Health Technology Briefing
November 2023

Rilzabrutinib for treating persistent or chronic immune thrombocytopenia

Company/Developer	Sanofi

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 30538	NICE ID: Not available	UKPS ID: 666468

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Rilzabrutinib is currently in clinical development for the treatment of persistent or chronic immune thrombocytopenia (ITP) in adult. ITP is an auto-immune disease that arises when the body's immune system attacks platelet cells resulting in a decreased number of platelets (platelet count) and impairs platelet production. Platelets are a specialised type of blood cell that help blood to clot following damage to a blood vessel wall so if there is a decreased platelet count there is an increased risk of frequent bleeding or severe bleeding. This results in the symptoms associated with ITP such as petechial (pin prick rash of blood spots), bruising, nosebleeds, gum bleeds, fatigue and heavy periods. Despite the range of available therapies, a need remains for safer therapy that results in durable increases in platelet count, eliminates related long-term toxic effects, and improves quality of life.

Rilzabrutinib is given as an oral tablet that works by blocking the activity of an enzyme called Bruton's tyrosine kinase (BTK). This enzyme is involved in activating the immune system, leading to damage to platelets. By blocking BTK, the medicine is expected to reduce platelet damage caused by the immune system and improve symptoms of the condition. If licensed, rilzabrutinib could offer an additional treatment option for patients with persistent or chronic ITP who have had limited response to previous therapy.

Proposed Indication

Treatment of adult patients with persistent or chronic immune thrombocytopenia (ITP) who are refractory or relapsed to any appropriate courses of standard of care ITP therapy.[1,2]

Technology

Description

Rilzabrutinib (PRN1008) is an oral, reversible, potent Bruton's tyrosine kinase (BTK) inhibitor that was designed for the treatment of immune-mediated diseases. BTK is widely expressed in many cells and plays a critical role in B-cell maturation, antibody production, and Fcγ receptor–mediated signaling pathways. BTK inhibition has the potential to reduce Fcγ receptor–mediated macrophage function and reduce autoantibody production. The covalent binding of rilzabrutinib contributes to long BTK-target engagement and durable inhibition with limited drug exposure, a clinical advantage that is accompanied by rapid systemic clearance, which reduces the potential for off-target toxic effects, for example, atrial fibrillation.[3,4] A preclinical study identified simultaneous mechanisms of rapid anti-inflammatory effects, neutralisation of pathogenic autoantibody signaling, and prevention of new autoantibody production.[4,5]

Rilzabrutinib is currently in clinical development for the treatment of persistent or chronic immune thrombocytopenia. In the phase III clinical trial (LUNA 3, NCT04562766), patients receive rilzabrutinib 400mg orally twice daily for up to 24 weeks followed by 28 weeks of open label period.[1]

Key Innovation

Despite the range of available therapies for the treatment of ITP, durable responses or long-term remissions are not guaranteed. A need remains for safer therapy that results in durable increases in platelet counts, prolongs remission, eliminates glucocorticoid use and related long-term toxic effects, and improves quality of life.[4] The high specificity of rilzabrutinib is thought to decrease the risk of off-target toxic effects (e.g., atrial fibrillation) by means of the phosphatidylinositol 3-kinase (PI3K)–AKT signalling pathway, which is associated with other BTK inhibitors.[5] An early clinical study involving healthy volunteers showed rapid, sustained, and high BTK occupancy (the level of drug binding to BTK) with no evidence of the clinically significant adverse events that have been reported with other BTK inhibitors.[3] In contrast to the known effects that have been observed with other BTK inhibitors, rilzabrutinib use did not alter platelet aggregation in healthy volunteers or in patients with immune thrombocytopenia.[4,5] If licensed, rilzabrutinib will offer an additional treatment option for patients with persistent or chronic ITP who have had limited response to previous therapy.

Regulatory & Development Status

Rilzabrutinib does not currently have marketing authorisation in the EU/UK for any indication.

Rilzabrutinib has the following regulatory designations/awards:

- Orphan designation by the EMA for treatment of immune thrombocytopenia in June 2020 [6]
- Fast track designation by FDA for treatment of immune thrombocytopenia in November 2020 [6,7]

Rilzabrutinib is currently also in phase II/III clinical trials for the following indications:[8]

- Warm autoimmune hemolytic anemia (wAIHA)
- Immunoglobulin G4 related disease
- Asthma

- Atopic dermatitis
- Chronic spontaneous urticaria

Patient Group

Disease Area and Clinical Need

ITP (formerly known as idiopathic thrombocytopenic purpura) is an autoimmune bleeding disorder characterised by abnormally low levels of blood cells called platelets, a situation referred to as thrombocytopenia.[9,10] Platelets are specialised blood cells that help maintain the integrity of the walls of blood vessels and help prevent and stop bleeding by accelerating clotting where it is needed.[9] The fundamental abnormality in ITP is that the patient's immune system tags their own platelets as "foreign", leading their B-lymphocytes and plasma cells to produce self-reactive anti-platelet antibodies that attach to platelet surfaces. A type of white blood cells in the spleen and in other organs, called macrophages, normally recognise antibody-coated particles. In ITP, antibody-coated platelets are ingested and subsequently destroyed within the macrophages.[11] Patients with ITP often develop symptoms unexpectedly, such as abnormal bleeding into the skin resulting in either bruising (purpura), or tiny red dots on the skin called petechiae. Bleeding from mucous membranes such as the nose and mouth, and less commonly the stomach, gastrointestinal and urinary tracts may also occur.[9] In addition, a substantial disease burden is observed in patients with primary ITP beyond bleeding, as ITP has been shown to significantly affect individuals' health-related quality of life (HRQoL) due to anxiety about complications, depression, fatigue, and/or impact on ability to perform daily activities. Physicians have also reported HRQoL impacts in ITP patients due to their disease and treatment.[12,13]

