A Multi-arm Phase 1b Study of Talquetamab With Other Anticancer Therapies in Participants with Multiple Myeloma

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This study has been transitioned to CTIS with ID 2023-503620-60-00 check the CTIS register for the current data. The purpose of this study is to characterize the safety and tolerability of talquetamab when administered in different combination…

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

Summary

ID

NL-OMON53994

Source
ToetsingOnline

Brief title
64407564MMY1004 (monumenTAL-2)

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
Kahler's disease, Multiple Myeloma

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag

Source(s) of monetary or material Support: the sponsor of the study

Intervention

Keyword: Combination therapy, Multiple Myeloma, Safety, Talquetamab

Outcome measures

Primary outcome

- Number of Participants with Adverse Events (AEs) as a Measure of Safety and Tolerability

- Number of Participants with AEs by Severity

- Number of Participants with Clinically Significant Abnormalities in Laboratory Parameters

- Number of Participants with Dose Limiting Toxicity (DLT)

Secondary outcome

- Overall Response Rate (ORR)

- Very Good Partial Response (VGPR) or Better Response Rate

- Complete Response (CR) or Better Response Rate

- Stringent Complete Response (sCR)

- Duration of Response

- Time to Response

- Serum Concentration of Talquetamab

- Serum Concentration of Daratumumab

- Number of Participants with Anti-Drug Antibodies to Talquetamab

- Number of Participants with Anti-Drug Antibodies to Daratumumab

- Number of Participants with Anti-Drug Antibodies to Recombinant Human

Hyaluronidase PH20 Enzyme (rHuPH20)

Study description

Background summary

Multiple myeloma is currently a disease state with considerable unmet needs. Synergistic combinations that target various mechanisms to overcome drug resistance need to be examined in order to realize the full potential of talquetamab and may lead to a better response. To this end, talquetamab is being investigated as part of multidrug regimens. This study is designed to encompass a broad population of patients with unmet medical needs based on different exposures and refractoriness to prior therapies. The main objective is to establish safety in the different combination regimens; data which will be used to inform later phase studies.

Study objective

This study has been transitioned to CTIS with ID 2023-503620-60-00 check the CTIS register for the current data.

The purpose of this study is to characterize the safety and tolerability of talquetamab when administered in different combination regimens and to identify the safe dose(s) of talquetamab combination regimens.

Study design

This is an open-label, nonrandomized, multicenter, Phase 1b study to evaluate the safety and tolerability of talquetamab combination regimens in the treatment of participants with multiple myeloma.
Participants will be assigned to 1 of the following treatment regimens based on the participant*s disease characteristics and prior treatment for multiple myeloma:
- Treatment Regimen A (talquetamab + carfilzomib)
- Treatment Regimen B (talquetamab + daratumumab + carfilzomib)
- TreatmentRegimen C (talquetamab + lenalidomide)
- Treatment Regimen D (talquetamab + daratumumab + lenalidomide)
- Treatment Regimen E (talquetamab + pomalidomide)

The study consists of a Screening Period (up to 28 days), a Treatment Period, and a Posttreatment Follow-up Period (up to 16 weeks).

A patient will remain in the study and continue to get the study drug for as long as it is of benefit to the patient or*until:**

• There is evidence that the study drugs are not controlling the patient's disease well enough.
• The patient develops unacceptable side effects, or is not well enough to continue with the study drugs
• A patient has become pregnant.
• A patient has received another type of anticancer therapy or medicine.
• A patient wants to stop participating in the study.
• The investigator thinks it is better the patient to stop.
• The patient does not follow the investigator*s and/or study staff*s instructions.
• A patient no longer meets the eligibility criteria.
• The sponsor, government or METC decides that the study should stop.

Intervention

Participants will be assigned to 1 of the following treatment regimens based on the participant*s disease characteristics and prior treatment for multiple myeloma:
- Treatment Regimen A: Participants will receive talquetamab subcutaneously (SC) in combination with carfilzomib as an intravenous (IV) infusion.
- Treatment Regimen B: Participants will receive talquetamab SC in combination with daratumumab SC and carfilzomib as an IV infusion.
- Treatment Regimen C: Participants will receive talquetamab SC in combination with lenalidomide orally.
- Treatment Regimen D: Participants will receive talquetamab SC in combination with daratumumab SC and lenalidomide orally.
- Treatment Regimen E: Participants will receive talquetamab SC in combination with pomalidomide orally.

