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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Wayrilz (Rilzabrutinib)
Treatment of immune thrombocytopenia
EU/3/20/2278

Sponsor: Sanofi B.V.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance(s)	Rilzabrutinib
Other name(s)	Wayrilz, Rilzabrutinib
International Non-Proprietary Name	Rilzabrutinib
Tradename	Wayrilz
Orphan condition	Treatment of immune thrombocytopenia
Sponsor's details:	Sanofi B.V. Paasheuvelweg 25 1105 BP Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Clinical Network Services (NL) B.V.
COMP opinion	23 April 2020
EC decision	4 June 2020
EC registration number	EU/3/20/2278
Post-designation procedural history	
Transfer of sponsorship	Transfer from Clinical Network Services (NL) B.V. to Sanofi B.V. – EC decision of 10 February 2022
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Daniela Philadelphy / Alexandre Moreau
Applicant	Sanofi B.V.
Application submission	26 September 2024
Procedure start	31 October 2024
Procedure number	EMA/H/C/006425/0000
Invented name	Wayrilz
Therapeutic indication	Wayrilz is indicated for the treatment of immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments. Further information on Wayrilz can be found in the European public assessment report (EPAR) on the Agency's website : https://www.ema.europa.eu/en/medicines/human/EPAR/Wayrilz
CHMP opinion	16 October 2025
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Frauke Naumann-Winter / Cécile Dop
Sponsor's report submission	31 January 2025
COMP discussion	4-6 November 2025
COMP opinion	6 November 2025

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2020 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing rilzabrutinib was considered justified based on preliminary clinical observations showing increase in platelet counts in patients with relapsed chronic immune thrombocytopenia;
- the condition is life-threatening and chronically debilitating due to bleeding, which may occur without an obvious precipitating event and can involve the skin, oral cavity and gastrointestinal tract, as well as manifest with intracranial haemorrhage;
- the condition was estimated to be affecting less than 3 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing rilzabrutinib will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients who did not respond to previous existing treatments responded to treatment with the proposed product. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing rilzabrutinib as an orphan medicinal product for the orphan condition: treatment of immune thrombocytopenia.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Immune thrombocytopenia (ITP) is an acquired immune-mediated disorder defined by isolated thrombocytopenia with platelet counts persistently below 100 × 10^9/L (Matzdorff et al., 2018). Most cases (~80%) are primary with no identifiable cause, reflecting the disorder's immune basis (Provan et al., 2010). Its aetiology is multifactorial, involving genetic susceptibility and environmental triggers (Cooper and Bussel, 2006). Although familial ITP is rare, polymorphisms in immune-regulatory genes such as LTA and Fcγ receptors may contribute to disease risk or chronicity (Carcao et al., 2003;

Johnsen, 2012). Secondary ITP may occur in association with autoimmune or lymphoproliferative disorders, infections, drug exposures, vaccinations, or post-transfusion purpura (Cines et al., 2009).

ITP pathophysiology reflects both increased platelet destruction and impaired production. Autoantibodies drive Fc-mediated platelet clearance (Grozovsky et al., 2015a, 2015b; Swinkels et al., 2018), while autoreactive B cells, plasma cells, and dysregulated BAFF impair immune tolerance (Zufferey et al., 2017). T-cell cytotoxicity and reduced regulatory T-cell activity further contribute (Olsson et al., 2003). Megakaryocyte injury and inadequate thrombopoietin responses can limit thrombopoiesis (Fielder et al., 1996; Grozovsky et al., 2015b). Mechanisms in secondary ITP differ by underlying trigger (Cines et al., 2009).

Clinical presentation is variable and not strictly correlated with platelet count (Arnold, 2015). Bleeding ranges from petechiae to rare intracranial haemorrhage, with severe bleeding risk increasing substantially below 30 × 10^9/L (Matzdorff et al., 2018). Nonetheless, 30–40% of chronic ITP patients remain asymptomatic (Bussel et al., 2009; Gernsheimer et al., 2010). One to two thirds eventually achieve remission, and overall mortality in adults is low (Kuter et al., 2008; Neunert et al., 2013; Tarantino et al., 2016). Beyond bleeding, fatigue, cognitive symptoms, reduced quality of life, and thromboembolic events are common (Cooper et al., 2021; Neunert et al., 2019; Frith et al., 2012; Lafaurie et al., 2021). Active disease is associated with increased inflammasome activation and endothelial and neutrophil activation markers (Garabet et al., 2020; Qiao et al., 2016; Hill et al., 2015).

