A Four-Part, Open Label, Randomized, Parallel Assignment Study to Evaluate the Pharmacodynamics of Nirogacestat on B-Cell Maturation Antigen (BCMA)

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Part 1In Part 1 of the study, no study compound will be administered, but a bone marrow aspiration and a blood sample will be taken to evaluate an assay that will be used for Part 2 and Part 3 of the study. Because no nirogacestat is given, we can…

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

Summary

ID

NL-OMON53403

Source
ToetsingOnline

Brief title
Phase I pharmacodynamic, pharmacokinetics study of Nirogacestat on BCMA

Condition

- Other condition
- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
multiple myeloma

Health condition

multiple myeloma

Research involving
Human

Sponsors and support

Primary sponsor: SpringWorks Therapeutics, Inc.
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: BCMA, Nirogacestat, pharmacodynamics, pharmacokinetics

Outcome measures

Primary outcome

•To evaluate the pharmacodynamics (PD) of nirogacestat on BCMA

• To evaluate the serum nirogacestat exposure-response relationship to

membrane-bound BCMA (mbBCMA) and soluble BCMA (sBCMA) kinetics after single

dose administration of nirogacestat

Secondary outcome

• To evaluate the pharmacokinetics of serum nirogacestat after single and

multiple dose administration of nirogacestat

• To evaluate the safety and tolerability of single and multiple dose

nirogacestat in healthy male participants

Study description

Background summary

Nirogacestat is a new compound that may potentially be used for the treatment of a specific type of bone marrow cancer, which is called multiple myeloma. Multiple myeloma tumor cells carry a protein on their cell surface. This protein is called *B-cell maturation antigen* or BCMA. BCMA is not only present on multiple myeloma tumor cells but is also present on normal B-cells. BCMA plays an important role in the survival and multiplication of the myeloma tumor

cells and normal B-cells. BCMA can be either bound to the cell surface or can be secreted by the cell as a soluble protein. BCMA can be used as a target for specific anti-cancer drugs. The anti-cancer drugs will be more effective if the BCMA is bound to the cell surface and not secreted as a soluble protein. Nirogacestat will prevent that BCMA is secreted from the cells so that BCMA remains on the cell surface. In this way, anti-cancer drugs will become more effective when these agents are combined with nirogacestat.

Study objective

Part 1
In Part 1 of the study, no study compound will be administered, but a bone marrow aspiration and a blood sample will be taken to evaluate an assay that will be used for Part 2 and Part 3 of the study. Because no nirogacestat is given, we can use these samples as a type of blank measurement (baseline) which we can compare to samples from participants who did receive the study compound.

The test evaluated in this part of the study is a flow cytometry assay, which is a technique used in general to determine which different types of cells and how many cells are present in for example blood samples. This type of essay is even precise enough to measure differences in the amount of proteins bound to the cells. The degree of binding of certain proteins (BMCA) to specific cell types (B-cells) is a measure of the effectiveness of the study compound

Part 2 and 3
In Parts 2 and 3 of this study, we will investigate how safe the new compound nirogacestat is and how well it is tolerated when it is used by healthy participants.

We also investigate how quickly and to what extent nirogacestat is absorbed, transported, and eliminated from the body. In addition, we look at the effect of nirogacestat on B-cells, which is a type of white blood cell.

We also look at the effect of genetic information on the body*s response to nirogacestat. This part of the study is mandatory.

Nirogacestat has been used by humans before. In addition, it has been extensively tested in the laboratory and on animals.

Part 4
In Part 1 of the study, no nirogacestat, also referred to as the study compound, was administered. A bone marrow sample and a blood sample were taken to develop an assay used in the evaluation of these samples. As no nirogacestat was given in Part 1, we used these samples as controls to establish a baseline for information we obtain from the assay. This assay was then used during Part 2 and Part 3 of the study, where participants were given nirogacestat,

which allowed us to compare the information from
control samples to samples from participants who did receive the study
compound. In Part 4, bone marrow samples and blood
samples will be taken from participants who were not administered study
compound. These samples will be handled and
processed differently and evaluated using the same assay in Parts 1-3. The
purpose of Part 4 is to evaluate if different handling
and processing of the samples has an effect on the information we obtain from
the assay.

