Improved Health-Related Quality of Life (HRQoL) With Oral Bruton Tyrosine Kinase Inhibitor (BTKi) Rilzabrutinib vs Placebo in Adults With Previously Treated Immune Thrombocytopenia (ITP): Phase 3 LUNA 3 Multicenter Study

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#2552

INTRODUCTION

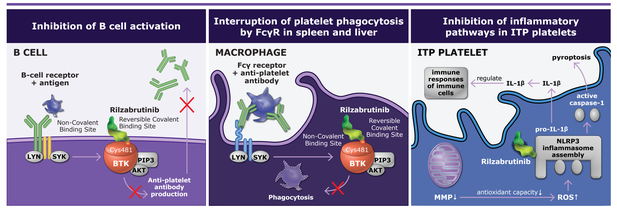
Immune Thrombocytopenia

- Immune thrombocytopenia (ITP) is characterized by low platelet count with consequent increased bleeding risk, fatigue, and diminished overall health-related quality of life (HRQoL)[1-4]
- ITP symptoms can negatively impact overall patient well-being due to[3,4]
  - Prolonged persistence of the disease
  - High incidence of comorbid conditions
  - Elevated risk for bleeding
  - Impaired HRQoL
- A wide spectrum of ITP effects may profoundly impact energy levels, daily activities, social and emotional health, and work productivity[3-6]
- Current ITP therapy while effective in raising platelet counts in many patients, often fails to address HRQoL issues, especially fatigue[2,6]
- Restoring and maintaining patient HRQoL is an important additional goal of ITP therapy

Rilzabrutinib

- Rilzabrutinib is an oral Bruton tyrosine kinase (BTK) inhibitor optimized for safety and efficacy in autoimmune and/or inflammatory diseases[7]
- BTK inhibition impacts different mechanisms that target key aspects of ITP disease pathophysiology[8,12-14]
- Mechanisms for rilzabrutinib in ITP may include inhibiting B cell activation, reducing pathogenic autoantibody production, interrupting platelet phagocytosis by FcγR in spleen and liver, and inhibiting inflammatory pathways (Figure 1)[8]
- Clinical evidence for rilzabrutinib in the phase 2 LUNA 2 study showed rapid and durable platelet responses, favorable safety, and improved fatigue and HRQoL with rilzabrutinib in previously treated ITP patients[9-11]

Figure 1. Rilzabrutinib is an Oral, Reversible, Potent BTK Inhibitor



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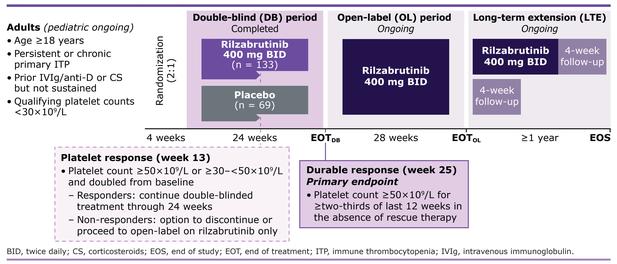
METHODS

LUNA 3 Study Design

- LUNA 3 is a multicenter, placebo-controlled, phase 3 study (NCT04562766, 2020-002063-60; Figure 2)[12]
- Adults ≥18 y and pediatric patients 10–<18 y with previously treated primary persistent/chronic ITP for >3 mo and platelet counts <30×10⁹/L within 2 weeks of treatment were enrolled (only adults reported here; pediatric ongoing)
- Primary endpoint was durable platelet response defined as platelet counts ≥50×10⁹/L for ≥8 of the last 12 weeks of the 24-week blinded period without rescue therapy
- Presented here are the first HRQoL results from the multicenter phase 3 LUNA 3 study of rilzabrutinib vs placebo in adults with ITP

Figure 2. LUNA 3 Study Design



BID, twice daily; CS, corticosteroids; EOS, end of study; EOT, end of treatment; ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin.

