

**TREATMENT OF CHRONIC SPONTANEOUS URTICARIA BY ADMINISTERING
(R)-2-[3-[4-AMINO-3-(2-FLUORO-4-PHENOXY-PHENYL)PYRAZOLO[3,4-
D]PYRIMIDIN-1-YL]PIPERIDINE-1-CARBONYL]-4-METHYL-4-[4-(OXETAN-3-
YL)PIPERAZIN-1-YL]PENT-2-ENENITRILE**

[001] Disclosed herein are methods for treating chronic spontaneous urticaria. BTK inhibitors and pharmaceutical compositions comprising the same are also disclosed.

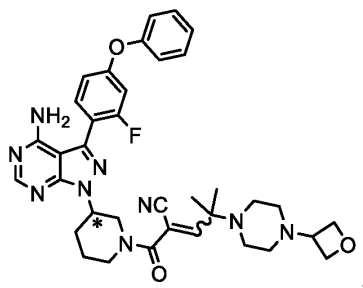
[002] Chronic spontaneous urticaria (CSU), formerly known as chronic idiopathic urticaria (CIU) is a common condition characterized by the spontaneous appearance of pruritic hives and wheals with or without angioedema for more than 6 weeks without a clear inciting factor. CSU has a prevalence between 0.5% and 1% (Maurer et al. 2011). It more commonly affects females than males, and the peak incidence occurs between 20 and 40 years of age. Patients with CSU experience substantial disease burden, including sleep impairment, body image issues, diminished physical and emotional well-being, and impaired performance at school and work (Can et al. 2023; Kolkhir et al. 2022). CSU can thus have significant detrimental impacts on quality of life, productivity, and psychological health (Maurer et al. 2017).

[003] Although the molecular mechanisms are still being elucidated, CSU is thought to be driven by pathogenic activation of mast cells and basophils leading to local release of degranulation products. Of these degranulation products, histamine is felt to play a central role in CSU pathogenesis, driving the pruritus and local vascular permeability (leading to urticaria/angioedema) characteristic of this disease. Of note, emerging data suggest that mast cell and basophil activation in CSU is mediated by activation of the high-affinity IgE receptor, FcεRI, either from development of IgE to autoantigens such as thyroid peroxidase (autoimmune Type I phenotype) or development of activating IgG autoantibodies to IgE or FcεRI (autoimmune Type IIb phenotype) (Bracken et al. 2019; Giménez-Arnau et al. 2021; Kolkhir et al. 2017). Current approved treatments for CSU are targeted against either mast cell degranulation products or the IgE receptor. H1-antihistamines (H1-AH) are first-line therapy in most practice settings. However, approximately 50% of patients fail to achieve symptomatic control with H1-AH at a standard dose. Second-line treatment includes escalation up to four-fold the standard dose of H1-AHs; however, the success rate for patients remains around 45-55%, and dose escalation may be associated with increased somnolence compared to standard dosing of H1-AHs (Armstrong et al. 2023; Kaplan et al. 2023; Kolkhir et al. 2022; Xiao et al. 2023). Omalizumab, an anti-IgE monoclonal antibody which reduces

both serum IgE and cell-surface FcεRI, has emerged as an effective treatment for CSU with inadequate response to H1-AH. However, it has been reported that nearly 50% of patients who receive omalizumab have an inadequate response to this therapy (Metz et al. 2017). In particular, patients with Type IIb autoimmunity are less likely to respond to treatment with H1-AH or omalizumab (Marcelino et al. 2021). As such, there is a need for additional treatments for CSU.

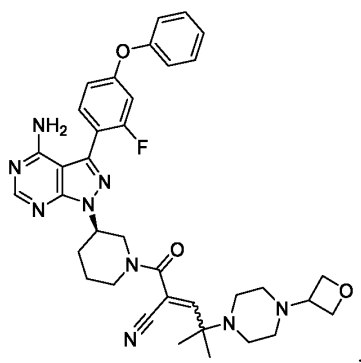
[004] Emerging evidence suggests that Bruton's tyrosine kinase (BTK), a non-receptor-tyrosine kinase and a member of the TEC family of kinases, plays a role in signal amplification after FcεRI cross-linking, leading to enhanced activation of mast cells and basophils. Consistent with this observation, BTK antagonists have demonstrated an inhibitory effect on basophil activation by allergens or anti-IgE antibodies. Given its importance in both the generation of antibodies and signaling through FcεRI, BTK has great potential as a target in CSU therapy, as evidenced by multiple clinical studies investigating the effect of BTK inhibitors on patients with CSU who are refractory to treatment with H1-AH, and are omalizumab-naïve.

[005] Compound (**I**) is a BTK inhibitor of the following structure:



wherein *C is a stereochemical center. *See* PCT Publication No. WO 2014/039899, which is incorporated herein by reference, e.g., Example 31.

(R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, having the following structure:



is also known as rilzabrutinib. This compound has been disclosed in several patent publications, such as, e.g., PCT Publication Nos. WO 2014/039899, WO 2015/127310, WO 2016/100914, WO 2016/105531, WO 2018/005849, and WO 2021/150723, the contents of each of which are incorporated by reference herein.

[006] Rilzabrutinib is a novel, highly selective, and potent small molecule inhibitor of non-T cell white blood cell signaling via B-cell receptor, FcγR, and/or FcεR signaling of the BTK pathway. In the context of ITP, rilzabrutinib has the potential to (1) inhibit B cell activation and (2) interrupt antibody-coated cell phagocytosis by FCγR in the spleen and liver (Bradshaw et al. 2021, Langrish et al. 2021, Owens et al. 2022).

[007] Rilzabrutinib functions as a reversible covalent BTK inhibitor and is capable of both non-covalently and covalently binding to its target; in particular, its reversible cysteine binding enables high selectivity and precise BTK inhibition without a permanent modification of proteins and peptides (Langrish et al. 2021, Owens et al. 2022, Smith PF et al. 2017). Taken together, these properties allow for enhanced selectivity and extended inhibition with low systemic exposure. In comparison to first and second generation BTKi, rilzabrutinib has shown minimal cross-reactivity with other molecules and is low risk for off-target effects (Smith PF et al. 2017). Importantly, rilzabrutinib's reversible binding minimizes the likelihood of permanently modified peptides (Serafimova IM 2012). In addition, rilzabrutinib shows improved kinase selectivity relative to the covalent BTK inhibitor ibrutinib. Preclinical studies in a broad kinase enzyme inhibition panel showed that 1 μ M rilzabrutinib achieved >90% inhibition of just 6 of 251 kinases sharing a common cysteine in their active site. By contrast, 1 μ M ibrutinib inhibited 21 kinases. Rilzabrutinib's IC₅₀ values were 1.3 nM for BTK, 0.8 nM for tyrosine protein kinase TEC, 1.0 nM for bone marrow tyrosine kinase on chromosome X (BMX), 1.2 nM for receptor-like kinase (RLK), 6.3 nM for

B cell lymphocyte kinase (BLK), and 11 nM for ERBB4. Further preclinical assays with rilzabrutinib showed that binding to BTK persisted while that for other TEC family members decayed rapidly over time.

[008] Rilzabrutinib has shown encouraging results for the treatment of immune-mediated diseases. In humans, rilzabrutinib is rapidly absorbed following oral administration, with a fast half-life (3-4 h) and variable pharmacokinetics (Smith PF et al., 2017).

[009] In Phase 1 studies of rilzabrutinib with 114 healthy volunteers, target BTK occupancy levels were safely and consistently exceeded, suggesting rilzabrutinib may be highly effective in treating autoimmune diseases. Moreover, preclinical and clinical pharmacokinetic and pharmacodynamic data showed that treatment effects endured even after the compound was cleared from circulation, consistent with an extended target residence time (Hill R et al., 2015) and high target occupancy rate (> 90% within four hours and high sustained occupancy over 24 h) (Smith PF et al., 2015).

[0010] Rilzabrutinib has also demonstrated a favorable safety profile in clinical studies. In contrast with non-selective, irreversible BTK inhibitors, rilzabrutinib does not alter platelet aggregation in healthy volunteers or patients with ITP and thus does not lead to bleeding problems (Langrish et al. 2021, von Hundelshausen and Seiss 2021). As an additional point of contrast with irreversible BTK inhibitors, rilzabrutinib treatment does not exert clinically relevant effects on cardiac repolarization (electrocardiogram parameters including corrected QT interval) in healthy volunteers (N=51), even when administered at supratherapeutic doses (Lipsky and Lamanna 2020). Indeed, the most commonly reported adverse events in healthy volunteers were gastrointestinal adverse events, including nausea/vomiting and diarrhea. No serious adverse events or deaths were reported, and no participants discontinued treatment due to an adverse event (Smith PF 2017). Moreover, based on preclinical reproductive toxicity studies, rilzabrutinib is not expected to harm fetal development or male fertility.

[0011] The efficacy of rilzabrutinib has been evaluated in both nonclinical and clinical studies. Rilzabrutinib demonstrated blockade of the rat Arthus reaction, full disease reversal of a rat collagen-induced arthritis model, and reduction in platelet loss in a mouse model of immune thrombocytopenia. The therapeutic effects of rilzabrutinib in pemphigus was studied in dogs with newly diagnosed, naturally occurring pemphigus foliaceus (PF). The drug safely controlled disease without the need for corticosteroid (CS) in 4 of 4 cases. The clinical efficacy of rilzabrutinib was further demonstrated in an open-label, Phase 1/2 study in

immune thrombocytopenic purpura (ITP). In this trial, 50% of participants achieved the primary response endpoint after treatment with rilzabrutinib for at least 12 weeks. Furthermore, there were no treatment-emergent serious adverse events (TESAEs) observed. Collectively, these and other studies have shown rilzabrutinib to be a safe and effective inhibitor of BTK.

[0012] There is preliminary evidence to support the role of BTK inhibition in patients with CSU, including in patients with CSU who are both refractory to treatment with H1-AH and are omalizumab-naïve (Maurer et al. 2021; Metz et al. 2020). Notably, results from studies on the BTK inhibitor fenebrutinib suggest a differential response based on basophil histamine release assay (BHRA) status, wherein BHRA-positive patients may be more sensitive to BTK inhibition, especially at lower doses, compared to BHRA-negative patients (Metz et al. 2020). Separately, studies suggest that CSU patients who are BHRA-positive are more likely to have a poorer response to omalizumab compared to those who are BHRA-negative. As patients with prior omalizumab use, including omalizumab-incomplete responders may be enriched for BHRA-positive CSU patients, who are in turn more likely to have Type IIb autoimmunity and be less responsive to available treatments, they may be best poised to benefit from BTK inhibition. Patients with prior omalizumab use, including omalizumab-incomplete responders who are BHRA-negative may also stand to benefit from BTK inhibition, although this benefit may be seen at higher doses compared to BHRA-positive patients (Gericke et al. 2016). Accordingly, a dose-ranging Phase 2 study was initiated to assess the efficacy and safety of rilzabrutinib in patients with moderate-to-severe CSU.

[0013] Accordingly, disclosed herein are methods of treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, comprising administering to the human patient in need thereof a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof.

[0014] Further disclosed herein are methods of treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, comprising administering to the human patient a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-

4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, wherein the human patient in need thereof has CSU refractory to H1 antihistamines (H1-AH) treatment.

[0015] Further disclosed herein is a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for use in treating chronic spontaneous urticaria (CSU) in a human patient in need thereof.

[0016] Further disclosed herein is a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for use in the manufacture of a medicament for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof.

[0017] Further disclosed herein is the use of a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof.

[0018] Further disclosed herein is the use of a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for the manufacture of a medicament for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof.

[0019] Further disclosed herein is a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for use in treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, wherein the human patient in need thereof has CSU refractory to H1 antihistamines (H1-AH) treatment.

[0020] Further disclosed herein is a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for use in the manufacture of a medicament for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, wherein the human patient in need thereof has CSU refractory to H1 antihistamines (H1-AH) treatment.

[0021] Further disclosed herein is the use of a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, wherein the human patient in need thereof has CSU refractory to H1 antihistamines (H1-AH) treatment.

[0022] Further disclosed herein is the use of a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, wherein the human patient in need thereof has CSU refractory to H1 antihistamines (H1-AH) treatment.

BRIEF DESCRIPTION OF DRAWINGS

[0023] **Fig. 1A** shows the graphical study design.

[0024] **Fig. 1B** shows patient disposition up to Week 12.

[0025] **Fig. 2** shows a waterfall plot of UAS7 at Week 12 by treatment group (omalizumab-naïve population). Circles and triangles indicate scores for individual patients at baseline and Week 12, respectively.

[0026] **Fig. 3** shows a waterfall plot of UAS7 at Week 12 by treatment group (patients with prior omalizumab use, including omalizumab-incomplete responders in ITT population). Circles and triangles indicate scores for individual patients at baseline and Week 12, respectively.

[0027] **Fig. 4** shows the cumulative probability function of change from baseline in UAS7 at Week 12 (omalizumab-naïve population).

[0028] **Fig. 5** shows a plot of LS mean change from baseline in UAS7 over time up to Week 12 (ITT population).

[0029] **Fig. 6** shows a plot of LS mean change from baseline in UAS7 over time up to Week 12 (omalizumab-naïve population).

[0030] **Fig. 7** shows a plot of LS mean change from baseline in UAS7 over time up to Week 12 (omalizumab-naïve population with outlier removed from analysis).

[0031] **Fig. 8** shows a plot of mean change from baseline in UAS7 over time up to Week 12 (patients with prior omalizumab use, including omalizumab-incomplete responders in ITT population).

[0032] **Fig. 9** shows a plot of the proportion of participants with UAS7 ≤ 6 over time up to Week 12 (ITT population).

[0033] **Fig. 10** shows a plot of the proportion of participants with UAS7 ≤ 6 over time up to Week 12 (omalizumab-naïve population).

[0034] **Fig. 11** shows a plot of the proportion of participants with UAS7 = 0 over time up to Week 12 (ITT population).

[0035] **Fig. 12** shows a plot of the proportion of participants with UAS7 = 0 over time up to Week 12 (omalizumab-naïve population).

[0036] **Fig. 13** shows a plot of the proportion of participants with UAS7 reduction from baseline of 10 points or more over time up to Week 12 (ITT population).

[0037] **Fig. 14** shows a plot of the proportion of participants with UAS7 reduction from baseline of 10 points or more over time up to Week 12 (omalizumab-naïve population).

[0038] **Fig. 15** shows a cumulative probability function of change from baseline in ISS7 at Week 12 (omalizumab-naïve population).

[0039] **Fig. 16** shows a waterfall plot of ISS7 at Week 12 by treatment group (omalizumab-naïve population). Circles and triangles indicate scores for individual patients at baseline and Week 12, respectively.

[0040] **Fig. 17** shows a waterfall plot of ISS7 at Week 12 by treatment group (patients with prior omalizumab use, including omalizumab-incomplete responders in the ITT population). Circles and triangles indicate scores for individual patients at baseline and Week 12, respectively.

[0041] **Fig. 18** shows a plot of LS mean change from baseline in ISS7 over time up to Week 12 (ITT population).

[0042] **Fig. 19** shows a plot of LS mean change from baseline in ISS7 over time up to Week 12 (omalizumab-naïve population).

[0043] **Fig. 20** shows a plot of LS mean change from baseline in ISS7 over time up to Week 12 (omalizumab-naïve population with outlier removed from analysis).

[0044] **Fig. 21** shows a plot of mean change from baseline in ISS7 over time up to Week 12 (patients with prior omalizumab use, including omalizumab-incomplete responders in the ITT population).

[0045] **Fig. 22** shows a cumulative probability function of change from baseline in HSS7 at Week 12 (omalizumab-naïve population).

[0046] **Fig. 23** shows a waterfall plot of HSS7 at Week 12 by treatment group (omalizumab-naïve population). Circles and triangles indicate scores for individual patients at baseline and Week 12, respectively.

[0047] **Fig. 24** shows a waterfall plot of HSS7 at Week 12 by treatment group (patients with prior omalizumab use, including omalizumab-incomplete responders in the ITT population). Circles and triangles indicate scores for individual patients at baseline and Week 12, respectively.

[0048] **Fig. 25** shows a plot of LS mean change from baseline in HSS7 over time up to Week 12 (ITT population).

[0049] **Fig. 26** shows a plot of LS mean change from baseline in HSS7 over time up to Week 12 (omalizumab-naïve population).

[0050] **Fig. 27** shows a plot of LS mean change from baseline in HSS7 over time up to Week 12 (omalizumab-naïve population with outlier removed from analysis).

[0051] **Fig. 28** shows a plot of mean change from baseline in HSS7 over time up to Week 12 (patients with prior omalizumab use, including omalizumab-incomplete responders in the ITT population).

[0052] **Fig. 29** shows a plot of LS mean change from baseline in AAS7 over time up to Week 12 in participants with angioedema at baseline (ITT population).

[0053] **Fig. 30** shows a plot of LS mean change from baseline in AAS7 over time up to Week 12 in participants with angioedema at baseline (omalizumab-naïve population).

[0054] **Fig. 31** shows a cumulative probability function of change from baseline in AAS7 at Week 12 in participants with angioedema at baseline (omalizumab-naïve population).

[0055] **Fig. 32** shows a waterfall plot of AAS7 at Week 12 by treatment group in participants with angioedema at baseline (omalizumab-naïve population). Circles and triangles indicate scores for individual patients at baseline and Week 12, respectively.

[0056] **Fig. 33** shows a plot of the proportion of participants with AAS7 = 0 over time up to Week 12 (participants with angioedema at baseline in the omalizumab-naïve population).

[0057] **Fig. 34** shows a plot of proportion of participants with AAS7 = 0 over time up to Week 12 (omalizumab-naïve population with outlier removed from the analysis).

[0058] **Fig. 35** shows a plot of LS mean change from baseline in UCT over time up to Week 12 (ITT population).

[0059] **Fig. 36** shows a plot of LS mean change from baseline in UCT over time up to Week 12 (omalizumab-naïve population).

[0060] **Fig. 37** shows a plot of proportion of participants with UCT ≥ 12 over time up to Week 12 (omalizumab-naïve population).

[0061] **Fig. 38** shows a plot of LS mean change from baseline in PGIS over time up to Week 12 (omalizumab-naïve population).

[0062] **Fig. 39** shows a plot of LS mean change from baseline in PGIC over time up to Week 12 (omalizumab-naïve population).

[0063] **Fig. 40A-E** shows a plot of the median percentage change from baseline (with interquartile range) for (A) sMRGPRX2, (B) IL-31, (C) IgG anti-TPO, (D) IgG anti-Fc ϵ RI, and (E) IgG anti-IgE.

[0064] **Fig. 41** shows a plot of the median percentage change from baseline (with interquartile range) for eosinophils.

Definitions:

[0065] Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meanings. All undefined technical and scientific terms used in this Application have the meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0066] As used herein, “a” or “an” entity refers to one or more of that entity; for example, a compound refers to one or more compounds or at least one compound unless stated

otherwise. As such, the terms “a” (or “an”), “one or more”, and “at least one” can be used interchangeably herein.

[0067] As used herein, the term “about” is used herein to mean approximately, in the region of, roughly, or around. When the term “about” is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term “about” is used herein to modify a numerical value above and below the stated value by a variance of 5%. With regard to specific values, it should be understood that specific values described herein for subject populations (e.g., the subject of the described clinical trial) represent median, mean, or statistical numbers, unless otherwise provided. Accordingly, aspects of the present disclosure requiring a particular value in a subject are supported herein by population data in which the relevant value is assessed to be a meaningful delimitation on the subject population.

[0068] As used herein, the term “active pharmaceutical ingredient” or “therapeutic agent” (“API”) refers to a biologically active compound.

[0069] As used herein, the term “approved treatment” refers to a medication that has received regulatory authorization, in any country, for its intended use.

[0070] As used herein, the terms “administer,” “administering,” or “administration” herein refer to providing, giving, dosing, and/or prescribing by either a health practitioner or an authorized agent and/or putting into, taking, or consuming by the patient or person himself or herself. For example, “administration” of an API to a patient refers to any route (e.g., oral delivery) of introducing or delivering the API to the patient. Administration includes self-administration and administration by another.

[0071] As used herein, the term “baseline” refers to a measurement or an average of measurements taken on or before day 1 (D1) of initiating rilzabrutinib treatment. By way of non-limiting example, baseline can be determined for, e.g., UAS7, ISS7, UCT, and AAS7.

[0072] As used herein, “BID” and “bid” are used interchangeably to refer to twice a day.

[0073] As used herein, the term “in combination with,” when referring to two or more compounds, agents, or additional active pharmaceutical ingredients, means the administration of two or more compounds, agents, or active pharmaceutical ingredients to the patient prior to, concurrent with, or subsequent to each other during a treatment period. Unless specified otherwise, the two or more compounds, agents, or active pharmaceutical ingredients may be administered on different schedules during the treatment period, such as, e.g., with one or

more compounds, agents, or active pharmaceutical ingredients being administered once a day and one or more other compounds, agents, or active pharmaceutical ingredients being administered twice a day.

[0074] As used herein, an amount expressed in terms of “mg of [X]” refers to the total amount in milligrams of [X], i.e., the free base. In some embodiments, rilzabrutinib may be administered as a pharmaceutically acceptable salt of rilzabrutinib, in which case an amount expressed in terms of “mg of rilzabrutinib” refers to the total amount in milligrams of rilzabrutinib, i.e., the free base, plus the equivalent amount of one or more pharmaceutically acceptable salts of rilzabrutinib based on the weight of free base therein. For example, “400 mg of at least one compound chosen from rilzabrutinib and pharmaceutically acceptable salts thereof” includes 400 mg of rilzabrutinib and a concentration of one or more pharmaceutically acceptable salts of rilzabrutinib equivalent to 400 mg of rilzabrutinib.

[0075] As used herein, “moderate-to-severe” CSU encompasses both patients with moderate CSU and patients with severe CSU.

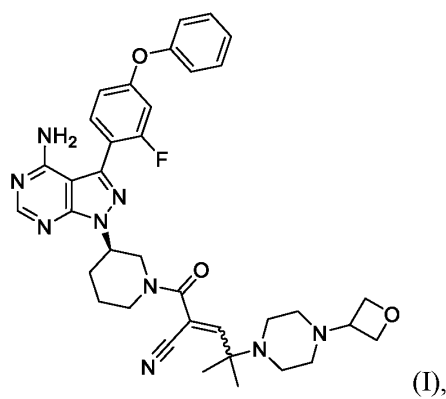
[0076] As used herein, the terms “prior use of omalizumab” “omalizumab-incomplete responder,” “omalizumab-incomplete responder,” “incomplete responder,” and “incomplete responders” refer to participants who were previously treated with omalizumab and/or exhibited inadequate control of CSU symptoms despite treatment with omalizumab as prescribed.

[0077] As used herein, a “pharmaceutically acceptable carrier or excipient” means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, and neither biologically nor otherwise undesirable, such as, e.g., a carrier or an excipient that is acceptable for mammalian pharmaceutical use.

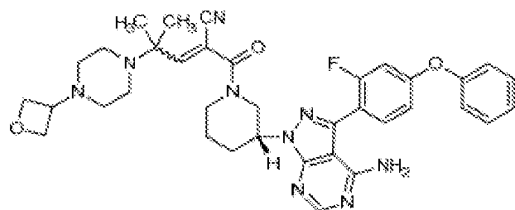
[0078] As used herein, the term “pharmaceutically acceptable salt” refers to a salt form, e.g., an acid addition salt, of an active pharmaceutical agent that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the API of which the salt is made. Pharmaceutically acceptable salts are well known in the art and include those derived from suitable inorganic and organic acids. Such salts include, but are not limited to, salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, and the like; or formed with organic acids such as formic acid, acetic acid, propionic acid, hexanoic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic

acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, benzenesulfonic acid, 4-toluenesulfonic acid, and the like. S. M. Berge et al. describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19.

[0079] As used herein, the terms “rilzabrutinib,” “(R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile,” “the compound of Formula (I),” and “2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]-pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile” are used interchangeably to refer to a compound having the structure:



which is also referred to as 2-[(3R)-2-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-(E and Z)-pent-2-enenitrile; (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile; 1-piperidinepropanenitrile, 3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-α-[2-methyl-2-[4-(3-oxetanyl)-1-piperazinyl]propylidene]-β-oxo-, (3R)-; (EZ)-2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile; and also by the International Nonproprietary Names for Pharmaceutical Substances (INN) as published by the World Health Organization ([https://cdn.who.int/media/docs/default-source/international-nonproprietary-names-\(inn\)/pl121.pdf?sfvrsn=69617906_15&download=true](https://cdn.who.int/media/docs/default-source/international-nonproprietary-names-(inn)/pl121.pdf?sfvrsn=69617906_15&download=true)) having the following structure:



The compound of Formula (I) includes E and Z isomers, as indicated by the wavy bond in the structure shown above. The compound of Formula (I) may be present as a salt form.

[0080] A dose of the (E) isomer of rilzabrutinib may contain the corresponding (Z) isomer as an impurity in less than about 1% by weight; a dose of the (Z) isomer of rilzabrutinib may contain the corresponding (E) isomer as an impurity in less than about 1% by weight. When rilzabrutinib is denoted as a mixture of (E) and (Z) isomers of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, it means that the amount of (E) or (Z) isomer in the mixture is greater than about 1% by weight. In some embodiments, the molar ratio of (E) to (Z) isomer is 9:1. rilzabrutinib or a pharmaceutically acceptable salt thereof may also be referred to herein as a “drug,” “active agent,” “a therapeutically active agent,” or “API.”

[0081] As used herein, “QD” and “qd” are used interchangeably to refer to once a day.

[0082] As used herein, the terms “refractory” or “refractory to H1 antihistamines” encompasses patients diagnosed with CSU who continue to exhibit symptoms despite treatment with up to 4 times the recommended dose of H1-AH, for example 2 times the recommended dose, 2.5 times the recommended dose, 3 times the recommended dose, 3.5 times the recommended dose, or 4 times the recommended dose.

[0083] As used herein, the term “therapeutically effective amount” refers to that of a compound that produces the desired effect for which it is administered (e.g., improvement in CSU or a symptom of CSU, or lessening the severity of CSU or a symptom of CSU). The exact amount of an effective dose will depend on the purpose of the treatment and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lloyd (1999) The Art, Science and Technology of Pharmaceutical Compounding).

[0084] As used herein, “TID” and “tid” are used interchangeably to refer to three times a day.

[0085] As used herein, the term “treat,” “treating,” or “treatment,” when used in connection with a disorder or condition, includes any effect, e.g., lessening, reducing, modulating, ameliorating, or eliminating, that results in the improvement of the disorder or condition.

Improvements in or lessening the severity of any symptom of the disorder or condition can be readily assessed according to standard methods and techniques known in the art.

[0086] The present disclosure provides methods of treating chronic spontaneous urticaria (CSU) in a human patient in need thereof. In some embodiments, the methods comprise administering to the human patient in need thereof a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof. In some embodiments, the methods comprise administering to the human patient a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, wherein the human patient in need thereof has CSU refractory to H1 antihistamines (H1-AH) treatment. In at least one embodiment, rilzabrutinib is administered to the human patient.

[0087] In some embodiments, the human patient has moderate-to-severe CSU. In some embodiments, the human patient has moderate CSU. In some embodiments, the human patient has severe CSU. In some embodiments, the human patient has CSU refractory to H1 antihistamine (H1-AH) treatment.

[0088] In some embodiments, the human patient has Type I autoimmune CSU. In some embodiments, the human patient has Type IIb autoimmune CSU.

[0089] In some embodiments, the human patient has angioedema. In some embodiments, the human patient does not have angioedema.

[0090] In some embodiments, the human patient achieves a Urticaria Activity Score (UAS7) that is lower than baseline UAS7. In some embodiments, the human patient achieves a UAS7 that is lower than baseline UAS7 within 52 weeks of initiating rilzabrutinib. In some embodiments, the human patient achieves a UAS7 that is lower than baseline UAS7 within 24 weeks of initiating rilzabrutinib. In some embodiments, the human patient achieves a UAS7 that is lower than baseline UAS7 within 12 weeks of initiating rilzabrutinib. In some embodiments, the human patient achieves a UAS7 that is lower than baseline UAS7 within 4 weeks of initiating rilzabrutinib. In some embodiments, the human patient achieves a UAS7

that is lower than baseline UAS7 within 3 weeks of initiating rilzabrutinib. In some embodiments, the human patient achieves a UAS7 that is lower than baseline UAS7 within 2 weeks of initiating rilzabrutinib. In some embodiments, the human patient achieves a UAS7 that is lower than baseline UAS7 within 1 week of initiating rilzabrutinib.

[0091] In some embodiments, the human patient achieves a UAS7 ≤ 6 . In some embodiments, the human patient achieves a UAS7 ≤ 6 within 12 weeks of initiating rilzabrutinib treatment.

[0092] In some embodiments, the human patient achieves a UAS7 of 0. In some embodiments, the human patient achieves a UAS7 of 0 within 12 weeks of initiating rilzabrutinib treatment.

[0093] In some embodiments, the human patient achieves a UAS7 that is at least 10 points lower than baseline UAS7. In some embodiments, the human patient achieves a UAS7 that is at least 12 points lower than baseline UAS7.

[0094] In some embodiments, the human patient achieves an Itch Severity Score (ISS7) that is lower than baseline ISS7. In some embodiments, the human patient achieves an ISS7 that is lower than baseline ISS7 within 52 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves an ISS7 that is lower than baseline ISS7 within 24 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves an ISS7 that is lower than baseline ISS7 within 12 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves an ISS7 that is lower than baseline ISS7 within 4 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves an ISS7 that is lower than baseline ISS7 within 3 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves an ISS7 that is lower than baseline ISS7 within 2 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves an ISS7 that is lower than baseline ISS7 within 1 week of initiating rilzabrutinib treatment.

[0095] In some embodiments, the human patient achieves an ISS7 that is at least 5 points lower than a baseline ISS7. In some embodiments, the human patient achieves an ISS7 that is at least 6 points lower than a baseline ISS7.

[0096] In some embodiments, the human patient achieves a Hives Severity Score (HSS7) that is lower than baseline HSS7. In some embodiments, the human patient achieves a HSS7 that is lower than baseline HSS7 within 52 weeks of initiating rilzabrutinib treatment.

In some embodiments, the human patient achieves a HSS7 that is lower than baseline HSS7 within 24 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a HSS7 that is lower than baseline HSS7 within 12 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a HSS7 that is lower than baseline HSS7 within 4 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a HSS7 that is lower than baseline HSS7 within 3 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a HSS7 that is lower than baseline HSS7 within 2 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a HSS7 that is lower than baseline HSS7 within 1 week of initiating rilzabrutinib treatment.

[0097] In some embodiments, the human patient achieves an Angioedema Activity Score (AAS7) that is lower than baseline AAS7. In some embodiments, the human patient achieves an AAS7 that is lower than baseline AAS7 within 52 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves an AAS7 that is lower than baseline AAS7 within 24 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves an AAS7 that is lower than baseline AAS7 within 12 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves an AAS7 that is lower than baseline AAS7 within 4 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves an AAS7 that is lower than baseline AAS7 within 3 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves an AAS7 that is lower than baseline AAS7 within 2 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves an AAS7 that is lower than baseline AAS7 within 1 week of initiating rilzabrutinib treatment.

[0098] In some embodiments, the human patient achieves a Urticaria Control Test (UCT) score that is higher than baseline UCT score. In some embodiments, the human patient achieves a UCT score that is higher than baseline UCT score within 52 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a UCT score that is higher than baseline UCT score within 24 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a UCT score that is higher than baseline UCT score within 12 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a UCT score that is higher than baseline UCT score within 8 weeks of initiating rilzabrutinib treatment.

In some embodiments, the human patient achieves a UCT score that is higher than baseline UCT score within 4 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a UCT score that is higher than baseline UCT score within 3 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a UCT score that is higher than baseline UCT score within 2 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a UCT score that is higher than baseline UCT score within 1 week of initiating rilzabrutinib treatment.

[0099] In some embodiments, the human patient achieves a UCT score ≥ 12 . In some embodiments, the human patient achieves a UCT score ≥ 12 within 12 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a UCT score ≥ 12 within 8 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a UCT score ≥ 12 within 4 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a UCT score ≥ 12 within 3 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a UCT score ≥ 12 within 2 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a UCT score ≥ 12 within 1 week of initiating rilzabrutinib treatment.

[00100] In some embodiments, the human patient achieves a change from baseline in health-related quality-of-life (HRQoL). In some embodiments, the human patient achieves a change from baseline in HRQoL as measured by the Patient Global Impression of Severity (PGIS). In some embodiments, the human patient achieves a change from baseline in HRQoL as measured by the PGIS within 12 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a change from baseline in HRQoL as measured by the PGIS within 8 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a change from baseline in HRQoL as measured by the PGIS within 4 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a change from baseline in HRQoL as measured by the PGIS within 3 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a change from baseline in HRQoL as measured by the PGIS within 2 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a change from baseline in HRQoL as measured by the PGIS within 1 week of initiating rilzabrutinib treatment.

[00101] In some embodiments, the human patient achieves a change from baseline in HRQoL as measured by the PGIC. In some embodiments, the human patient achieves a

change from baseline in HRQoL as measured by the PGIC within 12 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a change from baseline in HRQoL as measured by the PGIC within 8 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a change from baseline in HRQoL as measured by the PGIC within 4 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a change from baseline in HRQoL as measured by the PGIC within 3 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a change from baseline in HRQoL as measured by the PGIC within 2 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a change from baseline in HRQoL as measured by the PGIC within 1 week of initiating rilzabrutinib treatment.

[00102] In some embodiments, the human patient requires rescue therapy. In some embodiments, when the human patient requires rescue therapy, the total number of days for which the human patient requires rescue therapy is lower than the total number of days for which the human patient required rescue therapy during a baseline time period of the same length. In some embodiments, when the human patient requires rescue therapy, the human patient receives rescue therapy with an H1-AH.

[00103] In some embodiments, the human patient has a history of taking one or more anti-IgE therapy prior to the start of the treatment period, optionally wherein the one or more anti-IgE therapy is omalizumab. In some embodiments, the human patient has a history of taking omalizumab prior to the start of the treatment period.

[00104] In some embodiments, the human patient has had an incomplete response to omalizumab. In some embodiments, the human patient is omalizumab naïve.

[00105] In some embodiments, the human patient has a positive basophil histamine release assay (BHRA) status. In some embodiments, the human patient has a negative BHRA status.

[00106] In some embodiments, the human patient receives concomitant treatment with an H1-AH.

[00107] In some embodiments, the human patient has previously been identified as having increased sMRGPRX2 serum levels. In some embodiments, the human patient has previously been identified as having increased mast cell MRGPRX2 expression. In some embodiments, the human patient achieves a reduction from baseline in sMRGPRX2 serum

levels. In some embodiments, the human patient achieves a reduction from baseline in sMRGPRX2 serum levels within 12 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in sMRGPRX2 serum levels within 10 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in sMRGPRX2 serum levels within 8 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in sMRGPRX2 serum levels within 6 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in sMRGPRX2 serum levels within 4 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in sMRGPRX2 serum levels within 2 weeks of initiating rilzabrutinib treatment.

[00108] In some embodiments, the human patient has previously been identified as having increased IL-31 serum levels. In some embodiments, the human patient has previously been identified as having increased IL-31 serum levels as a result of increased mast cell or basophil activation. In some embodiments, the human patient achieves a reduction from baseline in IL-31 serum levels. In some embodiments, the human patient achieves a reduction from baseline in IL-31 serum levels within 12 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in IL-31 serum levels within 10 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in IL-31 serum levels within 8 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in IL-31 serum levels within 6 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in IL-31 serum levels within 4 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in IL-31 serum levels within 2 weeks of initiating rilzabrutinib treatment.

[00109] In some embodiments, the human patient has previously been identified as having increased IgG anti-TPO serum levels. In some embodiments, the human patient achieves a reduction from baseline in IgG anti-TPO serum levels. In some embodiments, the human patient achieves a reduction from baseline in IgG anti-TPO serum levels within 12 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in IgG anti-TPO serum levels within 10 weeks of initiating

rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in IgG anti-TPO serum levels within 8 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in IgG anti-TPO serum levels within 6 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in IgG anti-TPO serum levels within 4 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in IgG anti-TPO serum levels within 2 weeks of initiating rilzabrutinib treatment.

[00110] In some embodiments, the human patient has previously been identified as having increased IgG anti-FCεRI serum levels. In some embodiments, the human patient has previously been identified as having increased mast cell or basophil activation as a result of increased IgG anti-FCεRI levels serum levels. In some embodiments, the human patient achieves a reduction from baseline in IgG anti-FCεRI serum levels. In some embodiments, the human patient achieves a reduction from baseline in IgG anti-FCεRI serum levels within 12 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in IgG anti-FCεRI serum levels within 10 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in IgG anti-FCεRI serum levels within 8 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in IgG anti-FCεRI serum levels within 6 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in IgG anti-FCεRI serum levels within 4 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in IgG anti-FCεRI serum levels within 2 weeks of initiating rilzabrutinib treatment.

[00111] In some embodiments, the human patient has previously been identified as having increased eosinophil levels. In some embodiments, the human patient has previously been identified as having increased mast cell activation as a result of increased eosinophil levels. In some embodiments, the human patient achieves a reduction from baseline in eosinophil levels. In some embodiments, the human patient achieves a reduction from baseline in eosinophil levels within 12 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in eosinophil levels within 10 weeks of initiating rilzabrutinib treatment. In some embodiments, the human

patient achieves a reduction from baseline in eosinophil levels within 8 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in eosinophil levels within 6 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in eosinophil levels within 4 weeks of initiating rilzabrutinib treatment. In some embodiments, the human patient achieves a reduction from baseline in eosinophil levels within 2 weeks of initiating rilzabrutinib treatment.

[00112] In some embodiments, the human patient does not achieve a reduction in total serum IgG or IgE levels.

[00113] In some embodiments, the treatment period is at least 12 weeks. In some embodiments, the treatment period is at least 52 weeks.

[00114] In some embodiments, the at least one compound consists of at least one compound chosen from the (E) isomer of rilzabrutinib and pharmaceutically acceptable salts thereof. In some embodiments, the at least one compound consists of at least one compound chosen from the (Z) isomer of rilzabrutinib and pharmaceutically acceptable salts thereof. In some embodiments, the at least one compound consists of a mixture of (E) and (Z) isomers of rilzabrutinib or a pharmaceutically acceptable salt of the foregoing.

[00115] In some embodiments, the method comprises administering to the human patient about 400 mg of at least one compound chosen from rilzabrutinib and pharmaceutically acceptable salts thereof once, twice, or thrice a day. In some embodiments, the method comprises administering to the human patient about 400 mg of at least one compound chosen from rilzabrutinib and pharmaceutically acceptable salts thereof once a day. In some embodiments, the method comprises administering to the human patient about 400 mg of at least one compound chosen from rilzabrutinib and pharmaceutically acceptable salts thereof twice a day. In some embodiments, the method comprises administering to the human patient about 400 mg of at least one compound chosen from rilzabrutinib and pharmaceutically acceptable salts thereof thrice a day.

[00116] In some embodiments, the method comprises administering to the human patient rilzabrutinib once, twice, or thrice a day. In some embodiments, the method comprises administering to the human patient rilzabrutinib once a day. In some embodiments, the method comprises administering to the human patient rilzabrutinib twice a day. In some

embodiments, the method comprises administering to the human patient rilzabrutinib thrice a day.

[00117] In some embodiments, the method comprises administering to the human patient 400 mg of rilzabrutinib once, twice, or thrice a day. In some embodiments, the method comprises administering to the human patient 400 mg of rilzabrutinib once a day. In some embodiments, the method comprises administering to the human patient 400 mg of rilzabrutinib twice a day. In some embodiments, the method comprises administering to the human patient 400 mg of rilzabrutinib thrice a day.

[00118] In some embodiments, the at least one compound is the (E) isomer of rilzabrutinib. In some embodiments, the at least one compound is the (Z) isomer of rilzabrutinib. In some embodiments, the at least one compound consists of a mixture of (E) and (Z) isomers of rilzabrutinib.

[00119] In some embodiments, the at least one compound is orally administered to the human patient. In some embodiments, the at least one compound is administered to the human patient in the form of at least one tablet. In some embodiments, the at least one compound is administered with water.

[00120] In some embodiments, the at least one compound is rilzabrutinib.

[00121] In some embodiments, the present disclosure provides a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for use in treating chronic spontaneous urticaria (CSU) in a human patient in need thereof.

[00122] In some embodiments, the present disclosure provides a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for use in the manufacture of a medicament for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof.

[00123] In some embodiments, the present disclosure provides for the use of a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-

4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof.

[00124] In some embodiments, the present disclosure provides for the use of a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for the manufacture of a medicament for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof.

[00125] In some embodiments, the present disclosure provides for a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for use in treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, wherein the human patient in need thereof has CSU refractory to H1 antihistamines (H1-AH) treatment.

[00126] In some embodiments, the present disclosure provides for a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for use in the manufacture of a medicament for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, wherein the human patient in need thereof has CSU refractory to H1 antihistamines (H1-AH) treatment.

[00127] In some embodiments, the present disclosure provides for the use of a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, wherein the human patient in need thereof has CSU refractory to H1 antihistamines (H1-AH) treatment.

[00128] In some embodiments, the present disclosure provides for the use of a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-

(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, wherein the human patient in need thereof has CSU refractory to H1 antihistamines (H1-AH) treatment.

Pharmaceutical Compositions:

[00129] In some embodiments of the present disclosure, rilzabrutinib is administered as part of a pharmaceutical composition comprising: at least one compound chosen from rilzabrutinib and pharmaceutically acceptable salts thereof; and at least one pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is in the form of at least one tablet.

[00130] In some embodiments, rilzabrutinib is administered in the form of a film-coated tablet.

[00131] In some embodiments of the present disclosure, rilzabrutinib is administered in the form of at least one tablet comprising: at least one compound chosen from rilzabrutinib and pharmaceutically acceptable salts thereof; and at least one pharmaceutically acceptable excipient. In some embodiments, rilzabrutinib is administered in the form of at least one tablet comprising: at least one compound chosen from rilzabrutinib and pharmaceutically acceptable salts thereof; at least one filler; at least one disintegrant; at least one lubricant; and at least one film coating.

[00132] In some embodiments, rilzabrutinib is administered with a glass of water.

[00133] The proportion and nature of any pharmaceutically acceptable excipient may be determined by the chosen route of administration and standard pharmaceutical practice. Except insofar as any conventional pharmaceutically acceptable excipient is incompatible with rilzabrutinib, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically composition, its use is contemplated to be within the scope of this disclosure.

[00134] Some non-limiting examples of materials which may serve as pharmaceutically acceptable excipients include: (1) sugars, such as, e.g., lactose, glucose, and sucrose; (2) starches, such as, e.g., corn starch and potato starch; (3) cellulose and its derivatives, such as, e.g., sodium carboxymethyl cellulose, ethyl cellulose, and cellulose

acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as, e.g., cocoa butter and suppository waxes; (9) oils, such as, e.g., peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; (10) glycols, such as, e.g., propylene glycol; (11) polyols, such as, e.g., glycerin, sorbitol, mannitol, and polyethylene glycol; (12) esters, such as, e.g., ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as, e.g., magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

[00135] Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D.B. Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York also discloses additional non-limiting examples of pharmaceutically acceptable excipients, as well as known techniques for preparing and using the same.

[00136] One skilled in the art can readily select the proper form and route of administration depending upon the disorder or condition to be treated, the stage of the disorder or condition, and other relevant circumstances.

EXAMPLES

[00137] The following example is intended to be illustrative and is not meant in any way to limit the scope of the disclosure.

Abbreviations:

AAS7	Angioedema activity score over 7 days
AE	Adverse event
AESI	Adverse event of special interest
API	Active pharmaceutical ingredient
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase

BHRA	Basophil histamine release assay
bid/BID	Twice daily (morning and evening)
BM	Biomarker
BMI	Body mass index
BTK	Bruton's Tyrosine Kinase
CD	Cluster of differentiation
CIU	Chronic idiopathic urticaria
CMH	Cochran-Mantel Haenzel test
CPK	Creatine phosphokinase
D	Day
DB	Double-blind
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
e-diary	Electronic diary
ED	Early discontinuation
EOT	End of treatment
EOS	End of study
FU	Follow-up
HbA1c	Glycated hemoglobin
H1-AH	H1 antihistamine
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HSS	Hives severity score
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IMP	Investigational medicinal product
INR	International normalized ratio

ISS	Itch severity score
ITP	Immune thrombocytopenia
LDH	Lactate dehydrogenase
LS	Least squares
MCID	Minimal clinically important difference
MI	Multiple imputation
MRGPRX2	Mas-related G-protein coupled receptor member X2
N	Number
OCS	Oral corticosteroids
OLE	Open-label extension phase
OR	Odds ratio
PBMC	Peripheral blood mononuclear cells
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PK	Pharmacokinetic
PRO	Patient-reported outcome
qd/QD	Once a day
QOL	Quality of Life
QPM	Once each evening
R	Randomization
RRD	Response rate difference
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
TB	Tuberculosis
TID	Three times daily/thrice daily
TPO	Thyroperoxidase
UAS7	Urticaria activity score over 7 days
UCT	Urticaria control test

ULN	Upper limit of normal
V	Visit
W	Week
WOCBP	Woman of childbearing potential
WOCF	Worst observation carried forward

Example 1: A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Dose-Ranging Phase 2 Study of Rilzabrutinib Followed by an Open-Label Extension Phase in Patients with Moderate-to-Severe Chronic Spontaneous Urticaria (CSU) Who Remain Symptomatic Despite the Use of H1 Antihistamine Treatments

Study Design

[00138] This study is a 52-week sequential Phase 2 study on the effects of rilzabrutinib in adult participants with moderate-to-severe CSU who remain symptomatic despite the use of H1 antihistamine (H1-AH) treatment. The study comprises a 12 week, randomized, double-blind, placebo-controlled, multi-center, dose-ranging efficacy and safety phase, followed by a 40 week open label extension (OLE) phase (see **Figure 1**).

[00139] Patients exhibited at least moderate disease activity (see inclusion criteria) despite the use of H1-AH. It was expected that ~40% of patients would have concomitant angioedema. Participants were to be randomized 1:1:1:1 to one of three doses of rilzabrutinib or placebo. The randomization was to be stratified by region and prior use of omalizumab.

[00140] The study is to evaluate the effect of rilzabrutinib on itch and hives, scored individually or as a composite score; on angioedema activity; on participant-reported urticaria control; and on HRQoL.

[00141] The study consists of three phases and an optional OLE phase. The phases are as follows:

- Screening period (up to 4 weeks)
- Double-blind IMP treatment period (12 weeks): participants were randomized 1:1:1:1 to one of the following treatments: rilzabrutinib 400 mg TID; rilzabrutinib 400 mg BID with matched placebo; rilzabrutinib 400 mg QPM with matched placebo; or matched placebo
- Optional OLE phase (40 weeks): for participants who completed the 12-week double-blind phase, eligible participants were given the option to continue to an OLE phase of the study. Participants in the OLE will be given rilzabrutinib 400 mg TID (the dose may be modified based on the 12-week safety and efficacy data) (all non-Germany countries). In Germany, participants in the OLE will be administered rilzabrutinib 400 mg BID.
- Follow-up period (4 weeks)

[00142] During the double-blind IMP treatment phase of this study, participants were to continue their established standard of care background therapy with an approved long-acting H1-AH, at up to 4-fold the recommended dose. If a participant was on an H1-AH dose higher than 4-fold the recommended dose at the screening visit, the Investigator may have adjusted the participant's dose to within the stipulated dose range at the screening visit. For participants on stable doses of nonstudy-approved H1-AH, Investigators may have switched participants to an equivalent dose of a study-approved H1-AH maintenance medication at the screening visit. Participants should have continued their screening dose of H1-AH throughout the double-blind phase of the study, unless they experienced a disease flare. Participants should also continue their baseline dose of H1-AH for the first 12 weeks of the OLE phase of the study. After 12 weeks in the OLE phase, Investigators may, at their discretion, reduce participants' H1-AH dose, but the antihistamine daily dose still may not exceed 4-fold the recommended dose (all non-Japan countries) or 2-fold the recommended dose (Japan only).

[00143] In the case that participants are considered for rescue therapy, participants on 1-, 2- or 3-fold the recommended H1-AH may receive additional doses of their study-approved H1-AH as rescue medication, as long as their daily dose does not exceed 4-fold the recommended daily dose of the H1-AH (all non-Japan countries) or 2-fold the recommended daily dose of the H1-AH (Japan only). At the investigator's discretion, participants may be prescribed a short course of oral corticosteroids (OCS) as rescue therapy during the treatment, OLE and follow up periods. Rescue therapy should start with an increase in H1-AH whenever possible, followed by a short course of OCS if needed. For analysis of urticaria activity (including itch and hives individually), angioedema activity, participant-reported urticaria control and HRQoL, data collected after OCS use will be set to missing and the worse post-baseline values before OCS therapy will be used.

[00144] The end of the study in the 12 week double-blind phase of the study is defined as the date of the last follow-up visit of the last participant in the double-blind phase of study. Participants were considered to have completed the 12 week double-blind phase of the study if they had completed the 12 week phase of the study, including the last follow-up visit.

[00145] The end of the study in the 40 week open-label phase of the study is defined as the date of the last follow-up visit of the last participant in the open-label phase of the study. Participants will be considered to have completed the 40 week open-label phase of the

study once they have completed the 40-week phase of the study including the last follow-up visit.

[00146] The assessments used in this study are standard endpoints in evaluation of disease activity and response to therapy in CSU. Clinically, CSU is characterized by the spontaneous and recurrent appearance of pruritic hives. The proposed primary endpoints were the UAS7 at Week 12 in EU and EU reference countries and the ISS7 in the US. Regardless of where a participant was from, all assessments were the same. The UAS7 score is a composite score containing both the HSS7 and the ISS7. This allowed a global assessment of the two key components of urticaria: hives and itch. The UAS7 score has been well-established as a prospective measure of CSU activity and has been used in a number of clinical studies as a primary outcome measure (Agache et al. 2021; Hawro et al. 2018; Maurer et al. 2019). As an independent score, ISS7 has also been well established and widely accepted as a primary outcome measure for CSU activity (Maurer et al. 2013).

[00147] Angioedema is present in up to 40.3% of patients with CSU and can have a significant negative impact on quality of life (Sussman et al. 2018). This study aimed to assess the effect of rilzabrutinib on angioedema activity. The weekly angioedema activity score (AAS7) was proposed as a tertiary endpoint. The AAS7 score is a validated tool determine angioedema activity and has previously been used in CSU clinical studies (Maurer et al. 2019; Weller et al. 2013).

[00148] This study also aimed to assess disease control from the perspective of participants. To this end, the UCT was proposed as a tertiary endpoint in this study. The UCT is a validated tool which has become the standard Patient-Reported Outcome (PRO) tool to determine disease control in CSU and other forms of chronic urticaria (Weller et al. 2014; Zuberbier et al. 2018). In addition to disease activity scores, this study aimed to assess the impact of rilzabrutinib on HRQoL in CSU. The dermatology life quality index (DLQI) was proposed as a tertiary endpoint in this study. The DLQI is a standard well-studied HRQoL score which has been validated for use in chronic urticaria (Lennox et al. 2004).

[00149] Blood samples were also collected through Week 12 to evaluate the change in baseline in various biomarkers, including sMRGPRX2, IgG anti-TPO, IgG anti-FCεRI, IgG anti-IgE, and IL-31.

[00150] In sum, the proposed primary, secondary and tertiary endpoints were intended to allow a determination of the efficacy of rilzabrutinib on disease activity, disease

symptoms, and HRQoL in participants with CSU.

[00151] Table 1. Objectives and Endpoints.

Objectives	Endpoints
Primary	
To demonstrate the efficacy of rilzabrutinib in study participants with CSU who remain symptomatic despite the use of H1-AH	• Change from baseline in weekly UAS7 at Week 12 (except US and US reference countries) • For US and US reference countries only: change from baseline in weekly ISS7 at Week 12
Secondary	
To demonstrate the efficacy of rilzabrutinib on urticaria activity composite endpoint and itch or hives, separately, at various time points	• Change from baseline in UAS7 at Week 4 • Change from baseline in ISS7 at Week 12 (except US and US reference countries) • For US and US reference countries only: change from baseline in UAS7 at Week 12 • Change from baseline in weekly HSS7 at Week 12 • Proportion of participants with UAS7 ≤ 6 at Week 12 • Proportion of participants with UAS7 = 0 at Week 12
To evaluate safety outcome measures	Incidence of TEAEs, SAEs, AESIs, and withdrawals due to TEAEs during the DB period and OLE
To assess the plasma PK of rilzabrutinib in participants with CSU	Plasma PK concentrations of rilzabrutinib in participants with CSU
Tertiary	
To demonstrate the efficacy of rilzabrutinib on urticaria activity composite endpoint and itch or hives, separately, at various time points	• Change from baseline in UAS7 at all time points (onset of action is assessed by the first $p < 0.05$ that remains significant at subsequent measures until Week 12) • Time to UAS7 minimal clinically important difference (MCID) in response (improvement from baseline =10) • Proportion of participants with UAS7 ≤ 6 at all time points • Change from baseline in ISS7 at all time points (onset of action is assessed by the first $p < 0.05$ that remains significant at subsequent measures until Week 12) • Time to ISS7 minimal clinically important difference (MCID) in response (improvement from baseline ≥ 5)

Objectives	Endpoints
	• Change from baseline in HSS7 at all time points (onset of action is assessed by the first $p < 0.05$ that remains significant at subsequent measures until Week 12) • Change from baseline in UAS7 at Week 24 and Week 52 • Change from baseline in ISS7 at Week 24 and Week 52 • Change from baseline in HSS7 at Week 24 and Week 52
To demonstrate the efficacy of rilzabrutinib on angioedema	• Change from baseline in AAS7 at all time points (onset of action is assessed by the first $p < 0.05$ that remains significant at subsequent measures until Week 12) • Change from baseline in AAS7 at Week 24 and Week 52
To demonstrate the efficacy of rilzabrutinib on urticaria control	• Change from baseline in UCT at Week 4, at Week 8 and at Week 12 • Proportion of well-controlled participants ($UCT \geq 12$) at Week 4, at Week 8 and at Week 12 • Change from baseline in UCT at Week 24 and Week 52
To demonstrate improvement in health-related quality-of-life and overall disease status and severity	• Change from baseline in HRQoL as measured by Dermatology Life Quality Index (DLQI) at Week 4, at Week 8 and Week 12; by Patient Global Impression of Severity (PGIS) at Week 2, Week 4, Week 8, and Week 12; by Patient Global Impression of Change (PGIC) at Week 2, Week 4, Week 8, and Week 12 • Change from baseline in DLQI at Week 24 and week 52
To evaluate the ability of rilzabrutinib in reducing the need for oral corticosteroids	• Time-to-event of participants receiving rescue therapy with OCS for CSU during the double-blind phase • Proportion of participants receiving rescue therapy with OCS for CSU during the double-blind phase • Total number of days each participant requires rescue therapy with OCS for CSU during the double-blind phase

Study Population

[00152] Inclusion criteria are summarized in **Table 2**. Participants were eligible to be included in the study only if they met all of the inclusion criteria.

[00153] **Table 2. Inclusion Criteria.**

Age	Participants must have been 18-80 years of age (inclusive) at the time of signing the informed consent
Disease characteristics	Participants must have had a diagnosis of CSU refractory to H1-AH at the time of randomization, as defined by all of the following: • Diagnosis of CSU ≥ 3 months prior to screening visit (Visit 1) • The presence of itch and hives for ≥ 6 consecutive weeks at any time prior to screening visit (Visit 1) despite the use of H1-AH during this time period. • Participants must have been using a study defined H1-AH for CSU treatment. For participants on stable doses of non-study-approved H1-AH, investigators may switch participants to an equivalent dose of a study-approved H1-AH maintenance medication. Note: participants should have remained on their prescreening non-sedating H1-AH dose. Only up to 4-fold the recommended dose was allowed. If participants were on dose higher than 4-fold the recommended dose at screening, the Investigator could have adjusted the participant dose to the stipulated range at the screening visit (Visit 1). Participants were to remain on this dose of antihistamine for at least 3 consecutive days before screening assessment of UAS7 and ISS7 is initiated. • Participants who were omalizumab-naïve OR with prior omalizumab use, including omalizumab-incomplete responders (as determined by the Site Investigator and defined as inadequate control of CSU symptoms despite treatment with omalizumab 300 mg every 4 weeks for at least 3 months (minimum 3 injections). Note: Documentation of incomplete response must have been documented in the patient's medical records). • During the 7 days before randomization, patients must have had a UAS7 ≥ 16, ISS7 ≥ 8, with no missing e-diary UAS7 or ISS7 records
Sex, contraceptive/barrier method and pregnancy testing requirements	• Male participants must have agreed to the following during the study intervention period and for at least 13 weeks after the last administration of study intervention: -refrain from donating or cryopreserving sperm -abstain from heterosexual or homosexual intercourse as their preferred and usual lifestyle (<i>i.e.</i>, must have been abstinent on a long term and persistent basis) and agree to remain abstinent; or use contraception and a barrier (<i>i.e.</i>, a male condom and an additional highly effective contraceptive method when having sexual intercourse with a WOCBP who is not currently pregnant;

	or a male condom when engaging in any activity that allows for passage of ejaculate to another person) • Female participants must not have been pregnant or breastfeeding and must have met the following criteria: -be a WONCBP; or agree to use a highly-effective contraceptive method (<i>i.e.</i>, a contraceptive method with a failure rate of <1% per year), preferably with low user dependency, during the study intervention period. The contraceptive method must be effective before starting the intervention and for at least 4 weeks after the last administration of study intervention. The participant must agree not to donate or cryopreserve eggs (ova/oocytes) for the purpose of reproduction during this period). Eligible WOCBP participants must have a negative highly sensitive pregnancy test (serum as required by local regulations) within 28 days before the first administration of study intervention. If a urine test cannot be confirmed as negative (<i>e.g.</i>, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
Informed consent	Participants must have been capable of giving signed informed consent.
Additional criteria	Participants must have been willing and able to complete a daily symptom e-diary for the duration of the study

[00154] Exclusion criteria are summarized in **Table 3**. Participants were excluded from the study if any of the criteria applied.

[00155] **Table 3. Exclusion Criteria.**

Medical Conditions	Participants must not have had any of the following medical conditions: • Clearly defined underlying etiology for CUs other than CSU (main manifestation being physical urticaria). • Presence of skin morbidities other than CSU that may interfere with the assessment of the study outcomes • Active atopic dermatitis (AD) • Severe concomitant illness(es) that, in the Investigator's judgment, would adversely affect the patient's participation in the study. • Known or suspected immunodeficiency, or otherwise recurrent infections of abnormal frequency or prolonged duration suggesting an immune compromised status, as judged by the Investigator. • History of serious infections requiring intravenous (IV) therapy with the potential for recurrence, or currently active moderate to
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	severe infection at Screening (Grade 2 or higher), including active coronavirus disease 2019 (COVID-19) • Live vaccine except Bacille Calmette Guerin-vaccination within 28 days prior to Day 1 or plan to receive one during the trial; Bacille Calmette Guerin-vaccination within 12 months prior to Screening. • Active malignancy or history of malignancy within 5 years before Day 1, • Conditions that may predispose the participant to excessive bleeding • An uncontrolled disease state as judged by the Investigator, such as asthma, psoriasis, or an inflammatory bowel disease, etc. that is typically treated with oral and/or parenteral corticosteroids
Prior/concurrent clinical study experience	• Previous use of a BTK inhibitor • Use of any investigational drug (or current use of an investigational device) within the 30 days before Day 1, or at least 5 times the respective elimination half-life time (whichever is longer) • Previous exposure to another investigative drug for CSU
Diagnostic Assessments	• Positive HIV antibody test • Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) with positive DNA test result at screening or within 3 months prior to the screening visit (all non-Japan countries) • Presence of hepatitis B surface antigen (HBsAg) with/without positive HBV DNA test result or presence of hepatitis B core antibody (HBcAb) or presence of hepatitis B surface antibody (HBsAb) with positive HBV DNA test result at screening or within 3 months prior to the screening visit (Japan only) • Positive hepatitis C antibody test result at screening or within 3 months prior to the screening visit. • Exclusions related to tuberculosis infection (TBI) • Any laboratory abnormalities at the screening visit

Screen Failures

[00156] Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

[00157] If a participant failed to complete 2 or fewer days of their UAS7 evaluation at screening, or if their e-diary device failed, that participant may have been rescreened once.

However, if a participant did not meet the minimum UAS7 or ISS7 score in screening, that participant was not eligible for rescreening.

[00158] In cases where original screen failure was due to reasons expected to change at re-screening and based upon the Investigator's clinical judgment, the participant may have been rescreened one time for this study after notification of the Sponsor. Rescreened participants were to be assigned a new participant number for the re-screening event. There was no requirement for a waiting period between the screen-failure and the re-screening. A new consent form must have been signed and Visit 1 procedures must have been repeated for re-screened participants.

Study Intervention(s) Administered

[00159] Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. **Tables 4 and 5** provide an overview of interventions administered in the present study.

[00160] Consecutive doses were to be administered approximately 6 hours apart (and not less than 4 hours apart).

[00161] Table 4. Overview of Study Interventions Administered

Intervention label	Rilzabrutinib	Placebo
Intervention name	Rilzabrutinib	Placebo
Type	Drug	Drug
Dose formulation	Tablets tablets/caplets)	Placebo to match rilzabrutinib tablets (/caplets)
Unit dose strength(s)	400 mg	0 mg
Dosage level(s)	400 mg (1 tablet) BID, QPM, or TID	1 tablet BID, QPM, or TID
Route of administration	Oral	Oral
Use	Experimental	Experimental
IMP or NIMP	IMP	IMP
Packaging and labeling	During the double-blind phase, IMP was to be provided in wallets of 1 blister pack, and each wallet was to be labeled as required per country requirement; during the open-label phase, IMP was to be supplied in white plastic bottles, and each bottle was to be labeled as required per country requirement	During the double-blind phase, IMP was to be provided in wallets of 1 blister pack, and each wallet was to be labeled as required per country requirements
Current/Former name(s) or aliases	Rilzabrutinib	Placebo

[00162] Table 5. Arms and Associated Interventions

Arm name	Placebo	400 mg QPM	400 mg BID	400 mg TID
Associated interventions (intervention label(s))	Rilzabrutinib or placebo	Rilzabrutinib or placebo	Rilzabrutinib or placebo	Rilzabrutinib or placebo

Noninvestigational Medicinal Products

[00163] Participants were to continue their established standard of care background therapy with a long-acting, non-sedating H1-AH during the study. For participants on stable doses of non-study-approved H1-AH, investigators may have switched participants to an equivalent dose of a study-approved H1-AH maintenance medication. Only up to 4-fold (all non-Japan countries) or 2-fold (Japan only) the recommended dose was allowed. If participants were

on dose higher than 4-fold the recommended dose at screening, the Investigator could have adjusted the participant dose to the stipulated range at the screening visit (Visit 1). Participants must have remained on this dose of antihistamine for at least 3 consecutive days before screening assessment of UAS7 and ISS7 is initiated. Participants were to continue to take the same daily dose throughout the study unless they experience a flare for which rescue therapy may have been initiated. During the OLE phase, participants are to also continue their baseline dose of H1-AH for the first 12 weeks of the OLE phase. After 12 weeks in the OLE phase, Investigators may, at their discretion, decide to reduce or discontinue participants' maintenance antihistamines dose, but the antihistamine daily dose still may not exceed 4-fold the recommended dose; the dose of rilzabrutinib will remain the same.

[00164] Because rilzabrutinib is a mild inhibitor of CYP3A, only the following study-approved antihistamines and recommended were allowed as background therapy to minimize the possibility of rilzabrutinib altering their pharmacokinetics: cetirizine (10 mg QD); levocetirizine dihydrochloride (5 mg QD); fexofenadine (60 mg BID or 180 mg QD); desloratadine (5 mg QD); and bilastine (20 mg QD).

Dose Modification

[00165] Rilzabrutinib dose modification was not allowed during the double-blind phase. For the OLE phase, the dose may be modified based on the 12 week safety and efficacy data.

Concomitant Therapy

[00166] Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant was receiving at the time of enrollment or received during the study must have been recorded along with the reason for use, the dates of administration (including the start and end dates), and dosage information (including dose and frequency). The sponsor should have been contacted if there were any questions regarding concomitant or prior therapy.

[00167] Participants were to abstain from taking nonprescription drugs (including vitamins and dietary or herbal supplements) within 2 weeks or 5 half-lives (whichever was longer) before the start of study intervention until completion of the follow-up visit, unless, in

the opinion of the Investigator, the medication would not interfere with the study. New or chronic prescription medications could have been used if needed at the discretion of the Investigator. The Medical Monitor was to be contacted if there were any questions regarding new or chronic medications.

[00168] Clinically relevant drugs that are substrates of CYP3A, including those considered to be sensitive CYP3A substrates were permitted. Appropriate caution was to be used when co-administering sensitive CYP3A substrates with rilzabrutinib and a benefit-risk assessment was to be conducted for each medication. Consideration was also to have been given to avoidance of high doses, dose reduction, or replacement of sensitive and narrow therapeutic index CYP3A substrate drug. Systemic strong and moderate inhibitors (including foods such as grapefruit juice) and inducers of CYP3A were to be avoided.

