Rilzabrutinib Reduces IgG Anti-Thyroid Peroxidase (anti-TPO), Soluble Mas-Related G Protein-Coupled Receptor X2 (sMRGPRX2), and Eosinophils at 12 Weeks in Patients With Chronic Spontaneous Urticaria

Presenter: Prof. Dr. Marcus Maurer

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Oral Session (OAS) 10

Advances in Chronic Urticaria treatment

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Table of Content

1 Introduction

CSU, characterized by recurrent wheals and/or angioedema, is driven by the **pathogenic activation of cutaneous mast cells** by various mechanisms[1,2]

Biomarkers can provide clinicians and researchers with **insights related to disease monitoring, predicted drug efficacy**, as well as **mechanism of action**[3]

2 main autoimmune mechanisms of CSU: Type I associated with IgE autoantibodies and type IIb associated with IgG autoantibodies[2]

Use of biomarkers in CSU treatment may enable better **patient stratification and personalized treatment** based on CSU endotype[4]

- **type IIb CSU** is characterized by **poor response to antihistamines and currently available biologics**

1. Church MK, et al. *Immunol Rev.* 2018;282(1):232-247; 2. Kolkhir P, et al. *J Allergy Clin Immunol.* 2022;149(6):1819-1831; 3. FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [internet]. Silver Spring and Bethesda, MD: US Food and Drug Administration and National Institutes of Health. January 28, 2016 (Updated January 25, 2021). Kaplan A, et al. *Allergy.* 2023;78(2):389-401.

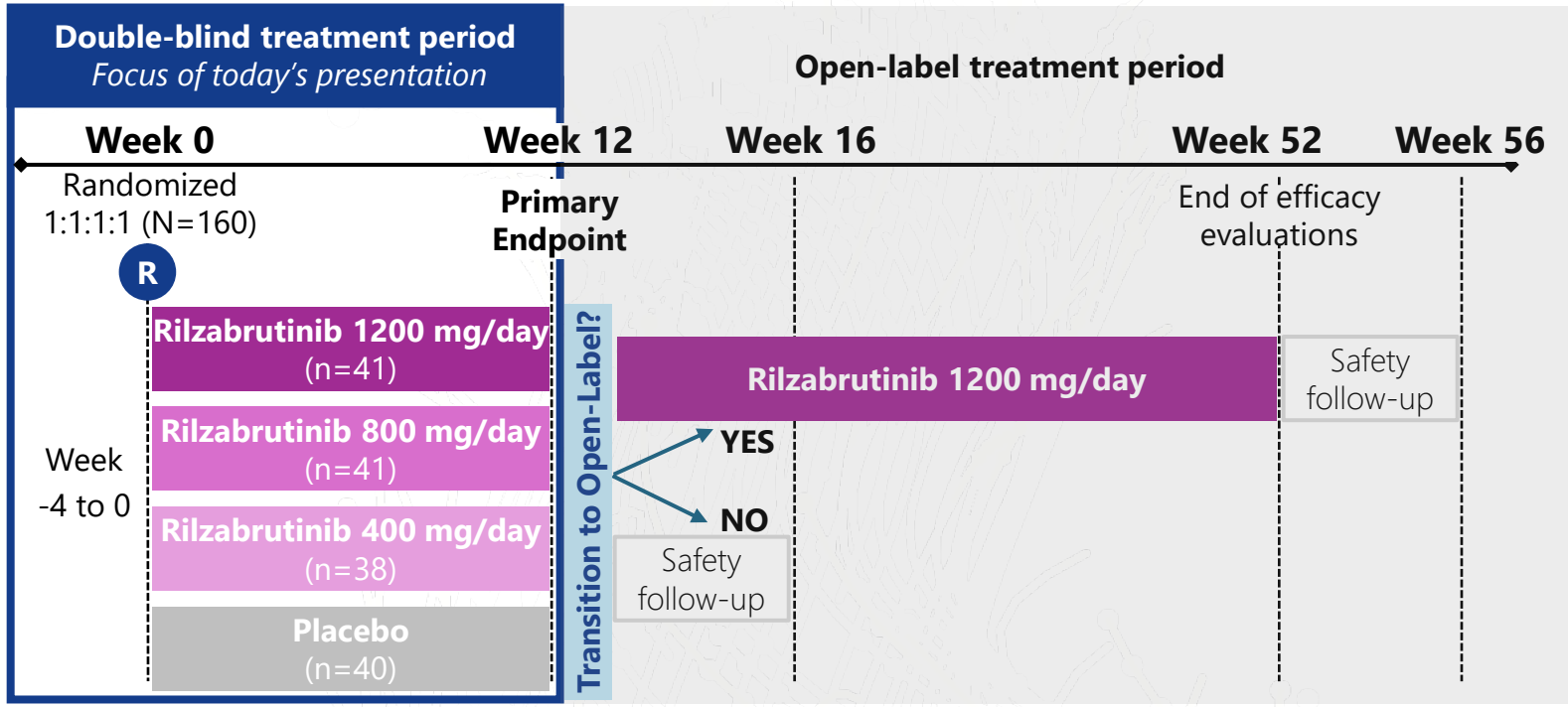
2 Objective

Objective

Explore the effect of rilzabrutinib on **CSU-relevant biomarkers** during the Phase 2 study (RILECSU) evaluating the efficacy and safety of rilzabrutinib in adults with CSU whose disease is uncontrolled with antihistamines

3 Study design

RILECSU Phase 2 trial (NCT05107115)



Primary analysis population: omalizumab-naïve patients (N=143)
Intent-to-treat population: omalizumab-naïve and omalizumab-incomplete responders[a] (N=160)

Note: Rilzabrutinib tablets were taken orally.
[a]Omalizumab-incomplete responders randomized as follows: 400 mg/day arm (n=1); 800 mg/day (n=6); 1200 mg/day (n=6); and placebo (n=4).