Study design

Part 1
Screening -> Day -35 up to Day -2 prior to Day 1
Arrival -> Day -1
In-house stay -> Day -1 up to Day 1
Departure -> Day 1 (at least 1 hour after the bone marrow aspirate)

During Part 1 of the study, no study compound will be given.

Part 2
Screening -> Day -35 up to Day -3 prior to the Day of (first) dosing
Arrival -> Day -2
In-house stay -> Day -2 up to Day 2 or 3 as explained below
Departure -> Day 2 (if bone marrow aspirate on Day 1 or Day 2), or Day 3 (if
bone marrow aspirate on Day 3)
Follow-up (per phone call) -> Between Day 31 and Day 33

Subjects will receive nirogacestat as oral tablets with 240 milliliters (mL) of
(tap) water.

Part 3
Screening -> Day -35 up to Day 3 prior to the Day of (first) dosing
Arrival -> Day -2
In-house stay -> Day -2 up to Day 2 or 3 as explained below
Departure -> In case of single dose: Day 2 after completion of the final safety
assessments and sample collection
-> In case of multiple doses: Day 3 after completion of the final safety
assessments and sample collection.
Follow-up (per phone call) -> In case of single dose: Between Day 31 and Day 33
-> In case of multiple doses: Between Day 32 and Day 34

Subjects will receive nirogacestat as oral tablets with 240 milliliters (mL) of
(tap) water.

Part 4
Screening -> Day -35 up to Day -2 prior to Day 1

Arrival -> Day -1
In-house stay -> Day -1 up to Day 2
Departure -> Day 2 (at least 1 hour after the bone marrow aspirate)
During Part 4 of the study, no study compound will be given.

Intervention

Part 1
During Part 1 of the study, no study compound will be given.

Part 2
Subjects will receive a single oral dose with 150 mg nirogacestat (3 tablets of 50 mg each) on Day 1.

Part 3
The dose and the number of doses subjects will receive will be based on the outcome of Part 2 of the study. They will be informed about the dose they will receive on the day they will enter the research center.

The dose(s) could be as follows:
• a single dose of between 50 mg (1 tablet of 50 mg) to 300 mg (6 tablets of 50 mg) nirogacestat, or
• multiple doses of 100 mg twice daily (2 tablets of 50 mg in the morning and in the evening) for 1 or 2 days (maximum of 4 doses of nirogacestat). The highest nirogacestat doses given in previous studies are: 330 mg nirogacestat twice daily for 21 days in patients, 95 mg once daily for 14 days in healthy participants and 150 mg once in healthy participants.

Part 4
During Part 4 of the study, no study compound will be given.

Study burden and risks

Blood draw
Drawing blood may be painful or cause some bruising. The use of the indwelling cannula can sometimes lead to inflammation, swelling, hardening of the vein, blood clotting, and bleeding in the environment (bruising) of the puncture site. In some individuals, a blood draw can sometimes cause pallor, nausea, sweating, low heart rate, or drop in blood pressure with dizziness or fainting.

In total, we will take about 26 (in part 1), 113 (in part 2) and 173 (in part 3) milliliters (mL) of blood from screening to follow-up. This amount does not cause any problems in adults. To compare: a blood donation involves 500 mL of blood being taken each time at once. If the investigator thinks it is necessary for the safety of a participant, extra samples might be taken for possible additional testing. If this happens, the total amount of blood drawn may be

more than the amount indicated above.

Heart tracing
To make a heart tracing, electrodes will be placed on arms, chest and legs. Prolonged use of these electrodes can cause skin irritation (rash and itching).