ITP is classified by duration as newly diagnosed (<3 months), persistent (3–12 months), or chronic (≥12 months), guiding expectations regarding remission and treatment strategy (Matzdorff et al., 2018) and responsiveness to treatment. Management focuses on preventing bleeding, promoting remission where possible, and optimizing long-term quality of life.

The condition is acceptable for orphan designation.

The approved therapeutic indication "WAYRILZ is indicated for the treatment of immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (see section 5.1)″ falls within the scope of the designated orphan condition "Treatment of immune thrombocytopenia".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

ITP remains a chronically debilitating and potentially life-threatening condition, consistent with its status at the time of rilzabrutinib's orphan designation. Bleeding is the most serious complication, contributing substantially to morbidity, mortality, quality-of-life impairment, and treatment decisions (Neunert et al., 2015). Clinical manifestations range from petechiae and mucosal bleeding to life-threatening intracranial haemorrhage, which occurs more frequently in adults (1.4%) than children (0.4%) (Neunert et al., 2015). Fatal bleeding risk increases with age, reaching up to 7% in older adults (Matzdorff et al., 2018).

Chronic ITP impairs health-related quality of life (HRQoL), affecting emotional, functional, and physical domains (Matzdorff et al., 2018). Fatigue is burdensome and difficult to treat, reported by 39–59% of adults (Provan et al., 2019). Patients demonstrate markedly worse outcomes than the general population in physical and mental fatigue, activity levels, and overall HRQoL, with persistent ITP

associated with clinically meaningful deficits across multiple SF-36 domains (Provan et al., 2019). HRQoL studies in adults and children highlight the impact of fatigue, work and school limitations, and activity restrictions advised for safety (Trotter and Hill, 2018). Multiple instruments have been used to capture these patient-reported outcomes (Provan et al., 2019).

Infections represent another cause of morbidity and mortality. Newly diagnosed adults have an estimated 24% infection rate, largely driven by immunosuppressive therapies such as corticosteroids or splenectomy, although the relative contribution of disease versus treatment remains unclear (Qu et al., 2018; Sandvad et al., 2021). Infections are associated with poorer treatment responses and lower platelet counts. Chronic bleeding may also lead to iron-deficiency anaemia, contributing to fatigue and functional impairment (Matzdorff et al., 2018).

Number of people affected or at risk

The sponsor estimated the prevalence of immune thrombocytopenia (ITP) in the European Union (EU) following the methodological framework outlined in the "*Points to consider on the estimation and reporting on the prevalence of a condition for the purpose of orphan designation."* The analysis incorporated both prevalence and incidence data for primary and secondary ITP, across paediatric and adult populations, and included newly diagnosed, persistent, and chronic disease stages.

For this purpose, a comprehensive literature search was conducted in PubMed (US National Library of Medicine and National Institutes of Health on 5 November 2019 and updated on 4 November 2024 using relevant terms. The initial search yielded 1,134 hits, with an additional 733 results identified in the updated search. Titles and abstracts were screened to identify relevant publications reporting ITP prevalence or incidence data in the EU and comparable territories. Prevalence estimates were compiled for the 27 EU Member States, Iceland, Norway, Liechtenstein, and England.

The sponsor noted that many publications reported prevalence for specific ITP subgroups (e.g., chronic or primary forms) and therefore applied correction factors to estimate total ITP prevalence. These included:

- Adjustment for chronic disease proportion in adults (60%) (Matzdorff et al., 2018) and in children (25%) (Heitink-Pollé et al., 2014);
- Adjustment for the proportion of primary versus secondary ITP (80% primary, 20% secondary) (Matzdorff et al., 2018);
- Adjustment for the adult-to-paediatric case ratio, assuming 70% of ITP patients are adults (Terrell et al., 2013).

