A Phase 3 Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Rozanolixizumab in Adult Study Participants With Persistent or Chronic Primary Immune Thrombocytopenia (ITP)

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Primary:* To demonstrate the clinical efficacy of rozanolixizumab in maintenance treatment in study participants with primary ITPSecondary:* To assess the safety and tolerability of rozanolixizumabExploratory:* To evaluate the clinical efficacy as...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Haematological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON49073

Source
ToetsingOnline

Brief title
myOpportunITy2

Condition

- Haematological disorders NEC
- Autoimmune disorders

Synonym

Chronic Primary Immune Thrombocytopenia / ITP

Research involving
Human

Sponsors and support

Primary sponsor: UCB Pharma
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: ITP, Phase 3, Rozanolixizumab

Outcome measures

Primary outcome

The primary efficacy endpoint is:

* Durable Clinically Meaningful Platelet Response of *50x109/L, as defined by

proportion of study participants who have platelet responses fromfor at least 8

out of 12 weeks during the last 12 weeks (Week 13 to 25)

The secondary efficacy endpoints are:

* Cumulative number of visits with Clinically Meaningful Platelet Response of

*50x109/L

* Response defined as platelet count *30x109/L and at least a 2-fold increase

of the Baseline count confirmed on at least 2 separate occasions at two

adjacent nominal visits at least 7 days apart, and absence of bleeding by visit

a,b

* Complete Response defined as platelet count *100x109/L confirmed on at least

2 separate occasions at two adjacent nominal visits at least 7 days apart, and

absence of bleeding by visit a,b

* Time to Clinically Meaningful Platelet Response of *50x109/L: time from

starting treatment to achievement of first response of *50x109/L

* Clinically Meaningful Platelet Response of *50x109/L by Day 8

* Time to first rescue therapy

* Response defined as change from Baseline at or above the defined threshold for ITP Patient Assessment Questionnaire (ITP-PAQ) Symptoms Score

The other efficacy endpoints are:

* Duration of Clinically Meaningful Platelet Response of *50x109/L: measured from achievement of first Response to loss of Response (loss of Response defined as platelet count <50x109/L)

* Time to first Response: time from starting treatment to achievement of Response

* Time to first Complete Response: time from starting treatment to achievement of Complete Response

* Duration of first Complete Response: measured from achievement of Complete Response to loss of Complete Response (loss of Complete Response defined as platelet count <100x109/L or bleeding. Platelet counts confirmed on at least 2 separate occasions)

* Usage of rescue therapy

Secondary outcome

Secondary:

The safety endpoints are:

* Occurrence of treatment-emergent adverse events (TEAEs)

* Occurrence of TEAEs leading to withdrawal of investigational medicinal product (IMP)

The other safety endpoints are:

* Occurrence of serious TEAEs

* Occurrence of treatment related TEAEs

* Occurrence of adverse events of special monitoring (AESM)

* Vital signs change from Baseline (blood pressure [BP], pulse rate, body temperature) at each scheduled assessment during Treatment and Safety Follow-up (SFU) Periods

* 12-lead electrocardiogram (ECG) change from Baseline at each scheduled ECG visit

* Laboratory change from Baseline (hematology including coagulation parameters, clinical chemistry, and urinalysis) at each scheduled assessment during Treatment and SFU Periods

* Change from Baseline in concentrations of total protein, albumin, * globulin, and *-globulin

* Change from Baseline in serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a) at each scheduled assessment during the study (for study participants experiencing infusion reactions or hypersensitivity reactions)

* Change from Baseline in cytokines during the study (for study participants experiencing infusion reactions or hypersensitivity reactions)

Exploratory:

* ITP bleeding score over time and number of bleeding events

* Change from Baseline in European Quality of Life 5 5 Levels Dimension Assessment (EQ 5D 5L)