[00169] Medications that have not been listed as exclusion criteria were permitted for use during the trial. These include the following:

- Oral corticosteroid rinses (mouth washes) are allowed.
- H2 antihistamine (H2-AH) receptor blocking drugs were permitted provided they were taken once daily only and were taken 2-3 hours after administration of the evening rilzabrutinib or placebo dose.
- Antacids were permitted provided they were given 2 hours or more apart from rilzabrutinib or placebo dose.
- COVID-19 vaccines

[00170] Participants were to continue their established standard of care background therapy with a long acting, non-sedating H1-AH (defined as noninvestigational medicinal product (NIMP)). During the OLE phase, participants should also continue their baseline dose of H1-AH for the first 12 weeks of the OLE phase. After 12 weeks in the OLE phase, Investigators may, at their discretion, decide to reduce or discontinue participants' maintenance antihistamines dose; the dose of rilzabrutinib will remain the same. In addition, participants should continue to take only allowed concomitant therapy, as defined for the first phase of the study (*i.e.*, 12-week double-blind period).

[00171] A list of prohibited concomitant therapies is provided in **Table 6**.

[00172] Table 6. Prohibited Concomitant Therapy

Drug Category	Drug Name
Immunosuppressants	Mycophenolate mofetil
	Azathioprine
	Methotrexate
	Cyclosporine
	Dapsone
	Anakinra (Kineret)
	Etanercept (Enbrel)
	Topical corticosteroids, topical calcineurin inhibitors, and topical antihistamines (non-Italy countries only)
	Systemic corticosteroids (except for OCS used as rescue)
	Immunosuppressant drugs
Biologics or targeted-synthetic disease modifiers	Omalizumab (non-Italy countries only)
	Infliximab
	Adalimumab
	Golimumab
	Abatacept
	Tocilizumab
	Sarilumab
	Certolizumab
	Secukinumab
	IFN- γ
	JAK inhibitors
	Dupilumab
	Other biologic or targeted-synthetic disease modifiers
Anti-CD20 drugs	Rituximab
	Ofatumumab
	Other long-acting biologics
Antifibrinolytic	Tranexamic acid
	Epsilon-aminocaproic acid
Leukotriene receptor antagonists and 5-lipoxygenase inhibitors (Note: OK to continue if used for an indication other than CSU)	Montelukast
	Zafirlukast
	Zileuton (non-Italy countries only)
H2 receptor antagonists (Note: OK to continue if used for an indication other than CSU)	Cimetidine
	Ranitidine
	Famotidine
	Nizatidine
	Roxatidine
	Lafutidine
	Other H2 Receptor antagonists
Proton pump inhibitors	Omeprazole

	Esomeprazole
	Lansoprazole
	Pantoprazole
	Other proton pump inhibitors
Immunomodulator therapy	Intravenous immunoglobulin (IVIG); subcutaneous immunoglobulin (SCIG) (non-Italy countries only)
	Plasmapheresis
Antidepressant	Doxepin
Systemic strong-to-moderate inhibitors and inducers of cytochrome P450 CYP3A	Strong CYP3A inducers: apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort
	Moderate CYP3A inducers: Bosentan, efavirenz, etravirine, phenobarbital, primidone
	Strong CYP3A inhibitors: boceprevir, clarithromycin, cobicistat, danoprevir/ritonavir, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, paritaprevir/ritonavir and ombitasvir and/or dasabuvir, posaconazole, ritonavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole
	Moderate CYP3A inhibitors: aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil

This table provides a list of the most common medications within the classes of prohibited concomitant drugs but is not exhaustive.

Rescue Medicine

[00173] As rescue medication, up to 4-fold of the approved dose of the participants usual H1-AH could have been given on days where pruritus and wheal development were severe. The total daily H1-AH dose was not to exceed 4-fold the recommended dose during the screening, treatment and follow-up period.

[00174] The initial maintenance antihistamine dose should have remained stable throughout the 12-week double-blind phase and the first 12 weeks of the OLE phase, and participants were to continue their maintenance dose once rescue treatment is no longer required. After 12 weeks in the OLE phase, Investigators may, at their discretion, decide to reduce or discontinue participants' maintenance antihistamines dose, but the antihistamine daily dose still may not exceed 4-fold the recommended dose.

[00175] If needed, or if unable to increase H1-AH as an initial step for rescue therapy, participants may have been prescribed a short course of OCS. After any use of OCS, participants would have needed to seek immediate medical attention to ensure that the initial reaction had been successfully controlled and/or to evaluate for additional therapeutic steps. In order to ensure consistency, when possible, it was recommended to use OCS for 5 to 7 days with a starting dose of oral prednisone 40 mg (or clinically comparable OCS) followed by taper per the Investigator's judgment. The use of OCS was to be delayed, if possible, for at least 8 weeks following the initiation of the investigational treatment. The date and time of OCS administration as well as the name and dosage regimen of the OCS was to be recorded.

[00176] Unless permanently discontinued from the study, all participants were to complete the scheduled study visits and assessments whether or not they completed study treatment and whether or not they received rescue treatment for CSU. Investigators were to make every attempt to conduct efficacy and safety assessments immediately before administering any rescue treatment. An unscheduled visit may have been used for this purpose, if necessary. Participants who received rescue therapy with OCS during the study treatment were considered "treatment failures" for the analysis of all efficacy endpoints.

Efficacy Assessments

[00177] Efficacy data was to be collected via electronic devices. The e-diary was to be used for daily recording of PRO such as the UAS7 and AAS7 questionnaires, and use of H1-AH medication. This device was to be dispensed at Screening (Visit 1), including instructions for use. Additionally, participants were to be instructed on the use of the device.

[00178] Participants were to fill in UCT, DLQI, PGIC, and PGIS questionnaires during their site visit.

Urticaria Activity Score

[00179] The UAS is a validated PRO measure. The daily UAS is the sum of the daily Hive Severity Score (HSS, ranging from 0 = None to 3 = more than 50 hives) and the daily Itch Severity Score (ISS, ranging from 0 = None to 3 = intense), the 2 key urticaria signs and symptoms which are wheals and itch. The daily UAS scores range from 0 to 6 point/day. Daily

UAS scores are summed over 7-day period to create the UAS7, ranging from 0 to 42, and are composed of the HSS7 and ISS7 components. The UAS7 is an established and widely accepted PRO tool to prospectively measure CSU activity (Mlynek et al. 2008). It has been used in most clinical trials in CSU in recent years as a main outcome parameter and medical practice (Maurer et al. 2013; Metz et al. 2020). A minimal important difference (MID) value ranging from 9.5 to 10.5 has been defined to help interpretation of the change in score in CSU participants (Hawro et al. 2018; Hollis et al. 2018; Mathias et al. 2012). Patients were to complete the UAS using the e-diary. The e-diary was to be used once daily on the same time of each day recording of participant's answers to the urticaria activity score over 7 days (UAS7) questionnaire. For participants who entered the OLE phase, their answers to the UAS7 questionnaire were also to be collected from Week 20 to Week24 and from Week 48 to Week 52.

Angioedema Activity Score

[00180] The AAS is a validated PRO measure that assesses angioedema activity (Weller et al. 2013). The AAS is a diary in which participants document on a daily basis the presence or absence of angioedema during the past 24 hours. If angioedema is present, participants answer 5 additional questions about the time of the day the swelling episode occurred, and the severity and impact on daily functioning and appearance this swelling episode has had. Each AAS item is scored between 0 and 3 points, that is, the minimum and maximum daily AASs are 0 and 15 points. The daily AASs are summed up to 7-day scores (AAS7), with 7-day scores ranging from 0 to 105 (Weller et al. 2013). A MID of the AAS7 of around 8 points has been established (Weller et al. 2013). Patients were to complete the AAS using the e-diary. The e-diary was to be used once daily on the same time of each day recording of participant's answers to the angioedema activity score over 7 days (AAS7) questionnaire. For participants who entered the OLE phase, their answers to the AAS7 questionnaire were also to be collected from Week 20 to Week24 and from Week 48 to Week 52.

Urticaria Control Test

[00181] The UCT is a validated PRO measure for assessing urticaria control (Weller et al. 2014) based on 4 items (severity of pruritus and wheals urticaria symptoms; frequency of

treatment being not sufficient; QoL impairment; overall urticarial control). Each item is rated on a 5-point Likert-type scale (scored with 0 to 4 points). Low scores indicate high disease activity and low disease control. The UCT total score is calculated by adding all 4 individual item scores. Accordingly, the minimum and maximum UCT scores are 0 and 16, with a score of 16 points indicating complete disease control (Weller et al. 2014). The recall period is the previous 4 weeks. Patients were to complete the UCT questionnaire during their site visit.

Dermatology Life Quality Index

[00182] The DLQI is a PRO developed to measure dermatology-specific HRQoL in adult participants (Finlay and Khan 1994). The instrument comprises 10 items assessing the impact of skin disease on participants' HRQoL over the previous week with an average completion time of 126 seconds (Loo et al. 2003). The items cover symptoms, leisure activities, work/school or holiday time, personal relationships including intimate, the side effects of treatment, and emotional reactions to having a skin disease. It is a validated questionnaire used in clinical practice and clinical trials (Chernyshov 2019). Response scale is a 4-point Likert scale (0 = "not at all" and 3 = "very much") for 9 items. The remaining 1 item about work/studying asks whether work/study has been prevented and then (if "No") to what degree the skin condition has been a problem at work/study; the item is rated on a 3-point Likert scale ("Not at all" to "A lot"). Overall scoring ranges from 0 to 30, with a high score indicative of a poor HRQoL. Using an integrated analysis of distribution and anchor-based approaches using the change in DLQI total score and participant-assessed itch severity scores, the MID for the DLQI in participants with CIU was reported to be in the range of 2.24 to 3.10 points (Shiklar et al. 2005). The recall period is the previous week. Patients were to complete the DLQI questionnaire during their site visit.

Patient Global Impression of Change of CSU Disease and Patient Global Impression of Severity of CSU Disease

[00183] The PGIS is a 1-item measure that asks participants to provide a self-assessment of their overall CSU severity for the past week on a 4 point scale. Response choices are: "None", "Mild", "Moderate" and "Severe". The PGIC is a 1-item measure that asks the participant to provide a self-assessment of overall change in their CSU since the participant started taking the

study medication on a 7-point scale. The response options range from “Very Much Better” to “Very Much Worse.” Patients were to complete questionnaires for the 2 items during their site visit.

Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

[00184] An AE is defined as any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention¹.

[00185] Events meeting the AE definition include any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (*e.g.*, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (*i.e.*, not related to progression of underlying disease), *e.g.*, events that are symptomatic; events that require either corrective treatment or consultation; events that lead to IMP discontinuation or modification of dosing; events that fulfill a seriousness criterion; and/or events defined as an AESI. Events meeting the AE definition further include the exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition; a new condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study; signs, symptoms, or clinical sequelae of a suspected drug-drug interaction; and/or signs, symptoms, or clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

[00186] An SAE is defined as any AE that, at any dose, results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

[00187] The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.

¹ An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

[00188] In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

[00189] The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

[00190] Other situations may also have been considered SAEs. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that did not result in hospitalization, or development of drug dependency or drug abuse.

[00191] The Investigator was to make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: an event that was easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: an event that caused sufficient discomfort to interfere with normal everyday activities.
- Severe: an event that prevented normal everyday activities. An AE that was assessed as severe should not have been confused with an SAE. "Severe" is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, and not when it is rated as severe.

Adverse Events of Special Interest

[00192] An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may have required further investigation in order to characterize and understand them. AESIs may have been added, modified, or removed during a study by protocol amendment. Exemplary AESIs are listed below.

- Pregnancy of a female participant entered in the study, or pregnancy occurring in a female partner of a male participant entered in the clinical trial. Such a pregnancy was to be qualified as an SAE only if it fulfilled one of the seriousness criteria. In the event of pregnancy in a female participant, the IMP was to be discontinued. Follow-up of the pregnancy in a female participant or in a female partner of a male participant was mandatory until the outcome had been determined.
- Symptomatic overdose (serious or nonserious) with an IMP or NIMP. An overdose (accidental or intentional) with the IMP was an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as a single ingestion of a dose equal to or greater than 1,200 mg (≥ 3 times the indicated single dose of 400 mg), provided that it had been taken at once or over 2-hour period. An overdose (accidental or intentional) with the NIMP was an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as at least twice the maximum allowed daily dose, within the intended therapeutic interval. For H1-AH only, an overdose is defined as any dose that exceeds the maximum allowed daily dose in this protocol.
- Increase in ALT. For participants with an increase in ALT $> 3 \times$ ULN, report the ALT $> 3 \times$ ULN together with total bilirubin value including normal ranges and confirm the elevation within 72 hours.
- Other project specific AESIs. This may have included severe infections, including opportunistic infections; tuberculosis or initiation of medications for suspected tuberculosis; diagnosed and biologically proven SARS-CoV-2 infection; major hemorrhagic events, including symptomatic bleeding in a critical area or organ such as the central nervous system (CNS), or intraocular bleeding, resulting in an SAE;

severe or serious AEs (or non-serious AEs with a severity level consistent with Grade 3 Common Terminology Criteria for AE (CTCAE) of cytopenia v 5.0; and atrial fibrillation.

Pharmacokinetics

[00193] Plasma samples were to be obtained for PK characterization of rilzabrutinib. Selected residual plasma samples may have been utilized to assess PK of relevant metabolites of rilzabrutinib. Concentrations at each time point were to be reported.

Biomarkers

[00194] Collection of biological samples for other biomarker research was also part of this study. The following samples for biomarker research were required and were to be collected from all participants in this study:

- Serum and plasma samples for soluble biomarkers and cellular tests. Analytes included IgG anti-IgE, IgG anti-FcεRI, IgG anti-TPO, IgE anti-TPO, IL-31, and sMRGPRX2.
- Blood samples for immune cell phenotyping, including measurement of eosinophil levels
- Blood samples for BTK occupancy in peripheral blood mononuclear cells (PBMCs) at selected sites

[00195] For each patient, serum samples were to be collected on each of four visits (Visits 2, 4, 6, and end of study/follow up).

[00196] Serum analyte testing was to be performed using the antibodies and antigens listed below:

- hIgG anti-FcεRI (Cat. No. #130-122-308; Miltenyi)
- hIgG anti-IgE-biotin (Cat. No. #130-117-938; Miltenyi)
- Anti-IgE-HRP (Cat. No. #5220-0329; SeraCare)
- Anti-hIgG HRP (Cat. No. #109-035-008; Jackson IR)
- Purified TPO (Cat. No. #043/20; In.vent Diagnostica)

- Recombinant human FcεRIα (HIS-tag) (Cat. No. #FCA-H5228; AcroBiosystems)
- Human IgE (myeloma) (Cat. No. #401152; Merck Millipore)
- IvIg (Kiovig) (Cat. No. #LE-07-43020; Baxter AG/Shire)
- IgE anti-TPO (SP1.4-IgE anti-TPO purified from hybridoma supernatants) (Guo et al. 1996)

[00197] Serum analyte testing was to be performed using the following commercial assays:

- sMRGPRX2 ELISA (Cat. No. #MBS933336; MyBioSource)
- IL-31 HTRF assay (Cat. No. #62HIL31PEG; Cisbio/PerkinElmer)
- IgG anti-TPO ELISA (Cat. No. #ORG503; Orgentec Diagnostica GmbH)

[00198] All chemical and biological reagents used for serum analyte testing were of analytical grade and were used without further purification. Any water used for dilution, *e.g.*, for the washing buffer, was to be deionized and obtained directly from the facilities installation.

[00199] The following commercial reagents and consumables were to be used:

- ECL prime (Cat. No. #10308449; Cytiva/FisherScientific)
- Streptavidin HRP (Cat. No. #DY998; R&D Systems)
- PBS (Cat. No. #14190094; Gibco)
- Protein-free blocking buffer (Cat. No. #927-90001; LI-COR)
- TritonX-100 (Cat. No. #T8532; SigmaAldrich)
- Tween-20 (Cat. No. #M147; VWR LifeSciences)
- NaCl
- MaxiSorp 384 well plates (Cat. No. #P6491; Nunc/SigmaAldrich)

[00200] Assay buffer was to be prepared using PBS, Tween-20, TritonX-100, and NaCl. TBS was to comprise 10 mM Tris, 150 mM NaCl, pH 7.4. TBST was to comprise TBS and Tween-20.

[00201] Laboratory equipment was to include a Multimode Plate Reader (VICTOR5; Perkin Elmer).

[00202] If dilutions were to be prepared, the same dilutions were to be prepared twice from each sample. These were to be measured on different plates. Each plate was to include a standard curve. Samples were to be measured twice for all biomarkers except for sMRGPRX2. Mean measurement values were to be calculated, and the concentration of the biomarker was to be calculated using GraphPad Prism 9 software (4-PL model).

[00203] Biomarker assays were performed as described below.

[00204] For the IgG anti-IgE ELISA, MaxiSorp plates were coated overnight with 1 µg/mL human IgE antigen and blocked with 10% protein-free blocking buffer diluted in assay buffer. Following the addition of serum samples (1:100 dilution in assay buffer) or the hIgG anti-IgE standard (1:2 serial dilution in assay buffer), the plates were incubated at room temperature. Next, the anti-IgG-HRP detection antibody was added to all samples. Development was performed using ECL-prime solution, and chemiluminescent signal intensity was measured on the Victor5 multimode plate reader.

[00205] For the IgG anti-FcεRI ELISA, MaxiSorp plates were coated overnight with 1 µg/mL recombinant human FcεRIα and blocked with 10% protein-free blocking buffer diluted in assay buffer. Following the addition of serum samples (1:100 in assay buffer) or the hIgG anti-FcεRI standard (1:2 serial dilution in assay buffer), the plates were incubated at room temperature. Next, the anti-IgG-HRP detection antibody was added to all samples. Development was performed using ECL-prime solution and chemiluminescent signal intensity was measured on the Victor5 multimode plate reader.

[00206] The IgG anti-TPO ELISA was performed according to the manufacturer's instructions.

[00207] For the IgE anti-TPO ELISA, plates were coated with purified human TPO and blocked with 1% fetal bovine serum (FBS) diluted in TBST. Serum samples (1:5 in TBS) or the SP1.4-IgE anti-TPO standard (1:2 serial dilution in assay buffer) were incubated at room temperature. Next, the anti-IgE-HRP antibody was added to all samples. Development was

performed using ECL-prime solution and chemiluminescent signal intensity was measured on the Victor5 multimode plate reader.

[00208] The IL-31 HTRF assay was performed according to the manufacturer's instructions.

[00209] For the sMRGPRX2 ELISA, measurements were performed according to the manufacturer's instructions. Single measurements were obtained for all samples.

[00210] Assay data ranges are described below.

- sMRGPRX2: 0.1 ng/mL-10 ng/mL
- IgG anti-FCεRI: 0-10000 arbitrary units (AU)
- IgG anti-TPO: 0-3000 international units (IU)
- IgE anti-TPO: 0-500 AU
- IgG anti-IgE: 0-100000 AU
- IL-31: 0.1 ng/mL-20 ng/mL

Statistical Considerations

[00211] In this study, the statistical hypotheses for comparing each of rilzabrutinib groups against placebo on the primary endpoint of change from baseline in ISS7 at Week 12 (for US and US reference countries), and the primary endpoint of change from baseline in UAS7 at Week 12 (for countries except US and US reference countries) were as follows:

- Null hypothesis H0: there is no treatment difference between rilzabrutinib and placebo.
- Alternative hypothesis H1: there is a treatment difference between rilzabrutinib and placebo.

[00212] The statistical hypotheses to be tested on secondary efficacy endpoints could be specified similarly as those on the primary endpoint.

[00213] Participants were randomized to the intervention group in a ratio of 1:1:1:1.

[00214] An absolute change of 5 in ISS7 score is considered the minimal clinically important difference (MCID) and an absolute change of 10 in UAS7 score is considered the MCID. Based upon an SD of 7, a change of 5 in the ISS7 would correspond to an effect size of

approximately 0.71. Based upon a SD of 14, a change of 10 in the UAS7 would correspond to an effect size of approximately 0.71. Based on this assumption, plus the assumption of a 15% dropout rate before Week 12, it was estimated that 38 patients per group would provide approximate 80% power to detect an effect size of 0.71 or higher between the rilzabrutinib arm and placebo using a 2-sided t-test with $\alpha = 0.05$. This sample size estimate applies to both ISS7 (primary endpoint for US and US reference countries) and UAS7 (primary endpoint for all countries except US and US reference countries).

[00215] The sample size calculations were performed using EAST 6.5.

[00216] The randomization was to be stratified by region and prior use of omalizumab (yes or no). Note: prior use of omalizumab = yes represents patients with prior omalizumab use, including omalizumab-incomplete responders, and prior use of omalizumab = no represents omalizumab-naïve patients. Patients with prior omalizumab use, including omalizumab-incomplete responders were only to be randomized to the 400 mg BID, 400 mg TID and placebo arms, and they were to be capped at up to 15% of the patients in that arm.

Populations for Analyses

[00217] The populations for analyses are defined in **Table 7**.

Table 7. Populations for Analyses

Population	Description
Screened	All participants who signed the ICF
Randomized	All participants from screened population who were allocated to a randomized intervention by IRT regardless of whether the intervention was received
Intent-to-treat (ITT)	All randomized participants. Participants were to be analyzed according to the intervention allocated by randomization.
Omalizumab-naïve	All randomized omalizumab-naïve participants. Participants were to be analyzed according to the intervention they actually received.
Safety	All randomized participants who took at least one dose of study intervention. Participants

	were to be analyzed according to the intervention they actually received
Pharmacokinetic (PK)	All randomized and treated participants (safety population) without important deviation related to IMP administration, and with at least one post-baseline PK sample with adequate documentation of dosing and sampling dates and times. Participants having received only placebo were not to be part of the PK population. Participants were to be analyzed according to the intervention they actually received.
Open-label extension (OLE)	All participants who received at least one dose of intervention during the open-label extension phase.

[00218] The efficacy endpoints analyses were to be primarily based on the omalizumab-naïve population. The ITT population was to be used as the supplementary analysis for selected efficacy endpoints.

Primary Endpoints

[00219] The primary endpoint was change from baseline in UAS7 at Week 12 (except US and US reference countries). For US and US reference countries, the primary endpoint was change from baseline in ISS7 at Week 12.

[00220] The summary of primary estimand for the primary endpoint is provided in **Table 8**.

Table 8. Primary Estimand for the Primary Endpoint

Treatment	Rilzabrutinib 400 mg QPM, 400 mg BID, 400 mg TID, and placebo, along with established standard of care background therapy with a long-acting, non-sedating H1-AH.
Population	Omalizumab-naïve
Variables	Change from baseline in UAS7 at Week 12 (except US and US reference countries). Change from baseline in ISS7 at Week 12 (for US and US reference countries only).
Intercurrent events and handling strategy for missing data handlings	For participants who discontinued the study intervention, all data collected after discontinuation were to be used in the analysis (treatment policy strategy). After discontinuation of

	the study intervention due to lack of efficacy prior to Week 12, WOCF approach was to be used to impute missing data if needed. After discontinuation of the study intervention due to reasons other than lack of efficacy prior to Week 12, MI approach was to be used to impute missing endpoint values, and this MI was to use all participants excluding participants who had taken selected prohibited medications and/or rescue medications prior to Week 12. • For participants who took selected prohibited medications and/or rescue medications prior to Week 12, data were to be set to missing values after the medication usage, and the participant's worst postbaseline value on or before the time of the medication usage was to be used to impute missing endpoint values. For participants whose postbaseline values were all missing, the participant's baseline value was to be used to impute the missing endpoint value (hypothetical strategy).
Population-level summary	An analysis of covariance model with intervention groups, region (combined countries) and baseline value of the endpoint as covariates was to be used. Statistical inference obtained from all imputed data was to be combined using Rubin's rule. Descriptive statistics including number of subjects, mean, standard error, and LS mean changes (and standard error) score will be provided. In addition, difference of the rilzabrutinib group against placebo in LS means and the corresponding 95% CI was to be provided along with the p-values.

Supplementary Analysis

[00221] The primary endpoint was also to be analyzed on ITT population. In addition, descriptive statistics for patients with prior omalizumab use, including omalizumab-incomplete responders, were to be provided.

[00222] As-observed analysis (including all data after taking the prohibited and/or rescue medications) and other supplementary analyses were to be performed to provide additional insights into the understanding of the treatment effect.

[00223] In addition to the comparison between each dose level of rilzabrutinib and placebo in a pairwise manner, a pooled analysis of the BID and TID doses may have been performed as appropriate.

Secondary Endpoint(s)

[00224] The following secondary endpoints were to be analyzed using the same approach as for the primary endpoint:

- Change from baseline in UAS7 at Week 4
- Change from baseline in UAS7 at Week 12 (for US and US reference countries)
- Change from baseline in ISS7 at Week 12 (except US and US reference countries)
- Change from baseline in HSS7 at Week 12

[00225] The following responder secondary endpoints were to be analyzed using the Cochran-Mantel-Haenszel test adjusted by region:

- Proportion of participants with $UAS7 \leq 6$ at Week 12
- Proportion of participants with $UAS7 = 0$ at Week 12

[00226] Participants who received selected prohibited medications and/or rescue medications were to be considered as non-responders for time points after the medication usage. For other participants, all available data including those collected during the off-treatment period were to be used to determine the responder/non-responder status. Missing data were to be considered as non-responders.

[00227] No multiplicity adjustment for the secondary efficacy endpoints was to be made. A pooled analysis of the BID and TID doses may have been performed as appropriate.

Safety Analysis

[00228] All safety analysis was to be based on the safety population according to the intervention group to which the participants are exposed. The safety analysis was to be conducted separately for double-blind period and open-label period.

Example 2: Double-Blind Treatment Phase Results

[00229] A study was initiated to evaluate the effect of rilzabrutinib treatment in patients with moderate-to-severe chronic spontaneous urticaria (CSU) whose disease was not controlled with H1-antihistamines (H1-AH) alone. Over the course of this 12-week, double-blind, placebo-controlled study, N=160 patients were administered one of three doses of rilzabrutinib (400 mg QD, 400 mg BID, or 400 mg TID) or a placebo.

[00230] Patients exhibited significant improvement across all disease components, including urticaria activity, itch severity, and hives. These improvements, which were observed from Week 1, were sustained through Week 12. Moreover, improvements were observed in both the intent-to-treat (ITT) and omalizumab-naïve participant populations.

[00231] Primary endpoints for this study included the change from baseline in weekly urticaria activity score (UAS7) at Week 12 (all non-US countries) and the change from baseline in weekly itch severity score (ISS7) at Week 12 (US only). Secondary and tertiary endpoints are described in **Table 1**.

[00232] For patients receiving 400 mg TID rilzabrutinib, the study met the primary endpoints for both non-US countries and the US. Additionally, for patients receiving 400 mg TID rilzabrutinib, the study met several secondary endpoints, including the proportion of participants with well-controlled disease ($UAS7 \leq 6$) at Week 12 and the percent change from baseline in weekly hives severity score (HSS7) at Week 12.

[00233] Evidence of a dose-response relationship was observed for patients treated with rilzabrutinib. While there was no difference between patients receiving 400 mg QPM rilzabrutinib and patients receiving the placebo, patients receiving 400 mg BID rilzabrutinib showed positive improvements across all endpoints when compared to patients receiving the placebo.

[00234] Moreover, rilzabrutinib was generally safe, with no evidence of new safety concerns or dose-related AEs.

Participant Demographics

[00235] The 160 patients enrolled in the phase 2 study were characterized by the demographic information provided in **Tables 9-12**. Of the 160 patients randomized, 142 (88.75%) completed the double-blind period. Baseline demographics and disease characteristics were generally well balanced across treatment arms (**Tables 9 and 10**). The omalizumab-naïve patient population was similar to the ITT population.

[00236] The median age of enrolled patients was 44. At enrollment, patients had CSU for a median duration of 3.0 years, and 11.6% had previously received omalizumab (patients with prior omalizumab use, including omalizumab-incomplete responders). Additionally, 36.9% of patients had a history of angioedema.

Table 9. Demographics and Participant Characteristics at Baseline (Randomized Population)

	Placebo (N=40)	Rilzabrutinib 400mg QPM (N=38)	Rilzabrutinib 400mg BID (N=41)	Rilzabrutinib 400mg TID (N=41)	All (N=160)
Age (years)					
Number	40	38	41	41	160
Mean (SD)	40.2 (14.0)	42.1 (12.7)	45.5 (13.4)	48.5 (12.2)	44.1 (13.4)
Median	39.5	41.0	43.0	49.0	44.0
Q1 ; Q3	27.0 ; 50.5	33.0 ; 50.0	34.0 ; 57.0	40.0 ; 56.0	33.0 ; 54.5
Min ; Max	19 ; 70	20 ; 66	24 ; 73	22 ; 77	19 ; 77
Age group (years) [n (%)]					
Number	40	38	41	41	160
18-39	20 (50.0)	16 (42.1)	17 (41.5)	10 (24.4)	63 (39.4)
40-64	18 (45.0)	21 (55.3)	22 (53.7)	27 (65.9)	88 (55.0)
≥65	2 (5.0)	1 (2.6)	2 (4.9)	4 (9.8)	9 (5.6)
Age group (years) [n (%)]					
Number	40	38	41	41	160
< 44 (Median)	25 (62.5)	20 (52.6)	21 (51.2)	13 (31.7)	79 (49.4)
≥ 44 (Median)	15 (37.5)	18 (47.4)	20 (48.8)	28 (68.3)	81 (50.6)
Region ^a [n (%)]					
Number	40	38	41	41	160
Asia	9 (22.5)	10 (26.3)	8 (19.5)	8 (19.5)	35 (21.9)
Latin America	14 (35.0)	14 (36.8)	11 (26.8)	9 (22.0)	48 (30.0)
Eastern Europe	3 (7.5)	4 (10.5)	3 (7.3)	5 (12.2)	15 (9.4)
Western Countries	14 (35.0)	10 (26.3)	19 (46.3)	19 (46.3)	62 (38.8)
Sex [n (%)]					
Number	40	38	41	41	160
Male	14 (35.0)	10 (26.3)	16 (39.0)	8 (19.5)	48 (30.0)

	Placebo (N=40)	Rilzabrutinib 400mg QPM (N=38)	Rilzabrutinib 400mg BID (N=41)	Rilzabrutinib 400mg TID (N=41)	All (N=160)
Female	26 (65.0)	28 (73.7)	25 (61.0)	33 (80.5)	112 (70.0)
Race [n (%)]					
Number	40	38	41	41	160
White	31 (77.5)	27 (71.1)	33 (80.5)	30 (73.2)	121 (75.6)
Black or African American	0	0	0	0	0
Asian	9 (22.5)	11 (28.9)	8 (19.5)	10 (24.4)	38 (23.8)
Japanese	2 (5.0)	3 (7.9)	2 (4.9)	3 (7.3)	10 (6.3)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
American Indian or Alaska Native	0	0	0	1 (2.4)	1 (0.6)
Multiple	0	0	0	0	0
Not reported	0	0	0	0	0
Unknown	0	0	0	0	0
Ethnicity [n (%)]					
Number	40	38	41	41	160
Hispanic or Latino	13 (32.5)	17 (44.7)	12 (29.3)	11 (26.8)	53 (33.1)
Not Hispanic or Latino	27 (67.5)	21 (55.3)	28 (68.3)	28 (68.3)	104 (65.0)
Not reported	0	0	1 (2.4)	1 (2.4)	2 (1.3)
Unknown	0	0	0	1 (2.4)	1 (0.6)
Weight (kg)					
Number	40	38	41	41	160
Mean (SD)	74.86 (18.00)	72.31 (16.45)	75.68 (18.99)	74.52 (16.37)	74.38 (17.38)
Median	72.65	67.35	75.00	75.00	72.90
Q1 ; Q3	58.60 ; 87.40	60.50 ; 81.90	61.00 ; 87.00	64.00 ; 81.50	60.75 ; 85.00
Min ; Max	44.0 ; 110.6	48.9 ; 118.0	49.8 ; 141.5	43.4 ; 114.8	43.4 ; 141.5
Weight group (kg) [n (%)]					
Number	40	38	41	41	160
< 72.9 (Median)	21 (52.5)	23 (60.5)	20 (48.8)	16 (39.0)	80 (50.0)
≥ 72.9 (Median)	19 (47.5)	15 (39.5)	21 (51.2)	25 (61.0)	80 (50.0)
Weight group (kg) [n (%)]					
Number	40	38	41	41	160
<60	11 (27.5)	7 (18.4)	9 (22.0)	8 (19.5)	35 (21.9)
≥60 - <90	20 (50.0)	28 (73.7)	24 (58.5)	28 (68.3)	100 (62.5)
≥90	9 (22.5)	3 (7.9)	8 (19.5)	5 (12.2)	25 (15.6)
BMI (kg/m ²)					
Number	40	38	41	41	160
Mean (SD)	27.04 (5.73)	26.01 (5.48)	27.01 (6.18)	27.69 (5.25)	26.95 (5.65)
Median	25.30	25.20	24.90	27.80	25.90
Q1 ; Q3	23.65 ; 31.00	21.70 ; 30.50	22.60 ; 30.10	24.50 ; 29.20	22.90 ; 29.95
Min ; Max	17.9 ; 42.4	18.4 ; 38.6	17.3 ; 43.2	17.6 ; 42.2	17.3 ; 43.2

	Placebo (N=40)	Rilzabrutinib 400mg QPM (N=38)	Rilzabrutinib 400mg BID (N=41)	Rilzabrutinib 400mg TID (N=41)	All (N=160)
BMI group (kg/m ²) [n (%)]					
Number	40	38	41	41	160
<25	17 (42.5)	18 (47.4)	21 (51.2)	12 (29.3)	68 (42.5)
≥25 - <30	12 (30.0)	10 (26.3)	9 (22.0)	21 (51.2)	52 (32.5)
≥30	11 (27.5)	10 (26.3)	11 (26.8)	8 (19.5)	40 (25.0)

^a Asia: South Korea, Taiwan, Japan; Latin America: Argentina, Chile; Eastern Europe: Poland; Western Countries: Spain, Italy, Germany, Canada, Greece, Netherlands.

Table 10. Demographics and Participant Characteristics at Baseline (Omalizumab-Naïve Population)

	Placebo (N=36)	Rilzabrutini b 400mg QPM (N=37)	Rilzabrutini b 400mg BID (N=35)	Rilzabrutini b 400mg TID (N=35)	All (N=143)
Age (years)					
Number	36	37	35	35	143
Mean (SD)	39.3 (13.7)	41.9 (12.9)	45.5 (13.6)	48.7 (12.8)	43.8 (13.6)
Median	38.0	41.0	44.0	49.0	43.0
Q1 ; Q3	27.0 ; 49.5	33.0 ; 50.0	33.0 ; 57.0	40.0 ; 59.0	31.0 ; 54.0
Min ; Max	19 ; 70	20 ; 66	24 ; 73	22 ; 77	19 ; 77
Age group (years) [n (%)]					
Number	36	37	35	35	143
18-39	19 (52.8)	16 (43.2)	15 (42.9)	8 (22.9)	58 (40.6)
40-64	15 (41.7)	20 (54.1)	18 (51.4)	23 (65.7)	76 (53.1)
≥65	2 (5.6)	1 (2.7)	2 (5.7)	4 (11.4)	9 (6.3)
Age group (years) [n (%)]					
Number	36	37	35	35	143
< 44 (Median)	24 (66.7)	20 (54.1)	17 (48.6)	11 (31.4)	72 (50.3)
≥ 44 (Median)	12 (33.3)	17 (45.9)	18 (51.4)	24 (68.6)	71 (49.7)
Region ^a [n (%)]					
Number	36	37	35	35	143
Asia	9 (25.0)	10 (27.0)	8 (22.9)	8 (22.9)	35 (24.5)
Latin America	13 (36.1)	14 (37.8)	10 (28.6)	8 (22.9)	45 (31.5)
Eastern Europe	3 (8.3)	4 (10.8)	3 (8.6)	4 (11.4)	14 (9.8)
Western Countries	11 (30.6)	9 (24.3)	14 (40.0)	15 (42.9)	49 (34.3)
Sex [n (%)]					
Number	36	37	35	35	143
Male	13 (36.1)	9 (24.3)	13 (37.1)	7 (20.0)	42 (29.4)
Female	23 (63.9)	28 (75.7)	22 (62.9)	28 (80.0)	101 (70.6)
Race [n (%)]					
Number	36	37	35	35	143
White	27 (75.0)	26 (70.3)	27 (77.1)	25 (71.4)	105 (73.4)
Black or African American	0	0	0	0	0

	Placebo (N=36)	Rilzabrutini b 400mg QPM (N=37)	Rilzabrutini b 400mg BID (N=35)	Rilzabrutini b 400mg TID (N=35)	All (N=143)
Asian	9 (25.0)	11 (29.7)	8 (22.9)	10 (28.6)	38 (26.6)
Japanese	2 (5.6)	3 (8.1)	2 (5.7)	3 (8.6)	10 (7.0)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
American Indian or Alaska Native	0	0	0	0	0
Multiple	0	0	0	0	0
Not reported	0	0	0	0	0
Unknown	0	0	0	0	0
Ethnicity [n (%)]					
Number	36	37	35	35	143
Hispanic or Latino	12 (33.3)	16 (43.2)	11 (31.4)	10 (28.6)	49 (34.3)
Not Hispanic or Latino	24 (66.7)	21 (56.8)	23 (65.7)	23 (65.7)	91 (63.6)
Not reported	0	0	1 (2.9)	1 (2.9)	2 (1.4)
Unknown	0	0	0	1 (2.9)	1 (0.7)
Weight (kg)					
Number	36	37	35	35	143
Mean (SD)	73.33 (17.55)	72.64 (16.55)	74.13 (19.95)	72.62 (15.08)	73.17 (17.19)
Median	71.75	67.70	71.90	75.00	71.90
Q1 ; Q3	58.20 ; 84.60	60.70 ; 81.90	56.70 ; 84.00	62.00 ; 81.50	60.20 ; 82.70
Min ; Max	44.0 ; 110.6	48.9 ; 118.0	49.8 ; 141.5	43.4 ; 110.0	43.4 ; 141.5
Weight group (kg) [n (%)]					
Number	36	37	35	35	143
< 72.9 (Median)	20 (55.6)	22 (59.5)	19 (54.3)	15 (42.9)	76 (53.1)
≥ 72.9 (Median)	16 (44.4)	15 (40.5)	16 (45.7)	20 (57.1)	67 (46.9)
Weight group (kg) [n (%)]					
Number	36	37	35	35	143
<60	11 (30.6)	7 (18.9)	9 (25.7)	8 (22.9)	35 (24.5)
≥60 - <90	18 (50.0)	27 (73.0)	19 (54.3)	24 (68.6)	88 (61.5)
≥90	7 (19.4)	3 (8.1)	7 (20.0)	3 (8.6)	20 (14.0)
BMI (kg/m ²)					
Number	36	37	35	35	143
Mean (SD)	26.48 (5.32)	26.22 (5.41)	26.49 (6.07)	27.19 (4.82)	26.59 (5.38)
Median	25.25	25.40	24.50	27.10	25.40
Q1 ; Q3	23.35 ; 30.05	21.80 ; 30.50	22.40 ; 31.30	24.20 ; 29.10	22.60 ; 29.60
Min ; Max	17.9 ; 39.7	18.4 ; 38.6	17.3 ; 43.2	17.6 ; 41.4	17.3 ; 43.2
BMI group (kg/m ²) [n (%)]					
Number	36	37	35	35	143
<25	17 (47.2)	17 (45.9)	20 (57.1)	11 (31.4)	65 (45.5)
≥25 - <30	10 (27.8)	10 (27.0)	6 (17.1)	18 (51.4)	44 (30.8)
≥30	9 (25.0)	10 (27.0)	9 (25.7)	6 (17.1)	34 (23.8)

BMI: Body mass index

^a Asia: South Korea, Taiwan, Japan; Latin America: Argentina, Chile; Eastern Europe: Poland; Western Countries: Spain, Italy, Germany, Canada, Greece, Netherlands.

Table 11. Demographics and Participant Characteristics at Baseline (Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders in ITT Population)

	Placebo (N=4)	Rilzabrutini b 400mg QPM (N=1)	Rilzabrutini b 400mg BID (N=6)	Rilzabrutini b 400mg TID (N=6)	All (N=17)
Age (years)					
Number	4	1	6	6	17
Mean (SD)	48.0 (16.5)	48.0 (NC)	45.7 (12.8)	47.0 (8.9)	46.8 (11.3)
Median	53.0	48.0	41.5	50.0	47.0
Q1 ; Q3	36.0 ; 60.0	48.0 ; 48.0	34.0 ; 59.0	39.0 ; 54.0	39.0 ; 55.0
Min ; Max	25 ; 61	48 ; 48	34 ; 64	34 ; 55	25 ; 64
Age group (years) [n (%)]					
Number	4	1	6	6	17
18-39	1 (25.0)	0	2 (33.3)	2 (33.3)	5 (29.4)
40-64	3 (75.0)	1 (100)	4 (66.7)	4 (66.7)	12 (70.6)
≥65	0	0	0	0	0
Age group (years) [n (%)]					
Number	4	1	6	6	17
< 44 (Median)	1 (25.0)	0	4 (66.7)	2 (33.3)	7 (41.2)
≥ 44 (Median)	3 (75.0)	1 (100)	2 (33.3)	4 (66.7)	10 (58.8)
Region ^a [n (%)]					
Number	4	1	6	6	17
Latin America	1 (25.0)	0	1 (16.7)	1 (16.7)	3 (17.6)
Eastern Europe	0	0	0	1 (16.7)	1 (5.9)
Western Countries	3 (75.0)	1 (100)	5 (83.3)	4 (66.7)	13 (76.5)
Sex [n (%)]					
Number	4	1	6	6	17
Male	1 (25.0)	1 (100)	3 (50.0)	1 (16.7)	6 (35.3)
Female	3 (75.0)	0	3 (50.0)	5 (83.3)	11 (64.7)
Race [n (%)]					
Number	4	1	6	6	17
White	4 (100)	1 (100)	6 (100)	5 (83.3)	16 (94.1)
Black or African American	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
American Indian or Alaska Native	0	0	0	1 (16.7)	1 (5.9)
Multiple	0	0	0	0	0
Not reported	0	0	0	0	0
Unknown	0	0	0	0	0
Ethnicity [n (%)]					
Number	4	1	6	6	17
Hispanic or Latino	1 (25.0)	1 (100)	1 (16.7)	1 (16.7)	4 (23.5)
Not Hispanic or Latino	3 (75.0)	0	5 (83.3)	5 (83.3)	13 (76.5)
Not reported	0	0	0	0	0

	Placebo (N=4)	Rilzabrutini b 400mg QPM (N=1)	Rilzabrutini b 400mg BID (N=6)	Rilzabrutini b 400mg TID (N=6)	All (N=17)
Unknown	0	0	0	0	0
Weight (kg)					
Number	4	1	6	6	17
Mean (SD)	88.55 (18.49)	60.10 (NC)	84.73 (8.01)	85.63 (20.59)	84.50 (16.08)
Median	89.85	60.10	88.00	76.00	84.00
Q1 ; Q3	72.85 ; 104.25	60.10 ; 60.10	84.00 ; 89.40	75.00 ; 108.00	75.00 ; 90.00
Min ; Max	68.7 ; 105.8	60.1 ; 60.1	69.0 ; 90.0	64.0 ; 114.8	60.1 ; 114.8
Weight group (kg) [n (%)]					
Number	4	1	6	6	17
< 72.9 (Median)	1 (25.0)	1 (100)	1 (16.7)	1 (16.7)	4 (23.5)
≥ 72.9 (Median)	3 (75.0)	0	5 (83.3)	5 (83.3)	13 (76.5)
Weight group (kg) [n (%)]					
Number	4	1	6	6	17
<60	0	0	0	0	0
≥60 - <90	2 (50.0)	1 (100)	5 (83.3)	4 (66.7)	12 (70.6)
≥90	2 (50.0)	0	1 (16.7)	2 (33.3)	5 (29.4)
BMI (kg/m ²)					
Number	4	1	6	6	17
Mean (SD)	32.05 (7.69)	18.50 (NC)	30.03 (6.54)	30.60 (7.09)	30.03 (7.05)
Median	30.35	18.50	28.70	28.60	28.70
Q1 ; Q3	26.30 ; 37.80	18.50 ; 18.50	26.90 ; 30.10	25.00 ; 35.70	25.10 ; 33.20
Min ; Max	25.1 ; 42.4	18.5 ; 18.5	23.3 ; 42.5	23.5 ; 42.2	18.5 ; 42.5
BMI group (kg/m ²) [n (%)]					
Number	4	1	6	6	17
<25	0	1 (100)	1 (16.7)	1 (16.7)	3 (17.6)
≥25 - <30	2 (50.0)	0	3 (50.0)	3 (50.0)	8 (47.1)
≥30	2 (50.0)	0	2 (33.3)	2 (33.3)	6 (35.3)

BMI: Body mass index

^a Asia: South Korea, Taiwan, Japan; Latin America: Argentina, Chile; Eastern Europe: Poland; Western Countries: Spain, Italy, Germany, Canada, Greece, Netherlands.

Table 12. Disease and Other Characteristics at Baseline (Randomized Population)

	Placebo (N=40)	Rilzabrutinib 400mg QPM (N=38)	Rilzabrutinib 400mg BID (N=41)	Rilzabrutinib 400mg TID (N=41)	All (N=160)
Age at onset of CSU (years)					
Number	40	38	41	41	160
Mean (SD)	34.7 (12.2)	37.3 (14.1)	41.9 (15.3)	42.0 (13.4)	39.0 (14.0)
Median	31.5	38.0	41.0	42.0	38.0
Q1 ; Q3	25.0 ; 43.5	25.0 ; 49.0	31.0 ; 54.0	33.0 ; 49.0	28.0 ; 49.0
Min ; Max	17 ; 62	12 ; 65	2 ; 71	8 ; 70	2 ; 71

Time since first diagnosis of CSU (years)^a

	Placebo (N=40)	Rilzabrutinib 400mg QPM (N=38)	Rilzabrutinib 400mg BID (N=41)	Rilzabrutinib 400mg TID (N=41)	All (N=160)
Number	40	38	41	41	160
Mean (SD)	6.13 (8.89)	5.26 (5.56)	4.11 (6.96)	6.99 (11.37)	5.63 (8.51)
Median	3.50	3.63	2.00	3.08	3.00
Q1 ; Q3	1.21 ; 6.79	1.17 ; 6.00	1.08 ; 4.17	1.08 ; 7.25	1.08 ; 6.00
Min ; Max	0.3 ; 39.0	0.6 ; 24.0	0.3 ; 41.0	0.3 ; 53.0	0.3 ; 53.0
Prior use of Omalizumab [n (%)]					
Number	40	38	41	41	160
Yes	4 (10.0)	1 (2.6)	6 (14.6)	6 (14.6)	17 (10.6)
No	36 (90.0)	37 (97.4)	35 (85.4)	35 (85.4)	143 (89.4)
History of allergy ^b					
Number	40	38	41	41	160
Allergic	6 (15.0)	10 (26.3)	13 (31.7)	12 (29.3)	41 (25.6)
Non-Allergic	34 (85.0)	28 (73.7)	28 (68.3)	29 (70.7)	119 (74.4)
History of atopic dermatitis					
Number	40	38	41	41	160
Yes	1 (2.5)	0	1 (2.4)	1 (2.4)	3 (1.9)
No	39 (97.5)	38 (100)	40 (97.6)	40 (97.6)	157 (98.1)
History of angioedema					
Number	40	38	41	41	160
Yes	18 (45.0)	16 (42.1)	12 (29.3)	13 (31.7)	59 (36.9)
No	22 (55.0)	22 (57.9)	29 (70.7)	28 (68.3)	101 (63.1)
Number of angioedema episodes in past 6 months					
Number	18	17	12	13	60
Mean (SD)	9.5 (14.6)	8.6 (14.4)	11.4 (20.3)	14.5 (16.0)	10.7 (15.9)
Median	4.0	1.0	1.5	6.0	2.5
Q1 ; Q3	1.0 ; 10.0	0.0 ; 12.0	1.0 ; 17.5	3.0 ; 30.0	1.0 ; 16.5
Min ; Max	0 ; 60	0 ; 48	0 ; 70	0 ; 48	0 ; 70
Time since last angioedema episode (months)					
Number	18	16	12	13	59
Mean (SD)	7.14 (21.22)	6.62 (11.64)	21.31 (64.64)	10.39 (29.51)	10.60 (34.22)
Median	1.41	2.83	1.81	1.87	1.58
Q1 ; Q3	0.92 ; 3.19	0.71 ; 8.20	0.76 ; 4.63	1.02 ; 3.29	0.76 ; 4.50
Min ; Max	0.5 ; 91.8	0.4 ; 48.2	0.5 ; 226.4	0.2 ; 108.4	0.2 ; 226.4
Baseline UAS7 score					
Number	40	38	41	41	160
Mean (SD)	30.0 (8.6)	31.4 (7.3)	30.2 (7.2)	29.9 (8.6)	30.3 (7.9)
Median	29.0	30.0	28.0	29.0	29.0
Q1 ; Q3	23.0 ; 37.5	27.0 ; 38.0	25.0 ; 35.0	25.0 ; 36.0	25.0 ; 37.0
Min ; Max	16 ; 42	16 ; 42	18 ; 42	0 ; 42	0 ; 42
Baseline UAS7 score [n (%)]					
Number	40	38	41	41	160
<28	15 (37.5)	10 (26.3)	16 (39.0)	14 (34.1)	55 (34.4)
≥28	25 (62.5)	28 (73.7)	25 (61.0)	27 (65.9)	105 (65.6)
Baseline ISS7 score					
Number	40	38	41	41	160
Mean (SD)	15.6 (4.2)	16.5 (3.5)	15.8 (3.7)	15.9 (4.4)	15.9 (4.0)

	Placebo (N=40)	Rilzabrutinib 400mg QPM (N=38)	Rilzabrutinib 400mg BID (N=41)	Rilzabrutinib 400mg TID (N=41)	All (N=160)
Median	14.5	16.5	15.0	15.0	15.0
Q1 ; Q3	12.0 ; 20.5	14.0 ; 20.0	13.0 ; 19.0	14.0 ; 20.0	14.0 ; 20.0
Min ; Max	8 ; 21	9 ; 21	8 ; 21	0 ; 21	0 ; 21
Baseline ISS7 score [n (%)]					
Number	40	38	41	41	160
<13	11 (27.5)	5 (13.2)	7 (17.1)	4 (9.8)	27 (16.9)
≥13	29 (72.5)	33 (86.8)	34 (82.9)	37 (90.2)	133 (83.1)
Baseline HSS7 score					
Number	40	38	41	41	160
Mean (SD)	14.4 (4.9)	14.9 (4.3)	14.4 (4.3)	14.0 (4.8)	14.4 (4.5)
Median	14.0	14.0	14.0	14.0	14.0
Q1 ; Q3	11.0 ; 18.9	12.0 ; 18.0	12.0 ; 17.0	12.0 ; 17.0	12.0 ; 18.0
Min ; Max	7 ; 21	7 ; 21	7 ; 21	0 ; 21	0 ; 21
Baseline AAS7>0 [n (%)]					
Number	40	38	41	41	160
Yes	30 (75.0)	28 (73.7)	28 (68.3)	26 (63.4)	112 (70.0)
No	10 (25.0)	10 (26.3)	13 (31.7)	15 (36.6)	48 (30.0)
Baseline AAS7 score for participants with angioedema ^c					
Number	30	28	28	26	112
Mean (SD)	59.7 (27.1)	54.0 (25.2)	46.1 (25.7)	46.0 (22.3)	51.7 (25.6)
Median	61.5	56.0	44.5	50.5	51.0
Q1 ; Q3	42.0 ; 86.0	39.0 ; 71.0	24.0 ; 67.5	27.0 ; 61.0	32.0 ; 68.0
Min ; Max	8 ; 101	6 ; 99	2 ; 92	9 ; 91	2 ; 101
Baseline UCT score					
Number	35	36	41	40	152
Mean (SD)	4.2 (3.1)	4.0 (2.2)	4.2 (3.1)	4.5 (3.5)	4.3 (3.0)
Median	4.0	4.0	4.0	4.0	4.0
Q1 ; Q3	2.0 ; 6.0	2.0 ; 5.5	2.0 ; 6.0	2.0 ; 6.5	2.0 ; 6.0
Min ; Max	0 ; 12	0 ; 9	0 ; 13	0 ; 15	0 ; 15
Baseline PGIS score					
Number	40	38	41	40	159
Mean (SD)	2.4 (0.6)	2.5 (0.6)	2.2 (0.6)	2.4 (0.7)	2.4 (0.6)
Median	2.0	3.0	2.0	2.0	2.0
Q1 ; Q3	2.0 ; 3.0	2.0 ; 3.0	2.0 ; 3.0	2.0 ; 3.0	2.0 ; 3.0
Min ; Max	1 ; 3	1 ; 3	1 ; 3	0 ; 3	0 ; 3
Baseline Eosinophils (10 ⁹ /L)					
Number	40	38	41	41	160
Mean (SD)	0.194 (0.104)	0.189 (0.134)	0.192 (0.150)	0.200 (0.144)	0.194 (0.133)
Median	0.180	0.155	0.160	0.180	0.165
Q1 ; Q3	0.115 ; 0.290	0.110 ; 0.250	0.090 ; 0.260	0.090 ; 0.290	0.090 ; 0.280
Min ; Max	0.03 ; 0.45	0.02 ; 0.67	0.02 ; 0.62	0.02 ; 0.64	0.02 ; 0.67
Baseline Eosinophils (10 ⁹ /L) [n (%)]					
Number	40	38	41	41	160
< 0.165 (Median)	19 (47.5)	20 (52.6)	22 (53.7)	19 (46.3)	80 (50.0)
≥ 0.165 (Median)	21 (52.5)	18 (47.4)	19 (46.3)	22 (53.7)	80 (50.0)
Baseline Eosinophils (10 ⁹ /L) [n (%)]					

	Placebo (N=40)	Rilzabrutinib 400mg QPM (N=38)	Rilzabrutinib 400mg BID (N=41)	Rilzabrutinib 400mg TID (N=41)	All (N=160)
Number	40	38	41	41	160
< 0.3	31 (77.5)	33 (86.8)	33 (80.5)	32 (78.0)	129 (80.6)
≥ 0.3	9 (22.5)	5 (13.2)	8 (19.5)	9 (22.0)	31 (19.4)
Baseline Basophils (10 ⁹ /L)					
Number	40	38	41	41	160
Mean (SD)	N/A	N/A	N/A	N/A	N/A
Median	0.040	0.040	0.040	0.040	0.040
Q1 ; Q3	(0.023; 0.050)	(0.015; 0.070)	(0.015; 0.060)	(0.030; 0.050)	(0.015; 0.060)
Min ; Max	N/A	N/A	N/A	N/A	N/A
Baseline Total IgE (IU/mL)					
Number	39	37	41	40	157
Mean (SD)	319.6 (530.2)	433.3 (669.8)	275.7 (487.3)	389.0 (638.7)	352.6 (581.9)
Median	142.6	158.0	111.1	116.8	123.8
Q1 ; Q3	40.4 ; 349.5	37.6 ; 533.6	38.7 ; 314.6	34.7 ; 407.9	37.6 ; 351.1
Min ; Max	0 ; 2608	3 ; 2843	1 ; 2634	1 ; 2882	0 ; 2882
Baseline Total IgE (IU/mL) [n (%)]					
Number	39	37	41	40	157
<300	27 (69.2)	25 (67.6)	29 (70.7)	28 (70.0)	109 (69.4)
≥300	12 (30.8)	12 (32.4)	12 (29.3)	12 (30.0)	48 (30.6)
Baseline Total IgE (IU/mL) [n (%)]					
Number	39	37	41	40	157
<100	18 (46.2)	15 (40.5)	19 (46.3)	18 (45.0)	70 (44.6)
≥100	21 (53.8)	22 (59.5)	22 (53.7)	22 (55.0)	87 (55.4)
Baseline Total IgG (g/L)					
Number	40	38	41	41	160
Mean (SD)	12.4 (3.2)	11.6 (2.0)	11.3 (2.3)	11.7 (2.1)	11.7 (2.5)
Median	11.9	11.1	11.4	11.7	11.5
Q1 ; Q3	10.2 ; 14.0	9.9 ; 13.0	10.2 ; 12.4	10.4 ; 12.9	10.1 ; 13.0
Min ; Max	6 ; 24	8 ; 17	6 ; 19	7 ; 18	6 ; 24
Baseline Total IgG (g/L) [n (%)]					
Number	40	38	41	41	160
<7	1 (2.5)	0	1 (2.4)	0	2 (1.3)
7-16	33 (82.5)	37 (97.4)	39 (95.1)	40 (97.6)	149 (93.1)
>16	6 (15.0)	1 (2.6)	1 (2.4)	1 (2.4)	9 (5.6)
Baseline Total IgM (g/L)					
Number	39	37	41	41	158
Mean (SD)	1.1 (0.6)	1.1 (0.5)	1.2 (0.7)	1.3 (0.8)	1.2 (0.6)
Median	1.0	1.1	1.1	1.1	1.1
Q1 ; Q3	0.7 ; 1.3	0.7 ; 1.5	0.7 ; 1.4	0.7 ; 1.6	0.7 ; 1.4
Min ; Max	0 ; 3	0 ; 2	0 ; 4	0 ; 4	0 ; 4
Baseline Total IgM (g/L) [n (%)]					
Number	39	37	41	41	158
<0.4	0	2 (5.4)	1 (2.4)	1 (2.4)	4 (2.5)
0.4-2.3	36 (92.3)	35 (94.6)	38 (92.7)	34 (82.9)	143 (90.5)
>2.3	3 (7.7)	0	2 (4.9)	6 (14.6)	11 (7.0)
Baseline IgG anti-IgE (Arbitrary U)					
Number	40	38	41	41	160

	Placebo (N=40)	Rilzabrutinib 400mg QPM (N=38)	Rilzabrutinib 400mg BID (N=41)	Rilzabrutinib 400mg TID (N=41)	All (N=160)
Mean (SD)	N/A	N/A	N/A	N/A	N/A
Median	5982.6	6983.4	6911.4	6230.8	6437.3
Q1 ; Q3	(3954.8; 9595.8)	(3807.8; 11618.6)	(5329.0; 10065.8)	(4608.6; 9534.6)	(4608.6; 10147.6)
Min ; Max	N/A	N/A	N/A	N/A	N/A
Baseline BHRA [n (%)]					
Number	40	36	41	41	158
BHRA+	5 (12.5)	4 (11.1)	7 (17.1)	6 (14.6)	22 (13.9)
BHRA-	35 (87.5)	32 (88.9)	34 (82.9)	35 (85.4)	136 (86.1)
Baseline IgG anti-FceRI (Arbitrary U)					
Number	40	38	41	41	160
Mean (SD)	312.3 (530.0)	931.6 (4512.2)	1591.8 (7225.6)	214.9 (298.3)	762.3 (4275.0)
Median	141.6	174.7	208.2	134.2	160.1
Q1 ; Q3	56.1 ; 308.9	53.7 ; 250.0	99.8 ; 425.0	46.4 ; 308.9	53.5 ; 317.6
Min ; Max	0 ; 2762	0 ; 27990	0 ; 46369	0 ; 1695	0 ; 46369
Baseline IgE anti-TPO (Arbitrary U)					
Number	40	38	41	41	160
Mean (SD)	2.7 (0.6)	2.9 (1.3)	2.7 (0.5)	2.8 (0.7)	2.8 (0.8)
Median	2.5	2.5	2.6	2.6	2.6
Q1 ; Q3	2.2 ; 3.2	2.4 ; 3.2	2.4 ; 2.9	2.2 ; 3.0	2.3 ; 3.1
Min ; Max	2 ; 4	2 ; 10	2 ; 4	2 ; 5	2 ; 10
Baseline IL-31					
Number	40	38	41	41	160
Median	4.0	4.1	5.0	4.2	4.2
Q1 ; Q3	(2.9; 5.3)	(3.2; 5.7)	(3.8; 8.4)	(3.3; 6.7)	(3.3; 6.4)
Baseline sMRGPRX2 (ng/mL)					
Number	40	38	41	41	160
Median	21.1	26.5	17.5	21.8	21.2
Q1 ; Q3	(13.1; 30.6)	(17.5; 33.6)	(10.4; 28.3)	(14.3; 30.3)	(13.6; 31.2)
Baseline IgG anti-TPO (IU)					
Number	40	38	40	41	159
Mean (SD)	18.7 (50.0)	35.4 (107.4)	47.7 (182.1)	36.1 (80.7)	34.5 (115.2)
Median	0.0	0.0	3.1	1.6	0.4
Q1 ; Q3	0.0 ; 6.8	0.0 ; 8.3	0.0 ; 9.7	0.0 ; 19.9	0.0 ; 10.3
Min ; Max	0 ; 205	0 ; 429	0 ; 1133	0 ; 338	0 ; 1133
Baseline H1-antihistamines dose [n (%)]					
Number	40	38	41	40	159
<1-fold	1 (2.5)	0	0	0	1 (0.6)
1-fold	22 (55.0)	21 (55.3)	16 (39.0)	24 (60.0)	83 (52.2)
2-fold to 3-fold	9 (22.5)	14 (36.8)	14 (34.1)	9 (22.5)	46 (28.9)
4-fold	8 (20.0)	3 (7.9)	11 (26.8)	7 (17.5)	29 (18.2)
Frequency of alcohol drinking in the past 12 months [n (%)]					
Number	40	38	41	41	160
Never	19 (47.5)	17 (44.7)	19 (46.3)	22 (53.7)	77 (48.1)
Occasional	16 (40.0)	15 (39.5)	18 (43.9)	16 (39.0)	65 (40.6)
At least monthly	1 (2.5)	0	2 (4.9)	0	3 (1.9)

	Placebo (N=40)	Rilzabrutinib 400mg QPM (N=38)	Rilzabrutinib 400mg BID (N=41)	Rilzabrutinib 400mg TID (N=41)	All (N=160)
At least weekly	2 (5.0)	5 (13.2)	1 (2.4)	2 (4.9)	10 (6.3)
At least daily	2 (5.0)	1 (2.6)	1 (2.4)	1 (2.4)	5 (3.1)
Number of drinks on a typical day of alcohol drinking in the past 12 months [n (%)]					
Number	21	21	22	19	83
1 to 3	21 (100)	21 (100)	21 (95.5)	19 (100)	82 (98.8)
>3	0	0	1 (4.5)	0	1 (1.2)

^a Derived as (Year of randomization - Year of first diagnosis of CSU) + (month of randomization-month of first diagnosis of CSU)/12

^b Defined as having a medical history of atopic dermatitis, allergic rhinitis, allergic conjunctivitis, asthma, food allergy, chronic rhinosinusitis, nasal polyps or eosinophilic esophagitis.

^c Participants with an AAS7 baseline score >0.

Note: A low score indicates good outcome for ISS7 (range 0-21), UAS7 (range 0-42), HSS7 (range 0-21), AAS7 (0-105), UCT (range 0-16), and PGIS (range 1-4).

UAS7

[00237] Treatment with rilzabrutinib yielded significant improvements in UAS7. In particular, patients receiving 400 mg TID rilzabrutinib saw a significant reduction in UAS7 at Week 12, thereby meeting the primary endpoint in the non-United States countries (see **Figures 2-4** and **Tables 13-16**). In the ITT population, participants receiving 400 mg TID rilzabrutinib showed a LS mean change from baseline at Week 12 of -17.95 (p=0.00116) points, while patients receiving the placebo showed a LS mean change of -11.20 from baseline to Week 12 (see **Table 13**). Consistent results were observed for omalizumab-naïve patients receiving 400 mg TID rilzabrutinib, both prior to (LS mean change of -16.89, p=0.0159; see **Table 14**) and following (LS mean reduction of -17.50, p=0.0079; see **Table 15**) the removal of a non-symptomatic outlier (UAS7/ISS7=0 at baseline) who was erroneously randomized into the 400 mg TID rilzabrutinib arm.

[00238] In the 400 mg TID arm, all patients except for one showed improvement in the weekly UAS7. Moreover, a clear separation was observed between patients receiving 400 mg TID rilzabrutinib and patients receiving the placebo across all response thresholds (see **Figure 4**).

[00239] Subgroup analysis of the omalizumab-naïve population further supports the efficacy of rilzabrutinib treatment in CSU (see **Table 16**). Overall, treatment with 400 mg TID rilzabrutinib was efficacious across subgroups, regardless of baseline demographic characteristics. Moreover, 400 mg TID rilzabrutinib treatment led to improvements in patients

with a low IgE concentration, positive BHRA status, history of angioedema, or characteristics of difficult-to-treat CSU.