METHODS

HRQoL-Specific Analyses

- Change from baseline in ITP-PAQ item 10 (physical fatigue) at week 13 was a key secondary endpoint measured in all patients and among durable responders/non-responders
- HRQoL was measured from 0 worst to 100 best possible using ITP Patient Assessment Questionnaire (ITP-PAQ)[15,16] and EuroQol Visual Analog Scale (EQ-VAS)[17] scales
- For ITP-PAQ, minimum important differences (MID) represented clinically meaningful changes[16]
  - 8- to 12-point changes for symptoms, bother-physical health, psychological health, overall HRQOL, social activity, and women's reproductive health
  - 10- to 15-point changes for fatigue and activity
- Anchor-based psychometric analyses from LUNA 3 blinded data determined between-group meaningful score difference (MSD) thresholds for ITP-PAQ item 10 (physical fatigue) using change from baseline data to weeks 13 and 25
- Between-group mean change scores and mixed-models for repeated measures (MMRMs) were used to estimate between-group MSD threshold range of 8-18

RESULTS

Patients

- As of data cutoff on March 14, 2024, 202 adults were randomized to either rilzabrutinib (n = 133) or placebo (n = 69)
- Baseline demographics and disease characteristics were generally similar between arms (Table 1)

Table 1. Baseline Characteristics and Prior/Concomitant Therapy

	Rilzabrutinib (n = 133)	Placebo (n = 69)
Median age, y (range)	47 (18–80)	46 (19–79)
Female, n (%)	78 (59)	49 (71)
Median duration of ITP, y (range)	8.1 (0.3–52.2)	6.2 (0.3–35.8)
Median baseline platelet count, ×10⁹/L (range)*	15 (1-32)	15 (1-54)
Median number of unique prior ITP therapies† (range)	4 (1-15)	5 (1-12)
≥5 prior therapies, n (%)	57 (43)	36 (52)
Prior splenectomy, n (%)	37 (28)	19 (28)

*Averaged first and second qualifying screening platelet counts and study day 1 platelet count. †Identified using standard medication term, different corticosteroids counted as one therapy, and splenectomy could be counted as one prior ITP therapy. Patients could receive more than one therapy.

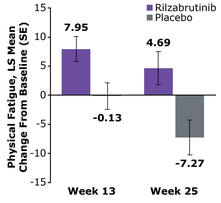
Efficacy

- Platelet response (ie, responders: ≥50×10⁹/L or ≥30–<50×10⁹/L and doubled from baseline) at week 13 was achieved in 86 (65%) rilzabrutinib vs 23 (33%) placebo patients
- The primary endpoint of durable response was met in 31 (23%) rilzabrutinib vs 0 placebo patients (*P*<0.0001)
- As of the data cutoff date for double-blind and open-label periods combined, durable response has been met in 38/133 (29%) rilzabrutinib-randomized patients
- Significant improvements with rilzabrutinib over placebo were seen in all secondary efficacy endpoints, including week 13 physical fatigue

Physical Fatigue by ITP-PAQ

- Mean (SE) baseline ITP-PAQ item 10 scores for physical fatigue were similar between arms: 52.5 (2.7) for rilzabrutinib and 54.7 (3.5) for placebo
  - ITP patients with platelet counts in normal ranges of 100-149×10⁹/L and ≥150×10⁹/L have been shown to have ITP-PAQ fatigue scores of 62 and 71, respectively[18]
- Physical fatigue showed statistically significant and clinically meaningful improvements with rilzabrutinib vs placebo at weeks 13 and 25 (Figure 3)
  - LS mean change from baseline at week 13: 7.95 rilzabrutinib vs -0.13 placebo (*P*=0.01)
  - LS mean change from baseline at week 25: 4.69 rilzabrutinib vs -7.27 placebo (*P*=0.0003)
- Improvements in physical fatigue with rilzabrutinib were observed as early as week 5 (Figure 4)

