Efficacy and Safety of Rilzabrutinib in Patients With Moderate to Severe Atopic Dermatitis: A Proof-of-Concept Phase 2 Clinical Trial

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Introduction

- Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin disease, which is currently treated with topical and systemic therapies (ie, biologics and Janus kinase inhibitors). However, many patients with moderate-to-severe AD are unable to achieve adequate disease control.[1-3]
- Bruton's tyrosine kinase (BTK) is expressed in B cells, as well as mast cells and basophils, which play a critical role in multiple inflammatory diseases, including AD.[4]
- Rilzabrutinib is an oral, reversible, covalent BTK inhibitor.[5]

Objective

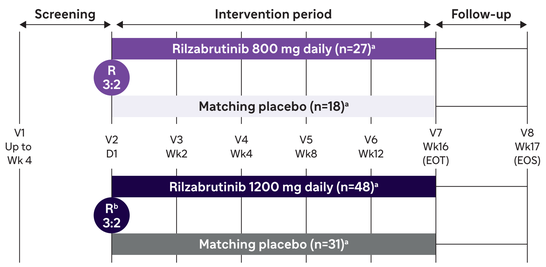
- To evaluate the efficacy and safety of rilzabrutinib in adults with moderate-to-severe AD and inadequate response or intolerance to topical corticosteroids

Methods

Study Design

- Phase 2, randomised, double-blind, placebo-controlled, multicentre, proof-of-concept (POC) clinical trial (**Figure 1**)
- Eligible adults (≥18 years; N=124) with moderate-to-severe AD and inadequate response or intolerance to TCS
- Enrolled into 2 staggered dose regimen cohorts: 800 mg/day (n=45) or 1200 mg/day (n=79)
- Randomised 3:2 to receive rilzabrutinib or placebo for 16 weeks

Figure 1. Study Design (NCT05018806)



[a]Rilzabrutinib and the matching placebo were administered orally; [b]The randomisation of 1200 mg daily cohort started after the enrolment of the 800 mg daily cohort.

- **Primary endpoint**: Percentage change in EASI score from baseline to week 16
- **Key secondary endpoints**: At week 16, proportion of participants achieving:
  - — IGA 0/1 — EASI-75 — Reduction in PP-NRS ≥4
- **Safety endpoints**: Assess safety from baseline to week 16

Key Conclusions

1 Treatment with rilzabrutinib 800 or 1200 mg/day did not show significant statistical improvements compared with placebo in the lesions (primary and secondary endpoints).

2 Consistent trends favouring rilzabrutinib in pruritus/itch were confirmed by rapid improvement in absolute and relative changes in PP-NRS.

3 Rilzabrutinib was well tolerated with an acceptable safety profile.

4 There is potential for rilzabrutinib to be explored further in diseases where itch is a key component.

Results

Baseline Demographics and Disease Characteristics

- Generally well balanced across the rilzabrutinib and placebo groups
  - — Mean baseline EASI score: 26.1 in 800 mg/day cohort; 27.8 in 1200 mg/day cohort
  - — Mean baseline weekly average of PP-NRS score: 7.2 in 800 mg/day cohort; 7.38 in 1200 mg/day cohort

Primary and Secondary Endpoints

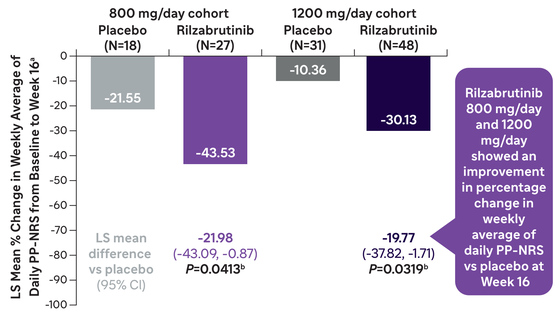
- The primary and key secondary endpoints were not met for the rilzabrutinib 800 or 1200 mg/day dose (**Table 1**).
  - — Inconsistent trends in the proportion of EASI-75 and IGA 0/1 responders were observed between the 2 cohorts.
- Proportion of participants with a reduction in weekly average of daily PP-NRS of ≥4 from baseline at week 16 was numerically greater with rilzabrutinib vs placebo (**Table 1**).
- The consistent trend favouring rilzabrutinib 800 and 1200 mg/day vs placebo observed in participants reaching PP-NRS of ≥4 was further confirmed by improvement in absolute and relative changes in weekly average of daily PP-NRS from baseline to week 16 (**Table 1, Figure 2**).
  - — Improvements in absolute and relative changes in weekly average of daily PP-NRS were seen as early as Week 1 with 1200 mg/day and Week 2 with 800 mg/day.

