Long-Term Efficacy and Safety With Oral Bruton Tyrosine Kinase Inhibitor Rilzabrutinib in Patients With Immune Thrombocytopenia

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Disclosures for David J. Kuter

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- Current equity holder in publicly traded company: Rubius
- Patents and royalties: Up-to-date
- Membership on entity's board of directors or advisory committees: Platelet Disorder Support Association

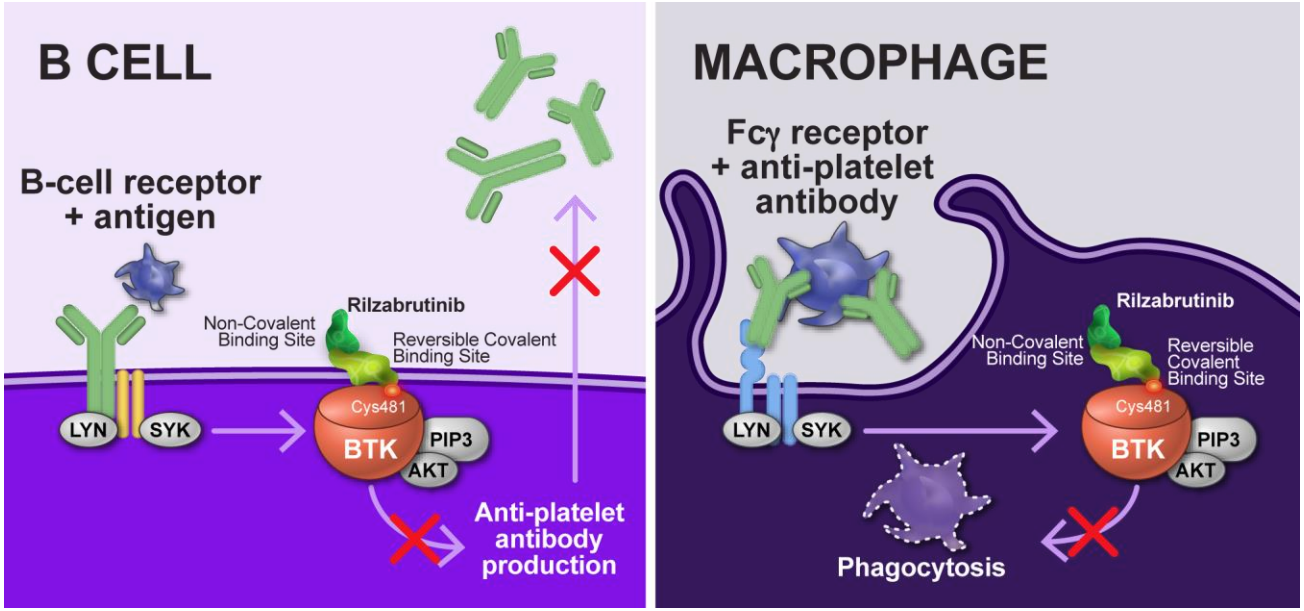
Presentation Learning Objectives

At the conclusion of this presentation, participants will be able to:

- Describe the key mechanistic effects of BTK inhibition with rilzabrutinib in ITP
- Discuss the safety and efficacy results for long-term use of rilzabrutinib in adult patients with ITP
- Summarize the long term platelet responses following extended rilzabrutinib treatment and safety profile

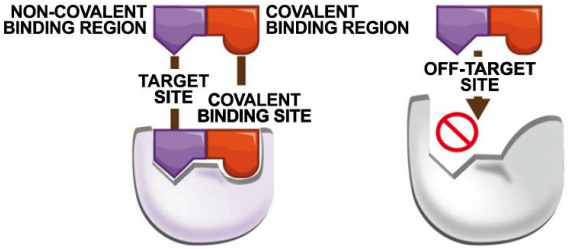
Bruton Tyrosine Kinase Inhibitor Rilzabrutinib Is Specifically Designed for Immune-Mediated Diseases