Studies with methodological limitations or uncertain validity were excluded from computation. To avoid bias, only one value per country was retained when multiple prevalence estimates were available. Based on the corrected dataset, the mean prevalence across the EU was estimated at approximately 1.2 per 10,000 persons.

Given the chronic and fluctuating nature of ITP, prevalence was also derived from incidence data using disease duration estimates. The sponsor identified that most adult ITP cases are chronic (Despotovic and Grimes, 2018; Cuker et al., 2015), while the majority of paediatric cases resolve within 6–12 months, with only 20–25% progressing to chronic disease (Heitink-Pollé et al., 2014). Duration estimates were supported by clinical trial data in adults, where median disease duration ranged between 1.6 and 8.5 years (Bussel et al., 2018; Kuter et al., 2013).

To approximate mean disease duration, studies reporting both incidence and prevalence were used (Christiansen et al., 2019; Matzdorff et al., 2018; Gonzalez-Lopez et al., 2024), resulting in an estimated average duration of 5.8 years (range: 3.6–7.2 years). Prevalence was then calculated by multiplying incidence rates by this duration, assuming a steady-state population. Sensitivity analyses were performed with alternative durations (5.8 and 7.5 years for adults and all ages; 3 years for paediatric cases) to reflect uncertainty and population differences.

Using this approach, the mean estimated prevalence derived from incidence data was 2.78 per 10,000 persons when a 5.8-year duration was applied, and 3.46 per 10,000 persons for a 7.5-year duration. The sponsor considered the estimate of 2.78 per 10,000 (95% CI: 2.05–3.52; n=16 studies) as the most representative and conservative value for the EU population.

The sponsor noted discrepancies between prevalence directly reported in epidemiological studies (mean 1.2/10,000) and those derived from incidence-based calculations (mean 2.78/10,000). This divergence was attributed to potential underestimation in field studies due to difficulties in capturing relapsing-remitting courses of ITP, variability in data quality and case ascertainment across healthcare databases, and challenges in distinguishing acute from chronic cases within registry data.

In contrast, incidence-based estimates were considered more robust due to standardized diagnostic ascertainment and easier capture of new cases. Therefore, prevalence derived from incidence data was prioritized for the final estimate.

The final calculated value of 2.78 per 10,000 (95% CI: 2.05–3.52) is consistent with prior estimates submitted to the EMA for similar designations (1.8–3.5 per 10,000).

Assessing ITP prevalence is complex because the disorder is highly heterogeneous including both primary and secondary forms as well has having both acute (and transient) and chronic developments. Reliance on purely administrative data as e.g. in Lawrie et al. 2023, risks overestimating true prevalence.

The COMP therefore agrees with the sponsors approach and concludes on a prevalence of approximately 3 per 10,000 persons. This estimate was selected as a conservative and comprehensive representation of the condition’s frequency, considering both adult and paediatric populations and the chronic-relapsing nature of the disease.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The therapeutic objective in primary immune thrombocytopenia (ITP) is not to normalise platelet counts, but to achieve and maintain platelet levels that minimize bleeding risk, while considering treatment toxicity and preserving quality of life. Current guidelines emphasize individualised treatment based on bleeding severity, comorbidities, patient lifestyle, and treatment preferences. Recommended therapeutic goals include (i) prevention of severe bleeding episodes, (ii) maintaining platelet counts generally >20–30 × 10^9/L in symptomatic patients, (iii) minimizing treatment toxicity, and (iv) improving health-related quality of life.

Treatment strategies differ between adults and children due to differences in disease course. In adults, ITP is more often persistent or chronic, whereas in younger children it is frequently acute and self-limited.

- **Adults**

First-line treatment

Systemic corticosteroids are the standard initial therapy. They suppress autoantibody-mediated platelet destruction and enhance platelet production (Khan et al., 2017). Although initial responses occur in 70–90% of patients, lasting remissions are uncommon (~5–6%), and adverse effects (hypertension, metabolic disturbance, osteoporosis) limit long-term use. Intravenous immunoglobulin (IVIg) is also widely used in the first-line setting, particularly when a rapid rise in platelet counts is required (e.g. before surgery or in active bleeding). IVIg produces transient responses (~80%), usually within 1–4 days but lasting only 1–2 weeks (Martínez-Carballeira et al., 2024). Anti-D immunoglobulin has been withdrawn from the EU market.

