THERAPEUTIC ADVANCES in
Hematology

Study Protocol

Rilzabrutinib *versus* placebo in adults and adolescents with persistent or chronic immune thrombocytopenia: LUNA 3 phase III study

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David J. Kuter, James B. Bussel, Waleed Ghanima, Nichola Cooper, Terry Gernsheimer, Michele P. Lambert, Howard A. Liebman, Michael D. Tarantino, Michelle Lee, Hailing Guo and Ahmed Daak

Abstract

Background: Immune thrombocytopenia (ITP) is characterized by primarily autoantibody-mediated platelet destruction and impaired platelet production resulting in thrombocytopenia and an increased risk of bleeding. Other manifestations include increased risk of thrombosis and diminished quality of life. Current treatment approaches are directed toward lowering the rate of platelet destruction or stimulating platelet production to prevent bleeding. Rilzabrutinib is an oral, reversible, potent Bruton tyrosine kinase inhibitor that was specifically designed to treat immune-mediated diseases and mediates its therapeutic effect through a dual mechanism of action: (1) inhibiting B-cell activation and (2) interrupting antibody-coated cell phagocytosis by Fc gamma receptor in spleen and liver. A 24-week dose-finding phase I/II study of rilzabrutinib in patients with ITP showed a 40% platelet response (≥2 consecutive platelet counts of $\geq 50 \times 10^9$/L and increase from baseline $\geq 20 \times 10^9$/L without rescue medication use) and a well-tolerated safety profile with only grade 1/2 transient adverse events across dose levels.

Objectives: Assess the efficacy and safety of oral rilzabrutinib in adult and adolescent patients with persistent or chronic ITP.

Design: Rilzabrutinib 400 mg BID is being evaluated in the ongoing LUNA 3 multicenter, double-blind, placebo-controlled phase III study.

Methods and analysis: The primary endpoint is durable platelet response, defined as achieving platelet counts of $\geq 50 \times 10^9$/L for at least two-thirds of ≥8 available weekly scheduled platelet measurements during the last 12 weeks (including ≥2 available measurements within the last 6 weeks) of the 24-week blinded treatment period in the absence of rescue therapy.

Ethics: Ethical guidelines and informed consent are followed.

Discussion: The LUNA 3 trial will further investigate rilzabrutinib's safety and efficacy in adult and adolescent patients, with the primary goal of addressing a major objective in treating patients with ITP: durability of platelet response.

Trail Registration: ClinicalTrials.gov NCT04562766: https://clinicaltrials.gov/ct2/show/NCT04562766; EU Clinical Trials Register EudraCT 2020-002063-60: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2020-002063-60.

Keywords: autoimmunity, B cells, bleeding, BTK inhibition, immune thrombocytopenia, platelets, rilzabrutinib

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Correspondence to:
David J. Kuter
Hematology Division, Massachusetts General Hospital, Harvard Medical School, Bartlett Hall 150, 140 Blossom Street, Boston, MA 02114-2603, USA
kuter.david@mgh.harvard.edu

James B. Bussel
Division of Pediatric Hematology/Oncology, Department of Pediatrics, Weill Cornell Medicine, New York, NY, USA

Waleed Ghanima
Østfold Hospital Trust, Grålum, Norway

Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Nichola Cooper
Department of Immunology and Inflammation, Imperial College London, London, UK

Terry Gernsheimer
University of Washington Medical Center and Fred Hutchinson Cancer Center, Seattle, WA, USA

Michele P. Lambert
Department of Pediatrics, Children's Hospital of Philadelphia Division of Hematology and Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Howard A. Liebman
Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Michael D. Tarantino
The Bleeding and Clotting Disorders Institute, University of Illinois College of Medicine Peoria, Peoria, IL, USA

Michelle Lee
Hailing Guo
Sanofi, Bridgewater, NJ, USA

Ahmed Daak
Sanofi, Cambridge, MA, USA

Background

Immune thrombocytopenia

Immune thrombocytopenia (ITP) is an acquired autoimmune blood disease with an estimated worldwide prevalence of 10–23 per 100,000 people and an incidence of approximately 2–4 per 100,000 person-years in the general population, including patients under 18 years of age.[1–7] ITP is characterized by primarily autoantibody-mediated platelet destruction and impaired platelet production, which results in thrombocytopenia (i.e. platelet count below 100×10^9/L), an increased risk of bleeding and thrombosis, and diminished quality of life.[8–10]

Current treatment approaches are directed toward lowering the rate of platelet destruction or stimulating platelet production to prevent bleeding.[11,12] The standard therapy for adult patients with newly diagnosed ITP consists of corticosteroids (CS), such as high-dose dexamethasone or oral prednisone/prednisolone, the prolonged use should be avoided due to potential adverse events.[11,13] Although most patients respond to initial CS therapy, responses are typically not durable, are associated with significant toxicities, and have a low rate of lasting remission.[11] Other first-line therapies include intravenous immunoglobulins (IVIG) and anti-D. Second-line treatment options of rituximab and thrombopoietin receptor agonists (TPO-RA) have shown durable treatment response rates of 60–80%, whereas durable response rates with fostamatinib have reported 18% in a very heavily pretreated set of ITP patients.[13–15] Splenectomy as a second-line treatment choice has the benefit of high responses along with durable off-treatment remission rates of 60–70%. However, splenectomy might be associated with short-term surgery-related complications and long-term increased risks of thrombosis and infection.[14,15]

The disease burden is more significant in patients with severe and chronic thrombocytopenia requiring ongoing treatment and those who are unresponsive to current therapy, contributing to elevated mortality rates relative to the general population.[16,17] Adult patients with chronic thrombocytopenia have up to a 10% risk of bleeding or hemorrhage that increases with age, and intracranial hemorrhage has been reported in ~1–2% of patients.[8,16,18] In addition, patients with chronic and refractory ITP may experience significant fatigue, cognitive impairment, fear of bleeding, and a negative impact on social and work activities, reinforcing the significant unmet need for these patients.[19–21]

The pathophysiology of ITP includes pathogenic anti-platelet immunoglobulin G autoantibodies that target surface antigens [e.g. glycoproteins αIIbβ3 (GPIIb/IIIA), GPIa/IIa, and/or GPIb-IX-V].[22–24] The binding of autoantibodies to various platelet glycoproteins results in platelet phagocytosis through binding of autoantibodies to Fc gamma receptors (FcγRs) on macrophages, platelet clearance by a C-type lectin receptor (CLEC4F) on hepatic Kupffer cells, platelet lysis by the membrane attack complex and/or phagocytosis due to classical complement pathway activation, T-cell-mediated cytotoxicity, and/or impaired megakaryocyte viability.[23–27] Considering the heterogeneity of mechanisms underlying ITP development, a single therapy that targets multiple pathogenic pathways or a combination of therapies is likely to be needed to induce sufficient and durable platelet response.