Primary endpoint

- Change from baseline at **Week 12** in **weekly Urticaria Activity Score (UAS7)**

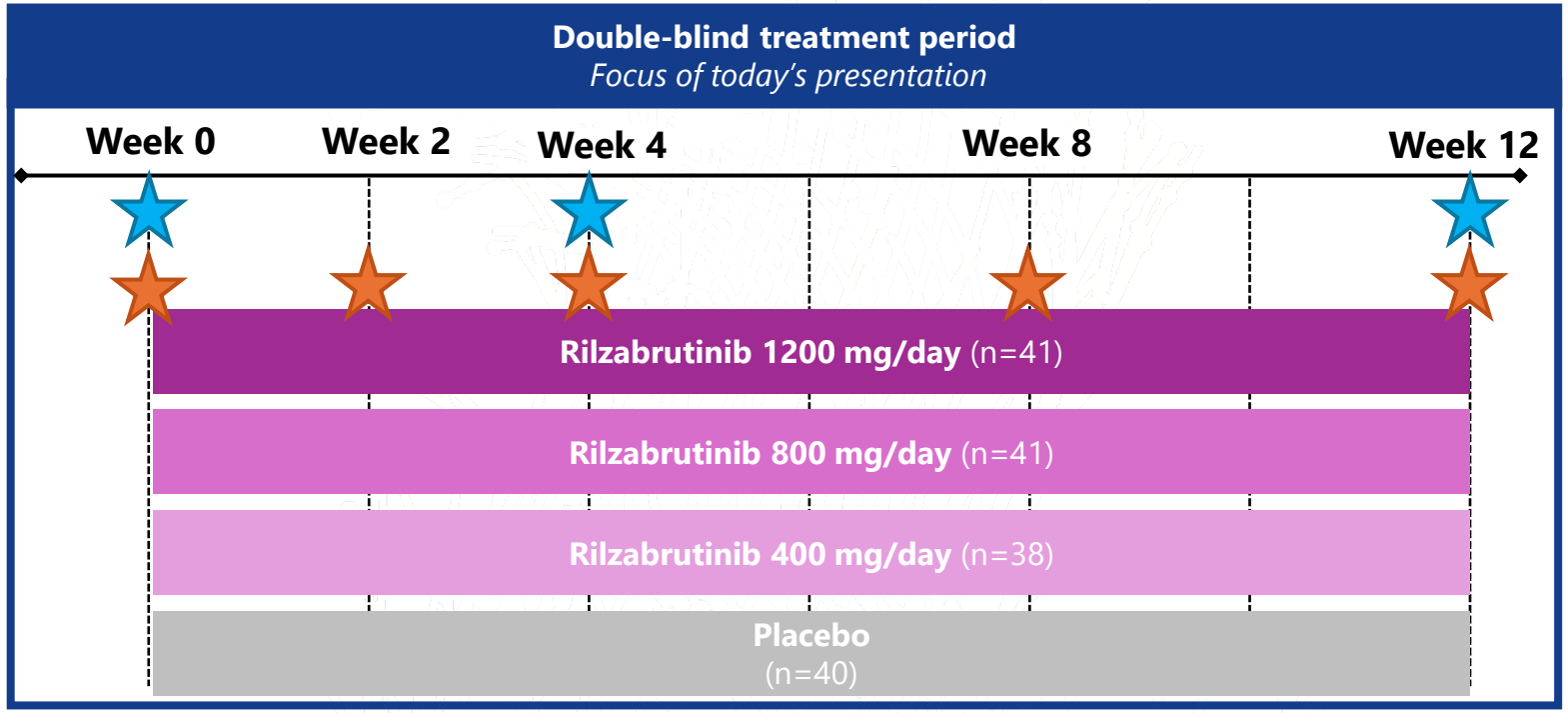
Secondary endpoints

- Change from baseline in:
  - weekly Itch Severity Score **(ISS7) at Week 12**
  - weekly Hives Severity Score **(HSS7) at Week 12**
  - **UAS7 at Week 4**
- Proportion of participants with:
  - **UAS7≤6 at Week 12**
  - **UAS7=0 at Week 12**
- **Safety**

Biomarkers

3 Study design

RILECSU Phase 2 trial (NCT05107115)



Biomarkers included:

- IgG anti-high-affinity IgE receptor **(IgG anti-FcεRI)**
- IgG anti-thyroid peroxidase **(IgG anti-TPO)**
- **IL-31**
- Soluble Mas-related G protein-coupled receptor X2 **(sMRGPRX2)**