Second-line treatment

Most adult patients relapse after corticosteroid tapering; therefore second-line treatments are used for inadequate response, relapse, or steroid intolerance. Treatment choice is individualized with increased attention to long-term toxicity, comorbidities, and patient preference.

Thrombopoietin receptor agonists (TPO-RAs)
Romiplostim, eltrombopag, and avatrombopag are centrally authorised in the EU for adult patients with ITP refractory to other treatments, the latter only for chronic ITP. They increase platelet production and induce lasting responses in 40–60% of patients. Key limitations include the risk of thromboembolic events, concerns regarding bone marrow reticulin changes, variable platelet stability requiring ongoing monitoring, and fatigue, which is common in ITP and may worsen on treatment. TPO-RAs have markedly reduced the frequency of splenectomy in Europe.

Fostamatinib (SYK inhibitor)
Fostamatinib is indicated for chronic ITP refractory to other treatments. In placebo-controlled studies, stable platelet responses were observed in ~17% of treated patients. Time to benefit is typically rapid (~2 weeks). Its use is limited by adverse events such as hypertension, diarrhoea, hepatotoxicity, and increased infection risk. It is contraindicated in children due to effects on bone development.

Rituximab
Rituximab (off-label) leads to B-cell depletion and has demonstrated remission in a subset of patients; however, long-term sustained responses remain low (~20% at 5 years). Infection risk and delayed immunosuppression are relevant considerations.

Splenectomy
Splenectomy remains an established option for patient's refractory to several medical therapies, with sustained response rates of 50–75% at 5 years. Surgical and long-term infectious risks (including overwhelming post-splenectomy sepsis) have reduced its early use.

Other options
Azathioprine, mycophenolate mofetil, cyclosporine A, danazol, dapsone and vincristine may be considered, although evidence is limited and toxicity may constrain use.

- **Children**

In children with newly diagnosed ITP and minimal bleeding, observation is preferred even with very low platelet counts, given the typical spontaneous recovery. Where treatment is indicated, first-line options mirror adults (corticosteroids, IVIg). Second- or third-line therapies for persistent or chronic paediatric ITP are not standardized; combination therapy is often applied (Matzdorff et al., 2018, Provan et al., 2019). Romiplostim and eltrombopag are approved in children ≥1 year refractory to first-line therapies. Fostamatinib is contraindicated in paediatric ITP.

- **Approved medicinal products in the EU/EEA**

Multiple products are authorised for ITP in the EU/EEA, including intravenously administered immunoglobulins, systemic corticosteroids, TPO-RAs, and fostamatinib. Table 1 summarises the centrally and nationally authorised medicinal products currently available for ITP treatment.

Trade name	Active substance	Authorisation	Indication	Date of Authorisation	Market Authorisation Holder
Octagam	Human normal immunoglobulin	National procedure	Immunomodulation in adults, children and adolescents (0-18 years), in primary immune thrombocytopenia (ITP) where patients are at high risk of bleeding or prior to surgery to correct the platelet count	21/05/1997	Octapharma Limited
Vigam Liquid	Human normal immunoglobulin	National procedure	Immunomodulation in adults, children and adolescents (0-18 years), in ITP where patients are at high risk of bleeding or prior to surgery to correct the platelet count	29/10/1997	Bio Products Laboratory Ltd
Intratect	Human normal immunoglobulin	National procedure	Immunomodulation in adults, children and adolescents (0-18 years), in ITP where patients are at high risk of bleeding or prior to surgery to correct the platelet count	10/01/2006	Biotest (UK) Ltd
Kiovig	Human normal immunoglobulin	Centralised procedure	Immunomodulation in adults, children and adolescents (0-18 years), in ITP where patients are at high risk of bleeding or prior to surgery to correct the platelet count	18/01/2006	Baxter AG
Gamunex	Human normal immunoglobulin	National procedure	Immunomodulation in adults, children and adolescents (0-18 years), in ITP where patients are at high risk of bleeding or prior to surgery to correct the platelet count	27/07/2006	Grifols UK Ltd