Inhibition of Bruton tyrosine kinase by rilzabrutinib

Bruton tyrosine kinase (BTK) is expressed in B cells and innate immune cells and is a key therapeutic target in immune-mediated diseases due to its role in B-cell differentiation and development, antibody production, and FcγR-mediated signaling pathways and its direct regulation of key innate inflammatory machinery, nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome.[28–31] Through these various pathways, BTK inhibition may decrease autoantibody production and inhibit macrophage function through the FcγR, Fc epsilon receptor (FcεR)-induced mast cell degranulation, and granulocyte migration and mediator release, thereby targeting multiple pathways involved in inflammation and autoimmunity.[28,29]

Rilzabrutinib is an oral, reversible, potent BTK inhibitor specifically designed to treat immune-mediated diseases and can mediate its therapeutic effect through a dual mechanism of action: (1) inhibition of B-cell activation and (2) interruption of antibody-coated cell phagocytosis by FcγR in

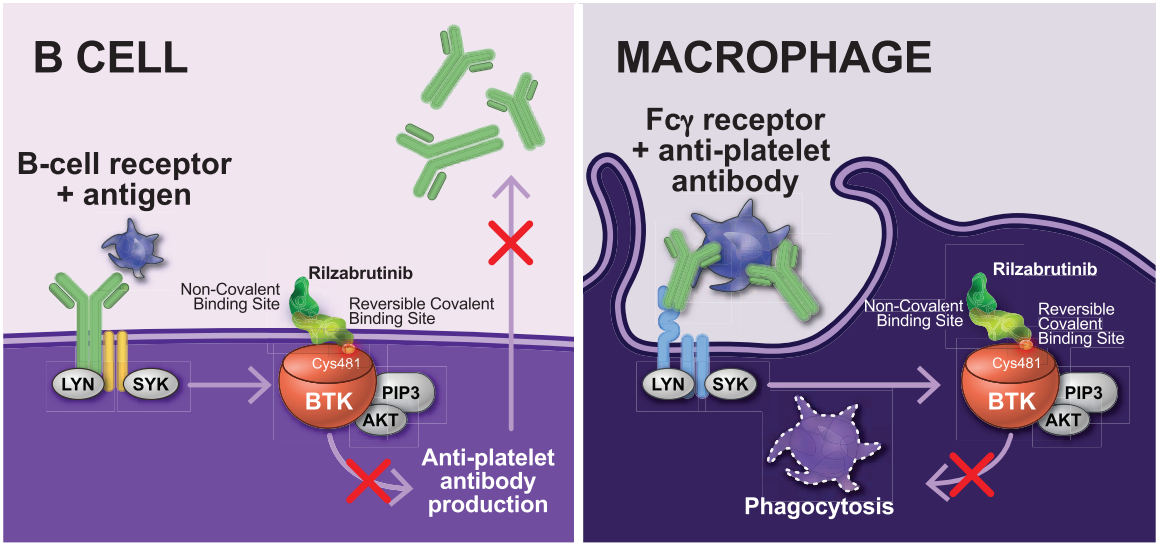

Figure 1. Rilzabrutinib mechanism of action in ITP. BTK regulates both B-cell receptor signaling upon antigen binding in B lymphocytes and FcγR signaling through binding of immune complexes in macrophages. By concerted action of the LYN and SYK tyrosine kinases, the PI3K/AKT signaling pathway is activated, leading to the generation of PIP3, which, in turn, results in the recruitment and activation of BTK. Through its noncovalent/reversible covalent binding sites, rilzabrutinib inhibits BTK and blocks its downstream effects.
AKT, Ak strain transforming kinase; serine-threonine kinase; BTK, Bruton tyrosine kinase; FcγR, Fc gamma receptor; ITP, immune thrombocytopenia; PI3K, phosphatidylinositol-3 kinase; PIP3, phosphatidylinositol-3,4,5-triphosphate kinase.

spleen and liver (Figure 1).[32–34] In addition, rilzabrutinib has a short half-life (~3–4h), durable target occupancy (>90% within 4h and sustained high occupancy maintained over 24h), and contains both covalent and noncovalent binding regions; this reversible cysteine binding enables high selectivity and precise BTK inhibition without permanently modifying proteins and peptides.[33–35] Furthermore, rilzabrutinib in contrast to non-selective, irreversible BTK inhibition does not alter platelet aggregation in patients with ITP or healthy volunteers and thus does not seem to lead to bleeding problems.[33,36] In addition, based on potential adverse bleeding and cardiac effects observed with many other irreversible BTK inhibitors,[37] a two-part phase I study showed that rilzabrutinib (even at supratherapeutic doses) had no clinically relevant effects on cardiac repolarization (electrocardiogram parameters including corrected QT interval) in healthy volunteers ($N=51$).[38]

In an international, adaptive, open-label, dose-finding phase I/II clinical trial, treatment with rilzabrutinib resulted in a rapid and durable therapeutic effect in ITP patients who were previously treated with multiple therapies and was generally well tolerated.[39] All treatment-related adverse events (primarily diarrhea, nausea, and fatigue) were transient, grade 1 or 2 with no related grade ⩾2 bleeding or thrombotic events.[39] The oral 400mg BID dose of rilzabrutinib is being evaluated in a placebo-controlled, phase III study, the protocol of which is described here.

Methods and analysis

LUNA 3 phase III study

LUNA 3 is an ongoing, multicenter, randomized, double-blind, placebo-controlled, parallel-group, interventional phase III study evaluating the efficacy and safety of oral rilzabrutinib in adults and adolescents with persistent or chronic ITP (ClinicalTrials.gov NCT04562766,[40] EudraCT 2020-002063-60[41]). This study is being conducted at approximately 160 global ITP clinical study sites in North America, South America, Europe, and Asia/Pacific (Figure 2). To our knowledge, LUNA 3 is one of the largest clinical trials conducted in patients with primary ITP to date that is uniquely designed to include both 194 adult and 30 adolescent patients.