- Total serum **IgE**
- Total serum **IgG**
- Eosinophils **(Eos)**

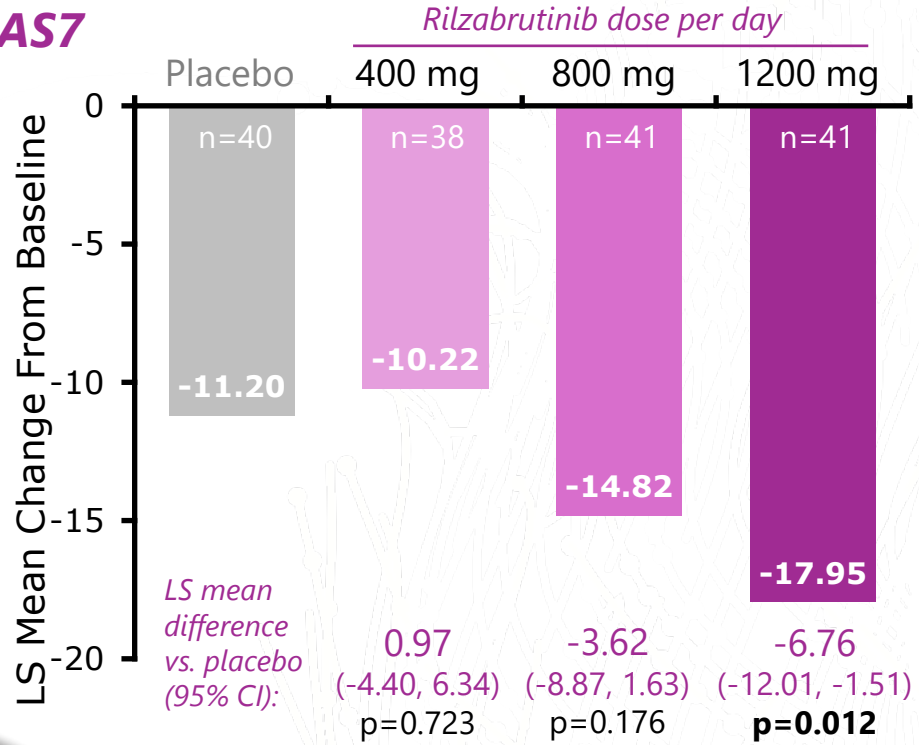
Primary analysis population: omalizumab-naïve patients (N=143)
Intent-to-treat population: omalizumab-naïve and omalizumab-incomplete responders[a] (N=160)

Note: Rilzabrutinib tablets were taken orally.
[a]Omalizumab-incomplete responders randomized as follows: 400 mg/day arm (n=1); 800 mg/day (n=6); 1200 mg/day (n=6); and placebo (n=4).

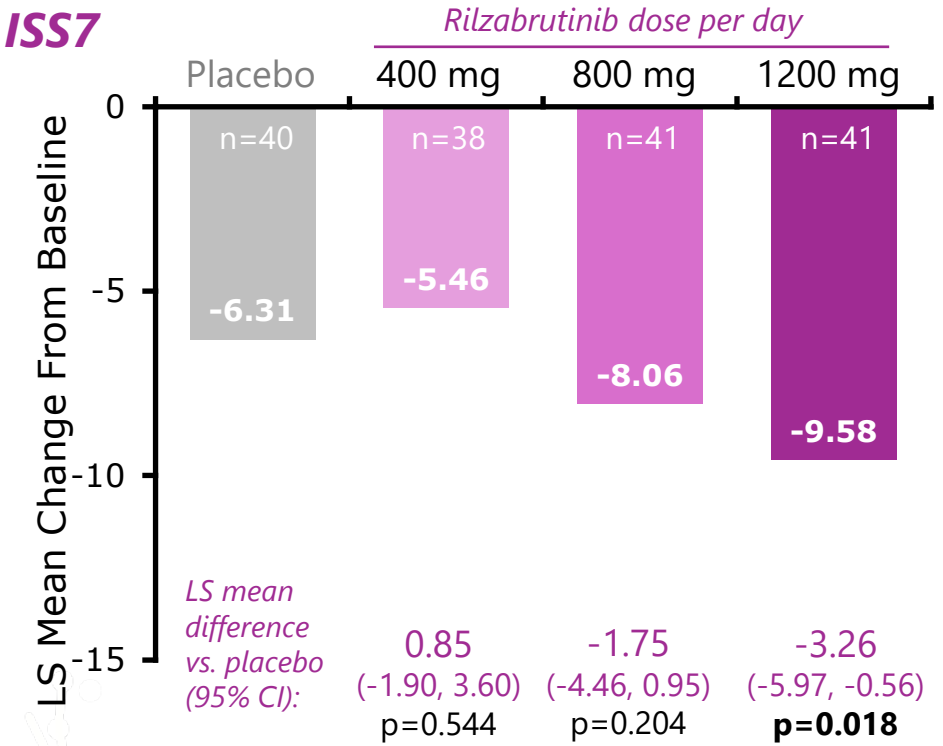
4 Results

Significant reduction in UAS7 and ISS7 from baseline at Week 12 with rilzabrutinib 1200 mg vs placebo

UAS7



ISS7



CI, confidence interval; ISS7, weekly Itch Severity Score; LS, least squares; UAS7, weekly Urticaria Activity Score.