Table 13. Supplementary Analysis: Change from Baseline in UAS7 at Week 12 (ITT Population)

UAS7	Placebo (N=40)	Rilzabrutinib 400mg QPM (N=38)	Rilzabrutinib 400mg BID (N=41)	Rilzabrutinib 400mg TID (N=41)
Baseline				
Number	40	38	41	41
Mean (SD)	29.97 (8.56)	31.37 (7.32)	30.21 (7.19)	29.88 (8.57)
Median	29.00	30.00	28.00	29.00
Q1 ; Q3	23.00 ; 37.50	27.00 ; 38.00	25.00 ; 35.00	25.00 ; 36.00
Min ; Max	16.0 ; 42.0	16.0 ; 42.0	18.0 ; 42.0	0.0 ; 42.0
Week 12				
Number (observed/imputed)	35 (33/2)	31 (28/3)	30 (27/3)	33 (30/3)
Mean (SD)	19.27 (13.49)	21.80 (10.94)	14.70 (14.29)	10.52 (10.26)
Median	17.50	22.40	12.00	9.00
Q1 ; Q3	7.00 ; 29.00	14.00 ; 28.00	0.00 ; 26.00	0.00 ; 16.80
Min ; Max	0.0 ; 42.0	0.0 ; 42.0	0.0 ; 42.0	0.0 ; 35.0
Change from baseline				
Number (observed/imputed)	35 (33/2)	31 (28/3)	30 (27/3)	33 (30/3)
Mean (SD)	-10.76 (13.99)	-11.04 (9.56)	-16.02 (13.29)	-20.30 (12.41)
Median	-8.00	-9.40	-13.50	-20.33
Q1 ; Q3	-21.00 ; -0.50	-17.50 ; -3.67	-27.00 ; -4.00	-31.00 ; -10.00
Min ; Max	-40.8 ; 20.5	-31.0 ; 3.3	-42.0 ; 1.0	-42.0 ; -1.0
LS Mean (SE) ^a	-11.20 (1.98)	-10.22 (2.01)	-14.82 (1.98)	-17.95 (1.95)
LS Mean Diff vs. placebo (95% CI) ^a		0.97 (-4.40, 6.34)	-3.62 (-8.87, 1.63)	-6.76 (-12.01, -1.51)
P-value vs. placebo ^a		0.7230	0.1763	0.0116

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

Note: Data collected after study intervention discontinuation were included. Data post selected prohibited/rescue medications (high/medium impact on efficacy confirmed through blinded medical review) were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF; other missing data were imputed by MI.

Descriptive statistics at Week 12 include participants with WOCF imputation at Week 12, and participants whose values were imputed by MI at Week 12 were excluded from the descriptive analysis.

Table 14. Primary Analysis: Change from Baseline in UAS7 at Week 12 (Omalizumab-Naïve Population)

UAS7	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Baseline				
Number	36	37	35	35
Mean (SD)	28.97 (8.39)	31.11 (7.24)	29.73 (7.11)	29.34 (8.08)
Median	28.00	30.00	28.00	28.00
Q1 ; Q3	22.00 ; 35.00	27.00 ; 38.00	24.50 ; 35.00	25.00 ; 35.00
Min ; Max	16.0 ; 42.0	16.0 ; 42.0	18.0 ; 42.0	0.0 ; 42.0
Week 12				
Number (observed/imputed)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)

UAS7	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Mean (SD)	19.32 (13.04)	22.00 (11.07)	15.61 (13.91)	11.00 (9.90)
Median	17.75	22.87	14.00	12.25
Q1 ; Q3	8.17 ; 28.50	14.00 ; 28.00	2.00 ; 26.00	1.00 ; 17.15
Min ; Max	0.0 ; 42.0	0.0 ; 42.0	0.0 ; 42.0	0.0 ; 35.0
Change from baseline				
Number (observed/imputed)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)
Mean (SD)	-9.71 (13.20)	-10.57 (9.36)	-14.49 (12.08)	-19.04 (11.40)
Median	-8.00	-8.70	-12.80	-18.92
Q1 ; Q3	-18.50 ; -0.50	-17.33 ; -3.67	-22.00 ; -4.00	-28.50 ; -8.75
Min ; Max	-35.0 ; 20.5	-31.0 ; 3.3	-40.8 ; 1.0	-42.0 ; -1.0
LS Mean (SE) ^a	-10.14 (2.05)	-9.74 (2.00)	-14.24 (2.06)	-16.89 (2.04)
LS Mean Diff vs. placebo (95% CI) ^a		0.40 (-5.08, 5.89)	-4.09 (-9.59, 1.40)	-6.75 (-12.23, -1.26)
P-value vs. placebo ^a		0.8856	0.1441	0.0159

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

Note: Data collected after study intervention discontinuation were included. Data post selected prohibited/rescue medications (high/medium impact on efficacy confirmed through blinded medical review) were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF; other missing data were imputed by MI.

Descriptive statistics at Week 12 include participants with WOCF imputation at Week 12, and participants whose values were imputed by MI at Week 12 were excluded from the descriptive analysis.

Table 15. Change from Baseline in UAS7 at Week 12 (Omalizumab-Naïve Population with Outlier Removed from Analysis)

UAS7	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=34)
Baseline				
Number	36	37	35	34
Mean (SD)	28.97 (8.39)	31.11 (7.24)	29.73 (7.11)	30.21 (6.36)
Median	28.00	30.00	28.00	28.50
Q1 ; Q3	22.00 ; 35.00	27.00 ; 38.00	24.50 ; 35.00	25.00 ; 35.00
Min ; Max	16.0 ; 42.0	16.0 ; 42.0	18.0 ; 42.0	17.0 ; 42.0
Week 12				
Number (observed/imputed)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)
Mean (SD)	19.32 (13.04)	22.00 (11.07)	15.61 (13.91)	11.00 (9.90)
Median	17.75	22.87	14.00	12.25
Q1 ; Q3	8.17 ; 28.50	14.00 ; 28.00	2.00 ; 26.00	1.00 ; 17.15
Min ; Max	0.0 ; 42.0	0.0 ; 42.0	0.0 ; 42.0	0.0 ; 35.0
Change from baseline				
Number (observed/imputed)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)
Mean (SD)	-9.71 (13.20)	-10.57 (9.36)	-14.49 (12.08)	-19.04 (11.40)
Median	-8.00	-8.70	-12.80	-18.92
Q1 ; Q3	-18.50 ; -0.50	-17.33 ; -3.67	-22.00 ; -4.00	-28.50 ; -8.75
Min ; Max	-35.0 ; 20.5	-31.0 ; 3.3	-40.8 ; 1.0	-42.0 ; -1.0
LS Mean (SE) ^a	-10.01 (2.01)	-9.93 (1.96)	-14.30 (2.06)	-17.50 (2.06)
LS Mean Diff vs. placebo (95% CI) ^a		0.08 (-5.29, 5.46)	-4.29 (-9.74, 1.16)	-7.50 (-13.02, -1.97)
P-value vs. placebo ^a		0.9759	0.1232	0.0079

^a Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group and region as covariates.

Table 16. Subgroup Analysis: Change from Baseline in UAS7 at Week 12 by Subgroups (Omalizumab-Naïve Population)

	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Age group (years)				
< 44 (Median)				
Number (observed/imputed)	21 (20/1)	16 (14/2)	12 (12/0)	8 (8/0)
Mean (SD)	-8.66 (13.45)	-10.45 (10.67)	-11.98 (9.69)	-18.69 (10.55)
LS Mean (SE) ^a	-8.39 (2.53)	-9.54 (2.74)	-13.80 (2.95)	-16.19 (3.68)
LS Mean Diff vs. placebo (95% CI) ^a		-1.15 (-8.58, 6.27)	-5.42 (-13.05, 2.21)	-7.80 (-16.46, 0.86)
P-value vs. placebo ^a		0.7607	0.1642	0.0775
≥ 44 (Median)				
Number (observed/imputed)	11 (11/0)	14 (13/1)	14 (12/2)	20 (19/1)
Mean (SD)	-11.71 (13.10)	-10.71 (7.99)	-16.63 (13.80)	-19.17 (11.98)
LS Mean (SE) ^a	-11.56 (3.28)	-8.84 (2.81)	-15.12 (2.72)	-17.54 (2.39)
LS Mean Diff vs. placebo (95% CI) ^a		2.72 (-5.76, 11.20)	-3.56 (-11.91, 4.80)	-5.98 (-13.92, 1.95)
P-value vs. placebo ^a		0.5296	0.4045	0.1393
Overall p-value for interaction ^b				0.9595
Age group (years)				
< 65				
Number (observed/imputed)	30 (29/1)	29 (26/3)	25 (23/2)	24 (23/1)
Mean (SD)	-10.62 (12.74)	-10.37 (9.46)	-13.91 (11.95)	-18.19 (11.00)
LS Mean (SE) ^a	-10.41 (2.02)	-9.12 (1.96)	-13.99 (2.04)	-16.30 (2.11)
LS Mean Diff vs. placebo (95% CI) ^a		1.30 (-4.27, 6.86)	-3.58 (-9.19, 2.03)	-5.88 (-11.58, -0.19)
P-value vs. placebo ^a		0.6475	0.2106	0.0430
≥ 65				
Number (observed/imputed)	2 (2/0)	1 (1/0)	1 (1/0)	4 (4/0)
Mean (SD)	4.00 (16.97)	-16.33 (NC)	-29.00 (NC)	-24.13 (14.17)
LS Mean (SE) ^a	1.46 (10.15)	-1.73 (17.36)	-21.85 (10.98)	-23.81 (7.07)
LS Mean Diff vs. placebo (95% CI) ^a		-3.19 (-44.28, 37.89)	-23.31 (-51.77, 5.15)	-25.27 (-49.57, -0.97)
P-value vs. placebo ^a		0.8790	0.1084	0.0416
Overall p-value for interaction ^b				0.2251
Gender				
Male				
Number (observed/imputed)	11 (11/0)	8 (8/0)	9 (8/1)	5 (5/0)
Mean (SD)	-6.91 (13.75)	-9.58 (10.13)	-16.87 (13.20)	-12.72 (5.65)
LS Mean (SE) ^a	-6.70 (3.52)	-8.84 (4.15)	-16.67 (3.54)	-11.21 (4.99)
LS Mean Diff vs. placebo (95% CI) ^a		-2.15 (-12.83, 8.54)	-9.97 (-19.70, -0.25)	-4.51 (-16.53, 7.51)
P-value vs. placebo ^a		0.6937	0.0445	0.4622
Female				
Number (observed/imputed)	21 (20/1)	22 (19/3)	17 (16/1)	23 (22/1)
Mean (SD)	-11.17 (12.99)	-10.93 (9.28)	-13.23 (11.66)	-20.41 (11.94)
LS Mean (SE) ^a	-11.39 (2.38)	-9.27 (2.22)	-12.97 (2.46)	-18.51 (2.16)
LS Mean Diff vs. placebo (95% CI) ^a		2.13 (-4.34, 8.59)	-1.57 (-8.27, 5.12)	-7.12 (-13.39, -0.85)
P-value vs. placebo ^a		0.5190	0.6450	0.0260

	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Overall p-value for interaction ^b				0.3631
Baseline weight (kg)				
< 72.9 (Median)				
Number (observed/imputed)	18 (18/0)	17 (16/1)	16 (15/1)	13 (13/0)
Mean (SD)	-11.18 (11.95)	-7.98 (7.20)	-12.97 (9.84)	-20.83 (13.25)
LS Mean (SE) ^a	-10.84 (2.51)	-7.76 (2.45)	-13.03 (2.58)	-18.62 (2.85)
LS Mean Diff vs. placebo (95% CI) ^a		3.08 (-3.85, 10.01)	-2.19 (-9.21, 4.84)	-7.78 (-15.19, -0.37)
P-value vs. placebo ^a		0.3833	0.5418	0.0397
≥ 72.9 (Median)				
Number (observed/imputed)	14 (13/1)	13 (11/2)	10 (9/1)	15 (14/1)
Mean (SD)	-7.82 (14.89)	-13.96 (10.98)	-16.91 (15.27)	-17.48 (9.72)
LS Mean (SE) ^a	-7.93 (3.02)	-11.30 (3.07)	-15.67 (3.01)	-16.27 (2.71)
LS Mean Diff vs. placebo (95% CI) ^a		-3.37 (-11.78, 5.05)	-7.75 (-16.17, 0.68)	-8.35 (-16.31, -0.38)
P-value vs. placebo ^a		0.4330	0.0715	0.0400
Overall p-value for interaction ^b				0.4144
Baseline weight (kg)				
< 60				
Number (observed/imputed)	10 (10/0)	6 (5/1)	7 (7/0)	8 (8/0)
Mean (SD)	-8.75 (11.17)	-7.82 (8.01)	-10.00 (9.76)	-19.50 (14.84)
LS Mean (SE) ^a	-8.01 (3.53)	-6.74 (4.50)	-11.36 (3.92)	-19.90 (4.01)
LS Mean Diff vs. placebo (95% CI) ^a		1.28 (-9.97, 12.52)	-3.35 (-13.61, 6.91)	-11.88 (-22.36, -1.40)
P-value vs. placebo ^a		0.8237	0.5222	0.0262
≥ 60 - <90				
Number (observed/imputed)	15 (14/1)	21 (19/2)	16 (14/2)	17 (17/0)
Mean (SD)	-10.84 (13.46)	-10.49 (9.74)	-15.04 (13.16)	-18.74 (10.60)
LS Mean (SE) ^a	-11.19 (2.81)	-9.11 (2.26)	-13.31 (2.65)	-15.74 (2.43)
LS Mean Diff vs. placebo (95% CI) ^a		2.08 (-5.04, 9.20)	-2.12 (-9.70, 5.46)	-4.55 (-11.84, 2.73)
P-value vs. placebo ^a		0.5666	0.5832	0.2205
> 90				
Number (observed/imputed)	7 (7/0)	3 (3/0)	3 (3/0)	3 (2/1)
Mean (SD)	-8.64 (16.85)	-16.67 (9.07)	-22.00 (9.00)	-19.44 (9.03)
LS Mean (SE) ^a	-8.78 (4.74)	-14.44 (7.38)	-20.74 (5.01)	-20.81 (7.30)
LS Mean Diff vs. placebo (95% CI) ^a		-5.66 (-22.88, 11.55)	-11.96 (-25.48, 1.56)	-12.03 (-29.07, 5.01)
P-value vs. placebo ^a		0.5190	0.0829	0.1663
Overall p-value for interaction ^b				0.7259
Baseline BMI (kg/m ²)				
< 25				
Number (observed/imputed)	15 (15/0)	14 (13/1)	17 (16/1)	11 (11/0)
Mean (SD)	-8.97 (10.73)	-7.00 (7.22)	-14.44 (11.30)	-17.02 (13.10)
LS Mean (SE) ^a	-8.65 (2.64)	-6.27 (2.66)	-14.48 (2.43)	-17.23 (3.19)
LS Mean Diff vs. placebo (95% CI) ^a		2.37 (-4.98, 9.73)	-5.83 (-12.83, 1.16)	-8.58 (-16.69, -0.47)

	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
P-value vs. placebo ^a		0.5266	0.1020	0.0381
≥ 25 - <30				
Number (observed/imputed)	9 (8/1)	7 (6/1)	5 (4/1)	13 (13/0)
Mean (SD)	-5.13 (16.32)	-10.92 (12.01)	-13.03 (16.22)	-19.44 (10.56)
LS Mean (SE) ^a	-9.33 (3.97)	-7.48 (3.95)	-11.34 (4.80)	-14.99 (2.89)
LS Mean Diff vs. placebo (95% CI) ^a		1.85 (-9.71, 13.42)	-2.01 (-14.35, 10.33)	-5.67 (-15.50, 4.16)
P-value vs. placebo ^a		0.7535	0.7493	0.2585
≥ 30				
Number (observed/imputed)	8 (8/0)	9 (8/1)	4 (4/0)	4 (3/1)
Mean (SD)	-16.25 (12.62)	-15.85 (8.40)	-16.50 (13.23)	-23.25 (10.60)
LS Mean (SE) ^a	-14.22 (4.23)	-14.65 (3.89)	-15.87 (4.21)	-21.80 (5.17)
LS Mean Diff vs. placebo (95% CI) ^a		-0.43 (-11.59, 10.72)	-1.65 (-13.49, 10.19)	-7.58 (-20.66, 5.50)
P-value vs. placebo ^a		0.9391	0.7849	0.2561
Overall p-value for interaction ^b				0.9352
Region ^c				
Asia				
Number (observed/imputed)	8 (8/0)	9 (9/0)	8 (8/0)	6 (6/0)
Mean (SD)	-7.46 (11.36)	-9.59 (9.91)	-11.25 (10.32)	-13.93 (11.07)
LS Mean (SE) ^a	-6.47 (3.67)	-9.00 (3.50)	-11.32 (3.76)	-14.25 (3.99)
LS Mean Diff vs. placebo (95% CI) ^a		-2.53 (-12.50, 7.44)	-4.86 (-15.18, 5.46)	-7.78 (-18.32, 2.76)
P-value vs. placebo ^a		0.6187	0.3562	0.1479
Latin America				
Number (observed/imputed)	11 (10/1)	10 (7/3)	8 (6/2)	6 (6/0)
Mean (SD)	-13.32 (15.08)	-13.28 (10.78)	-10.23 (11.81)	-14.07 (12.07)
LS Mean (SE) ^a	-11.88 (3.39)	-10.74 (3.14)	-9.26 (3.71)	-11.50 (4.23)
LS Mean Diff vs. placebo (95% CI) ^a		1.14 (-7.86, 10.15)	2.62 (-7.19, 12.43)	0.38 (-10.12, 10.88)
P-value vs. placebo ^a		0.8035	0.6003	0.9434
Eastern Europe				
Number (observed/imputed)	2 (2/0)	4 (4/0)	3 (3/0)	4 (4/0)
Mean (SD)	-10.00 (18.38)	-5.79 (5.45)	-20.14 (18.13)	-21.88 (11.40)
LS Mean (SE) ^a	-19.72 (8.80)	-5.35 (5.65)	-6.34 (10.64)	-25.97 (6.17)
LS Mean Diff vs. placebo (95% CI) ^a		14.37 (-6.40, 35.15)	13.37 (-19.79, 46.54)	-6.26 (-24.55, 12.03)
P-value vs. placebo ^a		0.1751	0.4292	0.5025
Western Countries				
Number (observed/imputed)	11 (11/0)	7 (7/0)	7 (7/0)	12 (11/1)
Mean (SD)	-7.68 (12.86)	-10.70 (8.61)	-20.62 (10.65)	-23.13 (10.61)
LS Mean (SE) ^a	-7.98 (3.38)	-8.74 (4.03)	-20.19 (3.23)	-19.49 (3.03)
LS Mean Diff vs. placebo (95% CI) ^a		-0.76 (-11.10, 9.58)	-12.21 (-21.37, - 3.06)	-11.51 (-20.42, - 2.61)
P-value vs. placebo ^a		0.8853	0.0090	0.0113
Overall p-value for interaction ^b				0.4154
Race				

	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
White				
Number (observed/imputed)	24 (23/1)	21 (18/3)	18 (16/2)	20 (19/1)
Mean (SD)	-10.46 (13.90)	-10.99 (9.33)	-15.92 (12.79)	-20.70 (11.84)
LS Mean (SE) ^a	-10.65 (2.36)	-9.37 (2.37)	-15.38 (2.37)	-17.97 (2.44)
LS Mean Diff vs. placebo (95% CI) ^a		1.28 (-5.33, 7.88)	-4.73 (-11.30, 1.84)	-7.33 (-13.95, 0.70)
P-value vs. placebo ^a		0.7052	0.1579	0.0303
All the Others				
Number (observed/imputed)	8 (8/0)	9 (9/0)	8 (8/0)	8 (8/0)
Mean (SD)	-7.46 (11.36)	-9.59 (9.91)	-11.25 (10.32)	-14.86 (9.62)
LS Mean (SE) ^a	-6.51 (3.58)	-8.43 (3.32)	-11.33 (3.66)	-14.94 (3.44)
LS Mean Diff vs. placebo (95% CI) ^a		-1.92 (-11.55, 7.72)	-4.82 (-14.87, 5.24)	-8.43 (-18.08, 1.23)
P-value vs. placebo ^a		0.6967	0.3477	0.0871
Overall p-value for interaction ^b				0.9692
Ethnicity				
Hispanic				
Number (observed/imputed)	10 (10/0)	12 (10/2)	8 (6/2)	8 (8/0)
Mean (SD)	-14.65 (15.20)	-10.26 (9.92)	-10.23 (11.81)	-15.49 (12.69)
LS Mean (SE) ^a	-12.54 (3.60)	-8.80 (2.97)	-10.31 (3.59)	-13.76 (3.78)
LS Mean Diff vs. placebo (95% CI) ^a		3.74 (-5.35, 12.83)	2.24 (-7.72, 12.19)	-1.22 (-11.34, 8.91)
P-value vs. placebo ^a		0.4198	0.6597	0.8139
Non-Hispanic				
Number (observed/imputed)	22 (21/1)	18 (17/1)	17 (17/0)	18 (17/1)
Mean (SD)	-7.46 (11.88)	-10.78 (9.25)	-16.52 (12.39)	-22.02 (10.28)
LS Mean (SE) ^a	-8.25 (2.37)	-9.79 (2.59)	-16.16 (2.46)	-19.24 (2.48)
LS Mean Diff vs. placebo (95% CI) ^a		-1.54 (-8.49, 5.41)	-7.92 (-14.63, -1.20)	-10.99 (-17.71, -4.28)
P-value vs. placebo ^a		0.6636	0.0209	0.0013
Overall p-value for interaction ^b				0.2878
History of angioedema				
Yes				
Number (observed/imputed)	15 (14/1)	11 (8/3)	8 (6/2)	9 (8/1)
Mean (SD)	-10.17 (12.72)	-13.08 (11.63)	-8.60 (9.01)	-16.58 (10.23)
LS Mean (SE) ^a	-9.67 (2.91)	-11.20 (2.97)	-11.58 (3.69)	-15.33 (3.68)
LS Mean Diff vs. placebo (95% CI) ^a		-1.53 (-9.72, 6.65)	-1.91 (-11.17, 7.35)	-5.66 (-14.82, 3.50)
P-value vs. placebo ^a		0.7135	0.6863	0.2255
No				
Number (observed/imputed)	17 (17/0)	19 (19/0)	18 (18/0)	19 (19/0)
Mean (SD)	-9.30 (13.98)	-9.12 (7.74)	-17.10 (12.56)	-20.20 (12.00)
LS Mean (SE) ^a	-9.88 (2.69)	-7.72 (2.58)	-15.01 (2.39)	-17.97 (2.40)
LS Mean Diff vs. placebo (95% CI) ^a		2.16 (-5.19, 9.52)	-5.13 (-12.18, 1.92)	-8.09 (-15.14, 1.03)
P-value vs. placebo ^a		0.5644	0.1538	0.0246
Overall p-value for interaction ^b				0.7199

	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Baseline UAS7 score				
< 28				
Number (observed/imputed)	12 (12/0)	6 (6/0)	11 (9/2)	11 (11/0)
Mean (SD)	-3.75 (12.65)	-8.39 (3.86)	-11.43 (8.06)	-13.43 (7.05)
LS Mean (SE) ^a	-4.40 (2.72)	-5.87 (3.45)	-8.89 (2.76)	-11.75 (2.89)
LS Mean Diff vs. placebo (95% CI) ^a		-1.46 (-10.06, 7.14)	-4.49 (-12.35, 3.38)	-7.34 (-15.21, 0.52)
P-value vs. placebo ^a		0.7388	0.2634	0.0670
≥ 28				
Number (observed/imputed)	20 (19/1)	24 (21/3)	15 (15/0)	17 (16/1)
Mean (SD)	-13.28 (12.47)	-11.12 (10.28)	-16.73 (14.20)	-22.66 (12.35)
LS Mean (SE) ^a	-13.11 (2.72)	-11.17 (2.39)	-17.23 (2.81)	-19.91 (2.64)
LS Mean Diff vs. placebo (95% CI) ^a		1.94 (-5.16, 9.03)	-4.13 (-11.78, 3.52)	-6.81 (-14.23, 0.62)
P-value vs. placebo ^a		0.5925	0.2903	0.0722
Overall p-value for interaction ^b				0.9282
Baseline ISS7 score				
< 13				
Number (observed/imputed)	10 (10/0)	2 (2/0)	6 (5/1)	2 (2/0)
Mean (SD)	-5.50 (12.18)	-5.83 (3.06)	-10.78 (8.33)	-10.75 (6.01)
LS Mean (SE) ^a	-4.91 (3.05)	-3.27 (5.21)	-9.30 (4.02)	-9.24 (6.48)
LS Mean Diff vs. placebo (95% CI) ^a		1.64 (-10.30, 13.58)	-4.39 (-14.52, 5.74)	-4.33 (-18.30, 9.63)
P-value vs. placebo ^a		0.7870	0.3954	0.5433
≥ 13				
Number (observed/imputed)	22 (21/1)	28 (25/3)	20 (19/1)	26 (25/1)
Mean (SD)	-11.62 (13.46)	-10.91 (9.59)	-15.60 (12.97)	-19.67 (11.53)
LS Mean (SE) ^a	-10.75 (2.45)	-10.47 (2.13)	-15.07 (2.33)	-18.70 (2.15)
LS Mean Diff vs. placebo (95% CI) ^a		0.28 (-6.08, 6.64)	-4.32 (-10.91, 2.27)	-7.95 (-14.32, 1.57)
P-value vs. placebo ^a		0.9304	0.1991	0.0145
Overall p-value for interaction ^b				0.8561
Duration of disease (years)				
< 2				
Number (observed/imputed)	14 (13/1)	10 (9/1)	14 (13/1)	12 (11/1)
Mean (SD)	-7.17 (10.41)	-12.50 (9.27)	-14.54 (10.00)	-19.20 (11.00)
LS Mean (SE) ^a	-7.07 (2.94)	-10.62 (3.36)	-16.30 (2.66)	-17.20 (3.03)
LS Mean Diff vs. placebo (95% CI) ^a		-3.55 (-12.28, 5.17)	-9.24 (-17.02, 1.46)	-10.14 (-18.42, 1.86)
P-value vs. placebo ^a		0.4248	0.0200	0.0164
2 - 10				
Number (observed/imputed)	15 (15/0)	16 (16/0)	11 (10/1)	12 (12/0)
Mean (SD)	-13.42 (14.67)	-10.83 (9.70)	-15.56 (14.75)	-17.51 (11.39)
LS Mean (SE) ^a	-12.83 (2.86)	-9.73 (2.58)	-12.88 (3.03)	-16.44 (3.07)
LS Mean Diff vs. placebo (95% CI) ^a		3.11 (-4.51, 10.72)	-0.05 (-8.24, 8.14)	-3.61 (-11.80, 4.58)
P-value vs. placebo ^a		0.4239	0.9909	0.3878
> 10				

	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Number (observed/imputed)	3 (3/0)	4 (2/2)	1 (1/0)	4 (4/0)
Mean (SD)	-3.00 (16.52)	-4.70 (7.74)	-1.83 (NC)	-23.13 (14.76)
LS Mean (SE) ^a	-5.92 (6.96)	-1.05 (6.12)	8.87 (12.67)	-18.73 (5.22)
LS Mean Diff vs. placebo (95% CI) ^a		4.87 (-13.68, 23.41)	14.79 (-14.26, 43.85)	-12.81 (-29.81, 4.20)
P-value vs. placebo ^a		0.6071	0.3183	0.1399
Overall p-value for interaction ^b				0.5067
Baseline H1-antihistamines dose				
1-fold				
Number (observed/imputed)	17 (17/0)	16 (14/2)	11 (10/1)	18 (17/1)
Mean (SD)	-12.60 (13.61)	-8.61 (9.50)	-18.22 (14.88)	-15.87 (11.07)
LS Mean (SE) ^a	-12.27 (2.76)	-7.64 (2.73)	-15.75 (3.11)	-14.92 (2.59)
LS Mean Diff vs. placebo (95% CI) ^a		4.64 (-2.96, 12.23)	-3.48 (-11.69, 4.73)	-2.65 (-10.05, 4.76)
P-value vs. placebo ^a		0.2316	0.4057	0.4837
2 to 4-fold standard dose				
Number (observed/imputed)	14 (13/1)	14 (13/1)	15 (14/1)	10 (10/0)
Mean (SD)	-6.32 (12.80)	-12.81 (9.00)	-11.75 (9.14)	-24.73 (10.10)
LS Mean (SE) ^a	-6.56 (2.90)	-10.93 (2.77)	-12.98 (2.55)	-20.96 (3.15)
LS Mean Diff vs. placebo (95% CI) ^a		-4.37 (-12.30, 3.56)	-6.42 (-13.94, 1.10)	-14.41 (-22.75, 6.07)
P-value vs. placebo ^a		0.2798	0.0942	0.0007
Overall p-value for interaction ^b				0.1610
Baseline Eosinophils (10 ⁹ /L)				
<0.150				
Number	16	N/A	11	14
Mean (SD)	N/A	N/A	N/A	N/A
LS Mean (SE)	-13.06 (2.87)	N/A	-13.60 (3.19)	-20.09 (3.11)
LS Mean Diff vs. placebo (95% CI)		N/A	-0.54 (-8.95, 7.87)	-7.04 (-15.34, 1.27)
P-value vs. placebo		N/A	N/A	N/A
≥0.150				
Number	16	N/A	15	14
Mean (SD)	N/A	N/A	N/A	N/A
LS Mean (SE)	-6.89 (2.77)	N/A	-14.57 (2.57)	-14.80 (2.58)
LS Mean Diff vs. placebo (95% CI)		N/A	-7.68 (-15.25, - 0.11)	-7.92 (-15.27, - 0.56)
P-value vs. placebo		N/A	N/A	N/A
Baseline Eosinophils (10 ⁹ /L)				
< 0.165 (Median)				
Number (observed/imputed)	17 (17/0)	16 (14/2)	13 (12/1)	14 (14/0)
Mean (SD)	-12.63 (13.99)	-9.46 (8.63)	-11.24 (8.98)	-21.57 (13.01)
LS Mean (SE) ^a	-12.47 (2.71)	-7.71 (2.71)	-14.30 (2.83)	-19.82 (2.96)
LS Mean Diff vs. placebo (95% CI) ^a		4.76 (-2.75, 12.26)	-1.83 (-9.50, 5.84)	-7.36 (-15.23, 0.52)
P-value vs. placebo ^a		0.2139	0.6397	0.0673
≥ 0.165 (Median)				
Number (observed/imputed)	15 (14/1)	14 (13/1)	13 (12/1)	14 (13/1)

	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Mean (SD)	-6.40 (11.83)	-11.84 (10.30)	-17.73 (14.16)	-16.50 (9.30)
LS Mean (SE) ^a	-7.12 (2.93)	-10.83 (2.83)	-14.13 (2.87)	-14.63 (2.71)
LS Mean Diff vs. placebo (95% CI) ^a		-3.71 (-11.80, 4.38)	-7.01 (-15.24, 1.22)	-7.52 (-15.32, 0.28)
P-value vs. placebo ^a		0.3686	0.0948	0.0590
Overall p-value for interaction ^b				0.3253
Baseline Eosinophils (10 ⁹ /L)				
< 0.3				
Number (observed/imputed)	29 (28/1)	25 (22/3)	20 (19/1)	23 (22/1)
Mean (SD)	-9.51 (13.70)	-10.75 (8.91)	-14.90 (12.30)	-19.99 (12.00)
LS Mean (SE) ^a	-10.16 (2.13)	-9.19 (2.15)	-15.05 (2.31)	-18.29 (2.31)
LS Mean Diff vs. placebo (95% CI) ^a		0.97 (-5.00, 6.93)	-4.89 (-11.04, 1.26)	-8.14 (-14.29, - 1.98)
P-value vs. placebo ^a		0.7505	0.1188	0.0096
≥ 0.3				
Number (observed/imputed)	3 (3/0)	5 (5/0)	6 (5/1)	5 (5/0)
Mean (SD)	-11.67 (8.14)	-9.69 (12.55)	-13.11 (12.32)	-14.65 (7.48)
LS Mean (SE) ^a	-7.66 (5.36)	-9.66 (4.84)	-11.06 (3.93)	-13.16 (4.09)
LS Mean Diff vs. placebo (95% CI) ^a		-2.00 (-16.22, 12.21)	-3.40 (-16.66, 9.86)	-5.51 (-18.58, 7.57)
P-value vs. placebo ^a		0.7820	0.6148	0.4085
Overall p-value for interaction ^b				0.9380
Baseline Total IgE (IU/mL)				
< 300				
Number (observed/imputed)	23 (22/1)	21 (18/3)	18 (16/2)	18 (18/0)
Mean (SD)	-7.80 (13.81)	-10.61 (9.62)	-15.35 (12.23)	-20.66 (12.39)
LS Mean (SE) ^a	-8.06 (2.36)	-9.07 (2.38)	-14.78 (2.46)	-18.19 (2.47)
LS Mean Diff vs. placebo (95% CI) ^a		-1.01 (-7.60, 5.59)	-6.72 (-13.41, - 0.03)	-10.13 (-16.83, - 3.44)
P-value vs. placebo ^a		0.7649	0.0490	0.0030
≥ 300				
Number (observed/imputed)	9 (9/0)	8 (8/0)	8 (8/0)	10 (9/1)
Mean (SD)	-14.59 (10.63)	-9.60 (9.52)	-12.53 (12.31)	-16.12 (9.22)
LS Mean (SE) ^a	-12.46 (3.64)	-8.04 (3.57)	-14.22 (3.59)	-14.94 (3.46)
LS Mean Diff vs. placebo (95% CI) ^a		4.42 (-5.58, 14.42)	-1.77 (-12.00, 8.47)	-2.48 (-12.37, 7.41)
P-value vs. placebo ^a		0.3860	0.7351	0.6230
Overall p-value for interaction ^b				0.5123
Baseline Total IgE (IU/mL)				
< 100				
Number (observed/imputed)	15 (14/1)	11 (10/1)	11 (10/1)	13 (13/0)
Mean (SD)	-6.59 (15.16)	-11.05 (9.70)	-16.26 (11.38)	-21.03 (13.37)
LS Mean (SE) ^a	-7.30 (3.09)	-8.49 (3.25)	-15.72 (3.24)	-17.40 (3.01)
LS Mean Diff vs. placebo (95% CI) ^a		-1.19 (-10.05, 7.67)	-8.43 (-17.18, 0.33)	-10.10 (-18.54, - 1.65)
P-value vs. placebo ^a		0.7926	0.0593	0.0191
≥ 100				

	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Number (observed/imputed)	17 (17/0)	18 (16/2)	15 (14/1)	15 (14/1)
Mean (SD)	-12.46 (10.92)	-9.90 (9.51)	-13.19 (12.80)	-17.31 (9.51)
LS Mean (SE) ^a	-11.51 (2.59)	-8.97 (2.49)	-13.17 (2.55)	-17.08 (2.69)
LS Mean Diff vs. placebo (95% CI) ^a		2.53 (-4.52, 9.59)	-1.67 (-8.84, 5.51)	-5.57 (-12.83, 1.69)
P-value vs. placebo ^a		0.4814	0.6486	0.1328
Overall p-value for interaction ^b				0.6477
Baseline BHRA				
BHRA+				
Number (observed/imputed)	3 (3/0)	3 (2/1)	6 (5/1)	4 (4/0)
Mean (SD)	-8.83 (8.78)	-19.94 (5.28)	-19.50 (10.03)	-22.13 (16.40)
LS Mean (SE) ^a	-9.49 (6.28)	-17.03 (6.45)	-19.58 (5.46)	-22.12 (5.72)
LS Mean Diff vs. placebo (95% CI) ^a		-7.53 (-24.53, 9.46)	-10.09 (-27.02, 6.84)	-12.63 (-29.25, 4.00)
P-value vs. placebo ^a		0.3849	0.2428	0.1365
BHRA-				
Number (observed/imputed)	29 (28/1)	26 (24/2)	20 (19/1)	24 (23/1)
Mean (SD)	-9.80 (13.68)	-9.96 (9.08)	-12.98 (12.46)	-18.52 (10.75)
LS Mean (SE) ^a	-9.97 (2.05)	-8.95 (2.08)	-12.39 (2.21)	-16.51 (2.11)
LS Mean Diff vs. placebo (95% CI) ^a		1.02 (-4.73, 6.78)	-2.42 (-8.35, 3.52)	-6.53 (-12.28, -0.79)
P-value vs. placebo ^a		0.7271	0.4247	0.0258
Overall p-value for interaction ^b				0.4945

^a Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value and intervention group as covariates. Analysis was based on the same imputed dataset using WOCF/MI from primary analysis of the primary endpoint.

^b Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value and intervention group as covariates, plus the subgroup variable and the subgroup-by-intervention interaction. Analysis was based on the same imputed dataset using WOCF/MI from primary analysis of the primary endpoint.

^c Asia: South Korea, Taiwan, Japan; Latin America: Argentina, Chile; Eastern Europe: Poland; Western Countries: Spain, Italy, Germany, Canada, Greece, Netherlands.

Note: Descriptive statistics include participants with WOCF imputation at Week 12 and participants whose Week 12 values were imputed by MI were excluded from the descriptive analysis.

[00240] Additionally, participants exhibited a rapid and sustained improvement in symptoms, with significant reductions in UAS7 observed following one week of treatment (see **Figures 5-8** and **Tables 17-20**). In the ITT population, participants receiving 400 mg BID rilzabrutinib had an LS mean change in UAS7 from baseline to Week 12 of -10.01 ($p=0.0024$; see **Table 18**). Consistent with rilzabrutinib's dose-dependent effect on UAS7, participants receiving 400 mg TID showed an LS mean change in UAS7 from baseline to Week 12 of -12.72 ($p<0.0001$), reflecting a 40.18% decrease from baseline. Notably, the overall reduction in UAS7 observed in both the 400 mg BID and TID arms exceeded the minimal clinically important difference (MCID) of 10 points.

[00241] Similar results were observed for the omalizumab-naïve population (see **Table 19**). Omalizumab-naïve participants in the 400 mg BID and TID rilzabrutinib arms experienced an LS mean reduction in UAS7 of -9.79 ($p=0.0040$) and -11.44 ($p=0.0003$) from baseline to Week 12, respectively. Similar data were obtained when these analyses were repeated following the removal of the asymptomatic outlier (see **Table 20**).

Table 17. Summary of UAS7 by Week in the Double-Blind Period (Omalizumab-Naïve Population and Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders)

UAS7	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
Baseline								
Number	36	37	35	35	4	1	6	6
Mean (SD)	28.97 (8.39)	31.11 (7.24)	29.73 (7.11)	29.34 (8.08)	38.96 (3.53)	41.00 (NC)	33.00 (7.67)	33.03 (11.40)
Median	28.00	30.00	28.00	28.00	39.92	41.00	35.00	38.00
Q1 ; Q3	22.00 ; 35.00	27.00 ; 38.00	24.50 ; 35.00	25.00 ; 35.00	36.50 ; 41.42	41.00 ; 41.00	27.00 ; 38.00	22.17 ; 42.00
Min ; Max	16.0 ; 42.0	16.0 ; 42.0	18.0 ; 42.0	0.0 ; 42.0	34.0 ; 42.0	41.0 ; 41.0	21.0 ; 42.0	16.0 ; 42.0
Week 1								
Number (observed/imputed)	36 (36/0)	37 (37/0)	35 (35/0)	35 (35/0)	4 (4/0)	1 (1/0)	6 (5/1)	6 (6/0)
Mean (SD)	25.80 (10.44)	23.81 (8.78)	19.77 (11.32)	17.77 (10.26)	31.50 (9.04)	25.00 (NC)	21.17 (12.48)	12.17 (8.54)
Median	27.00	25.00	21.00	18.00	31.50	25.00	23.50	12.00
Q1 ; Q3	21.50 ; 32.50	18.00 ; 29.00	10.00 ; 28.00	8.00 ; 27.00	24.50 ; 38.50	25.00 ; 25.00	14.00 ; 30.00	4.00 ; 16.00
Min ; Max	0.0 ; 42.0	5.0 ; 42.0	0.0 ; 42.0	0.0 ; 35.0	21.0 ; 42.0	25.0 ; 25.0	1.0 ; 35.0	3.0 ; 26.0
Change from baseline								
Number (observed/imputed)								
Mean (SD)	36 (36/0)	37 (37/0)	35 (35/0)	35 (35/0)	4 (4/0)	1 (1/0)	6 (5/1)	6 (6/0)
Median	-3.17 (8.91)	-7.30 (9.14)	-9.96 (8.81)	-11.57 (10.61)	-7.46 (7.56)	-16.00 (NC)	-11.83 (12.14)	-20.86 (9.80)
Q1 ; Q3	-0.50	-6.00	-9.00	-10.00	-5.92	-16.00	-7.50	-21.00
Min ; Max	-7.50 ; 1.50	-12.00 ; -1.00	-19.00 ; -4.00	-21.00 ; -3.00	-12.00 ; -2.92	-16.00 ; -16.00	-26.00 ; -2.00	-30.00 ; -13.00
	-30.0 ; 17.0	-35.0 ; 8.0	-29.0 ; 3.0	-36.0 ; 5.0	-18.0 ; 0.0	-16.0 ; -16.0	-28.0 ; 0.0	-32.0 ; -8.2
Percent change from baseline								
Number (observed/imputed)								
Mean (SD)	36 (36/0)	37 (37/0)	35 (35/0)	34 (34/0)	4 (4/0)	1 (1/0)	6 (5/1)	6 (6/0)
Median	-9.17 (34.38)	-21.72 (26.65)	-35.41 (33.69)	-38.05 (33.56)	-19.52 (19.33)	-39.02 (NC)	-35.59 (37.55)	-63.75 (22.12)
Q1 ; Q3	-1.56	-17.95	-26.19	-30.95	-15.97	-39.02	-20.53	-69.05
Min ; Max	-31.18 ; 4.70	-36.36 ; -3.33	-61.54 ; -13.79	-65.63 ; -13.79	-31.90 ; -7.14	-39.02 ; -39.02	-66.67 ; -9.52	-81.25 ; -38.10
	-100.0 ; 70.8	-87.5 ; 27.6	-100.0 ; 12.0	-94.4 ; 17.9	-46.2 ; 0.0	-39.0 ; -39.0	-96.3 ; 0.0	-88.2 ; -36.8
Week 2								
Number (observed/imputed)								
Mean (SD)	35 (35/0)	37 (37/0)	34 (34/0)	35 (35/0)	4 (4/0)	1 (1/0)	6 (5/1)	6 (6/0)
Median	23.49 (10.05)	23.44 (8.97)	19.59 (10.86)	15.65 (10.66)	27.29 (15.37)	22.00 (NC)	19.00 (13.67)	8.33 (9.77)
Q1 ; Q3	25.00	23.00	18.10	14.00	29.58	22.00	23.00	5.50
Min ; Max	18.00 ; 29.00	20.00 ; 29.00	11.00 ; 28.00	7.00 ; 22.40	15.08 ; 39.50	22.00 ; 22.00	5.00 ; 28.00	0.00 ; 14.00
	0.0 ; 42.0	6.0 ; 42.0	0.0 ; 42.0	0.0 ; 38.0	8.0 ; 42.0	22.0 ; 22.0	0.0 ; 35.0	0.0 ; 25.0
Change from baseline								

UAS7	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
Week 3	Number (observed/imputed)	35 (35/0)	37 (37/0)	34 (34/0)	35 (35/0)	4 (4/0)	1 (1/0)	6 (6/0)
	Mean (SD)	-5.11 (9.01)	-7.67 (8.84)	-10.10 (8.61)	-13.69 (11.66)	-11.67 (13.80)	-19.00 (NC)	-14.00 (14.98)
	Median	-3.00	-5.00	-10.00	-11.00	-7.83	-19.00	-10.00
	Q1 ; Q3	-8.00 ; 0.00	-13.00 ; 0.00	-14.00 ; -2.00	-23.00 ; -5.60	-21.42 ; -1.92	-19.00 ; -19.00	-27.00 ; 0.00
	Min ; Max	-32.0 ; 12.0	-32.0 ; 2.5	-31.0 ; 3.0	-35.0 ; 7.0	-31.0 ; 0.0	-19.0 ; -19.0	-37.0 ; 0.0
	Percent change from baseline							
	Number (observed/imputed)	35 (35/0)	37 (37/0)	34 (34/0)	34 (34/0)	4 (4/0)	1 (1/0)	6 (5/1)
	Mean (SD)	-16.27 (32.44)	-23.23 (26.34)	-35.50 (31.03)	-45.70 (36.18)	-30.92 (35.56)	-46.34 (NC)	-40.50 (43.43)
	Median	-9.38	-16.67	-35.71	-46.67	-22.10	-46.34	-27.44
	Q1 ; Q3	-30.95 ; 0.00	-39.39 ; 0.00	-50.00 ; -11.11	-80.56 ; -21.08	-57.15 ; -4.69	-46.34 ; -46.34	-88.10 ; 0.00
Min ; Max	-100.0 ; 50.0	-80.6 ; 9.1	-100.0 ; 13.3	-100.0 ; 25.0	-79.5 ; 0.0	-46.3 ; -46.3	-100.0 ; 0.0	
Week 4	Number (observed/imputed)	35 (35/0)	37 (37/0)	35 (35/0)	35 (35/0)	4 (4/0)	1 (1/0)	6 (6/0)
	Mean (SD)	22.60 (10.89)	22.01 (9.00)	17.71 (11.91)	15.37 (9.87)	23.30 (14.48)	19.00 (NC)	17.19 (13.86)
	Median	23.00	22.00	16.80	14.00	26.43	19.00	18.58
	Q1 ; Q3	17.50 ; 30.00	15.00 ; 28.00	10.00 ; 25.00	7.00 ; 21.00	14.63 ; 31.97	19.00 ; 19.00	3.00 ; 28.00
	Min ; Max	0.0 ; 42.0	5.0 ; 42.0	0.0 ; 42.0	0.0 ; 35.0	3.0 ; 37.3	19.0 ; 19.0	0.0 ; 35.0
	Change from baseline							
	Number (observed/imputed)	35 (35/0)	37 (37/0)	35 (35/0)	35 (35/0)	4 (4/0)	1 (1/0)	6 (5/1)
	Mean (SD)	-6.00 (9.80)	-9.10 (8.78)	-12.02 (10.63)	-13.97 (12.14)	-15.66 (14.49)	-22.00 (NC)	-15.81 (16.39)
	Median	-3.00	-7.00	-9.00	-14.00	-11.58	-22.00	-15.00
	Q1 ; Q3	-12.00 ; 0.00	-15.33 ; -2.00	-21.20 ; -2.00	-23.00 ; -7.00	-25.88 ; -5.45	-22.00 ; -22.00	-24.00 ; 0.00
Min ; Max	-33.0 ; 7.0	-27.0 ; 2.0	-39.0 ; 1.0	-35.0 ; 21.0	-36.0 ; -3.5	-22.0 ; -22.0	-42.0 ; 1.2	
Week 4	Number (observed/imputed)	35 (35/0)	37 (37/0)	35 (35/0)	34 (34/0)	4 (4/0)	1 (1/0)	6 (6/0)
	Mean (SD)	-19.11 (37.23)	-28.09 (25.63)	-41.11 (35.05)	-48.87 (33.07)	-40.04 (36.80)	-53.66 (NC)	-44.47 (44.78)
	Median	-9.00	-26.67	-32.14	-48.08	-29.63	-53.66	-41.73
	Q1 ; Q3	-36.67 ; 0.00	-46.15 ; -9.09	-69.05 ; -8.00	-76.67 ; -25.00	-64.90 ; -15.17	-53.66 ; -53.66	-88.89 ; 0.00
	Min ; Max	-100.0 ; 43.8	-82.8 ; 10.0	-100.0 ; 5.6	-100.0 ; 28.0	-92.3 ; -8.6	-53.7 ; -53.7	-100.0 ; 5.6
	Percent change from baseline							
	Number (observed/imputed)	35 (35/0)	37 (37/0)	35 (35/0)	34 (34/0)	4 (4/0)	1 (1/0)	6 (5/1)
	Mean (SD)	-19.11 (37.23)	-28.09 (25.63)	-41.11 (35.05)	-48.87 (33.07)	-40.04 (36.80)	-53.66 (NC)	-44.47 (44.78)
	Median	-9.00	-26.67	-32.14	-48.08	-29.63	-53.66	-41.73
	Q1 ; Q3	-36.67 ; 0.00	-46.15 ; -9.09	-69.05 ; -8.00	-76.67 ; -25.00	-64.90 ; -15.17	-53.66 ; -53.66	-88.89 ; 0.00
Min ; Max	-100.0 ; 43.8	-82.8 ; 10.0	-100.0 ; 5.6	-100.0 ; 28.0	-92.3 ; -8.6	-53.7 ; -53.7	-100.0 ; 5.6	
Week 4	Number (observed/imputed)	34 (34/0)	37 (36/1)	33 (33/0)	32 (32/0)	4 (4/0)	1 (1/0)	5 (4/1)
								6 (6/0)

UAS7	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Change from baseline								
Number (observed/imputed)								
Mean (SD)	22.09 (12.20)	21.92 (8.82)	15.92 (11.71)	14.65 (9.61)	19.83 (10.96)	18.00 (NC)	13.60 (16.55)	10.08 (10.62)
Median	23.50	21.00	14.00	14.00	20.65	18.00	3.00	8.58
Q1 ; Q3	14.00 ; 29.00	17.00 ; 28.00	6.00 ; 22.17	8.50 ; 19.00	11.75 ; 27.90	18.00 ; 18.00	1.00 ; 28.00	2.33 ; 11.00
Min ; Max	0.0 ; 42.0	2.0 ; 42.0	0.0 ; 42.0	0.0 ; 38.0	6.0 ; 32.0	18.0 ; 18.0	1.0 ; 35.0	0.0 ; 30.0
Percent change from baseline								
Number (observed/imputed)								
Mean (SD)	34 (34/0)	37 (36/1)	33 (33/0)	32 (32/0)	4 (4/0)	1 (1/0)	5 (4/1)	6 (6/0)
Median	-6.64 (11.17)	-9.18 (9.24)	-13.49 (10.97)	-15.51 (9.79)	-19.13 (10.10)	-23.00 (NC)	-21.80 (16.62)	-22.94 (13.84)
Q1 ; Q3	-3.42	-7.00	-11.00	-14.00	-17.35	-23.00	-26.00	-22.50
Min ; Max	-14.00 ; 0.00	-14.00 ; -1.00	-22.50 ; -5.00	-22.50 ; -8.50	-25.60 ; -12.67	-23.00 ; -23.00	-10.00 ; -31.67	-12.00 ; -42.0 ; -7.0
Percent change from baseline								
Number (observed/imputed)								
Mean (SD)	34 (34/0)	37 (36/1)	33 (33/0)	32 (32/0)	4 (4/0)	1 (1/0)	5 (4/1)	6 (6/0)
Median	-21.54 (41.63)	-27.91 (26.53)	-46.55 (35.69)	-51.19 (29.70)	-49.53 (26.13)	-56.10 (NC)	-62.33 (45.90)	-67.07 (27.75)
Q1 ; Q3	-13.83	-21.88	-41.94	-51.09	-45.93	-56.10	-91.43	-68.48
Min ; Max	-55.56 ; 0.00	-48.39 ; -4.55	-76.92 ; -18.52	-73.39 ; -30.70	-66.57 ; -32.48	-56.10 ; -56.10	-26.32 ; -93.14	-43.75 ; -100.0 ; -28.6
Percent change from baseline								
Number (observed/imputed)								
Mean (SD)	33 (33/0)	36 (35/1)	34 (33/1)	33 (33/0)	4 (4/0)	1 (1/0)	4 (3/1)	6 (5/1)
Median	18.31 (9.22)	20.63 (9.18)	17.22 (13.36)	13.41 (10.60)	27.52 (11.12)	19.00 (NC)	9.75 (16.94)	8.92 (10.94)
Q1 ; Q3	16.33	18.63	16.50	14.00	28.38	19.00	2.00	5.50
Min ; Max	12.00 ; 24.50	15.28 ; 27.50	5.00 ; 24.00	5.00 ; 19.83	18.00 ; 37.04	19.00 ; 19.00	0.00 ; 19.50	2.00 ; 10.50
Percent change from baseline								
Number (observed/imputed)								
Mean (SD)	33 (33/0)	36 (35/1)	34 (33/1)	33 (33/0)	4 (4/0)	1 (1/0)	4 (3/1)	6 (5/1)
Median	-10.66 (8.95)	-10.65 (9.52)	-12.56 (11.55)	-16.74 (11.67)	-11.44 (8.17)	-22.00 (NC)	-25.00 (18.42)	-24.11 (14.81)
Q1 ; Q3	-10.00	-8.50	-12.67	-15.17	-11.33	-22.00	-29.00	-20.50
Min ; Max	-17.00 ; -4.00	-15.33 ; -2.88	-21.67 ; -2.00	-24.00 ; -9.00	-18.50 ; -4.38	-22.00 ; -22.00	-38.50 ; -11.50	-40.00 ; -11.67 ; -10.0
Percent change from baseline								
Number (observed/imputed)								
Mean (SD)	33 (33/0)	36 (35/1)	34 (33/1)	33 (33/0)	4 (4/0)	1 (1/0)	4 (3/1)	6 (5/1)
Median	-35.69 (29.51)	-32.46 (26.63)	-44.07 (39.75)	-54.42 (33.80)	-30.69 (23.32)	-53.66 (NC)	-71.30 (48.04)	-70.71 (27.72)
Q1 ; Q3	-40.48	-27.86	-40.89	-50.00	-29.91	-53.66	-92.59	-73.90
Min ; Max	-40.48	-27.86	-40.89	-50.00	-29.91	-53.66	-92.59	-73.90

UAS7	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)		Rilzabrutinib 400mg QPM (N=37)		Rilzabrutinib 400mg BID (N=35)		Rilzabrutinib 400mg QPM (N=1)	
	Rilzabrutinib 400mg QPM (N=36)	Rilzabrutinib 400mg BID (N=37)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
Q1 ; Q3	-50.00 ; -13.89	-48.70 ; -12.02	-80.56 ; -7.69	-82.14 ; -30.30	-50.83 ; -10.56	-53.66 ; -53.7	-100.00 ; -42.59	-95.24 ; -52.63
Min ; Max	-100.0 ; 43.8	-100.0 ; 2.4	-100.0 ; 44.8	-100.0 ; 8.3	-52.9 ; -10.0	-53.7 ; -53.7	-100.0 ; 0.0	-100.0 ; -28.6
Week 6								
Number (observed/imputed)	32 (31/1)	34 (33/1)	34 (33/1)	31 (31/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (5/1)
Mean (SD)	19.67 (10.97)	20.21 (10.42)	17.02 (12.76)	14.10 (11.23)	27.25 (11.24)	17.00 (NC)	13.03 (15.45)	7.00 (11.49)
Median	21.00	18.25	16.50	14.00	26.00	17.00	5.83	3.00
Q1 ; Q3	10.50 ; 28.00	14.00 ; 28.00	4.00 ; 26.83	4.67 ; 21.00	19.50 ; 35.00	17.00 ; 17.00	1.00 ; 23.33	0.00 ; 6.00
Min ; Max	0.0 ; 42.0	0.0 ; 42.0	0.0 ; 42.0	0.0 ; 40.0	15.0 ; 42.0	17.0 ; 17.0	0.0 ; 35.0	0.0 ; 30.0
Change from baseline								
Number (observed/imputed)	32 (31/1)	34 (33/1)	34 (33/1)	31 (31/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (5/1)
Mean (SD)	-9.36 (11.33)	-11.79 (10.56)	-12.76 (11.42)	-15.94 (12.03)	-11.71 (8.21)	-24.00 (NC)	-18.97 (18.81)	-26.03 (14.05)
Median	-7.50	-9.00	-11.08	-15.00	-13.92	-24.00	-26.00	-26.58
Q1 ; Q3	-14.40 ; -0.25	-22.67 ; -2.67	-24.00 ; -2.00	-27.00 ; -4.83	-17.00 ; -6.42	-24.00 ; -24.00	-35.00 ; 0.00	-39.00 ; -12.00
Min ; Max	-40.0 ; 12.0	-31.0 ; 3.3	-32.0 ; 3.0	-37.0 ; 3.5	-19.0 ; 0.0	-24.0 ; -24.0	-36.2 ; 2.3	-42.0 ; -10.0
Percent change from baseline								
Number (observed/imputed)	32 (31/1)	34 (33/1)	34 (33/1)	31 (31/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (5/1)
Mean (SD)	-29.60 (39.51)	-35.97 (30.17)	-43.89 (39.18)	-52.07 (35.76)	-31.44 (23.35)	-58.54 (NC)	-54.26 (54.98)	-78.40 (28.08)
Median	-26.59	-37.30	-38.06	-47.83	-34.95	-58.54	-86.11	-89.66
Q1 ; Q3	-56.07 ; -1.39	-58.12 ; -10.00	-83.33 ; -8.33	-81.33 ; -17.90	-47.17 ; -15.71	-58.54 ; -58.54	-96.30 ; 0.00	-100.00 ; -62.50
Min ; Max	-100.0 ; 75.0	-100.0 ; 10.0	-100.0 ; 13.3	-100.0 ; 12.5	-55.9 ; 0.0	-58.5 ; -58.5	-100.0 ; 11.1	-100.0 ; -28.6
Week 7								
Number (observed/imputed)	33 (32/1)	33 (31/2)	34 (33/1)	30 (30/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (5/1)
Mean (SD)	19.78 (10.84)	21.11 (10.03)	15.55 (11.97)	13.54 (9.34)	30.35 (10.52)	17.00 (NC)	11.60 (15.79)	12.17 (10.21)
Median	21.00	18.20	14.88	14.00	31.30	17.00	2.00	11.50
Q1 ; Q3	11.20 ; 28.00	14.00 ; 28.00	5.60 ; 26.00	6.00 ; 18.67	22.90 ; 37.80	17.00 ; 17.00	0.00 ; 21.00	6.00 ; 14.00
Min ; Max	0.0 ; 42.0	0.0 ; 42.0	0.0 ; 42.0	0.0 ; 36.0	16.8 ; 42.0	17.0 ; 17.0	0.0 ; 35.0	0.0 ; 30.0
Change from baseline								
Number (observed/imputed)	33 (32/1)	33 (31/2)	34 (33/1)	30 (30/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (5/1)
Mean (SD)	-9.19 (10.67)	-10.92 (10.06)	-14.03 (11.20)	-16.56 (10.48)	-8.61 (7.11)	-24.00 (NC)	-20.40 (19.58)	-20.86 (14.89)
Median	-7.00	-9.00	-12.75	-15.00	-8.62	-24.00	-25.00	-16.00

UAS7	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
Q1 ; Q3	-14.00 ; -2.50	-21.00 ; -3.00	-22.00 ; -4.00	-23.00 ; -9.00	-13.60 ; -3.62	-24.00 ; -24.00	-35.00 ; 0.00	-36.00 ; -8.17
Min ; Max	-40.0 ; 12.0	-29.0 ; 3.3	-39.0 ; 2.0	-36.0 ; 3.5	-17.2 ; 0.0	-24.0 ; -24.0	-42.0 ; 0.0	-42.0 ; -7.0
Percent change from baseline								
Number (observed/imputed)	33 (32/1)	33 (31/2)	34 (33/1)	30 (30/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (5/1)
Mean (SD)	-29.76 (37.90)	-33.33 (28.49)	-48.14 (36.14)	-54.22 (30.59)	-23.49 (21.01)	-58.54 (NC)	-58.52 (53.51)	-58.95 (28.44)
Median	-21.88	-36.11	-48.28	-52.50	-21.68	-58.54	-92.59	-51.29
Q1 ; Q3	-55.00 ; -10.00	-57.14 ; -7.89	-81.58 ; -22.22	-76.00 ; -28.21	-38.11 ; -8.86	-58.54 ; -100.00	0.00 ; 0.00	-85.71 ; -36.84
Min ; Max	-100.0 ; 75.0	-100.0 ; 8.8	-100.0 ; 6.9	-100.0 ; 12.5	-50.6 ; 0.0	-58.5 ; -58.5	-100.0 ; 0.0	-100.0 ; -28.6
Week 8								
Number (observed/imputed)	33 (32/1)	33 (30/3)	33 (32/1)	28 (28/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (5/1)
Mean (SD)	19.31 (11.99)	21.16 (10.52)	13.98 (13.06)	13.36 (9.81)	23.52 (13.09)	16.00 (NC)	11.00 (15.67)	7.50 (11.26)
Median	18.00	21.00	10.00	14.00	20.20	16.00	1.00	3.00
Q1 ; Q3	10.50 ; 29.40	14.00 ; 28.00	4.00 ; 22.00	4.00 ; 19.13	14.83 ; 32.20	16.00 ; 16.00	0.00 ; 19.00	2.00 ; 7.00
Min ; Max	0.0 ; 42.0	0.0 ; 42.0	0.0 ; 42.0	0.0 ; 35.0	11.7 ; 42.0	16.0 ; 16.0	0.0 ; 35.0	0.0 ; 30.0
Change from baseline								
Number (observed/imputed)	33 (32/1)	33 (30/3)	33 (32/1)	28 (28/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (5/1)
Mean (SD)	-9.66 (11.77)	-10.63 (9.70)	-15.64 (11.76)	-16.89 (10.13)	-15.44 (10.42)	-25.00 (NC)	-21.00 (19.13)	-25.53 (12.52)
Median	-7.00	-10.80	-16.00	-15.17	-19.72	-25.00	-26.00	-25.58
Q1 ; Q3	-18.00 ; -0.50	-17.33 ; -2.00	-24.00 ; -5.00	-23.00 ; -10.00	-21.67 ; -9.22	-25.00 ; -25.00	-35.00 ; -2.00	-35.00 ; -13.00
Min ; Max	-37.0 ; 11.4	-31.0 ; 3.3	-42.0 ; 4.0	-37.0 ; 1.0	-22.3 ; 0.0	-25.0 ; -25.0	-42.0 ; 0.0	-42.0 ; -12.0
Percent change from baseline								
Number (observed/imputed)	33 (32/1)	33 (30/3)	33 (32/1)	28 (28/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (5/1)
Mean (SD)	-32.03 (39.69)	-33.68 (30.26)	-54.37 (38.23)	-55.66 (31.25)	-41.17 (28.71)	-60.98 (NC)	-61.16 (51.62)	-78.96 (25.66)
Median	-23.81	-31.82	-64.29	-55.83	-49.49	-60.98	-96.30	-84.90
Q1 ; Q3	-57.58 ; -1.28	-54.17 ; -6.25	-89.47 ; -15.38	-82.48 ; -35.91	-59.77 ; -22.57	-60.98 ; -100.00	-9.52 ; -94.12	-81.25
Min ; Max	-100.0 ; 63.3	-100.0 ; 8.8	-100.0 ; 16.0	-100.0 ; 5.9	-65.7 ; 0.0	-61.0 ; -61.0	-100.0 ; 0.0	-100.0 ; -28.6
Week 9								
Number (observed/imputed)	32 (31/1)	34 (31/3)	29 (28/1)	29 (29/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (5/1)
Mean (SD)	20.65 (11.21)	20.25 (10.25)	14.64 (14.43)	12.57 (9.72)	21.35 (13.88)	18.00 (NC)	11.17 (15.78)	7.89 (11.07)
Median	20.00	19.33	11.00	12.00	15.40	18.00	1.00	4.00
Q1 ; Q3	14.00 ; 28.00	14.00 ; 26.83	2.33 ; 22.00	4.00 ; 18.00	13.30 ; 29.40	18.00 ; 18.00	0.00 ; 19.83	2.33 ; 7.00
Min ; Max	0.0 ; 42.0	0.0 ; 42.0	0.0 ; 42.0	0.0 ; 35.0	12.6 ; 42.0	18.0 ; 18.0	0.0 ; 35.0	0.0 ; 30.0

UAS7	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)		Rilzabrutinib 400mg BID (N=35)		Placebo (N=4)		Rilzabrutinib 400mg QPM (N=1)	
	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)	Rilzabrutinib 400mg TID (N=6)
Change from baseline								
Number (observed/imputed)								
Mean (SD)	32 (31/1)	34 (31/3)	29 (28/1)	29 (29/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (5/1)
Median	-8.35 (11.00)	-11.75 (9.99)	-14.51 (11.46)	-17.88 (11.04)	-17.61 (12.62)	-23.00 (NC)	-20.83 (19.15)	-25.14 (12.48)
Q1 ; Q3	-7.00	-11.00	-17.00	-17.00	-21.10	-23.00	-27.00	-24.92
Min ; Max	-14.00 ; -0.25	-17.00 ; -5.00	-22.00 ; -4.00	-25.00 ; -10.00	-26.62 ; -8.60	-23.00 ; -23.00	-35.00 ; -1.17	-35.00 ; -12.00
	-35.0 ; 13.7	-38.0 ; 3.3	-35.7 ; 6.0	-39.0 ; 4.0	-28.2 ; 0.0	-23.0 ; -23.0	-41.0 ; 0.0	-42.0 ; -12.0
Percent change from baseline								
Number (observed/imputed)								
Mean (SD)	32 (31/1)	34 (31/3)	29 (28/1)	29 (29/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (5/1)
Median	-26.90 (38.08)	-36.26 (27.83)	-53.27 (40.38)	-57.42 (32.58)	-45.96 (31.62)	-56.10 (NC)	-60.63 (52.86)	-77.44 (25.29)
Q1 ; Q3	-22.88	-32.58	-59.77	-60.00	-57.35	-56.10	-97.62	-85.78
Min ; Max	-49.07 ; -1.39	-51.72 ; -16.67	-91.67 ; -15.38	-82.14 ; -35.71	-66.62 ; -25.29	-56.10 ; -56.10	-100.00 ; -5.56	-89.47 ; -75.00
	-100.0 ; 56.3	-100.0 ; 8.8	-100.0 ; 24.0	-100.0 ; 23.5	-69.1 ; 0.0	-56.1 ; -56.1	-100.0 ; 0.0	-100.0 ; -28.6
Week 10								
Number (observed/imputed)								
Mean (SD)	33 (32/1)	34 (31/3)	28 (27/1)	30 (30/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (4/2)
Median	19.73 (12.24)	20.27 (10.69)	15.22 (14.36)	12.61 (9.89)	16.78 (17.90)	16.00 (NC)	12.60 (14.98)	7.83 (11.43)
Q1 ; Q3	19.83	17.00	13.50	12.83	11.40	16.00	4.00	4.00
Min ; Max	10.50 ; 28.00	14.00 ; 28.00	0.00 ; 23.50	4.00 ; 17.50	4.17 ; 29.40	16.00 ; 16.00	3.00 ; 21.00	0.00 ; 9.00
	0.0 ; 42.0	0.0 ; 42.0	0.0 ; 42.0	0.0 ; 35.0	2.3 ; 42.0	16.0 ; 16.0	0.0 ; 35.0	0.0 ; 30.0
Change from baseline								
Number (observed/imputed)								
Mean (SD)	33 (32/1)	34 (31/3)	28 (27/1)	30 (30/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (4/2)
Median	-9.24 (11.57)	-11.73 (10.20)	-14.01 (11.59)	-17.75 (10.50)	-22.18 (17.32)	-25.00 (NC)	-19.40 (18.66)	-25.19 (15.27)
Q1 ; Q3	-8.00	-10.00	-14.50	-20.00	-25.10	-25.00	-23.00	-25.08
Min ; Max	-16.33 ; 0.00	-18.50 ; -3.00	-24.00 ; -4.50	-23.00 ; -10.00	-35.75 ; -8.60	-25.00 ; -25.00	-35.00 ; 0.00	-40.00 ; -12.00
	-35.0 ; 14.0	-34.0 ; 3.3	-32.0 ; 8.0	-37.0 ; 0.5	-38.5 ; 0.0	-25.0 ; -25.0	-39.0 ; 0.0	-42.0 ; -7.0
Percent change from baseline								
Number (observed/imputed)								
Mean (SD)	33 (32/1)	34 (31/3)	28 (27/1)	30 (30/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (4/2)
Median	-30.98 (42.20)	-36.15 (29.79)	-50.88 (41.19)	-58.08 (31.82)	-57.37 (42.59)	-60.98 (NC)	-55.61 (51.03)	-73.42 (30.92)
Q1 ; Q3	-33.33	-36.70	-51.79	-59.49	-67.60	-60.98	-85.19	-84.09
Min ; Max	-53.33 ; 0.00	-62.07 ; -10.34	-100.00 ; -	-84.00 ; -28.00	-89.45 ; -25.29	-60.98 ; -60.98	-92.86 ; 0.00	-100.00 ; -43.75
	-100.0 ; 56.3	-100.0 ; 10.0	-100.0 ; 32.0	-100.0 ; 2.9	-94.3 ; 0.0	-61.0 ; -61.0	-100.0 ; 0.0	-100.0 ; -28.6

