Phase 3, Two-Stage, Randomized, Multicenter, Open-label Study Comparing Iberdomide, Daratumumab and Dexamethasone (IberDd) versus Daratumumab, Bortezomib, and Dexamethasone (DVd) in Subjects with Relapsed or Refractory Multiple Myeloma (RRMM)

Published: 26-05-2021
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This study has been transitioned to CTIS with ID 2024-510800-35-00 check the CTIS register for the current data. Primary objective:To compare the efficacy of iberdomide, daratumumab and dexamethasone (IberDd) to that of daratumumab, bortezomib and…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	White blood cell disorders
Study type	Interventional

Summary

ID

NL-OMON54280

Source
ToetsingOnline

Brief title
CC-220-MM-002

Condition

- White blood cell disorders

Synonym
Multiple Myeloma; cancer of pasma cells (a type of white blood cells)

Research involving
Human

Sponsors and support

Primary sponsor: Celgene Corporation
Source(s) of monetary or material Support: Farmaceutisch bedrijf

Intervention

Keyword: CC-220, Iberdomide, Multiple Myeloma

Outcome measures

Primary outcome

Overview of Key Efficacy Assessments

• Myeloma paraprotein (serum and 24-hour urine)

• Serum immunofixation

• Serum immunoglobulins

• Serum free light chains

• Bone marrow aspiration/biopsy

• Percent plasma cells in the bone marrow

• Radiographic assessments of lytic bone lesions

• Extramedullary plasmacytoma (EMP) assessments

• Minimal residual disease assessment

• Response per International Myeloma Working Group (IMWG) criteria

Overview of Key Safety Assessments

• Adverse events (AEs)

• Complete physical examination including vital signs and venous thromboembolism

• (VTE) monitoring

• Clinical laboratory evaluations (hematology, chemistry)

• Electrocardiogram (ECG)

• Pregnancy testing/counselling

• Concomitant medications and procedures

Secondary outcome

not applicable

Study description

Background summary

The purpose of this study is to see how well a new investigational drug, iberdomide (CC-220), works to treat relapsed or refractory multiple myeloma when combined with daratumumab and dexamethasone. This iberdomide combination has already been tested for safety and effectiveness in a smaller number of patients with relapsed or refractory multiple myeloma to establish the dose that will be used for this study. In this study, this iberdomide combination will be compared to a combination already approved for the treatment of multiple myeloma that includes bortezomib, daratumumab and dexamethasone. Iberdomide is a medication that comes in the form of capsules that is taken by mouth. It belongs to a group of drugs known as CELMoDs, which are medicines that can modify or regulate how the immune system works.

Study objective

This study has been transitioned to CTIS with ID 2024-510800-35-00 check the CTIS register for the current data.

Primary objective:
To compare the efficacy of iberdomide, daratumumab and dexamethasone (IberDd) to that of daratumumab, bortezomib and dexamethasone (DVd) in terms of progression-free survival (PFS) in subjects with RRMM

Secondary objectives:
• In Stage 1, to determine the dose of IberDd in combination with dexamethasone

and daratumumab to continue in Stage 2 of the study
• In Stage 1, to assess the PK of IberDd in combination with daratumumab and dexamethasone
• To evaluate overall survival in subjects with RRMM treated with IberDd compared to DVd
• To evaluate achievement of minimal residual disease (MRD) negative status in subjects with RRMM (who achieve complete response [CR] or better) when treated with IberDd compared to DVd
• To evaluate additional efficacy parameters in subjects with RRMM treated with IberDd compared to DVd
• To evaluate safety of IberDd compared to DVd in subjects with RRMM
• To evaluate cancer-related symptoms and health-related quality of life (HRQoL) using the European Organization for Research and Treatment of Cancer - Quality of Life C30 questionnaire (EORTC QLQ-C30) and the European Quality of Life Multiple Myeloma Module (EORTC QLQ-MY20) in subjects with RRMM treated with IberDd compared to DVd

