An Adaptive, Open-Label, Dose-Finding, Phase 1/2 Study Investigating the Safety, Pharmacokinetics, and Clinical Activity of Rilzabrutinib (PRN1008), an Oral BTK Inhibitor, in Patients with Relapsed Immune Thrombocytopenia

Published: 05-02-2019
Last updated: 07-09-2024

This study has been transitioned to CTIS with ID 2023-509397-39-00 check the CTIS register for the current data. Part A: Safety:• To characterize the safety and tolerability of up to four dose levels of rilzabrutinibin patients with ITPEfficacy:• To...

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

Summary

ID

NL-OMON52638

Source
ToetsingOnline

Brief title
PRN1008-010

Condition

- Platelet disorders

Synonym
Immune Thrombocytopenic Purpura (ITP), low platelets

Research involving

Human

Sponsors and support

Primary sponsor: Principia Biopharma, a Sanofi Company
Source(s) of monetary or material Support: Industry;payed by the sponsor

Intervention

Keyword: BTK inhibitor, Immune thrombocytopenic purpura, Open-label, PRN1008-010

Outcome measures

Primary outcome

Outcome Measures of the Study: Part A

Primary Safety Endpoints

Safety will be assessed by the incidence, severity, and relationship of TEAEs,

including

clinically significant changes in physical examination, laboratory tests, and

vital signs.

Treatment-emergent adverse events in the post treatment follow-up period will

also be assessed

and examined for possible relationship to the prior rilzabrutinib treatment.

Adverse events (AEs)

will be categorized as treatment emergent after the first dose of rilzabrutinib

has been received.

Primary Efficacy Endpoint

Proportion of patients able to achieve platelet counts >=50,000/µL on at least 8

out of the last 12 weeks of the 24-week treatment period without the use of

rescue medication.

Outcome Measures of the Study: Part B

Primary Safety Endpoints

Safety will be assessed by the incidence, severity, and relationship of TEAEs, including

clinically significant changes in physical examination, laboratory tests, and vital signs. Bleeding

TEAEs will be tabulated and a proportion of patients with a Grade 2 or higher bleeding event

will be provided.

Primary Efficacy Endpoint

Proportion of patients able to achieve platelet counts >=50,000/µL on at least 8 out of the last

12 weeks of the 24-week treatment period without the use of rescue medication after 10 weeks

of active treatment.

Secondary outcome

Secondary Endpoints

Safety Endpoints

In addition, safety will be assessed by the following endpoints,

• Proportion of patients receiving rescue medication at each dosing level and overall

• Proportion of patients with a Grade 2 or higher bleeding event at each dosing level

and overall

• Bleeding scale (ITP-BAT) at the end of treatment period for each dosing level

Efficacy Endpoints

Part A:

• Percent of weeks with platelet counts >= 50,000/µL by dose level and overall

• Proportion of patients with 4 out of the final 8 platelet counts >= 50,000/µL

across all

dose levels

• Change from baseline to the average of the post Day 1 platelet counts by dose

level and

overall for patients who had >4 weeks of study drug on that given dose level

• Number of weeks with platelet counts >= 50,000/µL across all dose levels

• Number of weeks with platelet counts >= 30,000/µL across all dose levels

• Time to first platelet count >= 50,000/µL across all dose levels

Part B:

• Number of weeks with platelet count >=50,000/µL OR >=30,000/µL and doubling the

baseline in the absence of rescue therapy (platelet counts will be censored for

4 weeks

after the use of rescue medication, if given)

• Proportion of all treated patients able to achieve two or more consecutive

platelet counts,

separated by at least 5 days, of >=50,000/µL AND an increase of platelet count

of >=20,000/µL from baseline without use of rescue medication in the 4 weeks

prior to the

latest elevated platelet count

• Number of weeks with platelet counts >= 30,000/µL and doubling from baseline

over the

24-week treatment period (platelet counts will be censored for 4 weeks after

the use of

rescue medication, if given)

• Proportion of patients receiving rescue medication

• Change from baseline in ITP Bleeding Assessment Tool (ITP-BAT)

Study description

Background summary

Rilzabrutinib is a high-affinity, inhibitor of BTK. Pertinent to the treatment of ITP, Rilzabrutinib treatment in profoundly inhibited human B cell activation and blocked antibody- (IgG, IgE) mediated activation of immune cells via Fc receptor signaling. In nonclinical studies, Rilzabrutinib demonstrated a significant dose-dependent reduction of platelet-loss in a mouse model of immune thrombocytopenia. Rilzabrutinib also showed rapid and significant anti-inflammatory effects in rat collagen-induced arthritis model, rat antibody-mediated arthus model, and spontaneous canine pemphigus disease.