Trade name	Active substance	Authorisation	Indication	Date of Authorisation	Market Authorisation Holder
Flebogamma DIF	Human normal immunoglobulin	Centralised procedure	Immunomodulation in adults, children and adolescents (0-18 years), in ITP where patients are at high risk of bleeding or prior to surgery to correct the platelet count	23/07/2007	Instituto Grifols S.A.
Privigen	Human normal immunoglobulin	Centralised procedure	Immunomodulation in adults, children and adolescents (0-18 years), in ITP where patients are at high risk of bleeding or prior to surgery to correct the platelet count	24/04/2008	CSL Behring GmbH
Nplate	Romiplostim	Centralised procedure	Nplate is indicated for the treatment of primary immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1). Paediatrics: Nplate is indicated for the treatment of chronic primary immune thrombocytopenia (ITP) in paediatric patients one year of age and older who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).	04/02/2009	Amgen Europe B.V.
Revolade	Eltrombopag olamine	Centralised procedure	Revolade is indicated for the treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Revolade is indicated for the treatment of paediatric patients aged 1 year and above with primary immune thrombocytopenia (ITP) lasting 6 months or	11/03/2010	Novartis Europharm Limited

Trade name	Active substance	Authorisation	Indication	Date of Authorisation	Market Authorisation Holder
			longer from diagnosis and who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)		
Gammaplex	Human normal immunoglobulin	National procedure	Immunomodulation in adults, children and adolescents (0-18 years), in ITP where patients are at high risk of bleeding or prior to surgery to correct the platelet count	05/10/2014	Bio Products Laboratory Ltd
Panzyga	Human normal immunoglobulin	National procedure	Immunomodulation in adults, children and adolescents (0-18 years), in ITP where patients are at high risk of bleeding or prior to surgery to correct the platelet count	24/02/2016	Octapharma Ltd.
IQYMUNE	Human normal immunoglobulin	National procedure	Immunomodulation in adults, children and adolescents (0-18 years), in ITP where patients are at high risk of bleeding or prior to surgery to correct the platelet count	08/03/2016	LFB Biopharmaceuticals Limited
Doptelet	Avatrombopag	Centralised procedure	Doptelet is indicated for the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)	20/06/2019	Swedish Orphan Biovitrum AB
Tavlesse	Fostamatinib	Centralised Procedure	Tavlesse is indicated for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (see section 5.1)	09/01/2020	Instituto Grifols S.A.

Trade name	Active substance	Authorisation	Indication	Date of Authorisation	Market Authorisation Holder
Multiple	Azathioprine	Decentralised procedure	chronic refractory idiopathic thrombocytopenic purpura	Multiple	Multiple
Multiple	Dexamethasone	National procedure	treatment of diseases of the blood (e.g. idiopathic thrombocytopenic purpura in adults)	Multiple	Multiple
Multiple	Methylprednisolone	Decentralised	Idiopathic thrombocytopenic purpura in adults	Multiple	Multiple
Multiple	Prednisone	National, decentralised	Thrombocytopenic purpura Thrombocytopenia	Multiple	Multiple
Multiple	Prednisolone	National	idiopathic thrombo-cytopenic purpura.	Multiple	Multiple
Multiple	Vincristine	National	Idiopathic thrombocytopenic purpura. Patients with true ITP refractory to splenectomy and short-term treatment with adrenocortical steroids may respond to vincristine but the medicinal product is not recommended as primary treatment of this	Multiple	Multiple

Trade name	Active substance	Authorisation	Indication	Date of Authorisation	Market Authorisation Holder
			disorder. Recommended weekly doses of vincristine given for 3 to 4 weeks have produced permanent remissions in some patients. If patients fail to respond after 3 to 6 doses, it is unlikely that there will be any beneficial results with additional doses.		

In accordance with Article 3(1)(b) of Regulation (EC) No 141/2000, the assessment of satisfactory methods is based on whether there are any authorised medicinal products in the Union that are indicated for the same condition as that covered by the authorised indication of WAYRILZ, or for a broader patient population.

WAYRILZ (rilzabrutinib) is indicated for the treatment of immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments.

Corticosteroids, intravenous immunoglobulins, romiplostim, and eltrombopag are considered to cover the same or a broader patient population than WAYRILZ and are therefore defined as satisfactory methods.

