Efficacy and Safety of Rilzabrutinib in Patients With Chronic Spontaneous Urticaria: 12-Week Results From the RILECSU Phase 2 Dose-Ranging Study

Poster # L38

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Introduction

- Chronic spontaneous urticaria (CSU) is a common immunologic skin disease characterized by intensely itchy recurrent wheals, angioedema, or both[1]
- Current therapies include H1-antihistamines (H1-AH) and biologic therapy (eg, omalizumab); however, many patients may not respond to available treatments, leaving an unmet need[1]
- CSU is driven mainly by the activation of cutaneous mast cells by various mechanisms, including autoantibodies[2]
- Bruton's tyrosine kinase (BTK), expressed in B cells and mast cells, plays a critical role in multiple immune-mediated disease processes[3]
- Rilzabrutinib (SAR444671) is an investigational oral, reversible, covalent BTK inhibitor[4]

Objective

- Assess the efficacy and safety of rilzabrutinib in adults with moderate-to-severe CSU, who remain symptomatic despite H1-AH treatment, at 12 weeks in a phase 2 dose-ranging study (RILECSU)

Methods

Study Design

- RILECSU (NCT05107115) is a 52-week phase 2 study comprising:
  - Part 1 (completed and presented here): 12-week randomized, double-blind, placebo-controlled, dose-ranging, efficacy and safety period
  - Part 2 (ongoing): 40-week open-label extension
- Adults (18 to 80 years; N=160) with moderate-to-severe CSU whose disease is not adequately controlled with H1-AH treatment (omalizumab-naïve and incomplete responders) were randomized 1:1:1:1 to receive:
  - Rilzabrutinib 400 mg once every evening (QPM; N=38)
  - Rilzabrutinib 400 mg twice a day (BID; N=41)
  - Rilzabrutinib 400 mg three times a day (TID; N=41)
  - Matching placebo (N=40)

Endpoints

- **Primary endpoint:** Change from baseline in weekly itch severity score (ISS7) at Week 12
- **Secondary endpoints:**
  - Change from baseline in weekly urticaria activity score (UAS7) at Wk 12
  - Change from baseline in UAS7 at Wk 4
  - Change from baseline in weekly hives severity score (HSS7) at Wk 12
  - Proportion of participants with UAS7 ≤ 6 at Wk 12
  - Proportion of participants with UAS7 = 0 at Wk 12
- **Safety**
- Intent-to-treat (ITT) analysis included all randomized participants (omalizumab-naïve and incomplete responders)
- Data collected after discontinuing study intervention were included. Data post selected prohibited/rescue medications were set to missing and imputed by worst observation carried forward (WOCF). Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF; other missing data were imputed by multiple imputation
- No multiplicity adjustment was made for the analyses in the ITT population

Key Conclusions

1. Rilzabrutinib 400 mg TID dose met its primary endpoint demonstrating a significant reduction in ISS7 at Week 12 from baseline vs placebo. Significant changes were seen as early as Week 1.
2. Rilzabrutinib 400 mg TID dose also showed significant reduction at Week 12 from baseline in UAS7 and HSS7 vs placebo
3. Rilzabrutinib was well tolerated, with no instances of BTK inhibitor class-effect AEs of cytopenia, bleeding, or atrial fibrillation
4. RILECSU Part 2 (open-label extension) is ongoing and will provide insight into safety and efficacy through Week 52

Results

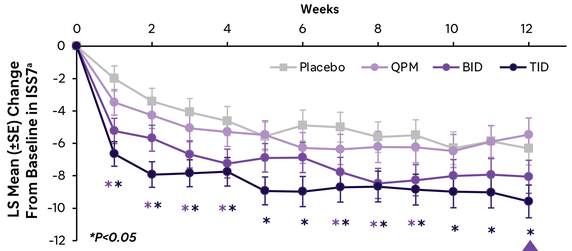
Baseline Demographics and Disease Characteristics

- Baseline demographics and disease characteristics were generally balanced
  - Age, mean (SD): 44.1 (13.4) years
  - Predominantly White females
  - CSU duration, mean (SD): 5.63 (8.51) years
  - ISS7, mean (SD): 15.9 (4.0)
  - UAS7, mean (SD): 30.3 (7.9)
  - HSS7, mean (SD): 14.4 (4.5)

Primary and Secondary Endpoints

- Primary and secondary endpoints were met for rilzabrutinib 400 mg TID **(Figure 1, Figure 2,** and **Table 1)**
  - Evidence of a fast and dose-response relationship was observed
  - Although no treatment difference was observed for the rilzabrutinib 400 mg QPM dose vs placebo, the rilzabrutinib 400 mg BID dose showed positive trends (without statistical significance) across all endpoints

