Pooled Analysis of the Efficacy and Safety of Oral Bruton Tyrosine Kinase Inhibitor Rilzabrutinib in Patients With Previously Treated Immune Thrombocytopenia: Phase 2 Study

David J. Kuter,[1] Robert Bird,[2] A. J. Gerard Jansen,[3] Umer Khan,[4] Ahmed Daak,[5] and Nichola Cooper[6]

[1]Hematology Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA;
[2]Princess Alexandra Hospital, Woolloongabba, Australia; [3]Erasmus MC, University Medical Center, Rotterdam, Netherlands;
[4]Biostatistics, Sanofi, Bridgewater, NJ, USA; [5]Sanofi, Cambridge, MA, USA; [6]Hammersmith Hospital, London, United Kingdom

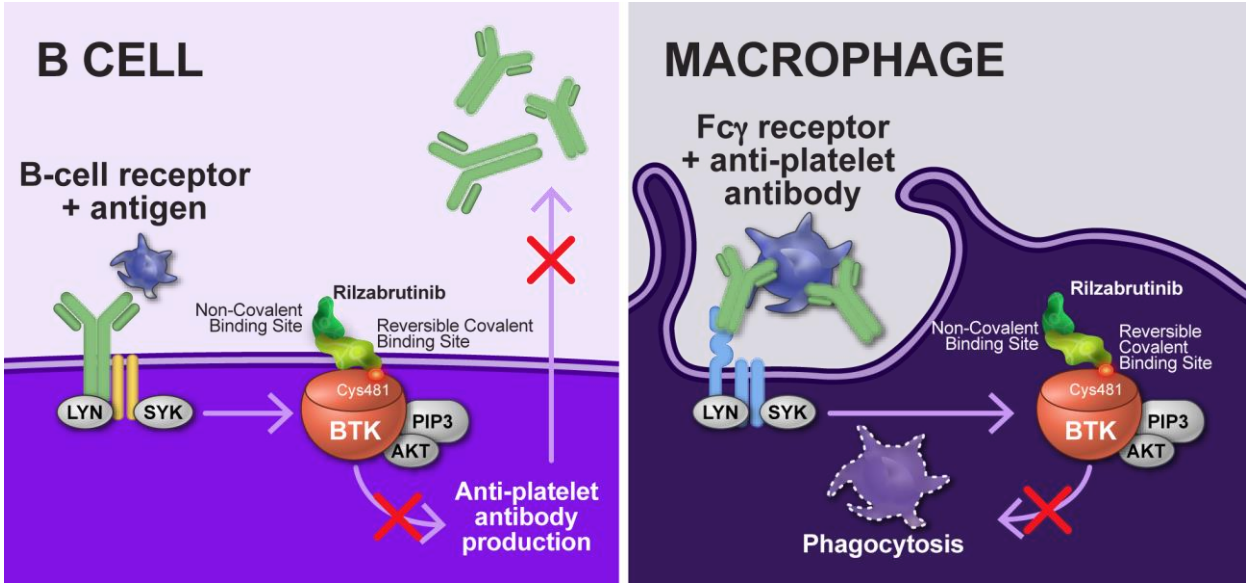
ISTH 2024 BANGKOK

Disclosures for David J. Kuter

- Employment: Massachusetts General Hospital
- Research funding for institution: Novartis, Rigel, Sanofi (Principia), Takeda (Bioverativ), UCB
- Consulting fees: AIRx, Alexion (Syntimmune), Alnylam, Alpine, Amgen, argenx, BioCryst, Bristol Myers Squibb, Caremark, Cellularity, Cellphire, Chugai, CRICO, Daiichi Sankyo, Hengrui, Immunovant, Incyte, Inmagene Biopharmaceuticals, Merck Sharp Dohme, Momenta, Novartis, Nuvig, Pfizer, Platelet Disorder Support Association, Protagonist, Rigel, Sanofi (Bioverativ), Sanofi (Principia), Sanofi (Genzyme), Sobi (Dova), Takeda, UCB, UpToDate, Zafgen
- Membership on entity's board of directors or advisory committees: Platelet Disorder Support Association