Significant benefit

To support the significant benefit arguments, the sponsor argues that the therapeutic goal in ITP is to maintain platelet counts at levels sufficient to prevent clinically relevant bleeding while minimising treatment-related toxicity and addressing non-haematological symptoms such as fatigue. The sponsor states that current treatments, although often effective at transiently increasing platelet counts, do not fully address the broader symptom burden of ITP and may introduce additional risks. In their view, corticosteroids and immunosuppressants are associated with infection and metabolic complications; thrombopoietin receptor agonists (TPO-RAs) with an increased risk of thrombosis; and fostamatinib and certain TPO-RAs (romiplostim, avatrombopag) with fatigue, further impairing quality of life.

In this context, the sponsor proposes that rilzabrutinib, a reversible covalent Bruton's tyrosine kinase (BTK) inhibitor, offers a novel mechanism of action and provides a clinically relevant advantage for adult patients with ITP refractory to prior therapies based on their clinical trial in the persistent and chronic setting. According to the sponsor, rilzabrutinib addresses key unmet needs by delivering durable platelet responses, reducing bleeding, improving health-related quality of life - particularly fatigue - and maintaining an acceptable safety profile.

Significant benefit of rilzabrutinib over corticosteroids and intravenous immunoglobulins (IVIg)

Corticosteroids and IVIg remain the standard first-line therapies for immune thrombocytopenia (ITP). Both interventions typically produce transient platelet increases but are associated with limitations. Corticosteroids are linked to metabolic and immunological toxicity, and their prolonged use does not improve response rates (Matzdorff et al., 2018; Provan et al., 2019). IVIg provides a rapid but short-lived increase in platelet counts and is generally reserved for emergency management or pre-surgical interventions due to its transient efficacy and potential adverse effects, including thromboembolic complications.

The pivotal Phase 3 study LUNA-3 (PRN1008-018) enrolled patients with persistent or chronic ITP who were refractory to one or more prior therapies. The median number of previous unique ITP treatments was four (range 1–15), including corticosteroids and IVIg for 95% and 54% of patients, respectively. These baseline data reflect a population representative of patients who had failed conventional first-line therapies.

- Efficacy in corticosteroid-refractory patients

Subgroup analyses in participants with prior corticosteroid exposure showed that 23.6% of patients treated with rilzabrutinib achieved a durable platelet response, compared with 0% in the placebo group (Table 2), which was consistent with the overall trial result. Comparable response rates were reported irrespective of concomitant corticosteroid use during the double-blind period. Among patients with

prior corticosteroid use, but no concomitant corticosteroids, 23.6% achieved a durable response (placebo: 0%), and among those with both prior and concomitant corticosteroid use, 23.5% achieved a durable response (placebo: 0%). In the subgroup receiving both concomitant corticosteroids and TPO-RAs, 23.8% achieved a durable response with rilzabrutinib versus 0% with placebo.

During the long-term extension (LTE), 47% (16/34) of patients receiving concomitant corticosteroids reduced their corticosteroid dose by more than 50%, and 23% (11/47) discontinued all concomitant ITP therapies (corticosteroids or TPO-RAs) while maintaining platelet counts on rilzabrutinib monotherapy.

Table 1. Subgroup analysis (prior and/or concomitant ITP medications excluding rescue therapy) on primary endpoint durable platelet response - Adult ITT population.