UAS7	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
Week 11								
Number (observed/imputed)								
Mean (SD)	33 (32/1)	33 (30/3)	29 (28/1)	31 (31/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (4/2)
Median	19.89 (12.32)	21.17 (11.16)	15.06 (13.80)	13.16 (10.54)	17.58 (17.21)	18.00 (NC)	11.57 (15.45)	7.08 (11.77)
Q1 ; Q3	21.00	20.00	11.20	13.00	13.00	18.00	2.00	1.75
Q1 ; Q3	9.33 ; 28.00	14.00 ; 28.00	4.00 ; 22.00	4.00 ; 20.00	6.17 ; 29.00	18.00 ; 18.00	1.00 ; 19.83	0.00 ; 9.00
Min ; Max	0.0 ; 42.0	0.0 ; 42.0	0.0 ; 42.0	0.0 ; 37.8	2.3 ; 42.0	18.0 ; 18.0	0.0 ; 35.0	0.0 ; 30.0
Change from baseline								
Number (observed/imputed)								
Mean (SD)	33 (32/1)	33 (30/3)	29 (28/1)	31 (31/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (4/2)
Median	-9.08 (11.91)	-11.28 (9.60)	-14.86 (11.83)	-17.13 (11.53)	-21.38 (16.53)	-23.00 (NC)	-20.43 (19.00)	-25.94 (15.41)
Q1 ; Q3	-10.20	-11.00	-19.00	-17.00	-23.50	-23.00	-25.00	-26.33
Q1 ; Q3	-18.00 ; 0.00	-16.00 ; -3.00	-23.80 ; 4.00	-27.00 ; -8.00	-33.75 ; -9.00	-23.00 ; -23.00	-35.00 ; -1.17	-42.00 ; -12.00
Min ; Max	-35.0 ; 16.0	-31.0 ; 3.3	-38.0 ; 6.0	-38.0 ; 9.8	-38.5 ; 0.0	-23.0 ; -23.0	-41.0 ; 0.0	-42.0 ; -7.0
Percent change from baseline								
Number (observed/imputed)								
Mean (SD)	33 (32/1)	33 (30/3)	29 (28/1)	31 (31/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (4/2)
Median	-29.69 (45.40)	-35.34 (30.18)	-51.82 (39.20)	-56.01 (34.22)	-55.40 (40.61)	-56.10 (NC)	-59.15 (51.57)	-76.09 (31.89)
Q1 ; Q3	-33.33	-34.19	-57.14	-60.00	-63.65	-56.10	-92.59	-92.11
Q1 ; Q3	-61.11 ; 0.00	-50.00 ; -12.82	-85.19 ; -21.05	-88.89 ; -33.33	-84.32 ; -26.47	-56.10 ; -56.10	-97.62 ; -5.56	-100.00 ; -43.75
Min ; Max	-100.0 ; 75.0	-100.0 ; 8.8	-100.0 ; 24.0	-100.0 ; 35.0	-94.3 ; 0.0	-56.1 ; -56.1	-100.0 ; 0.0	-100.0 ; -28.6
Week 12								
Number (observed/imputed)								
Mean (SD)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)	3 (2/1)	1 (1/0)	4 (3/1)	5 (3/2)
Median	19.32 (13.04)	22.00 (11.07)	15.61 (13.91)	11.00 (9.90)	18.67 (21.39)	16.00 (NC)	8.75 (17.50)	7.80 (13.01)
Q1 ; Q3	17.75	22.87	14.00	12.25	14.00	16.00	0.00	0.00
Q1 ; Q3	8.17 ; 28.50	14.00 ; 28.00	2.00 ; 26.00	1.00 ; 17.15	0.00 ; 42.00	16.00 ; 16.00	0.00 ; 17.50	0.00 ; 9.00
Min ; Max	0.0 ; 42.0	0.0 ; 42.0	0.0 ; 42.0	0.0 ; 35.0	0.0 ; 42.0	16.0 ; 16.0	0.0 ; 35.0	0.0 ; 30.0
Change from baseline								
Number (observed/imputed)								
Mean (SD)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)	3 (2/1)	1 (1/0)	4 (3/1)	5 (3/2)
Median	-9.71 (13.20)	-10.57 (9.36)	-14.49 (12.08)	-19.04 (11.40)	-21.94 (20.59)	-25.00 (NC)	-26.00 (18.38)	-27.40 (16.76)
Q1 ; Q3	-8.00	-8.70	-12.80	-18.92	-25.00	-25.00	-31.00	-34.00
Q1 ; Q3	-18.50 ; -0.50	-17.33 ; -3.67	-22.00 ; -4.00	-28.50 ; -8.75	-40.83 ; 0.00	-25.00 ; -25.00	-38.50 ; -13.50	-42.00 ; -12.00
Min ; Max	-35.0 ; 20.5	-31.0 ; 3.3	-40.8 ; 1.0	-42.0 ; -1.0	-40.8 ; 0.0	-25.0 ; -25.0	-42.0 ; 0.0	-42.0 ; -7.0
Percent change from baseline								

UAS7	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)		Rilzabrutinib 400mg QPM (N=37)		Rilzabrutinib 400mg BID (N=35)		Rilzabrutinib 400mg TID (N=35)	
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
Number (observed/imputed)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)	3 (2/1)	1 (1/0)	4 (3/1)	5 (3/2)
Mean (SD)	-31.31 (48.12)	-33.23 (28.33)	-50.20 (37.89)	-62.32 (31.89)	-54.70 (50.66)	-60.98 (NC)	-75.00 (50.00)	-74.46 (35.38)
Median	-26.76	-29.67	-47.76	-60.00	-64.10	-60.98	-100.00	-100.00
Q1 ; Q3	-68.36 ; -2.03	-48.15 ; -12.50	-91.67 ; -16.67	-97.14 ; -34.52	-100.00 ; 0.00	-60.98 ; -60.98	-100.00 ; -50.00	-100.00 ; -43.75
Min ; Max	-100.0 ; 113.9	-100.0 ; 8.8	-100.0 ; 2.9	-100.0 ; -2.8	-100.0 ; 0.0	-61.0 ; -61.0	-100.0 ; 0.0	-100.0 ; -28.6
End of Study								
Number (observed/imputed)	5 (3/2)	7 (3/4)	5 (3/2)	5 (3/2)	0 (0/0)	0 (0/0)	0 (0/0)	2 (0/2)
Mean (SD)	22.10 (13.19)	11.70 (16.82)	15.60 (17.52)	21.40 (11.74)				15.58 (9.31)
Median	24.50	5.00	14.00	20.00				15.58
Q1 ; Q3	23.00 ; 28.00	0.00 ; 30.33	0.00 ; 22.00	14.00 ; 30.00				9.00 ; 22.17
Min ; Max	0.0 ; 35.0	0.0 ; 41.0	0.0 ; 42.0	7.0 ; 36.0				9.0 ; 22.2
Change from baseline								
Number (observed/imputed)	5 (3/2)	7 (3/4)	5 (3/2)	5 (3/2)	0 (0/0)	0 (0/0)	0 (0/0)	2 (0/2)
Mean (SD)	-7.30 (10.21)	-21.44 (16.26)	-14.40 (13.79)	-11.40 (6.62)				-3.50 (4.95)
Median	-11.00	-28.00	-13.00	-14.00				-3.50
Q1 ; Q3	-14.00 ; 0.00	-36.40 ; 0.00	-28.00 ; -2.00	-14.00 ; -12.00				-7.00 ; 0.00
Min ; Max	-18.0 ; 6.5	-38.0 ; 0.3	-29.0 ; 0.0	-17.0 ; 0.0				-7.0 ; 0.0
Percent change from baseline								
Number (observed/imputed)	5 (3/2)	7 (3/4)	5 (3/2)	5 (3/2)	0 (0/0)	0 (0/0)	0 (0/0)	2 (0/2)
Mean (SD)	-25.92 (50.26)	-66.12 (46.34)	-51.30 (48.04)	-38.24 (25.31)				-21.88 (30.94)
Median	-32.35	-86.67	-48.15	-45.95				-21.88
Q1 ; Q3	-33.33 ; 0.00	-100.00 ; 0.00	-100.00 ; -8.33	-50.00 ; -28.57				-43.75 ; 0.00
Min ; Max	-100.0 ; 36.1	-100.0 ; 1.1	-100.0 ; 0.0	-66.7 ; 0.0				-43.8 ; 0.0

Note: Data collected after study intervention discontinuation were included. Data post selected prohibited/rescue medications (high/medium impact on efficacy confirmed through blinded medical review) were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF.

Table 18. Change and Percent Change from Baseline in UAS7 over Time up to Week 12 (ITT population)

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo		% Change difference for rilzabrutinib vs. placebo ^a			
					LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	
Week 1										
Rilzabrutinib 400mg TID (N=41)	41	29.88 (8.57)	16.95 (10.13)	-12.72 (1.45)	-8.89 (-13.65, -4.13)	<.0001	-40.18 (5.17)	-29.94 (-43.87, -16.00)	<.0001	
Rilzabrutinib 400mg BID (N=41)	41	30.21 (7.19)	19.98 (11.35)	-10.01 (1.48)	-6.18 (-10.92, -1.44)	0.0024	-34.18 (5.22)	-23.93 (-37.73, -10.14)	0.0007	
Rilzabrutinib 400mg QPM (N=38)	38	31.37 (7.32)	23.84 (8.66)	-7.44 (1.50)	-3.61 (-8.44, 1.23)	0.0785	-22.47 (5.29)	-12.22 (-26.29, 1.85)	0.0887	
Placebo (N=40)	40	29.97 (8.56)	26.37 (10.35)	-3.83 (1.48)			-10.25 (5.23)			
Week 2										
Rilzabrutinib 400mg TID (N=41)	41	29.88 (8.57)	14.58 (10.74)	-15.06 (1.50)	-8.72 (-12.78, -4.67)	<.0001	-48.69 (5.12)	-29.83 (-43.69, -15.96)	<.0001	
Rilzabrutinib 400mg BID (N=41)	40	30.21 (7.19)	19.50 (11.13)	-10.82 (1.53)	-4.49 (-8.54, -0.44)	0.0296	-36.13 (5.18)	-17.26 (-30.96, -3.56)	0.0135	
Rilzabrutinib 400mg QPM (N=38)	38	31.37 (7.32)	23.40 (8.85)	-8.14 (1.55)	-1.80 (-5.93, 2.32)	0.3911	-25.19 (5.23)	-6.32 (-20.30, 7.65)	0.3751	
Placebo (N=40)	39	29.97 (8.56)	23.88 (10.51)	-6.33 (1.53)			-18.87 (5.20)			
Week 3										
Rilzabrutinib 400mg TID (N=41)	41	29.88 (8.57)	14.42 (9.77)	-15.15 (1.57)	-7.56 (-11.83, -3.30)	0.0005	-49.95 (5.25)	-28.32 (-42.50, -14.13)	<.0001	
Rilzabrutinib 400mg BID (N=41)	41	30.21 (7.19)	17.63 (12.02)	-12.33 (1.60)	-4.74 (-8.99, -0.49)	0.0290	-39.97 (5.30)	-18.34 (-32.39, -4.29)	0.0105	
Rilzabrutinib 400mg QPM (N=38)	38	31.37 (7.32)	21.93 (8.89)	-9.50 (1.63)	-1.91 (-6.25, 2.43)	0.3889	-29.55 (5.37)	-7.92 (-22.26, 6.42)	0.2790	
Placebo (N=40)	39	29.97 (8.56)	22.67 (11.08)	-7.59 (1.62)			-21.63 (5.34)			
Week 4										
Rilzabrutinib 400mg TID (N=41)	38	29.88 (8.57)	13.93 (9.77)	-14.78 (1.64)	-6.71 (-11.14, -2.27)	0.0030	-48.94 (5.48)	-25.68 (-40.58, -10.78)	0.0007	
Rilzabrutinib 400mg BID (N=41)	38	30.21 (7.19)	15.62 (12.20)	-13.41 (1.67)	-5.34 (-9.76, -0.93)	0.0177	-44.02 (5.54)	-20.76 (-35.44, -6.08)	0.0056	
Rilzabrutinib 400mg QPM (N=38)	38	31.37 (7.32)	21.82 (8.73)	-9.55 (1.68)	-1.48 (-5.98, 3.01)	0.5181	-29.23 (5.56)	-5.97 (-20.90, 8.96)	0.4329	
Placebo (N=40)	38	29.97 (8.56)	21.85 (11.96)	-8.07 (1.68)			-23.26 (5.57)			

				Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
				Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Week 5									
Rilzabrutinib 400mg TID (N=41)	39	29.88 (8.57)	12.72 (10.63)	-16.68 (1.65)	-6.47 (-10.92, -2.03)	0.0043	-54.01 (5.30)	-22.21 (-36.58, -7.85)	0.0024
Rilzabrutinib 400mg BID (N=41)	38	30.21 (7.19)	16.44 (13.70)	-12.81 (1.68)	-2.61 (-7.06, 1.84)	0.2503	-42.67 (5.37)	-10.88 (-25.10, 3.34)	0.1338
Rilzabrutinib 400mg QPM (N=38)	37	31.37 (7.32)	20.58 (9.05)	-10.47 (1.69)	-0.26 (-4.77, 4.25)	0.9091	-32.52 (5.40)	-0.72 (-15.19, 13.75)	0.9222
Placebo (N=40)	37	29.97 (8.56)	19.30 (9.71)	-10.20 (1.68)			-31.80 (5.40)		
Week 6									
Rilzabrutinib 400mg TID (N=41)	37	29.88 (8.57)	12.95 (11.42)	-16.68 (1.78)	-7.54 (-12.35, -2.72)	0.0022	-54.12 (5.89)	-27.22 (-43.32, -11.13)	0.0009
Rilzabrutinib 400mg BID (N=41)	39	30.21 (7.19)	16.51 (12.98)	-12.78 (1.79)	-3.64 (-8.40, 1.12)	0.1341	-41.66 (5.92)	-14.76 (-30.55, 1.03)	0.0669
Rilzabrutinib 400mg QPM (N=38)	35	31.37 (7.32)	20.12 (10.28)	-11.02 (1.82)	-1.88 (-6.78, 3.02)	0.4515	-34.14 (6.02)	-7.24 (-23.38, 8.91)	0.3795
Placebo (N=40)	36	29.97 (8.56)	20.51 (11.10)	-9.14 (1.82)			-26.90 (6.05)		
Week 7									
Rilzabrutinib 400mg TID (N=41)	36	29.88 (8.57)	13.31 (9.35)	-16.36 (1.70)	-7.30 (-11.86, -2.74)	0.0017	-52.94 (5.57)	-25.60 (-40.60, -10.59)	0.0008
Rilzabrutinib 400mg BID (N=41)	39	30.21 (7.19)	15.04 (12.35)	-14.56 (1.71)	-5.50 (-10.02, -0.98)	0.0170	-47.80 (5.58)	-20.46 (-35.24, -5.68)	0.0067
Rilzabrutinib 400mg QPM (N=38)	34	31.37 (7.32)	20.98 (9.91)	-10.95 (1.74)	-1.89 (-6.55, 2.77)	0.4271	-34.50 (5.71)	-7.16 (-22.48, 8.17)	0.3600
Placebo (N=40)	37	29.97 (8.56)	20.92 (11.17)	-9.06 (1.72)			-27.34 (5.65)		
Week 8									
Rilzabrutinib 400mg TID (N=41)	34	29.88 (8.57)	12.33 (10.15)	-16.52 (1.81)	-6.17 (-11.06, -1.29)	0.0132	-54.62 (5.88)	-22.78 (-38.64, -6.92)	0.0049
Rilzabrutinib 400mg BID (N=41)	38	30.21 (7.19)	13.59 (13.23)	-15.96 (1.78)	-5.61 (-10.36, -0.86)	0.0205	-53.24 (5.86)	-21.40 (-36.98, -5.82)	0.0071
Rilzabrutinib 400mg QPM (N=38)	34	31.37 (7.32)	21.01 (10.40)	-10.88 (1.83)	-0.53 (-5.43, 4.37)	0.8324	-35.22 (5.96)	-3.38 (-19.31, 12.56)	0.6780
Placebo (N=40)	37	29.97 (8.56)	19.76 (11.99)	-10.35 (1.81)			-31.84 (5.90)		

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
					LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	
Rilzabrutinib 400mg TID (N=41)	35	29.88 (8.57)	11.76 (9.95)	-16.69 (1.82)	-7.09 (-12.04, -2.14)	0.0050	-54.53 (6.02)	-26.48 (-42.71, - 10.25)	0.0014	
Rilzabrutinib 400mg BID (N=41)	34	30.21 (7.19)	14.13 (14.43)	-15.45 (1.85)	-5.85 (-10.77, -0.92)	0.0199	-52.21 (5.98)	-24.16 (-39.96, - 8.36)	0.0027	
Rilzabrutinib 400mg QPM (N=38)	35	31.37 (7.32)	20.18 (10.10)	-11.33 (1.85)	-1.73 (-6.68, 3.21)	0.4925	-36.53 (6.04)	-8.48 (-24.69, 7.74)	0.3055	
Placebo (N=40)	36	29.97 (8.56)	20.73 (11.30)	-9.60 (1.85)			-28.05 (5.98)			
Week 10										
Rilzabrutinib 400mg TID (N=41)	36	29.88 (8.57)	11.82 (10.15)	-17.20 (1.88)	-6.30 (-11.39, -1.21)	0.0153	-56.75 (6.13)	-23.22 (-39.70, - 6.74)	0.0057	
Rilzabrutinib 400mg BID (N=41)	33	30.21 (7.19)	14.82 (14.24)	-15.36 (1.94)	-4.46 (-9.57, 0.65)	0.0874	-51.13 (6.28)	-17.60 (-34.05, - 1.16)	0.0359	
Rilzabrutinib 400mg QPM (N=38)	35	31.37 (7.32)	20.15 (10.55)	-11.66 (1.94)	-0.76 (-5.94, 4.43)	0.7746	-37.35 (6.27)	-3.82 (-20.62, 12.97)	0.6555	
Placebo (N=40)	37	29.97 (8.56)	19.41 (12.68)	-10.90 (1.92)			-33.52 (6.21)			
Week 11										
Rilzabrutinib 400mg TID (N=41)	37	29.88 (8.57)	12.17 (10.81)	-17.15 (1.87)	-6.74 (-11.78, -1.71)	0.0087	-55.80 (6.27)	-25.03 (-42.07, - 7.99)	0.0040	
Rilzabrutinib 400mg BID (N=41)	34	30.21 (7.19)	14.55 (13.86)	-14.95 (1.92)	-4.55 (-9.58, 0.48)	0.0761	-49.87 (6.37)	-19.11 (-36.01, - 2.21)	0.0267	
Rilzabrutinib 400mg QPM (N=38)	34	31.37 (7.32)	21.08 (11.00)	-10.92 (1.93)	-0.52 (-5.67, 4.64)	0.8440	-36.39 (6.38)	-5.62 (-22.69, 11.45)	0.5185	
Placebo (N=40)	37	29.97 (8.56)	19.64 (12.65)	-10.40 (1.90)			-30.76 (6.34)			
Week 12										
Rilzabrutinib 400mg TID (N=41)	33	29.88 (8.57)	10.52 (10.26)	-17.95 (1.95)	-6.76 (-12.01, -1.51)	0.0116	-59.16 (6.41)	-26.23 (-43.53, - 8.93)	0.0030	
Rilzabrutinib 400mg BID (N=41)	30	30.21 (7.19)	14.70 (14.29)	-14.82 (1.98)	-3.62 (-8.87, 1.63)	0.1763	-49.34 (6.68)	-16.41 (-33.90, 1.08)	0.0660	
Rilzabrutinib 400mg QPM (N=38)	31	31.37 (7.32)	21.80 (10.94)	-10.22 (2.01)	0.97 (-4.40, 6.34)	0.7230	-35.03 (6.66)	-2.09 (-19.80, 15.61)	0.8167	
Placebo (N=40)	35	29.97 (8.56)	19.27 (13.49)	-11.20 (1.98)			-32.93 (6.46)			

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

Table 19. Change and Percent Change from Baseline in UAS7 over Time up to Week 12 (Omalizumab-Naïve Population)

				Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
				LS Mean (95% CI) ^a	p-value ^a		LS Mean (95% CI) ^a	p-value ^a	
				Change from baseline LS Mean (SE) ^a		Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	% Change from baseline LS Mean (SE) ^a	
				LS Mean (SE) ^a		Mean (SD)			
				n	Baseline Mean (SD)				
Week 1									
Rilzabrutinib 400mg TID	35	29.34 (8.08)	17.77 (10.26)	-11.44 (1.56)	-7.89 (-12.98, -2.81)	0.0003	-36.60 (5.66)	-27.13 (-42.27, -11.98)	0.0004
(N=35)									
Rilzabrutinib 400mg BID	35	29.73 (7.11)	19.77 (11.32)	-9.79 (1.58)	-6.24 (-11.31, -1.18)	0.0040	-34.48 (5.64)	-25.01 (-39.96, -10.06)	0.0010
(N=35)									
Rilzabrutinib 400mg QPM	37	31.11 (7.24)	23.81 (8.78)	-7.06 (1.52)	-3.51 (-8.52, 1.50)	0.0983	-21.67 (5.45)	-12.19 (-26.98, 2.60)	0.1062
(N=37)									
Placebo (N=36)	36	28.97 (8.39)	25.80 (10.44)	-3.55 (1.56)			-9.48 (5.57)		
Week 2									
Rilzabrutinib 400mg TID	35	29.34 (8.08)	15.65 (10.66)	-13.63 (1.56)	-7.73 (-11.91, -3.54)	0.0003	-44.90 (5.51)	-27.13 (-41.93, -12.34)	0.0003
(N=35)									
Rilzabrutinib 400mg BID	34	29.73 (7.11)	19.59 (10.86)	-10.44 (1.57)	-4.55 (-8.72, -0.37)	0.0327	-36.05 (5.50)	-18.28 (-32.86, -3.71)	0.0140
(N=35)									
Rilzabrutinib 400mg QPM	37	31.11 (7.24)	23.44 (8.97)	-7.71 (1.52)	-1.81 (-5.93, 2.31)	0.3884	-24.37 (5.29)	-6.60 (-21.02, 7.82)	0.3693
(N=37)									
Placebo (N=36)	35	28.97 (8.39)	23.49 (10.05)	-5.90 (1.55)			-17.76 (5.44)		
Week 3									
Rilzabrutinib 400mg TID	35	29.34 (8.08)	15.37 (9.87)	-13.83 (1.65)	-6.90 (-11.35, -2.45)	0.0024	-47.14 (5.69)	-27.19 (-42.43, -11.95)	0.0005
(N=35)									
Rilzabrutinib 400mg BID	35	29.73 (7.11)	17.71 (11.91)	-11.96 (1.67)	-5.04 (-9.48, -0.61)	0.0259	-40.11 (5.66)	-20.16 (-35.23, -5.10)	0.0087
(N=35)									
Rilzabrutinib 400mg QPM	37	31.11 (7.24)	22.01 (9.00)	-9.10 (1.61)	-2.17 (-6.56, 2.22)	0.3319	-28.93 (5.48)	-8.98 (-23.89, 5.93)	0.2377
(N=37)									
Placebo (N=36)	35	28.97 (8.39)	22.60 (10.89)	-6.92 (1.66)			-19.95 (5.62)		
Week 4									
Rilzabrutinib 400mg TID	32	29.34 (8.08)	14.65 (9.61)	-13.66 (1.72)	-6.60 (-11.22, -1.97)	0.0052	-46.75 (5.92)	-26.33 (-42.23, -10.43)	0.0012
(N=35)									
Rilzabrutinib 400mg BID	33	29.73 (7.11)	15.92 (11.71)	-12.89 (1.73)	-5.82 (-10.43, -1.22)	0.0132	-43.62 (5.88)	-23.20 (-38.83, -7.56)	0.0036
(N=35)									
Rilzabrutinib 400mg QPM	37	31.11 (7.24)	21.92 (8.82)	-9.14 (1.66)	-2.08 (-6.63, 2.47)	0.3699	-28.63 (5.66)	-8.22 (-23.72, 7.28)	0.2988
(N=37)									
Placebo (N=36)	34	28.97 (8.39)	22.09 (12.20)	-7.06 (1.72)			-20.42 (5.86)		
Week 5									

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
					LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	
Rilzabrutinib 400mg TID (N=35)	33	29.34 (8.08)	13.41 (10.60)	-15.54 (1.72)	-5.10 (-9.74, -0.45)	0.0314	-52.02 (5.69)	-19.17 (-34.55, -3.79)	0.0146	
Rilzabrutinib 400mg BID (N=35)	34	29.73 (7.11)	17.22 (13.36)	-12.04 (1.72)	-1.60 (-6.18, 2.98)	0.4942	-41.58 (5.68)	-8.73 (-23.98, 6.52)	0.2620	
Rilzabrutinib 400mg QPM (N=37)	36	31.11 (7.24)	20.63 (9.18)	-10.08 (1.67)	0.36 (-4.19, 4.90)	0.8770	-31.92 (5.50)	0.93 (-14.21, 16.06)	0.9046	
Placebo (N=36)	33	28.97 (8.39)	18.31 (9.22)	-10.44 (1.72)			-32.85 (5.72)			
Week 6										
Rilzabrutinib 400mg TID (N=35)	31	29.34 (8.08)	14.10 (11.23)	-15.12 (1.90)	-5.94 (-11.02, -0.87)	0.0218	-50.65 (6.35)	-24.10 (-41.21, -7.00)	0.0058	
Rilzabrutinib 400mg BID (N=35)	34	29.73 (7.11)	17.02 (12.76)	-12.21 (1.87)	-3.03 (-8.03, 1.97)	0.2347	-41.23 (6.32)	-14.68 (-31.55, 2.19)	0.0881	
Rilzabrutinib 400mg QPM (N=37)	34	31.11 (7.24)	20.21 (10.42)	-10.46 (1.82)	-1.28 (-6.26, 3.70)	0.6143	-33.30 (6.14)	-6.75 (-23.47, 9.97)	0.4286	
Placebo (N=36)	32	28.97 (8.39)	19.67 (10.97)	-9.18 (1.88)			-26.55 (6.32)			
Week 7										
Rilzabrutinib 400mg TID (N=35)	30	29.34 (8.08)	13.54 (9.34)	-15.80 (1.80)	-6.37 (-11.19, -1.55)	0.0096	-52.91 (6.13)	-24.35 (-40.66, -8.04)	0.0034	
Rilzabrutinib 400mg BID (N=35)	34	29.73 (7.11)	15.55 (11.97)	-13.94 (1.77)	-4.51 (-9.23, 0.22)	0.0617	-47.01 (5.97)	-18.46 (-34.43, -2.48)	0.0236	
Rilzabrutinib 400mg QPM (N=37)	33	31.11 (7.24)	21.11 (10.03)	-10.55 (1.74)	-1.12 (-5.86, 3.63)	0.6443	-34.23 (5.85)	-5.67 (-21.60, 10.26)	0.4852	
Placebo (N=36)	33	28.97 (8.39)	19.78 (10.84)	-9.43 (1.77)			-28.56 (5.99)			
Week 8										
Rilzabrutinib 400mg TID (N=35)	28	29.34 (8.08)	13.36 (9.81)	-15.04 (1.96)	-5.11 (-10.30, 0.07)	0.0532	-50.90 (6.49)	-20.07 (-37.26, -2.87)	0.0222	
Rilzabrutinib 400mg BID (N=35)	33	29.73 (7.11)	13.98 (13.06)	-15.47 (1.87)	-5.54 (-10.53, -0.54)	0.0299	-53.47 (6.30)	-22.63 (-39.45, -5.82)	0.0083	
Rilzabrutinib 400mg QPM (N=37)	33	31.11 (7.24)	21.16 (10.52)	-10.40 (1.83)	-0.47 (-5.46, 4.52)	0.8534	-34.61 (6.22)	-3.78 (-20.49, 12.94)	0.6578	
Placebo (N=36)	33	28.97 (8.39)	19.31 (11.99)	-9.93 (1.87)			-30.84 (6.24)			
Week 9										

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
					LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	
Rilzabrutinib 400mg TID (N=35)	29	29.34 (8.08)	12.57 (9.72)	-15.75 (1.93)	-7.07 (-12.19, -1.96)	0.0067	-52.54 (6.34)	-25.99 (-43.04, -8.94)	0.0028	
Rilzabrutinib 400mg BID (N=35)	29	29.73 (7.11)	14.64 (14.43)	-14.84 (1.91)	-6.16 (-11.24, -1.09)	0.0173	-52.38 (6.34)	-25.82 (-42.66, -8.98)	0.0026	
Rilzabrutinib 400mg QPM (N=37)	34	31.11 (7.24)	20.25 (10.25)	-11.03 (1.86)	-2.36 (-7.42, 2.70)	0.3609	-35.89 (6.15)	-9.34 (-26.06, 7.39)	0.2740	
Placebo (N=36)	32	28.97 (8.39)	20.65 (11.21)	-8.67 (1.90)			-26.56 (6.30)			
Week 10										
Rilzabrutinib 400mg TID (N=35)	30	29.34 (8.08)	12.61 (9.89)	-16.20 (1.97)	-6.54 (-11.80, -1.28)	0.0149	-54.80 (6.67)	-24.83 (-42.85, -6.81)	0.0069	
Rilzabrutinib 400mg BID (N=35)	28	29.73 (7.11)	15.22 (14.36)	-14.89 (2.00)	-5.22 (-10.50, 0.05)	0.0523	-51.13 (6.68)	-21.17 (-38.85, -3.48)	0.0190	
Rilzabrutinib 400mg QPM (N=37)	34	31.11 (7.24)	20.27 (10.69)	-11.25 (1.92)	-1.58 (-6.76, 3.60)	0.5492	-37.03 (6.40)	-7.06 (-24.72, 10.60)	0.4332	
Placebo (N=36)	33	28.97 (8.39)	19.73 (12.24)	-9.66 (1.95)			-29.97 (6.65)			
Week 11										
Rilzabrutinib 400mg TID (N=35)	31	29.34 (8.08)	13.16 (10.54)	-15.86 (1.96)	-6.58 (-11.85, -1.31)	0.0143	-53.47 (6.81)	-25.26 (-43.63, -6.89)	0.0071	
Rilzabrutinib 400mg BID (N=35)	29	29.73 (7.11)	15.06 (13.80)	-14.56 (1.97)	-5.29 (-10.53, -0.05)	0.0479	-49.86 (6.78)	-21.65 (-39.78, -3.52)	0.0193	
Rilzabrutinib 400mg QPM (N=37)	33	31.11 (7.24)	21.17 (11.16)	-10.63 (1.93)	-1.36 (-6.58, 3.86)	0.6091	-35.67 (6.65)	-7.47 (-25.41, 10.47)	0.4145	
Placebo (N=36)	33	28.97 (8.39)	19.89 (12.32)	-9.27 (1.94)			-28.20 (6.73)			
Week 12										
Rilzabrutinib 400mg TID (N=35)	28	29.34 (8.08)	11.00 (9.90)	-16.89 (2.04)	-6.75 (-12.23, -1.26)	0.0159	-56.89 (6.92)	-26.61 (-45.20, -8.01)	0.0050	
Rilzabrutinib 400mg BID (N=35)	26	29.73 (7.11)	15.61 (13.91)	-14.24 (2.06)	-4.09 (-9.59, 1.40)	0.1441	-48.13 (6.91)	-17.85 (-36.39, 0.69)	0.0592	
Rilzabrutinib 400mg QPM (N=37)	30	31.11 (7.24)	22.00 (11.07)	-9.74 (2.00)	0.40 (-5.08, 5.89)	0.8856	-34.79 (6.80)	-4.51 (-22.99, 13.98)	0.6327	
Placebo (N=36)	32	28.97 (8.39)	19.32 (13.04)	-10.14 (2.05)			-30.28 (6.89)			

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

Table 20. Change and Percent Change from Baseline in UAS7 over Time up to Week 12 (Omalizumab-Naïve Population with Outlier Removed from Analysis)

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo		% Change difference for rilzabrutinib vs. placebo			
					LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	
Week 1										
Rilzabrutinib 400mg TID (N=34)	34	30.21 (6.36)	18.29 (9.93)	-11.59 (1.59)	-7.98 (-13.13, -2.83)	0.0003	-36.85 (5.65)	-27.32 (-45.67, - 8.97)	0.0006	
Rilzabrutinib 400mg BID (N=35)	35	29.73 (7.11)	19.77 (11.32)	-9.85 (1.58)	-6.25 (-11.33, -1.16)	0.0041	-34.55 (5.64)	-25.02 (-43.14, - 6.90)	0.0013	
Rilzabrutinib 400mg QPM (N=37)	37	31.11 (7.24)	23.81 (8.78)	-7.14 (1.53)	-3.54 (-8.57, 1.49)	0.0971	-21.78 (5.44)	-12.25 (-30.18, - 5.68)	0.1068	
Placebo (N=36)	36	28.97 (8.39)	25.80 (10.44)	-3.60 (1.56)			-9.53 (5.57)			
Week 2										
Rilzabrutinib 400mg TID (N=34)	34	30.21 (6.36)	16.03 (10.59)	-13.89 (1.58)	-7.96 (-12.18, -3.73)	0.0002	-44.94 (5.49)	-27.17 (-41.88, - 12.47)	0.0003	
Rilzabrutinib 400mg BID (N=35)	34	29.73 (7.11)	19.59 (10.86)	-10.50 (1.58)	-4.57 (-8.75, -0.39)	0.0321	-36.40 (5.49)	-18.63 (-33.17, - 4.09)	0.0121	
Rilzabrutinib 400mg QPM (N=37)	37	31.11 (7.24)	23.44 (8.97)	-7.82 (1.52)	-1.89 (-6.02, 2.24)	0.3700	-24.47 (5.29)	-6.70 (-21.07, 7.68)	0.3612	
Placebo (N=36)	35	28.97 (8.39)	23.49 (10.05)	-5.93 (1.56)			-17.77 (5.42)			
Week 3										
Rilzabrutinib 400mg TID (N=34)	34	30.21 (6.36)	15.20 (9.97)	-14.55 (1.64)	-7.70 (-12.10, -3.31)	0.0006	-47.26 (5.69)	-27.10 (-42.36, - 11.83)	0.0005	
Rilzabrutinib 400mg BID (N=35)	35	29.73 (7.11)	17.71 (11.91)	-11.96 (1.63)	-5.12 (-9.46, -0.78)	0.0207	-40.21 (5.67)	-20.05 (-35.13, - 4.97)	0.0092	
Rilzabrutinib 400mg QPM (N=37)	37	31.11 (7.24)	22.01 (9.00)	-9.28 (1.58)	-2.44 (-6.74, 1.86)	0.2659	-29.02 (5.48)	-8.86 (-23.79, 6.08)	0.2451	
Placebo (N=36)	35	28.97 (8.39)	22.60 (10.89)	-6.84 (1.62)			-20.16 (5.64)			
Week 4										
Rilzabrutinib 400mg TID (N=34)	32	30.21 (6.36)	14.65 (9.61)	-14.31 (1.71)	-7.25 (-11.83, -2.67)	0.0019	-46.87 (5.93)	-26.13 (-41.99, - 10.27)	0.0012	
Rilzabrutinib 400mg BID (N=35)	33	29.73 (7.11)	15.92 (11.71)	-12.88 (1.70)	-5.82 (-10.34, -1.30)	0.0116	-43.62 (5.90)	-22.88 (-38.52, - 7.25)	0.0041	
Rilzabrutinib 400mg QPM (N=37)	37	31.11 (7.24)	21.92 (8.82)	-9.30 (1.64)	-2.24 (-6.70, 2.22)	0.3244	-28.65 (5.66)	-7.91 (-23.33, 7.51)	0.3148	

				Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
				Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
n	Baseline Mean (SD)	Post-baseline Mean (SD)							
Placebo (N=36)	28.97 (8.39)	22.09 (12.20)	-7.06 (1.68)				-20.74 (5.82)		
Week 5									
Rilzabrutinib 400mg TID (N=34)	30.21 (6.36)	13.41 (10.60)	-16.07 (1.72)	-5.61 (-10.23, -0.99)	0.0172	-51.99 (5.73)	-19.26 (-34.65, -3.86)	0.0142	
Rilzabrutinib 400mg BID (N=35)	29.73 (7.11)	17.22 (13.36)	-12.04 (1.71)	-1.59 (-6.13, 2.96)	0.4931	-41.62 (5.69)	-8.89 (-24.04, 6.26)	0.2499	
Rilzabrutinib 400mg QPM (N=37)	31.11 (7.24)	20.63 (9.18)	-10.29 (1.65)	0.16 (-4.35, 4.67)	0.9433	-32.16 (5.50)	0.57 (-14.46, 15.59)	0.9411	
Placebo (N=36)	28.97 (8.39)	18.31 (9.22)	-10.45 (1.71)			-32.73 (5.69)			
Week 6									
Rilzabrutinib 400mg TID (N=34)	30.21 (6.36)	14.10 (11.23)	-15.69 (1.88)	-6.44 (-11.46, -1.43)	0.0118	-50.57 (6.35)	-23.48 (-40.46, -6.49)	0.0067	
Rilzabrutinib 400mg BID (N=35)	29.73 (7.11)	17.02 (12.76)	-12.20 (1.86)	-2.96 (-7.92, 2.01)	0.2434	-41.32 (6.30)	-14.22 (-31.04, 2.59)	0.0973	
Rilzabrutinib 400mg QPM (N=37)	31.11 (7.24)	20.21 (10.42)	-10.66 (1.81)	-1.41 (-6.38, 3.55)	0.5767	-33.42 (6.12)	-6.33 (-23.11, 10.46)	0.4602	
Placebo (N=36)	28.97 (8.39)	19.67 (10.97)	-9.24 (1.87)			-27.10 (6.34)			
Week 7									
Rilzabrutinib 400mg TID (N=34)	30.21 (6.36)	13.54 (9.34)	-16.24 (1.78)	-6.73 (-11.50, -1.96)	0.0057	-52.77 (6.02)	-24.12 (-40.27, -7.97)	0.0034	
Rilzabrutinib 400mg BID (N=35)	29.73 (7.11)	15.55 (11.97)	-14.01 (1.76)	-4.50 (-9.19, 0.19)	0.0598	-47.24 (5.95)	-18.59 (-34.47, -2.70)	0.0218	
Rilzabrutinib 400mg QPM (N=37)	31.11 (7.24)	21.11 (10.03)	-10.66 (1.72)	-1.15 (-5.83, 3.52)	0.6289	-34.18 (5.81)	-5.53 (-21.38, 10.31)	0.4938	
Placebo (N=36)	28.97 (8.39)	19.78 (10.84)	-9.51 (1.76)			-28.65 (5.95)			
Week 8									
Rilzabrutinib 400mg TID (N=34)	30.21 (6.36)	13.36 (9.81)	-15.70 (1.90)	-5.68 (-10.80, -0.56)	0.0298	-51.40 (6.43)	-20.31 (-37.72, -2.91)	0.0222	
Rilzabrutinib 400mg BID (N=35)	29.73 (7.11)	13.98 (13.06)	-15.43 (1.86)	-5.41 (-10.40, -0.43)	0.0332	-53.10 (6.28)	-22.01 (-38.88, -5.14)	0.0106	
Rilzabrutinib 400mg QPM (N=37)	31.11 (7.24)	21.16 (10.52)	-10.60 (1.81)	-0.58 (-5.54, 4.37)	0.8181	-35.12 (6.14)	-4.03 (-20.86, 12.79)	0.6385	
Placebo (N=36)	28.97 (8.39)	19.31 (11.99)	-10.02 (1.87)			-31.09 (6.33)			

		Change difference for rilzabrutinib vs. placebo				% Change difference for rilzabrutinib vs. placebo			
		Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	LS Mean (95% CI) ^a	p-value ^a	
Week 9									
Rilzabrutinib 400mg TID (N=34)	29	30.21 (6.36)	12.57 (9.72)	-16.22 (1.96)	-7.36 (-12.59, -2.14)	0.0058	-52.11 (6.55)	-25.28 (-42.68, -7.89)	0.0044
Rilzabrutinib 400mg BID (N=35)	29	29.73 (7.11)	14.64 (14.43)	-14.88 (1.92)	-6.02 (-11.15, -0.89)	0.0215	-52.05 (6.41)	-25.22 (-42.33, -8.12)	0.0039
Rilzabrutinib 400mg QPM (N=37)	34	31.11 (7.24)	20.25 (10.25)	-11.11 (1.85)	-2.25 (-7.32, 2.82)	0.3846	-35.85 (6.16)	-9.02 (-25.91, 7.86)	0.2949
Placebo (N=36)	32	28.97 (8.39)	20.65 (11.21)	-8.86 (1.91)			-26.83 (6.34)		
Week 10									
Rilzabrutinib 400mg TID (N=34)	30	30.21 (6.36)	12.61 (9.89)	-16.56 (1.98)	-6.91 (-12.19, -1.64)	0.0103	-54.21 (6.69)	-23.84 (-41.69, -5.99)	0.0089
Rilzabrutinib 400mg BID (N=35)	28	29.73 (7.11)	15.22 (14.36)	-15.06 (1.99)	-5.41 (-10.69, -0.13)	0.0445	-51.72 (6.74)	-21.34 (-39.16, -3.52)	0.0189
Rilzabrutinib 400mg QPM (N=37)	34	31.11 (7.24)	20.27 (10.69)	-11.49 (1.88)	-1.84 (-7.00, 3.33)	0.4863	-37.24 (6.37)	-6.86 (-24.33, 10.60)	0.4410
Placebo (N=36)	33	28.97 (8.39)	19.73 (12.24)	-9.65 (1.95)			-30.37 (6.58)		
Week 11									
Rilzabrutinib 400mg TID (N=34)	31	30.21 (6.36)	13.16 (10.54)	-16.34 (1.95)	-7.03 (-12.30, -1.76)	0.0090	-53.14 (6.75)	-24.83 (-43.04, -6.61)	0.0076
Rilzabrutinib 400mg BID (N=35)	29	29.73 (7.11)	15.06 (13.80)	-14.46 (1.99)	-5.15 (-10.44, 0.15)	0.0567	-49.79 (6.87)	-21.48 (-39.77, -3.19)	0.0214
Rilzabrutinib 400mg QPM (N=37)	33	31.11 (7.24)	21.17 (11.16)	-10.76 (1.90)	-1.45 (-6.67, 3.77)	0.5864	-36.00 (6.57)	-7.69 (-25.74, 10.36)	0.4037
Placebo (N=36)	33	28.97 (8.39)	19.89 (12.32)	-9.31 (1.95)			-28.31 (6.74)		
Week 12									
Rilzabrutinib 400mg TID (N=34)	28	30.21 (6.36)	11.00 (9.90)	-17.50 (2.06)	-7.50 (-13.02, -1.97)	0.0079	-57.01 (7.01)	-26.35 (-45.10, -7.61)	0.0059
Rilzabrutinib 400mg BID (N=35)	26	29.73 (7.11)	15.61 (13.91)	-14.30 (2.06)	-4.29 (-9.74, 1.16)	0.1232	-49.10 (7.03)	-18.45 (-37.01, 0.12)	0.0515
Rilzabrutinib 400mg QPM (N=37)	30	31.11 (7.24)	22.00 (11.07)	-9.93 (1.96)	0.08 (-5.29, 5.46)	0.9759	-34.40 (6.66)	-3.75 (-21.98, 14.48)	0.6869
Placebo (N=36)	32	28.97 (8.39)	19.32 (13.04)	-10.01 (2.01)			-30.65 (6.81)		
LS: least squares; WOCF: Worst observation carried forward; MI: multiple imputation									

LS: least squares, WOCF: Worst observation carried forward; MI: multiple imputation

n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo		% Change difference for rilzabrutinib vs. placebo	
				LS Mean (95% CI) ^a	p-value ^a	LS Mean (95% CI) ^a	p-value ^a
				% Change from baseline LS Mean (SE) ^a			

^a Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group and region as covariates.

[00242] Over the course of the study, a substantial proportion of patients in both the ITT and omalizumab-naïve population achieved a UAS7 score of ≤6 (a non-limiting representative criterion for well-controlled disease), with a smaller population of participants achieving a UAS7 score of 0 (see **Figures 9-12** and **Tables 21-22**). At Week 12, 20.0% of omalizumab-naïve participants receiving 400 mg BID rilzabrutinib and 34.3% of omalizumab-naïve participants receiving 400 mg TID rilzabrutinib had a UAS7 of ≤6. Meanwhile, 14.3% of omalizumab-naïve participants in the BID cohort and 20.0% of omalizumab-naïve patients in the TID cohort had a UAS7 of 0. Additionally, a substantial percentage of patients experienced an MCID (a reduction in UAS7 of at least 10 points relative to baseline) that was sustained over the course of the double-blind treatment phase (see **Figures 13-14** and **Table 23**).

Table 21. Proportion of Participants with UAS7 ≤6 Over Time up to Week 12 (ITT and Omalizumab-Naïve Population)									
	ITT Population				Omalizumab-Naïve Population				
	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^a	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)
Baseline									
Rilzabrutinib 400mg TID (N=41)	0	41 (100)	0				0	35 (100)	0
Rilzabrutinib 400mg BID (N=41)	0	41 (100)	0				0	35 (100)	0
Rilzabrutinib 400mg QPM (N=38)	0	38 (100)	0				0	37 (100)	0
Placebo (N=40)	0	40 (100)	0				0	36 (100)	0

ITT Population												Omalizumab-Naïve Population			
Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b				
Week 1															
Rilzabrutinib 400mg TID (N=41)	10 (24.4)	31 (75.6)	0	17.6 (2.90, 32.38)	5.673 (1.111, 28.967)	8 (22.9)	27 (77.1)	0	15.9 (0.19, 31.52)	4.809 (0.890, 25.993)	0.0600				
Rilzabrutinib 400mg BID (N=41)	7 (17.1)	34 (82.9)	1 (2.4)	10.3 (-2.73, 23.37)	3.469 (0.658, 18.287)	6 (17.1)	29 (82.9)	0	9.9 (-4.25, 24.02)	3.183 (0.576, 17.573)	0.1789				
Rilzabrutinib 400mg QPM (N=38)	2 (5.3)	36 (94.7)	0	0.4 (-9.14, 10.01)	1.099 (0.137, 8.792)	2 (5.4)	35 (94.6)	0	-0.0 (-10.23, 10.17)	0.994 (0.125, 7.921)	0.9954				
Placebo (N=40)	2 (5.0)	38 (95.0)	0			2 (5.6)	34 (94.4)	0							
Week 2															
Rilzabrutinib 400mg TID (N=41)	11 (26.8)	30 (73.2)	0	19.4 (4.20, 34.60)	6.049 (1.232, 29.703)	8 (22.9)	27 (77.1)	0	15.3 (-0.43, 31.10)	4.455 (0.852, 23.298)	0.0693				
Rilzabrutinib 400mg BID (N=41)	6 (14.6)	35 (85.4)	2 (4.9)	7.7 (-4.55, 19.88)	2.834 (0.511, 15.715)	4 (11.4)	31 (88.6)	1 (2.9)	4.4 (-7.93, 16.65)	1.917 (0.304, 12.087)	0.4975				
Rilzabrutinib 400mg QPM (N=38)	1 (2.6)	37 (97.4)	0	-2.3 (-10.71, 6.12)	0.517 (0.043, 6.233)	1 (2.7)	36 (97.3)	0	-2.7 (-11.88, 6.43)	0.489 (0.042, 5.701)	0.5668				
Placebo (N=40)	2 (5.0)	38 (95.0)	1 (2.5)			2 (5.6)	34 (94.4)	1 (2.8)							
Week 3															
Rilzabrutinib 400mg TID (N=41)	11 (26.8)	30 (73.2)	0	14.9 (-1.46, 31.22)	3.055 (0.845, 11.040)	8 (22.9)	27 (77.1)	0	13.6 (-2.78, 30.07)	3.239 (0.735, 14.279)	0.1209				
Rilzabrutinib 400mg BID (N=41)	10 (24.4)	31 (75.6)	1 (2.4)	12.5 (-3.67, 28.69)	2.554 (0.730, 8.938)	8 (22.9)	27 (77.1)	0	13.3 (-3.54, 30.09)	2.894 (0.713, 11.743)	0.1292				
Rilzabrutinib 400mg QPM (N=38)	2 (5.3)	36 (94.7)	0	-3.9 (-15.41, 7.63)	0.553 (0.092, 3.325)	2 (5.4)	35 (94.6)	0	-2.5 (-14.01, 8.99)	0.666 (0.102, 4.335)	0.6724				
Placebo (N=40)	4 (10.0)	36 (90.0)	1 (2.5)			3 (8.3)	33 (91.7)	1 (2.8)							

ITT Population										Omalizumab-Naïve Population									
Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	P-value vs. placebo ^b	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	P-value vs. placebo ^b				
Rilzabrutinib 400mg TID (N=41)	7 (17.1)	34 (82.9)	3 (7.3)	2.4 (-13.00, 17.75)	0.7677	5 (14.3)	30 (85.7)	3 (8.6)	1.8 (-13.62, 17.23)	1.185 (0.278, 5.048)	0.8243								
Rilzabrutinib 400mg BID (N=41)	13 (31.7)	28 (68.3)	4 (9.8)	16.7 (-0.68, 34.05)	0.0676	10 (28.6)	25 (71.4)	2 (5.7)	15.8 (-2.29, 33.91)	2.950 (0.814, 10.692)	0.0963								
Rilzabrutinib 400mg QPM (N=38)	2 (5.3)	36 (94.7)	1 (2.6)	-6.0 (-18.20, 6.10)	0.3471	2 (5.4)	35 (94.6)	1 (2.7)	-5.0 (-17.29, 7.31)	0.486 (0.080, 2.962)	0.4367								
Placebo (N=40)	5 (12.5)	35 (87.5)	2 (5.0)			4 (11.1)	32 (88.9)	2 (5.6)											
Week 5																			
Rilzabrutinib 400mg TID (N=41)	14 (34.1)	27 (65.9)	3 (7.3)	26.0 (9.94, 42.11)	0.0030	10 (28.6)	25 (71.4)	2 (5.7)	19.7 (3.09, 36.22)	5.923 (1.166, 30.099)	0.0254								
Rilzabrutinib 400mg BID (N=41)	13 (31.7)	28 (68.3)	5 (12.2)	24.3 (8.61, 39.95)	0.0037	10 (28.6)	25 (71.4)	2 (5.7)	21.1 (4.62, 37.65)	6.525 (1.284, 33.153)	0.0152								
Rilzabrutinib 400mg QPM (N=38)	2 (5.3)	36 (94.7)	2 (5.3)	0.3 (-9.40, 9.99)	0.9539	2 (5.4)	35 (94.6)	2 (5.4)	-0.1 (-10.46, 10.32)	0.986 (0.128, 7.566)	0.9892								
Placebo (N=40)	2 (5.0)	38 (95.0)	3 (7.5)			2 (5.6)	34 (94.4)	3 (8.3)											
Week 6																			
Rilzabrutinib 400mg TID (N=41)	13 (31.7)	28 (68.3)	5 (12.2)	14.2 (-4.24, 32.56)	0.1405	8 (22.9)	27 (77.1)	4 (11.4)	3.7 (-14.85, 22.33)	1.274 (0.384, 4.230)	0.7003								
Rilzabrutinib 400mg BID (N=41)	12 (29.3)	29 (70.7)	4 (9.8)	13.6 (-4.03, 31.14)	0.1450	9 (25.7)	26 (74.3)	2 (5.7)	8.8 (-9.86, 27.50)	1.743 (0.532, 5.708)	0.3678								
Rilzabrutinib 400mg QPM (N=38)	3 (7.9)	35 (92.1)	4 (10.5)	-6.3 (-20.67, 8.03)	0.3899	3 (8.1)	34 (91.9)	4 (10.8)	-7.8 (-22.93, 7.40)	0.481 (0.111, 2.083)	0.3189								
Placebo (N=40)	6 (15.0)	34 (85.0)	6 (15.0)			6 (16.7)	30 (83.3)	5 (13.9)											
Week 7																			

ITT Population												Omalizumab-Naïve Population					
Responder n (%)		Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	P-value vs. placebo ^b						
Week 8																	
Rilzabrutinib 400mg TID (N=41)	11 (26.8)	30 (73.2)	6 (14.6)	16.1 (-0.40, 32.60)	3.247 (0.898, 11.746)	0.0691	9 (25.7)	26 (74.3)	5 (14.3)	13.4 (-4.18, 31.05)	2.685 (0.704, 10.244)	0.1522					
Rilzabrutinib 400mg BID (N=41)	12 (29.3)	29 (70.7)	4 (9.8)	17.8 (0.98, 34.66)	3.425 (0.989, 11.863)	0.0465	9 (25.7)	26 (74.3)	2 (5.7)	13.6 (-4.13, 31.42)	2.622 (0.714, 9.632)	0.1456					
Rilzabrutinib 400mg QPM (N=38)	1 (2.6)	37 (97.4)	6 (15.8)	-7.3 (-18.32, 3.75)	0.278 (0.033, 2.339)	0.1981	1 (2.7)	36 (97.3)	6 (16.2)	-8.3 (-20.15, 3.52)	0.249 (0.029, 2.154)	0.1674					
Placebo (N=40)	4 (10.0)	36 (90.0)	5 (12.5)				4 (11.1)	32 (88.9)	4 (11.1)								
Week 9																	
Rilzabrutinib 400mg TID (N=41)	13 (31.7)	28 (68.3)	8 (19.5)	12.7 (-4.90, 30.33)	2.257 (0.723, 7.043)	0.1663	9 (25.7)	26 (74.3)	7 (20.0)	6.3 (-12.17, 24.68)	1.513 (0.448, 5.104)	0.5163					
Rilzabrutinib 400mg BID (N=41)	16 (39.0)	25 (61.0)	5 (12.2)	21.8 (3.07, 40.46)	3.297 (1.126, 9.656)	0.0279	13 (37.1)	22 (62.9)	3 (8.6)	18.5 (-1.55, 38.58)	2.745 (0.891, 8.452)	0.0799					
Rilzabrutinib 400mg QPM (N=38)	3 (7.9)	35 (92.1)	7 (18.4)	-7.0 (-21.26, 7.28)	0.502 (0.118, 2.138)	0.3464	3 (8.1)	34 (91.9)	7 (18.9)	-8.4 (-23.55, 6.78)	0.454 (0.105, 1.963)	0.2869					
Placebo (N=40)	6 (15.0)	34 (85.0)	5 (12.5)				6 (16.7)	30 (83.3)	4 (11.1)								
Week 9																	
Rilzabrutinib 400mg TID (N=41)	15 (36.6)	26 (63.4)	7 (17.1)	22.0 (4.85, 39.06)	4.680 (1.311, 16.709)	0.0151	11 (31.4)	24 (68.6)	6 (17.1)	16.7 (-1.21, 34.64)	3.358 (0.885, 12.743)	0.0781					
Rilzabrutinib 400mg BID (N=41)	13 (31.7)	28 (68.3)	9 (22.0)	19.4 (2.08, 36.75)	3.540 (1.061, 11.804)	0.0309	10 (28.6)	25 (71.4)	7 (20.0)	15.6 (-2.80, 34.02)	2.797 (0.796, 9.830)	0.0998					
Rilzabrutinib 400mg QPM (N=38)	3 (7.9)	35 (92.1)	6 (15.8)	-2.2 (-15.39, 10.92)	0.773 (0.169, 3.540)	0.7375	3 (8.1)	34 (91.9)	6 (16.2)	-3.0 (-16.97, 10.87)	0.715 (0.154, 3.319)	0.6671					
Placebo (N=40)	4 (10.0)	36 (90.0)	6 (15.0)				4 (11.1)	32 (88.9)	5 (13.9)								
Week 10																	

ITT Population												Omalizumab-Naïve Population					
Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b						
Week 11																	
Rilzabrutinib 400mg TID (N=41)	14 (34.1)	27 (65.9)	7 (17.1)	12.9 (-5.77, 31.54)	2.074 (0.709, 6.063)	10 (28.6)	25 (71.4)	5 (14.3)	12.1 (-6.36, 30.46)	2.241 (0.642, 7.824)	0.2111						
Rilzabrutinib 400mg BID (N=41)	12 (29.3)	29 (70.7)	10 (24.4)	8.6 (-9.13, 26.41)	1.699 (0.567, 5.093)	9 (25.7)	26 (74.3)	8 (22.9)	9.9 (-8.41, 28.23)	1.923 (0.566, 6.530)	0.2961						
Rilzabrutinib 400mg QPM (N=38)	2 (5.3)	36 (94.7)	6 (15.8)	-11.9 (-25.79, 2.04)	0.279 (0.055, 1.407)	2 (5.4)	35 (94.6)	6 (16.2)	-8.6 (-22.21, 5.00)	0.357 (0.066, 1.940)	0.2263						
Placebo (N=40)	7 (17.5)	33 (82.5)	5 (12.5)			5 (13.9)	31 (86.1)	4 (11.1)									
Week 12																	
Rilzabrutinib 400mg TID (N=41)	15 (36.6)	26 (63.4)	6 (14.6)	15.0 (-3.73, 33.81)	2.322 (0.795, 6.782)	11 (31.4)	24 (68.6)	4 (11.4)	11.2 (-8.12, 30.44)	1.971 (0.605, 6.420)	0.2662						
Rilzabrutinib 400mg BID (N=41)	13 (31.7)	28 (68.3)	9 (22.0)	11.8 (-6.40, 30.04)	1.991 (0.676, 5.862)	10 (28.6)	25 (71.4)	7 (20.0)	10.3 (-8.89, 29.45)	1.853 (0.578, 5.939)	0.3072						
Rilzabrutinib 400mg QPM (N=38)	3 (7.9)	35 (92.1)	7 (18.4)	-9.4 (-24.19, 5.35)	0.418 (0.101, 1.739)	3 (8.1)	34 (91.9)	7 (18.9)	-8.5 (-23.75, 6.80)	0.456 (0.107, 1.946)	0.2834						
Placebo (N=40)	7 (17.5)	33 (82.5)	5 (12.5)			6 (16.7)	30 (83.3)	4 (11.1)									
Week 12																	
Rilzabrutinib 400mg TID (N=41)	15 (36.6)	26 (63.4)	11 (26.8)	20.9 (3.11, 38.70)	3.721 (1.141, 12.137)	12 (34.3)	23 (65.7)	8 (22.9)	20.3 (1.86, 38.75)	3.980 (1.064, 14.887)	0.0394						
Rilzabrutinib 400mg BID (N=41)	10 (24.4)	31 (75.6)	14 (34.1)	10.0 (-6.37, 26.39)	2.067 (0.616, 6.930)	7 (20.0)	28 (80.0)	11 (31.4)	7.9 (-8.61, 24.44)	1.904 (0.488, 7.430)	0.3661						
Rilzabrutinib 400mg QPM (N=38)	2 (5.3)	36 (94.7)	10 (26.3)	-7.6 (-20.17, 5.06)	0.378 (0.069, 2.072)	2 (5.4)	35 (94.6)	10 (27.0)	-6.1 (-18.87, 6.62)	0.438 (0.076, 2.527)	0.3551						
Placebo (N=40)	5 (12.5)	35 (87.5)	7 (17.5)			4 (11.1)	32 (88.9)	5 (13.9)									

^a OR: odds ratio; RRD: response rate difference; derived from the Mantel-Haenszel estimator

^b CMH test was performed on the association between the responder status and intervention group, stratified by region.