For all regimens, talquetamab will be administered SC; the initial dose regimen for talquetamab will comprise 2 step-up doses separated by approximately 2 to 4 days followed by weekly or biweekly treatment doses. Based on the safety of each treatment regimen, the SET (Safety Evaluation Team) will decide if the doses or schedule of the agents in the combination regimens are confirmed or need modification. Furthermore, an Independent data monitoring committee (IDMC) will be commissioned to review safety data from the study on a periodic basis.

Study burden and risks

Every medicine has risks and side effects. These can differ per person. Side effects can be mild or very serious in nature. Most side effects disappear after treatment is stopped, but some can last for a long time. The side effects seen in the studies may be due to the disease being treated, the drug to be studied, other drugs being ingested, other illnesses the patient has, or a combination thereof. Some potential risks are mentioned below.
Cytokine Release Syndrome (CRS), Infusion related reactions, Neurological

problems, Immune related effects. See section 2.3 in the protocol.

There is potential risk for overlapping toxicities, specifically the unknown effect of IMiDs and daratumumab on CRS, which is a known AE associated with talquetamab. Risk-mitigation measures are planned for this study and include amongst others:
- implementation of step-up doses of talquetamab to reduce risk or severity of CRS,
- close monitoring of participants during the first few doses of talquetamab when CRS risk is highest,
- initiating IMiD administration on Cycle 2 Day 1, outside the highest-risk window for CRS,
- implementing count start criteria for IMiD-containing regimens to decrease overlapping toxicities of cytopenias,
- initiating carfilzomib administration on Cycle 2 Day 2, outside the highest-risk window for CRS, and with the first dose of carfilzomib given at least 20 hours after talquetamab,
- implementation of inclusion and exclusion criteria designed to limit enrollment to participants at lower risk of adverse outcomes associated with study treatment,
- recommendation of use of antimicrobial prophylaxis to reduce risk of infection,
- provision of guidance regarding management strategies for potential toxicities and
- inclusion of treatment regimen stopping rules.

Given the clinical experience to date, it is considered likely that the benefit-risk profile will be positive for participants enrolled in the treatment regimens. The addition of talquetamab to these treatment regimens offers a unique mechanism of action of T-cell redirection that could lead to synergistic antimyeloma effects.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Be >=18 years of age.
2. Sign an ICF indicating that the participant understands the purpose of, and procedures required for, the study and is willing to participate in the study, including the requirement to provide information during the Posttreatment Follow-up Period. Consent must be obtained prior to the initiation of any study-related tests or procedures that are not part of standard of care for the participant*s disease.
3. Have documented initial diagnosis of multiple myeloma according to IMWG diagnostic criteria.
4. Meet treatment regimen-specific requirements as follows:
a. Treatment Regimen A (talquetamab + carfilzomib): Participants with multiple myeloma who have received >=3 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb
b. Treatment Regimen B (talquetamab + daratumumab + carfilzomib): Participants with multiple myeloma who have received >=3 prior lines of therapy, including a PI and an IMiD
c. Treatment Regimen C (talquetamab + lenalidomide): Participants with multiple myeloma who have received >=1 prior lines of therapy, including a PI and an IMiD
d. Treatment Regimen D (talquetamab + daratumumab + lenalidomide):
o Participants with >=1 prior lines, including a PI and an IMiD.
o Participants who are lenalidomide naïve or have newly diagnosed disease. Any newly diagnosed participants must be transplant ineligible. Where local treatment guidelines allow, newly diagnosed transplant-eligible participants who chose to defer ASCT as initial therapy may also be enrolled.
e. Treatment Regimen E (talquetamab + pomalidomide): Participants with multiple