	Placebo (N=69)			**Rilzabrutinib 400 mg BID (N=133)**			**vs.Placebo**	
Subset, n (%)	N	n (%)	95% CI[a]	N	n (%)	95% CI[a]	Difference[b]	95% CI[b]
Prior CS								
No	3	0 (0.0)	0.00 , 0.00	6	1 (16.7)	0.00 , 46.49	16.7	-13.15 , 46.49
Yes	66	0 (0.0)	0.00 , 0.00	127	30 (23.6)	16.23 , 31.01	23.6	16.23 , 31.01
No concomitant CS	32	0 (0.0)	0.00 , 0.00	72	17 (23.6)	13.80 , 33.42	23.6	13.80 , 33.42
Concomitant CS	20	0 (0.0)	0.00 , 0.00	34	8 (23.5)	9.27 , 37.79	23.5	9.27 , 37.79
Concomitant CS and TPO-RA	14	0 (0.0)	0.00 , 0.00	21	5 (23.8)	5.59 , 42.03	23.8	5.59 , 42.03
Prior TPO-RA								
No	18	0 (0.0)	0.00 , 0.00	45	11 (24.4)	11.89 , 37.00	24.4	11.89 , 37.00
Yes	51	0 (0.0)	0.00 , 0.00	88	20 (22.7)	13.97 , 31.48	22.7	13.97 , 31.48
No concomitant TPO-RA	25	0 (0.0)	0.00 , 0.00	42	6 (14.3)	3.70 , 24.87	14.3	3.70 , 24.87
Concomitant TPO-RA	12	0 (0.0)	0.00 , 0.00	25	9 (36.0)	17.18 , 54.82	36.0	17.18 , 54.82
Concomitant TPO-RA and CS	14	0 (0.0)	0.00 , 0.00	21	5 (23.8)	5.59 , 42.03	23.8	5.59 , 42.03
Prior CS or TPO-RA								
Prior Neither *	0	0 (NA)	NA , NA	3	0 (0.0)	0.00 , 0.00		
Prior Either	69	0 (0.0)	0.00 , 0.00	130	31 (23.8)	16.52 , 31.17	23.8	16.52 , 31.17
Concomitant neither *	23	0 (0.0)	0.00 , 0.00	50	9 (18.0)	7.35 , 28.65	18.0	7.35 , 28.65
Concomitant either	46	0 (0.0)	0.00 , 0.00	80	22 (27.5)	17.72 , 37.28	27.5	17.72 , 37.28

	Placebo (N=69)			**Rilzabrutinib 400 mg BID (N=133)**			**vs.Placebo**	
Concomitant CS/TPO-RA medications								
CS but no TPO-RA	20	0 (0.0)	0.00 , 0.00	34	8 (23.5)	9.27 , 37.79	23.5	9.27 , 37.79
TPO-RA but no CS	12	0 (0.0)	0.00 , 0.00	25	9 (36.0)	17.18 , 54.82	36.0	17.18 , 54.82
Both CS and TPO-RA	14	0 (0.0)	0.00 , 0.00	21	5 (23.8)	5.59 , 42.03	23.8	5.59 , 42.03
Neither CS nor TPO-RA**	23	0 (0.0)	0.00 , 0.00	53	9 (17.0)	6.87 , 27.09	17.0	6.87 , 27.09
Prior ITP medication category [n (%)]								
Prior 1st line [c]	7	0 (0.0)	0.00 , 0.00	26	6 (23.1)	6.88 , 39.27	23.1	6.88 , 39.27
Prior 2nd line plus [d]	62	0 (0.0)	0.00 , 0.00	107	25 (23.4)	15.35 , 31.38	23.4	15.35 , 31.38

CI: confidence interval, TPO-RA: Thrombopoietin receptor agonist, CS: Corticosteroid.
Durable platelet response is defined as the proportion of 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.
[a]Asymptotic confidence interval
[b]The treatment difference for each subgroup is estimated via normal approximation without being adjusted by stratification factors
[c]1st line includes CS, IVIG, anti-D, danazol only (alone or in combination).
[d]2nd line plus includes any other medications except for the 1st line medications.
* Monotherapy.
** Monotherapy total.
Source: PRODOPS/SAR444671/EFC17093/CSR_01/REPORT/OUTPUT/eff_subgrp_plt_resp1_db_i_t_i.rtf (14JUN2024), eff_itp_duresp_db_posthoc_r_t_x.rtf (13MAR2025). PRODOPS/SAR444671/OVERALL/ITP_EMA_01/REPORT/OUTPUT/ eff_subgrp_cm_itp_db_i_t_i.rtf (11APR2025).
CI: confidence interval, TPO-RA: Thrombopoietin receptor agonist, CS: Corticosteroid.

- Efficacy in IVIg-refractory patients

Although IVIg was not permitted as rescue therapy during the study, approximately half of the participants had received IVIg before entering the study. In this subgroup, the proportion of patients achieving durable platelet response with rilzabrutinib was consistent with the overall study population, indicating benefit in patients with prior IVIg exposure and refractoriness.