4 Results

Baseline biomarker levels were generally well balanced across treatment arms

Median Biomarker Levels (Q1; Q3 range)	Placebo (n=40)	Rilzabrutinib 400 mg/day (n=38)	Rilzabrutinib 800 mg/day (n=41)	Rilzabrutinib 1200 mg/day (n=41)	Total (N=160)
Total IgE (IU/mL)	142.6 (40.4; 349.5)	158.0 (37.6; 533.6)	111.1 (38.7; 314.6)	116.8 (34.7; 407.9)	123.8 (37.6; 351.1)
Total IgG (g/L)	11.9 (10.2; 14.0)	11.1 (9.9; 13.0)	11.4 (10.2; 12.4)	11.7 (10.4; 12.9)	11.5 (10.1; 13.0)
IgG anti-FcεRI (arbitrary unit)	141.6 (56.1; 308.9)	174.7 (53.7; 250.0)	208.2 (99.8; 425.0)	134.2 (46.4; 308.9)	160.1 (53.5; 317.6)
IgG anti-TPO (IU)	0.0 (0.0; 6.8)	0.0 (0.0; 8.3)	3.1 (0.0; 9.7)	1.6 (0.0; 19.9)	0.4 (0.0; 10.3)
IL-31 (ng/mL)	4.0 (2.9; 5.3)	4.1 (3.2; 5.7)	5.0 (3.8; 8.4)	4.2 (3.3; 6.7)	4.2 (3.3; 6.4)
sMRGPRX2 (ng/mL)	21.1 (13.1; 30.6)	26.5 (17.5; 33.6)	17.5 (10.4; 28.3)	21.8 (14.3: 30.3)	21.2 (13.6; 31.2)
Eosinophils (10^9/L)	0.18 (0.12; 0.29)	0.16 (0.11; 0.25)	0.16 (0.09; 0.26)	0.18 (0.09; 0.29)	0.17 (0.09; 0.28)

Ig, immunoglobulin; IL, interleukin; Q, quartile; sMRGPRX2, soluble Mas-related G-protein coupled receptor X2; TPO, thyroid peroxidase.

4 Results

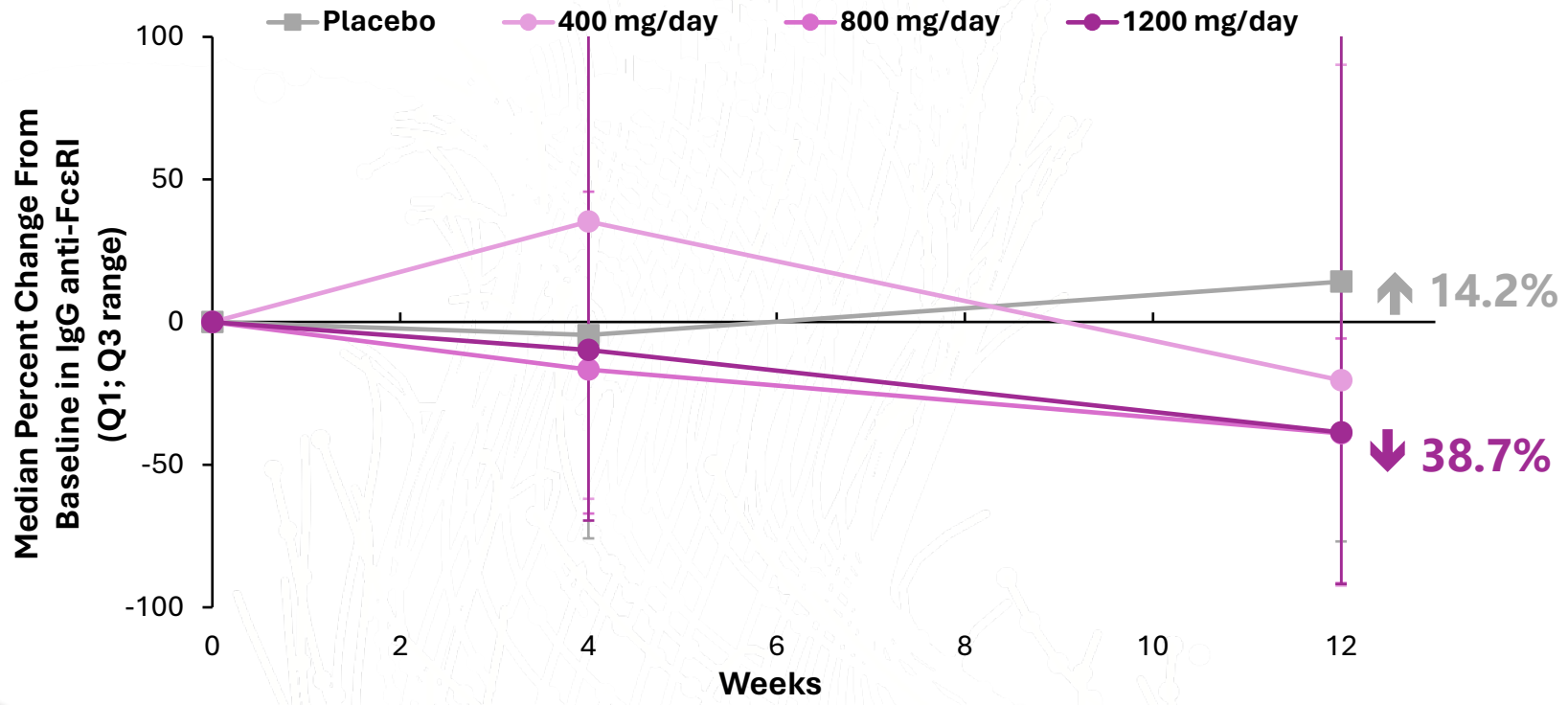
Reductions in CSU-related biomarkers from baseline to Week 12 with Rilzabrutinib (median percent change)

