A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study with an Open-Label Extension to Evaluate the Efficacy and Safety of Oral Rilzabrutinib (PRN1008) in Adults and Adolescents with Persistent or Chronic Immune Thrombocytopenia (ITP)

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Primary Efficacy Objective (Blinded Treatment Period)• To demonstrate the efficacy of rilzabrutinib versus placebo in participants with refractory/relapsed ITP, based on the durability of platelet response during the last12 weeks of the 24-week...

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

Summary

ID

NL-OMON53830

Source
ToetsingOnline

Brief title
LUNA 3

Condition

- Platelet disorders
- Autoimmune disorders

Synonym
ITP, platelet disorder

Research involving
Human

Sponsors and support

Primary sponsor: Principia Biopharma, Inc.
Source(s) of monetary or material Support: Sponsor funding

Intervention

Keyword: Immune Thrombocytopenia

Outcome measures

Primary outcome

Primary Efficacy Endpoint (Blinded Treatment Period)

• Durable platelet response defined as a proportion of participants able to achieve platelet counts at or above 50,000/µL for >= two-thirds of at least 8 non-missing weekly scheduled platelet measurements during the last 12 weeks of the 24 week blinded treatment period in the absence of rescue therapy, provided that at least 2 non-missing weekly scheduled platelet measurements are at or above 50,000/µL during the last 6 weeks of the 24-week blinded treatment period; see Appendix 10.7 for country specific definition of durable platelet response (EU [EEA countries] and UK).

Secondary outcome

Key Secondary Efficacy Endpoints (Blinded Treatment Period)

• Number of weeks with platelet count >=50,000/µL OR between >=30,000/µL and <50,000/µL and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy

• Number of weeks with platelet counts >=30,000/µL and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy

• Time to first platelet count of >=50,000/µL OR between >=30,000/µL and <50,000/µL and doubled from baseline

• Proportion of participants requiring rescue therapy during the 24-week blinded treatment period

• Change from baseline on Item 10 of the ITP-PAQ (ie, physical fatigue) in adult participants (>=18 years) at Week 13

See Appendix 10.7 for EU (EEA countries) and UK specific requirements.

Other Secondary Endpoints

Efficacy Endpoint

• Stability of response defined as the proportion of participants able to achieve stable platelet response, which is defined as no 2 scheduled visits, at least 4 weeks apart, with a platelet count less than 50,000/µL, without an intervening visit with a platelet count >=50,000/µL, within a period of 24 weeks following initial achievement of the platelet response (initial platelet response defined as platelet count >=50,000/µL within 12 weeks of initiation of treatment with rilzabrutinib during the study)

Safety Endpoints

• Frequency and severity of TEAEs

• Frequency and severity of bleeding TEAEs

• Change from baseline in physical examination, ECG, vital signs and clinical

laboratory tests results: serum chemistry and hematology (except for platelet

counts included in the primary efficacy endpoint)

Pharmacokinetic Endpoints

• Plasma concentrations of rilzabrutinib

Quality of Life (QOL) Endpoints

• Change from baseline on the Symptoms, Bother and Activity domains of the ITP

Patient Assessment Questionnaire (ITP-PAQ) in adult participants (>=18 years)

• Change from baseline in disease-specific QoL as measured by the Kids* ITP

Tools (ITP-KIT) score in pediatric participants

Study description

Background summary

Immune Thrombocytopenia (ITP) is characterized by autoantibody-mediated destruction of platelets and impaired platelet production, which result in thrombocytopenia and a predisposition to bleeding associated with morbidity and mortality.
In general, pharmacotherapy (corticosteroids [CSs], intravenous immunoglobulin [IVIg] or Anti D) is used for symptomatic patients with low platelet counts for reducing platelet destruction. While a majority of patients respond initially to CSs, the rate of continued remission is low. Second line therapies include rituximab and splenectomy and are associated with risk of sepsis and immune suppression. Thrombopoietin (TPO) mimetics (Bussel 2007) are approved for the treatment of patients with chronic ITP who have not had sufficient responses to CSs, IVIg, or splenectomy. Second-line treatment with TPO-RAs have a clinical response rate of 80%, however approximately one third of patients discontinue TPO-RAs due to lack of response (Ghanima 2019). Novel, safe and effective, oral treatments to maintain platelet counts in this setting would be a significant therapeutic advantage. Thus, there remains a high unmet medical need for novel, safe and effective oral therapies for ITP.