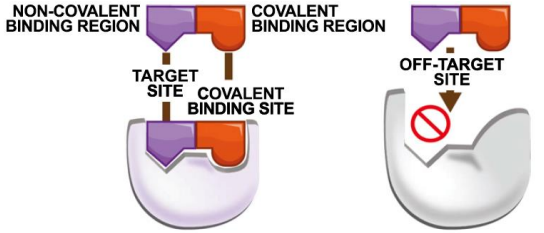
Bruton Tyrosine Kinase (BTK) Inhibitor Rilzabrutinib Is Specifically Designed for Immune-Mediated Diseases

- 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



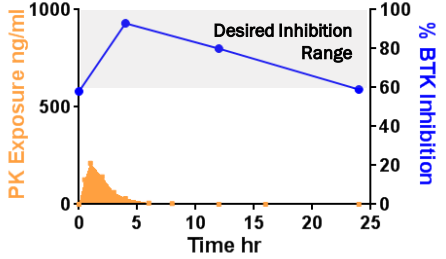
1. Langrish C, et al. *J Immunol*. 2021;206:1454-1468. 2. Owens TD, et al. *J Med Chem*. 2022;65:5300-5316. 3. Kuter DJ, et al. *Ther Adv Hematol*. 2023;14. doi: 10.1177/20406207231205431.

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



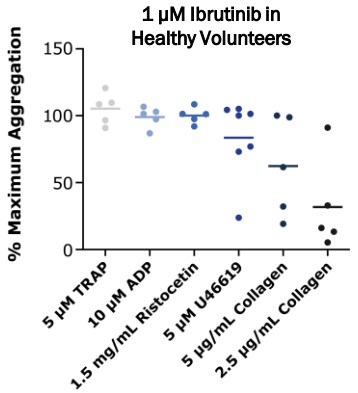
Selective/Reversible

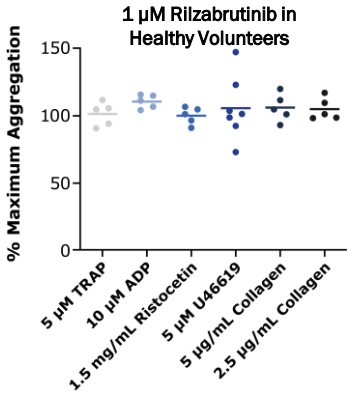
Precise Inhibition;
No Permanent Modification of Proteins and Peptides

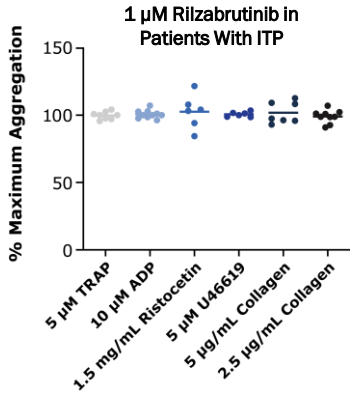


Durable BTK Inhibition With Low Exposure

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.

Phase 2 Study of Oral Rilzabrutinib in Relapsed/Refractory ITP

Eligibility criteria for ITP patients

- Aged 18-80 years
- Platelet counts <30×10^9/L
- Response to ≥1 prior ITP therapy but no response to the previous or concomitant therapy maintained at baseline
- Stable concomitant CS and/or TPO-RA allowed

Oral Rilzabrutinib 400 mg BID for 24 weeks
(main treatment period)

Part A (dose-finding) (included n=45 initiating 400 mg BID)	**Part B** (single-dose) (n=26)

Aim: Analyze pooled results from parts A and B with rilzabrutinib monotherapy or rilzabrutinib with concomitant ITP therapy

Primary endpoints: safety and efficacy

- **Overall platelet response (part A):** ≥2 consecutive platelet counts ≥50×10^9/L and increased ≥20×10^9/L from baseline without rescue medication
- **Durable platelet response (part B):** ≥50×10^9/L on ≥8 of the last 12 weeks of 24-week main treatment period without rescue medication

ClinicalTrials.gov: NCT03395210; EudraCT: 2017-004012-19.
BID, twice daily; CS, corticosteroid; ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist.

