A randomized, open-label, phase I/II open platform study evaluating safety and efficacy of novel ruxolitinib combinations in myelofibrosis patients

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To characterize the safety, tolerability, and recommended phase 2 dose (RP2D) of each combination partner used with ruxolitinib (Part 1)To evaluate the preliminary efficacy of each novel ruxolitinib combination treatment arm (Parts 2 & 3)

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Haematological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON52828

Source
ToetsingOnline

Brief title
CINC424H12201 (ADORE)

Condition

- Haematological disorders NEC

Synonym
myelofibrosis

Research involving
Human

Sponsors and support

Primary sponsor: Novartis

Source(s) of monetary or material Support: Novartis Pharma B.V.

Intervention

Keyword: 5 novel agents, myelofibrosis, ruxolitinib (INC424)

Outcome measures

Primary outcome

The efficacy assessments for the primary objectives are:

**Laboratory hemoglobin assessments taken at the end of Cycle 6 compared to baseline

**MRI or CT imaging of the spleen will be performed at screening, at the end of Cycle 6, the end of Cycle 12 and at end of treatment (EOT)

**total symptom score (TSS) assessed by MFSAF v4.0 at baseline and at the end of Cycle 6

Secondary outcome

To assess the proportion of subjects in each treatment arm who achieve an Hb improvement of * 2.0 g/dL or * 1.5 g/dL from baseline to the end of Cycle 6 and end of Cycle 12

To evaluate the changes in spleen size in each treatment arm measured by change in spleen length (by palpation) and spleen volume (by magnetic resonance imaging (MRI)/computed topography (CT)) from baseline

To evaluate changes in symptoms of myelofibrosis in each treatment arm using MFSAF v4.0 and European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) patient reported outcomes (PROs) from baseline

To characterize the pharmacokinetic profile of ruxolitinib administered in

combination with siremadlin, crizanlizumab, sabatolimab, LTT462 and NIS793.

Study description

Background summary

MF is defined by progressive bone marrow fibrosis, Anemia is among the cardinal features of MF. Nearly 40% of MF patients have hemoglobin (Hb) levels < 10 g/dL at diagnosis, and nearly one-quarter are already red blood cell (RBC) transfusiondependent. All patients with MF will eventually develop anemia, which has consistently been associated with inferior QoL measures. Furthermore, anemia is the disease feature most consistently associated with poor prognosis in MF.

Ruxolitinib demonstrated improvements in splenomegaly and constitutional symptoms. However, not all patients respond to ruxolitinib, with some losing response while on treatment, and some having to discontinue treatment owing to toxicities. Ruxolitinib does not improve cytopenias but may aggravate anemia due to transient suppression of the erythropoiesis, which at least partially resolves over time on continuous therapy. Current treatment options for these patients are limited in their efficacy, durability and tolerability. Anemia and thrombocytopenia have remained challenges in the management of MF and represent a high unmet medical need. Combination therapies of ruxolitinib with novel agents may deliver transformational clinical benefits such as improvement of PFS, associated with an improvement of cytopenia and in particular anemia, as well as improvement in QoL.
The purpose of this study is to investigate the safety, pharmacokinetics and preliminary efficacy of combinations treatment of ruxolitinib with five novel compounds: siremadlin, crizanlizumab, sabatolimab, LTT462 and NIS793 in MF subjects.

Study objective

To characterize the safety, tolerability, and recommended phase 2 dose (RP2D) of each combination partner used with ruxolitinib (Part 1)
To evaluate the preliminary efficacy of each novel ruxolitinib combination treatment arm (Parts 2 & 3)

Study design

This is an open-label, multi-center, three-part, phase Ib/II open platform study to assess safety and efficacy of ruxolitinib in combination with novel compounds in myelofibrosis patients. The study consists of three parts:
**Part 1: Dose escalation and safety-run-in (recommended Phase II dose

confirmation)
**Part 2: Selection
**Part 3: Expansion

Intervention

In Part 1 of the study, subjects will be allocated during screening to one of the following 5 treatment arms:
- Arm 1: Ruxolitinib 5-25 mg PO BID and siremadlin at various dose levels (either 10 mg, 20 mg (starting dose), 30 mg or 40 mg) PO on Days 1 to 5 of a 28-day cycle
- Arm 2: Ruxolitinib 5-25 mg PO BID and crizanlizumab 5 mg/kg IV Q4W
- Arm 3: Ruxolitinib 5-25 mg PO BID and MBG453 800 mg IV Q4
- Arm 4: Ruxolitinib 5-25 mg PO BID and LTT462 100-300mg PO QD (in a 28 day cycle)
- Arm 5: Ruxolitinib 5-25 mg PO BID and NIS793 2100 mg IV Q3W