- Rilzabrutinib can mediate its therapeutic effect in ITP patients through a dual mechanism of action[1-3]
  - Inhibition of B cell activation
  - Interruption of platelet phagocytosis by FcγR in spleen and liver



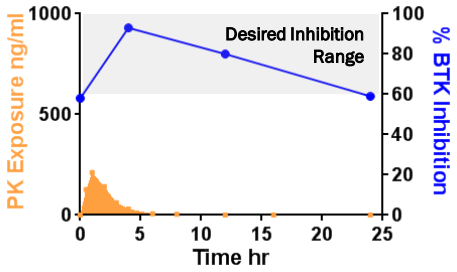
1. Bradshaw JM, et al. *Nat Chem Biol.* 2015;11:525–531. 2. Langrish C, et al. *J Immunol.* 2021;206:1454–1468. 3. Owens TD, et al. *J Med Chem.* 2022;65:5300–5316.

Rilzabrutinib Is an Oral, Reversible, Potent BTK Inhibitor and Does Not Impact Platelet Aggregation[1]



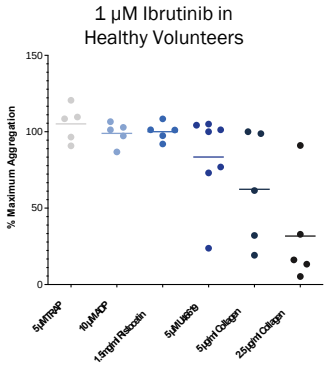
Selective/Reversible

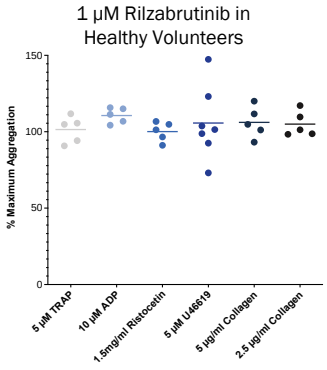
Precise Inhibition;
No Permanent Modification Of Proteins and Peptides

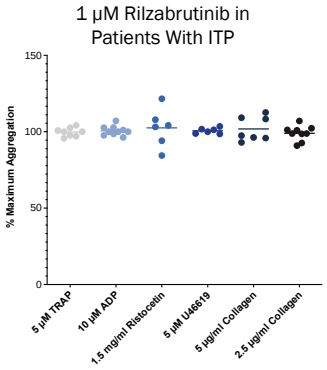


Durable BTK Inhibition With Low Exposure

Potential Optimized Clinical Benefit







No Inhibition of Platelet Aggregation

Potential Reduced Risk of Bleeding

1. Langrish CL, et al. *J Immunol.* 2021;206:1454-1468.

ISth 2023

Adaptive, Open-Label, Dose-Finding, Phase 1/2 Study of Oral Rilzabrutinib in Relapsed/Refractory ITP

Key inclusion criteria

- 18-80 years
- Response to ≥1 prior ITP therapy but no response to the previous or concomitant therapy maintained at baseline
- Platelet counts $<30\times10^9$/L on 2 occasions ≥7 days apart in the 15 days before study entry
- Stable concomitant CS and/or TPO-RA allowed

Phase 1/2: Intrapatient dose escalation

Oral Rilzabrutinib 200 and 400 mg QD, or 300 and 400 mg BID (24 wk)

Primary endpoints
- Safety
- Platelet response*

Additional endpoints
- Durable response
- Rescue medication use, bleeding grade ≥2 and scores
- Subgroup analyses

Long-term Extension (LTE)