Overall assessment

Overall, based on the data available from the Phase 3 study and the subgroup analyses, rilzabrutinib showed clinically relevant improvements in durable platelet response and bleeding outcomes compared with placebo in patients previously treated with corticosteroids or IVIg. These effects, together with observed reductions in concomitant corticosteroid use support the conclusion that rilzabrutinib provides a significant benefit over corticosteroids and IVIg in patients with persistent or chronic ITP refractory to these treatments.

Significant benefit of rilzabrutinib over thrombopoietin receptor agonists (TPO-RAs)

TPO-Ras, including the defined satisfactory methods for this procedure romiplostim and eltrombopag, are established second-line therapies for immune thrombocytopenia (ITP). These agents stimulate platelet production through activation of the thrombopoietin receptor on megakaryocytes with approximately 40–60% of patients achieving a lasting response. A proportion lose responsiveness over time or experience treatment-related toxicity such as thromboembolic events, hepatotoxicity (particularly with eltrombopag), and bone marrow reticulin formation. Fatigue is also commonly reported with several agents, negatively impacting quality of life. In practice, a subset of patients remains refractory, intolerant, or contraindicated to TPO-RA therapy, representing an unmet clinical need.

- Efficacy in TPO-RA–refractory patients

In the pivotal Phase 3 LUNA-3 study (PRN1008-018), prior exposure to TPO-RAs was frequent, occurring in 66.2% of participants in the rilzabrutinib arm and 73.9% in the placebo arm. Around one-third of these patients (34.6% and 37.7%, respectively) continued TPO-RA treatment concomitantly during the double-blind period (Table 2).

Subgroup analyses showed that durable platelet responses with rilzabrutinib were observed across categories defined by prior and concomitant TPO-RA use. Among participants with prior TPO-RA exposure, 22.7% achieved a durable response with rilzabrutinib compared with 0% in the placebo group. In those with both prior and concomitant TPO-RA use, durable response occurred in 36% versus 0%, and in those with prior but no concomitant TPO-RA use, 14% versus 0%, respectively. These results were consistent with the overall study findings.

During the long-term extension (LTE), 15 of 27 patients (56%) receiving concomitant TPO-RAs reduced or discontinued TPO-RA treatment while maintaining platelet counts on rilzabrutinib. Among all patients receiving any concomitant ITP medication (corticosteroids and/or TPO-RAs), 23% (11/47) discontinued background therapy and remained on rilzabrutinib monotherapy. These observations indicate that platelet responses were maintained in a proportion of patients despite reduction or withdrawal of concomitant therapy.

Overall assessment

Overall, the subgroup and long-term extension data indicate that durable platelet responses with rilzabrutinib were observed in patients with prior and/or concomitant TPO-RA use, and that a proportion of patients were able to reduce or discontinue background ITP therapy while maintaining

platelet counts. While interpretation is limited by the exploratory nature of subgroup analyses and the absence of a direct comparator for treatment reduction, the results are consistent with the primary efficacy findings and support the use of rilzabrutinib in patients previously treated with TPO-RAs, including those receiving concomitant therapy at baseline.

Overall, significant benefit over the relevant comparators was established based on the totality of evidence from the pivotal Phase 3 study, supported by subgroup analyses, reductions in concomitant therapy, and the comparative information submitted for corticosteroids, IVIg, and TPO-RAs, while acknowledging the limitations inherent to indirect comparisons.

4. COMP position adopted on 06 November 2025

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of immune thrombocytopenia (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 3 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to bleeding, which may occur without an obvious precipitating event and can involve the skin, oral cavity and gastrointestinal tract, as well as manifest with intracranial haemorrhage;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the claim that Wayrilz is of significant benefit to those affected by the orphan condition is established.
- In the phase 3 study, durable platelet responses were observed even in patients who had failed multiple prior therapies (including corticosteroids, intravenous immunoglobulins and thrombopoietin receptor agonists) and in those receiving concomitant standard treatment during the trial. These results support that rilzabrutinib provides a clinically relevant advantage in the refractory immune thrombocytopenia population.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Wayrilz, rilzabrutinib, for treatment of immune thrombocytopenia (EU/3/20/2278) is not removed from the Community Register of Orphan Medicinal Products.