* Change from Baseline in Short form 36 item (SF 36) Survey

* Change from Baseline in the ITP-PAQ Score

* Number and length of hospitalizations

* Change from Baseline in Physical Fatigue Instrument

* Change from Baseline in Patient Global Impression of Severity (PGI-S)

* Change from Baseline in Patient Global Impression of Change (PGI-C)

* Plasma concentration of rozanolixizumab

* ADAs at each scheduled assessment

The exploratory PD endpoints are:

* Minimum value and maximum decrease from Baseline in total serum IgG concentration

* Change from Baseline in serum IgG subclass concentration

* Change from Baseline in serum immunoglobulin concentrations (IgA, IgE, IgM)

* Change from Baseline in ITP-specific autoantibodies in serum

The other exploratory endpoints are:

* Change from Baseline in exploratory biomarkers (for study participants experiencing severe headache or gastrointestinal [GI] related AESM)

* For consenting study participants, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), genetic, and epigenetic changes that may be measured to understand the cause, progression, and appropriate treatment of ITP

* Exploratory biomarkers such as but not limited to B-cell activating factor and circulating immune complexes may be measured to evaluate the effect of

rozanolixizumab

* Proteins and metabolite changes may be measured to understand the cause,

progression, and appropriate treatment of ITP

* Percent change from Baseline in vaccination titers against Streptococcus

pneumoniae, Neisseria meningitidis, and Haemophilus influenzae in

splenectomized study participants

* Percent change from Baseline in vaccination titers against tetanus in all

study participants

Study description

Background summary

ITP is a rare autoimmune disorder. The immune system is our body*s defense system against infections. Antibodies are the defenders which give us this protection. In case of an autoimmune disorder like ITP, your antibodies cannot tell the difference between foreign proteins that should be eliminated (from bacteria or viruses or other substances) and your own proteins. As a result, they end up targeting and destroying certain healthy or normal cells such as platelets.
Platelets are components of your blood that help it to clot when there is an injury to a blood vessel. In ITP, the antibodies target and destroy the platelets and the cells producing them. This leads to an overall reduction in the number of platelets in the body.
When the number of platelets in your blood falls to a certain level, you develop a tendency to bleed or bruise easily.
The study drug is an antibody that works as a medicine to reduce the number of defective antibodies in your blood. This may allow the number of your platelets (also called platelet count) to increase.
The purpose of this study is to help us understand how effective the study drug will be in achieving and maintaining an adequate platelet count in study participants with ITP.

Study objective

Primary:

* To demonstrate the clinical efficacy of rozanolixizumab in maintenance treatment in study participants with primary ITP

Secondary:
* To assess the safety and tolerability of rozanolixizumab

Exploratory:
* To evaluate the clinical efficacy as measured by the ITP bleeding score
* To assess the effect of rozanolixizumab on health-related quality of life (HRQoL)
* To assess hospitalizations due to ITP
* To assess the effect of rozanolixizumab on patient reported outcomes (PROs)
* To assess the plasma concentrations of rozanolixizumab administered by subcutaneous (sc) infusion
* To evaluate the incidence and emergence of antidrug antibodies (ADAs) of rozanolixizumab
* To assess the pharmacodynamic (PD) effects of rozanolixizumab
* To evaluate the effects of rozanolixizumab on exploratory biomarkers
* To assess the influence of rozanolixizumab treatment on vaccination titers