The proposed study is a dose-finding study that uses an intrapatient dose-escalation design to explore a range of potential biologically active doses within each patient, starting with an expected *no effect dose.* This design allows for evaluation of a full range of potentially active doses in all patients in the study and accounts for the biological variation in response in each patient. Compared to a parallel dose-response study, this design will expose fewer patients to ineffective dose levels and is appropriate to the planned population. The dose-finding portion of the study (Part A) is complete and all newly-admitted patients are initiating active treatment at the recommended dose of 400 mg rilzabrutinib twice daily (B.I.D.)

Study objective

This study has been transitioned to CTIS with ID 2023-509397-39-00 check the CTIS register for the current data.

Part A:

Safety:

• To characterize the safety and tolerability of up to four dose levels of rilzabrutinib
in patients with ITP
Efficacy:
• To explore the clinical activity of up to four dose levels of rilzabrutinib
in relapsed/refractory patients with ITP
• To identify a potential dose regimen to use in future studies of rilzabrutinib in
patients with ITP
Pharmacokinetics:
• To characterize the pharmacokinetics of rilzabrutinib in patients with ITP
Exploratory:
• To explore effect of rilzabrutinib on platelet autoantibody levels
• To explore effect of rilzabrutinib on markers of hemolysis
• To explore effect of rilzabrutinib on thrombopoietin (TPO) levels
• To explore effect of rilzabrutinib on quality of life (QOL) using the Euro-QoL 5-Dimension Visual Analog Scale (EQ-5D VAS)
• To characterize plasma metabolites of rilzabrutinib

Part B:
Safety:
To characterize the safety and tolerability of the selected dose of 400 mg BID of rilzabrutinib in patients with ITP
Efficacy:
• To further explore the clinical activity and durability of response of the selected dose
of 400 mg BID of rilzabrutinib in patients with ITP who have relapsed or have an insufficient response to prior therapies
• To evaluate the predictive value of platelet response to rilzabrutinib therapy in the
first 8 weeks of active treatment for the achievement of the primary endpoint
Pharmacokinetics:
• To characterize the pharmacokinetics of rilzabrutinib in patients with ITP
Exploratory:
• To explore effect of rilzabrutinib on markers of hemolysis
• To explore effect of rilzabrutinib on thrombopoietin (TPO) levels
• To explore effect of rilzabrutinib on IgG, IgG1, IgG4, IgM, IgE levels
• To explore effect of rilzabrutinib on quality of life (QOL) using the EQ-5D VAS
and Immune Thrombocytopenic Purpura Patient Assessment Questionnaire (ITP-PAQ)

Study design

This is an adaptive, open-label, dose-finding study of rilzabrutinib in patients with ITP who are refractory or relapsed with no available and approved therapeutic options, with a platelet count <30,000/µL on two counts no sooner than 7 days apart in the 15 days before treatment begins.
The active treatment period is 24 weeks and the post-treatment follow-up period is 4 weeks.

Intervention

Part A:
PRN1008 100 mg, 300 mg and 400 mg tablets. Tablets should be taken with a glass (~8 oz.) of water and may be taken with or without food.
Part B:
PRN1008 400 mg tablets. Tablets should be taken with a glass (~8 oz.) of water and may be taken with or without food.

Study burden and risks

Possible risks / burden related to the IMP:

Possible Adverse Events (AE) such as diarrhea or *loose stools*, nausea, abdominal distension, vomiting, abdominal discomfort, lab abnormalities, headache, abdominal pain or bloating, change in immune system and allergic reaction risks

Possible risks / burden associated with blood collection:

Discomfort, pain, irritation, infection, light-headedness or fainting, a feeling of weakness accompanied by sweating, slowing of heart beat, and a decrease in blood pressure.