Exploratory objectives:
• In Stage 1, to evaluate benefit-risk score of different dose levels of iberdomide in subjects with RRMM treated with IberDd
• In Stage 1, to assess the relationship between genomic, molecular, immune biomarkers, and clinical outcomes in subjects with RRMM treated with IberDd at different dose levels of iberdomide
• To evaluate the sustainability of MRD negativity in subjects with RRMM treated with IberDd compared to DVd
• To assess the relationship between genomic, molecular, immune biomarkers, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serologic status, and clinical outcomes in subjects with RRMM treated with IberDd compared to DVd
• To assess the PK of iberdomide at the selected dose in combination with daratumumab and dexamethasone(IberDd)
• To assess the overall health status and utility using the European Quality of Life 5-Dimension 5-Level instrument (EQ-5D-5L) in subjects with RRMM treated with IberDd compared to DVd
• To compare healthcare resource utilization in subjects with RRMM treated with IberDd compared to DVd

Study design

This is a two-stage multicenter, randomized, controlled, open-label Phase 3 study comparing the efficacy and safety of IberDd versus DVd in subjects with RRMM.

After informed consent has been obtained, subjects will undergo screening procedures to determine eligibility. Eligible subjects in both stages of the study will be randomized using an Interactive Response Technology (IRT), and stratified by the following factors:
1. Number of prior lines: 1 prior line versus 2 prior lines

2. Age : <= 70 years old versus > 70 years
3. International Staging System (ISS) staging at study entry: I and II versus III

Subjects in all treatment arms will continue to receive treatment until confirmed progressive disease (PD), unacceptable toxicity or withdrawal of consent. To ensure accuracy and completeness of the primary endpoint assessment of PFS, subjects who permanently discontinue study treatment for any reason, other than confirmed PD or withdrawal of consent, will continue to be followed for disease assessment. Subjects should not start any other anti-myeloma therapy prior to PD

All subjects will be followed for subsequent anti-myeloma therapies (including subsequent dates of progression), European Quality of Life 5-Dimension 5-Level instrument (EQ-5D-5L) assessments, second primary malignancies and survival status every 4 months for at least 5 years after the last subject is randomized into the study.

In Stage 1 of the study, at least 200 subjects will be initially randomized 1:1:1:1 (at least 50 subjects in each arm) to one of three iberdomide dose levels of 1, 1.3, or 1.6 mg in combination with daratumumab and dexamethasone (Treatment Arms A1, A2, or A3), or to the DVd comparatorarm(Treatment Arm B).

In Stage 2 of the study,approximately 664 additional subjects will be randomized 1:1 between 2 treatment arms:
• Approximately 332 subjects will be randomized to receive Treatment Arm A (IberDd)
• Approximately 332 subjects will be randomized to receive Treatment Arm B (DVd)

The total number of subjects enrolled in Stage 2 will be adjusted according to the number of subjects enrolled in the selected iberdomide dose level arm and in the DVd arm during Stage 1.
Overall, approximately 764 subjects are planned to be enrolled in these 2 arms considering Stage 1 and Stage 2 combined.

Intervention

Stage 1 Treatment Arms A1, A2 and A3 and Stage 2 Arm A (iberdomide, daratumumab and dexamethasone):
- Oral iberdomide at 1, 1.3 and 1.6 mg once daily from Days 1 to 21 of a 28-day cycle
- Daratumumab administered as 1800 mg subcutaneously co-formulated with 30,000 units of recombinant human hyaluronidase (rHuPH20) for:
• Cycles 1 and 2 on Days 1, 8, 15 and 22 of a 28-day cycle
• Cycles 3 to 6 on Days 1 and 15 of a 28-day cycle
• Cycles 7+ on Day 1 of a 28-day cycle
- Oral dexamethasone will be administered at a total dose of 40 mg weekly on

Days 1, 8, 15 and 22. For subjects older than 75 years, underweight (body mass index [BMI] < 18.5), have poorly controlled diabetes, or prior intolerance/adverse event to steroid therapy, dexamethasone may be administered at a dose of 20 mg weekly on Days 1, 8, 15 and 22.
• On daratumumab administration days, dexamethasone will be utilized as the treatment dose of steroid for that particular day, as well as the required premedication prior to the daratumumab administration.