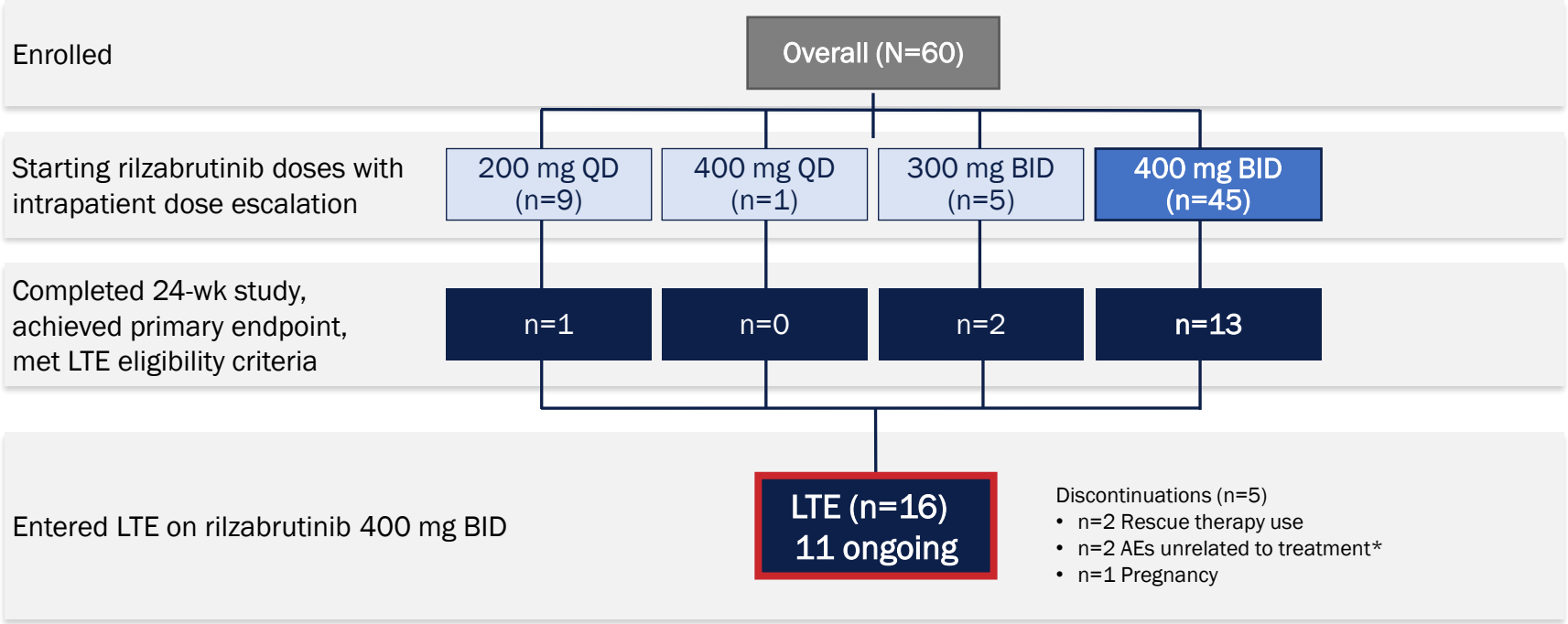
Oral Rilzabrutinib 400 mg BID

LTE endpoints
- Safety
- Platelet counts

- Initial rilzabrutinib phase 1/2 trial in ITP patients showed a 40% platelet response* and only grade 1 or 2 adverse events at all dose levels[1]
- Rilzabrutinib **400 mg BID** was identified for further testing
- Rilzabrutinib showed rapid and durable clinical activity that improved with duration of treatment

ClinicalTrials.gov: NCT03395210 EudraCT: 2017-004012-19.
*Defined as ≥2 consecutive platelet counts (separated by ≥5 days) of $\geq50\times10^9$/L and an increase from baseline of $\geq20\times10^9$/L without the use of rescue medication for ITP in the 4 weeks before the latest elevated platelet count.
BID, twice daily; CS, corticosteroid; QD, once daily; TPO-RA, thrombopoietin receptor agonist.
1. Kuter DJ, et al. *N Engl J Med.* 2022;386:1421–1431.

Patient Disposition



Data cutoff for LTE: 21 Jan 2022.
*Non-dose limiting toxicity adverse events (AEs): grade 4 thrombocytopenia and pneumonia/pulmonary embolism.