Contacts

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US
Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Part A
Inclusion Criteria:
1. Male or female patients, aged 18 to 80 years old (Czech Republic and Norway only: 18 to 65 years old)
2. Immune-related ITP (both primary and secondary)
3. Refractory or relapsed patients with no available and approved therapeutic options
with a platelet count of <30,000/µL on two occasions no less than 7 days apart in
the 15 days prior to beginning study treatment.
4. A history of response (two or more platelet counts >=50,000/µL with an increase
of at least 20,000/µL) to at least one prior line of therapy (with splenectomy being
considered a line of therapy)
5. Adequate hematologic, hepatic, and renal function (absolute neutrophil count >=1.5 × 109/L, hemoglobin [Hgb] >9 g/dL, AST/ALT <=1.5 × ULN, albumin >=3 g/dL, total bilirubin <=1.5 × ULN, estimated glomerular filtration rate [eGFR] > 60 mL/min (Cockcroft and Gault method) (C1D1 pre-dose may be checked up to Day -3 prior to C1D1)
6. Female patients who are of reproductive potential must agree for the duration of
active treatment in the study to use a highly effective means of contraception (hormonal contraception methods that inhibits ovulation, intrauterine device,

intrauterine hormone-releasing system, bilateral tubal ligation, vasectomized partner, or true abstinence; when this is in line with the preferred and usual lifestyle of the patient). Unless surgically sterile, postmenopausal females should
have menopause confirmed by follicle-stimulating hormone (FSH) testing.
7. Able to provide written informed consent and agreeable to the schedule of assessments
Part B
Inclusion Criteria:
1. Male or female patients, aged 18 to 80 years old
2. Patients with immune-related ITP (both primary and secondary) as defined by current guidelines with at least 3 months duration
3. Patients who had a response (achievement of platelet count >=50,000/µL) to IVIg/anti-D or corticosteroid that was not sustained and failed at least one other
ITP therapy (that was not IVIg or corticosteroid 4. Patients with a platelet count of <30,000/µL on two occasions no less than 7 days
apart in the 15 days before treatment begins, and no platelet count above 35,000/µL on Study Day 1.
5. Patients with adequate hematologic, hepatic, and renal function (absolute neutrophil count >=1.5 × 109/L, Hgb >9 g/dL, AST/ALT <=1.5 × ULN, albumin >=3 g/dL, total bilirubin <=1.5 × ULN, eGFR >50 mL/min (Cockcroft and Gault method) (pre-dose may be checked up to Day -3)
6. Female patients who are of reproductive potential must agree for the duration of active treatment in the study to use a highly effective means of contraception
(hormonal contraception methods that inhibits ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal ligation, vasectomized partner, or true abstinence; when this is in line with the preferred and usual lifestyle of the patient). Unless surgically sterile, postmenopausal females should
have menopause confirmed by FSH testing.
7. Able to provide written informed consent and agreeable to the schedule of assessments

Exclusion criteria

Part A:
Exclusion Criteria:
1. Pregnant or lactating women
2. ECG findings of QTcF >450 msec (males) or >470 msec (females), poorly controlled atrial fibrillation (i.e., symptomatic patients or a ventricular rate above
100 beats/min on ECG), or other clinically significant abnormalities 3. History of current, active malignancy requiring or likely to require

chemotherapeutic or surgical treatment during the trial, with the exception of non-melanoma skin cancer
4. Transfusion with blood or blood products or plasmapheresis within 2 weeks before
Day 1
5. Change in corticosteroid and/or TPO agonist dose within 2 weeks prior to Day 1
(more than 10% variation from Day 1 daily doses)
6. Use of rescue medications other than corticosteroids or TPO in Exclusion Criterion
#5 in the two weeks before Day 1
7. Immunosuppressant drugs other than corticosteroids - these drugs should be discontinued for at least 14 days before Day 1
8. Treatment with rituximab or splenectomy within the 3 months prior to Day 1
9. Ongoing need for the use of proton pump inhibitor drugs such as omeprazole and esomeprazole (it is acceptable to change patient to H2 receptor blocking drugs
prior to Day 1)
10. Concomitant use of known strong-to-moderate inducers or inhibitors of CYP3A within 3 days or 5 half-lives (whichever is longer) of Day 1
11. Use of CYP3A-sensitive substrate drugs with a narrow therapeutic index within
3 days or 5 half-lives (whichever is longer) of study drug dosing including, but not
limited to, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or terfenadine
12. Planned or concomitant use of any anticoagulants and platelet aggregation inhibiting drugs such as aspirin, non-steroidal anti-inflammatory drugs (NSAIDs),
thienopyridenes (within 14 days of planned dosing through end of follow-up)
13. 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); patient should not be using an investigational device at the
time of dosing
14. Current drug or alcohol abuse
15. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate study drug absorption
16. History of solid organ transplant
17. Positive screening for human immunodeficiency virus (HIV), hepatitis B (surface
antigen and core antibodies unrelated to vaccination), or hepatitis C (anti-HCV antibody confirmed with HCV RNA)
18. History of serious infections requiring intravenous therapy within the last 3 months
before Day 1