Baseline Characteristics and Prior/Concomitant Therapy

Characteristic	Patients (N=71)
Median age, years (range)	52 (19-75)
Female, n (%)	43 (61)
Median duration of ITP, years (range)	7.3 (0.4-53)
Median platelet count, $\times 10^9$/L (range)	14 (2-33)
Median number of unique prior ITP therapies (range)	6 (1-21)
Splenectomy, n (%)	23 (32)
Median number of prior unique failed ITP therapies* (range)	2 (1-19)
Rilzabrutinib study treatment, n (%)	
Monotherapy	24 (34)
Plus concomitant ITP therapy (n=24 TPO-RA, n=15 CS, n=8 both)	47 (66)

Data cutoff for part A (n=45) was 09Apr2021; part B (n=26) was 31Jan2023.
*Defined as failed to reach platelet counts >50×10^9/L for a given treatment.

Efficacy: Main Treatment Period

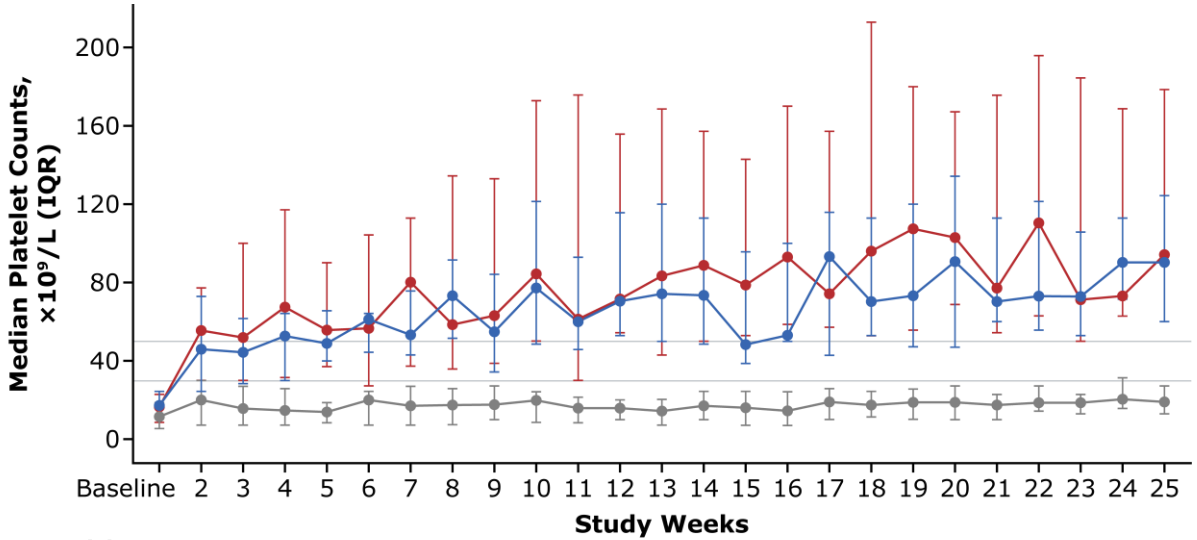
- 41% pooled part A and B patients achieved the overall platelet response (ie, responders)
  - 21 of 29 (72%) responder patients were early responders (ie, platelet counts ≥30×10^9/L at week 2)
  - Response was consistent with rilzabrutinib monotherapy or plus concomitant ITP therapy
- 28% of patients had durable platelet response, and 35% achieved complete response

Efficacy, n (%)	Patients (N=71)
Overall platelet response: ≥50×10^9/L and increased ≥20×10^9/L from baseline	**29 (41)**
Rilzabrutinib monotherapy	**10/24 (42)**
Rilzabrutinib + concomitant ITP therapy	**19/47 (40)**
Durable platelet response: ≥8 of the last 12 platelet counts ≥50×10^9/L	**20 (28)**
Complete platelet response: platelet counts ≥100×10^9/L	**25 (35)**

Data cutoff for part A was 09Apr2021; part B was 31Jan2023.