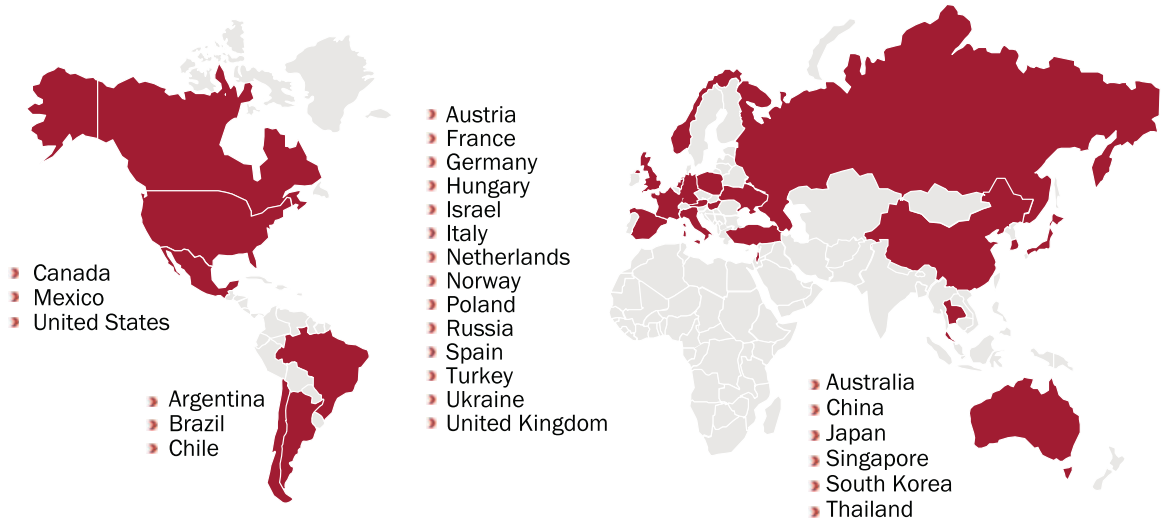

Figure 2. LUNA 3 recruiting countries.

Patient eligibility and recruitment

Eligible patients must have primary ITP[42] with a duration of >3 months if aged ⩾18 years or a duration of >6 months if aged 12 to <18 years. Patients should have an average of two platelet counts of $<30\times10^9$/L at least 5 days apart during the screening period, and no single platelet count $>35\times10^9$/L within 14 days before the first dose of rilzabrutinib. Patients should have had a previous response (platelet counts $\geqslant50\times10^9$/L) to CS or IVIG/anti-D. Either the prior response is not sustained or the patient has a documented intolerance, insufficient response, or any contraindication to any appropriate courses of standard ITP therapy. Patients receiving a stable dose of CS and/or TPO-RA are eligible to participate. Adequate hematologic, hepatic, and renal function [absolute neutrophil count $\geqslant1.5\times10^9$/L, aspartate aminotransferase/alanine aminotransferase ⩽1.5x upper limit of normal (ULN), albumin ⩾3 g/dL, total bilirubin ⩽1.5× ULN (unless documented Gilbert syndrome), estimated glomerular filtration rate >50 by Cockcroft and Gault method], and hemoglobin levels >9 g/dL (within 1 week before study day 1) are required. Additional eligibility criteria are outlined in Table 1.

Patients with known secondary ITP are not eligible to enroll. Key exclusion criteria also include platelet transfusions or use of any other rescue medications (e.g. IVIG) with the intent to increase platelet counts, changes in CS and/or TPO-RA dose (>10% variation from current doses) within 2 weeks before the study entry, and receipt of a live vaccine within 28 days before study day 1 or plan to receive one during the study. Because of recent reports suggesting exacerbation of ITP following COVID-19 vaccination,[43,44] administering a COVID-19 vaccine specifically within 2 weeks before study treatment and during the last 12 weeks of the blinded treatment period is not allowed due to potential confounding effects on the primary endpoint.

Study design and interventions

After providing written informed consent, patients enter a 28-day screening period and eligible patients are randomized 2:1 to receive oral treatment with either rilzabrutinib 400 mg BID or placebo with optional stable doses of standard CS and/or TPO-RA therapy.

Randomization is stratified by splenectomy status (yes/no) and severity of disease (platelet counts $<15\times10^9$/L *versus* $\geqslant15\times10^9$/L) and is carried out separately for adult and adolescent patients. After randomization, patients start a blinded treatment period for up to 24 weeks, followed by a 28-week open-label period when all patients receive rilzabrutinib, and then a 4-week safety follow-up or long-term extension (LTE) phase (Figure 3). Stable doses of concomitant ITP medication (oral CS and/or TPO-RA) are

Table 1. Key eligibility criteria.

Inclusion criteria	Exclusion criteria

• Primary ITP for >3 months if aged ⩾18 years or >6 months if aged 12 to <18 years
  - In EU countries, children aged 10–18 years are eligible
• Previous response (platelet count ⩾50×10^9/L) to CS or IVIG/anti-D that was not sustained, or documented intolerance, insufficient response, or any contraindication to any appropriate courses of standard-of-care ITP therapy
• An average of two platelet counts ⩾5 days apart of <30×10^9/L during screening and no single platelet count >35×10^9/L within 2 weeks before study treatment
  - If aged 12 to <18 years, must require ITP treatment per clinical investigator's assessment
• Adequate hematologic, hepatic, and renal function [absolute neutrophil count ⩾1.5×10^9/L, AST/ALT ⩽1.5 × ULN, albumin ⩾3 g/dL, total bilirubin ⩽1.5 × ULN (unless documented Gilbert syndrome), estimated glomerular filtration rate >50 (Cockcroft and Gault method)]
• Hemoglobin >9 g/dL within 1 week before study treatment
	• Secondary ITP
	• Pregnant or lactating women
	• Electrocardiogram (ECG) findings
	  - Aged ⩾10 and <16 years: QTcF >449 ms (males) or >457 ms (females)
	  - Aged ⩾16 and <18 years: QTcF >450 ms (males) or >460 ms (females)
	  - Aged ⩾18 years, of QTcF >450 ms (males) or >470 ms (females), poorly controlled atrial fibrillation (i.e. symptomatic participants or a ventricular rate >100 beats/min on ECG), or other clinically significant abnormalities
	• Transfusions or use of any other rescue medications with intent to increase platelet count within 2 weeks before study treatment
	• Change in CS and/or TPO-RA dose within 2 weeks before study treatment (>10% variation from current doses)
	• Use of immunosuppressants other than CS within five times the elimination half-life of the drug or within 2 weeks before study treatment, whichever is longer
	• Treatment with rituximab or splenectomy within 3 months before study treatment
	• Prior rilzabrutinib therapy
	• History (within 5 years of study day 1) of current active malignancy requiring or likely to require chemotherapeutic or surgical treatment during the study, except for non-melanoma skin cancer
	• History of solid organ transplant or planned surgery
	• Myelodysplastic syndrome
	• COVID-19 vaccine within 2 weeks prior or planned during the last 12 weeks of blinded treatment
	• Planned or concomitant use of any anticoagulants and platelet aggregation inhibiting drugs such as aspirin (except for low-dose aspirin up to 100 mg/day), nonsteroidal anti-inflammatory drugs, and/or thienopyridines within 14 days of treatment initiation and until the end of the active treatment period
	• Any other clinically significant disease, condition, known allergy to any of the study medications, their analogs, or excipients in the various formulations of any agent, 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

AST/ALT, aspartate aminotransferase/alanine aminotransferase; CS, corticosteroids; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; TPO-RA, thrombopoietin receptor agonist; ULN, upper limit of normal.

permitted in both treatment arms, with dose reductions allowed for associated safety concerns only. CS and/or TPO-RA administration should follow corresponding current package inserts/summary of product characteristics of the country-specific marketing authorization.