Figure 3. Physical Fatigue (ITP-PAQ Item 10) at Weeks 13 and 25

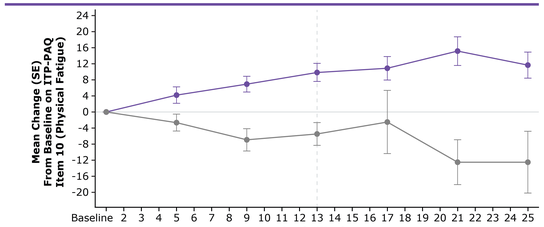


Physical Fatigue Score	Rilzabrutinib (n = 133)	Placebo (n = 69)
Baseline: mean (SD)	**54.7 (29.48)**	**52.5 (31.29)**
Change from baseline at week 13 (key secondary endpoint)		
LS mean (SE)	7.95 (2.13)	-0.13 (2.86)
LS mean difference vs placebo (95% CI)	8.08 (1.82-14.34)	
P value	0 .0114	
Change from baseline at week 25		
LS mean (SE)	4.69 (2.26)	-7.27 (2.99)
LS mean difference vs placebo (95% CI)	11.95 (5.42-18.49)	
P value	0.0003	

CI, confidence interval; LS, least squares; SD, standard deviation; SE, standard error.

RESULTS

Figure 4. Mean Change from Baseline on Physical Fatigue (ITP-PAQ Item 10) Over Time



Number at Risk							
Rilzabrutinib (N)	131	125	119	117	62	61	60
Placebo (N)	69	66	65	64	10	10	10

Vertical dashed line at week 13 represents measurement of patient response and continuation of responders to treatment through 24 weeks.

Physical Fatigue by Durable Responder Status

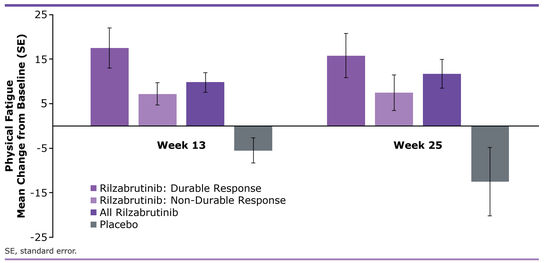
- Descriptive physical fatigue scores increased from baseline at weeks 13 and 25 for patients receiving rilzabrutinib and decreased or were similar in placebo patients (Table 2)
- Among durable responder patients receiving rilzabrutinib, physical fatigue score improved with mean changes (SE) from baseline at weeks 13 and 25 of 17.5 (4.5) and 15.8 (5.0), respectively (Figure 5)
- Additionally, non-durable responders receiving rilzabrutinib also showed improvement in physical fatigue, with mean changes (SE) from baseline at weeks 13 and 25 of 7.2 (2.5) and 7.5 (4.0), respectively (Figure 5)
- Patients receiving placebo (none who were durable responders) exhibited no improvement in physical fatigue

Table 2. Descriptive Physical Fatigue (ITP-PAQ Item 10) Score by Treatment and Durable Platelet Response Status

Mean Score (SE)	Rilzabrutinib: Durable Responders (n = 31)	Rilzabrutinib: Non-Durable Responders (n = 102)	Rilzabrutinib: All Rilzabrutinib (n = 133)	Placebo (n = 69)
Baseline	54.2 (5.5) n = 30	52.0 (3.2) n = 101	52.5 (2.7) n = 131	54.7 (3.5) n = 69
Week 13	69.4 (4.9) n = 31	58.8 (3.2) n = 88	61.6 (2.7) n = 119	51.2 (3.8) n = 64
Week 25	68.5 (4.9) n = 31	65.3 (5.5) n = 31	66.9 (3.7) n = 62	55.0 (9.0) n = 10

SE, standard error.
ITP-PAQ score ranges from 0 worst to 100 best.

Figure 5. Mean Change From Baseline in Descriptive Physical Fatigue (ITP-PAQ Item 10) Score by Durable Platelet Response Status



SE, standard error.