Table 22. Proportion of Participants with UAS7 =0 over Time up to Week 12 (ITT Population and Omalizumab-Naïve Participants)

	ITT Population				Omalizumab-Naïve Population						
	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^b	P-value vs. placebo ^b	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	P-value for rilzabrutinib vs. placebo ^b
Baseline											
Rilzabrutinib 400mg TID (N=41)	0	41 (100)	0				0	35 (100)	0		
Rilzabrutinib 400mg BID (N=41)	0	41 (100)	0				0	35 (100)	0		
Rilzabrutinib 400mg QPM (N=38)	0	38 (100)	0				0	37 (100)	0		
Placebo (N=40)	0	40 (100)	0				0	36 (100)	0		
Week 1											
Rilzabrutinib 400mg TID (N=41)	1 (2.4)	40 (97.6)	0	0.2 (-6.20, 6.54)	1.084 (0.050, 23.369)	0.9622	1 (2.9)	34 (97.1)	0	0.2 (-6.96, 7.45)	1.111 (0.050, 24.475)
Rilzabrutinib 400mg BID (N=41)	3 (7.3)	38 (92.7)	1 (2.4)	4.7 (-4.53, 13.93)	3.132 (0.292, 33.570)	0.3406	3 (8.6)	32 (91.4)	0	5.6 (-5.06, 16.16)	3.242 (0.306, 34.369)
Rilzabrutinib 400mg QPM (N=38)	0	38 (100)	0	-2.6 (-7.54, 2.36)	0.000 (NE, NE)	0.3173	0	37 (100)	0	-2.9 (-8.32, 2.60)	0.000 (NE, NE)
Placebo (N=40)	1 (2.5)	39 (97.5)	0				1 (2.8)	35 (97.2)	0		
Week 2											
Rilzabrutinib 400mg TID (N=41)	6 (14.6)	35 (85.4)	0	11.0 (-0.61, 22.60)	6.522 (0.677, 62.812)	0.0852	4 (11.4)	31 (88.6)	0	8.3 (-3.37, 19.87)	4.736 (0.439, 51.037)
Rilzabrutinib 400mg BID (N=41)	3 (7.3)	38 (92.7)	2 (4.9)	4.2 (-4.81, 13.16)	2.893 (0.262, 31.979)	0.3887	2 (5.7)	33 (94.3)	1 (2.9)	2.5 (-6.51, 11.58)	2.024 (0.158, 25.945)
Rilzabrutinib 400mg QPM (N=38)	0	38 (100)	0	-2.6 (-7.54, 2.36)	0.000 (NE, NE)	0.3173	0	37 (100)	0	-2.9 (-8.32, 2.60)	0.000 (NE, NE)

ITT Population										Omalizumab-Naïve Population									
Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^b	P-value vs. placebo ^b	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for OR (95% CI) vs. placebo ^a	P-value vs. placebo ^b									
Week 3																			
Placebo (N=40)	1 (2.5)	39 (97.5)	1 (2.5)			1 (2.8)	35 (97.2)	1 (2.8)											
Rilzabrutinib 400mg TID (N=41)	4 (9.8)	37 (90.2)	0	6.9 (-3.14, 17.00)	0.2129	3 (8.6)	32 (91.4)	0	5.8 (-4.73, 16.32)	0.3109									
Rilzabrutinib 400mg BID (N=41)	4 (9.8)	37 (90.2)	1 (2.4)	6.3 (-3.66, 16.26)	0.2374	3 (8.6)	32 (91.4)	0	5.0 (-5.34, 15.43)	0.3569									
Rilzabrutinib 400mg QPM (N=38)	0	38 (100)	0	-2.6 (-7.54, 2.36)	0.3173	0	37 (100)	0	-2.9 (-8.32, 2.60)	0.2994									
Placebo (N=40)	1 (2.5)	39 (97.5)	1 (2.5)			1 (2.8)	35 (97.2)	1 (2.8)											
Week 4																			
Rilzabrutinib 400mg TID (N=41)	4 (9.8)	37 (90.2)	3 (7.3)	4.0 (-7.30, 15.30)	0.5079	3 (8.6)	32 (91.4)	3 (8.6)	2.5 (-9.62, 14.53)	0.6991									
Rilzabrutinib 400mg BID (N=41)	3 (7.3)	38 (92.7)	4 (9.8)	1.3 (-8.78, 11.36)	0.8091	3 (8.6)	32 (91.4)	2 (5.7)	1.9 (-9.53, 13.23)	0.7574									
Rilzabrutinib 400mg QPM (N=38)	0	38 (100)	1 (2.6)	-4.8 (-11.39, 1.89)	0.1917	0	37 (100)	1 (2.7)	-5.3 (-12.71, 2.03)	0.1696									
Placebo (N=40)	2 (5.0)	38 (95.0)	2 (5.0)			2 (5.6)	34 (94.4)	2 (5.6)											
Week 5																			
Rilzabrutinib 400mg TID (N=41)	7 (17.1)	34 (82.9)	3 (7.3)	13.2 (0.86, 25.45)	0.0523	6 (17.1)	29 (82.9)	2 (5.7)	13.2 (-0.23, 26.61)	0.0692									
Rilzabrutinib 400mg BID (N=41)	6 (14.6)	35 (85.4)	5 (12.2)	11.1 (-0.64, 22.79)	0.0771	4 (11.4)	31 (88.6)	2 (5.7)	8.1 (-3.64, 19.77)	0.1914									
Rilzabrutinib 400mg QPM (N=38)	1 (2.6)	37 (97.4)	2 (5.3)	0.0 (-6.93, 6.93)	1.0000	1 (2.7)	36 (97.3)	2 (5.4)	-0.2 (-7.56, 7.15)	0.9574									
Placebo (N=40)	1 (2.5)	39 (97.5)	3 (7.5)			1 (2.8)	35 (97.2)	3 (8.3)											

ITT Population												Omalizumab-Naïve Population			
Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b				
Week 6															
Rilzabrutinib 400mg TID (N=41)	9 (22.0)	32 (78.0)	5 (12.2)	17.2 (3.80, 30.65)	9.649 (1.140, 81.651)	7 (20.0)	28 (80.0)	4 (11.4)	15.6 (1.47, 29.81)	8.082 (0.897, 72.821)	0.0415				
Rilzabrutinib 400mg BID (N=41)	5 (12.2)	36 (87.8)	4 (9.8)	8.4 (-2.38, 19.23)	4.821 (0.522, 44.499)	4 (11.4)	31 (88.6)	2 (5.7)	7.6 (-3.96, 19.07)	4.048 (0.423, 38.762)	0.2081				
Rilzabrutinib 400mg QPM (N=38)	1 (2.6)	37 (97.4)	4 (10.5)	0.0 (-6.93, 6.93)	1.000 (0.056, 17.751)	1 (2.7)	36 (97.3)	4 (10.8)	-0.2 (-7.56, 7.15)	0.923 (0.052, 16.456)	0.9574				
Placebo (N=40)	1 (2.5)	39 (97.5)	6 (15.0)			1 (2.8)	35 (97.2)	5 (13.9)							
Week 7															
Rilzabrutinib 400mg TID (N=41)	4 (9.8)	37 (90.2)	6 (14.6)	6.9 (-3.14, 17.00)	4.480 (0.413, 48.581)	3 (8.6)	32 (91.4)	5 (14.3)	5.8 (-4.73, 16.32)	3.625 (0.312, 42.079)	0.3109				
Rilzabrutinib 400mg BID (N=41)	6 (14.6)	35 (85.4)	4 (9.8)	11.1 (-0.64, 22.79)	6.024 (0.684, 53.045)	4 (11.4)	31 (88.6)	2 (5.7)	8.1 (-3.64, 19.77)	4.254 (0.439, 41.171)	0.1914				
Rilzabrutinib 400mg QPM (N=38)	1 (2.6)	37 (97.4)	6 (15.8)	0.4 (-7.05, 7.92)	1.167 (0.081, 16.709)	1 (2.7)	36 (97.3)	6 (16.2)	0.2 (-7.72, 8.07)	1.061 (0.073, 15.484)	0.9644				
Placebo (N=40)	1 (2.5)	39 (97.5)	5 (12.5)			1 (2.8)	35 (97.2)	4 (11.1)							
Week 8															
Rilzabrutinib 400mg TID (N=41)	4 (9.8)	37 (90.2)	8 (19.5)	3.2 (-7.77, 14.20)	1.697 (0.273, 10.531)	3 (8.6)	32 (91.4)	7 (20.0)	1.9 (-9.95, 13.68)	1.351 (0.204, 8.952)	0.7599				
Rilzabrutinib 400mg BID (N=41)	8 (19.5)	33 (80.5)	5 (12.2)	13.4 (-0.62, 27.32)	4.083 (0.825, 20.197)	6 (17.1)	29 (82.9)	3 (8.6)	10.7 (-3.97, 25.45)	3.154 (0.607, 16.397)	0.1632				
Rilzabrutinib 400mg QPM (N=38)	1 (2.6)	37 (97.4)	7 (18.4)	-2.2 (-10.44, 6.12)	0.527 (0.042, 6.557)	1 (2.7)	36 (97.3)	7 (18.9)	-2.7 (-11.63, 6.26)	0.477 (0.039, 5.895)	0.5680				
Placebo (N=40)	2 (5.0)	38 (95.0)	5 (12.5)			2 (5.6)	34 (94.4)	4 (11.1)							

Omalizumab-Naïve Population											
ITT Population						Omalizumab-Naïve Population					
Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b
Week 9											
Rilzabrutinib 400mg TID (N=41)	4 (9.8)	37 (90.2)	7 (17.1)	0.8 (-11.22, 12.86)	1.117 (0.220, 5.670)	3 (8.6)	32 (91.4)	6 (17.1)	-0.9 (-13.88, 12.16)	0.893 (0.161, 4.971)	0.8989
Rilzabrutinib 400mg BID (N=41)	8 (19.5)	33 (80.5)	9 (22.0)	11.3 (-3.19, 25.78)	2.914 (0.694, 12.243)	6 (17.1)	29 (82.9)	7 (20.0)	8.4 (-6.86, 23.71)	2.249 (0.502, 10.063)	0.2940
Rilzabrutinib 400mg QPM (N=38)	1 (2.6)	37 (97.4)	6 (15.8)	-4.9 (-14.54, 4.76)	0.330 (0.032, 3.409)	1 (2.7)	36 (97.3)	6 (16.2)	-5.6 (-16.00, 4.83)	0.305 (0.029, 3.168)	0.3052
Placebo (N=40)	3 (7.5)	37 (92.5)	6 (15.0)			3 (8.3)	33 (91.7)	5 (13.9)			
Week 10											
Rilzabrutinib 400mg TID (N=41)	6 (14.6)	35 (85.4)	7 (17.1)	1.7 (-11.54, 14.96)	1.210 (0.276, 5.304)	4 (11.4)	31 (88.6)	5 (14.3)	-1.7 (-15.55, 12.11)	0.819 (0.163, 4.120)	0.8173
Rilzabrutinib 400mg BID (N=41)	9 (22.0)	32 (78.0)	10 (24.4)	10.9 (-4.98, 26.81)	2.322 (0.651, 8.283)	8 (22.9)	27 (77.1)	8 (22.9)	10.6 (-6.91, 28.09)	2.159 (0.588, 7.919)	0.2438
Rilzabrutinib 400mg QPM (N=38)	1 (2.6)	37 (97.4)	6 (15.8)	-7.9 (-18.71, 3.01)	0.235 (0.026, 2.134)	1 (2.7)	36 (97.3)	6 (16.2)	-8.7 (-20.44, 2.97)	0.219 (0.024, 2.012)	0.1517
Placebo (N=40)	4 (10.0)	36 (90.0)	5 (12.5)			4 (11.1)	32 (88.9)	4 (11.1)			
Week 11											
Rilzabrutinib 400mg TID (N=41)	7 (17.1)	34 (82.9)	6 (14.6)	10.4 (-2.82, 23.58)	3.449 (0.661, 18.002)	4 (11.4)	31 (88.6)	4 (11.4)	4.3 (-8.37, 17.01)	1.846 (0.304, 11.223)	0.5161
Rilzabrutinib 400mg BID (N=41)	6 (14.6)	35 (85.4)	9 (22.0)	8.2 (-4.30, 20.69)	2.892 (0.532, 15.710)	5 (14.3)	30 (85.7)	7 (20.0)	7.4 (-6.07, 20.83)	2.551 (0.444, 14.640)	0.2939
Rilzabrutinib 400mg QPM (N=38)	2 (5.3)	36 (94.7)	7 (18.4)	0.3 (-9.40, 9.99)	1.065 (0.136, 8.313)	2 (5.4)	35 (94.6)	7 (18.9)	-0.1 (-10.46, 10.32)	0.986 (0.128, 7.566)	0.9892
Placebo (N=40)	2 (5.0)	38 (95.0)	5 (12.5)			2 (5.6)	34 (94.4)	4 (11.1)			

ITT Population						Omalizumab-Naïve Population					
Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^b	P-value vs. placebo ^b	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^b	P-value vs. placebo ^b
Rilzabrutinib 400mg T1D (N=41)	10 (24.4)	31 (75.6)	11 (26.8)	9.4 (-7.01, 25.85)	1.995 (0.587, 6.780)	7 (20.0)	28 (80.0)	8 (22.9)	6.9 (-9.40, 23.14)	1.800 (0.444, 7.300)	0.4283
Rilzabrutinib 400mg BID (N=41)	8 (19.5)	33 (80.5)	14 (34.1)	5.4 (-10.49, 21.25)	1.511 (0.443, 5.159)	5 (14.3)	30 (85.7)	11 (31.4)	2.6 (-13.10, 18.22)	1.258 (0.308, 5.128)	0.7536
Rilzabrutinib 400mg QPM (N=38)	1 (2.6)	37 (97.4)	10 (26.3)	-10.0 (-21.65, 1.62)	0.194 (0.022, 1.698)	1 (2.7)	36 (97.3)	10 (27.0)	-8.7 (-20.44, 2.97)	0.219 (0.024, 2.012)	0.1517
Placebo (N=40)	5 (12.5)	35 (87.5)	7 (17.5)			4 (11.1)	32 (88.9)	5 (13.9)			

^a OR: odds ratio; RRD: response rate difference; derived from the Mantel-Haenszel estimator
^b CMH test was performed on the association between the responder status and intervention group, stratified by region.

Table 23. Proportion of participants with UAS7 reduction from baseline of 10 points or more over time up to Week 12 - ITT population

ITT Population						Omalizumab-Naïve Participants					
Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^b	P-value vs. placebo ^b
Week 1											
Rilzabrutinib 400mg T1D (N=41)	23 (56.1)	18 (43.9)	0	32.5 (12.09, 52.85)	4.196 (1.583, 11.120)	18 (51.4)	17 (48.6)	0	28.5 (6.70, 50.35)	3.580 (1.268, 10.109)	0.0162
Rilzabrutinib 400mg BID (N=41)	18 (43.9)	23 (56.1)	1 (2.4)	20.0 (0.12, 39.90)	2.607 (0.975, 6.973)	16 (45.7)	19 (54.3)	0	22.3 (0.93, 43.62)	2.862 (1.007, 8.140)	0.0475
Rilzabrutinib 400mg QPM (N=38)	12 (31.6)	26 (68.4)	0	10.5 (-9.62, 30.53)	1.672 (0.618, 4.526)	11 (29.7)	26 (70.3)	0	8.2 (-12.26, 28.61)	1.510 (0.535, 4.266)	0.4319
Placebo (N=40)	9 (22.5)	31 (77.5)	0			8 (22.2)	28 (77.8)	0			
Week 2											
Rilzabrutinib 400mg T1D (N=41)	28 (68.3)	13 (31.7)	0	40.6 (20.49, 60.75)	5.982 (2.230, 16.042)	22 (62.9)	13 (37.1)	0	39.0 (17.40, 60.57)	5.505 (1.931, 15.697)	0.0012
Rilzabrutinib 400mg BID (N=41)	22 (53.7)	19 (46.3)	2 (4.9)	27.8 (7.35, 48.28)	3.388 (1.308, 8.771)	18 (51.4)	17 (48.6)	1 (2.9)	28.9 (7.38, 50.39)	3.686 (1.307, 10.399)	0.0141

ITT Population										Omalizumab-Naïve Participants				
	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	ITT Population		P-value vs. placebo ^b	OR (95% CI) for placebo ^b	Non- responder n (%)	Imputed non- responder n (%)	RRD (%)	OR (95% CI) for placebo ^b	P-value vs. placebo ^b		
				responder n (%)	vs. placebo (95% CI) ^a									
Rilzabrutinib 400mg QPM (N=38)	15 (39.5)	23 (60.5)	0	16.6 (-3.87, 37.01)	2.169 (0.813, 5.785)	0.1176	14 (37.8)	23 (62.2)	0	16.6 (-4.45, 37.65)	2.174 (0.790, 5.983)	0.1263		
Placebo (N=40)	10 (25.0)	30 (75.0)	1 (2.5)				8 (22.2)	28 (77.8)	1 (2.8)					
Week 3														
Rilzabrutinib 400mg TID (N=41)	27 (65.9)	14 (34.1)	0	31.4 (9.76, 53.03)	3.444 (1.387, 8.548)	0.0057	21 (60.0)	14 (40.0)	0	27.1 (3.88, 50.28)	2.949 (1.124, 7.739)	0.0251		
Rilzabrutinib 400mg BID (N=41)	21 (51.2)	20 (48.8)	1 (2.4)	18.0 (-3.33, 39.36)	2.109 (0.854, 5.210)	0.1076	17 (48.6)	18 (51.4)	0	17.2 (-5.49, 39.84)	2.057 (0.781, 5.418)	0.1481		
Rilzabrutinib 400mg QPM (N=38)	16 (42.1)	22 (57.9)	0	11.7 (-9.57, 32.93)	1.663 (0.650, 4.256)	0.2880	15 (40.5)	22 (59.5)	0	11.4 (-10.23, 33.01)	1.665 (0.624, 4.445)	0.3118		
Placebo (N=40)	13 (32.5)	27 (67.5)	1 (2.5)				11 (30.6)	25 (69.4)	1 (2.8)					
Week 4														
Rilzabrutinib 400mg TID (N=41)	29 (70.7)	12 (29.3)	3 (7.3)	29.4 (8.33, 50.37)	3.520 (1.371, 9.039)	0.0078	24 (68.6)	11 (31.4)	3 (8.6)	31.2 (8.87, 53.45)	3.855 (1.396, 10.650)	0.0083		
Rilzabrutinib 400mg BID (N=41)	22 (53.7)	19 (46.3)	4 (9.8)	14.7 (-6.60, 36.10)	1.853 (0.751, 4.572)	0.1892	18 (51.4)	17 (48.6)	2 (5.7)	16.8 (-5.71, 39.38)	2.046 (0.772, 5.420)	0.1587		
Rilzabrutinib 400mg QPM (N=38)	15 (39.5)	23 (60.5)	1 (2.6)	4.4 (-16.40, 25.18)	1.224 (0.469, 3.190)	0.6858	14 (37.8)	23 (62.2)	1 (2.7)	6.0 (-15.25, 27.19)	1.322 (0.487, 3.588)	0.5916		
Placebo (N=40)	15 (37.5)	25 (62.5)	2 (5.0)				12 (33.3)	24 (66.7)	2 (5.6)					
Week 5														
Rilzabrutinib 400mg TID (N=41)	29 (70.7)	12 (29.3)	3 (7.3)	23.5 (2.40, 44.63)	2.703 (1.064, 6.869)	0.0352	24 (68.6)	11 (31.4)	2 (5.7)	22.4 (-0.46, 45.18)	2.512 (0.941, 6.705)	0.0629		
Rilzabrutinib 400mg BID (N=41)	22 (53.7)	19 (46.3)	5 (12.2)	5.2 (-16.49, 26.99)	1.238 (0.511, 3.003)	0.6393	19 (54.3)	16 (45.7)	2 (5.7)	7.0 (-16.15, 30.06)	1.329 (0.515, 3.430)	0.5596		
Rilzabrutinib 400mg QPM (N=38)	17 (44.7)	21 (55.3)	2 (5.3)	-1.3 (-23.67, 21.07)	0.950 (0.390, 2.313)	0.9084	16 (43.2)	21 (56.8)	2 (5.4)	-3.4 (-26.65, 19.95)	0.877 (0.354, 2.177)	0.7743		
Placebo (N=40)	19 (47.5)	21 (52.5)	3 (7.5)				17 (47.2)	19 (52.8)	3 (8.3)					
Week 6														
Rilzabrutinib 400mg TID (N=41)	25 (61.0)	16 (39.0)	5 (12.2)	14.2 (-7.59, 35.94)	1.787 (0.727, 4.392)	0.2012	20 (57.1)	15 (42.9)	4 (11.4)	14.6 (-9.14, 38.27)	1.770 (0.690, 4.539)	0.2249		
Rilzabrutinib 400mg BID (N=41)	21 (51.2)	20 (48.8)	4 (9.8)	4.9 (-16.84, 26.74)	1.222 (0.505, 2.956)	0.6576	18 (51.4)	17 (48.6)	2 (5.7)	9.8 (-13.40, 32.94)	1.486 (0.577, 3.825)	0.4130		

ITT Population										Omalizumab-Naïve Participants			
	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%)	OR (95% CI) for placebo vs. rilzabrutinib	P-value vs. placebo ^a	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%)	OR (95% CI) for placebo vs. rilzabrutinib	P-value vs. placebo ^b	
Rilzabrutinib 400mg QPM (N=38)	16 (42.1)	22 (57.9)	4 (10.5)	-1.0 (-22.78, 20.79)	0.959 (0.384, 2.394)	0.9298	15 (40.5)	22 (59.5)	4 (10.8)	-0.5 (-22.90, 21.98)	0.981 (0.382, 2.519)	0.9682	
Placebo (N=40)	18 (45.0)	22 (55.0)	6 (15.0)				15 (41.7)	21 (58.3)	5 (13.9)				
Week 7													
Rilzabrutinib 400mg TID (N=41)	25 (61.0)	16 (39.0)	6 (14.6)	18.7 (-1.93, 39.42)	2.334 (0.897, 6.074)	0.0837	22 (62.9)	13 (37.1)	5 (14.3)	22.3 (0.42, 44.16)	2.765 (0.982, 7.782)	0.0534	
Rilzabrutinib 400mg BID (N=41)	23 (56.1)	18 (43.9)	4 (9.8)	15.6 (-5.89, 37.05)	1.899 (0.774, 4.661)	0.1689	20 (57.1)	15 (42.9)	2 (5.7)	18.5 (-4.23, 41.15)	2.154 (0.819, 5.667)	0.1269	
Rilzabrutinib 400mg QPM (N=38)	16 (42.1)	22 (57.9)	6 (15.8)	3.5 (-18.15, 25.06)	1.159 (0.461, 2.913)	0.7571	15 (40.5)	22 (59.5)	6 (16.2)	2.2 (-20.27, 24.65)	1.096 (0.427, 2.814)	0.8496	
Placebo (N=40)	16 (40.0)	24 (60.0)	5 (12.5)				14 (38.9)	22 (61.1)	4 (11.1)				
Week 8													
Rilzabrutinib 400mg TID (N=41)	27 (65.9)	14 (34.1)	8 (19.5)	23.2 (1.88, 44.51)	2.657 (1.048, 6.735)	0.0359	22 (62.9)	13 (37.1)	7 (20.0)	25.7 (2.65, 48.81)	2.815 (1.057, 7.500)	0.0307	
Rilzabrutinib 400mg BID (N=41)	24 (58.5)	17 (41.5)	5 (12.2)	17.5 (-4.45, 39.55)	1.985 (0.826, 4.769)	0.1221	21 (60.0)	14 (40.0)	3 (8.6)	24.0 (0.44, 47.47)	2.484 (0.977, 6.318)	0.0492	
Rilzabrutinib 400mg QPM (N=38)	17 (44.7)	21 (55.3)	7 (18.4)	5.3 (-16.20, 26.83)	1.257 (0.498, 3.172)	0.6342	16 (43.2)	21 (56.8)	7 (18.9)	6.6 (-15.50, 28.73)	1.331 (0.511, 3.468)	0.5608	
Placebo (N=40)	16 (40.0)	24 (60.0)	5 (12.5)				13 (36.1)	23 (63.9)	4 (11.1)				
Week 9													
Rilzabrutinib 400mg TID (N=41)	28 (68.3)	13 (31.7)	7 (17.1)	26.2 (5.60, 46.73)	3.243 (1.218, 8.639)	0.0147	23 (65.7)	12 (34.3)	6 (17.1)	29.2 (6.92, 51.53)	3.460 (1.235, 9.698)	0.0114	
Rilzabrutinib 400mg BID (N=41)	21 (51.2)	20 (48.8)	9 (22.0)	10.6 (-12.31, 33.44)	1.471 (0.633, 3.419)	0.3507	18 (51.4)	17 (48.6)	7 (20.0)	16.0 (-8.61, 40.51)	1.764 (0.720, 4.325)	0.1862	
Rilzabrutinib 400mg QPM (N=38)	18 (47.4)	20 (52.6)	6 (15.8)	8.5 (-12.74, 29.70)	1.452 (0.567, 3.719)	0.4398	17 (45.9)	20 (54.1)	6 (16.2)	9.7 (-12.34, 31.72)	1.522 (0.581, 3.985)	0.3873	
Placebo (N=40)	16 (40.0)	24 (60.0)	6 (15.0)				13 (36.1)	23 (63.9)	5 (13.9)				
Week 10													
Rilzabrutinib 400mg TID (N=41)	27 (65.9)	14 (34.1)	7 (17.1)	15.7 (-5.15, 36.64)	2.018 (0.784, 5.194)	0.1447	23 (65.7)	12 (34.3)	5 (14.3)	19.8 (-2.84, 42.45)	2.327 (0.859, 6.308)	0.0882	
Rilzabrutinib 400mg BID (N=41)	21 (51.2)	20 (48.8)	10 (24.4)	2.8 (-19.65, 25.28)	1.113 (0.473, 2.623)	0.8053	18 (51.4)	17 (48.6)	8 (22.9)	7.2 (-16.87, 31.33)	1.312 (0.529, 3.255)	0.5549	

ITT Population														Omalizumab-Naïve Participants					
	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for placebo (95% CI) ^a	OR (95% CI) for placebo ^a	P-value vs. placebo ^b	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for placebo (95% CI) ^a	OR (95% CI) for placebo ^a	P-value vs. placebo ^b	P-value vs. placebo ^b						
Week 11																			
Rilzabrutinib 400mg QPM (N=38)	19 (50.0)	19 (50.0)	6 (15.8)	3.5 (-18.12, 25.03)	1.159 (0.460, 2.918)	0.7599	18 (48.6)	19 (51.4)	6 (16.2)	4.1 (-18.19, 26.30)	1.190 (0.459, 3.082)	0.7267							
Placebo (N=40)	19 (47.5)	21 (52.5)	5 (12.5)				16 (44.4)	20 (55.6)	4 (11.1)										
Week 12																			
Rilzabrutinib 400mg TID (N=41)	27 (65.9)	14 (34.1)	6 (14.6)	10.3 (-10.11, 30.69)	1.624 (0.618, 4.267)	0.3217	23 (65.7)	12 (34.3)	4 (11.4)	13.6 (-8.65, 35.92)	1.839 (0.669, 5.054)	0.2206							
Rilzabrutinib 400mg BID (N=41)	22 (53.7)	19 (46.3)	9 (22.0)	0.2 (-22.10, 22.56)	1.009 (0.426, 2.389)	0.9836	19 (54.3)	16 (45.7)	7 (20.0)	4.4 (-19.56, 28.37)	1.183 (0.474, 2.949)	0.7166							
Rilzabrutinib 400mg QPM (N=38)	19 (50.0)	19 (50.0)	7 (18.4)	-1.3 (-22.73, 20.13)	0.945 (0.373, 2.395)	0.9077	18 (48.6)	19 (51.4)	7 (18.9)	-1.3 (-23.40, 20.84)	0.946 (0.363, 2.465)	0.9118							
Placebo (N=40)	21 (52.5)	19 (47.5)	5 (12.5)				18 (50.0)	18 (50.0)	4 (11.1)										
Week 12																			
Rilzabrutinib 400mg TID (N=41)	23 (56.1)	18 (43.9)	11 (26.8)	11.7 (-9.78, 33.27)	1.638 (0.660, 4.062)	0.2871	20 (57.1)	15 (42.9)	8 (22.9)	14.0 (-8.89, 36.90)	1.805 (0.681, 4.784)	0.2342							
Rilzabrutinib 400mg BID (N=41)	18 (43.9)	23 (56.1)	14 (34.1)	1.0 (-21.02, 23.03)	1.041 (0.434, 2.493)	0.9295	15 (42.9)	20 (57.1)	11 (31.4)	1.7 (-21.77, 25.12)	1.069 (0.420, 2.719)	0.8897							
Rilzabrutinib 400mg QPM (N=38)	14 (36.8)	24 (63.2)	10 (26.3)	-4.0 (-25.52, 17.49)	0.841 (0.333, 2.125)	0.7203	13 (35.1)	24 (64.9)	10 (27.0)	-5.8 (-27.91, 16.37)	0.780 (0.300, 2.029)	0.6176							
Placebo (N=40)	17 (42.5)	23 (57.5)	7 (17.5)				15 (41.7)	21 (58.3)	5 (13.9)										

^a OR: odds ratio; RRD: response rate difference; derived from the Mantel-Haenszel estimator
^b CMH test was performed on the association between the responder status and intervention group, stratified by region.
Note: Participants who received selected prohibited/rescue medications (high/medium impact on efficacy confirmed through blinded medical review) before the given week were considered as non-responders, and participants with missing data at the given week were considered as non-responders up to Week 12.

ISS7

[00243] Rilzabrutinib treatment led to significant improvements in ISS7. Notably, participants receiving 400 mg TID rilzabrutinib exhibited a significant reduction in ISS7 at Week 12, thereby meeting the primary endpoint in the United States and United States Reference Countries (see **Figures 15-17** and **Tables 24-26**). In the ITT population, participants receiving 400 mg TID rilzabrutinib exhibited a LS mean change from baseline at Week 12 of -9.58 (p=0.0181) points, while patients receiving the placebo exhibited a LS mean change of -6.31 points (see **Table 24**). Similar results were observed for the omalizumab-naïve population, both prior to (LS mean change from baseline of -9.21, p=0.0168; see **Table 25**) and following (LS mean change from baseline of -9.57, p=0.0078; see **Table 26**) the removal of the asymptomatic outlier (UAS7/ISS7=0 at baseline) who was erroneously randomized into the 400 mg TID rilzabrutinib arm.

[00244] In the 400 mg TID arm, all patients except one showed improvement in the weekly ISS7. Moreover, a clear separation was observed between patients receiving 400 mg TID rilzabrutinib and patients receiving the placebo across all response thresholds (see **Figure 15**).

[00245] Further analysis of the omalizumab-naïve population supports the efficacy of rilzabrutinib treatment in CSU (see **Table 27**). Overall, baseline participant demographics did not appear to affect the efficacy of 400 mg TID rilzabrutinib. Moreover, 400 mg TID rilzabrutinib treatment was efficacious in patients with characteristics such as low IgE, a positive BHRA status, and a history of angioedema.

Table 24. Change from baseline in ISS7 at Week 12 (ITT population)

ISS7	Placebo (N=40)	Rilzabrutinib 400mg QPM (N=38)	Rilzabrutinib 400mg BID (N=41)	Rilzabrutinib 400mg TID (N=41)
Baseline				
Number	40	38	41	41
Mean (SD)	15.60 (4.24)	16.50 (3.53)	15.80 (3.68)	15.88 (4.37)
Median	14.50	16.50	15.00	15.00
Q1 ; Q3	12.00 ; 20.50	14.00 ; 20.00	13.00 ; 19.00	14.00 ; 20.00
Min ; Max	8.0 ; 21.0	9.0 ; 21.0	8.0 ; 21.0	0.0 ; 21.0
Week 12				
Number (observed/imputed)	35 (33/2)	31 (28/3)	30 (27/3)	33 (30/3)
Mean (SD)	9.96 (7.02)	11.37 (5.51)	7.61 (7.18)	5.59 (5.58)
Median	8.00	11.20	7.00	6.00
Q1 ; Q3	4.67 ; 14.00	7.00 ; 15.17	0.00 ; 13.00	0.00 ; 8.75
Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0

ISS7	Placebo (N=40)	Rilzabrutinib 400mg QPM (N=38)	Rilzabrutinib 400mg BID (N=41)	Rilzabrutinib 400mg TID (N=41)
Change from baseline				
Number (observed/imputed)	35 (33/2)	31 (28/3)	30 (27/3)	33 (30/3)
Mean (SD)	-5.67 (7.15)	-5.95 (4.87)	-8.21 (6.76)	-10.68 (6.50)
Median	-6.00	-5.67	-8.00	-10.67
Q1 ; Q3	-10.00 ; 0.00	-8.60 ; -1.40	-13.00 ; -3.00	-16.00 ; -4.25
Min ; Max	-21.0 ; 9.8	-19.0 ; 1.0	-21.0 ; 2.0	-21.0 ; 0.0
LS Mean (SE) ^a	-6.31 (1.02)	-5.46 (1.03)	-8.06 (1.02)	-9.58 (1.01)
LS Mean Diff ^a vs. placebo (95% CI) ^a		0.85 (-1.90, 3.60)	-1.75 (-4.46, 0.95)	-3.26 (-5.97, -0.56)
P-value vs. placebo ^a		0.5439	0.2041	0.0181

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

Note: Data collected after study intervention discontinuation were included. Data post selected prohibited/rescue medications (high/medium impact on efficacy confirmed through blinded medical review) were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF; other missing data were imputed by MI.

Descriptive statistics at Week 12 include participants with WOCF imputation at Week 12, and participants whose values were imputed by MI at Week 12 were excluded from the descriptive analysis.

Table 25. Primary Analysis: Change from Baseline in ISS7 at Week 12 (Omalizumab-Naïve Population)

ISS7	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Baseline				
Number	36	37	35	35
Mean (SD)	15.14 (4.16)	16.38 (3.50)	15.45 (3.72)	15.69 (4.26)
Median	14.00	16.00	14.00	14.00
Q1 ; Q3	12.00 ; 19.50	14.00 ; 20.00	13.00 ; 19.00	14.00 ; 19.00
Min ; Max	8.0 ; 21.0	9.0 ; 21.0	8.0 ; 21.0	0.0 ; 21.0
Week 12				
Number (observed/imputed)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)
Mean (SD)	10.02 (6.82)	11.51 (5.54)	8.09 (6.95)	5.77 (5.26)
Median	8.50	11.60	7.00	7.00
Q1 ; Q3	4.83 ; 14.00	7.00 ; 15.17	1.17 ; 13.00	0.00 ; 8.88
Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0
Change from baseline				
Number (observed/imputed)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)
Mean (SD)	-5.11 (6.70)	-5.69 (4.72)	-7.40 (6.12)	-10.27 (6.02)
Median	-5.50	-5.33	-7.00	-10.33
Q1 ; Q3	-9.00 ; -0.25	-8.17 ; -1.40	-11.00 ; -3.00	-14.50 ; -4.63
Min ; Max	-17.5 ; 9.8	-19.0 ; 1.0	-20.0 ; 2.0	-21.0 ; 0.0
LS Mean (SE) ^a	-5.77 (1.05)	-5.19 (1.02)	-7.73 (1.06)	-9.21 (1.05)
LS Mean Diff ^a vs. placebo (95% CI) ^a		0.58 (-2.24, 3.40)	-1.96 (-4.77, 0.86)	-3.44 (-6.25, -0.62)
P-value vs. placebo ^a		0.6869	0.1728	0.0168

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

ISS7	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
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Note: Data collected after study intervention discontinuation were included. Data post selected prohibited/rescue medications (high/medium impact on efficacy confirmed through blinded medical review) were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF; other missing data were imputed by MI.

Descriptive statistics at Week 12 include participants with WOCF imputation at Week 12, and participants whose values were imputed by MI at Week 12 were excluded from the descriptive analysis.

Table 26. Change from Baseline in ISS7 at Week 12 (Omalizumab-Naïve Population with Outlier Removed from Analysis)

ISS7	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=34)
Baseline				
Number	36	37	35	34
Mean (SD)	15.14 (4.16)	16.38 (3.50)	15.45 (3.72)	16.15 (3.32)
Median	14.00	16.00	14.00	14.50
Q1 ; Q3	12.00 ; 19.50	14.00 ; 20.00	13.00 ; 19.00	14.00 ; 19.00
Min ; Max	8.0 ; 21.0	9.0 ; 21.0	8.0 ; 21.0	9.0 ; 21.0
Week 12				
Number (observed/imputed)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)
Mean (SD)	10.02 (6.82)	11.51 (5.54)	8.09 (6.95)	5.77 (5.26)
Median	8.50	11.60	7.00	7.00
Q1 ; Q3	4.83 ; 14.00	7.00 ; 15.17	1.17 ; 13.00	0.00 ; 8.88
Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0
Change from baseline				
Number (observed/imputed)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)
Mean (SD)	-5.11 (6.70)	-5.69 (4.72)	-7.40 (6.12)	-10.27 (6.02)
Median	-5.50	-5.33	-7.00	-10.33
Q1 ; Q3	-9.00 ; -0.25	-8.17 ; -1.40	-11.00 ; -3.00	-14.50 ; -4.63
Min ; Max	-17.5 ; 9.8	-19.0 ; 1.0	-20.0 ; 2.0	-21.0 ; 0.0
LS Mean (SE) ^a	-5.71 (1.02)	-5.29 (1.01)	-7.76 (1.06)	-9.57 (1.06)
LS Mean Diff vs. placebo (95% CI) ^a		0.42 (-2.33, 3.18)	-2.05 (-4.84, 0.74)	-3.86 (-6.71, -1.02)
P-value vs. placebo ^a		0.7634	0.1491	0.0078

^a Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group and region as covariates.

Note: Data collected after study intervention discontinuation were included. Data post selected prohibited/rescue medications (high/medium impact on efficacy confirmed through blinded medical review) were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF; other missing data were imputed by MI.

Descriptive statistics at Week 12 include participants with WOCF imputation at Week 12, and participants whose values were imputed by MI at Week 12 were excluded from the descriptive analysis.

One patient was randomized to Rilzabrutinib 400mg TID group by mistake (baseline ISS7/UAS7=0). Removed this participant from the analysis.

Table 27. Subgroup Analysis: Change from Baseline in ISS7 at Week 12 by Subgroups (Omalizumab-naïve population)

	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Age group (years)				
< 44 (Median)				
Number (observed/imputed)	21 (20/1)	16 (14/2)	12 (12/0)	8 (8/0)
Mean (SD)	-4.31 (6.69)	-5.45 (5.57)	-5.97 (4.65)	-10.53 (5.94)
LS Mean (SE) ^a	-4.47 (1.30)	-4.68 (1.40)	-7.05 (1.52)	-9.04 (1.89)
LS Mean Diff vs. placebo (95% CI) ^a		-0.21 (-4.03, 3.62)	-2.58 (-6.51, 1.36)	-4.56 (-9.03, -0.09)
P-value vs. placebo ^a		0.9161	0.1987	0.0454
≥ 44 (Median)				
Number (observed/imputed)	11 (11/0)	14 (13/1)	14 (12/2)	20 (19/1)
Mean (SD)	-6.64 (6.75)	-5.95 (3.70)	-8.62 (7.08)	-10.16 (6.20)
LS Mean (SE) ^a	-6.60 (1.68)	-4.77 (1.45)	-8.10 (1.40)	-9.26 (1.23)
LS Mean Diff vs. placebo (95% CI) ^a		1.83 (-2.53, 6.19)	-1.50 (-5.80, 2.80)	-2.66 (-6.72, 1.41)
P-value vs. placebo ^a		0.4100	0.4943	0.2007
Overall p-value for interaction ^b				0.9294
Age group (years)				
< 65				
Number (observed/imputed)	30 (29/1)	29 (26/3)	25 (23/2)	24 (23/1)
Mean (SD)	-5.52 (6.47)	-5.68 (4.80)	-7.17 (6.13)	-9.73 (5.71)
LS Mean (SE) ^a	-5.66 (1.04)	-4.78 (1.01)	-7.37 (1.05)	-8.63 (1.09)
LS Mean Diff vs. placebo (95% CI) ^a		0.88 (-2.00, 3.75)	-1.71 (-4.59, 1.18)	-2.97 (-5.90, -0.03)
P-value vs. placebo ^a		0.5497	0.2453	0.0478
≥ 65				
Number (observed/imputed)	2 (2/0)	1 (1/0)	1 (1/0)	4 (4/0)
Mean (SD)	1.00 (9.90)	-5.83 (NC)	-13.00 (NC)	-13.50 (7.71)
LS Mean (SE) ^a	0.90 (3.84)	2.48 (6.23)	-13.32 (4.62)	-12.67 (2.73)
LS Mean Diff vs. placebo (95% CI) ^a		1.58 (-12.80, 15.96)	-14.22 (-25.98, -2.46)	-13.57 (-22.81, -4.32)
P-value vs. placebo ^a		0.8295	0.0178	0.0040
Overall p-value for interaction ^b				0.1940
Gender				
Male				
Number (observed/imputed)	11 (11/0)	8 (8/0)	9 (8/1)	5 (5/0)
Mean (SD)	-3.50 (7.05)	-5.20 (5.77)	-8.17 (6.82)	-7.08 (3.25)
LS Mean (SE) ^a	-3.55 (1.87)	-4.68 (2.21)	-8.42 (1.87)	-6.50 (2.65)
LS Mean Diff vs. placebo (95% CI) ^a		-1.14 (-6.82, 4.55)	-4.88 (-9.99, 0.23)	-2.95 (-9.38, 3.48)
P-value vs. placebo ^a		0.6946	0.0613	0.3683
Female				
Number (observed/imputed)	21 (20/1)	22 (19/3)	17 (16/1)	23 (22/1)
Mean (SD)	-5.95 (6.52)	-5.86 (4.42)	-6.99 (5.89)	-10.96 (6.30)
LS Mean (SE) ^a	-6.30 (1.20)	-4.77 (1.12)	-6.92 (1.24)	-9.80 (1.09)
LS Mean Diff vs. placebo (95% CI) ^a		1.52 (-1.76, 4.81)	-0.62 (-4.00, 2.75)	-3.50 (-6.68, -0.33)
P-value vs. placebo ^a		0.3627	0.7173	0.0305
Overall p-value for interaction ^b				0.3883

	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Baseline weight (kg)				
< 72.9 (Median)				
Number (observed/imputed)	18 (18/0)	17 (16/1)	16 (15/1)	13 (13/0)
Mean (SD)	-5.88 (6.08)	-4.51 (3.00)	-6.55 (5.45)	-11.22 (7.22)
LS Mean (SE) ^a	-5.75 (1.29)	-3.98 (1.27)	-6.60 (1.34)	-9.97 (1.47)
LS Mean Diff vs. placebo (95% CI) ^a		1.77 (-1.80, 5.35)	-0.84 (-4.46, 2.77)	-4.22 (-8.04, -0.39)
P-value vs. placebo ^a		0.3311	0.6472	0.0306
≥ 72.9 (Median)				
Number (observed/imputed)	14 (13/1)	13 (11/2)	10 (9/1)	15 (14/1)
Mean (SD)	-4.12 (7.53)	-7.22 (6.10)	-8.75 (7.15)	-9.44 (4.85)
LS Mean (SE) ^a	-4.65 (1.54)	-5.86 (1.55)	-8.28 (1.53)	-8.80 (1.38)
LS Mean Diff vs. placebo (95% CI) ^a		-1.21 (-5.49, 3.07)	-3.62 (-7.92, 0.67)	-4.15 (-8.21, -0.09)
P-value vs. placebo ^a		0.5791	0.0983	0.0451
Overall p-value for interaction ^b				0.4436
Baseline weight (kg)				
< 60				
Number (observed/imputed)	10 (10/0)	6 (5/1)	7 (7/0)	8 (8/0)
Mean (SD)	-4.70 (5.59)	-4.71 (2.89)	-5.29 (4.80)	-11.17 (7.60)
LS Mean (SE) ^a	-4.34 (1.79)	-4.12 (2.29)	-5.70 (2.01)	-11.07 (2.04)
LS Mean Diff vs. placebo (95% CI) ^a		0.22 (-5.52, 5.95)	-1.37 (-6.59, 3.86)	-6.74 (-12.06, -1.41)
P-value vs. placebo ^a		0.9410	0.6083	0.0131
≥ 60 - <90				
Number (observed/imputed)	15 (14/1)	21 (19/2)	16 (14/2)	17 (17/0)
Mean (SD)	-5.69 (7.04)	-5.28 (4.97)	-7.71 (6.96)	-9.91 (5.71)
LS Mean (SE) ^a	-6.06 (1.42)	-4.36 (1.15)	-7.08 (1.35)	-8.41 (1.24)
LS Mean Diff vs. placebo (95% CI) ^a		1.71 (-1.90, 5.31)	-1.01 (-4.85, 2.82)	-2.35 (-6.03, 1.34)
P-value vs. placebo ^a		0.3530	0.6049	0.2123
≥ 90				
Number (observed/imputed)	7 (7/0)	3 (3/0)	3 (3/0)	3 (2/1)
Mean (SD)	-4.45 (8.22)	-10.47 (4.01)	-10.67 (1.53)	-9.89 (4.55)
LS Mean (SE) ^a	-5.14 (2.38)	-8.76 (3.75)	-10.60 (2.52)	-10.90 (3.63)
LS Mean Diff vs. placebo (95% CI) ^a		-3.62 (-12.56, 5.32)	-5.46 (-12.33, 1.40)	-5.76 (-14.13, 2.61)
P-value vs. placebo ^a		0.4278	0.1187	0.1775
Overall p-value for interaction ^b				0.7163
Baseline BMI (kg/m ²)				
< 25				
Number (observed/imputed)	15 (15/0)	14 (13/1)	17 (16/1)	11 (11/0)
Mean (SD)	-4.50 (5.63)	-4.18 (3.14)	-7.34 (6.20)	-9.13 (7.05)
LS Mean (SE) ^a	-4.42 (1.40)	-3.64 (1.42)	-7.22 (1.29)	-9.17 (1.68)
LS Mean Diff vs. placebo (95% CI) ^a		0.77 (-3.14, 4.68)	-2.81 (-6.51, 0.90)	-4.75 (-9.04, -0.47)
P-value vs. placebo ^a		0.6983	0.1382	0.0297
≥ 25 - <30				

	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Number (observed/imputed)	9 (8/1)	7 (6/1)	5 (4/1)	13 (13/0)
Mean (SD)	-3.39 (8.46)	-5.60 (6.96)	-7.10 (7.55)	-10.74 (5.51)
LS Mean (SE) ^a	-5.55 (1.96)	-3.43 (1.97)	-6.90 (2.41)	-8.43 (1.46)
LS Mean Diff vs. placebo (95% CI) ^a		2.13 (-3.54, 7.80)	-1.35 (-7.44, 4.74)	-2.88 (-7.76, 2.00)
P-value vs. placebo ^a		0.4619	0.6647	0.2473
≥ 30				
Number (observed/imputed)	8 (8/0)	9 (8/1)	4 (4/0)	4 (3/1)
Mean (SD)	-8.19 (6.16)	-8.09 (4.22)	-8.00 (5.48)	-11.88 (5.44)
LS Mean (SE) ^a	-7.67 (2.06)	-7.49 (1.92)	-8.24 (2.10)	-10.85 (2.59)
LS Mean Diff vs. placebo (95% CI) ^a		0.17 (-5.29, 5.63)	-0.57 (-6.35, 5.21)	-3.19 (-9.64, 3.26)
P-value vs. placebo ^a		0.9508	0.8467	0.3327
Overall p-value for interaction ^b				0.9842
Region ^c				
Asia				
Number (observed/imputed)	8 (8/0)	9 (9/0)	8 (8/0)	6 (6/0)
Mean (SD)	-3.46 (5.86)	-5.66 (5.13)	-6.86 (5.22)	-8.21 (6.23)
LS Mean (SE) ^a	-3.45 (1.91)	-5.17 (1.81)	-6.99 (1.97)	-8.33 (2.09)
LS Mean Diff vs. placebo (95% CI) ^a		-1.72 (-6.88, 3.45)	-3.54 (-8.93, 1.85)	-4.87 (-10.41, 0.67)
P-value vs. placebo ^a		0.5148	0.1978	0.0848
Latin America				
Number (observed/imputed)	11 (10/1)	10 (7/3)	8 (6/2)	6 (6/0)
Mean (SD)	-7.29 (7.65)	-6.51 (5.89)	-4.42 (6.21)	-7.34 (5.81)
LS Mean (SE) ^a	-6.59 (1.75)	-5.19 (1.62)	-4.75 (1.94)	-6.07 (2.20)
LS Mean Diff vs. placebo (95% CI) ^a		1.40 (-3.23, 6.04)	1.84 (-3.27, 6.94)	0.52 (-4.93, 5.96)
P-value vs. placebo ^a		0.5532	0.4802	0.8521
Eastern Europe				
Number (observed/imputed)	2 (2/0)	4 (4/0)	3 (3/0)	4 (4/0)
Mean (SD)	-6.00 (8.49)	-5.54 (3.34)	-10.81 (7.84)	-13.17 (6.21)
LS Mean (SE) ^a	-12.67 (4.21)	-4.74 (2.49)	-4.38 (4.01)	-14.02 (2.49)
LS Mean Diff vs. placebo (95% CI) ^a		7.93 (-2.07, 17.93)	8.28 (-5.64, 22.21)	-1.35 (-10.49, 7.79)
P-value vs. placebo ^a		0.1201	0.2436	0.7720
Western Countries				
Number (observed/imputed)	11 (11/0)	7 (7/0)	7 (7/0)	12 (11/1)
Mean (SD)	-3.97 (6.35)	-4.61 (3.50)	-9.95 (5.74)	-11.79 (5.72)
LS Mean (SE) ^a	-4.55 (1.70)	-3.02 (2.04)	-10.12 (1.65)	-9.58 (1.54)
LS Mean Diff vs. placebo (95% CI) ^a		1.53 (-3.74, 6.79)	-5.57 (-10.21, -0.93)	-5.03 (-9.55, -0.51)
P-value vs. placebo ^a		0.5697	0.0186	0.0293
Overall p-value for interaction ^b				0.3768
Race				
White				
Number (observed/imputed)	24 (23/1)	21 (18/3)	18 (16/2)	20 (19/1)
Mean (SD)	-5.66 (6.98)	-5.70 (4.66)	-7.64 (6.60)	-10.88 (6.28)
LS Mean (SE) ^a	-6.01 (1.20)	-4.41 (1.21)	-7.91 (1.21)	-9.18 (1.24)
LS Mean Diff vs. placebo (95% CI) ^a		1.60 (-1.77, 4.97)	-1.90 (-5.24, 1.43)	-3.17 (-6.56, 0.21)
P-value vs. placebo ^a		0.3527	0.2635	0.0663

	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
All the Others				
Number (observed/imputed)	8 (8/0)	9 (9/0)	8 (8/0)	8 (8/0)
Mean (SD)	-3.46 (5.86)	-5.66 (5.13)	-6.86 (5.22)	-8.74 (5.36)
LS Mean (SE) ^a	-3.47 (1.86)	-4.94 (1.72)	-6.99 (1.92)	-8.74 (1.80)
LS Mean Diff vs. placebo (95% CI) ^a		-1.48 (-6.47, 3.52)	-3.52 (-8.76, 1.71)	-5.27 (-10.33, -0.21)
P-value vs. placebo ^a		0.5627	0.1874	0.0414
Overall p-value for interaction ^b				0.8028
Ethnicity				
Hispanic				
Number (observed/imputed)	10 (10/0)	12 (10/2)	8 (6/2)	8 (8/0)
Mean (SD)	-8.02 (7.65)	-5.04 (5.25)	-4.42 (6.21)	-8.13 (6.19)
LS Mean (SE) ^a	-7.01 (1.85)	-4.19 (1.52)	-5.19 (1.87)	-7.36 (1.94)
LS Mean Diff vs. placebo (95% CI) ^a		2.82 (-1.84, 7.47)	1.82 (-3.35, 6.98)	-0.35 (-5.55, 4.84)
P-value vs. placebo ^a		0.2356	0.4911	0.8936
Non-Hispanic				
Number (observed/imputed)	22 (21/1)	18 (17/1)	17 (17/0)	18 (17/1)
Mean (SD)	-3.79 (5.94)	-6.12 (4.43)	-8.59 (5.90)	-11.83 (5.76)
LS Mean (SE) ^a	-4.47 (1.21)	-5.29 (1.31)	-8.43 (1.26)	-10.16 (1.27)
LS Mean Diff vs. placebo (95% CI) ^a		-0.82 (-4.37, 2.73)	-3.96 (-7.39, -0.53)	-5.69 (-9.13, -2.25)
P-value vs. placebo ^a		0.6503	0.0236	0.0012
Overall p-value for interaction ^b				0.2235
History of angioedema				
Yes				
Number (observed/imputed)	15 (14/1)	11 (8/3)	8 (6/2)	9 (8/1)
Mean (SD)	-5.34 (6.25)	-6.31 (5.88)	-4.04 (5.66)	-9.01 (5.02)
LS Mean (SE) ^a	-5.25 (1.51)	-5.00 (1.53)	-6.26 (1.90)	-8.24 (1.90)
LS Mean Diff vs. placebo (95% CI) ^a		0.25 (-3.98, 4.47)	-1.01 (-5.77, 3.76)	-2.99 (-7.72, 1.75)
P-value vs. placebo ^a		0.9094	0.6793	0.2160
No				
Number (observed/imputed)	17 (17/0)	19 (19/0)	18 (18/0)	19 (19/0)
Mean (SD)	-4.90 (7.26)	-5.32 (4.04)	-8.89 (5.85)	-10.86 (6.47)
LS Mean (SE) ^a	-5.34 (1.39)	-4.56 (1.34)	-7.93 (1.24)	-9.56 (1.25)
LS Mean Diff vs. placebo (95% CI) ^a		0.78 (-3.03, 4.59)	-2.59 (-6.23, 1.05)	-4.22 (-7.88, -0.56)
P-value vs. placebo ^a		0.6884	0.1626	0.0239
Overall p-value for interaction ^b				0.9105
Baseline UAS7 score				
< 28				
Number (observed/imputed)	12 (12/0)	6 (6/0)	11 (9/2)	11 (11/0)
Mean (SD)	-2.68 (6.50)	-5.32 (3.03)	-6.29 (4.93)	-7.61 (4.20)
LS Mean (SE) ^a	-3.17 (1.42)	-3.33 (1.83)	-5.40 (1.42)	-6.43 (1.53)
LS Mean Diff vs. placebo (95% CI) ^a		-0.15 (-4.72, 4.41)	-2.22 (-6.23, 1.79)	-3.26 (-7.39, 0.88)
P-value vs. placebo ^a		0.9472	0.2773	0.1225
≥ 28				

	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Number (observed/imputed)	20 (19/1)	24 (21/3)	15 (15/0)	17 (16/1)
Mean (SD)	-6.57 (6.54)	-5.78 (5.10)	-8.21 (6.91)	-11.99 (6.49)
LS Mean (SE) ^a	-6.60 (1.38)	-5.59 (1.21)	-8.64 (1.44)	-10.62 (1.34)
LS Mean Diff vs. placebo (95% CI) ^a		1.01 (-2.59, 4.61)	-2.04 (-5.95, 1.86)	-4.02 (-7.78, -0.25)
P-value vs. placebo ^a		0.5815	0.3055	0.0365
Overall p-value for interaction ^b				0.9187
Baseline ISS7 score				
< 13				
Number (observed/imputed)	10 (10/0)	2 (2/0)	6 (5/1)	2 (2/0)
Mean (SD)	-3.42 (6.10)	-4.42 (0.82)	-5.28 (5.01)	-3.50 (0.71)
LS Mean (SE) ^a	-2.72 (1.55)	-1.87 (2.70)	-5.14 (1.96)	-3.73 (3.33)
LS Mean Diff vs. placebo (95% CI) ^a		0.85 (-5.28, 6.98)	-2.42 (-7.37, 2.52)	-1.01 (-8.29, 6.27)
P-value vs. placebo ^a		0.7852	0.3369	0.7855
≥ 13				
Number (observed/imputed)	22 (21/1)	28 (25/3)	20 (19/1)	26 (25/1)
Mean (SD)	-5.88 (6.95)	-5.78 (4.87)	-8.03 (6.38)	-10.79 (5.93)
LS Mean (SE) ^a	-5.74 (1.24)	-5.38 (1.08)	-7.87 (1.19)	-10.18 (1.09)
LS Mean Diff vs. placebo (95% CI) ^a		0.36 (-2.88, 3.59)	-2.14 (-5.49, 1.22)	-4.45 (-7.66, -1.23)
P-value vs. placebo ^a		0.8293	0.2124	0.0068
Overall p-value for interaction ^b				0.5628
Duration of disease (years)				
< 2				
Number (observed/imputed)	14 (13/1)	10 (9/1)	14 (13/1)	12 (11/1)
Mean (SD)	-3.63 (5.63)	-5.46 (4.49)	-7.53 (5.34)	-10.93 (5.46)
LS Mean (SE) ^a	-3.65 (1.54)	-4.83 (1.76)	-8.54 (1.41)	-9.77 (1.60)
LS Mean Diff vs. placebo (95% CI) ^a		-1.18 (-5.77, 3.41)	-4.89 (-8.99, -0.80)	-6.12 (-10.48, -1.75)
P-value vs. placebo ^a		0.6138	0.0191	0.0060
2 - 10				
Number (observed/imputed)	15 (15/0)	16 (16/0)	11 (10/1)	12 (12/0)
Mean (SD)	-7.08 (7.11)	-6.43 (5.07)	-8.05 (6.91)	-9.37 (5.98)
LS Mean (SE) ^a	-7.03 (1.42)	-5.24 (1.27)	-6.89 (1.50)	-8.84 (1.51)
LS Mean Diff vs. placebo (95% CI) ^a		1.79 (-1.98, 5.56)	0.14 (-3.91, 4.18)	-1.82 (-5.85, 2.22)
P-value vs. placebo ^a		0.3512	0.9476	0.3780
> 10				
Number (observed/imputed)	3 (3/0)	4 (2/2)	1 (1/0)	4 (4/0)
Mean (SD)	-2.17 (8.81)	-3.29 (3.90)	1.67 (NC)	-11.00 (8.91)
LS Mean (SE) ^a	-3.68 (3.26)	-0.20 (2.96)	5.36 (5.71)	-9.33 (2.48)
LS Mean Diff vs. placebo (95% CI) ^a		3.49 (-5.35, 12.33)	9.04 (-4.01, 22.09)	-5.64 (-13.66, 2.38)
P-value vs. placebo ^a		0.4391	0.1743	0.1678
Overall p-value for interaction ^b				0.4674
Baseline H1-antihistamines dose				
1-fold				
Number (observed/imputed)	17 (17/0)	16 (14/2)	11 (10/1)	18 (17/1)

	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Mean (SD)	-6.94 (6.90)	-5.09 (4.87)	-9.03 (7.91)	-8.88 (5.91)
LS Mean (SE) ^a	-6.83 (1.42)	-4.24 (1.40)	-8.44 (1.60)	-8.05 (1.33)
LS Mean Diff vs. placebo (95% CI) ^a		2.59 (-1.31, 6.49)	-1.60 (-5.81, 2.60)	-1.22 (-5.04, 2.59)
P-value vs. placebo ^a		0.1928	0.4541	0.5295
2 to 4-fold standard dose				
Number (observed/imputed)	14 (13/1)	14 (13/1)	15 (14/1)	10 (10/0)
Mean (SD)	-2.96 (6.24)	-6.37 (4.61)	-6.20 (4.30)	-12.76 (5.65)
LS Mean (SE) ^a	-3.48 (1.49)	-5.28 (1.43)	-6.73 (1.31)	-11.00 (1.62)
LS Mean Diff vs. placebo (95% CI) ^a		-1.80 (-5.90, 2.30)	-3.25 (-7.13, 0.62)	-7.52 (-11.82, -3.22)
P-value vs. placebo ^a		0.3893	0.1001	0.0006
Overall p-value for interaction ^b				0.1602
Baseline Eosinophils (10 ⁹ /L)				
<0.150				
Number	16	N/A	11	14
Mean (SD)	N/A	N/A	N/A	N/A
LS Mean (SE)	-6.78 (1.51)	N/A	-6.93 (1.69)	-10.28 (1.64)
LS Mean Diff vs. placebo (95% CI)		N/A	-0.15 (-4.60, 4.29)	-3.50 (-7.87, 0.87)
P-value vs. placebo		N/A	N/A	N/A
≥0.150				
Number	16	N/A	15	14
Mean (SD)	N/A	N/A	N/A	N/A
LS Mean (SE)	-3.99 (1.42)	N/A	-7.91 (1.29)	-8.30 (1.31)
LS Mean Diff vs. placebo (95% CI)		N/A	-3.92 (-7.74, -0.10)	-4.31 (-8.09, -0.53)
P-value vs. placebo		N/A	N/A	N/A
Baseline Eosinophils (10 ⁹ /L)				
< 0.165 (Median)				
Number (observed/imputed)	17 (17/0)	16 (14/2)	13 (12/1)	14 (14/0)
Mean (SD)	-6.64 (7.14)	-4.93 (4.13)	-5.92 (5.31)	-10.99 (6.77)
LS Mean (SE) ^a	-6.51 (1.42)	-4.00 (1.41)	-7.37 (1.49)	-10.22 (1.54)
LS Mean Diff vs. placebo (95% CI) ^a		2.51 (-1.40, 6.42)	-0.86 (-4.88, 3.15)	-3.71 (-7.81, 0.40)
P-value vs. placebo ^a		0.2080	0.6742	0.0767
> 0.165 (Median)				
Number (observed/imputed)	15 (14/1)	14 (13/1)	13 (12/1)	14 (13/1)
Mean (SD)	-3.38 (5.91)	-6.55 (5.33)	-8.88 (6.71)	-9.55 (5.32)
LS Mean (SE) ^a	-4.08 (1.51)	-5.54 (1.44)	-7.62 (1.45)	-8.24 (1.39)
LS Mean Diff vs. placebo (95% CI) ^a		-1.46 (-5.64, 2.72)	-3.53 (-7.69, 0.63)	-4.16 (-8.20, -0.11)
P-value vs. placebo ^a		0.4941	0.0959	0.0440
Overall p-value for interaction ^b				0.4740
Baseline Eosinophils (10 ⁹ /L)				
< 0.3				
Number (observed/imputed)	29 (28/1)	25 (22/3)	20 (19/1)	23 (22/1)
Mean (SD)	-4.98 (7.03)	-5.66 (4.16)	-7.62 (6.27)	-10.61 (6.31)
LS Mean (SE) ^a	-5.46 (1.09)	-4.64 (1.10)	-7.78 (1.19)	-9.46 (1.18)
LS Mean Diff vs. placebo (95% CI) ^a		0.83 (-2.24, 3.89)	-2.31 (-5.47, 0.85)	-3.99 (-7.15, -0.84)

	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
P-value vs. placebo ^a		0.5966	0.1514	0.0132
≥ 0.3				
Number (observed/imputed)	3 (3/0)	5 (5/0)	6 (5/1)	5 (5/0)
Mean (SD)	-6.33 (0.58)	-5.81 (7.57)	-6.67 (6.06)	-8.68 (4.62)
LS Mean (SE) ^a	-4.85 (2.85)	-5.53 (2.57)	-6.15 (2.12)	-8.12 (2.13)
LS Mean Diff vs. placebo (95% CI) ^a		-0.68 (-8.12, 6.76)	-1.29 (-8.43, 5.85)	-3.27 (-10.21, 3.67)
P-value vs. placebo ^a		0.8580	0.7219	0.3547
Overall p-value for interaction ^b				0.9753
Baseline Total IgE (IU/mL)				
< 300				
Number (observed/imputed)	23 (22/1)	21 (18/3)	18 (16/2)	18 (18/0)
Mean (SD)	-4.45 (6.94)	-5.41 (4.78)	-7.93 (6.60)	-11.12 (6.60)
LS Mean (SE) ^a	-4.51 (1.21)	-4.46 (1.23)	-7.94 (1.28)	-9.55 (1.28)
LS Mean Diff vs. placebo (95% CI) ^a		0.05 (-3.34, 3.44)	-3.43 (-6.90, 0.04)	-5.04 (-8.49, -1.58)
P-value vs. placebo ^a		0.9766	0.0524	0.0043
≥ 300				
Number (observed/imputed)	9 (9/0)	8 (8/0)	8 (8/0)	10 (9/1)
Mean (SD)	-6.80 (6.07)	-6.11 (5.05)	-6.20 (5.04)	-8.74 (4.73)
LS Mean (SE) ^a	-6.54 (1.94)	-4.90 (1.83)	-7.17 (1.88)	-8.12 (1.78)
LS Mean Diff vs. placebo (95% CI) ^a		1.64 (-3.67, 6.95)	-0.62 (-6.16, 4.91)	-1.58 (-6.77, 3.62)
P-value vs. placebo ^a		0.5443	0.8249	0.5523
Overall p-value for interaction ^b				0.5546
Baseline Total IgE (IU/mL)				
< 100				
Number (observed/imputed)	15 (14/1)	11 (10/1)	11 (10/1)	13 (13/0)
Mean (SD)	-4.06 (7.77)	-4.48 (4.37)	-8.52 (6.05)	-11.17 (7.09)
LS Mean (SE) ^a	-4.24 (1.58)	-3.37 (1.66)	-8.29 (1.67)	-9.19 (1.55)
LS Mean Diff vs. placebo (95% CI) ^a		0.87 (-3.65, 5.38)	-4.06 (-8.57, 0.46)	-4.95 (-9.29, -0.61)
P-value vs. placebo ^a		0.7062	0.0780	0.0253
> 100				
Number (observed/imputed)	17 (17/0)	18 (16/2)	15 (14/1)	15 (14/1)
Mean (SD)	-6.04 (5.66)	-6.28 (5.01)	-6.57 (6.24)	-9.49 (5.03)
LS Mean (SE) ^a	-6.03 (1.33)	-5.51 (1.28)	-6.91 (1.31)	-9.13 (1.38)
LS Mean Diff vs. placebo (95% CI) ^a		0.52 (-3.13, 4.18)	-0.88 (-4.57, 2.80)	-3.10 (-6.85, 0.65)
P-value vs. placebo ^a		0.7797	0.6380	0.1053
Overall p-value for interaction ^b				0.6170
Baseline BHRA				
BHRA+				
Number (observed/imputed)	3 (3/0)	3 (2/1)	6 (5/1)	4 (4/0)
Mean (SD)	-4.39 (5.43)	-9.13 (3.87)	-9.57 (4.88)	-12.42 (9.12)
LS Mean (SE) ^a	-5.38 (3.35)	-8.50 (3.41)	-8.42 (3.14)	-12.96 (3.21)
LS Mean Diff vs. placebo (95% CI) ^a		-3.12 (-12.22, 5.98)	-3.03 (-12.35, 6.28)	-7.58 (-16.53, 1.37)
P-value vs. placebo ^a		0.5015	0.5234	0.0967

	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
BHRA-				
Number (observed/imputed)	29 (28/1)	26 (24/2)	20 (19/1)	24 (23/1)
Mean (SD)	-5.18 (6.89)	-5.45 (4.73)	-6.75 (6.40)	-9.91 (5.54)
LS Mean (SE) ^a	-5.49 (1.04)	-4.66 (1.06)	-6.59 (1.13)	-8.82 (1.08)
LS Mean Diff vs. placebo (95% CI) ^a		0.83 (-2.10, 3.77)	-1.10 (-4.12, 1.91)	-3.33 (-6.25, -0.41)
P-value vs. placebo ^a		0.5791	0.4730	0.0256
Overall p-value for interaction ^b				0.5253

^a Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value and intervention group as covariates. Analysis was based on the same imputed dataset using WOCF/MI from primary analysis of the primary endpoint.

^b Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value and intervention group as covariates, plus the subgroup variable and the subgroup-by-intervention interaction. Analysis was based on the same imputed dataset using WOCF/MI from primary analysis of the primary endpoint.

^c Asia: South Korea, Taiwan, Japan; Latin America: Argentina, Chile; Eastern Europe: Poland; Western Countries: Spain, Italy, Germany, Canada, Greece, Netherlands.

Note: Descriptive statistics include participants with WOCF imputation at Week 12 and participants whose Week 12 values were imputed by MI were excluded from the descriptive analysis.

[00246] Additionally, participants exhibited a rapid, clinically meaningful improvement in symptoms, with significant reductions in ISS7 observed following one week of treatment (see **Figures 18-21** and **Tables 28-31**). In the ITT population, participants receiving 400 mg BID rilzabrutinib had an LS mean change in ISS7 of -5.23 points from baseline ($p=0.0024$; see **Table 29**). Consistent with rilzabrutinib's dose-dependent effect on ISS7, participants receiving 400 mg TID showed an LS mean change in ISS7 of -6.65 points ($p<0.0001$), reflecting a 40.41% decrease from baseline. Notably, the overall reduction in ISS7 observed in both the 400 mg BID and TID arms exceeded the minimal clinically important difference (MCID) of 5 points.

[00247] Similar results were observed for the omalizumab-naïve population. Omalizumab-naïve participants in the 400 mg BID and TID rilzabrutinib arms experienced an LS mean reduction in ISS7 of -5.06 ($p=0.0060$) and -6.13 ($p=0.0003$), respectively (see **Table 30**). Similar data were obtained when these analyses were repeated following the removal of the asymptomatic outlier (see **Table 31**).

[00248] As further demonstrated in **Tables 28-31**, these improvements were sustained over the course of the study.