Efficacy: Platelet Counts

- Median platelet counts over time were similar for responders receiving rilzabrutinib monotherapy or with concomitant ITP therapy

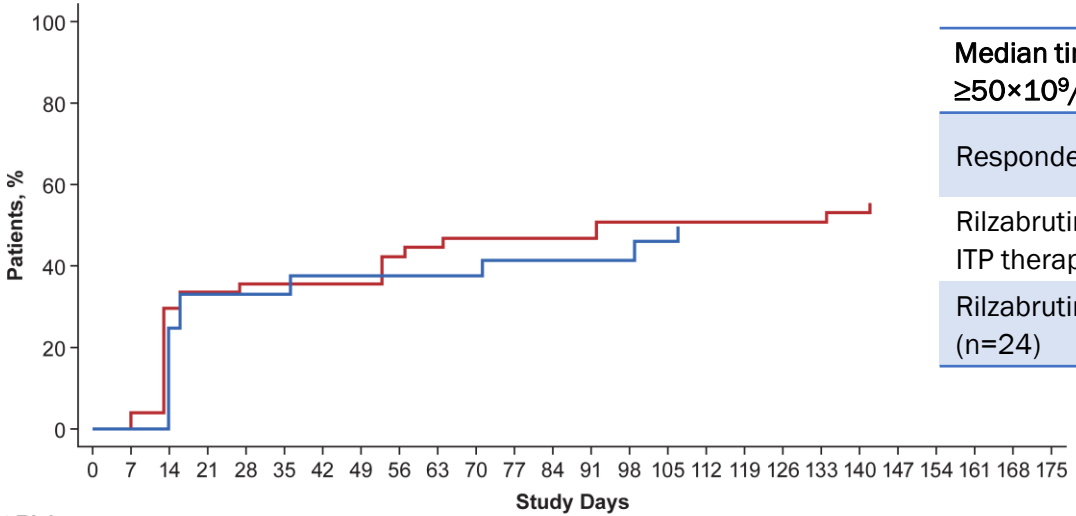


Number at Risk	Baseline	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Responder monotherapy	10	10	10	10	10	10	10	8	10	8	8	9	9	9	9	9	10	9	9	8	9	8	9	9	9
Responder concomitant therapy	19	19	19	19	19	18	17	18	19	18	19	17	18	15	17	17	16	16	16	13	16	15	16	16	17
Non-responder	42	39	38	34	36	33	35	34	34	30	29	30	28	25	25	23	25	22	22	20	21	18	18	18	18

Data cutoff for part A was 09Apr2021; part B was 31Jan2023.

Time to First Platelet Count ≥50×10^9/L

- Responders* had a median time to first platelet count ≥50×10^9/L of 12 days
- Results were similar with rilzabrutinib monotherapy or plus concomitant ITP therapy