Study design

This is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study with rozanolixizumab in study participants with persistent or chronic primary ITP defined as more than 3 months, or more than 12 months of duration respectively, since diagnosis.
The study participants will be male and female adults with persistent or chronic primary ITP, history of prior ITP treatment, a platelet count measurement at Screening and at Baseline with an average of the two <30x109/L (no single count may be >35x109/L) and a documented history of low platelet count (<30x109/L) any time prior to Screening.
Participants should previously have received one or more ITP therapies and should have initially responded to such therapy and have a current or history of a blood smear consistent with primary ITP.
Study participants who have previously undergone a splenectomy will be included in the study provided they meet the protocol defined exclusion criteria in order to optimize protection against overwhelming post-splenectomy infection (OPSI). Splenectomized study participants should be vaccinated against the encapsulated organisms such as Streptococcus pneumoniae (S. pneumoniae), Neisseria meningitidis (N. meningitidis), and Haemophilus influenzae (H. influenzae) (as per local/or a national guidance, as applicable) as evidenced from personal immunization records. Study participants, who are due to receive a booster, can be screened after they received the required booster.
Splenectomized study participants will be required to attend a Prescreening Period prior to the Screening Visit for the assessment of vaccination titers against the above-mentioned bacteria and to receive, if applicable, the required vaccinations (see Table 1-3).

The study will assess whether multiple sc infusions of rozanolixizumab will result in a durable Clinically Meaningful Platelet Count of *50x109/L for at least 8 out of 12 weeks during the last 12 weeks of the Treatment Period (Weeks 13 to 25). Starting at Week 2, platelet counts will be measured every week at a local laboratory. Home visits for assessment of platelet count may be done where local laboratory participation can be realized.
Once eligibility is confirmed, on Day 1 (Baseline Visit), study participants will enter the Treatment Period and will be randomized 2:1 to receive a one-time fixed-unit dose of rozanolixizumab equivalent to 15mg/kg sc or placebo, with randomization stratified by the degree of thrombocytopenia (platelet count < or *15x109/L) and history of splenectomy (yes or no; study participants with splenectomy within 2 years prior to Baseline will be excluded). Following the initial dose (equivalent to 15mg/kg), study participants will then receive a fixed-unit dose of rozanolixizumab equivalent to 10mg/kg or placebo, every 2 weeks (Q2W) until Week 23. The last assessment of the Treatment Period will take place at Week 25.
During the first 12 weeks in the study (Week 1 until Week 13) rozanolixizumab dose adaptations, depending on the observed levels of platelets as detailed in Table 1 1, will be allowed. The Dose Adaptation Period aims at achieving a rozanolixizumab dose regimen that sustains a platelet count *50x109/L to *200x109/L until Week 13. Following the initial dose, a dose equivalent to 10mg/kg Q2W is applied which can be adapted to dose equivalents to 7mg/kg Q2W or approximately 4mg/kg (280mg total dose) Q2W based on the platelet count. Following this Dose Adaptation Period, study participants will enter the Maintenance Period starting at Week 13 until Week 25. The dose regimen that achieves platelet stabilization in the adaptation period will be continued throughout the Maintenance Period. During the Maintenance Period the dose regimen should remain stable and further dose adaptations should be avoided if possible. However, adjustments for safety and efficacy reasons will still be allowed as outlined in Table 1 1 and Figure 1-1, which presents the dose titration for rozanolixizumab based on the platelet count.

Intervention

Study participants will be randomly assigned to IMP in a 2:1 ratio to either rozanolixizumab or placebo, respectively. A formal interim analysis will be conducted when approximately 30 eligible study participants have been treated and are evaluable for the primary endpoint analysis (ie, approximately 20 and 10 study participants in the rozanolixizumab and placebo arms, respectively). During the interim analysis, recruitment will be ongoing. If the study is not stopped for futility at this stage, then depending upon the calculation of conditional power, a further 30 to 75 study participants may be recruited into the study. Thus, the total sample size of the study could range between approximately 60 and 105 study participants if the study is not futile (for determination of sample size, see Section 9.8).

See study design for the dose of study medication.

Study burden and risks

The participants in this study will make at least 30 visits for this study (this may be more if the spleen is removed and the test subject needs extra vaccinations).
During these visits the test subjects will be subjected to:
Blood sampling (total 428 mL of blood)
Physical examinations
Measuring vital functions
pregnancy testing (if female)
ECG measurements
X-ray scan (is only done if researcher believes that the patient is at risk for TB, see protocol 8.2.5.1)
Filling in questionnaires on an electronic device. The questionnaires are about:
- General well-being
- Quality of life
- severity of symptoms
- Fatigue
- Daily functioning

Furthermore, the medication can cause side effects as described in E9.