At the end of 12 weeks of treatment (rilzabrutinib 400 mg BID or placebo), a single assessment of platelet response is performed, which is defined as platelet count of ⩾50×10^9/L or between ⩾30×10^9/L and <50×10^9/L and at least doubled from baseline at any time and in the absence of rescue medication in the 4 weeks before the elevated platelet count that met the platelet response criteria (Figure 4). The baseline is calculated as the average of two qualifying platelet counts at screening and day 1 before the first dose of treatment. Next, responders continue the blinded treatment period for 12 more weeks for a total of 24 weeks before entering the 28-week open-label period, whereas non-responders may

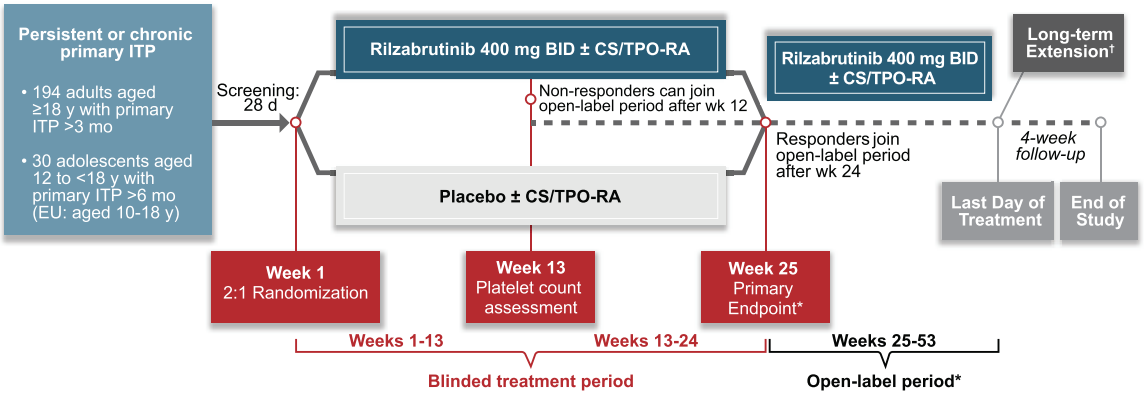

Figure 3. Study schema flow chart.[45] LUNA 3 is registered as NCT04562766 and EudraCT 2020-002063-60. *Week 25 is the last visit of the blinded treatment period and the start of the open-label period. †Following long-term extension completion, patients will undergo the last day of study drug and end of study assessments.
BID, twice daily; CS, corticosteroids; EU, European Union; ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist.

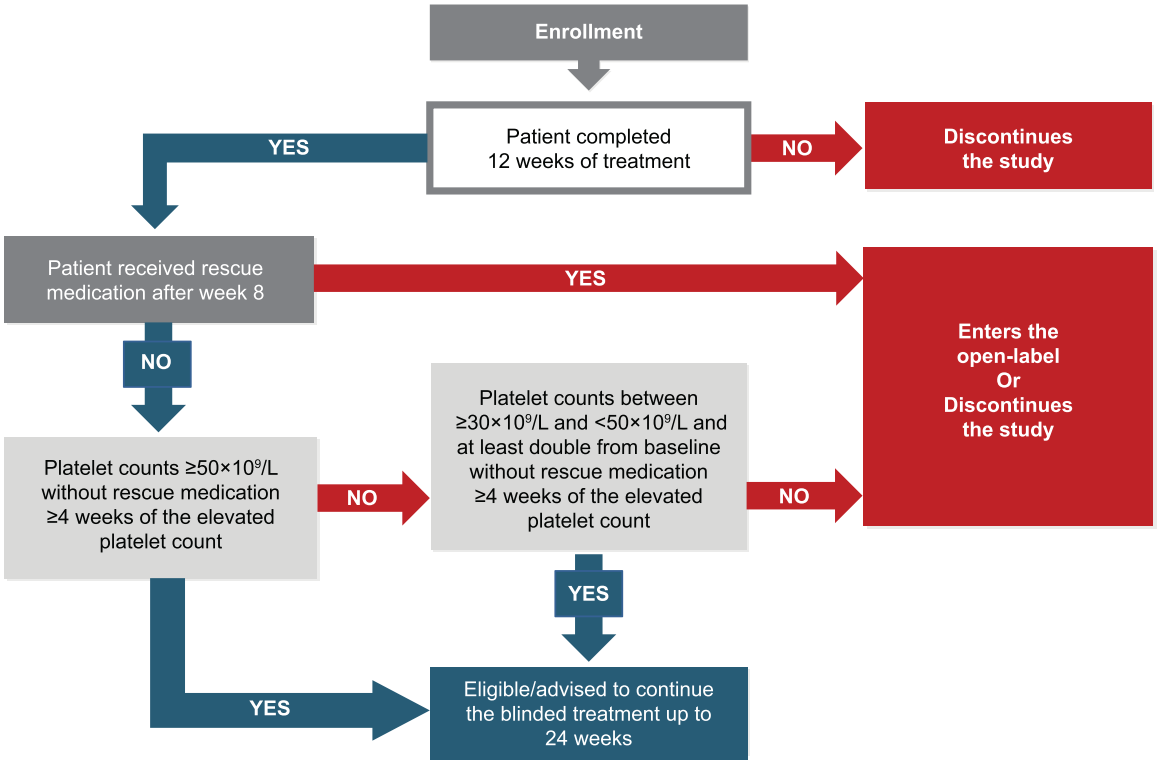

Figure 4. Decision flow for assessing response at week 13. After enrollment, patients will start a blinded treatment period for up to 24 weeks (rilzabrutinib or placebo treatment) followed by an open-label period of 28 weeks (where all patients receive rilzabrutinib), and then a 4-week safety follow-up period or long-term extension. Patients who do not complete the initial 12 weeks of treatment are not eligible to proceed to the open-label period. At the end of 12 weeks of treatment, participants will be assessed for platelet response ($\geq 50 \times 10^9$/L or between $\geq 30 \times 10^9$/L and $< 50 \times 10^9$/L and at least doubled from baseline at any time) and the presence or absence of rescue medication in the 4 weeks before elevated platelet counts meeting the platelet response criteria. Responders with no rescue medication use after week 8 will continue to be evaluated for eligibility to proceed to the blinded treatment period for a total of 24 weeks before entering the open-label period. Non-responders or those who did receive rescue medication after week 8 may discontinue the study or enter the 28-week open-label period at the end of week 12 and receive rilzabrutinib 400 mg BID.

discontinue the study or enter the 28-week open-label period at the end of week 12 while receiving rilzabrutinib 400 mg BID. Irrespective of the non-responder's choice, the initial study medication assignment remains blinded.