The UK incidence of adult ITP is estimated to be around 120 per year and 3,000–3,500 people are affected at any one time in England and Wales.[14] In England (2022-23), there were 12,729 finished consultant episodes (FCE) and 11,508 admissions for idiopathic thrombocytopenic purpura (ICD-10 code D69.3). This resulted in 10,727 FCE bed days and 8,648 day cases.[15]

Recommended Treatment Options

NICE currently recommends the following treatment options for ITP:

- Fostamatinib for treating refractory chronic immune thrombocytopenia[16]
- Romiplostim for the treatment of chronic immune thrombocytopenia[17]
- Avatrombopag for treating primary chronic immune thrombocytopenia[18]
- Eltromobopag for treating chronic immune thrombocytopenia[19]

Clinical Trial Information

Trial	NCT03395210; An Adaptive, Open-Label, Dose-Finding, Phase 1/2 Study Investigating the Safety, Pharmacokinetics, and Clinical Activity of PRN1008, an Oral BTK Inhibitor, in Patients With Relapsed Immune Thrombocytopenia **Phase I/II:** Active, not recruiting **Location(s):** 3 EU countries, UK, USA, Canada, Norway and Australia **Study completion date:** December 2025
Trial Design	Sequential assignment, open label

Population	N=81; male or female patients ages 18 to 80 years old; immune-related ITP (both primary and secondary)
Intervention(s)	Rilzabrutinib 400mg twice daily (oral)
Comparator(s)	-
Outcome(s)	Primary outcomes: • Part A and B: Incidence of treatment emergent adverse events (safety outcome measure) [Time Frame: 24 weeks of treatment, long term extension and 4 weeks of follow up post last dose] • Part A: Consecutive increased platelet counts (efficacy outcome measure) [Time Frame: 24 weeks] • Part B: Sustained increase in platelet counts (efficacy outcome measure) [Time Frame: 24 weeks] See trial record for further details on outcomes.
Results (efficacy)	Part A: All 60 patients could be evaluated for efficacy in this 24-week trial. The primary end point of platelet response was met in 24 patients (40%; 95% confidence interval [CI], 28 to 53). According to the dose level at any time during the trial (patients could have had a response at more than one dose level), 1 of 9 patients (11%) met the primary end point at a dose of 200 mg once daily, 2 of 8 (25%) at a dose of 400 mg once daily, 4 of 12 (33%) at a dose of 300 mg twice daily, and 20 of 52 (38%) at a dose of 400 mg twice daily (the highest dose). Of the 45 patients who had started rilzabrutinib at the highest dose, 18 (40%) met the primary end point of platelet response.[4]
Results (safety)	Part A: During the treatment period, 31 patients (52%) had at least one treatment-related adverse event; all these events were of grade 1 or 2 and were transient (Table 2 and S2). The most common treatment-related adverse events of any grade were diarrhea (in 32% of the patients), nausea (in 30%), and fatigue (in 10%). One patient had a treatment-related grade 1 contusion (bleeding), and 1 had treatment-related grade 2 erysipelas (infection) that resolved with treatment. There were no treatment-related bleeding or thrombotic events of grade 2 or higher. No treatment-related adverse events of grade 3 or higher or serious adverse events were observed. There were no other signs or symptoms of adverse events that have been typically associated with BTK inhibitors (i.e., neutropenia, treatment-related infection, bleeding, thrombotic events, fungal infection, or atrial fibrillation).[4]

Clinical Trial Information

Trial	**LUNA 3;** NCT04562766; 2020-002063-60; 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)

	Phase III: Recruiting **Location(s):** 8 EU countries, UK, USA, Canada and other countries **Primary completion date:** June 2025
Trial Design	Randomized, parallel assignment, quadruple masking
Population	N=194; male and female with primary ITP with duration of >6 months in paediatric participants aged 12 to <18 years; paediatric participants aged 10 to <12 years will be enrolled in the EU [EEA countries] only; duration of >3 months in ages 18 years and above
Intervention(s)	Rilzabrutinib 400mg twice daily (oral)
Comparator(s)	Matched placebo.
Outcome(s)	Primary outcomes: • Durable platelet response during the last 6 weeks of the 24-week blinded treatment period (not for EU and UK) [Time Frame: 24 weeks] • For EU and UK: Proportion of adult participants able to achieve platelet counts at or above 50,000/µL for at least 8 out of the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy [Time Frame: 24 weeks] See trial record for further details on outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The estimated cost of rilzabrutinib is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Avatrombopag for treating primary chronic immune thrombocytopenia (TA853). December 2022.
- NICE technology appraisal. Fostamatinib for treating refractory chronic immune thrombocytopenia. Technology appraisal guidance (TA835). October 2022.
- NICE technology appraisal. Eltrombopag for treating chronic immune thrombocytopenia (TA293). October 2018.
- NICE technology appraisal. Romiplostim for the treatment of chronic immune thrombocytopenia (TA221). October 2018.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Specialised Immunology (All ages). B09/S/a

Other Guidance

- American Society of Hematology (ASH). 2019 Guidelines for Immune Thrombocytopenia. 2019.[20]

Additional Information

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