Median Percent Change from Baseline (Q1; Q3 range)	Placebo (n=40)	Rilzabrutinib 400 mg/day (n=38)	Rilzabrutinib 800 mg/day (n=41)	Rilzabrutinib 1200 mg/day (n=41)	
Total IgE (IU/mL)	**0** (-13.8; 25.3)	**3.4** (-13.4; 22.2)	**3.9** (-13.0; 34.1)	**4.1** (-13.4; 53.7)	↔
Total IgG (g/L)	**2.76** (-2.29; 6.360	**-1.99** (-6.23; 5.89)	**0.96** (-2.21; 5.45)	**0.24** (-7.99; 4.61)	↔
IgG anti-FcεRI (arbitrary unit)	**14.2** (-76.9; 202.4)	**-20.4** (-92.4; 90.2)	**-39.0** (-91.5; -5.7)	**-38.7** (-91.8; 162.9)	↓
IgG anti-TPO (IU)	**-7.0** (-62.4; 53.0)	**-39.9** (-100.0; -0.7)	**-19.4** (-71.5; 16.7)	**-46.7** (-69.0; -7.4)	↓
IL-31 (ng/mL)	**15.4** (-11.1; 31.3)	**-11.6** (-24.7; 17.9)	**-6.8** (-28.6; 9.9)	**-8.1** (-22.3; 15.0)	↓
sMRGPRX2 (ng/mL)	**-4.5** (-47.6; 59.0)	**-31.1** (-47.4; -13.0)	**-29.3** (-44.9; 13.0)	**-22.8** (-57.7; -6.4)	↓
Eosinophils (10^9/L)	**3.6** (-25.0; 45.5)	**7.7** (-25.0; 33.3)	**-11.8** (-36.6; 8.7)	**-29.0** (-47.5; 0.0)	↓

Ig, immunoglobulin; IL, interleukin; Q, quartile; sMRGPRX2, soluble Mas-related G-protein coupled receptor X2; TPO, thyroid peroxidase.

4 Results

Rilzabrutinib reduced IgG anti-high-affinity IgE receptor (IgG anti-FcεRI) autoantibodies at Week 12