myeloma who have received >=2 prior lines of therapy, including a PI and lenalidomide
5. Have measurable disease at screening as defined by at least 1 of the following:
a. Serum M-protein level >=1.0 g/dL; or
b. Urine M-protein level >=200 mg/24 hours; or
c. Light chain multiple myeloma: Serum Ig FLC >=10 mg/dL and abnormal serum Ig kappa lambda FLC ratio.
6. Have an ECOG performance status score of 0 or 1 at screening and immediately before the start of study treatment administration.
7. Have clinical laboratory values meeting the following criteria during the Screening Period:
Hemoglobin 8.0 g/dL (5 mmol/L) (without prior RBC transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted)
Platelets 50×109/L (without transfusion support in the 7 days prior to the laboratory test)
ANC 1.0×109/L (prior growth factor support is permitted but must be without support for 7 days if received G-CSF or GM-CSF or 14 days if received peg-G-CSF)
AST and ALT <=2.5×ULN
Creatinine clearance 30 mL/min based upon Modified Diet in Renal Disease formula calculation (Appendix 7) or a 24-hour urine collection.
Total bilirubin <=1.5×ULN; except in participants with congenital bilirubinemia, such as Gilbert syndrome (in which case, direct bilirubin <=1.5×ULN is required)
Serum calcium corrected for albumin: <=14 mg/dL (<=3.5 mmol/L) or free ionized calcium <=6.5 mg/dL (<=1.6 mmol/L)
8. A woman of childbearing potential must have a negative highly sensitive serum (β-hCG) pregnancy test at screening and a negative urine or serum pregnancy test within 24 hours before the start of study treatment administration.
9. A woman must be:
a. Not of childbearing potential, or
b. Of childbearing potential and
-practicing true abstinence;
-or have a sole partner who is vasectomized;
-or practicing at least 1 highly effective user-independent method of contraception. If hormonal contraception is used (eg, oral estrogen/progestin), a male or female condom with or without spermicide (eg, spermicidal foam/gel/film/cream/suppository) must also be used.
•For participants enrolled in IMiD-containing regimens (Treatment Regimens C, D, and E), women of childbearing potential must be on 2 methods of reliable birth control simultaneously while receiving study treatment and until 100 days after last dose of study treatment: 1 highly effective form of contraception (tubal ligation, intrauterine device, hormonal [oral, injectable, transdermal patches, vaginal rings, or implants], or partner*s vasectomy), and 1 additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap).
-Agree to pregnancy testing (serum or urine) within 100 days after the last

dose of study
treatment.
10. A man must wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study and for 100 days after the last dose of study treatment. Male participants should also be advised of the benefit for a female partner to use a highly effective method of contraception as condoms may break or leak.
11. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 100 days after the last dose of study treatment.
12. A man must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 100 days after receiving the last dose of study treatment.
13. Be willing and able to adhere to the lifestyle restrictions specified in this protocol, including adherence to the applicable IMiD global PPP or local PPP/REMS program.

Please refer to protocol pages 91-94 for full inclusion criteria.

Exclusion criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:
1. Prior treatment with any therapy that targets GPRC5D.
2. Prior antitumor therapy as follows, in the specified time frame prior to the first dose of study treatment:
a. Targeted therapy, epigenetic therapy, or treatment with an investigational drug or an invasive investigational medical device within 21 days or at least 5 half lives, whichever is less.
b. Gene-modified adoptive cell therapy (eg, CAR modified T-cells, NK cells) within 3 months.
c. mAb treatment or bispecific T-cell redirector therapy for multiple myeloma within 21 days.
d. Cytotoxic therapy within 21 days.
e. PI therapy within 14 days.
f. Immunomodulatory agent therapy within 7 days.
g. Radiotherapy within 14 days. However, if palliative focal radiation is used, the participant is eligible irrespective of the end date of radiotherapy.
3. Live, attenuated vaccine within 4 weeks before the first dose of study treatment.
4. Non-hematologic toxicity from prior anticancer therapy that has not resolved to baseline levels or to Grade <=1 (except alopecia [any grade] or peripheral neuropathy Grade <=3).
5. Received a cumulative dose of corticosteroids equivalent to >=140 mg of prednisone within the 14-day period before the start of study treatment