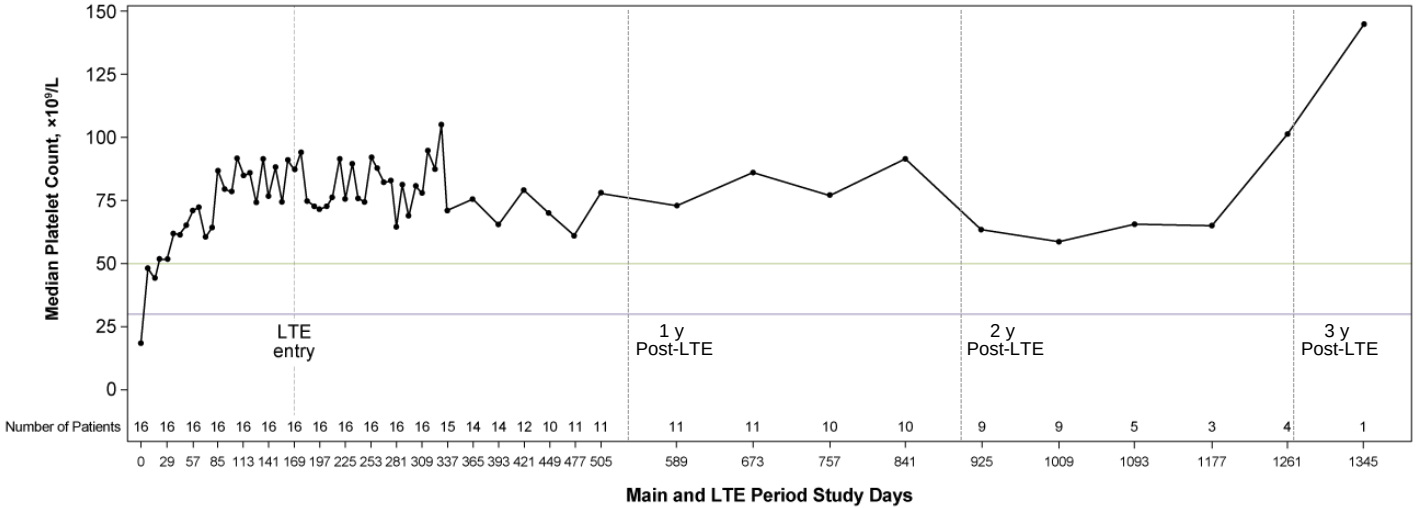
Baseline Characteristics and Prior Therapy

	All Patients (N=60)[1]	All LTE Patients (n=16)*
Median age, years (range)	50 (19-74)	49 (22-65)
Female, n (%)	34 (57)	9 (56)
Median duration of ITP, years (range)	6.3 (0.4-52.5)	4.3 (0.5-18.4)
Median platelet count, $\times 10^9$/L (range)	15 (2-33)	LTE entry: 87 (16-321)
Median number of unique prior ITP therapies (range)†	4 (1-17)	3 (1-9)
Splenectomy, n (%)	15 (25)	3 (19)
Median number of failed prior ITP therapies (range)‡	1 (0-11)	1 (0-3)

Data cutoff for main study period: 4 May 2021. Data cutoff for LTE: 21 Jan 2022/21 Dec 2022.
*Data were collected prior to entering LTE. †Unique ITP therapies were identified using standard criteria, and splenectomy was counted as one prior ITP therapy.
‡The number of failed prior ITP therapies was based on the latest record with no response. Only records with non-missing 'Was response achieved?' were included. Splenectomy was not included.
1. Kuter DJ, et al. *N Engl J Med.* 2022;386:1421–1431.

Platelet Counts in Patients Who Continued in the LTE (n=16)

- Median treatment duration was 1032 days (range, 318-1506)



	Median platelet counts
LTE entry (day 169)	87×10⁹/L
Post-LTE entry	
3 mo	92×10⁹/L
6 mo	71×10⁹/L
12 mo	61×10⁹/L
24 mo	64×10⁹/L

Data cutoff: 21 Dec 2022.

