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

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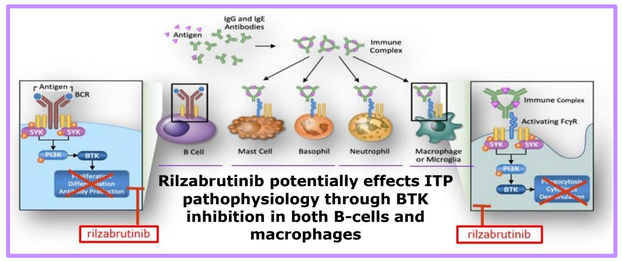
INTRODUCTION

- Immune thrombocytopenia (ITP) is an acquired autoimmune disease marked by immune-mediated platelet destruction and impaired platelet production, resulting in thrombocytopenia (i.e., platelet count <100×10^3/mm^3)[1]
- Rilzabrutinib's reversible covalent binding allows for long BTK-target engagement and durable inhibition, with limited drug exposure. This clinical advantage potentially reduces off-target toxic effects and does not alter platelet aggregation in healthy volunteers or patients with ITP[1,2]

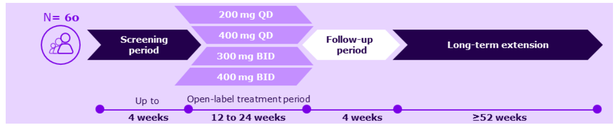


OBJECTIVES

- To report updated efficacy and safety results of rilzabrutinib 400 mg BID over 2 years in a long-term extension (LTE) study

METHODS

LUNA 2 Part A



Main treatment period:

- Adult ITP patients with baseline platelet counts <30×10^9/L on two occasions ≥7 days apart within the 15 days before trial entry, responded to ≥1 prior ITP therapy but were unable to maintain adequate response to prior/concomitant therapies were enrolled in the main study
- Endpoints included safety, platelet response, durable response, rescue medication use, bleeding grade ≥ 2 and scores, and subgroup analyses

Long-term extension:

- Patients in the main 24-week study were eligible for LTE if their platelet count was ≥50×10^9/L or ≥30×10^9/L plus a doubling of the baseline count for ≥50% of the patient's final 8 weeks of treatment
- Endpoints included safety and platelet count (percentage of weeks with platelet counts that increased ≥20×10^9/L above baseline, were ≥30×10^9/L, or ≥50×10^9/L; the proportion of patients with a platelet count of ≥100×10^9/L at any time; and ≥50×10^9/L for ≥50% of monthly/quarterly visits in the last 12 months of treatment)

RESULTS

Baseline Characteristics

- Of the 16 patients in the main treatment period that were eligible to continue to the LTE, median (range) treatment duration was 1032 days (318-1506)
- Among LTE patients, 5 (31%) received rilzabrutinib monotherapy and 11 (69%) received concomitant ITP medication: corticosteroid corticosteroid [CS] n=7, thrombopoietin receptor agonists [TPO-RA] n=2, and both CS plus TPO-RA n=2)

Table 1: Baseline Characteristics and Prior Therapies

Characteristic	All Patients (N=60)[1]	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, x10^9/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.
ITP, immune thrombocytopenia; LTE, long-term extension; n, number of patients in LTE group; N, total number of patients.

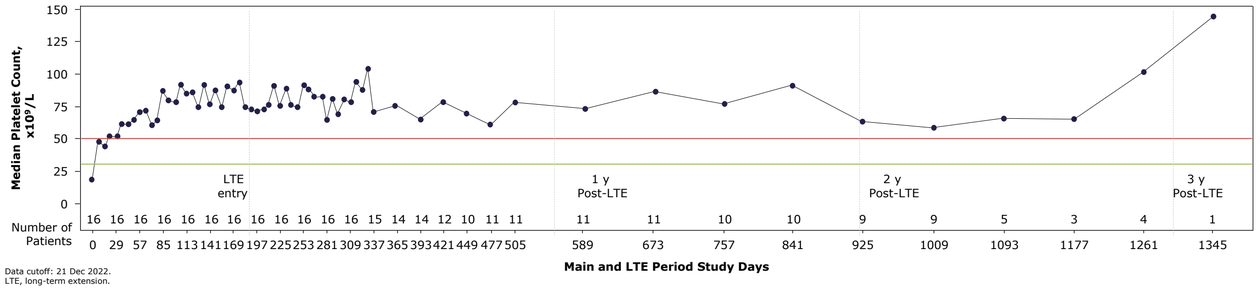
Platelet Response in LTE Patients

- Median platelet count at LTE entry was 87×10^9/L, with subsequent counts of 92×10^9/L, 71×10^9/L, 61×10^9/L, and 64×10^9/L at 3, 6, 12, and 24 months after LTE entry, respectively **(Figure 1)**
- Patients maintained above clinically meaningful thresholds throughout main treatment period and LTE, irrespective of the use of concomitant therapy