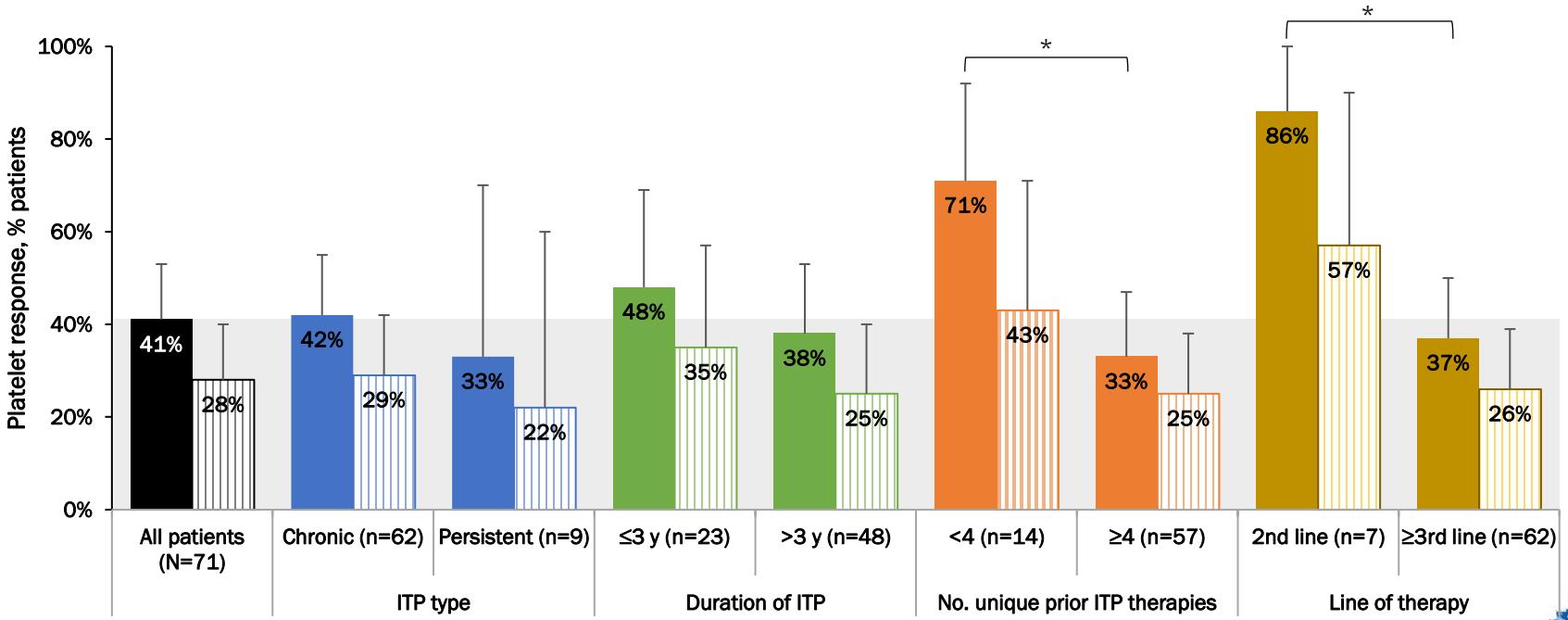


Median time to first platelet count ≥50×10^9/L, days (95% CI)	
Responders* (n=29)	12 (8, 16)
Rilzabrutinib + concomitant ITP therapy (n=47)	92 (27, NE)
Rilzabrutinib monotherapy (n=24)	NE (NE, NE)

Data cutoff for part A was 09Apr2021; part B was 31Jan2023. NE, not estimable (ie, does not reach 50% or confidence interval measurement).
*Responders achieved ≥2 consecutive platelet counts ≥50×10^9/L and increased ≥20×10^9/L from baseline without rescue medication.

Overall and Durable Platelet Responses by Baseline Variables

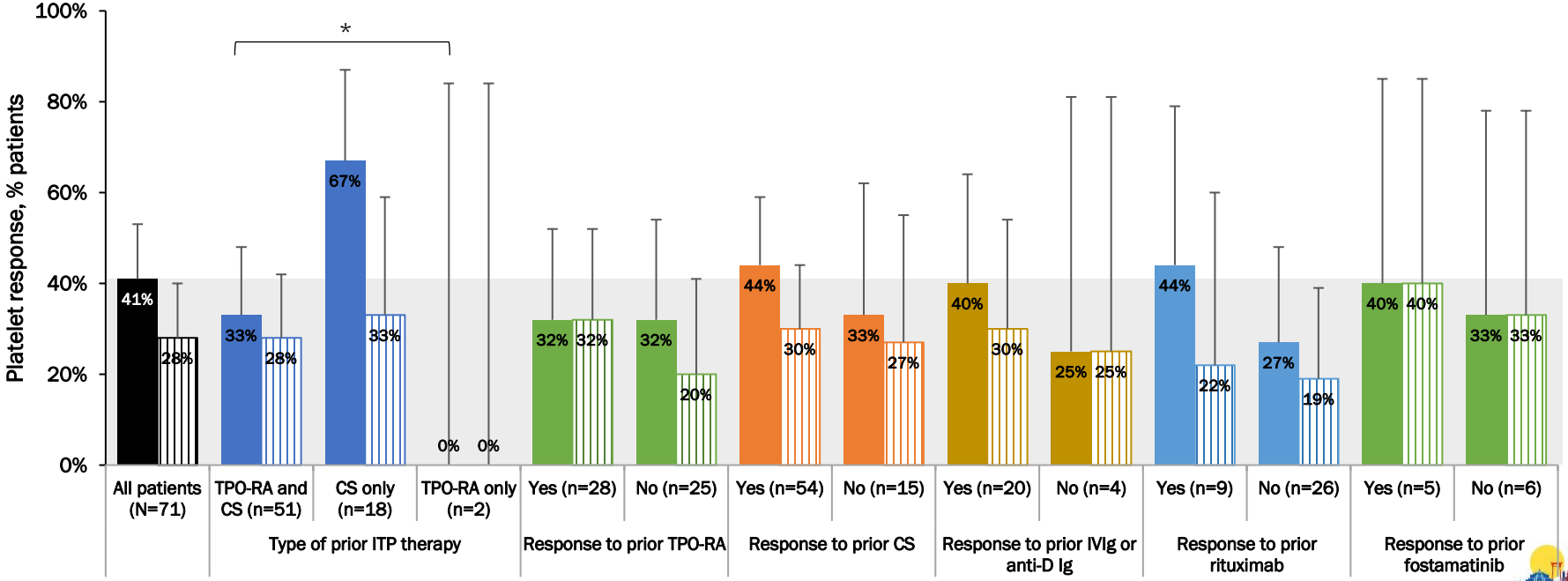
- Patients with fewer prior and earlier lines of ITP therapy had higher responses