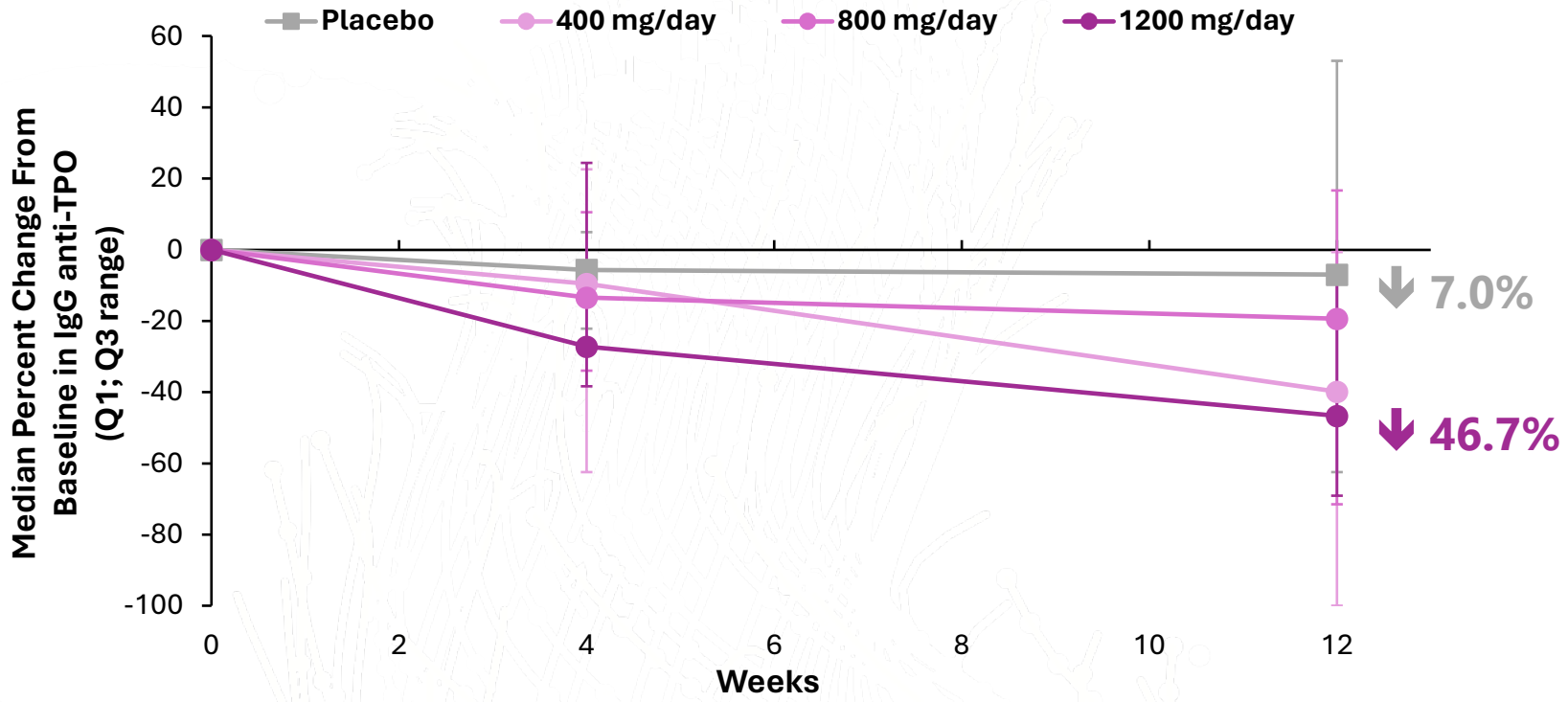


Reduction in IgG anti-FcεRI with BTK signaling inhibition may result in a reduction in mast-cell and basophil activation

BTK, Bruton's tyrosine kinase; Ig, immunoglobulin; Q, quartile.

4 Results

Rilzabrutinib reduced median immunoglobulin G anti-thyroid peroxidase (IgG anti-TPO) over 12 weeks



IgG anti-TPO recommended to be assessed in patients with CSU in the EAACI/GA²LEN/EuroGuiDerm/APAAACI urticaria guideline[1]

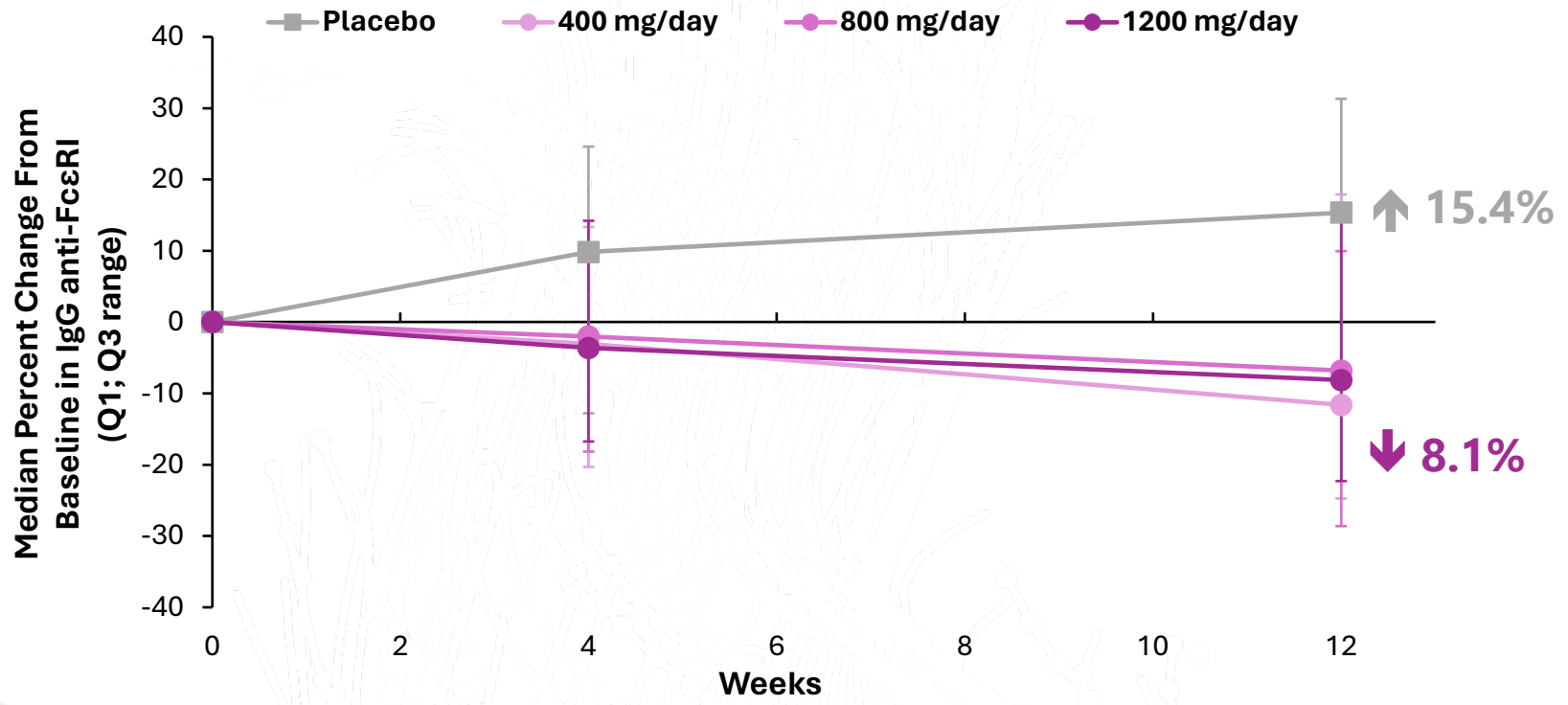
Inhibition of BTK signaling reduces IgG autoantibodies against TPO