Treatment Arm B (daratumumab, bortezomib and dexamethasone):
- Daratumumab administered as 1800 mg subcutaneously co-formulated with 30,000 units recombinant human hyaluronidase (rHuPH20) for:
• Cycles 1 to 3 on Days 1, 8 and 15 of a 21-day cycle
• Cycles 4 to 8 on Day 1 of a 21-day cycle
• Cycles 9+ on Day 1 of a 28-day cycle
- Bortezomib administered subcutaneously at a starting dose of 1.3 mg/m2 for:
• Cycles 1 to 8 on Days 1, 4, 8 and 11 of a 21-day cycle
- Oral dexamethasone will be administered at a starting dose of 20 mg for:
• Cycles 1 to 8 on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. For subjects older than 75 years, underweight (BMI < 18.5), have poorly controlled diabetes, or prior intolerance/adverse event to steroid therapy, dexamethasone may be administered at a dose of 10 mg on Days 1, 2, 4, 5, 8, 9, 11 and 12.
• On daratumumab administration days, dexamethasone will be utilized as the treatment dose of steroid for that particular day, as well as the required premedication prior to the daratumumab administration.

Study burden and risks

The purpose of this study is to see how well a new investigational drug, iberdomide (CC-220), works to treat relapsed or refractory multiple myeloma when combined with daratumumab and dexamethasone.

The maximum time in the study will depend on the response to treatment, when the multiple myeloma worsens, how well the study treatment is tolerated.

For the study, hospital visits are as follows:
Stage 1 Treatment Groups A1, A2 and A3 and Stage 2 Treatment Group A (28-day cycles):
• Cycle 1 and 2: weekly
• Cycle 3-6: bi-weekly
• Cycle 7 and beyond: once each cycle

Treatment Group B (Cycles 1-8: 21-day cycles; Cycles 9 and beyond: 28-day cycles):
• Cycle 1-3: twice per week in week 1 and 2, and once per week in week 3
• Cycle 4-8: twice per week in week 1 and 2
• Cycle 9 and beyond: once each cycle

Very common side effects of Iberdomide are: Low number of red blood cells (anemia, which may make you feel weaker or tired); Low number of neutrophil blood cells (neutropenia, which can cause increased risk of infection); Rash; Low number of platelet blood cells (thrombocytopenia, which can cause an increased risk of bleeding); Upper respiratory tract infection

Iberdomide may treat the multiple myeloma, but that is not certain. The condition may get better or worse during the study. However, the information collected during this study may help doctors learn more about the study treatment that could benefit people with multiple myeloma.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subject is >= 18 years of age at the time of signing the informed consent form (ICF).
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
4. Subject has documented diagnosis of MM and measurable disease, defined as any of the
following:
a. M-protein quantities >= 1 g/dL by serum protein electrophoresis (sPEP) or >= 200 mg/24-hour urine collection by urine protein electrophoresis (uPEP); or
b. Light chain MM without measurable disease in serum or urine: serum free light chain (FLC) levels > 100 mg/L (10 mg/dL) involved light chain and an abnormal kappa/lambda FLC ratio
5. Subject has received 1 to 2 prior lines of anti-myeloma therapy.
6. Subject achieved a response (partial response [PR] or better) to at least 1 prior antimyeloma regimen.
7. Subject must have documented disease progression during or after their last antimyeloma regimen.
8. Prior treatment with CD38-directed therapy:
In Stage 1, subjects with prior CD38-directed therapy are not eligible.
In Stage 2, prior treatment with CD38-directed therapy is permitted only if all the following are fulfilled:
a. Best response achieved during CD38-directed therapy was > PR.
b. Subject did not progress while receiving CD38-directed therapy or within 60 days of last dose of therapy.
c. Subject did not discontinue CD38-directed therapy due to a related AE.
d. Last dose of daratumumab was >= 3 months prior to randomization.
9. .Prior treatment with bortezomib therapy is permitted, if all the following are fulfilled:
a.Best response achieved during bortezomib-containing therapy was at least a minimal response (MR).
b.Subject did not progress while receiving bortezomib therapy or within 60 days of last dose of therapy.
10.Subject has an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1 or 2.
11. Females of childbearing potential (FCBP) must:
a. Have two negative pregnancy tests as verified by the Investigator prior to starting study treatment. She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. This applies even if the subject practices true abstinence* from heterosexual contact.
b. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with, 2 forms of contraception: one highly effective, and one

