Platform Study of Novel Ruxolitinib Combinations in Myelofibrosis Patients

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Main Information

Primary registry identifying number
LBCTR2022035001

Protocol number
CINC424H12201

MOH registration number

Study registered at the country of origin
Yes

Study registered at the country of origin: Specify

Type of registration
Prospective

Type of registration: Justify
N/A

Date of registration in national regulatory agency

Primary sponsor
Novartis Pharmaceuticals

Primary sponsor: Country of origin
Novartis Pharmaceuticals

Date of registration in primary registry
20/07/2022

Date of registration in national regulatory agency

Public title
Platform Study of Novel Ruxolitinib Combinations in Myelofibrosis Patients

Acronym
ADORE

Scientific title
A Randomized, Open-label, Phase I/II Open Platform Study Evaluating Safety and Efficacy of Novel Ruxolitinib Combinations in Myelofibrosis Patients

Acronym

Brief summary of the study: English
The purpose of this study is to investigate the safety, pharmacokinetics and preliminary efficacy of combinations treatment of ruxolitinib with 5 novel compounds: siremadlin, crizanlizumab, sabatolimab, LTT462 and NIS793 in myelofibrosis (MF) subjects.

Brief summary of the study: Arabic
دراسة لتقييم سلامة وفعاليّة استعمالات روكسوليتينيب مع أدوية جديدة لدى مرضى التليّف النقويّ

Health conditions/problem studied: Specify
Myelofibrosis

Interventions: Specify
- Drug: Ruxolitinib
5 mg tablets for oral use
Other Name: INC424, Jakavi
- Drug: Siremadlin
10 mg, 20 mg, or 40 mg capsules for oral use
Other Name: HDM201
- Drug: Crizanlizumab
100 mg/mL concentrate for infusion for intravenous use
Other Name: SEG101

- Drug: Sabatolimab
100 mg/mL or 400 mg/4 mL concentrate for infusion for intravenous use
Other Name: MBG453
- Drug: LTT462
100 mg capsule for oral use
- Drug: NIS793
700 mg/7 mL concentrate for intravenous use

Key inclusion and exclusion criteria: 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 from the left costal margin (LCM) to the point of greatest splenic protrusion 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 24 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 ≥ 8 weeks prior to first dose of study treatment

Key inclusion and exclusion criteria: Gender

Both

Key inclusion and exclusion criteria: Specify gender

Key inclusion and exclusion criteria: Age minimum

18

Key inclusion and exclusion criteria: Age maximum

99

Key inclusion and exclusion criteria: 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.

Type of study

Interventional

Type of intervention

Pharmaceutical

Type of intervention: Specify type

N/A

Trial scope

Therapy

Trial scope: Specify scope

N/A

Study design: Allocation

Randomized controlled trial

Study design: Masking

Open (masking not used)

Study design: Control

Active

Study phase

1 to 2

Study design: Purpose

Treatment

Study design: Specify purpose

N/A

Study design: Assignment

Parallel

Study design: Specify assignment

N/A

IMP has market authorization

No

IMP has market authorization: Specify

Name of IMP

Ruxolitinib

Year of authorization

Month of authorization

Type of IMP

Immunological

Pharmaceutical class

Janus Associated Kinase Inhibitor

Therapeutic indication

Myelofibrosis

Therapeutic benefit

progression free survival (PFS)

Study model

N/A

Study model: Explain model

N/A

Study model: Specify model

N/A

Time perspective

N/A

Time perspective: Explain time perspective

N/A

Time perspective: Specify perspective

N/A

Target follow-up duration

Target follow-up duration: Unit

Number of groups/cohorts

Biospecimen retention

Samples without DNA

Biospecimen description

Samples will be shipped to Covance Central Lab

Target sample size

4

Actual enrollment target size

Date of first enrollment: Type

Anticipated

Date of first enrollment: Date

28/04/2022

Date of study closure: Type

Anticipated

Date of study closure: Date

16/01/2024

Recruitment status

Suspended

Recruitment status: Specify

Date of completion

IPD sharing statement plan

IPD sharing statement description

Yes

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent expert panel on the basis of scientific merit. All data provided is anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

This trial data is currently available according to the process described on www.clinicalstudydatarequest.com.