Table 28. Summary of ISS7 by Week in the Double-Blind Period (Omalizumab-Naïve Population and Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders)

	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
Baseline								
Number	36	37	35	35	4	1	6	6
Mean (SD)	15.14 (4.16)	16.38 (3.50)	15.45 (3.72)	15.69 (4.26)	19.75 (2.50)	21.00 (NC)	17.83 (2.93)	17.00 (5.25)
Median	14.00	16.00	14.00	14.00	21.00	21.00	18.00	19.00
Q1 ; Q3	12.00 ; 19.50	14.00 ; 20.00	13.00 ; 19.00	14.00 ; 19.00	18.50 ; 21.00	21.00 ; 21.00	15.00 ; 21.00	14.00 ; 21.00
Min ; Max	8.0 ; 21.0	9.0 ; 21.0	8.0 ; 21.0	0.0 ; 21.0	16.0 ; 21.0	21.0 ; 21.0	14.0 ; 21.0	8.0 ; 21.0
Week 1								
Number (observed/imputed)	36 (36/0)	37 (37/0)	35 (35/0)	35 (35/0)	4 (4/0)	1 (1/0)	6 (5/1)	6 (6/0)
Mean (SD)	13.57 (5.31)	13.08 (4.52)	10.51 (5.88)	9.51 (5.64)	17.00 (4.08)	13.00 (NC)	11.50 (6.19)	7.33 (5.43)
Median	14.00	14.00	12.00	9.00	17.00	13.00	13.00	7.00
Q1 ; Q3	11.00 ; 17.25	11.00 ; 16.00	6.00 ; 14.00	4.00 ; 15.00	13.50 ; 20.50	13.00 ; 13.00	8.00 ; 16.00	2.00 ; 10.00
Min ; Max	0.0 ; 21.0	2.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	13.0 ; 21.0	13.0 ; 13.0	1.0 ; 18.0	2.0 ; 16.0
Change from baseline								
Number (observed/imputed)	36 (36/0)	37 (37/0)	35 (35/0)	35 (35/0)	4 (4/0)	1 (1/0)	6 (5/1)	6 (6/0)
Mean (SD)	-1.57 (4.47)	-3.30 (4.93)	-4.94 (4.65)	-6.17 (5.49)	-2.75 (3.59)	-8.00 (NC)	-6.33 (5.82)	-9.67 (5.32)
Median	0.00	-3.00	-4.00	-5.00	-1.50	-8.00	-4.50	-9.00
Q1 ; Q3	-3.75 ; 1.00	-5.00 ; 0.00	-10.00 ; -1.00	-11.00 ; -2.00	-5.00 ; -0.50	-8.00 ; -8.00	-13.00 ; -2.00	-15.00 ; -5.00
Min ; Max	-15.0 ; 8.0	-17.0 ; 6.0	-15.0 ; 2.0	-18.0 ; 3.0	-8.0 ; 0.0	-8.0 ; -8.0	-14.0 ; 0.0	-16.0 ; -4.0
Percent change from baseline								
Number (observed/imputed)	36 (36/0)	37 (37/0)	35 (35/0)	34 (34/0)	4 (4/0)	1 (1/0)	6 (5/1)	6 (6/0)
Mean (SD)	-8.95 (33.13)	-17.96 (28.66)	-33.91 (34.62)	-38.58 (33.51)	-13.84 (16.97)	-38.10 (NC)	-35.93 (34.83)	-58.16 (26.72)
Median	0.00	-19.05	-25.00	-31.37	-8.63	-38.10	-23.02	-66.07
Q1 ; Q3	-25.66 ; 7.42	-31.25 ; 0.00	-57.14 ; -7.14	-72.22 ; -16.67	-25.30 ; -2.38	-38.10 ; -38.10	-61.90 ; -14.29	-76.19 ; -28.57
Min ; Max	-100.0 ; 66.7	-89.5 ; 40.0	-100.0 ; 15.4	-92.9 ; 21.4	-38.1 ; 0.0	-38.1 ; -38.1	-93.3 ; 0.0	-88.2 ; -23.8
Week 2								
Number (observed/imputed)	35 (35/0)	37 (37/0)	34 (34/0)	35 (35/0)	4 (4/0)	1 (1/0)	6 (5/1)	6 (6/0)
Mean (SD)	12.38 (5.17)	12.53 (4.73)	10.32 (5.64)	8.40 (5.82)	14.63 (6.94)	9.00 (NC)	10.83 (6.85)	5.50 (6.95)
Median	13.00	12.00	11.00	8.00	15.25	9.00	13.50	4.00
Q1 ; Q3	9.00 ; 16.00	10.00 ; 15.75	7.00 ; 14.00	3.00 ; 11.20	8.75 ; 20.50	9.00 ; 9.00	5.00 ; 15.00	0.00 ; 7.00
Min ; Max	0.0 ; 21.0	3.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	7.0 ; 21.0	9.0 ; 9.0	0.0 ; 18.0	0.0 ; 18.0
Change from baseline								

ISS7	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
Number (observed/imputed)	35 (35/0)	37 (37/0)	34 (34/0)	35 (35/0)	4 (4/0)	1 (1/0)	6 (5/1)	6 (6/0)
	Mean (SD)	-2.59 (4.45)	-3.84 (4.75)	-5.00 (4.40)	-5.13 (6.38)	-12.00 (NC)	-7.00 (7.04)	-11.50 (6.92)
	Median	-2.00	-3.00	-5.00	-7.00	-3.25	-12.00	-10.50
	Q1 ; Q3	-5.00 ; 0.00	-6.00 ; -0.40	-8.00 ; -1.00	-13.00 ; -2.80	-9.75 ; -0.50	-12.00 ; -12.00	-15.00 ; 0.00
	Min ; Max	-15.0 ; 6.0	-16.0 ; 4.7	-16.0 ; 1.0	-17.0 ; 4.7	-14.0 ; 0.0	-12.0 ; -12.0	-16.0 ; 0.0
Percent change from baseline								
	Number (observed/imputed)	35 (35/0)	37 (37/0)	34 (34/0)	34 (34/0)	4 (4/0)	1 (1/0)	6 (5/1)
	Mean (SD)	-16.14 (31.66)	-22.08 (27.52)	-34.40 (31.27)	-46.12 (36.57)	-26.45 (30.82)	-57.14 (NC)	-38.76 (40.94)
	Median	-12.50	-17.11	-25.06	-46.89	-19.57	-57.14	-28.17
	Q1 ; Q3	-28.57 ; 0.00	-35.71 ; -2.00	-53.33 ; -7.14	-66.67 ; -21.43	-50.52 ; -2.38	-57.14 ; -57.14	-76.19 ; 0.00
Min ; Max	-100.0 ; 50.0	-84.2 ; 33.3	-100.0 ; 7.7	-100.0 ; 33.3	-66.7 ; 0.0	-57.1 ; -57.1	-100.0 ; 0.0	
Week 3								
	Number (observed/imputed)	35 (35/0)	37 (37/0)	35 (35/0)	35 (35/0)	4 (4/0)	1 (1/0)	6 (5/1)
	Mean (SD)	11.98 (5.40)	11.60 (4.68)	9.16 (6.09)	8.34 (5.42)	11.63 (6.46)	9.00 (NC)	9.53 (7.26)
	Median	13.00	11.00	9.00	8.40	12.43	9.00	10.50
	Q1 ; Q3	10.00 ; 15.17	8.00 ; 15.40	4.00 ; 13.00	3.00 ; 12.83	7.63 ; 15.63	9.00 ; 9.00	3.00 ; 15.17
Min ; Max	0.0 ; 21.0	3.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	3.0 ; 18.7	9.0 ; 9.0	0.0 ; 18.0	
Change from baseline								
	Number (observed/imputed)	35 (35/0)	37 (37/0)	35 (35/0)	35 (35/0)	4 (4/0)	1 (1/0)	6 (5/1)
	Mean (SD)	-2.99 (4.61)	-4.77 (4.84)	-6.29 (5.74)	-7.34 (6.48)	-8.12 (7.16)	-12.00 (NC)	-8.31 (8.28)
	Median	-2.00	-3.67	-5.00	-7.00	-6.08	-12.00	-9.00
	Q1 ; Q3	-7.00 ; 0.00	-8.00 ; -1.00	-11.00 ; -1.00	-12.00 ; -3.00	-13.38 ; -2.87	-12.00 ; -12.00	-12.00 ; 0.00
Min ; Max	-16.0 ; 4.0	-16.0 ; 2.0	-19.0 ; 0.0	-17.0 ; 14.0	-18.0 ; -2.3	-12.0 ; -12.0	-21.0 ; 1.2	
Percent change from baseline								
	Number (observed/imputed)	35 (35/0)	37 (37/0)	35 (35/0)	34 (34/0)	4 (4/0)	1 (1/0)	6 (5/1)
	Mean (SD)	-18.75 (33.73)	-27.79 (26.72)	-40.77 (35.75)	-49.02 (33.06)	-39.94 (33.06)	-57.14 (NC)	-44.35 (43.62)
	Median	-9.52	-23.81	-26.67	-48.53	-31.46	-57.14	-47.22
	Q1 ; Q3	-33.33 ; 0.00	-47.62 ; -8.33	-73.33 ; -11.11	-78.57 ; -22.22	-63.69 ; -16.18	-57.14 ; -57.14	-80.00 ; 0.00
Min ; Max	-100.0 ; 33.3	-84.2 ; 13.3	-100.0 ; 0.0	-100.0 ; 23.1	-85.7 ; -11.1	-57.1 ; -57.1	-100.0 ; 8.3	
Week 4								
	Number (observed/imputed)	34 (34/0)	37 (36/1)	33 (33/0)	32 (32/0)	4 (4/0)	1 (1/0)	5 (4/1)
Mean (SD)	11.51 (6.14)	11.39 (4.79)	8.32 (6.02)	7.79 (5.03)	9.84 (5.24)	8.00 (NC)	6.80 (8.53)	

ISS7	Omalizumab-Naïve Population						Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)		
Change from baseline Number (observed/imputed)	Median	12.33	11.00	7.00	10.68	8.00	1.00	5.42		
	Q1 ; Q3	7.00 ; 15.00	8.00 ; 15.00	3.00 ; 13.00	5.88 ; 13.80	8.00 ; 8.00	1.00 ; 14.00	1.17 ; 7.00		
	Min ; Max	0.0 ; 21.0	1.2 ; 21.0	0.0 ; 21.0	3.0 ; 15.0	8.0 ; 8.0	0.0 ; 18.0	0.0 ; 18.0		
Change from baseline Number (observed/imputed)	Median	34 (34/0)	37 (36/1)	33 (33/0)	4 (4/0)	1 (1/0)	5 (4/1)	6 (6/0)		
	Mean (SD)	-3.54 (5.46)	-4.99 (5.13)	-6.94 (6.13)	-9.91 (5.48)	-13.00 (NC)	-11.80 (8.35)	-10.83 (7.32)		
	Q1 ; Q3	-2.42	-4.00	-5.83	-7.83	-13.00	-14.00	-11.08		
	Min ; Max	-7.00 ; 0.00	-7.00 ; -1.00	-11.00 ; -2.00	-13.20 ; -6.63	-13.00 ; -13.00	-17.00 ; -7.00	-15.83 ; -3.00		
Percent change from baseline Number (observed/imputed)	Median	-17.0 ; 8.0	-17.8 ; 1.0	-19.0 ; 2.0	-18.0 ; -6.0	-13.0 ; -13.0	-21.0 ; 0.0	-21.0 ; -3.0		
	Mean (SD)	34 (34/0)	37 (36/1)	33 (33/0)	4 (4/0)	1 (1/0)	5 (4/1)	6 (6/0)		
	Q1 ; Q3	-22.34 (39.94)	-28.81 (27.96)	-44.87 (37.61)	-49.90 (24.88)	-61.90 (NC)	-64.22 (45.05)	-61.65 (32.63)		
	Min ; Max	-50.00 ; 0.00	-50.00 ; -6.67	-80.00 ; -15.38	-85.7 ; -28.6	-61.90 ; -61.90	-94.44 ; -33.33	-93.14 ; -37.50		
Week 5 Number (observed/imputed)	Median	-100.0 ; 61.5	-93.9 ; 6.7	-100.0 ; 22.2	-100.0 ; 0.0	-61.9 ; -61.9	-100.0 ; 0.0	-100.0 ; -14.3		
	Mean (SD)	33 (33/0)	36 (35/1)	34 (33/1)	33 (33/0)	1 (1/0)	4 (3/1)	6 (5/1)		
	Q1 ; Q3	9.75 (4.75)	11.00 (4.68)	8.88 (6.81)	6.92 (5.87)	11.00 (NC)	5.50 (8.54)	5.50 (6.53)		
	Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	11.0 ; 11.0	0.00 ; 11.00	2.00 ; 7.00		
Change from baseline Number (observed/imputed)	Median	7.00 ; 12.83	8.00 ; 14.00	3.00 ; 12.83	9.50 ; 17.21	11.00 ; 11.00	0.00 ; 11.00	2.00 ; 7.00		
	Mean (SD)	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	8.0 ; 18.7	11.0 ; 11.0	0.0 ; 18.0	0.0 ; 18.0		
	Q1 ; Q3									
	Min ; Max									
Change from baseline Number (observed/imputed)	Median	33 (33/0)	36 (35/1)	34 (33/1)	33 (33/0)	1 (1/0)	4 (3/1)	6 (5/1)		
	Mean (SD)	-5.35 (4.29)	-5.53 (4.98)	-6.55 (6.17)	-9.18 (6.46)	-10.00 (NC)	-12.50 (9.33)	-11.50 (7.58)		
	Q1 ; Q3	-5.00	-4.10	-6.42	-9.00	-10.00	-14.50	-10.50		
	Min ; Max	-8.00 ; -2.00	-8.50 ; -1.50	-11.83 ; -1.00	-13.60 ; -5.00	-10.00 ; -10.00	-19.50 ; -5.50	-19.00 ; -5.00		
Percent change from baseline Number (observed/imputed)	Median	-16.0 ; 3.0	-19.0 ; 1.0	-17.7 ; 6.0	-21.0 ; 1.4	-10.0 ; -10.0	-21.0 ; 0.0	-21.0 ; -3.0		
	Mean (SD)	33 (33/0)	36 (35/1)	34 (33/1)	33 (33/0)	1 (1/0)	4 (3/1)	6 (5/1)		
	Q1 ; Q3	-34.77 (28.93)	-31.93 (26.18)	-43.73 (41.21)	-55.68 (34.88)	-47.62 (NC)	-68.33 (47.26)	-66.60 (31.51)		
	Min ; Max	-50.00 ; -18.18	-48.16 ; -9.11	-80.00 ; -7.69	-85.71 ; -27.78	-47.62 ; -47.62	-100.00 ; -36.67	-90.48 ; -50.00		

ISS7	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
	Min ; Max	Min ; Max	Min ; Max	Min ; Max	Min ; Max	Min ; Max	Min ; Max	Min ; Max
Week 6								
Number (observed/imputed)								
Mean (SD)	32 (31/1) 10.58 (5.85)	34 (33/1) 10.27 (5.26)	34 (33/1) 8.85 (6.40)	31 (31/0) 7.32 (6.05)	4 (3/1) 13.17 (5.82)	1 (1/0) 9.00 (NC)	5 (4/1) 7.07 (8.32)	6 (5/1) 4.17 (6.88)
Median	11.60	10.25	10.00	7.00	12.33	9.00	2.33	2.00
Q1 ; Q3	5.50 ; 14.00	6.00 ; 14.00	2.00 ; 14.00	1.00 ; 10.50	9.33 ; 17.00	9.00 ; 9.00	1.00 ; 14.00	0.00 ; 3.00
Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	7.0 ; 21.0	9.0 ; 9.0	0.0 ; 18.0	0.0 ; 18.0
Change from baseline								
Number (observed/imputed)								
Mean (SD)	32 (31/1) -4.54 (5.55)	34 (33/1) -6.59 (5.45)	34 (33/1) -6.58 (5.90)	31 (31/0) -8.71 (6.32)	4 (3/1) -6.58 (4.43)	1 (1/0) -12.00 (NC)	5 (4/1) -10.13 (9.42)	6 (5/1) -12.83 (7.49)
Median	-4.00	-5.00	-5.75	-7.50	-8.50	-12.00	-14.00	-14.50
Q1 ; Q3	-7.40 ; -0.25	-11.00 ; -3.00	-12.00 ; -1.00	-14.00 ; -3.33	-9.17 ; -4.00	-12.00 ; -12.00	-18.00 ; 0.00	-19.00 ; -5.00
Min ; Max	-20.0 ; 6.0	-19.0 ; 1.0	-18.0 ; 2.0	-21.0 ; 2.3	-9.3 ; 0.0	-12.0 ; -12.0	-18.7 ; 0.0	-21.0 ; -3.0
Percent change from baseline								
Number (observed/imputed)								
Mean (SD)	32 (31/1) -28.70 (38.25)	34 (33/1) -38.20 (29.52)	34 (33/1) -42.90 (39.02)	31 (31/0) -53.59 (35.59)	4 (3/1) -34.70 (24.32)	1 (1/0) -57.14 (NC)	5 (4/1) -56.44 (51.68)	6 (5/1) -75.50 (33.00)
Median	-25.00	-31.67	-33.40	-50.00	-41.27	-57.14	-88.89	-88.10
Q1 ; Q3	-57.74 ; -2.27	-64.71 ; -20.00	-84.62 ; -6.67	-95.24 ; -25.00	-50.35 ; -19.05	-57.14 ; -57.14	-93.33 ; 0.00	-100.00 ; -62.50
Min ; Max	-100.0 ; 62.5	-100.0 ; 6.7	-100.0 ; 22.2	-100.0 ; 16.7	-56.3 ; 0.0	-57.1 ; -57.1	-100.0 ; 0.0	-100.0 ; -14.3
Week 7								
Number (observed/imputed)								
Mean (SD)	33 (32/1) 10.51 (5.70)	33 (31/2) 10.68 (5.34)	34 (33/1) 8.21 (6.16)	30 (30/0) 7.14 (5.35)	4 (3/1) 14.85 (5.21)	1 (1/0) 8.00 (NC)	5 (4/1) 6.80 (8.56)	6 (5/1) 7.06 (6.25)
Median	9.33	9.80	7.00	8.00	15.00	8.00	2.00	6.00
Q1 ; Q3	7.00 ; 14.00	7.00 ; 14.00	2.80 ; 12.00	3.00 ; 10.00	11.20 ; 18.50	8.00 ; 8.00	0.00 ; 14.00	3.00 ; 9.33
Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	8.4 ; 21.0	8.0 ; 8.0	0.0 ; 18.0	0.0 ; 18.0
Change from baseline								
Number (observed/imputed)								
Mean (SD)	33 (32/1) -4.58 (5.48)	33 (31/2) -6.11 (5.15)	34 (33/1) -7.28 (5.95)	30 (30/0) -8.96 (5.57)	4 (3/1) -4.90 (3.45)	1 (1/0) -13.00 (NC)	5 (4/1) -10.40 (9.91)	6 (5/1) -9.94 (7.89)
Median	-4.20	-5.20	-8.08	-9.00	-6.00	-13.00	-13.00	-7.33
Q1 ; Q3	-7.00 ; -0.83	-12.00 ; -1.17	-12.00 ; -2.00	-14.00 ; -5.25	-7.30 ; -2.50	-13.00 ; -13.00	-18.00 ; 0.00	-18.00 ; -3.00
Min ; Max	-20.0 ; 5.0	-14.0 ; 1.0	-19.0 ; 2.0	-20.0 ; 1.8	-7.6 ; 0.0	-13.0 ; -13.0	-21.0 ; 0.0	-21.0 ; -3.0

ISS7	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
Percent change from baseline								
Number (observed/imputed)								
Mean (SD)								
Median								
Q1 ; Q3								
Min ; Max								
Week 8								
Number (observed/imputed)								
Mean (SD)								
Median								
Q1 ; Q3								
Min ; Max								
Change from baseline								
Number (observed/imputed)								
Mean (SD)								
Median								
Q1 ; Q3								
Min ; Max								
Percent change from baseline								
Number (observed/imputed)								
Mean (SD)								
Median								
Q1 ; Q3								
Min ; Max								
Week 9								
Number (observed/imputed)								
Mean (SD)								
Median								
Q1 ; Q3								
Min ; Max								
Change from baseline								
Number (observed/imputed)								
Mean (SD)								
Median								
Q1 ; Q3								
Min ; Max								

ISS7	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
Percent change from baseline Number (observed/imputed)	Mean (SD)	-4.58 (5.77)	-6.39 (5.27)	-7.57 (6.14)	-9.25 (7.04)	-11.00 (NC)	-10.83 (9.53)	-12.36 (6.72)
	Median	-4.50	-5.42	-8.00	-10.80	-11.00	-15.00	-13.92
	Q1 ; Q3	-8.00 ; 0.00	-9.00 ; -2.50	-11.00 ; -3.00	-14.70 ; -3.80	-11.00 ; -11.00	-18.00 ; -1.17	-16.33 ; -6.00
	Min ; Max	-17.0 ; 8.0	-19.0 ; 1.0	-20.0 ; 3.0	-15.4 ; 0.0	-11.0 ; -11.0	-20.0 ; 0.0	-21.0 ; -3.0
Percent change from baseline Number (observed/imputed)	Mean (SD)	32 (31/1)	34 (31/3)	29 (28/1)	4 (3/1)	1 (1/0)	5 (4/1)	6 (5/1)
	Median	-28.39 (39.68)	-37.00 (28.06)	-51.57 (40.77)	-46.88 (33.11)	-52.38 (NC)	-60.71 (51.74)	-74.49 (30.89)
	Q1 ; Q3	-28.33	-33.33	-53.33	-57.08	-52.38	-95.24	-83.01
	Min ; Max	-55.00 ; 0.00	-53.33 ; -19.23	-91.67 ; -16.67	-70.00 ; -23.75	-52.38 ; -52.38	-100.00 ; -8.33	-91.67 ; -75.00
		-100.0 ; 61.5	-100.0 ; 5.0	-100.0 ; 23.1	-73.3 ; 0.0	-52.4 ; -52.4	-100.0 ; 0.0	-100.0 ; -14.3
Week 10								
Change from baseline Number (observed/imputed)	Mean (SD)	33 (32/1)	34 (31/3)	28 (27/1)	4 (3/1)	1 (1/0)	5 (4/1)	6 (4/2)
	Median	10.00 (6.49)	10.43 (5.30)	8.17 (7.29)	8.39 (8.95)	8.00 (NC)	7.40 (8.11)	4.83 (6.85)
	Q1 ; Q3	9.33	9.50	7.00	5.70	8.00	4.00	3.00
	Min ; Max	5.25 ; 14.00	7.00 ; 14.00	0.00 ; 11.50	2.08 ; 14.70	8.00 ; 8.00	1.00 ; 14.00	0.00 ; 5.00
		0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	1.2 ; 21.0	8.0 ; 8.0	0.0 ; 18.0	0.0 ; 18.0
Change from baseline Number (observed/imputed)	Mean (SD)	33 (32/1)	34 (31/3)	28 (27/1)	4 (3/1)	1 (1/0)	5 (4/1)	6 (4/2)
	Median	-5.09 (5.89)	-6.43 (5.26)	-7.07 (6.58)	-11.36 (9.29)	-13.00 (NC)	-9.80 (9.55)	-12.17 (8.26)
	Q1 ; Q3	-5.00	-6.00	-7.58	-12.80	-13.00	-11.00	-13.00
	Min ; Max	-8.17 ; 0.00	-9.00 ; -3.00	-12.50 ; -2.00	-18.92 ; -3.80	-13.00 ; -13.00	-18.00 ; 0.00	-20.00 ; -3.00
		-17.0 ; 8.0	-19.0 ; 2.2	-20.0 ; 5.0	-19.8 ; 0.0	-13.0 ; -13.0	-20.0 ; 0.0	-21.0 ; -3.0
Percent change from baseline Number (observed/imputed)	Mean (SD)	33 (32/1)	34 (31/3)	28 (27/1)	4 (3/1)	1 (1/0)	5 (4/1)	6 (4/2)
	Median	-33.59 (41.95)	-37.25 (29.62)	-47.10 (43.27)	-56.91 (43.07)	-61.90 (NC)	-53.71 (50.05)	-68.55 (36.38)
	Q1 ; Q3	-33.33	-39.23	-48.10	-66.61	-61.90	-73.33	-79.76
	Min ; Max	-55.79 ; 0.00	-57.14 ; -17.11	-100.00 ; -13.39	-90.08 ; -23.75	-61.90 ; -61.90	-95.24 ; 0.00	-100.00 ; -37.50
		-100.0 ; 61.5	-100.0 ; 24.4	-100.0 ; 38.5	-94.4 ; 0.0	-61.9 ; -61.9	-100.0 ; 0.0	-100.0 ; -14.3
Week 11								
Number (observed/imputed)	Mean (SD)	33 (32/1)	33 (30/3)	29 (28/1)	4 (3/1)	1 (1/0)	5 (4/1)	6 (4/2)
	Median	10.24 (6.31)	11.03 (5.55)	7.93 (6.94)	8.79 (8.61)	9.00 (NC)	6.77 (8.14)	4.42 (6.99)
		11.00	11.00	7.00	6.50	9.00	2.00	1.75

ISS7	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
Change from baseline Number (observed/imputed)	Q1 ; Q3	6.00 ; 14.00	7.00 ; 14.00	3.00 ; 10.00	2.33 ; 10.00	3.08 ; 14.50	9.00 ; 9.00	1.00 ; 12.83
	Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	1.2 ; 21.0	9.0 ; 9.0	0.0 ; 18.0
	Mean (SD)	-4.85 (6.05)	-6.07 (4.83)	-7.51 (6.18)	-9.23 (5.92)	-10.96 (8.81)	-12.00 (NC)	-10.43 (9.36)
	Median	-6.00	-6.00	-8.00	-9.00	-12.00	-12.00	-13.00
	Q1 ; Q3	-9.00 ; 0.00	-8.00 ; -3.00	-12.00 ; -2.80	-14.00 ; -5.20	-17.92 ; -4.00	-12.00 ; -12.00	-18.00 ; -1.17
Percent change from baseline Number (observed/imputed)	Min ; Max	-17.0 ; 8.0	-19.0 ; 1.0	-18.0 ; 4.0	-21.0 ; 4.2	-19.8 ; 0.0	-12.0 ; -12.0	-20.0 ; 0.0
	Mean (SD)	33 (32/1)	33 (30/3)	29 (28/1)	31 (31/0)	4 (3/1)	1 (1/0)	5 (4/1)
	Median	-30.60 (43.70)	-36.12 (28.12)	-49.75 (40.18)	-56.08 (33.60)	-55.16 (41.05)	-57.14 (NC)	-58.05 (49.51)
	Q1 ; Q3	-33.33	-30.00	-57.14	-60.00	-63.10	-57.14	-86.67
	Min ; Max	-56.25 ; 0.00	-50.00 ; -18.33	-80.95 ; -25.00	-85.71 ; -33.33	-85.32 ; -25.00	-57.14 ; -57.14	-95.24 ; -8.33
Week 12 Number (observed/imputed)	Min ; Max	-100.0 ; 61.5	-100.0 ; 5.0	-100.0 ; 23.5	-100.0 ; 30.0	-94.4 ; 0.0	-57.1 ; -57.1	-100.0 ; 0.0
	Mean (SD)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)	3 (2/1)	1 (1/0)	4 (3/1)
	Median	10.02 (6.82)	11.51 (5.54)	8.09 (6.95)	5.77 (5.26)	9.33 (10.69)	7.00 (NC)	4.50 (9.00)
	Q1 ; Q3	8.50	11.60	7.00	7.00	7.00	7.00	0.00
	Min ; Max	4.83 ; 14.00	7.00 ; 15.17	1.17 ; 13.00	0.00 ; 8.88	0.00 ; 21.00	7.00 ; 7.00	0.00 ; 5.00
Change from baseline Number (observed/imputed)	Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	7.0 ; 7.0	0.0 ; 18.0
	Mean (SD)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)	3 (2/1)	1 (1/0)	4 (3/1)
	Median	-5.11 (6.70)	-5.69 (4.72)	-7.40 (6.12)	-10.27 (6.02)	-11.67 (10.69)	-14.00 (NC)	-13.50 (9.33)
	Q1 ; Q3	-5.50	-5.33	-7.00	-10.33	-14.00	-14.00	-16.50
	Min ; Max	-9.00 ; -0.25	-8.17 ; -1.40	-11.00 ; -3.00	-14.50 ; -4.63	-21.00 ; 0.00	-14.00 ; -14.00	-19.50 ; -7.50
Percent change from baseline Number (observed/imputed)	Min ; Max	-17.5 ; 9.8	-19.0 ; 1.0	-20.0 ; 2.0	-21.0 ; 0.0	-21.0 ; 0.0	-14.0 ; -14.0	-21.0 ; 0.0
	Mean (SD)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)	3 (2/1)	1 (1/0)	4 (3/1)
	Median	-32.65 (46.69)	-33.81 (26.94)	-49.06 (38.85)	-62.66 (31.72)	-55.56 (50.92)	-66.67 (NC)	-75.00 (50.00)
	Q1 ; Q3	-31.67	-32.64	-45.00	-57.19	-66.67	-66.67	-100.00
	Min ; Max	-66.23 ; -2.27	-50.00 ; -8.33	-91.67 ; -26.67	-100.00 ; -34.52	-100.00 ; 0.00	66.67 ; -66.67	-100.00 ; -50.00
	Min ; Max	-100.0 ; 98.3	-100.0 ; 5.0	-100.0 ; 22.2	-100.0 ; 0.0	-100.0 ; 0.0	-66.7 ; -66.7	-100.0 ; 0.0
								-100.0 ; -14.3

ISS7	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
End of Study	Number (observed/imputed)	5 (3/2)	7 (3/4)	5 (3/2)	0 (0/0)	0 (0/0)	0 (0/0)	2 (0/2)
	Mean (SD)	12.17 (7.59)	5.74 (8.03)	7.80 (8.76)	11.40 (6.11)			9.50 (6.36)
	Median	13.00	2.00	7.00	10.00			9.50
	Q1 ; Q3	12.83 ; 14.00	0.00 ; 14.00	0.00 ; 11.00	7.00 ; 15.00			5.00 ; 14.00
	Min ; Max	0.0 ; 21.0	0.0 ; 20.0	0.0 ; 21.0	5.0 ; 20.0			5.0 ; 14.0
Change from baseline	Number (observed/imputed)	5 (3/2)	7 (3/4)	5 (3/2)	0 (0/0)	0 (0/0)	0 (0/0)	2 (0/2)
	Mean (SD)	-4.23 (5.39)	-11.40 (8.46)	-6.60 (7.33)	-6.20 (3.70)			-1.50 (2.12)
	Median	-7.00	-14.00	-8.00	-7.00			-1.50
	Q1 ; Q3	-7.00 ; 0.00	-19.00 ; 0.00	-13.00 ; 0.00	-9.00 ; -6.00			-3.00 ; 0.00
	Min ; Max	-10.0 ; 2.8	-20.0 ; 0.0	-14.0 ; 2.0	-9.0 ; 0.0			-3.0 ; 0.0
Percent change from baseline	Number (observed/imputed)	5 (3/2)	7 (3/4)	5 (3/2)	0 (0/0)	0 (0/0)	0 (0/0)	2 (0/2)
	Mean (SD)	-28.00 (48.01)	-66.19 (45.96)	-46.22 (56.25)	-38.05 (24.78)			-18.75 (26.52)
	Median	-33.33	-83.33	-53.33	-47.37			-18.75
	Q1 ; Q3	-35.00 ; 0.00	-100.00 ; 0.00	-100.00 ; 0.00	-50.00 ; -28.57			-37.50 ; 0.00
	Min ; Max	-100.0 ; 28.3	-100.0 ; 0.0	-100.0 ; 22.2	-64.3 ; 0.0			-37.5 ; 0.0

WOCF: Worst observation carried forward
Note: Data collected after study intervention discontinuation were included. Data post selected prohibited/rescue medications (high/medium impact on efficacy confirmed through blinded medical review) were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF.

Table 29. Change and Percent Change from Baseline in ISS7 Over Time Up to Week 12 (ITT Population)

n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo		% Change difference for rilzabrutinib vs. placebo ^a	
				LS Mean (95% CI) ^a	p-value ^a	LS Mean (95% CI) ^a	p-value ^a
Week 1							
Rilzabrutinib 400mg TID	41	15.88 (4.37)	9.20 (5.60)	-6.65 (0.76)	-4.65 (-7.14, -2.15)	-40.41 (5.24)	-29.95 (-44.08, -15.81)
(N=41)					<.0001		<.0001

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
				Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Rilzabrutinib 400mg BID (N=41)	41	15.80 (3.68)	10.65 (5.86)	-5.23 (0.78)	-3.23 (-5.72, -0.74)	0.0024	-34.02 (5.28)	-23.55 (-37.52, - 9.59)	0.0009
Rilzabrutinib 400mg QPM (N=38)	38	16.50 (3.53)	13.08 (4.46)	-3.47 (0.79)	-1.47 (-4.00, 1.07)	0.1716	-19.33 (5.35)	-8.87 (-23.12, 5.38)	0.2225
Placebo (N=40)	40	15.60 (4.24)	13.91 (5.26)	-2.00 (0.78)			-10.46 (5.30)		
Week 2									
Rilzabrutinib 400mg TIID (N=41)	41	15.88 (4.37)	7.97 (5.99)	-7.92 (0.79)	-4.51 (-6.65, -2.38)	<0001	-49.29 (5.21)	-29.81 (-43.92, - 15.69)	<0001
Rilzabrutinib 400mg BID (N=41)	40	15.80 (3.68)	10.40 (5.75)	-5.68 (0.80)	-2.27 (-4.39, -0.14)	0.0363	-36.11 (5.26)	-16.63 (-30.54, - 2.71)	0.0192
Rilzabrutinib 400mg QPM (N=38)	38	16.50 (3.53)	12.44 (4.70)	-4.27 (0.81)	-0.86 (-3.03, 1.30)	0.4345	-25.13 (5.32)	-5.64 (-19.84, 8.56)	0.4360
Placebo (N=40)	39	15.60 (4.24)	12.61 (5.31)	-3.41 (0.81)			-19.49 (5.28)		
Week 3									
Rilzabrutinib 400mg TIID (N=41)	41	15.88 (4.37)	7.93 (5.46)	-7.84 (0.83)	-3.76 (-6.00, -1.51)	0.0010	-50.07 (5.21)	-27.63 (-41.72, - 13.53)	0.0001
Rilzabrutinib 400mg BID (N=41)	41	15.80 (3.68)	9.21 (6.17)	-6.68 (0.84)	-2.60 (-4.83, -0.37)	0.0225	-40.88 (5.26)	-18.44 (-32.38, - 4.50)	0.0095
Rilzabrutinib 400mg QPM (N=38)	38	16.50 (3.53)	11.54 (4.63)	-5.06 (0.85)	-0.97 (-3.25, 1.31)	0.4036	-29.78 (5.33)	-7.34 (-21.57, 6.90)	0.3125
Placebo (N=40)	39	15.60 (4.24)	11.94 (5.42)	-4.08 (0.85)			-22.44 (5.30)		
Week 4									
Rilzabrutinib 400mg TIID (N=41)	38	15.88 (4.37)	7.54 (5.21)	-7.75 (0.88)	-3.13 (-5.50, -0.76)	0.0096	-48.97 (5.57)	-23.20 (-38.37, - 8.04)	0.0027
Rilzabrutinib 400mg BID (N=41)	38	15.80 (3.68)	8.12 (6.28)	-7.24 (0.89)	-2.62 (-4.98, -0.27)	0.0291	-44.30 (5.62)	-18.54 (-33.43, - 3.64)	0.0147
Rilzabrutinib 400mg QPM (N=38)	38	16.50 (3.53)	11.30 (4.76)	-5.29 (0.90)	-0.67 (-3.07, 1.73)	0.5838	-30.86 (5.64)	-5.09 (-20.26, 10.08)	0.5109
Placebo (N=40)	38	15.60 (4.24)	11.34 (6.01)	-4.62 (0.90)			-25.77 (5.66)		
Week 5									
Rilzabrutinib 400mg TIID (N=41)	39	15.88 (4.37)	6.70 (5.91)	-8.93 (0.86)	-3.36 (-5.69, -1.04)	0.0046	-54.96 (5.32)	-21.69 (-36.14, - 7.23)	0.0033

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
				LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	
Rilzabrutinib 400mg BID (N=41)	38	15.80 (3.68)	8.53 (6.95)	-6.89 (0.88)	0.2653	-43.12 (5.39)	-9.84 (-24.14, 4.45)	0.1769	
Rilzabrutinib 400mg QPM (N=38)	37	16.50 (3.53)	11.00 (4.61)	-5.48 (0.88)	0.9441	-32.42 (5.42)	0.86 (-13.68, 15.40)	0.9079	
Placebo (N=40)	37	15.60 (4.24)	10.14 (4.82)	-5.57 (0.88)		-33.27 (5.42)			
Week 6									
Rilzabrutinib 400mg TIID (N=41)	37	15.88 (4.37)	6.81 (6.20)	-8.97 (0.93)	0.0014	-55.31 (5.83)	-26.88 (-42.81, -10.95)	0.0009	
Rilzabrutinib 400mg BID (N=41)	39	15.80 (3.68)	8.62 (6.58)	-6.87 (0.93)	0.1157	-42.18 (5.84)	-13.75 (-29.35, 1.85)	0.0841	
Rilzabrutinib 400mg QPM (N=38)	35	16.50 (3.53)	10.23 (5.19)	-6.28 (0.95)	0.2855	-37.07 (5.96)	-8.64 (-24.62, 7.34)	0.2892	
Placebo (N=40)	36	15.60 (4.24)	10.87 (5.82)	-4.89 (0.95)		-28.43 (5.99)			
Week 7									
Rilzabrutinib 400mg TIID (N=41)	36	15.88 (4.37)	7.13 (5.42)	-8.71 (0.91)	0.0028	-53.83 (5.69)	-24.96 (-40.31, -9.62)	0.0014	
Rilzabrutinib 400mg BID (N=41)	39	15.80 (3.68)	8.03 (6.39)	-7.77 (0.91)	0.0243	-47.79 (5.68)	-18.93 (-34.00, -3.86)	0.0138	
Rilzabrutinib 400mg QPM (N=38)	34	16.50 (3.53)	10.60 (5.27)	-6.37 (0.93)	0.2799	-38.52 (5.84)	-9.66 (-25.33, 6.01)	0.2269	
Placebo (N=40)	37	15.60 (4.24)	10.98 (5.74)	-5.00 (0.92)		-28.86 (5.76)			
Week 8									
Rilzabrutinib 400mg TIID (N=41)	34	15.88 (4.37)	6.72 (5.76)	-8.66 (0.95)	0.0198	-54.76 (5.95)	-21.97 (-38.02, -5.91)	0.0073	
Rilzabrutinib 400mg BID (N=41)	38	15.80 (3.68)	7.18 (6.69)	-8.47 (0.93)	0.0243	-52.80 (5.92)	-20.00 (-35.73, -4.26)	0.0127	
Rilzabrutinib 400mg QPM (N=38)	34	16.50 (3.53)	10.61 (5.22)	-6.22 (0.96)	0.6407	-38.39 (6.03)	-5.60 (-21.72, 10.53)	0.4963	
Placebo (N=40)	37	15.60 (4.24)	10.34 (6.19)	-5.61 (0.94)		-32.80 (5.95)			
Week 9									
Rilzabrutinib 400mg TIID (N=41)	35	15.88 (4.37)	6.33 (5.52)	-8.85 (0.95)	0.0107	-55.43 (6.01)	-24.57 (-40.80, -8.33)	0.0030	

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
				Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Rilzabrutinib 400mg BID (N=41)	34	15.80 (3.68)	7.44 (7.20)	-8.27 (0.96)	-2.77 (-5.33, -0.21)	0.0337	-51.80 (5.94)	-20.94 (-36.69, - 5.20)	0.0091
Rilzabrutinib 400mg QPM (N=38)	35	16.50 (3.53)	10.45 (5.08)	-6.24 (0.96)	-0.74 (-3.32, 1.83)	0.5717	-37.93 (6.02)	-7.07 (-23.26, 9.12)	0.3920
Placebo (N=40)	36	15.60 (4.24)	10.54 (5.97)	-5.50 (0.96)			-30.86 (5.97)		
Week 10									
Rilzabrutinib 400mg TIID (N=41)	36	15.88 (4.37)	6.43 (5.48)	-8.98 (0.99)	-2.68 (-5.36, -0.00)	0.0496	-56.23 (6.14)	-18.42 (-34.98, - 1.86)	0.0293
Rilzabrutinib 400mg BID (N=41)	33	15.80 (3.68)	8.06 (7.29)	-8.01 (1.01)	-1.72 (-4.39, 0.96)	0.2088	-48.75 (6.31)	-10.95 (-27.46, 5.57)	0.1939
Rilzabrutinib 400mg QPM (N=38)	35	16.50 (3.53)	10.36 (5.24)	-6.47 (1.02)	-0.17 (-2.89, 2.55)	0.9030	-39.07 (6.29)	-1.26 (-18.15, 15.62)	0.8835
Placebo (N=40)	37	15.60 (4.24)	9.82 (6.66)	-6.30 (1.01)			-37.81 (6.23)		
Week 11									
Rilzabrutinib 400mg TIID (N=41)	37	15.88 (4.37)	6.57 (5.76)	-9.02 (0.96)	-3.15 (-5.75, -0.56)	0.0173	-55.75 (6.15)	-22.13 (-38.82, - 5.44)	0.0094
Rilzabrutinib 400mg BID (N=41)	34	15.80 (3.68)	7.76 (7.01)	-7.93 (0.99)	-2.07 (-4.65, 0.52)	0.1169	-49.45 (6.23)	-15.82 (-32.32, 0.67)	0.0601
Rilzabrutinib 400mg QPM (N=38)	34	16.50 (3.53)	10.97 (5.48)	-5.90 (0.99)	-0.04 (-2.69, 2.62)	0.9783	-36.92 (6.23)	-3.30 (-19.96, 13.36)	0.6977
Placebo (N=40)	37	15.60 (4.24)	10.09 (6.46)	-5.87 (0.98)			-33.62 (6.18)		
Week 12									
Rilzabrutinib 400mg TIID (N=41)	33	15.88 (4.37)	5.59 (5.58)	-9.58 (1.01)	-3.26 (-5.97, -0.56)	0.0181	-59.81 (6.28)	-23.23 (-40.11, - 6.35)	0.0070
Rilzabrutinib 400mg BID (N=41)	30	15.80 (3.68)	7.61 (7.18)	-8.06 (1.02)	-1.75 (-4.46, 0.95)	0.2041	-50.27 (6.54)	-13.69 (-30.83, 3.46)	0.1176
Rilzabrutinib 400mg QPM (N=38)	31	16.50 (3.53)	11.37 (5.51)	-5.46 (1.03)	0.85 (-1.90, 3.60)	0.5439	-35.23 (6.55)	1.35 (-16.05, 18.76)	0.8790
Placebo (N=40)	35	15.60 (4.24)	9.96 (7.02)	-6.31 (1.02)			-36.58 (6.30)		

^a Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group and regions as covariates.
Note: Data collected after study intervention discontinuation were included. Data post selected prohibited/rescue medications (high/medium impact on efficacy confirmed through blinded medical review) were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF; other missing data were imputed by MI.

n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
			Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a

Descriptive statistics at each week include participants with WOCF imputation at the week, and participants whose values were imputed by MI at the week were excluded from the descriptive analysis.

Table 30. Change and Percent Change from Baseline in ISS7 over Time up to Week 12 (Omalizumab-Naïve Population)

				Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Week 1									
Rilzabrutinib 400mg TID (N=35)	35	15.69 (4.26)	9.51 (5.64)	-6.13 (0.82)	-4.21 (-6.89, -1.52)	0.0003	-37.45 (5.78)	-27.33 (-42.78, -11.87)	0.0005
Rilzabrutinib 400mg BID (N=35)	35	15.45 (3.72)	10.51 (5.88)	-5.06 (0.83)	-3.14 (-5.80, -0.47)	0.0060	-33.92 (5.73)	-23.80 (-38.99, -8.60)	0.0021
Rilzabrutinib 400mg QPM (N=37)	37	16.38 (3.50)	13.08 (4.52)	-3.25 (0.80)	-1.33 (-3.97, 1.31)	0.2347	-18.38 (5.55)	-8.25 (-23.30, 6.80)	0.2827
Placebo (N=36)	36	15.14 (4.16)	13.57 (5.31)	-1.93 (0.82)			-10.12 (5.66)		
Week 2									
Rilzabrutinib 400mg TID (N=35)	35	15.69 (4.26)	8.40 (5.82)	-7.37 (0.82)	-4.14 (-6.35, -1.94)	0.0002	-46.27 (5.61)	-27.63 (-42.70, -12.56)	0.0003
Rilzabrutinib 400mg BID (N=35)	34	15.45 (3.72)	10.32 (5.64)	-5.49 (0.83)	-2.26 (-4.46, -0.07)	0.0431	-35.92 (5.58)	-17.28 (-32.06, -2.50)	0.0219
Rilzabrutinib 400mg QPM (N=37)	37	16.38 (3.50)	12.53 (4.73)	-3.99 (0.80)	-0.76 (-2.92, 1.41)	0.4948	-23.96 (5.37)	-5.32 (-19.96, 9.32)	0.4765
Placebo (N=36)	35	15.14 (4.16)	12.38 (5.17)	-3.23 (0.82)			-18.64 (5.51)		
Week 3									
Rilzabrutinib 400mg TID (N=35)	35	15.69 (4.26)	8.34 (5.42)	-7.29 (0.87)	-3.58 (-5.93, -1.24)	0.0027	-47.81 (5.64)	-27.20 (-42.33, -12.08)	0.0004
Rilzabrutinib 400mg BID (N=35)	35	15.45 (3.72)	9.16 (6.09)	-6.52 (0.87)	-2.82 (-5.15, -0.49)	0.0175	-40.91 (5.60)	-20.30 (-35.19, -5.41)	0.0076
Rilzabrutinib 400mg QPM (N=37)	37	16.38 (3.50)	11.60 (4.68)	-4.82 (0.85)	-1.12 (-3.43, 1.18)	0.3399	-28.99 (5.42)	-8.38 (-23.14, 6.38)	0.2659
Placebo (N=36)	35	15.14 (4.16)	11.98 (5.40)	-3.70 (0.87)			-20.61 (5.56)		
Week 4									
Rilzabrutinib 400mg TID (N=35)	32	15.69 (4.26)	7.79 (5.03)	-7.33 (0.92)	-3.23 (-5.71, -0.75)	0.0106	-47.50 (6.02)	-24.55 (-40.74, -8.36)	0.0030
Rilzabrutinib 400mg BID (N=35)	33	15.45 (3.72)	8.32 (6.02)	-6.96 (0.93)	-2.86 (-5.32, -0.40)	0.0227	-43.47 (5.96)	-20.53 (-36.37, -4.69)	0.0111
Rilzabrutinib 400mg QPM (N=37)	37	16.38 (3.50)	11.39 (4.79)	-5.03 (0.89)	-0.93 (-3.36, 1.50)	0.4535	-29.97 (5.75)	-7.02 (-22.76, 8.71)	0.3817
Placebo (N=36)	34	15.14 (4.16)	11.51 (6.14)	-4.10 (0.92)			-22.94 (5.94)		

				Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Rilzabrutinib 400mg TID (N=35)	33	15.69 (4.26)	6.92 (5.87)	-8.51 (0.91)	-2.88 (-5.34, -0.42)	0.0216	-53.64 (5.75)	-19.52 (-35.10, -3.93)	0.0141
Rilzabrutinib 400mg BID (N=35)	34	15.45 (3.72)	8.88 (6.81)	-6.55 (0.91)	-0.92 (-3.33, 1.50)	0.4561	-42.17 (5.73)	-8.04 (-23.43, 7.34)	0.3055
Rilzabrutinib 400mg QPM (N=37)	36	16.38 (3.50)	11.00 (4.68)	-5.30 (0.88)	0.33 (-2.07, 2.73)	0.7894	-31.89 (5.56)	2.23 (-13.08, 17.55)	0.7751
Placebo (N=36)	33	15.14 (4.16)	9.75 (4.75)	-5.63 (0.91)			-34.12 (5.78)		
Week 6									
Rilzabrutinib 400mg TID (N=35)	31	15.69 (4.26)	7.32 (6.05)	-8.27 (0.99)	-3.47 (-6.12, -0.82)	0.0103	-52.36 (6.28)	-24.70 (-41.62, -7.79)	0.0042
Rilzabrutinib 400mg BID (N=35)	34	15.45 (3.72)	8.85 (6.40)	-6.57 (0.97)	-1.76 (-4.36, 0.83)	0.1834	-41.28 (6.23)	-13.63 (-30.25, 3.00)	0.1082
Rilzabrutinib 400mg QPM (N=37)	34	16.38 (3.50)	10.27 (5.26)	-6.02 (0.95)	-1.21 (-3.81, 1.39)	0.3604	-36.29 (6.07)	-8.63 (-25.16, 7.90)	0.3060
Placebo (N=36)	32	15.14 (4.16)	10.58 (5.85)	-4.80 (0.98)			-27.66 (6.23)		
Week 7									
Rilzabrutinib 400mg TID (N=35)	30	15.69 (4.26)	7.14 (5.35)	-8.54 (0.97)	-3.43 (-6.01, -0.85)	0.0091	-54.42 (6.29)	-24.69 (-41.39, -7.99)	0.0038
Rilzabrutinib 400mg BID (N=35)	34	15.45 (3.72)	8.21 (6.16)	-7.47 (0.94)	-2.36 (-4.88, 0.16)	0.0664	-46.77 (6.08)	-17.04 (-33.33, -0.75)	0.0404
Rilzabrutinib 400mg QPM (N=37)	33	16.38 (3.50)	10.68 (5.34)	-6.16 (0.93)	-1.06 (-3.59, 1.48)	0.4144	-38.23 (5.98)	-8.51 (-24.78, 7.77)	0.3057
Placebo (N=36)	33	15.14 (4.16)	10.51 (5.70)	-5.11 (0.95)			-29.73 (6.10)		
Week 8									
Rilzabrutinib 400mg TID (N=35)	28	15.69 (4.26)	7.24 (5.51)	-7.93 (1.03)	-2.52 (-5.25, 0.20)	0.0697	-51.09 (6.57)	-19.18 (-36.57, -1.80)	0.0306
Rilzabrutinib 400mg BID (N=35)	33	15.45 (3.72)	7.33 (6.55)	-8.20 (0.98)	-2.79 (-5.41, -0.18)	0.0363	-52.58 (6.34)	-20.68 (-37.61, -3.74)	0.0167
Rilzabrutinib 400mg QPM (N=37)	33	16.38 (3.50)	10.72 (5.26)	-5.96 (0.96)	-0.55 (-3.17, 2.06)	0.6792	-37.54 (6.29)	-5.64 (-22.51, 11.23)	0.5122
Placebo (N=36)	33	15.14 (4.16)	10.15 (6.23)	-5.41 (0.98)			-31.90 (6.28)		
Week 9									

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
					LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	
Rilzabrutinib 400mg TID (N=35)	29	15.69 (4.26)	6.68 (5.31)	-8.45 (1.00)	-3.43 (-6.09, -0.77)	0.0114	-53.94 (6.32)	-24.44 (-41.44, -7.44)	0.0048	
Rilzabrutinib 400mg BID (N=35)	29	15.45 (3.72)	7.63 (7.11)	-7.96 (0.99)	-2.94 (-5.57, -0.32)	0.0282	-51.70 (6.32)	-22.21 (-38.97, -5.44)	0.0094	
Rilzabrutinib 400mg QPM (N=37)	34	16.38 (3.50)	10.46 (5.15)	-6.10 (0.96)	-1.08 (-3.70, 1.54)	0.4202	-37.27 (6.13)	-7.78 (-24.44, 8.89)	0.3604	
Placebo (N=36)	32	15.14 (4.16)	10.55 (5.94)	-5.02 (0.98)			-29.49 (6.26)			
Week 10										
Rilzabrutinib 400mg TID (N=35)	30	15.69 (4.26)	6.75 (5.25)	-8.59 (1.03)	-2.91 (-5.68, -0.13)	0.0400	-54.88 (6.72)	-20.32 (-38.47, -2.16)	0.0283	
Rilzabrutinib 400mg BID (N=35)	28	15.45 (3.72)	8.17 (7.29)	-7.77 (1.05)	-2.09 (-4.86, 0.69)	0.1405	-48.38 (6.69)	-13.81 (-31.52, 3.91)	0.1267	
Rilzabrutinib 400mg QPM (N=37)	34	16.38 (3.50)	10.43 (5.30)	-6.26 (1.01)	-0.58 (-3.31, 2.15)	0.6786	-38.74 (6.43)	-4.17 (-21.94, 13.59)	0.6454	
Placebo (N=36)	33	15.14 (4.16)	10.00 (6.49)	-5.68 (1.02)			-34.57 (6.68)			
Week 11										
Rilzabrutinib 400mg TID (N=35)	31	15.69 (4.26)	6.99 (5.53)	-8.50 (1.02)	-3.19 (-5.92, -0.45)	0.0224	-53.92 (6.66)	-22.62 (-40.61, -4.64)	0.0137	
Rilzabrutinib 400mg BID (N=35)	29	15.45 (3.72)	7.93 (6.94)	-7.75 (1.02)	-2.43 (-5.15, 0.28)	0.0790	-49.16 (6.63)	-17.86 (-35.62, -0.09)	0.0488	
Rilzabrutinib 400mg QPM (N=37)	33	16.38 (3.50)	11.03 (5.55)	-5.73 (1.00)	-0.42 (-3.12, 2.28)	0.7628	-36.17 (6.53)	-4.87 (-22.51, 12.77)	0.5885	
Placebo (N=36)	33	15.14 (4.16)	10.24 (6.31)	-5.32 (1.01)			-31.30 (6.59)			
Week 12										
Rilzabrutinib 400mg TID (N=35)	28	15.69 (4.26)	5.77 (5.26)	-9.21 (1.05)	-3.44 (-6.25, -0.62)	0.0168	-58.05 (6.73)	-23.84 (-41.97, -5.71)	0.0100	
Rilzabrutinib 400mg BID (N=35)	26	15.45 (3.72)	8.09 (6.95)	-7.73 (1.06)	-1.96 (-4.77, 0.86)	0.1728	-48.31 (6.75)	-14.10 (-32.26, 4.06)	0.1281	
Rilzabrutinib 400mg QPM (N=37)	30	16.38 (3.50)	11.51 (5.54)	-5.19 (1.02)	0.58 (-2.24, 3.40)	0.6869	-34.75 (6.64)	-0.54 (-18.55, 17.47)	0.9529	
Placebo (N=36)	32	15.14 (4.16)	10.02 (6.82)	-5.77 (1.05)			-34.21 (6.72)			

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

n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo		% Change difference for rilzabrutinib vs. placebo	
				LS Mean (95% CI) ^a	p-value ^a	LS Mean (95% CI) ^a	p-value ^a

Note: Data collected after study intervention discontinuation were included. Data post selected prohibited/rescue medications (high/medium impact on efficacy confirmed through blinded medical review) were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF; other missing data were imputed by MI.
Descriptive statistics at each week include participants with WOCF imputation at the week, and participants whose values were imputed by MI at the week were excluded from the descriptive analysis.

Table 31. Change and Percent Change from Baseline in ISS7 Over Time Up to Week 12 (Omalizumab-Naïve Population with Outlier Removed from Analysis)

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo		% Change difference for rilzabrutinib vs. placebo ^a		
					LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Week 1									
Rilzabrutinib 400mg TID (N=34)	34	16.15 (3.32)	9.79 (5.47)	-6.21 (0.84)	-4.25 (-6.97, -1.53)	0.0003	-37.73 (5.76)	-27.54 (-46.26, -8.82)	0.0006
Rilzabrutinib 400mg BID (N=35)	35	15.45 (3.72)	10.51 (5.88)	-5.10 (0.83)	-3.14 (-5.82, -0.46)	0.0062	-34.00 (5.73)	-23.81 (-42.23, -5.39)	0.0026
Rilzabrutinib 400mg QPM (N=37)	37	16.38 (3.50)	13.08 (4.52)	-3.30 (0.81)	-1.34 (-3.99, 1.31)	0.2324	-18.50 (5.54)	-8.32 (-26.56, 9.93)	0.2807
Placebo (N=36)	36	15.14 (4.16)	13.57 (5.31)	-1.96 (0.82)			-10.19 (5.67)		
Week 2									
Rilzabrutinib 400mg TID (N=34)	34	16.15 (3.32)	8.59 (5.80)	-7.53 (0.83)	-4.29 (-6.52, -2.06)	0.0002	-46.27 (5.57)	-27.63 (-42.59, -12.68)	0.0003
Rilzabrutinib 400mg BID (N=35)	34	15.45 (3.72)	10.32 (5.64)	-5.52 (0.83)	-2.27 (-4.47, -0.08)	0.0425	-36.28 (5.56)	-17.64 (-32.37, -2.92)	0.0189
Rilzabrutinib 400mg QPM (N=37)	37	16.38 (3.50)	12.53 (4.73)	-4.05 (0.80)	-0.80 (-2.97, 1.37)	0.4691	-24.02 (5.36)	-5.38 (-19.96, 9.19)	0.4692
Placebo (N=36)	35	15.14 (4.16)	12.38 (5.17)	-3.24 (0.82)			-18.64 (5.49)		
Week 3									
Rilzabrutinib 400mg TID (N=34)	34	16.15 (3.32)	8.18 (5.41)	-7.77 (0.85)	-4.12 (-6.42, -1.83)	0.0004	-47.94 (5.64)	-27.10 (-42.26, -11.94)	0.0005

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
					LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	
Rilzabrutinib 400mg BID (N=35)	35	15.45 (3.72)	9.16 (6.09)	-6.51 (0.85)	-2.87 (-5.12, -0.61)	0.0127	-41.02 (5.61)	-20.18 (-35.09, -5.26)	0.0080	
Rilzabrutinib 400mg QPM (N=37)	37	16.38 (3.50)	11.60 (4.68)	-4.94 (0.82)	-1.30 (-3.54, 0.94)	0.2544	-29.09 (5.42)	-8.25 (-23.04, 6.55)	0.2746	
Placebo (N=36)	35	15.14 (4.16)	11.98 (5.40)	-3.64 (0.84)			-20.84 (5.58)			
Week 4										
Rilzabrutinib 400mg TIID (N=34)	32	16.15 (3.32)	7.79 (5.03)	-7.78 (0.91)	-3.69 (-6.13, -1.25)	0.0031	-47.66 (6.02)	-24.30 (-40.44, -8.16)	0.0032	
Rilzabrutinib 400mg BID (N=35)	33	15.45 (3.72)	8.32 (6.02)	-6.96 (0.91)	-2.86 (-5.26, -0.46)	0.0193	-43.56 (5.98)	-20.20 (-36.06, -4.35)	0.0125	
Rilzabrutinib 400mg QPM (N=37)	37	16.38 (3.50)	11.39 (4.79)	-5.14 (0.87)	-1.05 (-3.42, 1.32)	0.3841	-30.05 (5.74)	-6.69 (-22.35, 8.98)	0.4028	
Placebo (N=36)	34	15.14 (4.16)	11.51 (6.14)	-4.09 (0.89)			-23.36 (5.91)			
Week 5										
Rilzabrutinib 400mg TIID (N=34)	33	16.15 (3.32)	6.92 (5.87)	-8.85 (0.91)	-3.21 (-5.65, -0.77)	0.0100	-53.59 (5.78)	-19.54 (-35.11, -3.96)	0.0140	
Rilzabrutinib 400mg BID (N=35)	34	15.45 (3.72)	8.88 (6.81)	-6.55 (0.90)	-0.91 (-3.31, 1.48)	0.4553	-42.26 (5.73)	-8.21 (-23.48, 7.06)	0.2920	
Rilzabrutinib 400mg QPM (N=37)	36	16.38 (3.50)	11.00 (4.68)	-5.44 (0.87)	0.20 (-2.17, 2.58)	0.8663	-32.18 (5.54)	1.87 (-13.30, 17.05)	0.8087	
Placebo (N=36)	33	15.14 (4.16)	9.75 (4.75)	-5.64 (0.90)			-34.06 (5.74)			
Week 6										
Rilzabrutinib 400mg TIID (N=34)	31	16.15 (3.32)	7.32 (6.05)	-8.61 (0.98)	-3.77 (-6.39, -1.15)	0.0047	-52.19 (6.28)	-23.97 (-40.79, -7.15)	0.0052	
Rilzabrutinib 400mg BID (N=35)	34	15.45 (3.72)	8.85 (6.40)	-6.56 (0.97)	-1.72 (-4.30, 0.87)	0.1928	-41.38 (6.22)	-13.16 (-29.74, 3.43)	0.1201	
Rilzabrutinib 400mg QPM (N=37)	34	16.38 (3.50)	10.27 (5.26)	-6.13 (0.94)	-1.29 (-3.88, 1.30)	0.3299	-36.45 (6.05)	-8.22 (-24.84, 8.40)	0.3323	
Placebo (N=36)	32	15.14 (4.16)	10.58 (5.85)	-4.84 (0.98)			-28.23 (6.27)			
Week 7										
Rilzabrutinib 400mg TIID (N=34)	30	16.15 (3.32)	7.14 (5.35)	-8.83 (0.95)	-3.69 (-6.24, -1.13)	0.0046	-54.22 (6.16)	-24.40 (-40.95, -7.85)	0.0039	

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
				Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Rilzabrutinib 400mg BID (N=35)	34	15.45 (3.72)	8.21 (6.16)	-7.50 (0.93)	-2.36 (-4.85, 0.14)	0.0640	-47.03 (6.06)	-17.21 (-33.40, - 1.02)	0.0372
Rilzabrutinib 400mg QPM (N=37)	33	16.38 (3.50)	10.68 (5.34)	-6.23 (0.91)	-1.09 (-3.58, 1.41)	0.3929	-38.17 (5.94)	-8.35 (-24.56, 7.86)	0.3129
Placebo (N=36)	33	15.14 (4.16)	10.51 (5.70)	-5.14 (0.94)			-29.82 (6.07)		
Week 8									
Rilzabrutinib 400mg TIID (N=34)	28	16.15 (3.32)	7.24 (5.51)	-8.34 (0.99)	-2.89 (-5.57, -0.21)	0.0343	-51.64 (6.49)	-19.50 (-37.05, - 1.95)	0.0295
Rilzabrutinib 400mg BID (N=35)	33	15.45 (3.72)	7.33 (6.55)	-8.18 (0.97)	-2.73 (-5.33, -0.13)	0.0394	-52.28 (6.33)	-20.13 (-37.11, - 3.16)	0.0201
Rilzabrutinib 400mg QPM (N=37)	33	16.38 (3.50)	10.72 (5.26)	-6.08 (0.95)	-0.63 (-3.22, 1.96)	0.6343	-38.14 (6.20)	-5.99 (-22.96, 10.98)	0.4887
Placebo (N=36)	33	15.14 (4.16)	10.15 (6.23)	-5.45 (0.97)			-32.14 (6.36)		
Week 9									
Rilzabrutinib 400mg TIID (N=34)	29	16.15 (3.32)	6.68 (5.31)	-8.79 (1.02)	-3.67 (-6.38, -0.96)	0.0079	-53.45 (6.52)	-23.53 (-40.91, - 6.16)	0.0080
Rilzabrutinib 400mg BID (N=35)	29	15.45 (3.72)	7.63 (7.11)	-7.98 (0.99)	-2.86 (-5.51, -0.21)	0.0344	-51.40 (6.37)	-21.48 (-38.50, - 4.47)	0.0133
Rilzabrutinib 400mg QPM (N=37)	34	16.38 (3.50)	10.46 (5.15)	-6.16 (0.95)	-1.04 (-3.67, 1.58)	0.4355	-37.28 (6.13)	-7.36 (-24.20, 9.48)	0.3915
Placebo (N=36)	32	15.14 (4.16)	10.55 (5.94)	-5.12 (0.98)			-29.92 (6.31)		
Week 10									
Rilzabrutinib 400mg TIID (N=34)	30	16.15 (3.32)	6.75 (5.25)	-8.88 (1.04)	-3.21 (-5.98, -0.44)	0.0230	-54.26 (6.73)	-19.20 (-37.21, - 1.20)	0.0366
Rilzabrutinib 400mg BID (N=35)	28	15.45 (3.72)	8.17 (7.29)	-7.86 (1.04)	-2.19 (-4.95, 0.57)	0.1198	-49.04 (6.78)	-13.98 (-31.91, 3.95)	0.1264
Rilzabrutinib 400mg QPM (N=37)	34	16.38 (3.50)	10.43 (5.30)	-6.41 (0.98)	-0.75 (-3.45, 1.96)	0.5891	-39.06 (6.40)	-3.99 (-21.57, 13.58)	0.6560
Placebo (N=36)	33	15.14 (4.16)	10.00 (6.49)	-5.67 (1.02)			-35.06 (6.61)		
Week 11									
Rilzabrutinib 400mg TIID (N=34)	31	16.15 (3.32)	6.99 (5.53)	-8.82 (1.00)	-3.49 (-6.21, -0.78)	0.0116	-53.60 (6.61)	-22.12 (-39.99, - 4.26)	0.0152

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
					LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	
Rilzabrutinib 400mg BID (N=35)	29	15.45 (3.72)	7.93 (6.94)	-7.71 (1.02)	-2.38 (-5.10, 0.33)	0.0851	-49.26 (6.74)	-17.79 (-35.67, 0.10)	0.0513	
Rilzabrutinib 400mg QPM (N=37)	33	16.38 (3.50)	11.03 (5.55)	-5.84 (0.98)	-0.51 (-3.21, 2.18)	0.7077	-36.51 (6.46)	-5.03 (-22.79, 12.72)	0.5785	
Placebo (N=36)	33	15.14 (4.16)	10.24 (6.31)	-5.32 (1.00)			-31.47 (6.58)			
Week 12										
Rilzabrutinib 400mg TID (N=34)	28	16.15 (3.32)	5.77 (5.26)	-9.57 (1.06)	-3.86 (-6.71, -1.02)	0.0078	-58.20 (6.85)	-23.57 (-41.96, - 5.17)	0.0120	
Rilzabrutinib 400mg BID (N=35)	26	15.45 (3.72)	8.09 (6.95)	-7.76 (1.06)	-2.05 (-4.84, 0.74)	0.1491	-49.36 (6.89)	-14.72 (-32.82, 3.38)	0.1109	
Rilzabrutinib 400mg QPM (N=37)	30	16.38 (3.50)	11.51 (5.54)	-5.29 (1.01)	0.42 (-2.33, 3.18)	0.7634	-34.35 (6.52)	0.29 (-17.53, 18.11)	0.9746	
Placebo (N=36)	32	15.14 (4.16)	10.02 (6.82)	-5.71 (1.02)			-34.64 (6.62)			
^a Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group and region as covariates. Note: Data collected after study intervention discontinuation were included. Data post selected prohibited/rescue medications (high/medium impact on efficacy confirmed through blinded medical review) were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at each week include participants with WOCF imputation at the week, and participants whose values were imputed by MI at the week were excluded from the descriptive analysis. One patient was randomized to Rilzabrutinib 400mg TID group by mistake (baseline ISS7/UAS7=0). Removed this participant from the analysis.										