A BTK inhibitor such as rilzabrutinib has the potential to target multiple pathways and cell types involved in inflammation and autoimmunity.
There is preliminary evidence to support the role of BTK inhibition in patients with autoimmune cytopenias (Rogers 2016, Montillo 2017), where sequential

episodes of severe autoimmune hemolytic anemia and ITP ceased after initiation of treatment with ibrutinib, a BTK/epidermal growth factor receptor /interleukin-2-inducible T-cell kinase inhibitor, in patients with chronic lymphatic leukemia (CLL).
Preliminary review of data from patients with ITP (Study PRN1008-010 Part A) demonstrated a potentially favorable platelet response in the patient population and in patients who received the 400 mg BID dose of rilzabrutinib. Participants that failed multiple treatments for ITP were able to achieve a rapid and durable platelet response.

Study objective

Primary Efficacy Objective (Blinded Treatment Period)
• To demonstrate the efficacy of rilzabrutinib versus placebo in participants with refractory/relapsed ITP, based on the durability of platelet response during the last
12 weeks of the 24-week blinded treatment period in the absence of rescue therapy

Key Secondary Efficacy Objectives (Blinded Treatment Period)
• To evaluate the effect of rilzabrutinib versus placebo on the number of weeks with platelet count >=50,000/µL OR between >=30,000/µL and <50,000/µL and at least doubled
from baseline, over the 24-week blinded treatment period in the absence of rescue therapy
• To evaluate the effect of rilzabrutinib versus placebo on the number of weeks with platelet counts >=30,000/µL and at least doubled from baseline over the 24-week blinded
treatment period in the absence of rescue therapy
• To evaluate the effect of rilzabrutinib versus placebo on the time to first platelet count of >=50,000/µL OR between >=30,000/µL and <50,000/µL and at least doubled from baseline
• To evaluate the effect of rilzabrutinib versus placebo on the proportion of participants requiring rescue therapy
• To evaluate the effect of rilzabrutinib versus placebo on the change from baseline on Item 10 of the ITP-PAQ (ie, physical fatigue) in adult participants (>=18 years) at Week 13

Study design

This is a global, randomized, parallel-group, double-blind, multicenter clinical study in patients with primary ITP who had a response to either intravenous immunoglobulin (IVIg) or corticosteroid (CS) that was not sustained. After providing informed consent, participants will enter a 28-day screening period. Upon completion of the screening period, participants who satisfy all the inclusion criteria and none of the exclusion criteria of this protocol will

be randomized in a 2:1 allocation ratio to one of two study arms: rilzabrutinib or placebo.
Randomization will be carried out separately for the two age groups. For the adult group, stratified permuted block randomization will be implemented; for the pediatric group, dynamic randomization algorithm (minimization) will be implemented. The factors used for stratification (for adults) or balance (for pediatric participants) are splenectomy status (yes/no), and by severity of thrombocytopenia (Inclusion Criteria 3 platelet counts <15,000/µL or >=15,000/µL).
After randomization, participants will start a blinded treatment period of up to 24 weeks followed by an open-label period of 28 weeks during which all participants will receive rilzabrutinib, and then a 4 week safety follow-up period or long-term extension.

At the end of 12 weeks of treatment, participants will be assessed for achieving a platelet response defined as:
a) platelet count of >=50,000/µL OR a platelet count between >=30,000/µL and <50,000/µL and at least doubled from baseline at any time during the first 12 weeks and
b) absence of rescue medication in the 4 weeks prior to the elevated platelet count that meets platelet response criteria.
Figure 1 depicts the decision process for assessing response. Baseline is defined as the average of all the participant*s predose platelet counts (Screening and Study Day 1).
• Participants who respond will continue the blinded treatment period for a total of 24 weeks before entering the open label period.
• Participants who do not respond (including participants who receive rescue medication after 8 weeks of treatment) may discontinue from the study or enter the 28-week open label period at the end of Week 12, receiving treatment with 400 mg twice daily (BID) of rilzabrutinib. The initial study medication assignment will remain blinded.