In Part 2 of the study, subjects will be randomized during screening to one of the following 6 treatment arms in a ratio of 1:1:1:1:1:1 with approximately 25 subjects per arm:
- Arm 1: ruxolitinib 5-25 mg PO BID and siremadlin at the RP2D from Part 1 PO on Days 1 to 5 of a 28-day cycle
- Arm 2: ruxolitinib 5-25 mg PO BID and crizanlizumab 5 mg/kg IV Q4W
- Arm 3: ruxolitinib 5-25 mg PO BID and MBG453 800 mg IV Q4W
- Arm 4: Ruxolitinib 5-25 mg PO BID and LTT462 (R2PD) PO QD (in a 28 day cycle)
- Arm 5: Ruxolitinib 5-25 mg PO BID and NIS793 2100 mg IV Q3W
- Arm 6: ruxolitinib 5-25 mg PO BID monotherapy control

In Part 3 of the study, subjects will be randomized during screening to one of the following 3 treatment arms in a ratio of 2:1:1 with approximately 20, 10, and 10 subjects per arm, respectively:
**Arm 1: Ruxolitinib 5-25 mg PO BID and novel compound from Part 2 (TBD)
**Arm 2: Ruxolitinib 5-25 mg PO BID and novel compound from Part 2 (TBD) for 3 cycles of treatment, followed by ruxolitinib cessation treatment (i.e. novel agent monotherapy control)
**Arm 3: Ruxolitinib 5-25 mg PO BID monotherapy control

Study burden and risks

Intensive PK sampling for all patients, infusions on day 1 of each cycle (compaed to standard treatment with ruxolitinib) for 2/3 of patients. Other 1/3 of patients will be randomised to siremadlin (oral capsules)

Risks: side effects of the medications (combinations) and of the test procedures like extra blooddraws.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

* Subjects have diagnosis of primary myelofibrosis (PMF) according to the 2016 World Health Organization (WHO) criteria, or diagnosis of post-essential thrombocythemia (ET) (PET-MF) or post-polycythemia vera (PV) myelofibrosis (PPV-MF) according to the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) 2007 criteria
* Palpable spleen of at least 5 cm or enlarged spleen volume of at least 450 cm3 per MRI or CT scan at baseline (a MRI/CT scan up to 8 weeks prior to first dose of study treatment can be accepted).
* Have been treated with ruxolitinib for at least 12 weeks prior to first dose of study treatment
* Are stable (no dose adjustments) on the prescribed ruxolitinib dose (between 5 and 25 mg twice a day (BID)) for * 4 weeks prior to first dose of study treatment.

* Hemoglobin < 11 g/dL
* Part 1: Platelet counts * 75 000/*L
* Part 2 and Part 3: Platelet counts * 50 000/*L

Exclusion criteria

* Not able to understand and to comply with study instructions and requirements.
* Received any investigational agent for the treatment of MF (except ruxolitinib) within 30 days of first dose of study treatment or within 5 half-lives of the study treatment, whichever is greater
* Peripheral blood blasts count of >10%.
* Received a monoclonal antibody (Ab) or immunoglobulin-based agent within 1 year of screening, or has documented severe hypersensitivity reactions/immunogenicity (IG) to a prior biologic
* Splenic irradiation within 6 months prior to the first dose of study drug
* Received blood platelet transfusion within 28 days prior to first dose of study treatment. PRBC transfusions are permitted
* Subjects with known TP53 mutation or deletion of TP53

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-01-2021
Enrollment:	7

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	crizanlizumab
Generic name:	crizanlizumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Jakavi
Generic name:	ruxolitinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	LTT462
Generic name:	LTT462
Product type:	Medicine
Brand name:	sabatolimab
Generic name:	sabatolimab
Product type:	Medicine
Brand name:	siremadlin
Generic name:	siremadlin

Ethics review

Approved WMO Date:	22-08-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-10-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-02-2020

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-06-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-06-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-09-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	05-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-01-2022
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:	01-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-06-2022
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	EUCTR2019-000373-23-NL
CCMO	NL70284.056.19