Additional data URL

https://clinicaltrials.gov/ct2/show/record/NCT04097821?term=CINC424H12201&draw=2&rank=1

Admin comments

Trial status

Approved

Secondary Identifying Numbers

Full name of issuing authority	Secondary identifying number
Clinicaltrials.gov	NCT04097821

Sources of Monetary or Material Support

Name
Novartis Pharmaceuticals

Secondary Sponsors

Name
N/A

Contact for Public/Scientific Queries

Contact type	Contact full name	Address	Country	Telephone	Email	Affiliation
Public	Ali Taher	Beirut	Lebanon	+9613755669	ataher@aub.edu.lb	American University of Beirut Medical Center
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Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
American University of Beirut Medical Center	Ali Taher	Hematology-Oncology	Approved

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
American University of Beirut Medical Center	24/01/2022	Fuad Ziyadeh	fz05@aub.edu.lb	+961 (0) 1 350 000 ext:5445

Countries of Recruitment

Name
Australia
Belgium
Canada
Denmark
Germany
Hungary
Italy
Netherlands
Russian Federation
Spain
Sweden
Switzerland
United Kingdom
Lebanon

Health Conditions or Problems Studied

Condition	Code	Keyword
Myelofibrosis	Other specified diseases of blood and blood-forming organs (D75.8)	Myelofibrosis

Interventions

Intervention	Description	Keyword
Consenting, IMP administration	Consenting, IMP administration	Consenting, IMP administration

Primary Outcomes

Name	Time Points	Measure
Incidence of dose limiting toxicities within the first 2 cycles	Baseline to the end of Cycle 2 (6 or 8 weeks)	Incidence and severity of dose limiting toxicities within the first 2 cycles (6 or 8 weeks) in Part 1 of the study
Response rate at the end of cycle 6 or cycle 8	Baseline to the end of Cycle 6 or 8 (24 weeks)	Composite of anemia improvement (hemoglobin level) and no spleen volume progression and no symptom worsening in Part 2 and Part 3 of the study. For a subject to be considered a responder, all three components of the composite have to be fulfilled

Key Secondary Outcomes

Name	Time Points	Measure
Proportion of subjects achieving an improvement in hemoglobin level of ≥ 1.5 g/dL from baseline	Baseline to the end of Cycle 6 or 8 (24 weeks), and end of Cycle 12 or 16 (48 weeks)	Proportion of subjects achieving an improvement in hemoglobin level of at least >= 1.5 g/dL from baseline at each time point in Part 2 and Part 3 of the study.
Proportion of subjects achieving an improvement in hemoglobin level of at least >= 2.0 g/dL from baseline	Baseline to the end of Cycle 6 or 8 (24 weeks), and end of Cycle 12 or 16 (48 weeks)	Proportion of subjects achieving an improvement in hemoglobin level of at least >= 2.0 g/dL from baseline at each time point in Part 2 and Part 3 of the study
Change in spleen length from baseline	Baseline to day 1 and day 15 of Cycle 1, 2 and 3, day 1 of all subsequent cycles, and the end of 12 or 16 cycles (48 weeks)	Change in spleen length measured in centimeters by manual palpation summarized at each time point using descriptive statistics in Part 2 and Part 3 of the study
Change in spleen volume from baseline	Baseline to the end of Cycle 6 or 8 (24 weeks), the end of Cycle 12 or 16 (48 weeks) and at the end of treatment if not performed in the past 12 weeks (up to 48 weeks)	Change in spleen volume measured by magnetic resonance imaging (MRI) or computed tomography (CT) summarized at each time point using descriptive statistics, in Part 2 and Part 3 of the study
Change in symptoms of MFSAF v4.0 from baseline	Baseline to day 1 of Cycle 1, day 1 of all subsequent cycles of treatment (each cycle is 28 days except for arms containing NIS793, which are 21 days), as well as the end of treatment visit (approximately 52 weeks)	Change in total symptom scores (TSS) assessed by the Myelofibrosis (MF Symptom Assessment Form version 4.0 (MFSAF v4.0) at each time point in Part 2 and Part 3 of the study. The MFSAF v4.0 questionnaire focuses on the 7 core symptoms of MF: fatigue, night sweats, pruritus, abdominal discomfort, pain under the ribs on the left side, early satiety and bone pain. Subjects record symptom severity at it worst for each of the 7 symptoms on an 11-point numeric rating scale, from 0 (absent) to 10 (worst imaginable). The Total Symptom Score (TSS) is the sum of all the scores for all 7 symptoms.