[00249] A significant proportion of patients in both the ITT and omalizumab-naïve population experienced a MCID (a reduction in ISS7 of at least 5 points) that was sustained over the course of the double-blind treatment phase (see Table 32).

Table 32. Proportion of Participants with ISS7 Reduction from Baseline of 5 Points or More Over Time up to Week 12 (ITT and Omalizumab-Naïve Populations)

	ITT Population					Omalizumab-Naïve Population						
	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for placebo ^b	P-value vs. placebo ^b
Week 1												
Rilzabrutinib 400mg	27 (65.9)	14 (34.1)	0	42.3 (22.48, 62.19)	6.428 (2.369, 17.441)	0.0002	22 (62.9)	13 (37.1)	0	40.1 (18.80, 5.851 (2.026, 0.0009 61.44)	16.899)	
T1D (N=41)												
Rilzabrutinib 400mg	20 (48.8)	21 (51.2)	1 (2.4)	25.5 (5.45, 45.48)	3.262 (1.222, 8.713)	0.0180	17 (48.6)	18 (51.4)	0	25.3 (3.89, 3.240 (1.139, 0.0267 46.70)	9.215)	
B1D (N=41)												
Rilzabrutinib 400mg	13 (34.2)	25 (65.8)	0	12.7 (-7.46, 32.82)	1.855 (0.686, 5.019)	0.2221	12 (32.4)	25 (67.6)	0	10.5 (-9.99, 1.691 (0.600, 0.3218 31.07)	4.768)	
QPM (N=38)												
Placebo (N=40)	9 (22.5)	31 (77.5)	0				8 (22.2)	28 (77.8)	0			
Week 2												
Rilzabrutinib 400mg	28 (68.3)	13 (31.7)	0	35.9 (15.40, 56.30)	4.772 (1.806, 12.610)	0.0013	23 (65.7)	12 (34.3)	0	36.4 (14.67, 4.876 (1.722, 0.0023 58.20)	13.807)	
T1D (N=41)												
Rilzabrutinib 400mg	22 (53.7)	19 (46.3)	2 (4.9)	23.6 (2.60, 44.66)	2.693 (1.073, 6.761)	0.0349	18 (51.4)	17 (48.6)	1 (2.9)	24.1 (2.00, 2.836 (1.042, 0.0420 46.13)	7.719)	
B1D (N=41)												
Rilzabrutinib 400mg	15 (39.5)	23 (60.5)	0	11.0 (-9.68, 31.70)	1.662 (0.634, 4.356)	0.3076	14 (37.8)	23 (62.2)	0	10.6 (-10.65, 1.637 (0.603, 0.3389 31.84)	4.439)	
QPM (N=38)												
Placebo (N=40)	12 (30.0)	28 (70.0)	1 (2.5)				10 (27.8)	26 (72.2)	1 (2.8)			
Week 3												
Rilzabrutinib 400mg	29 (70.7)	12 (29.3)	0	37.3 (15.73, 58.95)	4.110 (1.671, 10.108)	0.0011	23 (65.7)	12 (34.3)	0	34.3 (10.93, 3.637 (1.411, 0.0053 57.65)	9.374)	
T1D (N=41)												
Rilzabrutinib 400mg	22 (53.7)	19 (46.3)	1 (2.4)	21.5 (0.36, 42.64)	2.451 (0.981, 6.119)	0.0549	18 (51.4)	17 (48.6)	0	21.1 (-1.44, 2.418 (0.911, 0.0770 43.66)	6.416)	
B1D (N=41)												
Rilzabrutinib 400mg	18 (47.4)	20 (52.6)	0	15.9 (-6.26, 38.11)	1.881 (0.766, 4.618)	0.1588	17 (45.9)	20 (54.1)	0	16.0 (-6.65, 1.910 (0.749, 0.1686 38.62)	4.870)	
QPM (N=38)												
Placebo (N=40)	13 (32.5)	27 (67.5)	1 (2.5)				11 (30.6)	25 (69.4)	1 (2.8)			
Week 4												
Rilzabrutinib 400mg	28 (68.3)	13 (31.7)	3 (7.3)	18.8 (-2.90, 40.54)	2.155 (0.875, 5.310)	0.0939	24 (68.6)	11 (31.4)	3 (8.6)	25.1 (2.13, 2.777 (1.051, 0.0384 48.17)	7.333)	
T1D (N=41)												
Rilzabrutinib 400mg	22 (53.7)	19 (46.3)	4 (9.8)	5.6 (-16.31, 27.56)	1.252 (0.521, 3.011)	0.6227	18 (51.4)	17 (48.6)	2 (5.7)	9.7 (-13.58, 1.476 (0.577, 0.4279 33.00)	3.779)	
B1D (N=41)												
Rilzabrutinib 400mg	18 (47.4)	20 (52.6)	1 (2.6)	1.7 (-19.99, 23.44)	1.076 (0.430, 2.691)	0.8779	17 (45.9)	20 (54.1)	1 (2.7)	5.0 (-17.54, 1.231 (0.482, 0.6670 27.58)	3.146)	
QPM (N=38)												
Placebo (N=40)	19 (47.5)	21 (52.5)	2 (5.0)				15 (41.7)	21 (58.3)	2 (5.6)			

		ITT Population				Omalizumab-Naïve Population						
	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b
Week 5												
	Rilzabrutinib 400mg TID (N=41)	30 (73.2)	11 (26.8)	3 (7.3)	20.9 (-0.26, 42.03)	2.433 (0.960, 6.167)	0.0603	25 (71.4)	10 (28.6)	2 (5.7)	22.7 (-0.15, 2.535 (0.951, 45.54)	0.0599
	Rilzabrutinib 400mg BID (N=41)	23 (56.1)	18 (43.9)	5 (12.2)	2.7 (-19.28, 24.60)	1.112 (0.463, 2.675)	0.8143	20 (57.1)	15 (42.9)	2 (5.7)	7.3 (-16.20, 30.77)	0.5478
	Rilzabrutinib 400mg QPM (N=38)	17 (44.7)	21 (55.3)	2 (5.3)	-6.2 (-28.55, 16.17)	0.781 (0.321, 1.905)	0.5860	16 (43.2)	21 (56.8)	2 (5.4)	-6.3 (-29.76, 17.25)	0.5972
	Placebo (N=40)	21 (52.5)	19 (47.5)	3 (7.5)			18 (50.0)	18 (50.0)	3 (8.3)		1.938)	
Week 6												
	Rilzabrutinib 400mg TID (N=41)	25 (61.0)	16 (39.0)	5 (12.2)	11.1 (-10.74, 32.99)	1.574 (0.643, 3.851)	0.3257	20 (57.1)	15 (42.9)	4 (11.4)	11.3 (-12.38, 35.07)	0.3556
	Rilzabrutinib 400mg BID (N=41)	21 (51.2)	20 (48.8)	4 (9.8)	2.7 (-19.31, 24.65)	1.112 (0.463, 2.670)	0.8133	18 (51.4)	17 (48.6)	2 (5.7)	7.1 (-16.32, 30.44)	0.5593
	Rilzabrutinib 400mg QPM (N=38)	18 (47.4)	20 (52.6)	4 (10.5)	1.5 (-20.31, 23.37)	1.066 (0.428, 2.654)	0.8938	17 (45.9)	20 (54.1)	4 (10.8)	2.0 (-20.59, 24.65)	0.8639
	Placebo (N=40)	19 (47.5)	21 (52.5)	6 (15.0)			16 (44.4)	20 (55.6)	5 (13.9)		2.773)	
Week 7												
	Rilzabrutinib 400mg TID (N=41)	27 (65.9)	14 (34.1)	6 (14.6)	16.8 (-4.53, 38.17)	2.038 (0.810, 5.128)	0.1300	24 (68.6)	11 (31.4)	5 (14.3)	23.5 (1.00, 45.99)	0.0485
	Rilzabrutinib 400mg BID (N=41)	22 (53.7)	19 (46.3)	4 (9.8)	5.5 (-16.01, 27.10)	1.258 (0.515, 3.075)	0.6214	19 (54.3)	16 (45.7)	2 (5.7)	10.2 (-12.59, 33.02)	0.3942
	Rilzabrutinib 400mg QPM (N=38)	19 (50.0)	19 (50.0)	6 (15.8)	3.1 (-18.79, 25.00)	1.138 (0.458, 2.826)	0.7854	18 (48.6)	19 (51.4)	6 (16.2)	4.0 (-18.90, 26.93)	0.7346
	Placebo (N=40)	19 (47.5)	21 (52.5)	5 (12.5)			16 (44.4)	20 (55.6)	4 (11.1)		2.962)	
Week 8												
	Rilzabrutinib 400mg TID (N=41)	28 (68.3)	13 (31.7)	8 (19.5)	14.6 (-6.94, 36.13)	1.839 (0.738, 4.585)	0.1862	23 (65.7)	12 (34.3)	7 (20.0)	16.1 (-7.40, 39.61)	0.1770
	Rilzabrutinib 400mg BID (N=41)	25 (61.0)	16 (39.0)	5 (12.2)	8.3 (-13.74, 30.43)	1.388 (0.580, 3.321)	0.4623	22 (62.9)	13 (37.1)	3 (8.6)	13.7 (-10.03, 37.36)	0.2599
	Rilzabrutinib 400mg QPM (N=38)	18 (47.4)	20 (52.6)	7 (18.4)	-4.5 (-26.75, 17.83)	0.836 (0.342, 2.045)	0.6963	17 (45.9)	20 (54.1)	7 (18.9)	-4.4 (-27.59, 18.88)	0.7111
	Placebo (N=40)	21 (52.5)	19 (47.5)	5 (12.5)			18 (50.0)	18 (50.0)	4 (11.1)		2.100)	

		ITT Population					Omalizumab-Naïve Population						
	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for placebo ^b	OR (95% CI) for placebo ^a	P-value vs. placebo ^b	
Week 9													
Rilzabrutinib 400mg TID (N=41)	29 (70.7)	12 (29.3)	7 (17.1)	22.5 (1.82, 43.14)	2.730 (1.042, 7.150)	0.0383	24 (68.6)	11 (31.4)	6 (17.1)	25.1 (2.93, 47.37)	2.956 (1.064, 8.208)	0.0315	
Rilzabrutinib 400mg BID (N=41)	22 (53.7)	19 (46.3)	9 (22.0)	5.6 (-17.08, 28.33)	1.233 (0.528, 2.880)	0.6227	19 (54.3)	16 (45.7)	7 (20.0)	10.4 (-13.98, 34.88)	1.462 (0.596, 3.586)	0.3922	
Rilzabrutinib 400mg QPM (N=38)	20 (52.6)	18 (47.4)	6 (15.8)	5.8 (-15.33, 26.96)	1.294 (0.505, 3.321)	0.5965	19 (51.4)	18 (48.6)	6 (16.2)	6.5 (-15.49, 28.41)	1.328 (0.506, 3.483)	0.5653	
Placebo (N=40)	19 (47.5)	21 (52.5)	6 (15.0)				16 (44.4)	20 (55.6)	5 (13.9)				
Week 10													
Rilzabrutinib 400mg TID (N=41)	27 (65.9)	14 (34.1)	7 (17.1)	11.9 (-9.36, 33.15)	1.669 (0.662, 4.207)	0.2796	23 (65.7)	12 (34.3)	5 (14.3)	15.5 (-7.42, 38.40)	1.910 (0.719, 5.077)	0.1910	
Rilzabrutinib 400mg BID (N=41)	19 (46.3)	22 (53.7)	10 (24.4)	-6.2 (-28.29, 15.99)	0.786 (0.329, 1.875)	0.5921	16 (45.7)	19 (54.3)	8 (22.9)	-3.1 (-26.73, 20.43)	0.883 (0.349, 2.235)	0.7963	
Rilzabrutinib 400mg QPM (N=38)	24 (63.2)	14 (36.8)	6 (15.8)	11.2 (-10.58, 32.94)	1.593 (0.637, 3.986)	0.3280	23 (62.2)	14 (37.8)	6 (16.2)	11.9 (-10.94, 34.75)	1.614 (0.639, 4.080)	0.3157	
Placebo (N=40)	21 (52.5)	19 (47.5)	5 (12.5)				18 (50.0)	18 (50.0)	4 (11.1)				
Week 11													
Rilzabrutinib 400mg TID (N=41)	29 (70.7)	12 (29.3)	6 (14.6)	11.8 (-9.03, 32.68)	1.699 (0.661, 4.362)	0.2734	25 (71.4)	10 (28.6)	4 (11.4)	15.5 (-7.09, 38.00)	1.951 (0.720, 5.283)	0.1834	
Rilzabrutinib 400mg BID (N=41)	22 (53.7)	19 (46.3)	9 (22.0)	-4.5 (-26.51, 17.54)	0.837 (0.349, 2.007)	0.6935	19 (54.3)	16 (45.7)	7 (20.0)	-1.0 (-24.66, 22.75)	0.963 (0.383, 2.426)	0.9376	
Rilzabrutinib 400mg QPM (N=38)	21 (55.3)	17 (44.7)	7 (18.4)	-1.5 (-23.17, 20.15)	0.938 (0.374, 2.353)	0.8934	20 (54.1)	17 (45.9)	7 (18.9)	-1.7 (-24.23, 20.85)	0.932 (0.364, 2.385)	0.8852	
Placebo (N=40)	23 (57.5)	17 (42.5)	5 (12.5)				20 (55.6)	16 (44.4)	4 (11.1)				
Week 12													
Rilzabrutinib 400mg TID (N=41)	23 (56.1)	18 (43.9)	11 (26.8)	7.9 (-14.19, 29.98)	1.371 (0.566, 3.320)	0.4839	20 (57.1)	15 (42.9)	8 (22.9)	9.7 (-13.92, 33.30)	1.469 (0.572, 3.772)	0.4230	
Rilzabrutinib 400mg BID (N=41)	20 (48.8)	21 (51.2)	14 (34.1)	1.6 (-20.93, 24.12)	1.063 (0.452, 2.497)	0.8886	17 (48.6)	18 (51.4)	11 (31.4)	2.4 (-21.62, 26.39)	1.095 (0.440, 2.724)	0.8444	
Rilzabrutinib 400mg QPM (N=38)	17 (44.7)	21 (55.3)	10 (26.3)	-2.6 (-25.28, 20.14)	0.905 (0.377, 2.177)	0.8245	16 (43.2)	21 (56.8)	10 (27.0)	-4.2 (-27.77, 19.30)	0.851 (0.346, 2.092)	0.7237	

	ITT Population				Omalizumab-Naïve Population							
	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b
Placebo (N=40)	19 (47.5)	21 (52.5)	7 (17.5)				17 (47.2)	19 (52.8)	5 (13.9)			

^b CMH test was performed on the association between the responder status and intervention group, stratified by region.
Note: Participants who received selected prohibited/rescue medications (high/medium impact on efficacy confirmed through blinded medical review) before the given week were considered as non-responders, and participants with missing data at the given week were considered as non-responders up to Week 12.

HSS7

[00250] Rilzabrutinib treatment led to significant improvements in HSS7. Notably, participants receiving 400 mg TID rilzabrutinib exhibited a significant reduction in HSS7 at Week 12 (see **Figures 22-24** and **Tables 33-35**). In the ITT population, participants receiving 400 mg TID rilzabrutinib exhibited a median reduction in HSS7 of -8.31 ($p=0.0126$) points. Meanwhile, patients receiving the placebo exhibited a median reduction in HSS7 of -4.89 points (see **Table 33**). Similar results were observed for the omalizumab-naïve population, both prior to (median reduction of -7.64, $p=0.0257$; see **Table 34**) and following (median reduction of -7.89, $p=0.0156$; see **Table 35**) the removal of the asymptomatic outlier (UAS7/ISS7=0 at baseline) who was erroneously randomized into the 400 mg TID rilzabrutinib arm. Notably, in the 400 mg TID arm, all patients except one showed improvement in ISS7.

Table 33. Supplementary analysis: Change from baseline in HSS7 at Week 12 (ITT Population)

HSS7	Placebo (N=40)	Rilzabrutinib 400mg QPM (N=38)	Rilzabrutinib 400mg BID (N=41)	Rilzabrutinib 400mg TID (N=41)
Baseline				
Number	40	38	41	41
Mean (SD)	14.37 (4.89)	14.87 (4.29)	14.41 (4.26)	14.00 (4.77)
Median	14.00	14.00	14.00	14.00
Q1 ; Q3	11.00 ; 18.92	12.00 ; 18.00	12.00 ; 17.00	12.00 ; 17.00
Min ; Max	7.0 ; 21.0	7.0 ; 21.0	7.0 ; 21.0	0.0 ; 21.0
Week 12				
Number (observed/imputed)	35 (33/2)	31 (28/3)	30 (27/3)	33 (30/3)
Mean (SD)	9.31 (6.74)	10.47 (6.04)	7.08 (7.32)	4.92 (4.89)
Median	7.00	8.75	6.00	3.50
Q1 ; Q3	4.00 ; 14.00	7.00 ; 14.00	0.00 ; 13.00	0.00 ; 8.40
Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 15.2
Change from baseline				
Number (observed/imputed)	35 (33/2)	31 (28/3)	30 (27/3)	33 (30/3)
Mean (SD)	-5.09 (7.08)	-5.05 (5.64)	-7.81 (7.00)	-9.62 (6.34)
Median	-3.50	-4.00	-5.30	-9.00
Q1 ; Q3	-10.00 ; 0.00	-10.50 ; 0.00	-12.60 ; -3.00	-14.00 ; -4.00
Min ; Max	-19.8 ; 10.7	-17.0 ; 4.0	-21.0 ; 1.0	-21.0 ; 0.0
LS Mean (SE) ^a	-4.89 (1.02)	-4.75 (1.03)	-6.78 (1.02)	-8.31 (1.00)
LS Mean Diff vs. placebo (95% CI) ^a		0.14 (-2.62, 2.91)	-1.89 (-4.58, 0.80)	-3.42 (-6.11, -0.74)
P-value vs. placebo ^a		0.9186	0.1683	0.0126

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

Note: Data collected after study intervention discontinuation were included. Data post selected prohibited/rescue medications (high/medium impact on efficacy confirmed through blinded medical review) were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF; other missing data were imputed by MI.

HSS7	Placebo (N=40)	Rilzabrutinib 400mg QPM (N=38)	Rilzabrutinib 400mg BID (N=41)	Rilzabrutinib 400mg TID (N=41)
Descriptive statistics at Week 12 include participants with WOCF imputation at Week 12, and participants whose values were imputed by MI at Week 12 were excluded from the descriptive analysis.				

Table 34. Change from Baseline in HSS7 at Week 12 (Omalizumab-naïve Population)

HSS7	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Baseline				
Number	36	37	35	35
Mean (SD)	13.83 (4.85)	14.73 (4.26)	14.28 (4.21)	13.66 (4.47)
Median	14.00	14.00	14.00	14.00
Q1 ; Q3	9.50 ; 17.00	12.00 ; 18.00	12.00 ; 18.00	12.00 ; 16.00
Min ; Max	7.0 ; 21.0	7.0 ; 21.0	7.0 ; 21.0	0.0 ; 21.0
Week 12				
Number (observed/imputed)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)
Mean (SD)	9.31 (6.52)	10.52 (6.14)	7.52 (7.21)	5.23 (4.86)
Median	7.00	8.58	7.00	4.08
Q1 ; Q3	4.33 ; 14.00	7.00 ; 14.00	0.00 ; 13.00	0.58 ; 8.58
Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 15.2
Change from baseline				
Number (observed/imputed)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)
Mean (SD)	-4.60 (6.76)	-4.85 (5.63)	-7.09 (6.54)	-8.77 (5.84)
Median	-2.75	-4.00	-4.50	-8.00
Q1 ; Q3	-8.67 ; 0.00	-10.25 ; 0.00	-11.67 ; -3.00	-13.50 ; -3.72
Min ; Max	-18.0 ; 10.7	-17.0 ; 4.0	-21.0 ; 1.0	-21.0 ; 0.0
LS Mean (SE) ^a	-4.40 (1.06)	-4.49 (1.04)	-6.52 (1.07)	-7.64 (1.06)
LS Mean Diff vs. placebo (95% CI) ^a		-0.09 (-2.92, 2.75)	-2.12 (-4.97, 0.73)	-3.24 (-6.08, -0.39)
P-value vs. placebo ^a		0.9531	0.1450	0.0257

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

Note: Data collected after study intervention discontinuation were included. Data post selected prohibited/rescue medications (high/medium impact on efficacy confirmed through blinded medical review) were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF; other missing data were imputed by MI.

Descriptive statistics at Week 12 include participants with WOCF imputation at Week 12, and participants whose values were imputed by MI at Week 12 were excluded from the descriptive analysis.

Table 35. Change from Baseline in HSS7 at Week 12 (Omalizumab-Naïve Population with Outlier Removed from Analysis)

HSS7	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=34)
Baseline				
Number	36	37	35	34
Mean (SD)	13.83 (4.85)	14.73 (4.26)	14.28 (4.21)	14.06 (3.85)
Median	14.00	14.00	14.00	14.00
Q1 ; Q3	9.50 ; 17.00	12.00 ; 18.00	12.00 ; 18.00	12.00 ; 16.00
Min ; Max	7.0 ; 21.0	7.0 ; 21.0	7.0 ; 21.0	6.0 ; 21.0
Week 12				
Number (observed/imputed)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)

HSS7	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=34)
Mean (SD)	9.31 (6.52)	10.52 (6.14)	7.52 (7.21)	5.23 (4.86)
Median	7.00	8.58	7.00	4.08
Q1 ; Q3	4.33 ; 14.00	7.00 ; 14.00	0.00 ; 13.00	0.58 ; 8.58
Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 15.2
Change from baseline				
Number (observed/imputed)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)
Mean (SD)	-4.60 (6.76)	-4.85 (5.63)	-7.09 (6.54)	-8.77 (5.84)
Median	-2.75	-4.00	-4.50	-8.00
Q1 ; Q3	-8.67 ; 0.00	-10.25 ; 0.00	-11.67 ; -3.00	-13.50 ; -3.72
Min ; Max	-18.0 ; 10.7	-17.0 ; 4.0	-21.0 ; 1.0	-21.0 ; 0.0
LS Mean (SE) ^a	-4.35 (1.04)	-4.57 (1.02)	-6.56 (1.07)	-7.89 (1.07)
LS Mean Diff ^a vs. placebo (95% CI) ^a		-0.22 (-3.01, 2.57)	-2.20 (-5.04, 0.63)	-3.54 (-6.40, -0.67)
P-value vs. placebo ^a		0.8768	0.1279	0.0156

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

Note: Data collected after study intervention discontinuation were included. Data post selected prohibited/rescue medications (high/medium impact on efficacy confirmed through blinded medical review) were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF; other missing data were imputed by MI.

Descriptive statistics at Week 12 include participants with WOCF imputation at Week 12, and participants whose values were imputed by MI at Week 12 were excluded from the descriptive analysis.

One participant was randomized to Rilzabrutinib 400mg TID group by mistake (baseline ISS7/UAS7=0). Removed this participant from the analysis.

[00251] Participants exhibited a rapid and sustained improvement in hives symptoms, with significant reductions in HSS7 observed following one week of treatment (see **Figures 25-28** and **Tables 36-39**).

Table 36. Summary of HSS7 by Week in the Double-Blind Period (Omalizumab-Naïve Population and Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders)

HSS7	Omalizumab-Naïve Population							
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
Baseline								
Number	36	37	35	35	4	1	6	6
Mean (SD)	13.83 (4.85)	14.73 (4.26)	14.28 (4.21)	13.66 (4.47)	19.21 (1.47)	20.00 (NC)	15.17 (4.92)	16.03 (6.35)
Median	14.00	14.00	14.00	14.00	18.92	20.00	17.00	19.00
Q1 ; Q3	9.50 ; 17.00	12.00 ; 18.00	12.00 ; 18.00	12.00 ; 16.00	18.00 ; 20.42	20.00 ; 20.00	12.00 ; 17.00	8.17 ; 21.00
Min ; Max	7.0 ; 21.0	7.0 ; 21.0	7.0 ; 21.0	0.0 ; 21.0	18.0 ; 21.0	20.0 ; 20.0	7.0 ; 21.0	8.0 ; 21.0
Week 1								
Number (observed/imputed)	36 (36/0)	37 (37/0)	35 (35/0)	35 (35/0)	4 (4/0)	1 (1/0)	6 (5/1)	6 (6/0)
Mean (SD)	12.23 (5.49)	10.73 (4.90)	9.26 (5.76)	8.26 (4.91)	14.50 (5.32)	12.00 (NC)	9.67 (6.41)	4.83 (3.31)
Median	12.50	10.00	10.00	8.00	14.50	12.00	10.50	4.50
Q1 ; Q3	8.00 ; 16.00	8.00 ; 14.00	4.00 ; 14.00	4.00 ; 13.00	11.00 ; 18.00	12.00 ; 12.00	6.00 ; 14.00	2.00 ; 7.00
Min ; Max	0.0 ; 21.0	1.0 ; 21.0	0.0 ; 21.0	0.0 ; 16.0	8.0 ; 21.0	12.0 ; 12.0	0.0 ; 17.0	1.0 ; 10.0
Change from baseline								
Number (observed/imputed)	36 (36/0)	37 (37/0)	35 (35/0)	35 (35/0)	4 (4/0)	1 (1/0)	6 (5/1)	6 (6/0)
Mean (SD)	-1.60 (4.68)	-4.00 (4.92)	-5.02 (4.53)	-5.40 (5.44)	-4.71 (4.11)	-8.00 (NC)	-5.50 (6.41)	-11.19 (4.74)
Median	-1.00	-3.00	-5.00	-5.00	-4.42	-8.00	-3.00	-12.50
Q1 ; Q3	-3.50 ; 1.00	-6.00 ; 0.00	-9.00 ; 0.00	-9.00 ; 0.00	-7.42 ; -2.00	-8.00 ; -8.00	-12.00 ; 0.00	-15.00 ; -7.00
Min ; Max	-15.0 ; 9.0	-18.0 ; 2.0	-15.0 ; 1.0	-19.0 ; 2.0	-10.0 ; 0.0	-8.0 ; -8.0	-15.0 ; 0.0	-16.0 ; -4.2
Percent change from baseline								
Number (observed/imputed)	36 (36/0)	37 (37/0)	35 (35/0)	34 (34/0)	4 (4/0)	1 (1/0)	6 (5/1)	6 (6/0)
Mean (SD)	-8.04 (38.95)	-25.31 (29.00)	-36.53 (34.65)	-36.74 (35.15)	-25.54 (22.84)	-40.00 (NC)	-34.45 (41.48)	-70.33 (16.48)
Median	-7.74	-20.00	-28.57	-33.33	-23.30	-40.00	-17.65	-71.43
Q1 ; Q3	-26.79 ; 6.70	-44.44 ; 0.00	-52.38 ; 0.00	-61.11 ; 0.00	-39.96 ; -11.11	-40.00 ; -40.00	-71.43 ; 0.00	-87.50 ; -52.38
Min ; Max	-100.0 ; 85.7	-93.3 ; 15.4	-100.0 ; 14.3	-100.0 ; 16.7	-55.6 ; 0.0	-40.0 ; -40.0	-100.0 ; 0.0	-88.2 ; -51.0
Week 2								
Number (observed/imputed)	35 (35/0)	37 (37/0)	34 (34/0)	35 (35/0)	4 (4/0)	1 (1/0)	6 (5/1)	6 (6/0)
Mean (SD)	11.11 (5.32)	10.90 (4.97)	9.27 (5.49)	7.25 (5.05)	12.67 (8.67)	13.00 (NC)	8.17 (7.08)	2.83 (3.31)
Median	12.00	10.00	7.50	7.00	14.33	13.00	9.50	1.50
Q1 ; Q3	8.00 ; 14.00	8.00 ; 14.00	5.00 ; 14.00	4.00 ; 11.00	6.33 ; 19.00	13.00 ; 13.00	0.00 ; 13.00	0.00 ; 7.00
Min ; Max	0.0 ; 21.0	1.0 ; 21.0	0.0 ; 21.0	0.0 ; 17.0	1.0 ; 21.0	13.0 ; 13.0	0.0 ; 17.0	0.0 ; 7.0
Change from baseline								
Number (observed/imputed)	35 (35/0)	37 (37/0)	34 (34/0)	35 (35/0)	4 (4/0)	1 (1/0)	6 (5/1)	6 (6/0)

HSS7	Omalizumab-Naïve Population							
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)	
Percent change from baseline Number (observed/imputed)	Mean (SD)	-2.52 (4.98)	-3.83 (4.91)	-5.10 (4.74)	-6.40 (5.94)	-7.00 (NC)	-13.19 (5.74)	
	Median	-1.00	-3.00	-5.50	-6.00	-7.00	-14.00	
	Q1 ; Q3	-5.00 ; 1.00	-7.00 ; 0.00	-7.00 ; 0.00	-11.00 ; -1.17	-7.00 ; -7.00	-17.00 ; -7.17	
	Min ; Max	-17.0 ; 7.0	-16.0 ; 3.0	-16.0 ; 3.6	-18.0 ; 2.3	-7.0 ; -7.0	-21.0 ; -6.0	
Percent change from baseline Number (observed/imputed)	Mean (SD)	35 (35/0)	37 (37/0)	34 (34/0)	4 (4/0)	1 (1/0)	6 (6/0)	
	Median	-14.59 (39.41)	-23.50 (30.60)	-35.29 (34.55)	-35.98 (41.57)	-35.00 (NC)	-82.68 (15.48)	
	Q1 ; Q3	-12.50	-21.43	-37.50	-24.74	-35.00	-81.38	
	Min ; Max	-37.50 ; 6.25	-44.44 ; 0.00	-54.55 ; 0.00	-64.81 ; -7.14	-35.00 ; -35.00	-100.00 ; 0.00	
Week 3	Min ; Max	-100.0 ; 100.0	-93.3 ; 33.3	-100.0 ; 40.0	-100.0 ; 16.7	-35.0 ; -35.0	-100.0 ; -66.67	
	Number (observed/imputed)	35 (35/0)	37 (37/0)	35 (35/0)	4 (4/0)	1 (1/0)	6 (6/0)	
	Mean (SD)	10.62 (5.91)	10.41 (4.97)	8.55 (6.09)	11.67 (8.08)	10.00 (NC)	3.39 (2.63)	
	Median	11.00	9.00	7.00	14.00	10.00	2.67	
Change from baseline Number (observed/imputed)	Q1 ; Q3	7.00 ; 14.00	7.00 ; 14.00	3.50 ; 13.00	7.00 ; 16.33	10.00 ; 10.00	2.00 ; 6.00	
	Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 17.0	10.0 ; 10.0	0.0 ; 7.0	
	Mean (SD)	35 (35/0)	37 (37/0)	35 (35/0)	4 (4/0)	1 (1/0)	6 (6/0)	
	Median	-3.01 (5.52)	-4.32 (4.60)	-5.73 (5.31)	-7.54 (7.37)	-10.00 (NC)	-12.64 (6.13)	
Percent change from baseline Number (observed/imputed)	Q1 ; Q3	-2.00	-2.00	-5.00	-5.50	-10.00	-14.50	
	Min ; Max	-6.00 ; 0.00	-7.00 ; -0.83	-9.00 ; -2.00	-12.50 ; -2.58	-10.00 ; -10.00	-15.00 ; -5.83	
	Min ; Max	-17.0 ; 7.0	-15.0 ; 3.0	-20.0 ; 2.2	-18.0 ; 7.0	-10.0 ; -10.0	-21.0 ; -5.0	
	Percent change from baseline Number (observed/imputed)	Mean (SD)	35 (35/0)	37 (37/0)	34 (34/0)	4 (4/0)	1 (1/0)	6 (6/0)
Week 4	Median	-17.74 (46.09)	-27.98 (28.68)	-40.65 (36.39)	-40.36 (41.33)	-50.00 (NC)	-45.10 (46.71)	-76.71 (14.38)
	Q1 ; Q3	-12.50	-28.57	-41.67	-27.78	-50.00	-35.29	-71.43
	Min ; Max	-46.15 ; 0.00	-50.00 ; -6.25	-66.67 ; -9.52	-66.67 ; -14.05	-50.00 ; -50.00	-100.00 ; 0.00	-88.24 ; -66.67
	Min ; Max	-100.0 ; 100.0	-100.0 ; 37.5	-100.0 ; 24.4	-100.0 ; 33.3	-50.0 ; -50.0	-100.0 ; 0.0	-100.0 ; -62.5
Week 4	Number (observed/imputed)	34 (34/0)	37 (36/1)	33 (33/0)	4 (4/0)	1 (1/0)	5 (4/1)	6 (6/0)
	Mean (SD)	10.58 (6.36)	10.53 (4.74)	7.60 (6.00)	9.99 (5.80)	10.00 (NC)	6.80 (8.04)	3.92 (4.26)
	Median	12.00	10.00	7.00	9.98	10.00	2.00	3.17
	Q1 ; Q3	7.00 ; 14.00	8.00 ; 14.00	2.00 ; 11.00	5.88 ; 14.10	10.00 ; 10.00	1.00 ; 14.00	1.17 ; 4.00

HSS7	Omalizumab-Naïve Population							
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 19.0	3.0 ; 17.0	10.0 ; 10.0	0.0 ; 17.0	0.0 ; 12.0
Change from baseline								
Number (observed/imputed)	34 (34/0)	37 (36/1)	33 (33/0)	32 (32/0)	4 (4/0)	1 (1/0)	5 (4/1)	6 (6/0)
Mean (SD)	-3.10 (6.11)	-4.20 (4.74)	-6.54 (5.34)	-7.21 (5.24)	-9.22 (4.98)	-10.00 (NC)	-10.00 (8.34)	-12.11 (6.81)
Median	-0.50	-3.00	-6.00	-6.58	-9.53	-10.00	-12.00	-12.42
Q1 ; Q3	-6.00 ; 0.00	-6.00 ; 0.00	-10.00 ; -2.33	-10.00 ; -3.50	-12.40 ; -6.04	-10.00 ; -10.00	-15.00 ; -3.00	-17.00 ; -5.83
Min ; Max	-18.0 ; 7.0	-16.3 ; 2.0	-19.0 ; 2.0	-18.0 ; 2.0	-15.0 ; 2.8	-10.0 ; -10.0	-20.0 ; 0.0	-21.0 ; -4.0
Percent change from baseline								
Number (observed/imputed)	34 (34/0)	37 (36/1)	33 (33/0)	32 (32/0)	4 (4/0)	1 (1/0)	5 (4/1)	6 (6/0)
Mean (SD)	-18.42 (48.71)	-26.30 (29.41)	-47.44 (37.17)	-50.43 (33.03)	-48.92 (28.25)	-50.00 (NC)	-60.22 (47.52)	-73.06 (22.97)
Median	-2.38	-16.67	-42.86	-50.69	-49.03	-50.00	-88.24	-76.19
Q1 ; Q3	-59.17 ; 0.00	-45.45 ; 0.00	-85.71 ; -15.38	-71.43 ; -33.33	-67.36 ; -30.48	-50.00 ; -50.00	-95.24 ; -17.65	-93.14 ; -50.00
Min ; Max	-100.0 ; 100.0	-100.0 ; 25.0	-100.0 ; 14.3	-100.0 ; 16.7	-83.3 ; -14.3	-50.0 ; -50.0	-100.0 ; 0.0	-100.0 ; -42.9
Week 5								
Number (observed/imputed)	33 (33/0)	36 (35/1)	34 (33/1)	33 (33/0)	4 (4/0)	1 (1/0)	4 (3/1)	6 (5/1)
Mean (SD)	8.56 (4.98)	9.63 (5.13)	8.34 (6.75)	6.49 (5.14)	14.17 (6.62)	8.00 (NC)	4.25 (8.50)	3.42 (4.45)
Median	7.00	8.20	7.00	6.00	13.83	8.00	0.00	2.50
Q1 ; Q3	5.83 ; 12.00	6.50 ; 14.00	2.33 ; 13.00	2.80 ; 8.75	8.50 ; 19.83	8.00 ; 8.00	0.00 ; 8.50	0.00 ; 3.50
Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 19.0	8.0 ; 21.0	8.0 ; 8.0	0.0 ; 17.0	0.0 ; 12.0
Change from baseline								
Number (observed/imputed)	33 (33/0)	36 (35/1)	34 (33/1)	33 (33/0)	4 (4/0)	1 (1/0)	4 (3/1)	6 (5/1)
Mean (SD)	-5.32 (4.97)	-5.12 (5.22)	-6.01 (5.82)	-7.57 (5.71)	-5.04 (5.36)	-12.00 (NC)	-12.50 (9.11)	-12.61 (7.49)
Median	-4.00	-3.50	-7.00	-7.00	-5.67	-12.00	-14.50	-12.00
Q1 ; Q3	-8.17 ; -1.00	-9.33 ; -0.63	-9.83 ; -1.00	-11.20 ; -4.00	-9.50 ; -0.58	-12.00 ; -12.00	-19.00 ; -6.00	-21.00 ; -5.00
Min ; Max	-17.0 ; 4.0	-18.0 ; 1.0	-17.5 ; 7.0	-21.0 ; 2.0	-10.0 ; 1.2	-12.0 ; -12.0	-21.0 ; 0.0	-21.0 ; -4.7
Percent change from baseline								
Number (observed/imputed)	33 (33/0)	36 (35/1)	34 (33/1)	33 (33/0)	4 (4/0)	1 (1/0)	4 (3/1)	6 (5/1)
Mean (SD)	-36.12 (33.18)	-32.44 (31.06)	-43.27 (41.28)	-52.28 (34.93)	-27.70 (29.87)	-60.00 (NC)	-75.00 (50.00)	-75.12 (24.22)
Median	-41.67	-26.11	-42.86	-50.00	-30.56	-60.00	-100.00	-75.37
Q1 ; Q3	-50.00 ; -6.25	-56.92 ; -4.17	-83.33 ; -5.56	-80.00 ; -33.33	-52.78 ; -2.61	-60.00 ; -60.00	-100.00 ; -50.00	-100.00 ; -57.14
Min ; Max	-100.0 ; 50.0	-100.0 ; 10.0	-100.0 ; 50.0	-100.0 ; 18.2	-55.6 ; 5.9	-60.0 ; -60.0	-100.0 ; 0.0	-100.0 ; -42.9
Week 6								

HSS7	Omalizumab-Naïve Population							
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
	Number (observed/imputed)	32 (31/1)	34 (33/1)	34 (33/1)	31 (31/0)	4 (3/1)	1 (1/0)	5 (4/1)
	Mean (SD)	9.09 (5.60)	9.94 (5.76)	8.17 (6.62)	6.78 (5.55)	14.08 (5.76)	8.00 (NC)	5.97 (7.25)
	Median	8.50	8.28	7.00	6.00	13.67	8.00	3.50
	Q1 ; Q3	6.00 ; 14.00	7.00 ; 14.00	1.17 ; 13.00	2.00 ; 10.50	9.50 ; 18.67	8.00 ; 8.00	0.00 ; 9.33
	Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	8.0 ; 21.0	8.0 ; 8.0	0.0 ; 17.0
Change from baseline	Number (observed/imputed)	32 (31/1)	34 (33/1)	34 (33/1)	31 (31/0)	4 (3/1)	1 (1/0)	5 (4/1)
	Mean (SD)	-4.82 (6.12)	-5.20 (5.64)	-6.17 (6.01)	-7.22 (6.24)	-5.13 (4.33)	-12.00 (NC)	-8.83 (9.41)
	Median	-3.50	-4.50	-6.42	-7.00	-5.25	-12.00	-12.00
	Q1 ; Q3	-8.00 ; 0.00	-10.00 ; 0.00	-11.00 ; -1.00	-11.00 ; -1.50	-8.50 ; -1.75	-12.00 ; -12.00	-17.00 ; 0.00
	Min ; Max	-20.0 ; 7.0	-16.3 ; 4.0	-17.0 ; 4.0	-19.0 ; 1.2	-10.0 ; 0.0	-12.0 ; -12.0	-17.5 ; 2.3
Percent change from baseline	Number (observed/imputed)	32 (31/1)	34 (33/1)	34 (33/1)	31 (31/0)	4 (3/1)	1 (1/0)	5 (4/1)
	Mean (SD)	-29.90 (43.54)	-33.60 (35.00)	-43.56 (44.25)	-49.49 (37.97)	-28.02 (24.28)	-60.00 (NC)	-50.00 (62.36)
	Median	-25.76	-37.09	-47.73	-46.15	-28.27	-60.00	-83.33
	Q1 ; Q3	-54.76 ; 0.00	-61.11 ; 0.00	-85.71 ; -7.69	-90.48 ; -12.50	-47.22 ; -8.82	-60.00 ; -60.00	-100.00 ; 0.00
	Min ; Max	-100.0 ; 87.5	-100.0 ; 37.5	-100.0 ; 40.0	-100.0 ; 8.3	-55.6 ; 0.0	-60.0 ; -60.0	-100.0 ; 33.3
Week 7	Number (observed/imputed)	33 (32/1)	33 (31/2)	34 (33/1)	30 (30/0)	4 (3/1)	1 (1/0)	5 (4/1)
	Mean (SD)	9.27 (5.59)	10.43 (5.27)	7.34 (6.12)	6.40 (4.54)	15.50 (5.88)	9.00 (NC)	4.80 (7.46)
	Median	8.17	8.40	7.00	5.92	16.30	9.00	0.00
	Q1 ; Q3	5.60 ; 14.00	7.00 ; 14.00	2.00 ; 12.60	3.00 ; 9.00	10.70 ; 20.30	9.00 ; 9.00	0.00 ; 7.00
	Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 15.8	8.4 ; 21.0	9.0 ; 9.0	0.0 ; 17.0
Change from baseline	Number (observed/imputed)	33 (32/1)	33 (31/2)	34 (33/1)	30 (30/0)	4 (3/1)	1 (1/0)	5 (4/1)
	Mean (SD)	-4.60 (5.67)	-4.82 (5.35)	-6.75 (5.85)	-7.60 (5.60)	-3.71 (4.55)	-11.00 (NC)	-10.00 (9.67)
	Median	-5.00	-4.00	-7.00	-6.58	-2.62	-11.00	-12.00
	Q1 ; Q3	-7.00 ; 0.00	-10.00 ; 0.00	-9.83 ; -2.00	-11.00 ; -3.00	-7.30 ; -0.12	-11.00 ; -11.00	-17.00 ; 0.00
	Min ; Max	-20.0 ; 7.4	-15.0 ; 4.0	-20.0 ; 2.0	-18.0 ; 1.8	-9.6 ; 0.0	-11.0 ; -11.0	-21.0 ; 0.0
Percent change from baseline	Number (observed/imputed)	33 (32/1)	33 (31/2)	34 (33/1)	30 (30/0)	4 (3/1)	1 (1/0)	5 (4/1)
	Mean (SD)	-29.77 (42.69)	-29.76 (31.10)	-48.07 (38.31)	-52.36 (32.23)	-20.57 (25.33)	-55.00 (NC)	-60.00 (54.77)
	Median	-25.00	-35.71	-50.00	-50.69	-14.48	-55.00	-100.00

HSS7	Omalizumab-Naïve Population							
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)	
Week 8	Q1 : Q3	-56.25 ; 0.00	-55.56 ; 0.00	-84.44 ; -11.11	-80.95 ; -28.57	-55.00 ; -55.00	-100.00 ; 0.00	-85.71 ; -42.86
	Min ; Max	-100.0 ; 92.5	-100.0 ; 23.5	-100.0 ; 15.4	-53.3 ; 0.0	-55.0 ; -55.0	-100.0 ; 0.0	-100.0 ; -42.9
	Number (observed/imputed)	33 (32/1)	33 (30/3)	33 (32/1)	4 (3/1)	1 (1/0)	5 (4/1)	6 (5/1)
	Mean (SD)	9.16 (6.13)	10.47 (5.71)	6.66 (6.70)	11.61 (6.92)	9.00 (NC)	4.80 (7.46)	3.17 (4.45)
	Median	8.00	9.00	5.00	9.80	9.00	0.00	1.50
Change from baseline	Q1 : Q3	4.00 ; 14.00	7.00 ; 14.00	2.00 ; 11.00	6.42 ; 16.80	9.00 ; 9.00	0.00 ; 7.00	1.00 ; 3.00
	Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	5.8 ; 21.0	9.0 ; 9.0	0.0 ; 17.0	0.0 ; 12.0
	Number (observed/imputed)	33 (32/1)	33 (30/3)	33 (32/1)	4 (3/1)	1 (1/0)	5 (4/1)	6 (5/1)
	Mean (SD)	-4.72 (6.09)	-4.56 (5.35)	-7.49 (6.10)	-7.60 (5.49)	-11.00 (NC)	-10.00 (9.67)	-12.86 (6.28)
	Median	-3.00	-4.00	-7.00	-9.12	-11.00	-12.00	-12.50
Percent change from baseline	Q1 : Q3	-7.00 ; 0.00	-8.17 ; 0.00	-12.00 ; -2.00	-11.58 ; -3.62	-11.00 ; -11.00	-17.00 ; 0.00	-18.00 ; -7.17
	Min ; Max	-19.0 ; 6.0	-15.0 ; 4.0	-21.0 ; 2.0	-12.2 ; 0.0	-11.0 ; -11.0	-21.0 ; 0.0	-21.0 ; -6.0
	Number (observed/imputed)	33 (32/1)	33 (30/3)	33 (32/1)	4 (3/1)	1 (1/0)	5 (4/1)	6 (5/1)
	Mean (SD)	-31.47 (41.65)	-29.79 (35.34)	-54.71 (40.69)	-41.29 (30.62)	-55.00 (NC)	-60.00 (54.77)	-80.91 (20.45)
	Median	-23.81	-28.57	-74.07	-48.79	-55.00	-100.00	-86.73
Week 9	Q1 : Q3	-56.25 ; 0.00	-57.14 ; 0.00	-88.89 ; -14.29	-64.35 ; -18.24	-55.00 ; -55.00	-100.00 ; 0.00	-94.12 ; -75.00
	Min ; Max	-100.0 ; 75.0	-100.0 ; 27.3	-100.0 ; 16.7	-67.6 ; 0.0	-55.0 ; -55.0	-100.0 ; 0.0	-100.0 ; -42.9
	Number (observed/imputed)	32 (31/1)	34 (31/3)	29 (28/1)	4 (3/1)	1 (1/0)	5 (4/1)	6 (5/1)
	Mean (SD)	10.10 (5.69)	9.82 (5.59)	7.01 (7.58)	10.85 (6.80)	8.00 (NC)	4.80 (7.46)	3.25 (4.37)
	Median	9.00	9.20	3.50	7.70	8.00	0.00	2.00
Change from baseline	Q1 : Q3	7.00 ; 14.00	7.00 ; 14.00	0.00 ; 11.00	7.00 ; 14.70	8.00 ; 8.00	0.00 ; 7.00	1.17 ; 2.33
	Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	7.0 ; 21.0	8.0 ; 8.0	0.0 ; 17.0	0.0 ; 12.0
	Number (observed/imputed)	32 (31/1)	34 (31/3)	29 (28/1)	4 (3/1)	1 (1/0)	5 (4/1)	6 (5/1)
	Mean (SD)	-3.77 (5.51)	-5.33 (5.35)	-6.95 (6.00)	-8.36 (5.73)	-12.00 (NC)	-10.00 (9.67)	-12.78 (6.34)
	Median	-3.00	-4.92	-7.00	-10.30	-12.00	-12.00	-12.00
	Q1 : Q3	-7.00 ; 0.00	-8.00 ; 0.00	-11.00 ; -1.17	-11.92 ; -4.80	-12.00 ; -12.00	-17.00 ; 0.00	-18.67 ; -7.00
	Min ; Max	-18.0 ; 5.7	-19.0 ; 4.0	-19.0 ; 3.0	-12.8 ; 0.0	-12.0 ; -12.0	-21.0 ; 0.0	-21.0 ; -6.0

HSS7	Omalizumab-Naïve Population							
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
Percent change from baseline								
Number (observed/imputed)	32 (31/1)	34 (31/3)	29 (28/1)	29 (29/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (5/1)
Mean (SD)	-24.38 (38.78)	-34.46 (32.68)	-53.79 (43.28)	-55.85 (38.63)	-44.79 (30.23)	-60.00 (NC)	-60.00 (54.77)	-80.12 (19.92)
Median	-19.81	-33.59	-68.18	-57.14	-57.22	-60.00	-100.00	-86.97
Q1 ; Q3	-48.08 ; 0.00	-50.00 ; 0.00	-100.00 ; -5.56	-91.25 ; -28.57	-62.91 ; -26.67	-60.00 ; -60.00	-100.00 ; 0.00	-88.89 ; -75.00
Min ; Max	-100.0 ; 62.5	-100.0 ; 23.5	-100.0 ; 25.0	-100.0 ; 55.6	-64.7 ; 0.0	-60.0 ; -60.0	-100.0 ; 0.0	-100.0 ; -42.9
Week 10								
Number (observed/imputed)	33 (32/1)	34 (31/3)	28 (27/1)	30 (30/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (4/2)
Mean (SD)	9.73 (6.39)	9.88 (5.93)	7.05 (7.27)	5.87 (5.06)	8.39 (8.95)	8.00 (NC)	5.20 (7.19)	3.00 (4.65)
Median	10.50	8.00	6.50	4.50	5.70	8.00	2.00	1.00
Q1 ; Q3	5.25 ; 14.00	5.00 ; 14.00	0.00 ; 12.00	2.00 ; 8.00	2.08 ; 14.70	8.00 ; 8.00	0.00 ; 7.00	0.00 ; 4.00
Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 19.0	1.2 ; 21.0	8.0 ; 8.0	0.0 ; 17.0	0.0 ; 12.0
Change from baseline								
Number (observed/imputed)	33 (32/1)	34 (31/3)	28 (27/1)	30 (30/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (4/2)
Mean (SD)	-4.14 (6.14)	-5.27 (5.66)	-6.95 (5.65)	-8.20 (5.62)	-10.82 (8.12)	-12.00 (NC)	-9.60 (9.13)	-13.03 (7.21)
Median	-3.00	-4.00	-6.50	-9.00	-12.30	-12.00	-12.00	-13.00
Q1 ; Q3	-8.00 ; 0.00	-10.00 ; -1.00	-12.00 ; -2.50	-11.00 ; -4.00	-16.83 ; -4.80	-12.00 ; -12.00	-17.00 ; 0.00	-20.00 ; -7.17
Min ; Max	-18.0 ; 6.0	-17.0 ; 4.0	-16.0 ; 3.0	-19.0 ; 1.0	-18.7 ; 0.0	-12.0 ; -12.0	-19.0 ; 0.0	-21.0 ; -4.0
Percent change from baseline								
Number (observed/imputed)	33 (32/1)	34 (31/3)	28 (27/1)	30 (30/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (4/2)
Mean (SD)	-27.51 (45.53)	-33.86 (34.68)	-53.45 (42.56)	-57.32 (34.80)	-57.70 (42.16)	-60.00 (NC)	-58.10 (53.18)	-79.31 (25.96)
Median	-18.75	-28.64	-47.73	-63.10	-68.33	-60.00	-90.48	-91.50
Q1 ; Q3	-50.00 ; 0.00	-63.64 ; -5.56	-100.00 ; -16.30	-86.67 ; -25.00	-88.73 ; -26.67	-60.00 ; -60.00	-100.00 ; 0.00	-100.00 ; -50.00
Min ; Max	-100.0 ; 62.5	-100.0 ; 37.5	-100.0 ; 25.0	-100.0 ; 16.7	-94.1 ; 0.0	-60.0 ; -60.0	-100.0 ; 0.0	-100.0 ; -42.9
Week 11								
Number (observed/imputed)	33 (32/1)	33 (30/3)	29 (28/1)	31 (31/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (4/2)
Mean (SD)	9.64 (6.32)	10.18 (6.18)	7.13 (7.07)	6.17 (5.40)	8.79 (8.61)	9.00 (NC)	4.80 (7.46)	2.67 (4.84)
Median	9.00	9.33	5.83	5.83	6.50	9.00	0.00	0.00
Q1 ; Q3	4.67 ; 14.00	7.00 ; 14.00	2.00 ; 11.00	1.00 ; 9.80	3.08 ; 14.50	9.00 ; 9.00	0.00 ; 7.00	0.00 ; 4.00
Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 19.6	1.2 ; 21.0	9.0 ; 9.0	0.0 ; 17.0	0.0 ; 12.0
Change from baseline								
Number (observed/imputed)	33 (32/1)	33 (30/3)	29 (28/1)	31 (31/0)	4 (3/1)	1 (1/0)	5 (4/1)	6 (4/2)
Mean (SD)	-4.23 (6.15)	-5.18 (5.64)	-7.34 (6.14)	-7.90 (6.07)	-10.42 (7.82)	-11.00 (NC)	-10.00 (9.67)	-13.36 (7.26)

HSS7	Omalizumab-Naïve Population							
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)	
Percent change from baseline Number (observed/imputed)	Median	-4.60	-3.00	-7.00	-8.00	-11.50	-12.00	
	Q1 ; Q3	-9.00 ; 0.00	-9.67 ; 0.00	-12.00 ; -2.00	-14.00 ; -3.00	-15.83 ; -5.00	-17.00 ; 0.00	
	Min ; Max	-18.0 ; 8.0	-18.0 ; 4.0	-21.0 ; 3.0	-20.0 ; 5.6	-18.7 ; 0.0	-21.0 ; 0.0	
	Mean (SD)	33 (32/1)	33 (30/3)	29 (28/1)	31 (31/0)	4 (3/1)	5 (4/1)	
Percent change from baseline Number (observed/imputed)	Median	-27.83 (49.26)	-33.21 (36.21)	-52.82 (41.27)	-55.30 (37.59)	-55.00 (NC)	-60.00 (54.77)	
	Q1 ; Q3	-33.33	-30.00	-54.55	-61.11	-63.89	-100.00	
	Min ; Max	-60.00 ; 0.00	-50.88 ; 0.00	-89.47 ; -18.18	-93.75 ; -18.33	-83.17 ; -27.78	-100.00 ; 0.00	
	Mean (SD)	-100.0 ; 96.9	-100.0 ; 25.0	-100.0 ; 25.0	-100.0 ; 40.0	-94.1 ; 0.0	-100.0 ; 0.0	
Week 12	Number (observed/imputed)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)	3 (2/1)	4 (3/1)	
	Mean (SD)	9.31 (6.52)	10.52 (6.14)	7.52 (7.21)	5.23 (4.86)	9.33 (10.69)	4.25 (8.50)	
	Median	7.00	8.58	7.00	4.08	7.00	0.00	
	Q1 ; Q3	4.33 ; 14.00	7.00 ; 14.00	0.00 ; 13.00	0.58 ; 8.58	0.00 ; 21.00	0.00 ; 8.50	
Change from baseline	Min ; Max	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 21.0	0.0 ; 15.2	0.0 ; 21.0	0.0 ; 17.0	
	Number (observed/imputed)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)	3 (2/1)	4 (3/1)	
	Mean (SD)	-4.60 (6.76)	-4.85 (5.63)	-7.09 (6.54)	-8.77 (5.84)	-10.28 (9.94)	-12.50 (9.11)	
	Median	-2.75	-4.00	-4.50	-8.00	-11.00	-14.50	
Percent change from baseline Number (observed/imputed)	Q1 ; Q3	-8.67 ; 0.00	-10.25 ; 0.00	-11.67 ; -3.00	-13.50 ; -3.72	-19.83 ; 0.00	-19.00 ; -6.00	
	Min ; Max	-18.0 ; 10.7	-17.0 ; 4.0	-21.0 ; 1.0	-21.0 ; 0.0	-19.8 ; 0.0	-21.0 ; 0.0	
	Number (observed/imputed)	32 (31/1)	30 (27/3)	26 (24/2)	28 (27/1)	3 (2/1)	4 (3/1)	
	Mean (SD)	-29.00 (51.42)	-31.20 (34.88)	-49.56 (40.81)	-60.93 (34.27)	-53.70 (50.41)	-75.00 (50.00)	
Percent change from baseline Number (observed/imputed)	Median	-21.43	-33.18	-37.50	-64.29	-61.11	-100.00	
	Q1 ; Q3	-66.67 ; 0.00	-53.95 ; 0.00	-100.00 ; -16.67	-96.76 ; -31.67	-100.00 ; 0.00	-100.00 ; -50.00	
	Min ; Max	-100.0 ; 133.3	-100.0 ; 27.3	-100.0 ; 7.7	-100.0 ; 0.0	-100.0 ; 0.0	-100.0 ; 0.0	
	Mean (SD)	5 (3/2)	7 (3/4)	5 (3/2)	5 (3/2)	0 (0/0)	0 (0/0)	
End of Study	Number (observed/imputed)	9.93 (5.80)	6.13 (9.09)	7.80 (8.76)	10.00 (5.79)	0 (0/0)	0 (0/0)	
	Mean (SD)	11.67	1.40	7.00	10.00	0 (0/0)	0 (0/0)	
	Median	10.00 ; 14.00	0.00 ; 17.50	0.00 ; 11.00	7.00 ; 15.00	4.00 ; 8.17	4.00 ; 8.17	
	Q1 ; Q3	0.0 ; 14.0	0.0 ; 21.0	0.0 ; 21.0	2.0 ; 16.0	4.0 ; 8.2	4.0 ; 8.2	

HSS7	Onalizumab-Naïve Population						
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
Change from baseline							
Number (observed/imputed)	5 (3/2)	7 (3/4)	5 (3/2)	0 (0/0)	0 (0/0)	0 (0/0)	2 (0/2)
Mean (SD)	-3.07 (4.88)	-9.87 (8.34)	-7.80 (6.87)				-2.00 (2.83)
Median	-4.00	-12.00	-5.00				-2.00
Q1 ; Q3	-7.00 ; 0.00	-18.00 ; 0.00	-14.00 ; -4.00				-4.00 ; 0.00
Min ; Max	-8.0 ; 3.7	-19.6 ; 1.5	-16.0 ; 0.0				-4.0 ; 0.0
Percent change from baseline							
Number (observed/imputed)	5 (3/2)	7 (3/4)	5 (3/2)	0 (0/0)	0 (0/0)	0 (0/0)	2 (0/2)
Mean (SD)	-23.21 (53.23)	-64.85 (48.75)	-53.67 (44.85)				-25.00 (35.36)
Median	-28.57	-93.33	-41.67				-25.00
Q1 ; Q3	-33.33 ; 0.00	-100.00 ; 0.00	-100.00 ; -26.67				-50.00 ; 0.00
Min ; Max	-100.0 ; 45.8	-100.0 ; 9.4	-100.0 ; 0.0				-50.0 ; 0.0

Note: Data collected after study intervention discontinuation were included. Data post selected prohibited/rescue medications (high/medium impact on efficacy confirmed through blinded medical review) were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF.