Platelet Response in LTE Patients

- Patients maintained achieved target platelet counts above multiple clinically meaningful thresholds while in the LTE irrespective of the use of concomitant therapy
- Patients achieved platelet counts ≥50×10^9/L for 88% of visits
- 14 of 16 (88%) patients achieved platelet counts ≥100×10^9/L during the LTE

Median Number (Percentage) of Visits With Platelet Counts	LTE Patients (n=16)	Rilzabrutinib Monotherapy (n=5)	Concomitant Therapy* (n=11)
≥50×10^9/L	26 (88%)	29 (94%)	26 (76%)
Increased ≥20×10^9/L from baseline	29 (93%)	31 (97%)	29 (92%)
≥30×10^9/L	32 (100%)	32 (100%)	32 (100%)

Data cutoff: 21 Dec 2022.
*Concomitant therapy included n=7 corticosteroids (CS), n=2 thrombopoietin receptor agonists (TPO-RA), and n=2 CS and TPO-RA.

Concomitant Therapy in the LTE Period

- Protocol guidelines for concomitant therapy in LTE patients
  - Taper CS dose if platelet counts ≥100×10^9/L
  - Up-titrate CS dose if platelet counts <50×10^9/L on two consecutive measurements
  - Maintain TPO-RAs dose unless there were safety concerns
- At a median of 254 days (range, 152–274) in the LTE, 5 of 11 (45%) patients receiving concomitant therapy stopped using any ITP concomitant medication*

LTE Patients (n=5)	Median platelet counts, ×10^9/L (range)
After stopping concomitant medication	103 (90–218)
3-6 mo after stopping	106 (75–166)

Data cutoff: 21 Dec 2022.
*Concomitant therapy included n=2 CS, n=1 TPO-RA, and n=2 CS and TPO-RA.

Overview of TEAEs Due to Any Cause

Patients, n (%)	All Patients During Main Treatment Period (N=60)[1]	LTE Patients During LTE Period (n=16)
Any TEAE	48 (80)	13 (81)
Any treatment-related TEAE	31 (52)	4 (25)
Any grade ≥3 TEAE	8 (13)	5 (31)
Grade ≥2 infections (under SOC infections and infestations)	6 (10)	4 (25)*
SAEs		
Any treatment emergent SAE	8 (13)	5 (31)
Any treatment-related treatment emergent SAE	0	0
Discontinued treatment and/or study due to ≥1 TEAE	7 (12)	4 (25)†
Death due to a TEAE	1 (2)‡	0

Data cutoff for main study period: 4 May 2021. Data cutoff for LTE: 21 Dec 2022.
*4 patients experienced 5 infections/infestations: grade 2 COVID-19, upper respiratory tract infection (treatment-related), and bronchitis; grade 3 COVID-19; and grade 4 COVID-19.
†Treatment-emergent adverse events (TEAEs) leading to discontinuation were thrombocytopenia (n=2), pregnancy (n=1), and migraine/thrombocytosis (n=1).; all were unrelated to treatment.
‡Patient discontinued treatment due to exacerbation of Evans syndrome, then discontinued study on Sept 24, 2020, and died on Jan 22, 2021.
1. Kuter DJ, et al. *N Engl J Med.* 2022;386:1421-31.

Treatment-Related TEAEs

- In the LTE, 4 patients overall experienced related TEAEs
- All related TEAEs were transient, grade 1 or 2
- Two patients received rescue medication in the LTE (n=0 during main treatment period)
- There were no related bleeding or thrombotic events, serious AEs or deaths

Related TEAEs (≥5%), n (%)	All Patients During Main Treatment Period (N=60)[1]		LTE Patients During LTE Period (n=16)	
	Grade 1	Grade 2	Grade 1	Grade 2
All related TEAEs	27 (45)	15 (25)	3 (19)	2 (13)
Diarrhea	16 (27)	3 (5)	1 (6)	0
Nausea	16 (27)	2 (3)	1 (6)	0
Abdominal distension	4 (7)	0	0	0
Fatigue	5 (8)	1 (2)	0	0
Upper respiratory tract infection	0	0	0	1 (6)
Cough	0	0	1 (6)	0
Rhinorrhea	0	0	0	1 (6)
Vulvovaginal dryness	0	0	0	1 (6)

Data cutoff for main study period: 4 May 2021. Data cutoff for LTE: 21 Dec 2022.