Data cutoff for part A was 09Apr2021; part B was 31Jan2023.
Overall platelet response was defined as ≥50×10^9/L and increased ≥20×10^9/L from baseline. Durable platelet response was ≥8 of the last 12 platelet counts ≥50×10^9/L.
*Denotes *P*≤0.05 based on Fisher-exact method within the subgroup comparison.

Overall and Durable Platelet Responses by Prior Response to ITP Therapy

- Platelet response was consistent irrespective of response to prior ITP therapies



Data cutoff for part A was 09Apr2021; part B was 31Jan2023.
Overall platelet response was defined as ≥50×10^9/L and increased ≥20×10^9/L from baseline. Durable platelet response was ≥8 of the last 12 platelet counts ≥50×10^9/L.
*Denotes *P*≤0.05 based on Fisher-exact method within the subgroup comparison.

Summary of Adverse Events Due to Any Cause

- Median treatment duration was 167 days (range, 7-188)
- 3 (4%) patients received rescue therapy during the main treatment period

n (%)	Patients (N=71)
Any adverse event (AE)	61 (86)
Any treatment-related AE	43 (61)
Any grade ≥3 AE	12 (17)
Serious AE (SAE)	
Any SAE	8 (11)
Any treatment-related SAE	0
Any AE leading to study treatment discontinuation*	6 (8)
Death due to any AE (Evans syndrome unrelated to treatment)	1 (1)

Data cutoff for part A was 09Apr2021; part B was 31Jan2023.
*Discontinuations were due to treatment-related grade 1 hypokalemia, grade 2 diarrhea, and grade 2 frequent bowel movements; and unrelated grade 2 gastritis, grade 3 subcutaneous abscess, and grade 4 Evans syndrome.

Safety and Bleeding

- All treatment-related AEs were transient, grade 1 or 2
- Mean IBLS (ITP bleeding scale) score decreased from baseline to week 25
  - Baseline = 1.02 (SD, 0.67)
  - Week 25 = 0.82 (SD, 0.50)
  - Change from baseline to week 25 = –0.25 (SD, 0.36)
- No related bleeding or thrombotic events, SAEs, or deaths

Treatment Related AEs (>2 patients), n (%)	Patients (N=71)	
	Grade 1	Grade 2
All treatment-related AEs	38 (54)	19 (27)
Diarrhea	20 (28)	5 (7)
Nausea	16 (23)	2 (3)
Headache	7 (10)	1 (1)
Fatigue	3 (4)	1 (1)
Vomiting	2 (3)	2 (3)

Data cutoff for part A was 09Apr2021; part B was 31Jan2023.