APAAACI, Asia Pacific Association of Allergy, Asthma and Clinical Immunology; BTK, Bruton's tyrosine kinase; CSU, chronic spontaneous urticaria; EAACI; European Academy of Allergy and Clinical Immunology; GA²LEN, Global Allergy and Asthma European Network; Q, quartile.

1. Zuberbier T, et al. *Allergy*. 2022;77(3):734-766.

4 Results

IL-31, a pruritogenic proinflammatory cytokine, was reduced with 12 weeks of rilzabrutinib treatment

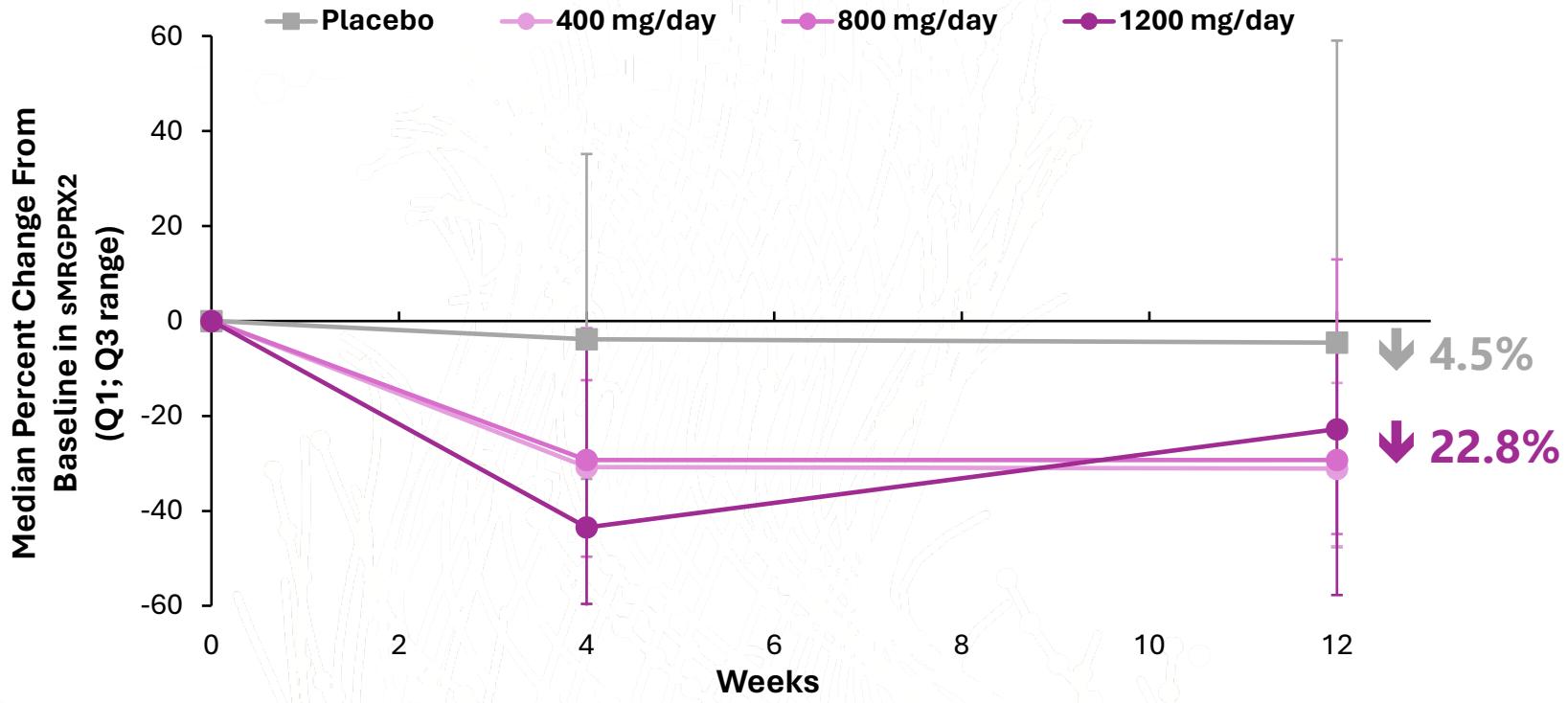


BTK signaling inhibition may reduce itch by reducing IL-31 secretion by mast cells and basophils

BTK, Bruton's tyrosine kinase; IL, interleukin; Q, quartile.

