disease with at least one of the following:
a. Serum M-protein >=0.5 g/dL (>=5 g/L)
b. Urine M-protein >=200 mg/24 hours
c. Serum free light chain (FLC) assay: Involved FLC level >=10 mg/dL (>= 100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65)
6. Participants with a history of autologous SCT are eligible for study participation provided the following eligibility criteria are met:
a. Transplant was >100 days prior to initiating study treatment
b. No active infection(s)
c. Participant meets the remainder of the protocol eligibility criteria
7. Adequate organ system functions as defined in Protocol Table 9

8. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
a. Male Participants:
Male participants are eligible to participate if they agree to the following during the intervention period and until 6 months* after the last dose of study intervention to allow for clearance of any altered sperm:
• Refrain from donating sperm
PLUS, either:
• Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
OR
• Must agree to use a male condom throughout study treatment including the 6 month* follow-up period even if they have undergone a successful vasectomy and a female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Protocol Appendix 4 when having sexual intercourse with a pregnant woman or a woman of childbearing potential (WOCBP) who is not currently pregnant.
*4 weeks for male participants on Treatment Arm 2 (pom/dex).
b. Female Participants:
A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
• Is not a WOCBP [Protocol Appendix 4]
OR
• Arm 1 (belantamab mafodotin): Use a contraceptive method that is highly effective (with a failure rate of <1% per year) which includes abstinence, preferably with low user dependency during the intervention period and for 4 months after the last dose of study treatment.
• Arm 2 (pom/dex): Due to pomalidomide being a thalidomide analogue with risk for embryofetal toxicity and prescribed under a pregnancy prevention/controlled distribution program, WOCBP participants will be eligible if they commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control (one method that is highly effective), beginning 4 weeks prior to initiating treatment with pomalidomide, during therapy, during dose interruptions and continuing for at least 4 weeks following discontinuation of pomalidomide treatment.
• 2 negative pregnancy tests must be obtained prior to initiating therapy. The 1st test should be performed within 10-14 days and the 2nd test within 24 hours prior to prescribing pomalidomide therapy.
• And agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period.
• The investigator should confirm the effectiveness of the contraceptive method(s) ahead of the 1st dose of study intervention.
Additional requirements for pregnancy testing during and after study

intervention are located in Protocol Appendix 4.
The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
9. All prior treatment-related toxicities (defined by National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 5.0, 2017) must be <=Grade 1 at the time of enrollment, except for alopecia and Grade 2 peripheral neuropathy.
10. In France, a participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

Exclusion criteria

1. Symptomatic amyloidosis, active POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes); active plasma cell leukemia at the time of screening.
2. Systemic anti-myeloma therapy or use of an investigational drug within <14 days or 5 half-lives, whichever is shorter, before the first dose of study intervention.
3. Prior treatment with an anti-MM monoclonal antibody within 30 days prior to receiving the first dose of study intervention.
4. Prior BCMA-targeted therapy or prior pomalidomide treatment.
5. Plasmapheresis within 7 days prior to the first dose of study intervention.
6. Prior allogeneic stem cell transplant.
NOTE - Participants who have undergone syngeneic transplant will be allowed only if no history of, or currently active GvHD.
7. Any major surgery within the last 4 weeks.
8. Presence of active renal condition (infection, requirement for dialysis or any other condition that could affect participant's safety). Participants with isolated proteinuria resulting from MM are eligible, provided they fulfil criteria included in Table 9 of the protocol.
9. Any serious and/or unstable pre-existing medical, psychiatric disorder, or other conditions (including lab abnormalities) that could interfere with participant's safety, obtaining informed consent, or compliance with study procedures.
10. History of (non-infectious) pneumonitis that required steroids, or current pneumonitis.
11. Evidence of active mucosal or internal bleeding.
12. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis.
NOTE: Stable chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) or hepatobiliary involvement of malignancy is

acceptable if participant otherwise meets entry criteria.
13. Participants with previous or concurrent malignancies other than multiple myeloma are excluded, unless the second malignancy has been considered medically stable for at least 2 years. The participant must not be receiving active therapy, other than hormonal therapy for this disease. NOTE - Participants with curatively treated non-melanoma skin cancer are allowed without a 2-year restriction.
14. Evidence of cardiovascular risk including any of the following:
a. QT interval corrected for heart rate by Fridericia's formula (QTcF) >= 480 msec
b. Evidence of current clinically significant uncontrolled arrhythmias including clinically significant electrocardiogram (ECG) abnormalities including 2nd degree (Mobitz Type II) or 3rd degree atrioventricular block.
c. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within 3 months of Screening.
d. Class III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system (Appendix 10 of the protocol)
e. Uncontrolled hypertension.
15. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to belantamab mafodotin, pomalidomide, dexamethasone or any of the components of the study intervention.
16. Pregnant or lactating female.
17. Active infection requiring treatment.
18. Known human immunodeficiency virus (HIV). unless the participant can meet all of the following criteria:
• Established anti-retroviral therapy (ART) for at least 4 weeks and HIV viral load <400 copies/mL
• CD4+ T-cell (CD4+) counts >=350 cells/uL
• No history of AIDS-defining opportunistic infections within the last 12 months
19. Patients with Hepatitis B will be excluded unless the following criteria can be met (see protocol).
20. Positive hepatitis C antibody test result or positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study intervention, unless the participant can meet the following criteria (see protocol).
21. Participants unable to tolerate thromboembolic prophylaxis
22. Current corneal epithelial disease except for mild punctate keratopathy

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-12-2020
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Dexamethason
Generic name:	n/a
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	GSK2857916
Generic name:	Belantamab mafodotin
Product type:	Medicine
Brand name:	Pomalidomide
Generic name:	Imnovid
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-01-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-04-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-08-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-09-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-02-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-05-2021
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-10-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-12-2023
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	CTIS2023-508962-14-00
EudraCT	EUCTR2018-004252-38-NL
ClinicalTrials.gov	NCT04162210
CCMO	NL72277.056.20