88% of visits: platelet counts ≥50×10^9/L

88% of patients: platelet counts ≥100×10^9/L

Figure 1: Median Platelet Counts in Main and LTE period study



Data cutoff: 21 Dec 2022.
LTE, long-term extension.

Concomitant Therapy in the LTE Period

45% of patients receiving concomitant therapy discontinued the use of any ITP concomitant medication (n=2 CS, n=1 TPO-RA, n=2 CS and TPO-RA)

- The median (range) platelet count after discontinuation of concomitant medications was 103×10^9/L (90×10^9/L–218×10^9/L) at first measurement and 106×10^9/L (75×10^9/L–166×10^9/L) at 3–6 months post cessation of concomitant ITP medication

Safety Outcomes

- During the LTE, 13 patients (81%) had ≥1 any-cause adverse events (AEs), with 3 patients (19%) experiencing grade ≥3 AEs **(Table 2)**
- During the main study, one death occurred, which was considered by the investigator to be unrelated to treatment, but no death was observed in LTE period **(Table 2)**
- Two patients received rescue medication in the LTE (n=0 during the main treatment period)

Table 2: Treatment-emergent adverse events (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/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 24 Sept 2020, and died on 22 Jan 2021.
COVID-19, coronavirus disease 2019; LTE, long-term extension; n, number of patients in LTE group; N, total number of patients; SAE, serious adverse event; SOC, standard of care; TEAE, treatment emergent adverse events.

Table 3: Treatment-Related TEAEs

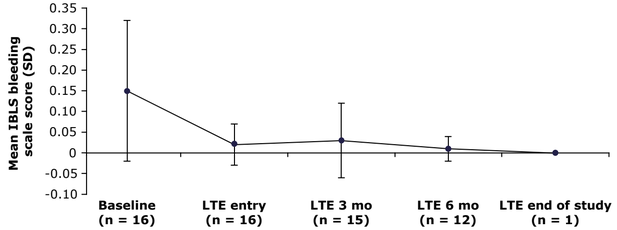
Related TEAEs (≥5%), n (%)	All Patients During Main Treatment Period (N=60)[1] Grade 1	All Patients During Main Treatment Period (N=60)[1] Grade 2	LTE Patients During LTE Period (n=16) Grade 1	LTE Patients During LTE Period (n=16) Grade 2
All treatment-related TEAEs	27 (45)	15 (25)	2 (13)	2 (13)
Diarrhea	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.
LTE, long-term extension; n/N, number of patients; TEAE, treatment emergent adverse events.

IBLS (Immune Thrombocytopenic Purpura Bleeding Scale) Scores

- LTE participants experienced decreased IBLS bleeding scores throughout the LTE period

Figure 2: IBLS bleeding scale scores at baseline, LTE entry (cycle 1, day 1), LTE 3 months (cycle 4, day 1), LTE 6 months (cycle 7, day 1), and LTE end of study



Bleeding symptoms were grouped by a total of 11 specific sites of bleeding and scored as 0=none; 1=1-5 bruises and/or scattered petechiae; and 2=>5 bruises with size >2 cm and/or diffuse petechiae.[5] The overall average (standard deviation) score is calculated from the arithmetic mean of 11 site-specific grades. If ≥1 site was missing, the average of the non-missing sites was used.
IBLS, Immune Thrombocytopenic Purpura Bleeding Scale; LTE, long-term extension; n, number of patients; SD, standard deviation.

CONCLUSIONS

- Overall, in both the phase 1/2 study and the extended treatment in the LTE study, rilzabrutinib demonstrated durable and stable platelet responses over time while maintaining a favorable safety profile
- Nearly 50% of patients on concomitant ITP therapy could discontinue concomitant medication and maintain an adequate platelet count
- Oral rilzabrutinib 400 mg BID remains well tolerated through the LTE

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