Patients are assessed for eligibility to enter the LTE at the end of the open-label period (i.e. 28 weeks of receiving treatment with rilzabrutinib 400 mg BID). After completing the open-label period, any participants who demonstrate platelet response defined as platelet counts $\geq 50 \times 10^9$/L or $\geq 30 \times 10^9$/L and at least doubled from baseline for ≥50% of the visits without receiving rescue therapy while on rilzabrutinib treatment during the last 8 weeks of the open-label period will be allowed to enter the LTE. In the LTE part, concomitant CS and/or TPO-RA dose reductions or discontinuations are allowed if platelet counts are $\geq 50 \times 10^9$/L on three scheduled visits over 12 weeks.

For the first study phase over 24 weeks, treatments are double-blinded to the investigator/clinical study team and patients, unless unblinding is deemed medically necessary by the investigator after consulting with the study sponsor's medical monitor and in accordance with local regulations/policies. The treating study investigator will be responsible for ensuring treatment is administered in compliance with the study protocol. Patients may discontinue the trial temporarily due to suspected adverse events or a regional or national emergency declared by a governmental agency (e.g. pandemic); reinitiate treatment under close supervision of the study investigator if continued eligibility criteria are met; or withdraw from the study due to life-threatening or grade 4 treatment-related adverse events, serious allergic reaction, pregnancy, any medical condition/personal circumstance deemed by the investigator to pose a significant risk to the patient, human immunodeficiency or hepatitis B/C viral infections, protocol violation compromising data interpretation, or abnormal liver tests.

Endpoints and assessments

The primary endpoint of this study is durable platelet response, defined as achieving platelet counts of $\geq 50 \times 10^9$/L for at least two-thirds of ≥8 available weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy, provided that ≥2 available weekly scheduled platelet measurements are $\geq 50 \times 10^9$/L during the last 6 weeks of the 24-week blinded treatment period (Table 2). Patients must have ≥2 available weekly scheduled platelet measurements of $\geq 50 \times 10^9$/L during the last 6 weeks of the 24-week blinded treatment period. Key secondary efficacy endpoints are the number of weeks with platelet counts $\geq 50 \times 10^9$/L or between $\geq 30 \times 10^9$/L and $< 50 \times 10^9$/L and at least doubled from baseline during the 24-week blinded treatment period in the absence of rescue medication, the number of weeks with platelet counts $\geq 30 \times 10^9$/L and at least doubled from baseline during the 24-week blinded treatment period in the absence of rescue medication, time to first platelet counts $\geq 50 \times 10^9$/L or between $\geq 30 \times 10^9$/L and $< 50 \times 10^9$/L and at least doubled from baseline, the proportion of patients requiring rescue therapy during the 24-week blinded treatment period, and changes from baseline on ITP Patient Assessment Questionnaire™ (ITP-PAQ™) physical fatigue score in adult patients (aged ≥18 years) at week 13 of treatment.

Secondary safety endpoints include evaluating the frequency and severity of treatment-emergent adverse events and bleeding events. Safety will be assessed by the incidence, severity, and causal relationship of treatment-emergent adverse events, including clinically significant changes in physical examination, vital signs, electrocardiogram, and laboratory parameters. The intensity of adverse events is graded based on the modified Common Terminology Criteria for Adverse Events, version 5.0 (National Cancer Institute). Additional endpoints are detailed in Table 2.

Disease-specific assessment tools include Idiopathic Thrombocytopenic Purpura Bleeding Scale, a bleeding assessment comprising 11 site-specific grades assessed at nine anatomical sites by history over the period before the visit; the ITP-PAQ™, a disease-specific instrument designed to measure quality of life of adult patients with ITP; and the Kids ITP Tools (KIT) assessment, which is based on a battery of three disease-specific instruments and a self-report form specifically designed for pediatric patients with ITP.[46–48] Generic health-related quality of life will be assessed using the EuroQOL-5 Dimension 5 Level (EQ-5D-5L)

Table 2. LUNA 3 study endpoints.

Primary endpoint	• Platelet counts $\geq 50 \times 10^9$/L for ≥two-thirds of ≥8 available weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue medication, provided that at least two available weekly scheduled platelet measurements are $\geq 50 \times 10^9$/L during the last 6 weeks of the 24-week blinded treatment period*
Key secondary endpoints	• Number of weeks with platelet counts $\geq 50 \times 10^9$/L or between $\geq 30 \times 10^9$/L and $< 50 \times 10^9$/L and at least doubled from baseline during the 24-week blinded treatment period in the absence of rescue medication • Number of weeks with platelet counts $\geq 30 \times 10^9$/L and at least doubled from baseline during the 24-week blinded treatment period in the absence of rescue medication • Time to first platelet counts $\geq 50 \times 10^9$/L or between $\geq 30 \times 10^9$/L and $< 50 \times 10^9$/L and at least doubled from baseline • Proportion of patients requiring rescue therapy during the 24-week blinded treatment period • Changes from baseline on ITP-PAQ physical fatigue score in adult patients (aged ≥18 years) at week 13 of treatment • Safety
Exploratory endpoints (24-week blinded period)	• Platelet counts of $\geq 50 \times 10^9$/L for 4 out of the last 8 weeks of treatment • Percentage of weeks with platelet counts of $\geq 50 \times 10^9$/L or between $\geq 30 \times 10^9$/L and $< 50 \times 10^9$/L and at least doubled from baseline • Complete response (defined as platelet counts of $\geq 100 \times 10^9$/L on two consecutive visits ≥5 days apart and no bleeding or rescue ITP medication use) • Platelet counts of $\geq 50 \times 10^9$/L on two consecutive visits at least 5 days apart with no rescue therapy on and through those two visits • Platelet counts $> 250 \times 10^9$/L or $> 450 \times 10^9$/L for patients receiving concomitant TPO-RA • Change from baseline in IBLS at weeks 13 and 25 • Changes in quality of life • Changes from baseline in thrombopoietin levels, T lymphocytes, B lymphocytes, natural kill cell counts, and immunoglobulin (IgG, IgG1, IgG4, IgM, and IgE) levels
Exploratory endpoints (open-label and LTE period)	• Platelet counts $\geq 50 \times 10^9$/L for two-thirds of ≥10 available weekly scheduled platelet measurements during the last 16 of 28 weeks in the open-label period in the absence of rescue medication, provided that at least three available weekly scheduled platelet measurements were $\geq 50 \times 10^9$/L during the last 8 weeks of the 28-week open-label period • Platelet counts of $\geq 50 \times 10^9$/L or between $\geq 30 \times 10^9$/L and $< 50 \times 10^9$/L and at least doubled from baseline • Complete response • Platelet counts $> 250 \times 10^9$/L or $> 450 \times 10^9$/L for patients receiving concomitant TPO-RA • Proportion of patients requiring rescue medication • Changes from baseline in IBLS and quality of life • Changes from baseline on CS or TPO-RA dose • Proportion of patients who switch to rilzabrutinib monotherapy during the first year of the LTE period