1. Kuter DJ, et al. *N Engl J Med.* 2022;386:1421-31.

Summary and Key Takeaways

Summary

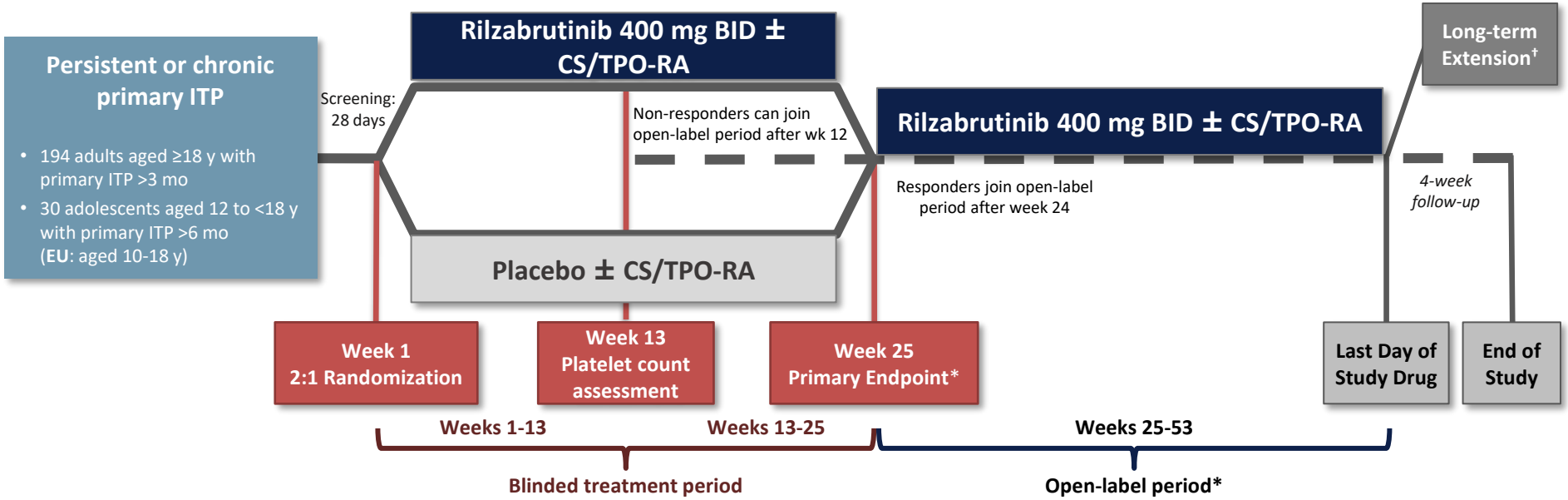
- Overall, platelet responses to rilzabrutinib in this phase 1/2 clinical trial were durable and stable over time with a favorable safety profile

Key Takeaways

- With extended rilzabrutinib treatment over a median treatment duration of 1032 days during the main + LTE periods, responses were durable with platelet counts $\geq 50 \times 10^9$/L reported in 88% of visits
- Oral rilzabrutinib 400 mg BID remains well tolerated through the LTE, with
  - Only grade 1/2 related TEAEs
  - No related thrombotic events or serious adverse events
  - No increased bleeding risk or BTK inhibitor class-associated AEs (eg, atrial fibrillation, neutropenia)

LUNA 3 Study Design

- LUNA 3 is a multicenter, double-blind, placebo-controlled phase 3 study assessing efficacy and safety of oral rilzabrutinib in adults and adolescents with persistent or chronic ITP



NCT04562766; EudraCT 2020-002063-60.
*Week 25 is the last visit of the blinded treatment period and the start of the open-label period. †Following LTE completion, patients will undergo last day of study drug and end of study assessments.

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