19. Clinically significant cognitive dysfunction (>= Grade 1) or medical history suggestive of increased risk for cognitive dysfunction during the study
20. Live vaccine within 28 days prior to 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, would interfere with patient safety, study evaluations,
and/or study procedures
Part B
1. Pregnant or lactating women
2. ECG findings of QTcF >450 msec (males) or >470 msec (females), poorly controlled atrial fibrillation (i.e., symptomatic patients or a ventricular rate above
100 beats/min on ECG), or other clinically significant abnormalities
3. History (within 5 years of SD1) or current, active malignancy requiring or likely to
require chemotherapeutic or surgical treatment during the trial, with the exception
of non-melanoma skin cancer
4. Transfusion with blood, blood products, IVIg, or plasmapheresis within 2 weeks
before SD1
5. Change in corticosteroid and/or TPO agonist dose within 2 weeks prior to SD1 (more than 10% variation)
6. Use of rescue medications in the 4 weeks before SD1
7. Treatment with immunosuppressant drugs other than corticosteroids within 2 weeks prior to SD1
8. Treatment with rituximab or splenectomy within the 3 months prior to SD1
• Patients treated with rituximab within 6 months from screening 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 patient to H2 receptor blocking drugs
prior to SD1)
10. Concomitant use of known strong-to-moderate inducers or inhibitors of CYP3A within 3 days or 5 half-lives (whichever is longer) of SD1
11. Use of CYP3A-sensitive substrate drugs with a narrow therapeutic index within
3 days or 5 half-lives (whichever is longer) of study drug dosing including, but not
limited to, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or terfenadine
12. Planned or concomitant use of any anticoagulants and platelet aggregation inhibiting drugs such as aspirin with the exception of up to 100 mg/day doses, NSAIDs, thienopyridenes (within 2 weeks of planned dosing through end of

follow-up)
13. 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); patient should not be using an investigational device at the
time of dosing • Patients who previously received treatment with BTK inhibitors within
30 days before receiving the first dose of study medication or who have previously received rilzabrutinib are not eligible for the study
14. Current drug or alcohol abuse
15. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate study drug absorption
16. History of solid organ transplant
17. Positive at screening for HIV, hepatitis B (surface antigen, core antibodies),
or hepatitis C (anti-HCV antibody confirmed with HCV RNA).
• Patients who are HBV surface antigen (HBsAg) positive will not be eligible.
• Patients who are HBsAg negative and HBV core 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.
• Patients who are HBcAb positive, HBsAg negative with HBsAb titer <100 IU/L or negative, are not eligible.
18. History of recurring (2 or more) serious infections requiring intravenous antibiotic
therapy within the last 3 months before SD1 or active serious or moderate infection ongoing on the day of the planned first dose of study drug
19. Myelodysplastic syndrome
20. Live vaccine within 28 days prior to SD1 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, would interfere with patient safety, study evaluations,
and/or study procedures

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-02-2020
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Rilzabrutinib (PRN1008)
Generic name:	Rilzabrutinib (PRN1008)

Ethics review

Approved WMO Date:	05-02-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-05-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	16-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-09-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-09-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-03-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-03-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-09-2020

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-10-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-02-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-04-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-04-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-05-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-11-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-11-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	08-02-2023
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
EU-CTR	CTIS2023-509397-39-00
EudraCT	EUCTR2017-004012-19-NL
CCMO	NL68745.078.19
Other	PRN1008-010 (DFI17124)