*In the European Union and the United Kingdom, the primary endpoint is defined as achieving platelet counts of $\geq 50 \times 10^9$/L for ≥8 of the last 12 weeks of the 24-week blinded treatment period in the absence of rescue medication.
CS, corticosteroids; IBLS, Idiopathic Thrombocytopenic Purpura Bleeding Scale; ITP, immune thrombocytopenia; ITP-PAQ™, Immune Thrombocytopenia Patient Assessment Questionnaire™; LTE, long-term extension; TPO-RA, thrombopoietin receptor agonist.

questionnaire and the Patient Global Impression of Severity Scales (generic, for fatigue, and change). These assessments will be done every 4 weeks during the blinded and open-label periods, and in the LTE, every 28 days for the first year of the LTE and every 3 months thereafter.

Statistical considerations

All randomized patients will be included in the intent-to-treat population and all randomized patients who are exposed to ⩾1 dose of study medication will be included in the safety population. Assessment of the primary response endpoint between the two arms will be performed using the Cochran–Mantel–Haenszel test. The adult sample size of approximately 194 was selected to achieve >85 power to detect a 20% difference in response rate (e.g. 25% *versus* 5% in the rilzabrutinib *versus* placebo arms, respectively) with approximately 129 adult patients (aged ⩾18 years) in the rilzabrutinib arm and 65 in the placebo arm. The adolescent sample size of 30 patients (20 on rilzabrutinib and 10 on placebo) was determined based on clinical practice and development experiences to adequately describe the safety and efficacy of these patients with ITP.

Data monitoring, collection, audit, and management plans are detailed in the study protocol to ensure data quality. To ensure patient safety, study investigators will proactively follow each patient and promptly notify the study sponsor of adverse events, and an independent data and safety monitoring board will regularly review and evaluate unblinded patient safety data. No formal interim analysis is planned for the double-blinded part of the study; the final analysis will be completed at the end of the study. Additional analyses with the open-label and LTE parts may be performed at the study sponsor's discretion.

Discussion

Results from an international phase I/II trial of rilzabrutinib in adult patients with previously treated ITP ($n=60$) provided evidence that this BTK inhibitor can confer a stable platelet response and has a tolerable safety profile.[39] The LUNA 3 phase III trial will compare the magnitude, durability, and stability of rilzabrutinib's efficacy and safety compared with placebo in adult patients with persistent or chronic ITP and explore findings in adolescent patients. The definition of durable response (the primary endpoint) in this trial is achieving platelet counts of $\geqslant 50\times10^9$/L for at least two-thirds of ⩾8 available weekly scheduled platelet measurements during the last 12 weeks (and including ⩾2 available measurements within the last 6 weeks) of the 24-week blinded treatment period in the absence of rescue therapy (e.g. in 8 of 12 or 6 of 9 counts).

The threshold for response ($\geqslant 50\times10^9$/L) is higher than the level adopted by the International Working Group consensus, which defines response as achieving any platelet count between 30×10^9/L and 100×10^9/L and at least doubling from the baseline count, and complete response is defined as any platelet count $\geqslant 100\times10^9$/L – both in the absence of bleeding.[10] Despite the lower guideline-based platelet level for response, a platelet count of $\geqslant 50\times10^9$/L is commonly used as the response threshold in clinical trials of approved ITP therapies.[49–52] Durable platelet response (i.e. platelet counts $\geqslant 30\times10^9$/L and at least doubling from the baseline at 6 months) is a goal for ITP therapies as an endpoint that measures sustained clinical benefit over time.[13] For recently approved fostamatinib, a durable response was demonstrated when two-thirds of platelet counts during the last 12 weeks (six visits) of the blinded period met the primary endpoint: platelet counts $\geqslant 50\times10^9$/L on ⩾4 of the six biweekly visits (weeks 14, 16, 18, 20, 22, and 24).[51,53] The LUNA 3 definition of durable response is based on the proportion of available platelet counts $\geqslant 50\times10^9$/L instead of the fixed timepoint of platelet counts $\geqslant 30\times10^9$/L and doubled from baseline at 6 months as defined in guidelines, which takes into account missing platelet counts.[13]

A significant number of both adults and children with ITP experience fatigue, which is thought to be associated with low platelets ($<30\times10^9$/L) and caused by a chronic inflammatory state and immune dysregulation.[20,54,55] To date, no available ITP therapies have shown significant improvement in fatigue in a randomized placebo-controlled clinical trial report. Considering rilzabrutinib's multipronged mechanisms of action, namely its potential anti-inflammatory effects, ITP-PAQ item 10 (fatigue domain) is being employed to quantify the impact of treatment with rilzabrutinib on fatigue as a key secondary endpoint.

Elucidating the mechanisms underlying ITP and designing novel therapies to address the current care gap continue to be active areas of research that are reviewed in detail elsewhere.[12,15,56] A growing number of therapies with various mechanisms of action are being investigated in late-phase clinical trials, with expected readouts within

the next 5 years. Among emerging therapeutic agents developed for ITP, the putative mechanisms of action of rilzabrutinib in ITP are thought to target both immune-mediated platelet destruction through blocking FcR-mediated platelet destruction and inhibition of platelet production, and by reducing the level of pathogenic antiplatelet antibodies due to suppression of autoreactive B cells.[28,29]

Patients enrolled in this trial are expected to have previously responded to at least one prior ITP therapy, supporting the diagnosis of ITP and not a 'look alike' thrombocytopenia. Preliminary findings based on phase II study results suggest that patients naive to rituximab and TPO-RA may achieve a better response rate,[57] thus providing a rationale to explore the effects of rilzabrutinib earlier in the disease course and relatively less refractory patients.

In summary, LUNA 3 is the first phase III trial assessing the efficacy and safety of rilzabrutinib in ITP and might demonstrate that BTK inhibition through treatment with rilzabrutinib may be a major improvement in therapy for patients with chronic ITP.