Table 1. Primary and Secondary Endpoints (ITT population)

Endpoints (Week 16)	800 mg/day cohort		1200 mg/day cohort	
	Placebo (N=18)	Rilzabrutinib (N=27)	Placebo (N=31)	Rilzabrutinib (N=48)
LS mean % change in EASI (SE)[a]	-47.33 (9.77)	-53.57 (8.25)	-43.33 (6.99)	-47.21 (6.26)
IGA 0/1, n (%)[b]	4 (22.2)	2 (7.4)	4 (12.9)	7 (14.6)
EASI-75 response, n (%)[b]	5 (27.8)	8 (29.6)	9 (29.0)	9 (18.8)
PP-NRS≥4, n (%)[b]	2 (11.1)	5 (18.5)	4 (12.9)	10 (20.8)
LS mean change in weekly average of daily PP-NRS from baseline (SE)[a]	-1.60 (0.66)	-3.11 (0.52)	-0.83 (0.51)	-2.07 (0.43)

[a]Analysed using an analysis of covariance (ANCOVA) model with intervention group, randomisation stratification of screening IgE levels (</≥300 UI/mL) as fixed effects, and baseline value of corresponding endpoint as covariates; [b]Analysed using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomisation stratification of screening IgE levels (</≥300 UI/mL).

Figure 2. Percentage Change in PP-NRS (ITT population)



[a]Analysed using an analysis of covariance (ANCOVA) model with intervention group, randomisation stratification of screening IgE levels (< or ≥300 UI/mL) as fixed effects, and baseline PP-NRS score as covariates; [b]Nominal *P* values are reported.

Results *(continued)*

Safety

- Rilzabrutinib was well tolerated with an acceptable safety profile (**Table 2**).
  - — Treatment-emergent AEs were mostly mild, with a low incidence of serious AEs (n=2) and no deaths.
  - — TEAEs occurring at a higher frequency with rilzabrutinib compared with placebo included diarrhoea and nausea.
  - — No ALT increases >3 ULN were reported with rilzabrutinib (vs 1 with placebo).

Table 2. Safety Summary Through Week 16

TEAEs through Week 16, n (%)[a]	800 mg/day cohort		1200 mg/day cohort	
	Placebo (N=18)	Rilzabrutinib (N=27)[b]	Placebo (N=31)	Rilzabrutinib (N=48)
TEAE	10 (55.6)	15 (55.6)	19 (61.3)	38 (79.2)
Severe TEAE	0	1 (3.7)	1 (3.2)	3 (6.3)
Treatment-emergent SAE	0	0	1 (3.2)	1 (2.1)
TEAE leading to death	0	0	0	0
TEAE leading to treatment discontinuation	0	2 (7.4)	2 (6.5)	9 (18.8)

[a]Reported as per the MedDRA version 26.0; [b]One participant in the rilzabrutinib 800 mg/day group had a pre-treatment AE leading to permanent study discontinuation, and this participant was not counted in this table.

References

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Abbreviations

AE, Adverse event; ALT, Alanine aminotransferase; CI, Confidence interval; D, Day; EASI, Eczema Area and Skin Severity Index; EOS, End of study; EOT, End of treatment; IGA, Investigator's Global Assessment; IgE, Immunoglobulin E; ITT, Intention-to-treat; LS, Least squares; MedDRA, Medical Dictionary for Regulatory Activities; N/n, Number of participants; PP-NRS, Peak Pruritus Numerical Rating Scale; R, Randomisation; SE, Standard error; ULN, Upper limit of normal; V, Visit; Wk, Week.

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Disclosures

Leon Kircik has served as an investigator, speaker, advisory board member, or consultant for AbbVie, Acambis, Amgen, Anacor Pharmaceuticals, AnaptysBio, Arcutis, Arena, Assos Pharmaceuticals, Astellas Pharma US, Asubio, BioMimetrix, Biosion, Dermavant, Dermira, Dow Pharmaceutical Sciences, Eli Lilly, Ferndale Laboratories, Galderma, Genentech, GlaxoSmithKline, Glenmark, HealthPoint, Incyte, Innocutis, Innovail, Kyowa Kirin, LEO Pharma, L'Oréal, Nano Bio, Nektar, Novartis, Nucryst Pharmaceuticals, Onset, Ortho Dermatologics, Ortho Neutrogena, PediaPharma, Pfizer, Pharmaderm, Promius, PuraCap, Quinnova, Regeneron, Sanofi, SkinMedica, Stiefel Laboratories, Sun Pharma, Taro, Triax, and Valeant Pharmaceuticals.
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Vincent Mikol, Gaowei Nian, Leda Mannent, and Lydie Baret-Cormel are employees of Sanofi and may hold stock and/or stock options in the company.

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