administration
6. Received either of the following:
a. An allogeneic SCT within 6 months before the first dose of study treatment. Participants who received an allogeneic transplant must be off all immunosuppressive medications during the 6 weeks before the start of study treatment administration without signs of graft-versus-host disease.
b. An autologous SCT within 12 weeks before the start of study treatment administration.
7. Active CNS involvement or exhibition of clinical signs of meningeal involvement of multiple
8. Active plasma cell leukemia (>2.0×109/L plasma cells by standard differential), Waldenstro*m*s macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes), or primary amyloid light chain amyloidosis.
9. Known to be seropositive for human immunodeficiency virus.
10. Seropositive for HBV, defined by a positive test for HbsAg. Participants with resolved infection (ie, participants who are HbsAg negative but positive for hepatitis B core antibody[anti-HBc] and/or positive for hepatitis B surface antibody [anti-HBs]) must be screened using real-time PCR measurement of HBV DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Participants with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR.
11. Active hepatitis C infection as measured by positive HCV-RNA testing. Participants with a history of HCV antibody positivity must undergo HCV-RNA testing.
12. Known allergies, hypersensitivity, or intolerance to any study treatment or their excipients
13. Any serious underlying medical condition, such as:
a. Evidence of serious active viral, bacterial, or uncontrolled systemic fungal infection.
b. Active autoimmune disease requiring systemic immunosuppressive therapy within 6 months before start of study treatment. EXCEPTION: Participants with vitiligo, type I diabetes, and prior autoimmune thyroiditis that is currently euthyroid based on clinical symptoms and laboratory testing are eligible regardless of when these conditions were diagnosed.
c. Disabling psychiatric conditions (eg, ongoing alcohol or drug abuse), severe dementia, or altered mental status.
d. Any other issue that would impair the ability of the participant to receive, absorb, or tolerate the planned treatment at the study site, to understand informed consent, or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise well-being) or that could prevent, limit, or confound the protocol-specified assessments.
14. History of stroke or seizure within 6 months prior to the first dose of study treatment.
15. Any of the following cardiac conditions:

a. New York Heart Association stage III or IV congestive heart failure.
b. Myocardial infarction, unstable angina, or coronary artery bypass graft <=6 months prior to enrollment.
c. History of clinically significant ventricular arrhythmia or unexplained syncope not believed to be vasovagal in nature or due to dehydration.
d. History of severe nonischemic cardiomyopathy. e. Treatment Regimen A (tal-cfz) and Treatment Regimen B (tal-dara-cfz) only: transthoracic echocardiography showing LVEF < 40%. Please refer to protocol pages 79-82 for full exclusion criteria.
16. Pregnant or breastfeeding or planning to become pregnant while enrolled in this study or within 100 days after the last dose of study treatment.
17. Planning to father a child while enrolled in this study or within 100 days after the last dose of study treatment.
18. Major surgery within 2 weeks of the first dose of study treatment, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to be treated in the study or within 2 weeks after the last dose of study treatment administration. Note: participants with planned surgical procedures to be conducted under local anesthesia may participate.
19. Treatment Regimen B (taldara-cfz) and Treatment Regimen D (taldaralen) only: Has either of the following:
a. COPD with FEV1<50% of predicted normal. Note that FEV1 testing is required for participants suspected of having COPD, and participants must be excluded if FEV1 is
<50% of predicted normal; testing done as standard of care within 6 months of the first dose of study treatment is acceptable for this criterion.
b. Moderate or severe persistent asthma within the past 2 years, or uncontrolled asthma of any classification. Note: participants who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study.
Cfr protocol p. 94-96 voor volledige exclusiecriteria.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-03-2022
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Carfilzomib
Generic name:	Kyprolis
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Daratumumab
Generic name:	Darzalex
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Lenalidomide
Generic name:	Revlimid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Pomalidomide
Generic name:	Imnovid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Talquetamab
Generic name:	Talvey
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	24-11-2021
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-11-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	12-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	23-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-12-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-02-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-02-2024
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	CTIS2023-503620-60-00

Register	ID
EudraCT	EUCTR2020-004502-55-NL
ClinicalTrials.gov	NCT05050097
CCMO	NL79182.056.21