Phase 2 Pooled Parts A and B Conclusions

Summary

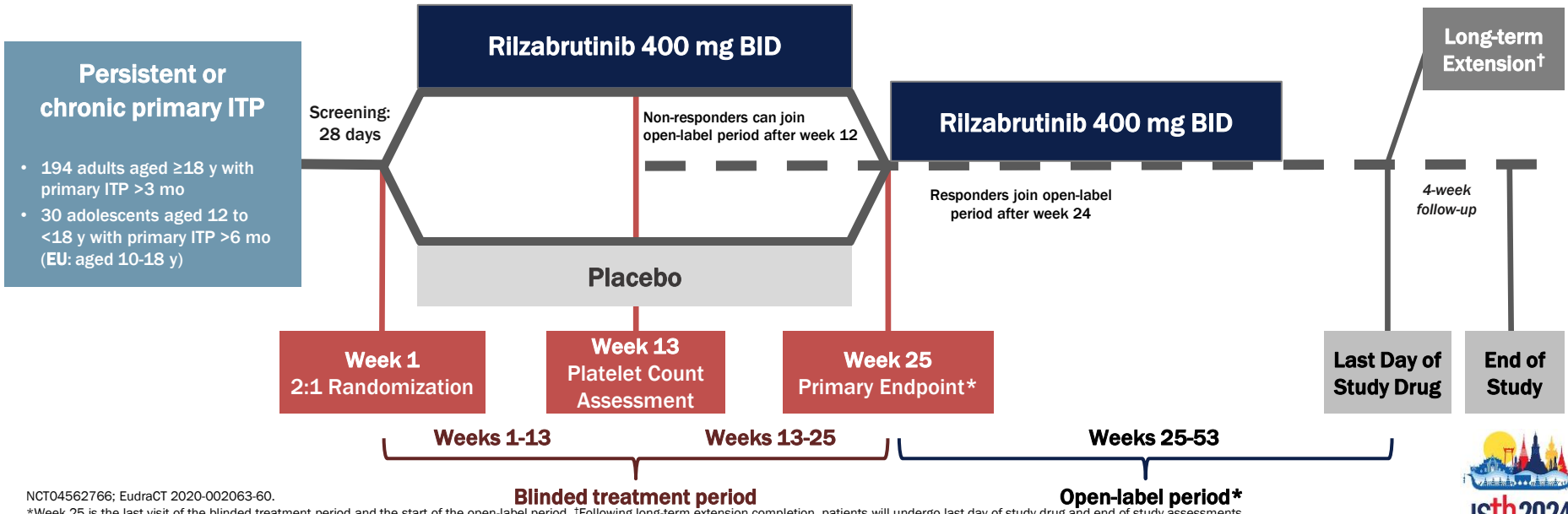
- Pooled analyses demonstrated rapid and durable platelet count increases in adults with ITP receiving rilzabrutinib monotherapy or rilzabrutinib with concomitant ITP therapy

Key Takeaways

- 41% of patients achieved the overall platelet response (ie, responders), consistent in patients receiving rilzabrutinib monotherapy (42%) or plus concomitant ITP therapy (40%)
  - Median time to first platelet count $\geq 50 \times 10^9$/L was rapid for responders at 12 days
- 28% of patients achieved durable platelet response and 35% complete response
- Patients with fewer prior and earlier lines of ITP therapy had higher platelet responses, irrespective of response to prior ITP therapy
- Oral rilzabrutinib 400 mg BID remains well tolerated in parts A and B
  - IBLS (ITP bleeding scale) score decreased from baseline to week 25
  - **All treatment-related AEs were transient, grade 1 or 2 events**
  - **No related thrombotic events, SAEs, or deaths**
  - 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 persistent or chronic ITP
  - Adult double-blinded portion is complete[1]; portion with adolescents is ongoing



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 long-term extension completion, patients will undergo last day of study drug and end of study assessments.
1. Sanofi press release, April 23, 2024.

Acknowledgments

- Patients, families, caregivers, and co-investigators who are participating in the rilzabrutinib ITP trial globally
- Sanofi for sponsoring the trial
- Publication support and critical feedback during development were provided by Erin Reineke, PhD and Matias Cordoba, MD of Sanofi
- Statistical support and analyses were provided by Umer Khan of Sanofi, and SCiAN Services
- Medical writing support was provided by Julie Kern, PhD, CMPP, of Second City Science, LLC, and funded by Sanofi