Declarations

Ethics approval and consent to participate

The LUNA 3 trial is being conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation E6 requirements. The protocol (version 3 dated 11 August 2022) and informed consent documents were approved by multiple country- and site-specific Ethics Committees and/or Institutional Review Boards; any amended protocols will require additional approval before implementation. The study is being monitored by an independent Data Monitoring Committee. All patients or the patient's parent/legal guardian(s) have or will provide written informed consent before enrollment. The submitted manuscript conforms with the ICMJE recommendations for the Conduct, Reporting Editing, and Publication of Scholarly Work in Medical Journals.

Consent for publication

Not applicable; no data from an individual person are included.

Author contributions

David J. Kuter: Conceptualization; Writing – review & editing.

James B. Bussel: Conceptualization; Writing – review & editing.

Waleed Ghanima: Conceptualization; Writing – review & editing.

Nichola Cooper: Conceptualization; Writing – review & editing.

Terry Gernsheimer: Conceptualization; Writing – review & editing.

Michele P. Lambert: Conceptualization; Writing – review & editing.

Howard A. Liebman: Conceptualization; Writing – review & editing.

Michael D. Tarantino: Conceptualization; Writing – review & editing.

Michelle Lee: Conceptualization; Writing – review & editing.

Hailing Guo: Conceptualization; Data curation; Formal analysis; Writing – review & editing.

Ahmed Daak: Conceptualization; Project administration/Medical Monitor; Writing – review & editing.

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Competing interests

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Availability of data and materials

Qualified researchers may request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org/.

ORCID iD

David J. Kuter https://orcid.org/0000-0003-2084-8810

References

1. Abrahamson PE, Hall SA, Feudjo-Tepie M, *et al.* The incidence of idiopathic thrombocytopenic purpura among adults: a population-based study and literature review. *Eur J Haematol* 2009; 83: 83–89.
2. Feudjo-Tepie MA, Robinson NJ and Bennett D. Prevalence of diagnosed chronic immune thrombocytopenic purpura in the US: analysis of a large US claim database: a rebuttal. *J Thromb Haemost* 2008; 6: 711–712.

3. Schoonen WM, Kucera G, Coalson J, *et al*. Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. *Br J Haematol* 2009; 145: 235–244.
4. Segal JB and Powe NR. Prevalence of immune thrombocytopenia: analyses of administrative data. *J Thromb Haemost* 2006; 4: 2377–2383.
5. Terrell DR, Beebe LA, Vesely SK, *et al*. The incidence of immune thrombocytopenic purpura in children and adults: a critical review of published reports. *Am J Hematol* 2010; 85: 174–180.
6. Yong M, Schoonen WM, Li L, *et al*. Epidemiology of paediatric immune thrombocytopenia in the General Practice Research Database. *Br J Haematol* 2010; 149: 855–864.
7. Christiansen CF, Bahmanyar S, Ghanima W, *et al*. Chronic immune thrombocytopenia in Denmark, Sweden and Norway: The Nordic Country Patient Registry for Romiplostim. *EClinicalMedicine* 2019; 14: 80–87.
8. Adelborg K, Kristensen NR, Norgaard M, *et al*. Cardiovascular and bleeding outcomes in a population-based cohort of patients with chronic immune thrombocytopenia. *J Thromb Haemost* 2019; 17: 912–924.
9. Efficace F, Mandelli F, Fazi P, *et al*. Health-related quality of life and burden of fatigue in patients with primary immune thrombocytopenia by phase of disease. *Am J Hematol* 2016; 91: 995–1001.
10. Rodeghiero F, Stasi R, Gernsheimer T, *et al*. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood* 2009; 113: 2386–2393.
11. Cooper N and Ghanima W. Immune thrombocytopenia. *N Engl J Med* 2019; 381: 945–955.
12. Kuter DJ. Novel therapies for immune thrombocytopenia. *Br J Haematol* 2022; 196: 1311–1328.
13. Neunert C, Terrell DR, Arnold DM, *et al*. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv* 2019; 3: 3829–3866.
14. Singh A, Uzun G and Bakchoul T. Primary immune thrombocytopenia: novel insights into pathophysiology and disease management. *J Clin Med* 2021; 10: 789.
15. Mingot-Castellano ME, Bastida JM, Caballero-Navarro G, *et al*. Novel therapies to address unmet needs in ITP. *Pharmaceuticals (Basel)* 2022; 15: 779.
16. Norgaard M, Jensen AO, Engebjerg MC, *et al*. Long-term clinical outcomes of patients with primary chronic immune thrombocytopenia: a Danish population-based cohort study. *Blood* 2011; 117: 3514–3520.
17. Frederiksen H, Maegbaek ML and Norgaard M. Twenty-year mortality of adult patients with primary immune thrombocytopenia: a Danish population-based cohort study. *Br J Haematol* 2014; 166: 260–267.
18. Neunert C, Noroozi N, Norman G, *et al*. Severe bleeding events in adults and children with primary immune thrombocytopenia: a systematic review. *J Thromb Haemost* 2015; 13: 457–464.
19. Frith J, Watson S, Bolton Maggs PH, *et al*. Cognitive symptoms are common in immune thrombocytopenia and associate with autonomic symptom burden. *Eur J Haematol* 2012; 88: 224–228.
20. Trotter P and Hill QA. Immune thrombocytopenia: improving quality of life and patient outcomes. *Patient Relat Outcome Meas* 2018; 9: 369–384.
21. Terrell DR, Neunert CE, Cooper N, *et al*. Immune thrombocytopenia (ITP): current limitations in patient management. *Medicina* 2020; 56: 667.
22. Al-Samkari H, Rosovsky RP, Karp Leaf RS, *et al*. A modern reassessment of glycoprotein-specific direct platelet autoantibody testing in immune thrombocytopenia. *Blood Adv* 2020; 4: 9–18.
23. Zufferey A, Kapur R and Semple JW. Pathogenesis and therapeutic mechanisms in immune thrombocytopenia (ITP). *J Clin Med* 2017; 6: 16.
24. Grodzielski M, Di Buduo CA, Goette NP, *et al*. Autoantibodies in immune thrombocytopenia affect the physiological interaction between megakaryocytes and bone marrow extracellular matrix proteins. *Br J Haematol* 2018; 183: 319–323.
25. Peerschke EI, Andemariam B, Yin W, *et al*. Complement activation on platelets correlates with a decrease in circulating immature platelets in patients with immune thrombocytopenic purpura. *Br J Haematol* 2010; 148: 638–645.
26. Reis ES, Mastellos DC, Hajishengallis G, *et al*. New insights into the immune functions

of complement. *Nat Rev Immunol* 2019; 19: 503–516.