4 Results

Over 12 weeks, rilzabrutinib reduced soluble Mas-related G protein-coupled receptor X2 (sMRGPRX2) levels



sMRGPRX2 in the serum has been shown to be higher in patients with severe CSU and correlates with urticaria severity[1]

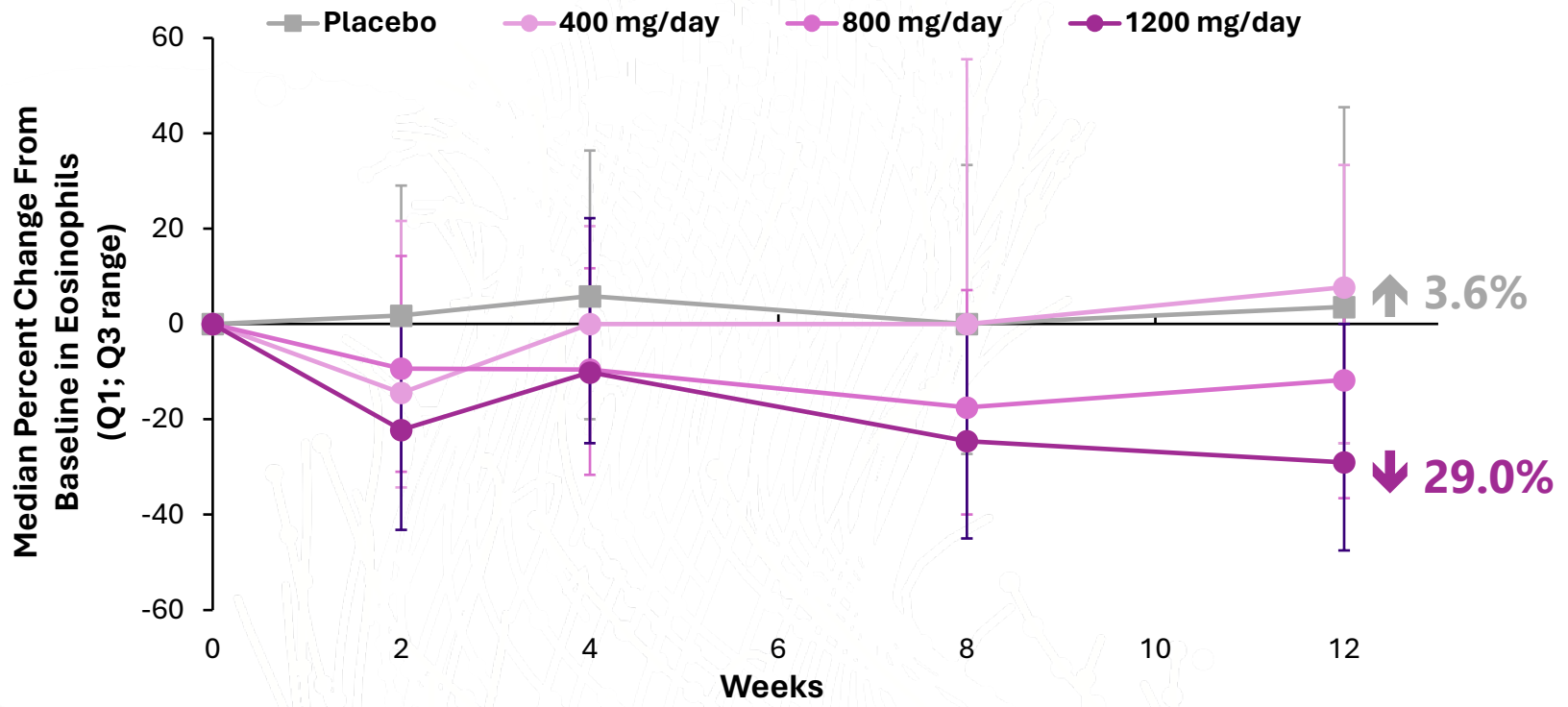
BTK signaling inhibition may reduce serum sMRGPRX2 levels by reducing MRGPRX2 expression on mast cells

BTK, Bruton's tyrosine kinase; CSU, chronic spontaneous urticaria; Q, quartile.

1. Cao TBT, et al. *Allergy Asthma Immunol Res.* 2021;13(3):498-506.

4 Results

Median serum eosinophil levels were reduced with rilzabrutinib at Week 12



Inhibition of BTK signaling reduces eosinophil levels, which may indirectly lower the activation of mast cells

BTK, Bruton's tyrosine kinase; Q, quartile.

5 Conclusions

Reductions in CSU-related biomarkers were observed with rilzabrutinib 1200 mg treatment, supporting a role for BTK in the pathogenesis of CSU

IgG anti-TPO and **IgG anti-FcεRI**, both markers of type IIb autoimmune CSU, were reduced with 12 weeks of rilzabrutinib treatment. No impact in total serum IgE or IgG levels

sMRGPRX2 and **IL-31**, markers associated with CSU disease activity and itch, respectively, were reduced with rilzabrutinib treatment over 12 weeks

Reductions in these biomarkers aligns with the clinical efficacy results in this study and supports the mechanism of action of rilzabrutinib in CSU

BTK, Bruton's tyrosine kinase; CSU, chronic spontaneous urticaria; Ig, immunoglobulin; IL, interleukin; sMRGPRX2, soluble Mas-related G-protein coupled receptor X2; TPO, thyroid peroxidase.

THANK YOU

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