Health Status by EQ-VAS

- Improvements in fatigue with rilzabrutinib were associated with improved EQ-VAS health status at weeks 13 and 25
- Mean (SD) baseline EQ-VAS scores were similar for rilzabrutinib at 71.7 (18.9) and placebo at 70.2 (21.9)
- At week 13, mean (SD) changes from baseline were 3.4 (12.6) in the rilzabrutinib group and –2.0 (14.5) with placebo
- Similarly, change from baseline at week 25 showed a mean (SD) increase of 5.2 (13.2) with rilzabrutinib (indicating continued improvement) vs –3.2 (10.0) with placebo

Changes from Baseline in ITP-PAQ Domains

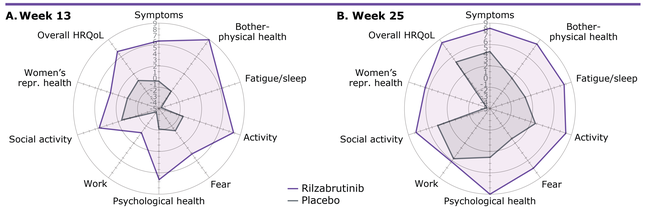
- Multiple ITP-PAQ domains showed improvements with rilzabrutinib vs placebo based on mean changes from baseline at weeks 13 and 25 (Table 3)
- All ITP-PAQ domains were increased from baseline at week 25 with rilzabrutinib (Figure 6)

Table 3. Changes from Baseline in ITP-PAQ Domains

Mean ITP-PAQ Domain Values	MID Reference*	Rilzabrutinib: Baseline (n = 131)	Rilzabrutinib: Change from Baseline at Week 13 (n = 117)	Rilzabrutinib: Change from Baseline at Week 25 (n = 60)	Placebo: Baseline (n = 69)	Placebo: Change from Baseline at Week 13 (n = 64)	Placebo: Change from Baseline at Week 25 (n = 10)
Symptoms	**8-12**	67.7	6.0	**10.3***	64.1	-0.5	2.1
Bother-physical health	**8-12**	65.6	**9.0***	**10.0***	61.2	-1.4	-4.7
Fatigue/sleep	**10-15**	63.1	5.6	9.3	64.0	-4.6	-5.0
Activity	**10-15**	64.3	7.9	**10.0***	55.6	-0.8	-1.3
Fear	**NE**	74.2	4.2	7.8	70.9	-0.4	-5.0
Psychological health	**8-12**	67.0	6.6	**11.9***	58.4	-1.7	-1.0
Work	**NE**	74.2	-0.2	4.9	65.9	-4.4	3.8
Social activity	**8-12**	68.5	5.2	**9.4***	64.4	1.4	1.3
Women's repr. health†	**8-12**	69.8	3.2	5.8	58.7	0.4	–16.7
Overall HRQoL	**8-12**	56.1	6.5	**10.6***	46.3	0.7	2.3

HRQoL, health-related quality of life; MID, minimal important difference; NE, not evaluated; repr, reproductive.
*Met minimal important difference (MID) reference range.[16] †Included n = 44 rilzabrutinib and n = 28 placebo applicable patients.

Figure 6. Spider Plot of Mean Change from Baseline in ITP-PAQ Domains



CONCLUSIONS

- **Statistically significant and clinically meaningful improvement in physical fatigue was observed with rilzabrutinib vs placebo at week 13, along with statistically significant increases at week 25**
- **Improvement in multiple measures of ITP-specific HRQoL (symptoms, bother-physical health, activity, psychological health, social activity, and overall HRQoL) were observed with rilzabrutinib vs placebo**
- **Improvements in fatigue were seen in both durable and non-durable responders to rilzabrutinib and other disease-specific HRQoL endpoints, indicative of potential multiple modalities of action**
- **These LUNA 3 phase 3 HRQoL results provide additional evidence of rilzabrutinib's effects beyond increased platelet counts and reduced bleeding in previously treated adults with ITP**

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