Contacts

Public
UCB Pharma

Allée de la Recherche 60
Brussels 1070
BE
Scientific
UCB Pharma

Allée de la Recherche 60
Brussels 1070
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

-Study participant must be *18 years of age at the time of the Screening Visit
-Study participant has a diagnosis of persistent (longer than 3 months duration) or chronic (longer than 12 months duration) primary immune thrombocytopenia (ITP) at the Screening Visit
-Study participant has documented intolerance or insufficient response to one or more appropriate courses of standard of care ITP medication prior to Screening
-Study participants must have prior history of a response to a previous ITP therapy
-If taking allowed immunosuppressive drugs, study participant must be on stable doses during defined time periods prior to Baseline (Day 1)
-Study participant has a documented history of low platelet count (less than 30x10^9/L) prior to Screening
-Study participant has a platelet count measurement at Screening and at Baseline (Day 1) with an average of the two less than 30x10^9/L and no single count may be greater than 35x10^9/L (using local laboratories)
-Study participant has a current or history of a peripheral blood smear consistent with ITP
-Study participants may be male or female:
a. A male participant must agree to use contraception during the Treatment Period and for at least 3 months after the final dose of study treatment and refrain from donating sperm during this period
b. A female participant is eligible to participate if she is not pregnant as confirmed by a negative serum pregnancy test or not planning to get pregnant during the participation in the study, not breastfeeding, and at least one of the following conditions applies:
Not a woman of childbearing potential (WOCBP)
OR
A WOCBP who agrees to follow the contraceptive guidance during the Treatment Period and for at least 3 months after the dose of study treatment

Exclusion criteria

-Participant has a history of arterial or venous thromboembolism (eg, stroke, transient ischemic attach, myocardial infarction, deep vein thrombosis or pulmonary embolism) within the 6 months prior to randomization or requires anticoagulant treatment
-Study participant has clinically significant bleeding that warrants immediate platelet adjustment (eg, menorrhagia with significant drop in hemoglobin)
-Study participant has a known hypersensitivity to any components of the investigational medicinal product (IMP) or comparative drugs (and/or an investigational device) as stated in this protocol
-Study participant has evidence of a secondary cause of immune thrombocytopenia from the past medical history (eg, bacterial or viral infection, past medical history of leukemia, lymphoma, common variable immunodeficiency, systemic lupus erythematosus, autoimmune thyroid disease) or to drug treatments (eg, heparin, quinine, antimicrobials, anticonvulsants) or participant has a multiple immune cytopenia, eg, Evan*s syndrome
-Study participant has a clinically relevant active infection (eg, sepsis, pneumonia, or abscess) in the opinion of the investigator, or had a serious infection (resulting in hospitalization or requiring parenteral antibiotic treatment) within 6 weeks prior to the dose of IMP
-Study participant with a known tuberculosis (TB) infection, at high risk of acquiring TB infection, or latent tuberculosis infection (LTBI), or current/history of nontuberculous mycobacterial infection (NTMBI)
-Study participant has a history of a major organ transplant or hematopoietic stem cell/marrow transplant
-Study participant has experienced intracranial bleed in the last 6 months prior to the Screening Visit
-Study participant has a history of coagulopathy disorders other than ITP
-Study participant has a Karnofsky Performance Status rating less than60% at the Screening Visit
-Study participant with current or medical history of immunoglobulin A (IgA) deficiency, or a measurement of IgA less than 50 mg/dL at the Screening Visit
-Study participant has undergone a splenectomy in the 2 years prior to the Baseline Visit

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	rozanolixizumab

Ethics review

Approved WMO Date:	03-03-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-05-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

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	EUCTR2019-003451-11-NL
ClinicalTrials.gov	NCT04224688
CCMO	NL72633.028.20