Change in symptoms of EORTC QLQ-C30 from baseline	Baseline to day 1 of Cycle 1, day 1 of all subsequent cycles of treatment (each cycle is 28 days except for arms containing NIS793, which are 21 days), as well as the end of treatment visit (approximately 52 weeks)	Change in symptom scores assessed by European Organization for Research and Treatment of Cancer 30-item core quality of life questionnaire (EORTC QLQ C-30) at each time point in Part 2 and Part 3 of the study. The EORTC QLQ-C30 includes 5 functional scales (physical, emotional, social, role, cognitive), eight symptom scales (fatigue, pain, nausea/vomiting, constipation, diarrhea, insomnia, dyspnea, and appetite loss), as well as global health/quality-of-life and financial impact. Subjects respond according to the past week recall period, with the exception of the first 5 questions that represent physical functioning and capture the subject's current status. Raw scores are linearly converted to a 0-100 scale. For functional and global health status/QoL higher scores indicate better QoL and level of functioning; for symptom scales, higher scores indicate greater level of symptoms or difficulties.
Progression free survival, per progressive splenomegaly, accelerated phase, deteriorating cytopenia, leukemic transformation or death from any cause	Baseline to disease progression, which is up to 24 weeks for Part 1 or through study completion, an average of 1 year, for Part 2 and Part 3	Progressive splenomegaly is assessed by increasing spleen volume (by MRI/CT) of ≥ 25% from baseline. Accelerated phase: a circulating peripheral blood blast content of > 10% but < 20% confirmed after 2 weeks. Deteriorating cytopenia (dCP) independent from treatment defined for all patients by platelet count < 35 x10^9/L or neutrophil count < 0.75 x 10^9/L that lasts for at least 4 weeks. Leukemic transformation, a peripheral blood blast content of ≥ 20% associated with an absolute blast count of ≥ 1x10^9/L that lasts for at least 2 weeks or a bone marrow blast count of ≥ 20%.
Proportion of subjects achieving an impovement in bone marrow fibrosis of ≥ 1 grade from baseline	Baseline to the end of Cycle 6 or 8 (24 weeks), the end of Cycle 12 or 16 (48 weeks) and at the end of treatment if not performed in the past 12 weeks (up to 48 weeks)	Proportion of subjects achieving an improvement in bone marrow fibrosis of >= 1 grade at each time point will be summarized in Part 2 and Part 3 of the study.
Area under the Plasma Concentration versus Time Curve (AUC)	Days 1 and 5 of Cycle 1 and 2 for siremadlin and ruxolitinib, and Cycle 1 and Cycle 3 for crizanlizumab, sabatolimab and NIS793, and Days 1 and 15 of Cycle 1 for LTT462	AUC for each investigational drug in Part 1, Part 2 and Part 3 of the study
Maximum (peak) observed plasma drug concentration (Cmax)	Days 1 and 5 of Cycle 1 and 2 for siremadlin and ruxolitinib, and Cycle 1 and Cycle 3 for crizanlizumab, sabatolimab and NIS793, and Days 1 and 15 of Cycle 1 for LTT462	Cmax for each investigational drug in Part 1, Part 2 and Part 3 of the study
Time to reach maximum (peak) plasma, blood, serum or other body fulid drug concentration after single dose administration (Tmax)	Days 1 and 5 of Cycle 1 and 2 for siremadlin and ruxolitinib, and Cycle 1 and Cycle 3 for crizanlizumab, sabatolimab and NIS793, and Days 1 and 15 of Cycle 1 for LTT462	Tmax for each investigational drug in Part 1, Part 2 and Part 3 of the study
Concentration versus time profile	Days 1 and 5 of Cycle 1 and 2 for siremadlin and ruxolitinib, and Cycle 1 and Cycle 3 for crizanlizumab, sabatolimab and NIS793, and Days 1 and 15 of Cycle 1 for LTT462	Concentration versus time profile for each investigational drug in Part 1, Part 2 and Part 3 of the study
Presence and/or concentration of anti-drug antibody	Baseline to 105 days after last study drug administration for crizanlizumab, to 150 days after last study drug administration for sabatolimab, or to 90 days after last study drug administration for NIS793	The presence and titer of anti-drug antibodies for crizanlizumab, sabatolimab and NIS793 in Part 1, Part 2 and Part 3 of the study

Trial Results

Summary results

Study results globally

Date of posting of results summaries

Date of first journal publication of results

Results URL link

Baseline characteristics

Participant flow

Adverse events

Outcome measures

URL to protocol files