additional effective (barrier) measure of contraception without interruption 28 days prior to starting study treatment, during the study treatment (including dose interruptions), and for at least 28 days after the last dose of iberdomide, 3 months after the last dose of daratumumab or 7 months after the last dose of bortezomib, whichever is longest.
12. Male subjects must:
a. Practice true abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 90 days after the last dose of iberdomide, 3 months after the last dose of daratumumab, or 4 months after the last dose of bortezomib, whichever is longer even if he has undergone a successful vasectomy.
13. Male subjects must agree to refrain from donating sperm while on study treatment, during dose interruptions and for at least 90 days following last dose of study treatment.
14. Subjects must agree to refrain from donating blood while on study treatment, during dose interruptions and for at least 28 days following the last dose of study treatment.
15. All male and female subjects must follow all requirements defined in the Pregnancy Prevention Program

Exclusion criteria

1. Subject has any significant medical condition, including active or uncontrolled infection, presence of laboratory abnormality, or psychiatric illness that places the subject at an unacceptable risk for treatment-related complications, if he/she were to participate in the study.
2. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection within 14 days for mild or asymptomatic infections or within 28 days for severe/critical illness prior to randomization. Acute symptoms must have resolved and there must be no sequelae that would place the subject at a higher risk of clinically significant complications from receiving study treatment, based on the Investigator*s assessment in consultation with the Sponsor Medical Monitor.
3. Subject has any condition that confounds the ability to interpret data from the study.
4. Subject has any of the following laboratory abnormalities:
a. Absolute neutrophil count (ANC) < 1,000 cells/µL. It is not permissible to administer granulocyte colony-stimulating factor (GCSF) to achieve minimum ANC levels.
b. Platelet count: < 75,000 cells/µL for subjects in whom < 50% of bone marrow nucleated cells are plasma cells; or a platelet count < 50,000 cells/µL for subjects in whom >= 50% of bone marrow nucleated cells are plasma cells. It is not permissible to transfuse subjects to achieve minimum platelet counts.
c. Hemoglobin < 8 g/dL (< 4.9 mmol/L).

d. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m2 or requiring dialysis. The eGFR can be calculated using the modification of diet in renal disease (MDRD) formula adjusted for actual BSA.
e. Corrected serum calcium > 13.5 mg/dL (> 3.4 mmol/L).
f. Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 × upper limit of normal (ULN).
g. Serum total bilirubin > 1.5 × ULN or > 3.0 mg/dL for subjects with documented Gilbert*s syndrome.
5. Subject has plasma cell leukemia, Waldenstrom*s macroglobulinemia or POEMS syndrome), or clinically significant amyloidosis.
6. Subject has peripheral neuropathy Grade 3, Grade 4 or Grade 2 with pain.
7. Subject has gastrointestinal disease that may significantly alter the absorption of iberdomide and/or other oral study treatment.
8. Subject has prior history of malignancies, other than MM, unless the subject has been free of the disease for >= 5 years with the exception of the following noninvasive malignancies:
• Basal cell carcinoma of the skin
• Squamous cell carcinoma of the skin in situ (stage 0)
• Carcinoma in situ of the cervix
• Carcinoma in situ of the breast
• Incidental histologic finding of prostate cancer (T1a or T1b using the TNM [tumor, nodes, metastasis] clinical staging system) or prostate cancer that is curative
9. Subject with known central nervous system involvement with MM.
10. Subject has received immunosuppressive medication within the last 14 days of initiating study treatment. The following are exceptions to this criterion:
• Intranasal, inhaled, topical or local corticosteroid injections (eg, intra-articular
• injection)
• Systemic corticosteroids at doses that do not exceed 10 mg/day of prednisone (or an
• equivalent dose of an alternative glucocorticoid, see Table 7)
• Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication)
11. Subject has impaired cardiac function or clinically significant cardiac disease, including:
a. Myocardial infarction within 1 year before randomization, or an unstable or uncontrolled disease/condition related to or affecting cardiac function
b. Uncontrolled cardiac arrhythmia or clinically significant electrocardiogram (ECG) abnormalities
12. Subject received prior therapy with iberdomide.
13. Subject received any of the following:
a. Plasmapheresis within the last 28 days of initiating study treatment
b. Major surgery (as defined by the Investigator) within 28 days of initiating study treatment
c. Radiation therapy, other than local palliative therapy, for myeloma associated bone lesions within 14 days of initiating study treatment