Concomitant ITP medications (an oral CS and/or a thrombopoietin receptor agonist [TPO RA]) will be permitted in both treatment arms and must be maintained at stable doses from 14 days before Study Day 1 until the last dose of study medication. Reductions in the doses of concomitant ITP medications will be permitted for associated safety concerns only.
The use of rescue medications (one of IVIg, high-dose CSs, platelet infusion, or anti-D immunoglobulin infusion) intended to increase platelet counts or prevent bleeding when platelet counts are less than 20,000/µL, or for bleeding or wet purpura, will be allowed.
After completing the open label period, participants who demonstrate a platelet response defined as platelet counts >=50,000/µL or >=30,000/µL and at least doubled from baseline at >=50% of the visits without receiving rescue therapy while on treatment during the last 8 weeks of the open label period, will be allowed to enter the LTE.

Participant(s) may continue in the LTE until:
a) The participant is no longer responding (platelet counts <30,000/µL or less than 20,000/µL above baseline on two consecutive visits)
b) The drug is no longer being developed by the Sponsor for ITP
c) The program is stopped for safety reasons or
d) The drug becomes commercially available in the participant*s country.

Safety Measures Due to COVID-19 Pandemic
Due to the COVID-19 pandemic, safety measures have been implemented to ensure continued supply of study medication and safety monitoring for participants. These measures are described in the *Guidelines to Sites for Delayed Participant Visits or Missed Visits due to travel restrictions and any foreseeable impacts of COVID-19.* When the COVID-19 pandemic resolves, the measures will be repealed back to the previous state as government rules and benefit/risk assessment allow.

Intervention

Participants will receive one 400 mg tablet of rilzabrutinib or placebo BID in the double-blind portion of the study. Participants will receive one 400 mg tablet of rilzabrutinib BID in the open label portion of the study and the LTE. Tablets should be taken with (~8oz/250mL) of water and may be taken with or without food.

Study burden and risks

Overall Risk-Benefit Assessment
Based on the review of the cumulative data, there are no important identified risks for rilzabrutinib. There are adverse events that have been reported during the administration of other drugs from the same therapeutic class (BTK inhibitors) as rilzabrutinib, but primarily for oncologic indications including B-cell malignancies (Lipsky 2020). Taken together, it is postulated that there is a low probability of occurrence of the above-mentioned *BTK inhibitor class* adverse events during the administration of rilzabrutinib.
ITP is associated with an increased risk of mortality due to bleeding, thrombosis, and reduced quality of life (QoL) (Trotter and Hill 2018). The disease burden is more significant in patients with severe and chronic thrombocytopenia and those who are unresponsive to current therapy. Patients with such severe thrombocytopenia have a high risk of hemorrhage which increases with age. Intracranial hemorrhage is the major cause of death which is reported to occur in 1.5% of adult patients (Neunert et al 2015). Besides the high risk of bleeding, patients with chronic ITP experience significant fatigue, cognitive impairment, fear of bleeding and a negative impact on social and work activities (Frith et al 2012; Trotter and Hill 2018). Treatment with rilzabrutinib may induce durable platelet response in patients not responsive to prior therapies.