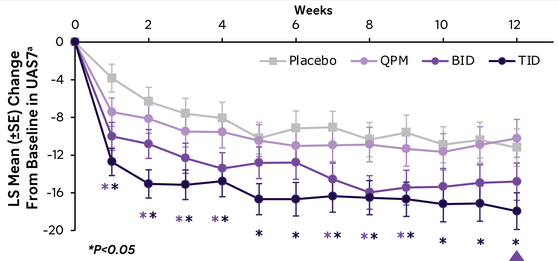
Figure 1. Change in ISS7 From Baseline to Week 12 (ITT population)



Rilzabrutinib 400 mg TID showed a fast (Week 1) and significant improvement vs. placebo up to Week 12

[a]All of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, and regions as covariates

Figure 2. Change in UAS7 From Baseline to Week 12 (ITT population)



Rilzabrutinib 400 mg TID showed a fast (Week 1) and significant improvement vs. placebo up to Week 12

[a]All of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, and regions as covariates

Table 1. Secondary Endpoints (ITT population)

Secondary Endpoints	Placebo (N=40)	Rilzabrutinib 400 mg QPM (N=38)	Rilzabrutinib 400 mg BID (N=41)	Rilzabrutinib 400 mg TID (N=41)
LS mean change from baseline in UAS7 at Week 4 (SE)[a]	-8.07 (1.68)	-9.55 (1.68)	-13.41* (1.67)	-14.78† (1.64)
LS mean change from baseline in HSS7 at Week 12 (SE)[a]	-4.89 (1.02)	-4.75 (1.03)	-6.78 (1.02)	-8.31* (1.00)
% of participants with UAS7≤6 at Week 12[b]	12.5	5.3	24.4	36.6*
% of participants with UAS7=0 at Week 12[b]	12.5	2.6	19.5	24.4

*P<0.0500; †P<0.0100

[a]All of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, and regions as covariates. [b]Cochran–Mantel–Haenszel test was performed on the association between the responder status and intervention group, stratified by region

Rilzabrutinib 400 mg TID showed reduction across disease components vs placebo

Results *(continued)*

Safety

- Rilzabrutinib was generally well tolerated with no evidence of new safety signals or apparent dose-related adverse events (AEs; **Table 2** and **Table 3**)
  - Few serious AEs (SAEs), similar incidence of severe AEs as placebo, and no deaths
  - Diarrhea and nausea were the most frequent treatment-emergent AEs (TEAEs) with rilzabrutinib 400 mg BID and TID; no evidence of dose effect
  - No events of cytopenia, bleeding, or atrial fibrillation

Table 2. Primary Safety Summary Through Week 12

TEAEs Through Week 12, n (%)	Placebo (N=40)	Rilzabrutinib 400 mg QPM (N=38)	Rilzabrutinib 400 mg BID (N=41)	Rilzabrutinib 400 mg TID (N=41)
TEAE	23 (57.5)	23 (60.5)	30 (73.2)	31 (75.6)
Severe TEAE	1 (2.5)	1 (2.6)	1 (2.4)	1 (2.4)
SAE	1 (2.5)	0	0	2 (4.9)
TEAE leading to death	0	0	0	0
TEAE leading to treatment discontinuation	0	0	1 (2.4)	1 (2.4)

Table 3. Most Frequent TEAEs Through Week 12 (>10% in any group)

TEAEs Through Week 12, n (%)	Placebo (N=40)	Rilzabrutinib 400 mg QPM (N=38)	Rilzabrutinib 400 mg BID (N=41)	Rilzabrutinib 400 mg TID (N=41)
Diarrhea	6 (15.0)	3 (7.9)	12 (29.3)	12 (29.3)
Nausea	2 (5.0)	5 (13.2)	7 (17.1)	8 (19.5)
Headache	0	2 (5.3)	6 (14.6)	4 (9.8)
Abdominal pain	2 (5.0)	1 (2.6)	5 (12.2)	0

References

1. Kaplan A, et al. *Allergy*. 2023;78:389–401.
2. Church MK, et al. *Immunol Rev*. 2018;282:232–247.
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4. Ucpinar S, et al. *Clin Transl Sci*. 2023;16:1210–1219.

Abbreviations

AE, adverse event; ANCOVA, analysis of covariance; BID, twice a day; BTK, Bruton's tyrosine kinase; CI, confidence interval; CSU, chronic spontaneous urticaria; H1-AH; H1-antihistamine; HSS7, weekly hives severity score; ISS7, weekly itch severity score; ITT, intent to treat; LS, least squares; QPM, once every evening; SAE, serious adverse event; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse event; TID, three times a day; UAS7, weekly urticaria activity score; Wk, Week; WOCF, worst observation carried forward.

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