Bone marrow sampling with local anesthetics (lidocaine injection)
The procedure will be performed by a hematologist and will be as follows: They will lie on their side (usually the left side) and the doctor first applies a local anesthetic to the back of the pelvis, where the puncture will then take place. The application of anesthetic (lidocaine injection) may hurt for a short period of time, because the outside of the bone has to be anesthetized. Disinfecting the puncture site may feel cold. When the anesthesia has taken effect, the doctor will puncture the bone marrow cavity with the puncture needle. Through this needle, the doctor can aspirate a small amount of bone marrow cells with a syringe. Aspirating bone marrow cells only takes a few seconds but can radiate painfully to the leg.
Usually the removal of the bone marrow cells is almost painless, although despite the anesthetic the procedure may still hurt a lot.
If it does hurt, it is important to mention this (during the puncturing of the bone), so extra anesthetic may be applied. The collection of the bone marrow may be painful or uncomfortable (unpleasant), but the pain should not last long (at the most 10 seconds), and they will always be warned in advance.
It is expected that the whole procedure (including anesthesia, sample collection, etc.) takes about 20 minutes. A plaster with gauze will be applied at the puncture site. Thereafter they will have to lie on their back for a while (usually about half an hour), to apply pressure to the puncture hole using their own weight. After it has been checked that any bleeding has stopped, they are allowed to get up and resume their activities. They cannot take a shower on the evening of the puncture, so that the *wound* can recover.
After 24 hours, the plaster with gauze may be removed.
After the sampling, the site may be sore, just like a large bruise, may hinder movement for the first few hours, and fever and/or blood loss from the puncture site may occur. If there is still pain afterwards, they can discuss with the study doctor whether they may use paracetamol. The second bone marrow sampling will be taken from the same area as the first sample.

Contacts

Public

SpringWorks Therapeutics, Inc.

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

2. Participant understands the study procedures, is willing to comply with all study requirements and restrictions and agrees to participate in the study by providing written informed consent as described in Appendix 1, prior to any study-related procedures being performed.
3. Participant is a male between 18 and 55 years of age (inclusive) at the time of informed consent.
4. Participant has a body mass index (BMI) >= 18 kg/m2 and <= 32 kg/m2 (inclusive) at Screening and a total body weight > 50 kg.
5. Participant is considered to be medically healthy, as determined by a responsible and experienced investigator, based on a clinical evaluation (including medical history, physical examination, clinical laboratory tests, vital sign measurements and a 12-lead ECG) performed as directed in the SoA (Section 1.3), Section 1.2.1; and the results of clinical chemistry, and hematology carried out at Screening and Day -1 (Parts 1 and 4) or Day -2 (Parts 2 and 3).

Exclusion criteria

1. Participant has a history or presence of oncologic, cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, ocular, endocrine, immunologic, dermatologic, musculoskeletal, neurological, psychiatric or other disease or condition or the laboratory test abnormality that in the investigator*s judgment poses a significant risk to the safety of the participant or the achievement of study objectives.
2. Participant has a medical history or abnormal findings at Screening or Day -1 (Parts 1 and 4) or Day -2 (Parts 2 and 3) that the investigator judges may put at risk achieving the objectives of the study or protecting the safety of the participant.
3. Participant has an acute illness with symptom or treatment that has started or persisted within 14 days prior to study treatment administration unless mild in severity and enrollment is approved by both Investigator and Sponsor*s medical monitor.
4. Participant has clinically significant infections (e.g., HBV, HCV, HIV) within 90 days prior to Day 1, as judged by the investigator, or evidence of any infection with the past 14 days prior to Day 1.
5. Participant has blood pressure (BP) that is greater than or equal to 140 mm Hg systolic or 90 mm Hg diastolic following at least 5 minutes of rest at Screening or Day -1 (Parts 1 and 4) or Day -2 (Parts 2 and 3). Additionally, BP that is less than 90 mm Hg systolic or 45 mmHg diastolic following at least 5 minutes of rest at Screening or Day -1 (Parts 1 and 4) or Day -2 (Parts 2 and 3).

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Completed

Start date (anticipated):	14-04-2022
Enrollment:	27
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	15-03-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-04-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	20-03-2023
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
EudraCT	EUCTR2022-000386-40-NL
CCMO	NL80762.056.22

Study results

Date completed:	05-05-2023
Results posted:	02-08-2024

First publication
18-06-2024