The safety of rilzabrutinib to date, and the resulting benefit risk balance profile, supports the continued investigation in patients with ITP. The adverse events seen with other BTK inhibitors (bleeding, cytopenia, atrial fibrillation) will be closely monitored.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

Patients may be included in the study if ALL of the following criteria are met:
1. Patients will be male and female with primary ITP with duration of >6 months in pediatric participants aged 12 to <18 years (pediatric participants aged 10 to <12 years will be enrolled in the EU [EEA countries] only; refer to Appendix

10.2, Appendix 10.3 and Appendix 10.7 for country-specific requirements) and duration of >3 months in adults aged >=18 years
2. Patients who had a response (achievement of platelet count >=50,000/µL) to IVIg/anti-D or CSs that was not sustained and who have documented intolerance, insufficient response or any contra-indication to any appropriate courses of standard of care ITP therapy
3. An average of 2 platelet counts at least 5 days apart of <30,000/µL during the screening period, and no single platelet count >35,000/µL within 14 days prior to the first dose of study drug
• Pediatric participants must additionally be determined to need treatment for ITP as per clinical assessment by the Investigator (see Appendix 10.7 for EU [EEA countries] specific requirements).
4. Adequate hematologic, hepatic, and renal function (absolute neutrophil count >=1.5 X 10^9/L, AST/ALT <=1.5 x upper limit of normal [ULN], albumin >=3 g/dL, total bilirubin <=1.5 x ULN [unless the participant has documented Gilbert syndrome], glomerular filtration rate >50 [Cockcroft and Gault method])
5. Hemoglobin >9 g/dL within 1 week prior to Study Day 1
6. All contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies
A) Male participants
Male participants are eligible to participate if they agree to the following during the intervention period and for at least 13 weeks after the last administration of study intervention:
• Refrain from donating or cryopreserving sperm
Plus either:
- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
OR
- Must agree to use contraception/barrier as detailed below
- A male condom; the participant should also be advised of the benefit for a female partner to use a highly effective method of contraception (as described in Appendix 13 Contraceptive and barrier guidance of the protocol) as a condom may break or leak when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant
B) Female participants
A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
• Is a woman of nonchildbearing potential (WONCBP) as defined in Appendix 13 of the protocol.
OR
• Is a woman of childbearing potential (WOCBP) and agrees to use a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, as described in Appendix 13 of the protocol, during the study intervention period (to be effective before starting the intervention) and for at least 4 weeks after the last administration of study

intervention AND agrees not to donate or cryopreserve eggs (ova, oocytes) for the purpose of reproduction during this period.
• A WOCBP must have a negative highly sensitive pregnancy test (serum) as required by local regulations) within 3 days before the first administration of study intervention
- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from
participation if the serum pregnancy result is positive.
7. Patients must be able to provide written informed consent or informed assent with corresponding informed consent obtained from the participant*s guardian and agree to the schedule of assessments.

Exclusion criteria

Patients will be excluded from the study if any of the following criteria are met:
1. Patients with secondary ITP
2. Pregnant or lactating women
3. Electrocardiogram (ECG) findings for participants:
o Aged >=10 and <16 years: QTcF >449 msec (males) or >457 msec (females)
o Aged >=16 and <18 years: QTcF >450 msec (males) or >460 msec (females)
o Aged >=18 years, of QTcF >450 msec (males) or >470 msec (females), poorly controlled atrial fibrillation (ie, symptomatic participants or a ventricular rate above 100 beats/min on ECG), or other clinically significant abnormalities
4. History (within 5 years of Study Day 1) or current, active malignancy requiring or likely to require chemotherapeutic or surgical treatment during the study, with the exception of non-melanoma skin cancer
5. Transfusion with blood, blood products, plasmapheresis, or use of any other rescue medications with intent to increase platelet count within 14 days before Study Day 1
6. Change in CS and/or TPO-RA dose within 14 days prior to Study Day 1 (more than 10% variation from current doses)
7. Immunosuppressant drugs other than CSs within 5 times the elimination half-life of the drug or 14 days of Study Day 1, whichever is longer
8. Treatment with rituximab or splenectomy within the 3 months prior to Study Day 1
- Patients treated with rituximab will have normal B-cell counts prior to enrollment
9. Ongoing need for the use of proton pump inhibitor drugs such as omeprazole and esomeprazole (it is acceptable to change participant to histamine 2 receptor blocking drugs prior to Study Day 1)
10. Use of known strong-to-moderate inducers or inhibitors of CYP3A within 14 days or 5 half-lives (whichever is longer) of Study Day 1 and until the end of the active treatment period