d. Use of any systemic anti-myeloma drug therapy within 14 days of initiating study treatment
14. Subject received any investigational agent within 28 days.
• Subjects who are participating in other interventional trials may not participate in BMS clinical trials, except for those who have completed treatment with the prior investigational agent(s) and are currently in Long-term Follow up.
• Trial participation for subjects whom have received an investigational vaccine (such as an investigational SARS-CoV-2 vaccine) will be determined by discussion between the Investigator and Sponsor Medical Monitor.
15. Subject has previously received a live vaccine within 3 months of initiating study treatment.
16. Concurrent administration of a strong inhibitor or inducer of cytochrome P450 (CYP3A4/5) (including within 14 days of initiating study treatment).
17. Subject is unable or unwilling to undergo protocol required thromboembolism or herpes zoster prophylaxis.
18. Subject has previously received allogeneic stem cell transplantation at any time during prior therapy or received autologous stem cell transplantation within 12 weeks of initiating study treatment.
19. Subject has known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) < 50% of predicted normal. Note that forced expiratory testing (FEV1) is required for subjects suspected of having COPD.
20. Subject has known moderate or severe persistent asthma within the last 2 years, or currently has uncontrolled asthma of any classification.
21. Subject is a female who is pregnant, nursing or breastfeeding, or who intends to become pregnant during participation in the study.
22. Subject is positive for human immunodeficiency virus (HIV), chronic or active hepatitis B, active hepatitis A, or active hepatitis C:
a. Known to be seropositive for HIV.
b. Seropositive for hepatitis B . Subjects with resolved infection must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) deoxyribonucleic acid (DNA) levels. Those who are PCR positive will be excluded.
c. Known to be seropositive for hepatitis C virus (HCV); anti-HCV antibody positive or HCV- ribonucleic acid (RNA) quantitation positive, except in the setting of a sustained virologic response (SVR), defined as aviremia at least 12 weeks after completion of antiviral therapy.
23. Subject has known allergies, hypersensitivity, or intolerance to boron or mannitol, hyaluronidase, sorbitol, corticosteroids, monoclonal antibodies or human proteins, cereblon modulating agents or their excipients or known sensitivity to mammalian-derived products.
24. Subject has any contraindications to daratumumab, bortezomib or dexamethasone, per local PI.
25. Vulnerable, under judicial protection, people without freedom by administrative or judicial decision, people with psychiatric conditions without their consent, people accepted in a health or social institution for other

purposes than the research, adults under legal guardianschip, curatorship, and people incapable of giving consent personally.

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):	06-12-2022
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bortezomib
Generic name:	Bortezomib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Daratumumab
Generic name:	Daratumumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Dexamethasone
Generic name:	Dexamethasone

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Iberdomide
Generic name:	Iberdomide

Ethics review

Approved WMO Date:	26-05-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-07-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	14-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-06-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-12-2023
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	CTIS2024-510800-35-00
EudraCT	EUCTR2020-00431-49-NL
CCMO	NL77115.056.21
Other	U1111-1260-2872