27. Jiang Y, Tang Y, Hoover C, *et al*. Kupffer cell receptor CLEC4F is important for the destruction of desialylated platelets in mice. *Cell Death Differ* 2021; 28: 3009–3021.
28. Lopez-Herrera G, Vargas-Hernandez A, Gonzalez-Serrano ME, *et al*. Bruton's tyrosine kinase – an integral protein of B cell development that also has an essential role in the innate immune system. *J Leukoc Biol* 2014; 95: 243–250.
29. Crofford LJ, Nyhoff LE, Sheehan JH, *et al*. The role of Bruton's tyrosine kinase in autoimmunity and implications for therapy. *Expert Rev Clin Immunol* 2016; 12: 763–773.
30. Weber ANR, Bittner Z, Liu X, *et al*. Bruton's tyrosine kinase: an emerging key player in innate immunity. *Front Immunol* 2017; 8: 1454.
31. Weber ANR, Bittner ZA, Shankar S, *et al*. Recent insights into the regulatory networks of NLRP3 inflammasome activation. *J Cell Sci* 2020; 133: jcs248344.
32. Bradshaw JM, McFarland JM, Paavilainen VO, *et al*. Prolonged and tunable residence time using reversible covalent kinase inhibitors. *Nat Chem Biol* 2015; 11: 525–531.
33. Langrish CL, Bradshaw JM, Francesco MR, *et al*. Preclinical efficacy and anti-inflammatory mechanisms of action of the Bruton tyrosine kinase inhibitor rilzabrutinib for immune-mediated disease. *J Immunol* 2021; 206: 1454–1468.
34. Owens TD, Brameld KA, Verner EJ, *et al*. Discovery of reversible covalent Bruton's tyrosine kinase inhibitors PRN473 and PRN1008 (rilzabrutinib). *J Med Chem* 2022; 65: 5300–5316.
35. Smith PF, Krishnarajah J, Nunn PA, *et al*. A phase I trial of PRN1008, a novel reversible covalent inhibitor of Bruton's tyrosine kinase, in healthy volunteers. *Br J Clin Pharmacol* 2017; 83: 2367–2376.
36. von Hundelshausen P and Siess W. Bleeding by Bruton tyrosine kinase-inhibitors: dependency on drug type and disease. *Cancers (Basel)* 2021; 13: 1103.
37. Lipsky A and Lamanna N. Managing toxicities of Bruton tyrosine kinase inhibitors. *Hematology Am Soc Hematol Educ Program* 2020; 2020: 336–345.
38. Ucpinar S, Darpo B, Neale A, *et al*. A thorough QTc study to evaluate the effects of oral rilzabrutinib administered alone and with ritonavir in healthy subjects. *Clin Transl Sci* 2022; 15: 1507–1518.
39. Kuter DJ, Efraim M, Mayer J, *et al*. Rilzabrutinib, an oral BTK inhibitor, in immune thrombocytopenia. *N Engl J Med* 2022; 386: 1421–1431.
40. Study to evaluate rilzabrutinib in adults and adolescents with persistent or chronic immune thrombocytopenia (ITP) (LUNA 3) (NCT04562766), https://clinicaltrials.gov/ct2/show/NCT04562766 (Accessed 28 October 2022).
41. 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) (EudraCT Number: 2020-002063-60), https://www.clinicaltrialsregister.eu (accessed 28 October 2022).
42. Provan D, Arnold DM, Bussel JB, *et al*. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. *Blood Adv* 2019; 3: 3780–3817.
43. Kuter DJ. Exacerbation of immune thrombocytopenia following COVID-19 vaccination. *Br J Haematol* 2021; 195: 365–370.
44. Lee EJ, Beltrami-Moreira M, Al-Samkari H, *et al*. SARS-CoV-2 vaccination and ITP in patients with de novo or preexisting ITP. *Blood* 2022; 139: 1564–1574.
45. Kuter DJ, Bussel JB, Cooper N, *et al*. LUNA3 phase III multicenter, double-blind, randomized, placebo-controlled trial of the oral BTK inhibitor rilzabrutinib in adults and adolescents with persistent or chronic immune thrombocytopenia. *Blood* 2021; 138(Suppl. 1): abstract 1010.
46. Mathias SD, Bussel JB, George JN, *et al*. A disease-specific measure of health-related quality of life in adults with chronic immune thrombocytopenic purpura: psychometric testing in an open-label clinical trial. *Clin Ther* 2007; 29: 950–962.
47. Mathias SD, Li X, Eisen M, *et al*. A phase 3, randomized, double-blind, placebo-controlled study to determine the effect of romiplostim on health-related quality of life in children with primary immune thrombocytopenia and associated burden in their parents. *Pediatr Blood Cancer* 2016; 63: 1232–1237.

48. Page LK, Psaila B, Provan D, *et al.* The immune thrombocytopenic purpura (ITP) bleeding score: assessment of bleeding in patients with ITP. *Br J Haematol* 2007; 138: 245–248.

49. Kuter DJ, Bussel JB, Lyons RM, *et al.* Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. *Lancet* 2008; 371: 395–403.

50. Ghanima W, Khelif A, Waage A, *et al.* Rituximab as second-line treatment for adult immune thrombocytopenia (the RITP trial): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2015; 385: 1653–1661.

51. Bussel J, Arnold DM, Grossbard E, *et al.* Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: results of two phase 3, randomized, placebo-controlled trials. *Am J Hematol* 2018; 93: 921–930.

52. Jurczak W, Chojnowski K, Mayer J, *et al.* Phase 3 randomised study of avatrombopag, a novel thrombopoietin receptor agonist for the treatment of chronic immune thrombocytopenia. *Br J Haematol* 2018; 183: 479–490.

53. Bussel JB, Arnold DM, Boxer MA, *et al.* Long-term fostamatinib treatment of adults with immune thrombocytopenia during the phase 3 clinical trial program. *Am J Hematol* 2019; 94: 546–553.

54. Newton JL, Reese JA, Watson SI, *et al.* Fatigue in adult patients with primary immune thrombocytopenia. *Eur J Haematol* 2011; 86: 420–429.

55. Hill QA and Newland AC. Fatigue in immune thrombocytopenia. *Br J Haematol* 2015; 170: 141–149.

56. Audia S and Bonnotte B. Emerging therapies in immune thrombocytopenia. *J Clin Med* 2021; 10: 1004.

57. Kuter DJ, Ghanima W, Khan U, *et al.* Clinical predictors of response to rilzabrutinib therapy in patients with immune thrombocytopenia: exploratory analysis of a phase 1/2 study. *Blood (ASH)* 2022; 140: abstract 2450.