11. Planned or concomitant use of any anticoagulants and platelet aggregation inhibiting drugs such as aspirin (except for low dose aspirin up to 100 mg per day), nonsteroidal
anti-inflammatory drugs, and/or thienopyridines within 14 days of Study Day 1 and until the end of the active treatment period
12. Has received any investigational drug within the 30 days before receiving the first dose of study medication, or at least 5 times elimination half-life of the drug (whichever is longer); participant should not be using an investigational device at the time of dosing
o Patients who previously received treatment with Bruton*s Tyrosine Kinase (BTK) inhibitors (except rilzabrutinib) within 30 days before the first dose of study drug are not
eligible
o Patients who previously received rilzabrutinib at any time are not eligible
13. Current drug or alcohol abuse
14. Refractory nausea and vomiting, malabsorption, external biliary shunt, significant bowel resection, or any other condition that would preclude adequate study drug absorption
15. History of solid organ transplant
16. Positive at Screening for human immunodeficiency virus (HIV), hepatitis B virus (HBV) (surface and core antibodies unrelated to vaccination), or hepatitis C virus (anti-HCV antibody confirmed with Hep C RNA)
o Patients who are hepatitis B virus surface antigen (HBsAg) positive will not be eligible.
o Patients who are HBsAg negative and hepatitis B core antigen antibody (HBcAb) positive will be tested for HBV surface antibody (HBsAb) and HBV DNA. If HBV DNA is
negative and HBsAb titer is >=100 IU/L, patients may be enrolled. Monthly HBV DNA monitoring will be required while on treatment and for 6 months after the last dose of the
study drug. Positive HBV DNA results will be managed appropriately as per local standard of care.
o Patients who are HBcAb positive and HBsAg negative with HBsAb titer <100 IU/L or negative, are not eligible.
17. Positive QuantiFERON®-TB Gold, or QuantiFERON®-TB Gold Plus (QFT Plus) at Screening unless all of the following 3 conditions are true (see Appendix 10 country-specific requirements):
a) Chest X-ray does not show evidence suggestive of active tuberculosis (TB) disease
b) There are no clinical signs and symptoms of pulmonary and/or extra-pulmonary TB disease
c) Documented receipt of one of the following prophylactic treatment regimens:
i. Oral daily Isoniazid for 6 months or
ii. Oral daily Rifampin for 4 months or
iii. Isoniazid and Rifapentine weekly for 3 months (3HP)
On a case-by-case basis, after discussion and approval by the Sponsor, a local TB test that is negative and is considered equivalent to 1 of the above tests

may be used for eligibility. For example, if a QuantiFERON®-TB Gold, or QuantiFERON-TB Gold Plus (QFT Plus) is indeterminate for any reason and a local blood test or T-Spot® TB test is negative, the patient may be enrolled using the local result upon approval of the Sponsor.
18. History of recurring (2 or more) serious infections requiring intravenous antibiotic, antivirals or antifungals therapy within the last 3 months before Study Day 1 or active serious or moderate infection ongoing on the day of randomization
19. Myelodysplastic syndrome
20. Live vaccine within 28 days prior to Study Day 1 or plan to receive one during the study
21. Planned surgery in the time frame of the dosing period
22. Any other clinically significant disease, condition, or medical history that, in the opinion of the Investigator or Sponsor*s medical monitor, would interfere with participant safety, study evaluations, and/or study procedures
23. Positive SARS-CoV-2 molecular test (if COVID-19 testing required per local guidelines to be determined for each site)
24. COVID-19 vaccine within 14 days prior to Study Day 1 or planned during the last 12 weeks of the blinded treatment period

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:	Recruitment stopped
Start date (anticipated):	30-08-2023
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Rilzabrutinib
Generic name:	Rilzabrutinib

Ethics review

Approved WMO Date:	02-03-2023
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-04-2023
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-07-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2020-002063-60-NL
ClinicalTrials.gov	NCT04562766
CCMO	NL83147.078.23