Table 37. Change and Percent Change from Baseline in HSS7 over Time up to Week 12 (ITT Population)

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo ^a	
					LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Week 1									
Rilzabrutinib 400mg TID (N=41)	41	14.00 (4.77)	7.76 (4.83)	-6.09 (0.74)	-4.26 (-6.67, -1.85)	<.0001	-39.34 (5.49)	-30.65 (-45.45, -15.85)	<.0001
Rilzabrutinib 400mg BID (N=41)	41	14.41 (4.26)	9.32 (5.77)	-4.79 (0.75)	-2.95 (-5.36, -0.55)	0.0041	-33.74 (5.55)	-25.04 (-39.70, -10.39)	0.0008
Rilzabrutinib 400mg QPM (N=38)	38	14.87 (4.29)	10.76 (4.83)	-3.98 (0.76)	-2.14 (-4.59, 0.31)	0.0398	-25.22 (5.61)	-16.53 (-31.46, -1.59)	0.0301
Placebo (N=40)	40	14.37 (4.89)	12.46 (5.45)	-1.84 (0.75)			-8.69 (5.56)		
Week 2									
Rilzabrutinib 400mg TID (N=41)	41	14.00 (4.77)	6.61 (5.06)	-7.16 (0.77)	-4.24 (-6.33, -2.15)	<.0001	-47.49 (5.64)	-30.93 (-46.17, -15.70)	<.0001
Rilzabrutinib 400mg BID (N=41)	40	14.41 (4.26)	9.11 (5.66)	-5.15 (0.79)	-2.23 (-4.31, -0.14)	0.0361	-34.94 (5.70)	-18.39 (-33.46, -3.31)	0.0168

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
				Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Rilzabrutinib 400mg QPM (N=38)	38	14.87 (4.29)	10.96 (4.91)	-3.87 (0.80)	-0.95 (-3.07, 1.17)	0.3805	-24.23 (5.75)	-7.67 (-23.03, 7.68)	0.3273
Placebo (N=40)	39	14.37 (4.89)	11.27 (5.61)	-2.92 (0.79)			-16.55 (5.72)		
Week 3									
Rilzabrutinib 400mg TID (N=41)	41	14.00 (4.77)	6.49 (4.72)	-7.29 (0.81)	-3.79 (-5.97, -1.61)	0.0007	-48.71 (5.82)	-29.56 (-45.28, - 13.85)	0.0002
Rilzabrutinib 400mg BID (N=41)	41	14.41 (4.26)	8.42 (6.15)	-5.64 (0.82)	-2.14 (-4.31, 0.04)	0.0544	-38.24 (5.88)	-19.09 (-34.67, - 3.50)	0.0164
Rilzabrutinib 400mg QPM (N=38)	38	14.87 (4.29)	10.40 (4.90)	-4.44 (0.83)	-0.94 (-3.15, 1.28)	0.4081	-28.70 (5.96)	-9.55 (-25.43, 6.33)	0.2387
Placebo (N=40)	39	14.37 (4.89)	10.73 (6.04)	-3.50 (0.83)			-19.15 (5.92)		
Week 4									
Rilzabrutinib 400mg TID (N=41)	38	14.00 (4.77)	6.39 (4.92)	-6.98 (0.82)	-3.53 (-5.74, -1.31)	0.0018	-47.90 (5.95)	-29.20 (-45.35, - 13.05)	0.0004
Rilzabrutinib 400mg BID (N=41)	38	14.41 (4.26)	7.50 (6.18)	-6.16 (0.83)	-2.71 (-4.92, -0.50)	0.0161	-43.10 (6.02)	-24.40 (-40.33, - 8.47)	0.0027
Rilzabrutinib 400mg QPM (N=38)	38	14.87 (4.29)	10.52 (4.68)	-4.23 (0.84)	-0.78 (-3.03, 1.46)	0.4947	-26.58 (6.02)	-7.88 (-24.05, 8.29)	0.3397
Placebo (N=40)	38	14.37 (4.89)	10.52 (6.24)	-3.45 (0.84)			-18.70 (6.04)		
Week 5									
Rilzabrutinib 400mg TID (N=41)	39	14.00 (4.77)	6.02 (5.11)	-7.73 (0.84)	-3.09 (-5.36, -0.81)	0.0078	-52.29 (5.80)	-23.13 (-38.86, - 7.41)	0.0039
Rilzabrutinib 400mg BID (N=41)	38	14.41 (4.26)	7.91 (6.94)	-5.93 (0.86)	-1.29 (-3.57, 0.99)	0.2659	-41.40 (5.88)	-12.25 (-27.81, 3.32)	0.1232
Rilzabrutinib 400mg QPM (N=38)	37	14.87 (4.29)	9.59 (5.07)	-4.97 (0.86)	-0.33 (-2.64, 1.97)	0.7765	-31.95 (5.91)	-2.80 (-18.63, 13.03)	0.7292
Placebo (N=40)	37	14.37 (4.89)	9.17 (5.37)	-4.64 (0.86)			-29.15 (5.91)		
Week 6									
Rilzabrutinib 400mg TID (N=41)	37	14.00 (4.77)	6.14 (5.55)	-7.75 (0.91)	-3.48 (-5.94, -1.02)	0.0055	-52.27 (6.61)	-28.20 (-46.23, - 10.17)	0.0022
Rilzabrutinib 400mg BID (N=41)	39	14.41 (4.26)	7.89 (6.65)	-5.90 (0.92)	-1.64 (-4.07, 0.79)	0.1859	-39.79 (6.64)	-15.72 (-33.44, 1.99)	0.0820

				Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Rilzabrutinib 400mg QPM (N=38)	35	14.87 (4.29)	9.89 (5.69)	-4.76 (0.93)	-0.50 (-3.00, 2.00)	0.6952	-31.19 (6.73)	-7.12 (-25.20, 10.96)	0.4401
Placebo (N=40)	36	14.37 (4.89)	9.65 (5.75)	-4.26 (0.93)			-24.07 (6.79)		
Week 7									
Rilzabrutinib 400mg TID (N=41)	36	14.00 (4.77)	6.18 (4.44)	-7.66 (0.86)	-3.58 (-5.87, -1.29)	0.0022	-51.12 (6.01)	-27.16 (-43.35, -10.98)	0.0010
Rilzabrutinib 400mg BID (N=41)	39	14.41 (4.26)	7.01 (6.25)	-6.79 (0.86)	-2.71 (-4.98, -0.44)	0.0193	-46.27 (6.01)	-22.31 (-38.25, -6.38)	0.0061
Rilzabrutinib 400mg QPM (N=38)	34	14.87 (4.29)	10.38 (5.19)	-4.61 (0.88)	-0.53 (-2.87, 1.81)	0.6575	-29.88 (6.15)	-5.92 (-22.43, 10.58)	0.4819
Placebo (N=40)	37	14.37 (4.89)	9.95 (5.88)	-4.08 (0.86)			-23.96 (6.09)		
Week 8									
Rilzabrutinib 400mg TID (N=41)	34	14.00 (4.77)	5.60 (4.81)	-7.81 (0.92)	-3.06 (-5.54, -0.58)	0.0156	-54.34 (6.35)	-25.27 (-42.38, -8.15)	0.0038
Rilzabrutinib 400mg BID (N=41)	38	14.41 (4.26)	6.41 (6.73)	-7.49 (0.91)	-2.74 (-5.15, -0.33)	0.0262	-52.52 (6.33)	-23.44 (-40.28, -6.61)	0.0063
Rilzabrutinib 400mg QPM (N=38)	34	14.87 (4.29)	10.43 (5.63)	-4.64 (0.93)	0.11 (-2.37, 2.59)	0.9319	-30.95 (6.43)	-1.88 (-19.05, 15.30)	0.8305
Placebo (N=40)	37	14.37 (4.89)	9.43 (6.16)	-4.75 (0.92)			-29.07 (6.37)		
Week 9									
Rilzabrutinib 400mg TID (N=41)	35	14.00 (4.77)	5.43 (4.93)	-7.79 (0.94)	-3.67 (-6.21, -1.13)	0.0046	-53.06 (6.70)	-29.14 (-47.15, -11.12)	0.0015
Rilzabrutinib 400mg BID (N=41)	34	14.41 (4.26)	6.69 (7.49)	-7.16 (0.96)	-3.04 (-5.57, -0.51)	0.0185	-51.53 (6.66)	-27.61 (-45.14, -10.07)	0.0020
Rilzabrutinib 400mg QPM (N=38)	35	14.87 (4.29)	9.77 (5.51)	-5.06 (0.95)	-0.94 (-3.47, 1.59)	0.4656	-34.23 (6.69)	-10.31 (-28.25, 7.64)	0.2602
Placebo (N=40)	36	14.37 (4.89)	10.18 (5.72)	-4.12 (0.95)			-23.93 (6.63)		
Week 10									
Rilzabrutinib 400mg TID (N=41)	36	14.00 (4.77)	5.39 (5.05)	-8.15 (0.96)	-3.55 (-6.13, -0.97)	0.0070	-56.54 (6.68)	-28.54 (-46.43, -10.65)	0.0018
Rilzabrutinib 400mg BID (N=41)	33	14.41 (4.26)	6.77 (7.18)	-7.32 (0.99)	-2.72 (-5.32, -0.11)	0.0410	-52.53 (6.82)	-24.54 (-42.40, -6.67)	0.0071

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
					LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	
Rilzabrutinib 400mg QPM (N=38)	35	14.87 (4.29)	9.82 (5.85)	-5.16 (0.98)	-0.56 (-3.19, 2.07)	0.6752	-34.70 (6.79)	-6.70 (-24.87, 11.46)	0.4694	
Placebo (N=40)	37	14.37 (4.89)	9.59 (6.57)	-4.60 (0.98)			-28.00 (6.74)			
Week 11										
Rilzabrutinib 400mg TID (N=41)	37	14.00 (4.77)	5.60 (5.41)	-8.09 (0.96)	-3.55 (-6.14, -0.95)	0.0074	-54.96 (6.95)	-28.42 (-47.32, - 9.53)	0.0032	
Rilzabrutinib 400mg BID (N=41)	34	14.41 (4.26)	6.79 (7.06)	-7.01 (0.99)	-2.46 (-5.05, 0.13)	0.0629	-49.14 (7.06)	-22.60 (-41.37, - 3.83)	0.0183	
Rilzabrutinib 400mg QPM (N=38)	34	14.87 (4.29)	10.15 (6.09)	-4.97 (0.99)	-0.43 (-3.08, 2.22)	0.7517	-34.56 (7.07)	-8.01 (-26.93, 10.90)	0.4062	
Placebo (N=40)	37	14.37 (4.89)	9.55 (6.46)	-4.54 (0.98)			-26.54 (7.04)			
Week 12										
Rilzabrutinib 400mg TID (N=41)	33	14.00 (4.77)	4.92 (4.89)	-8.31 (1.00)	-3.42 (-6.11, -0.74)	0.0126	-57.27 (7.06)	-29.54 (-48.60, - 10.47)	0.0024	
Rilzabrutinib 400mg BID (N=41)	30	14.41 (4.26)	7.08 (7.32)	-6.78 (1.02)	-1.89 (-4.58, 0.80)	0.1683	-46.86 (7.34)	-19.13 (-38.34, 0.09)	0.0510	
Rilzabrutinib 400mg QPM (N=38)	31	14.87 (4.29)	10.47 (6.04)	-4.75 (1.03)	0.14 (-2.62, 2.91)	0.9186	-33.48 (7.28)	-5.74 (-25.11, 13.62)	0.5609	
Placebo (N=40)	35	14.37 (4.89)	9.31 (6.74)	-4.89 (1.02)			-27.73 (7.11)			

^a Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group and regions as covariates.
Note: Data collected after study intervention discontinuation were included. Data post selected prohibited/rescue medications (high/medium impact on efficacy confirmed through blinded medical review) were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF; other missing data were imputed by MI.
Descriptive statistics at each week include participants with WOCF imputation at the week, and participants whose values were imputed by MI at the week were excluded from the descriptive analysis.

Table 38. Change and Percent Change from Baseline in HSS7 over Time up to Week 12 (Omalizumab-Naïve Population)

				Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
				LS Mean (95% CI) ^a	p-value ^a		LS Mean (95% CI) ^a	p-value ^a	
				Change from baseline LS Mean (SE) ^a			% Change from baseline LS Mean (SE) ^a		
				Post-baseline Mean (SD)	n	Baseline Mean (SD)			
Week 1									
Rilzabrutinib 400mg TID	35	13.66 (4.47)	8.26 (4.91)	-5.32 (0.79)	-3.68 (-6.26, -1.11)	0.0009	-34.85 (6.00)	-27.41 (-43.41, -11.41)	0.0008
(N=35)									
Rilzabrutinib 400mg BID	35	14.28 (4.21)	9.26 (5.76)	-4.73 (0.80)	-3.10 (-5.66, -0.53)	0.0048	-34.51 (5.97)	-27.07 (-42.90, -11.24)	0.0008
(N=35)									
Rilzabrutinib 400mg QPM	37	14.73 (4.26)	10.73 (4.90)	-3.79 (0.77)	-2.16 (-4.69, 0.37)	0.0444	-24.49 (5.76)	-17.05 (-32.67, -1.42)	0.0325
(N=37)									
Placebo (N=36)	36	13.83 (4.85)	12.23 (5.49)	-1.63 (0.79)			-7.44 (5.89)		
Week 2									
Rilzabrutinib 400mg TID	35	13.66 (4.47)	7.25 (5.05)	-6.28 (0.80)	-3.60 (-5.75, -1.45)	0.0010	-42.63 (6.08)	-27.36 (-43.65, -11.07)	0.0010
(N=35)									
Rilzabrutinib 400mg BID	34	14.28 (4.21)	9.27 (5.49)	-4.95 (0.81)	-2.26 (-4.41, -0.12)	0.0389	-34.80 (6.07)	-19.53 (-35.64, -3.42)	0.0175
(N=35)									
Rilzabrutinib 400mg QPM	37	14.73 (4.26)	10.90 (4.97)	-3.72 (0.78)	-1.03 (-3.15, 1.08)	0.3378	-23.62 (5.84)	-8.35 (-24.24, 7.54)	0.3028
(N=37)									
Placebo (N=36)	35	13.83 (4.85)	11.11 (5.32)	-2.68 (0.80)			-15.27 (6.00)		
Week 3									
Rilzabrutinib 400mg TID	35	13.66 (4.47)	7.03 (4.82)	-6.52 (0.85)	-3.28 (-5.57, -1.00)	0.0048	-45.07 (6.36)	-27.37 (-44.36, -10.37)	0.0016
(N=35)									
Rilzabrutinib 400mg BID	35	14.28 (4.21)	8.55 (6.09)	-5.45 (0.86)	-2.21 (-4.49, 0.07)	0.0571	-38.38 (6.33)	-20.68 (-37.52, -3.84)	0.0161
(N=35)									
Rilzabrutinib 400mg QPM	37	14.73 (4.26)	10.41 (4.97)	-4.25 (0.83)	-1.02 (-3.27, 1.23)	0.3745	-28.10 (6.12)	-10.40 (-27.02, 6.23)	0.2204
(N=37)									
Placebo (N=36)	35	13.83 (4.85)	10.62 (5.91)	-3.24 (0.85)			-17.70 (6.28)		
Week 4									
Rilzabrutinib 400mg TID	32	13.66 (4.47)	6.85 (4.96)	-6.26 (0.87)	-3.28 (-5.60, -0.96)	0.0056	-44.69 (6.50)	-28.82 (-46.18, -11.45)	0.0011
(N=35)									
Rilzabrutinib 400mg BID	33	14.28 (4.21)	7.60 (6.00)	-5.94 (0.87)	-2.96 (-5.27, -0.65)	0.0120	-43.11 (6.45)	-27.23 (-44.36, -10.10)	0.0018
(N=35)									
Rilzabrutinib 400mg QPM	37	14.73 (4.26)	10.53 (4.74)	-4.07 (0.83)	-1.08 (-3.36, 1.19)	0.3500	-26.07 (6.19)	-10.20 (-27.12, 6.73)	0.2378
(N=37)									
Placebo (N=36)	34	13.83 (4.85)	10.58 (6.36)	-2.98 (0.86)			-15.88 (6.41)		
Week 5									

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
				Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Rilzabrutinib 400mg TID (N=35)	33	13.66 (4.47)	6.49 (5.14)	-6.99 (0.88)	-2.17 (-4.52, 0.18)	0.0708	-49.42 (6.23)	-18.86 (-35.66, -2.07)	0.0277
Rilzabrutinib 400mg BID (N=35)	34	14.28 (4.21)	8.34 (6.75)	-5.50 (0.87)	-0.68 (-3.00, 1.65)	0.5686	-39.98 (6.23)	-9.42 (-26.13, 7.29)	0.2692
Rilzabrutinib 400mg QPM (N=37)	36	14.73 (4.26)	9.63 (5.13)	-4.75 (0.84)	0.07 (-2.23, 2.38)	0.9514	-31.12 (6.01)	-0.56 (-17.08, 15.96)	0.9468
Placebo (N=36)	33	13.83 (4.85)	8.56 (4.98)	-4.82 (0.87)			-30.56 (6.26)		
Week 6									
Rilzabrutinib 400mg TID (N=35)	31	13.66 (4.47)	6.78 (5.55)	-6.90 (0.98)	-2.51 (-5.12, 0.09)	0.0581	-48.15 (7.17)	-24.11 (-43.39, -4.84)	0.0142
Rilzabrutinib 400mg BID (N=35)	34	14.28 (4.21)	8.17 (6.62)	-5.67 (0.96)	-1.28 (-3.84, 1.29)	0.3295	-40.02 (7.13)	-15.99 (-35.02, 3.04)	0.0996
Rilzabrutinib 400mg QPM (N=37)	34	14.73 (4.26)	9.94 (5.76)	-4.47 (0.93)	-0.08 (-2.63, 2.47)	0.9525	-30.30 (6.90)	-6.27 (-25.06, 12.53)	0.5135
Placebo (N=36)	32	13.83 (4.85)	9.09 (5.60)	-4.39 (0.96)			-24.04 (7.13)		
Week 7									
Rilzabrutinib 400mg TID (N=35)	30	13.66 (4.47)	6.40 (4.54)	-7.27 (0.91)	-2.92 (-5.35, -0.49)	0.0185	-50.32 (6.67)	-24.63 (-42.34, -6.91)	0.0064
Rilzabrutinib 400mg BID (N=35)	34	14.28 (4.21)	7.34 (6.12)	-6.47 (0.89)	-2.12 (-4.51, 0.27)	0.0817	-45.57 (6.48)	-19.88 (-37.24, -2.52)	0.0248
Rilzabrutinib 400mg QPM (N=37)	33	14.73 (4.26)	10.43 (5.27)	-4.41 (0.88)	-0.06 (-2.46, 2.33)	0.9584	-29.51 (6.35)	-3.82 (-21.11, 13.47)	0.6649
Placebo (N=36)	33	13.83 (4.85)	9.27 (5.59)	-4.35 (0.90)			-25.69 (6.51)		
Week 8									
Rilzabrutinib 400mg TID (N=35)	28	13.66 (4.47)	6.12 (4.80)	-7.02 (1.00)	-2.47 (-5.11, 0.18)	0.0678	-50.37 (7.07)	-22.36 (-41.09, -3.64)	0.0192
Rilzabrutinib 400mg BID (N=35)	33	14.28 (4.21)	6.66 (6.70)	-7.26 (0.95)	-2.71 (-5.26, -0.16)	0.0375	-53.21 (6.86)	-25.21 (-43.54, -6.87)	0.0071
Rilzabrutinib 400mg QPM (N=37)	33	14.73 (4.26)	10.47 (5.71)	-4.41 (0.93)	0.14 (-2.40, 2.69)	0.9115	-30.42 (6.75)	-2.41 (-20.57, 15.74)	0.7944
Placebo (N=36)	33	13.83 (4.85)	9.16 (6.13)	-4.55 (0.95)			-28.01 (6.80)		
Week 9									

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
				Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Rilzabrutinib 400mg TID (N=35)	29	13.66 (4.47)	5.88 (4.98)	-7.21 (1.00)	-3.53 (-6.17, -0.89)	0.0088	-50.43 (7.09)	-27.94 (-47.00, -8.88)	0.0041
Rilzabrutinib 400mg BID (N=35)	29	14.28 (4.21)	7.01 (7.58)	-6.84 (0.99)	-3.16 (-5.79, -0.53)	0.0185	-52.03 (7.11)	-29.54 (-48.43, -10.65)	0.0022
Rilzabrutinib 400mg QPM (N=37)	34	14.73 (4.26)	9.82 (5.59)	-4.88 (0.96)	-1.19 (-3.81, 1.42)	0.3703	-33.42 (6.85)	-10.93 (-29.60, 7.74)	0.2511
Placebo (N=36)	32	13.83 (4.85)	10.10 (5.69)	-3.68 (0.98)			-22.49 (7.08)		
Week 10									
Rilzabrutinib 400mg TID (N=35)	30	13.66 (4.47)	5.87 (5.06)	-7.54 (1.02)	-3.52 (-6.23, -0.82)	0.0107	-53.73 (7.33)	-29.43 (-49.17, -9.70)	0.0035
Rilzabrutinib 400mg BID (N=35)	28	14.28 (4.21)	7.05 (7.27)	-7.11 (1.03)	-3.09 (-5.81, -0.38)	0.0256	-52.91 (7.33)	-28.62 (-48.06, -9.18)	0.0039
Rilzabrutinib 400mg QPM (N=37)	34	14.73 (4.26)	9.88 (5.93)	-4.92 (0.98)	-0.91 (-3.55, 1.74)	0.5023	-34.15 (7.01)	-9.86 (-29.14, 9.43)	0.3166
Placebo (N=36)	33	13.83 (4.85)	9.73 (6.39)	-4.02 (1.00)			-24.29 (7.29)		
Week 11									
Rilzabrutinib 400mg TID (N=35)	31	13.66 (4.47)	6.17 (5.40)	-7.31 (1.02)	-3.31 (-6.05, -0.57)	0.0179	-51.69 (7.63)	-27.64 (-48.19, -7.09)	0.0084
Rilzabrutinib 400mg BID (N=35)	29	14.28 (4.21)	7.13 (7.07)	-6.77 (1.02)	-2.77 (-5.49, -0.04)	0.0465	-49.42 (7.58)	-25.37 (-45.60, -5.14)	0.0140
Rilzabrutinib 400mg QPM (N=37)	33	14.73 (4.26)	10.18 (6.18)	-4.81 (1.00)	-0.81 (-3.52, 1.89)	0.5569	-33.39 (7.38)	-9.35 (-29.26, 10.56)	0.3575
Placebo (N=36)	33	13.83 (4.85)	9.64 (6.32)	-4.00 (1.01)			-24.05 (7.51)		
Week 12									
Rilzabrutinib 400mg TID (N=35)	28	13.66 (4.47)	5.23 (4.86)	-7.64 (1.06)	-3.24 (-6.08, -0.39)	0.0257	-54.23 (7.68)	-29.33 (-49.90, -8.75)	0.0052
Rilzabrutinib 400mg BID (N=35)	26	14.28 (4.21)	7.52 (7.21)	-6.52 (1.07)	-2.12 (-4.97, 0.73)	0.1450	-46.07 (7.64)	-21.17 (-41.70, -0.64)	0.0432
Rilzabrutinib 400mg QPM (N=37)	30	14.73 (4.26)	10.52 (6.14)	-4.49 (1.04)	-0.09 (-2.92, 2.75)	0.9531	-33.18 (7.52)	-8.28 (-28.75, 12.19)	0.4280
Placebo (N=36)	32	13.83 (4.85)	9.31 (6.52)	-4.40 (1.06)			-24.90 (7.64)		

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

n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo		% Change difference for rilzabrutinib vs. placebo	
				LS Mean (95% CI) ^a	p-value ^a	LS Mean (95% CI) ^a	p-value ^a
Note: Data collected after study intervention discontinuation were included. Data post selected prohibited/rescue medications (high/medium impact on efficacy confirmed through blinded medical review) were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF; other missing data were imputed by MI.							
Descriptive statistics at each week include participants with WOCF imputation at the week, and participants whose values were imputed by MI at the week were excluded from descriptive analysis.							

Table 39. Change and Percent Change from Baseline in HSS7 over Time up to Week 12 (Omalizumab-Naïve Population with Outlier Removed from Analysis)

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo		% Change difference for rilzabrutinib vs. placebo ^a		
					LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Week 1									
Rilzabrutinib 400mg TID (N=34)	34	14.06 (3.85)	8.50 (4.76)	-5.38 (0.80)	-3.72 (-6.32, -1.12)	0.0009	-35.11 (5.99)	-27.60 (-46.98, -8.21)	0.0009
Rilzabrutinib 400mg BID (N=35)	35	14.28 (4.21)	9.26 (5.76)	-4.76 (0.80)	-3.10 (-5.67, -0.52)	0.0049	-34.59 (5.97)	-27.08 (-46.27, -7.88)	0.0010
Rilzabrutinib 400mg QPM (N=37)	37	14.73 (4.26)	10.73 (4.90)	-3.83 (0.77)	-2.17 (-4.71, 0.37)	0.0444	-24.61 (5.76)	-17.09 (-36.03, 1.85)	0.0338
Placebo (N=36)	36	13.83 (4.85)	12.23 (5.49)	-1.66 (0.79)			-7.52 (5.90)		
Week 2									
Rilzabrutinib 400mg TID (N=34)	34	14.06 (3.85)	7.44 (5.01)	-6.39 (0.81)	-3.68 (-5.85, -1.50)	0.0009	-42.74 (6.08)	-27.42 (-43.65, -11.18)	0.0009
Rilzabrutinib 400mg BID (N=35)	34	14.28 (4.21)	9.27 (5.49)	-4.98 (0.81)	-2.27 (-4.42, -0.12)	0.0389	-35.26 (6.08)	-19.94 (-36.04, -3.84)	0.0152
Rilzabrutinib 400mg QPM (N=37)	37	14.73 (4.26)	10.90 (4.97)	-3.77 (0.78)	-1.05 (-3.18, 1.07)	0.3302	-23.80 (5.84)	-8.48 (-24.35, 7.39)	0.2948
Placebo (N=36)	35	13.83 (4.85)	11.11 (5.32)	-2.71 (0.80)			-15.32 (5.99)		
Week 3									
Rilzabrutinib 400mg TID (N=34)	34	14.06 (3.85)	7.03 (4.89)	-6.77 (0.85)	-3.54 (-5.82, -1.26)	0.0023	-45.23 (6.36)	-27.27 (-44.29, -10.26)	0.0017
Rilzabrutinib 400mg BID (N=35)	35	14.28 (4.21)	8.55 (6.09)	-5.46 (0.85)	-2.23 (-4.49, 0.03)	0.0529	-38.51 (6.34)	-20.55 (-37.40, -3.70)	0.0169

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
				Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Rilzabrutinib 400mg QPM (N=37)	37	14.73 (4.26)	10.41 (4.97)	-4.32 (0.82)	-1.09 (-3.32, 1.14)	0.3394	-28.21 (6.11)	-10.26 (-26.91, 6.39)	0.2272
Placebo (N=36)	35	13.83 (4.85)	10.62 (5.91)	-3.23 (0.84)			-17.96 (6.30)		
Week 4									
Rilzabrutinib 400mg TID (N=34)	32	14.06 (3.85)	6.85 (4.96)	-6.48 (0.87)	-3.47 (-5.78, -1.16)	0.0033	-44.85 (6.50)	-28.68 (-46.02, - 11.35)	0.0012
Rilzabrutinib 400mg BID (N=35)	33	14.28 (4.21)	7.60 (6.00)	-5.94 (0.86)	-2.93 (-5.22, -0.65)	0.0119	-43.08 (6.46)	-26.91 (-44.03, - 9.79)	0.0021
Rilzabrutinib 400mg QPM (N=37)	37	14.73 (4.26)	10.53 (4.74)	-4.12 (0.83)	-1.10 (-3.35, 1.14)	0.3359	-26.10 (6.19)	-9.93 (-26.78, 6.91)	0.2477
Placebo (N=36)	34	13.83 (4.85)	10.58 (6.36)	-3.01 (0.85)			-16.17 (6.37)		
Week 5									
Rilzabrutinib 400mg TID (N=34)	33	14.06 (3.85)	6.49 (5.14)	-7.19 (0.88)	-2.34 (-4.69, 0.01)	0.0514	-49.43 (6.29)	-19.00 (-35.86, - 2.14)	0.0272
Rilzabrutinib 400mg BID (N=35)	34	14.28 (4.21)	8.34 (6.75)	-5.51 (0.87)	-0.66 (-2.98, 1.66)	0.5779	-40.02 (6.24)	-9.59 (-26.21, 7.02)	0.2577
Rilzabrutinib 400mg QPM (N=37)	36	14.73 (4.26)	9.63 (5.13)	-4.83 (0.84)	0.02 (-2.28, 2.32)	0.9862	-31.37 (6.02)	-0.94 (-17.38, 15.50)	0.9109
Placebo (N=36)	33	13.83 (4.85)	8.56 (4.98)	-4.85 (0.87)			-30.43 (6.23)		
Week 6									
Rilzabrutinib 400mg TID (N=34)	31	14.06 (3.85)	6.78 (5.55)	-7.10 (0.97)	-2.66 (-5.24, -0.09)	0.0427	-48.07 (7.15)	-23.42 (-42.47, - 4.38)	0.0159
Rilzabrutinib 400mg BID (N=35)	34	14.28 (4.21)	8.17 (6.62)	-5.66 (0.96)	-1.22 (-3.78, 1.33)	0.3482	-40.11 (7.09)	-15.46 (-34.37, 3.44)	0.1089
Rilzabrutinib 400mg QPM (N=37)	34	14.73 (4.26)	9.94 (5.76)	-4.54 (0.93)	-0.10 (-2.65, 2.44)	0.9363	-30.40 (6.87)	-5.75 (-24.56, 13.05)	0.5487
Placebo (N=36)	32	13.83 (4.85)	9.09 (5.60)	-4.44 (0.96)			-24.65 (7.12)		
Week 7									
Rilzabrutinib 400mg TID (N=34)	30	14.06 (3.85)	6.40 (4.54)	-7.42 (0.90)	-3.01 (-5.42, -0.60)	0.0144	-50.21 (6.54)	-24.42 (-41.91, - 6.94)	0.0062
Rilzabrutinib 400mg BID (N=35)	34	14.28 (4.21)	7.34 (6.12)	-6.51 (0.89)	-2.10 (-4.48, 0.27)	0.0824	-45.82 (6.45)	-20.03 (-37.24, - 2.81)	0.0226

				Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Rilzabrutinib 400mg QPM (N=37)	33	14.73 (4.26)	10.43 (5.27)	-4.45 (0.87)	-0.04 (-2.40, 2.32)	0.9755	-29.53 (6.30)	-3.74 (-20.88, 13.40)	0.6688
Placebo (N=36)	33	13.83 (4.85)	9.27 (5.59)	-4.41 (0.89)			-25.79 (6.44)		
Week 8									
Rilzabrutinib 400mg TID (N=34)	28	14.06 (3.85)	6.12 (4.80)	-7.27 (0.98)	-2.65 (-5.28, -0.02)	0.0486	-50.94 (7.02)	-22.59 (-41.56, -3.62)	0.0196
Rilzabrutinib 400mg BID (N=35)	33	14.28 (4.21)	6.66 (6.70)	-7.25 (0.95)	-2.63 (-5.19, -0.07)	0.0443	-52.80 (6.83)	-24.45 (-42.85, -6.05)	0.0092
Rilzabrutinib 400mg QPM (N=37)	33	14.73 (4.26)	10.47 (5.71)	-4.49 (0.93)	0.13 (-2.41, 2.67)	0.9189	-30.95 (6.65)	-2.60 (-20.89, 15.69)	0.7806
Placebo (N=36)	33	13.83 (4.85)	9.16 (6.13)	-4.62 (0.96)			-28.35 (6.91)		
Week 9									
Rilzabrutinib 400mg TID (N=34)	29	14.06 (3.85)	5.88 (4.98)	-7.35 (1.02)	-3.55 (-6.27, -0.83)	0.0104	-50.03 (7.38)	-27.33 (-46.80, -7.85)	0.0060
Rilzabrutinib 400mg BID (N=35)	29	14.28 (4.21)	7.01 (7.58)	-6.87 (1.00)	-3.07 (-5.75, -0.40)	0.0241	-51.66 (7.19)	-28.96 (-48.16, -9.75)	0.0031
Rilzabrutinib 400mg QPM (N=37)	34	14.73 (4.26)	9.82 (5.59)	-4.89 (0.96)	-1.09 (-3.72, 1.53)	0.4145	-33.40 (6.87)	-10.69 (-29.52, 8.14)	0.2658
Placebo (N=36)	32	13.83 (4.85)	10.10 (5.69)	-3.80 (0.99)			-22.70 (7.10)		
Week 10									
Rilzabrutinib 400mg TID (N=34)	30	14.06 (3.85)	5.87 (5.06)	-7.62 (1.03)	-3.59 (-6.32, -0.86)	0.0099	-53.16 (7.35)	-28.45 (-48.02, -8.89)	0.0044
Rilzabrutinib 400mg BID (N=35)	28	14.28 (4.21)	7.05 (7.27)	-7.21 (1.04)	-3.18 (-5.92, -0.45)	0.0225	-53.63 (7.40)	-28.93 (-48.47, -9.38)	0.0037
Rilzabrutinib 400mg QPM (N=37)	34	14.73 (4.26)	9.88 (5.93)	-5.01 (0.97)	-0.99 (-3.65, 1.68)	0.4693	-34.33 (6.97)	-9.62 (-28.72, 9.48)	0.3234
Placebo (N=36)	33	13.83 (4.85)	9.73 (6.39)	-4.03 (1.01)			-24.71 (7.20)		
Week 11									
Rilzabrutinib 400mg TID (N=34)	31	14.06 (3.85)	6.17 (5.40)	-7.49 (1.03)	-3.43 (-6.19, -0.66)	0.0151	-51.42 (7.56)	-27.32 (-47.67, -6.96)	0.0085
Rilzabrutinib 400mg BID (N=35)	29	14.28 (4.21)	7.13 (7.07)	-6.73 (1.04)	-2.67 (-5.45, 0.11)	0.0601	-49.25 (7.67)	-25.15 (-45.61, -4.68)	0.0160

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo		% Change difference for rilzabrutinib vs. placebo		
					LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Rilzabrutinib 400mg QPM (N=37)	33	14.73 (4.26)	10.18 (6.18)	-4.85 (0.99)	-0.79 (-3.51, 1.93)	0.5709	-33.92 (7.28)	-9.82 (-29.88, 10.24)	0.3371
Placebo (N=36)	33	13.83 (4.85)	9.64 (6.32)	-4.06 (1.02)			-24.10 (7.53)		
Week 12									
Rilzabrutinib 400mg TID (N=34)	28	14.06 (3.85)	5.23 (4.86)	-7.89 (1.07)	-3.54 (-6.40, -0.67)	0.0156	-54.34 (7.78)	-28.97 (-49.68, - 8.27)	0.0061
Rilzabrutinib 400mg BID (N=35)	26	14.28 (4.21)	7.52 (7.21)	-6.56 (1.07)	-2.20 (-5.04, 0.63)	0.1279	-47.15 (7.75)	-21.78 (-42.31, - 1.25)	0.0376
Rilzabrutinib 400mg QPM (N=37)	30	14.73 (4.26)	10.52 (6.14)	-4.57 (1.02)	-0.22 (-3.01, 2.57)	0.8768	-32.82 (7.36)	-7.45 (-27.56, 12.65)	0.4674
Placebo (N=36)	32	13.83 (4.85)	9.31 (6.52)	-4.35 (1.04)			-25.37 (7.52)		

^a Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group and regions as covariates.
Note: Data collected after study intervention discontinuation were included. Data post selected prohibited/rescue medications (high/medium impact on efficacy confirmed through blinded medical review) were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF; other missing data were imputed by MI.
Descriptive statistics at each week include participants with WOCF imputation at the week, and participants whose values were imputed by MI at the week were excluded from the descriptive analysis.

AAS7

[00252] Treatment with rilzabrutinib was associated with meaningful improvements in AAS7 in patients with angioedema at baseline. Notably, participants receiving 400 mg TID rilzabrutinib exhibited a substantial reduction in AAS7 at Week 12 (see **Figures 29-32** and **Tables 40-42**). In the ITT population, participants receiving 400 mg TID rilzabrutinib exhibited a LS mean change from baseline at Week 12 of -43.36 ($p=0.1511$) points. By contrast, patients receiving the placebo had a LS mean change from baseline of -35.31 points (see **Table 41**). Similar results were observed for the omalizumab-naïve population, in which patients receiving the 400 mg TID rilzabrutinib intervention exhibited an LS mean change from baseline at Week 12 of -44.04 ($p=0.0797$), which represents an 84.63% decrease from baseline (see **Table 42**).

[00253] Improvement in AAS7 was dose-dependent, with participants randomized into the 400 mg BID rilzabrutinib treatment group also exhibiting a meaningful response.

[00254] Additionally, the reduction in AAS7 was rapid, with results observed as early as Week 1, and sustained throughout the study.

[00255] Table 40. Summary of AAS7 by Week in the Double-Blind Period in Participants with Angioedema at Baseline (Omalizumab-Naïve Population and Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders)

AAS7	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
Baseline								
Number	26	27	26	23	4	1	2	3
Mean (SD)	58.73 (26.52)	53.48 (25.55)	46.58 (26.66)	47.91 (22.78)	66.00 (34.21)	68.00 (NC)	39.50 (3.54)	31.28 (12.60)
Median	61.50	56.00	46.50	51.00	68.50	68.00	39.50	36.00
Q1 ; Q3	42.00 ; 84.00	35.00 ; 74.00	24.00 ; 68.00	27.00 ; 62.00	37.00 ; 95.00	68.00 ; 68.00	37.00 ; 42.00	17.00 ; 40.83
Min ; Max	8.0 ; 101.0	6.0 ; 99.0	2.0 ; 92.0	9.0 ; 91.0	29.0 ; 98.0	68.0 ; 68.0	37.0 ; 42.0	17.0 ; 40.8
Week 1								
Number (observed/imputed)	26 (26/0)	27 (27/0)	26 (26/0)	23 (23/0)	4 (4/0)	1 (1/0)	2 (2/0)	3 (3/0)
Mean (SD)	43.46 (28.75)	34.85 (21.86)	25.15 (31.33)	18.96 (23.24)	37.96 (36.04)	27.00 (NC)	0.00 (0.00)	6.33 (7.77)
Median	36.00	39.00	10.50	9.00	31.00	27.00	0.00	4.00
Q1 ; Q3	20.00 ; 65.00	17.00 ; 50.00	0.00 ; 48.00	0.00 ; 35.00	9.42 ; 66.50	27.00 ; 27.00	0.00 ; 0.00	0.00 ; 15.00
Min ; Max	0.0 ; 97.0	0.0 ; 77.0	0.0 ; 94.5	0.0 ; 82.0	5.8 ; 84.0	27.0 ; 27.0	0.0 ; 0.0	0.0 ; 15.0
Change from baseline								
Number (observed/imputed)	26 (26/0)	27 (27/0)	26 (26/0)	23 (23/0)	4 (4/0)	1 (1/0)	2 (2/0)	3 (3/0)
Mean (SD)	-15.27 (23.42)	-18.63 (22.01)	-21.44 (18.46)	-28.96 (27.34)	-28.04 (12.39)	-41.00 (NC)	-39.50 (3.54)	-24.94 (11.53)
Median	-13.00	-19.00	-22.00	-26.00	-27.58	-41.00	-39.50	-25.83
Q1 ; Q3	-30.00 ; -2.00	-39.00 ; 3.00	-32.00 ; -11.00	-55.00 ; -9.00	-37.50 ; -18.58	-41.00 ; -41.00	-42.00 ; -37.00	-36.00 ; -13.00
Min ; Max	-60.0 ; 44.0	-62.0 ; 12.0	-61.0 ; 7.0	-76.0 ; 19.0	-43.0 ; -14.0	-41.0 ; -41.0	-42.0 ; -37.0	-36.0 ; -13.0
Percent change from baseline								
Number (observed/imputed)	26 (26/0)	27 (27/0)	26 (26/0)	23 (23/0)	4 (4/0)	1 (1/0)	2 (2/0)	3 (3/0)
Mean (SD)	-18.83 (60.46)	-30.81 (44.93)	-62.04 (42.40)	-56.39 (51.49)	-53.01 (29.38)	-60.29 (NC)	-100.00 (0.00)	-79.91 (18.61)
Median	-18.98	-35.35	-82.71	-89.41	-58.93	-60.29	-100.00	-76.47
Q1 ; Q3	-59.38 ; -3.30	-69.64 ; 4.48	-100.00 ; -26.74	-100.00 ; -28.57	-75.50 ; -30.51	-60.29 ; -60.29	-100.00 ; -100.00	-100.00 ; -63.27
Min ; Max	-100.0 ; 200.0	-100.0 ; 45.5	-100.0 ; 12.5	-100.0 ; 84.2	-79.9 ; -14.3	-60.3 ; -60.3	-100.0 ; -100.0	-100.0 ; -63.3
Week 2								
Number (observed/imputed)	25 (25/0)	27 (27/0)	25 (25/0)	23 (23/0)	4 (4/0)	1 (1/0)	2 (2/0)	3 (3/0)
Mean (SD)	38.14 (29.33)	33.25 (23.40)	24.57 (29.12)	17.03 (20.90)	21.21 (38.63)	25.00 (NC)	0.00 (0.00)	4.00 (6.93)
Median	38.00	31.50	14.00	9.33	2.92	25.00	0.00	0.00
Q1 ; Q3	14.00 ; 63.00	14.00 ; 49.00	0.00 ; 37.80	0.00 ; 30.80	0.00 ; 42.42	25.00 ; 25.00	0.00 ; 0.00	0.00 ; 12.00

AAS7	Omalizumab-Naïve Population					Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders				
	Placebo (N=36)		Rilzabrutinib 400mg BID (N=35)		Rilzabrutinib 400mg TID (N=35)		Placebo (N=4)		Rilzabrutinib 400mg QPM (N=1)	
	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Rilzabrutinib 400mg TID (N=35)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)	Rilzabrutinib 400mg TID (N=6)
Min ; Max	0.0 ; 91.0	0.0 ; 77.0	0.0 ; 91.0	0.0 ; 68.0	0.0 ; 79.0	25.0 ; 25.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 12.0	0.0 ; 12.0
Change from baseline										
Number (observed/imputed)	25 (25/0)	27 (27/0)	25 (25/0)	23 (23/0)	4 (4/0)	1 (1/0)	2 (2/0)	2 (2/0)	3 (3/0)	3 (3/0)
Mean (SD)	-19.82 (22.48)	-20.23 (24.12)	-22.60 (18.31)	-30.89 (28.32)	-44.79 (33.47)	-43.00 (NC)	-39.50 (3.54)	-39.50 (3.54)	-27.28 (19.44)	-27.28 (19.44)
Median	-17.00	-11.00	-23.00	-27.00	-34.08	-43.00	-39.50	-39.50	-36.00	-36.00
Q1 ; Q3	-40.00 ; -5.00	-32.67 ; -1.67	-33.00 ; -11.00	-55.00 ; -9.00	-68.50 ; -21.08	-43.00 ; -43.00	-42.00 ; -37.00	-42.00 ; -37.00	-40.83 ; -5.00	-40.83 ; -5.00
Min ; Max	-66.0 ; 22.0	-75.0 ; 15.0	-57.0 ; 11.0	-75.0 ; 16.0	-92.0 ; -19.0	-43.0 ; -43.0	-42.0 ; -37.0	-42.0 ; -37.0	-40.8 ; -5.0	-40.8 ; -5.0
Percent change from baseline										
Number (observed/imputed)	25 (25/0)	27 (27/0)	25 (25/0)	23 (23/0)	4 (4/0)	1 (1/0)	2 (2/0)	2 (2/0)	3 (3/0)	3 (3/0)
Mean (SD)	-38.51 (43.99)	-36.22 (43.96)	-45.07 (90.72)	-58.84 (53.09)	-74.82 (38.15)	-63.24 (NC)	-100.00 (0.00)	-100.00 (0.00)	-76.47 (40.75)	-76.47 (40.75)
Median	-25.58	-31.31	-77.03	-81.97	-89.94	-63.24	-100.00	-100.00	-100.00	-100.00
Q1 ; Q3	-77.42 ; -9.85	-64.56 ; -2.49	-100.00 ; -26.56	-100.00 ; -28.57	-100.00 ; -49.64	-63.24 ; -63.24	-100.00 ; -	-100.00 ; -	-100.00 ; -29.41	-100.00 ; -29.41
Min ; Max	-100.0 ; 50.0	-100.0 ; 88.2	-100.0 ; 350.0	-100.0 ; 84.2	-100.0 ; -19.4	-63.2 ; -63.2	-100.0 ; -100.0	-100.0 ; -100.0	-100.0 ; -29.4	-100.0 ; -29.4
Week 3										
Number (observed/imputed)	25 (25/0)	27 (27/0)	26 (26/0)	23 (23/0)	4 (4/0)	1 (1/0)	2 (2/0)	2 (2/0)	3 (3/0)	3 (3/0)
Mean (SD)	33.14 (30.73)	32.60 (20.89)	15.95 (20.90)	14.08 (22.48)	24.15 (36.42)	29.00 (NC)	0.00 (0.00)	0.00 (0.00)	7.00 (7.00)	7.00 (7.00)
Median	22.40	34.00	6.50	0.00	9.80	29.00	0.00	0.00	7.00	7.00
Q1 ; Q3	5.00 ; 56.00	22.00 ; 46.00	0.00 ; 27.00	0.00 ; 24.00	0.00 ; 48.30	29.00 ; 29.00	0.00 ; 0.00	0.00 ; 0.00	0.00 ; 14.00	0.00 ; 14.00
Min ; Max	0.0 ; 93.0	0.0 ; 72.0	0.0 ; 68.0	0.0 ; 67.0	0.0 ; 77.0	29.0 ; 29.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 14.0	0.0 ; 14.0
Change from baseline										
Number (observed/imputed)	25 (25/0)	27 (27/0)	26 (26/0)	23 (23/0)	4 (4/0)	1 (1/0)	2 (2/0)	2 (2/0)	3 (3/0)	3 (3/0)
Mean (SD)	-24.82 (27.21)	-20.88 (26.24)	-30.63 (24.46)	-33.83 (29.99)	-41.85 (36.57)	-39.00 (NC)	-39.50 (3.54)	-39.50 (3.54)	-24.28 (18.46)	-24.28 (18.46)
Median	-17.00	-13.00	-25.88	-27.00	-33.00	-39.00	-39.50	-39.50	-33.83	-33.83
Q1 ; Q3	-47.00 ; -8.00	-49.00 ; -5.00	-51.00 ; -16.00	-59.00 ; -11.00	-68.50 ; -15.20	-39.00 ; -39.00	-42.00 ; -37.00	-42.00 ; -37.00	-36.00 ; -3.00	-36.00 ; -3.00
Min ; Max	-83.0 ; 21.0	-75.0 ; 23.0	-92.0 ; 10.8	-83.0 ; 26.8	-92.0 ; -9.4	-39.0 ; -39.0	-42.0 ; -37.0	-42.0 ; -37.0	-36.0 ; -3.0	-36.0 ; -3.0
Percent change from baseline										
Number (observed/imputed)	25 (25/0)	27 (27/0)	26 (26/0)	23 (23/0)	4 (4/0)	1 (1/0)	2 (2/0)	2 (2/0)	3 (3/0)	3 (3/0)
Mean (SD)	-45.13 (46.73)	-29.46 (63.83)	-45.93 (125.55)	-69.93 (48.65)	-63.46 (42.43)	-57.35 (NC)	-100.00 (0.00)	-100.00 (0.00)	-66.83 (43.45)	-66.83 (43.45)
Median	-38.46	-26.00	-89.45	-100.00	-66.21	-57.35	-100.00	-100.00	-82.86	-82.86
Q1 ; Q3	-92.42 ; -9.90	-70.89 ; -6.49	-100.00 ; -36.00	-100.00 ; -38.46	-100.00 ; -26.92	-57.35 ; -57.35	-100.00 ; -	-100.00 ; -	-100.00 ; -17.65	-100.00 ; -17.65

AAS7	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
	Min ; Max	Min ; Max	Min ; Max	Min ; Max	Min ; Max	Min ; Max	Min ; Max	Min ; Max
Week 4								
Number (observed/imputed)								
Mean (SD)								
Median								
Q1 ; Q3								
Min ; Max								
Change from baseline								
Number (observed/imputed)								
Mean (SD)								
Median								
Q1 ; Q3								
Min ; Max								
Percent change from baseline								
Number (observed/imputed)								
Mean (SD)								
Median								
Q1 ; Q3								
Min ; Max								
Week 5								
Number (observed/imputed)								
Mean (SD)								
Median								
Q1 ; Q3								
Min ; Max								
Change from baseline								
Number (observed/imputed)								
Mean (SD)								
Median								
Q1 ; Q3								
Min ; Max								

AAS7	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders											
	Placebo (N=36)		Rilzabrutinib 400mg BID (N=35)		Rilzabrutinib 400mg QPM (N=37)		Rilzabrutinib 400mg TID (N=35)		Placebo (N=4)		Rilzabrutinib 400mg QPM (N=1)		Rilzabrutinib 400mg BID (N=6)		Rilzabrutinib 400mg TID (N=6)	
Percent change from baseline																
Number (observed/imputed)																
Mean (SD)	23 (23/0)	26 (25/1)	25 (24/1)	23 (23/0)	23 (23/0)	4 (4/0)	1 (1/0)	2 (2/0)	3 (3/0)							
Median	-60.14 (58.83)	-55.69 (41.16)	-66.40 (54.16)	-73.55 (35.00)	-57.13 (31.75)	-51.76	-45.59 (NC)	-100.00 (0.00)	-44.59 (59.12)							
Q1 ; Q3	-81.13	-59.46	-100.00	-88.24	-79.35 ; -34.91	-79.35 ; -34.91	-45.59	-100.00 ; -	-100.00 ; 17.65							
Min ; Max	-100.00 ; -52.17	-100.00 ; -18.75	-100.00 ; -33.11	-100.00 ; -51.28	-100.00 ; 31.6	-100.00 ; -25.0	-45.6 ; -45.6	-100.0 ; -100.0	-100.0 ; 17.6							
Week 6																
Number (observed/imputed)																
Mean (SD)	22 (21/1)	24 (23/1)	25 (24/1)	21 (21/0)	21 (21/0)	4 (3/1)	1 (1/0)	2 (2/0)	3 (3/0)							
Median	25.43 (27.48)	28.26 (23.00)	13.26 (19.12)	13.55 (20.58)	31.83 (20.44)	30.17	21.00 (NC)	0.00 (0.00)	7.00 (8.19)							
Q1 ; Q3	16.70	24.38	3.00	0.00	14.50 ; 49.17	14.50 ; 49.17	21.00 ; 21.00	0.00 ; 0.00	5.00							
Min ; Max	0.00 ; 47.00	8.00 ; 46.50	0.00 ; 21.00	0.00 ; 16.00	0.00 ; 63.0	13.0 ; 54.0	21.0 ; 21.0	0.0 ; 0.0	0.00 ; 16.00							
Change from baseline																
Number (observed/imputed)																
Mean (SD)	22 (21/1)	24 (23/1)	25 (24/1)	21 (21/0)	21 (21/0)	4 (3/1)	1 (1/0)	2 (2/0)	3 (3/0)							
Median	-33.30 (33.06)	-28.36 (28.62)	-31.58 (23.39)	-32.35 (30.51)	-34.17 (16.81)	-35.00	-47.00 (NC)	-39.50 (3.54)	-24.28 (20.16)							
Q1 ; Q3	-27.00	-23.63	-24.00	-27.00	-45.83 ; -22.50	-45.83 ; -22.50	-47.00 ; -47.00	-42.00 ; -37.00	-35.83							
Min ; Max	-55.60 ; -11.00	-46.50 ; -7.17	-43.00 ; -14.00	-55.00 ; -11.00	-91.0 ; 26.8	-53.7 ; -13.0	-47.0 ; -47.0	-42.0 ; -37.0	-36.00 ; -1.00							
Percent change from baseline																
Number (observed/imputed)																
Mean (SD)	22 (21/1)	24 (23/1)	25 (24/1)	21 (21/0)	21 (21/0)	4 (3/1)	1 (1/0)	2 (2/0)	3 (3/0)							
Median	-53.45 (59.54)	-47.92 (45.31)	-70.72 (39.56)	-63.91 (58.28)	-53.00 (13.35)	-49.79	-69.12 (NC)	-100.00 (0.00)	-64.55 (51.17)							
Q1 ; Q3	-65.64	-55.14	-92.19	-100.00	-62.94 ; -43.07	-62.94 ; -43.07	-69.12 ; -69.12	-100.00 ; -	-87.76							
Min ; Max	-100.00 ; -22.95	-80.43 ; -19.31	-100.00 ; -45.83	-100.00 ; -52.38	-100.00 ; 100.0	-71.1 ; -41.3	-69.1 ; -69.1	-100.0 ; -100.0	-100.00 ; -5.88							
Week 7																
Number (observed/imputed)																
Mean (SD)	23 (22/1)	23 (21/2)	25 (24/1)	20 (20/0)	20 (20/0)	4 (3/1)	1 (1/0)	2 (2/0)	3 (3/0)							
Median	22.56 (25.96)	31.88 (21.51)	14.38 (19.63)	12.43 (15.87)	37.90 (31.72)	36.60	12.00 (NC)	1.00 (1.41)	9.72 (16.84)							
Q1 ; Q3	16.80	30.00	4.67	2.50	10.70 ; 65.10	8.4 ; 70.0	12.00 ; 12.00	0.00 ; 2.00	0.00							
Min ; Max	0.00 ; 38.00	14.00 ; 49.00	0.00 ; 22.00	0.00 ; 26.00	8.4 ; 70.0	8.4 ; 70.0	12.0 ; 12.0	0.0 ; 2.0	0.00 ; 29.17							

AAS7	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)		Rilzabrutinib 400mg BID (N=35)		Placebo (N=4)		Rilzabrutinib 400mg QPM (N=1)	
	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)	Rilzabrutinib 400mg TID (N=6)
Change from baseline								
Number (observed/imputed)								
Mean (SD)	23 (22/1)	23 (21/2)	25 (24/1)	20 (20/0)	4 (3/1)	1 (1/0)	2 (2/0)	3 (3/0)
Median	-36.31 (32.62)	-26.95 (30.21)	-33.54 (24.64)	-32.23 (26.57)	-28.10 (8.22)	-56.00 (NC)	-38.50 (2.12)	-21.56 (12.79)
Q1 ; Q3	-37.00	-28.00	-30.00	-27.00	-27.00	-56.00	-38.50	-17.00
Min ; Max	-62.00 ; -8.00	-55.00 ; -5.00	-47.00 ; -15.00	-51.00 ; -13.50	-34.90 ; -21.30	-56.00 ; -56.00	-40.00 ; -37.00	-36.00 ; -11.67
	-95.0 ; 32.8	-75.0 ; 42.8	-92.0 ; 1.0	-85.0 ; 26.5	-37.8 ; -20.6	-56.0 ; -56.0	-40.0 ; -37.0	-36.0 ; -11.7
Percent change from baseline								
Number (observed/imputed)								
Mean (SD)	23 (22/1)	23 (21/2)	25 (24/1)	20 (20/0)	4 (3/1)	1 (1/0)	2 (2/0)	3 (3/0)
Median	-56.79 (58.52)	-33.18 (69.78)	-68.05 (40.33)	-66.41 (55.40)	-51.16 (23.76)	-82.35 (NC)	-97.62 (3.37)	-76.19 (41.24)
Q1 ; Q3	-78.72	-50.00	-88.60	-93.41	-54.80	-82.35	-97.62	-100.00
Min ; Max	-100.00 ; -38.71	-76.00 ; -9.09	-100.00 ; -38.67	-100.00 ; -48.21	-71.07 ; -31.24	-82.35 ; -82.35	-100.00 ; -95.24	-100.00 ; -28.57
	-100.0 ; 149.2	-100.0 ; 225.4	-100.0 ; 50.0	-100.0 ; 139.5	-71.1 ; -23.9	-82.4 ; -82.4	-100.0 ; -95.2	-100.0 ; -28.6
Week 8								
Number (observed/imputed)								
Mean (SD)	23 (22/1)	23 (20/3)	24 (23/1)	19 (19/0)	4 (3/1)	1 (1/0)	2 (2/0)	3 (3/0)
Median	25.96 (27.00)	24.98 (23.29)	9.97 (16.69)	12.20 (13.05)	25.25 (22.35)	18.00 (NC)	0.00 (0.00)	4.67 (7.23)
Q1 ; Q3	26.00	18.00	0.00	11.00	27.50	18.00	0.00	1.00
Min ; Max	0.00 ; 39.00	0.00 ; 44.00	0.00 ; 16.00	0.00 ; 22.17	6.50 ; 44.00	18.00 ; 18.00	0.00 ; 0.00	0.00 ; 13.00
	0.0 ; 98.0	0.0 ; 70.0	0.0 ; 63.0	0.0 ; 40.6	0.0 ; 46.0	18.0 ; 18.0	0.0 ; 0.0	0.0 ; 13.0
Change from baseline								
Number (observed/imputed)								
Mean (SD)	23 (22/1)	23 (20/3)	24 (23/1)	19 (19/0)	4 (3/1)	1 (1/0)	2 (2/0)	3 (3/0)
Median	-32.91 (32.23)	-29.80 (30.38)	-36.21 (24.67)	-33.38 (24.94)	-40.75 (12.58)	-50.00 (NC)	-39.50 (3.54)	-26.61 (19.68)
Q1 ; Q3	-39.00	-28.00	-32.00	-25.00	-39.00	-50.00	-39.50	-36.00
Min ; Max	-61.00 ; -8.00	-56.00 ; -7.00	-52.50 ; -16.00	-51.00 ; -13.00	-51.00 ; -30.50	-50.00 ; -50.00	-42.00 ; -37.00	-39.83 ; -4.00
	-83.0 ; 52.2	-77.0 ; 42.8	-92.0 ; 1.5	-80.0 ; 5.6	-56.0 ; -29.0	-50.0 ; -50.0	-42.0 ; -37.0	-39.8 ; -4.0
Percent change from baseline								
Number (observed/imputed)								
Mean (SD)	23 (22/1)	23 (20/3)	24 (23/1)	19 (19/0)	4 (3/1)	1 (1/0)	2 (2/0)	3 (3/0)
Median	-49.15 (73.10)	-49.05 (70.23)	-74.90 (43.31)	-69.90 (38.13)	-69.56 (22.10)	-73.53 (NC)	-100.00 (0.00)	-73.69 (43.46)
Q1 ; Q3	-70.71	-66.00	-100.00	-85.88	-64.13	-73.53	-100.00	-97.55
Min ; Max	-100.00 ; -22.95	-100.00 ; -11.94	-100.00 ; -63.27	-100.00 ; -44.00	-85.56 ; -53.57	-73.53 ; -73.53	-100.00 ; -	-100.00 ; -23.53
	-100.0 ; 237.3	-100.0 ; 225.4	-100.0 ; 75.0	-100.0 ; 23.8	-100.0 ; -50.0	-73.5 ; -73.5	-100.0 ; -100.0	-100.0 ; -23.5

AAS7	Omalizumab-Naïve Population					Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders				
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)		
Week 9	Number (observed/imputed)	22 (21/1)	24 (21/3)	23 (22/1)	20 (20/0)	4 (3/1)	1 (1/0)	2 (2/0)	3 (3/0)	
	Mean (SD)	26.38 (25.55)	27.96 (21.62)	10.87 (18.30)	8.52 (12.19)	16.03 (5.68)	10.00 (NC)	0.00 (0.00)	4.39 (6.62)	
	Median	29.58	26.30	0.00	1.40	13.50	10.00	0.00	1.17	
	Q1 ; Q3	0.00 ; 40.00	9.50 ; 44.00	0.00 ; 12.00	0.00 ; 15.00	12.80 ; 19.25	10.00 ; 10.00	0.00 ; 0.00	0.00 ; 12.00	
	Min ; Max	0.0 ; 98.0	0.0 ; 71.0	0.0 ; 63.0	0.0 ; 34.0	12.6 ; 24.5	10.0 ; 10.0	0.0 ; 0.0	0.0 ; 12.0	
Change from baseline	Number (observed/imputed)	22 (21/1)	24 (21/3)	23 (22/1)	20 (20/0)	4 (3/1)	1 (1/0)	2 (2/0)	3 (3/0)	
	Mean (SD)	-32.17 (30.60)	-28.66 (27.25)	-34.83 (26.07)	-38.54 (26.30)	-49.98 (31.17)	-58.00 (NC)	-39.50 (3.54)	-26.89 (19.04)	
	Median	-38.50	-29.00	-32.00	-39.00	-49.75	-58.00	-39.50	-36.00	
	Q1 ; Q3	-58.80 ; -3.00	-52.50 ; -7.50	-46.00 ; -16.00	-55.00 ; -17.00	-75.75 ; -24.20	-58.00 ; -58.00	-42.00 ; -37.00	-39.67 ; -5.00	
	Min ; Max	-84.0 ; 22.3	-75.0 ; 42.8	-92.0 ; 4.0	-85.0 ; 3.5	-84.0 ; -16.4	-58.0 ; -58.0	-42.0 ; -37.0	-39.7 ; -5.0	
Percent change from baseline	Number (observed/imputed)	22 (21/1)	24 (21/3)	23 (22/1)	20 (20/0)	4 (3/1)	1 (1/0)	2 (2/0)	3 (3/0)	
	Mean (SD)	-47.50 (57.76)	-46.39 (66.49)	-67.10 (66.88)	-78.96 (34.18)	-71.69 (11.96)	-85.29 (NC)	-100.00 (0.00)	-75.52 (39.95)	
	Median	-62.54	-56.26	-100.00	-98.13	-72.24	-85.29	-100.00	-97.14	
	Q1 ; Q3	-100.00 ; -4.41	-83.27 ; -33.38	-100.00 ; -58.21	-100.00 ; -65.23	-79.54 ; -63.83	-85.29 ; -85.29	-100.00 ; -100.00	-100.00 ; -29.41	
	Min ; Max	-100.0 ; 101.5	-100.0 ; 225.4	-100.0 ; 200.0	-100.0 ; 16.7	-85.7 ; -56.6	-85.3 ; -85.3	-100.0 ; -100.0	-100.0 ; -29.4	
Week 10	Number (observed/imputed)	23 (22/1)	24 (21/3)	21 (20/1)	21 (21/0)	4 (3/1)	1 (1/0)	2 (2/0)	3 (2/1)	
	Mean (SD)	26.17 (27.80)	27.70 (22.96)	13.93 (20.43)	6.83 (9.73)	7.50 (5.57)	0.00 (NC)	0.00 (0.00)	9.00 (10.15)	
	Median	21.00	28.00	0.00	2.00	8.50	0.00	0.00	7.00	
	Q1 ; Q3	0.00 ; 41.00	0.00 ; 48.00	0.00 ; 24.00	0.00 ; 11.00	3.50 ; 11.50	0.00 ; 0.00	0.00 ; 0.00	0.00 ; 20.00	
	Min ; Max	0.0 ; 98.0	0.0 ; 70.0	0.0 ; 63.0	0.0 ; 32.0	0.0 ; 13.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 20.0	
Change from baseline	Number (observed/imputed)	23 (22/1)	24 (21/3)	21 (20/1)	21 (21/0)	4 (3/1)	1 (1/0)	2 (2/0)	3 (2/1)	
	Mean (SD)	-32.70 (32.03)	-28.93 (28.14)	-29.84 (25.74)	-39.26 (24.84)	-58.50 (37.18)	-68.00 (NC)	-39.50 (3.54)	-22.28 (21.92)	
	Median	-30.00	-28.92	-24.00	-40.00	-57.00	-68.00	-39.50	-33.83	
	Q1 ; Q3	-62.83 ; -8.00	-50.00 ; -9.00	-38.00 ; -14.00	-56.00 ; -18.00	-90.00 ; -27.00	-68.00 ; -68.00	-42.00 ; -37.00	-36.00 ; 3.00	
	Min ; Max	-91.0 ; 25.8	-75.0 ; 42.8	-92.0 ; 10.0	-85.0 ; 7.0	-98.0 ; -22.0	-68.0 ; -68.0	-42.0 ; -37.0	-36.0 ; 3.0	
Percent change from baseline										

AAS7	Omalizumab-Naïve Population						Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders																							
	Placebo (N=36)			Rilzabrutinib 400mg QPM (N=37)			Rilzabrutinib 400mg BID (N=35)			Rilzabrutinib 400mg TID (N=35)			Placebo (N=4)			Rilzabrutinib 400mg QPM (N=1)			Rilzabrutinib 400mg BID (N=6)			Rilzabrutinib 400mg TID (N=6)								
	Number (observed/imputed)	Mean (SD)	Median	Q1 ; Q3	Min ; Max		Number (observed/imputed)	Mean (SD)	Median	Q1 ; Q3	Min ; Max		Number (observed/imputed)	Mean (SD)	Median	Q1 ; Q3	Min ; Max		Number (observed/imputed)	Mean (SD)	Median	Q1 ; Q3	Min ; Max		Number (observed/imputed)	Mean (SD)	Median	Q1 ; Q3	Min ; Max	
Week 11	23 (22/1)	-48.53 (61.08)	-64.49	-100.00 ; -15.12	-100.00 ; -100.00		24 (21/3)	-46.90 (68.16)	-50.17	-100.00 ; -31.94	-100.00 ; -100.00		21 (20/1)	-45.78 (130.13)	-100.00	-100.00 ; -34.86	-100.00 ; -100.00		21 (21/0)	-82.44 (32.63)	-96.61	-100.00 ; -80.65	-100.00 ; -100.00		4 (3/1)	-84.03 (13.10)	-82.50	-100.00 ; -94.57	-100.00 ; -100.00	
Week 11	23 (22/1)	-48.53 (61.08)	-64.49	-100.00 ; -15.12	-100.00 ; -100.00		24 (21/3)	-46.90 (68.16)	-50.17	-100.00 ; -31.94	-100.00 ; -100.00		21 (20/1)	-45.78 (130.13)	-100.00	-100.00 ; -34.86	-100.00 ; -100.00		21 (21/0)	-82.44 (32.63)	-96.61	-100.00 ; -80.65	-100.00 ; -100.00		4 (3/1)	-84.03 (13.10)	-82.50	-100.00 ; -94.57	-100.00 ; -100.00	
Week 11	23 (22/1)	-48.53 (61.08)	-64.49	-100.00 ; -15.12	-100.00 ; -100.00		24 (21/3)	-46.90 (68.16)	-50.17	-100.00 ; -31.94	-100.00 ; -100.00		21 (20/1)	-45.78 (130.13)	-100.00	-100.00 ; -34.86	-100.00 ; -100.00		21 (21/0)	-82.44 (32.63)	-96.61	-100.00 ; -80.65	-100.00 ; -100.00		4 (3/1)	-84.03 (13.10)	-82.50	-100.00 ; -94.57	-100.00 ; -100.00	
Week 11	23 (22/1)	-48.53 (61.08)	-64.49	-100.00 ; -15.12	-100.00 ; -100.00		24 (21/3)	-46.90 (68.16)	-50.17	-100.00 ; -31.94	-100.00 ; -100.00		21 (20/1)	-45.78 (130.13)	-100.00	-100.00 ; -34.86	-100.00 ; -100.00		21 (21/0)	-82.44 (32.63)	-96.61	-100.00 ; -80.65	-100.00 ; -100.00		4 (3/1)	-84.03 (13.10)	-82.50	-100.00 ; -94.57	-100.00 ; -100.00	
Week 11	23 (22/1)	-48.53 (61.08)	-64.49	-100.00 ; -15.12	-100.00 ; -100.00		24 (21/3)	-46.90 (68.16)	-50.17	-100.00 ; -31.94	-100.00 ; -100.00		21 (20/1)	-45.78 (130.13)	-100.00	-100.00 ; -34.86	-100.00 ; -100.00		21 (21/0)	-82.44 (32.63)	-96.61	-100.00 ; -80.65	-100.00 ; -100.00		4 (3/1)	-84.03 (13.10)	-82.50	-100.00 ; -94.57	-100.00 ; -100.00	
Week 11	23 (22/1)	-48.53 (61.08)	-64.49	-100.00 ; -15.12	-100.00 ; -100.00		24 (21/3)	-46.90 (68.16)	-50.17	-100.00 ; -31.94	-100.00 ; -100.00		21 (20/1)	-45.78 (130.13)	-100.00	-100.00 ; -34.86	-100.00 ; -100.00		21 (21/0)	-82.44 (32.63)	-96.61	-100.00 ; -80.65	-100.00 ; -100.00		4 (3/1)	-84.03 (13.10)	-82.50	-100.00 ; -94.57	-100.00 ; -100.00	
Week 11	23 (22/1)	-48.53 (61.08)	-64.49	-100.00 ; -15.12	-100.00 ; -100.00		24 (21/3)	-46.90 (68.16)	-50.17	-100.00 ; -31.94	-100.00 ; -100.00		21 (20/1)	-45.78 (130.13)	-100.00	-100.00 ; -34.86	-100.00 ; -100.00		21 (21/0)	-82.44 (32.63)	-96.61	-100.00 ; -80.65	-100.00 ; -100.00		4 (3/1)	-84.03 (13.10)	-82.50	-100.00 ; -94.57	-100.00 ; -100.00	
Week 11	23 (22/1)	-48.53 (61.08)	-64.49	-100.00 ; -15.12	-100.00 ; -100.00		24 (21/3)	-46.90 (68.16)	-50.17	-100.00 ; -31.94	-100.00 ; -100.00		21 (20/1)	-45.78 (130.13)	-100.00	-100.00 ; -34.86	-100.00 ; -100.00		21 (21/0)	-82.44 (32.63)	-96.61	-100.00 ; -80.65	-100.00 ; -100.00		4 (3/1)	-84.03 (13.10)	-82.50	-100.00 ; -94.57	-100.00 ; -100.00	
Week 11	23 (22/1)	-48.53 (61.08)	-64.49	-100.00 ; -15.12	-100.00 ; -100.00		24 (21/3)	-46.90 (68.16)	-50.17	-100.00 ; -31.94	-100.00 ; -100.00		21 (20/1)	-45.78 (130.13)	-100.00	-100.00 ; -34.86	-100.00 ; -100.00		21 (21/0)	-82.44 (32.63)	-96.61	-100.00 ; -80.65	-100.00 ; -100.00		4 (3/1)	-84.03 (13.10)	-82.50	-100.00 ; -94.57	-100.00 ; -100.00	
Week 11	23 (22/1)	-48.53 (61.08)	-64.49	-100.00 ; -15.12	-100.00 ; -100.00		24 (21/3)	-46.90 (68.16)	-50.17	-100.00 ; -31.94	-100.00 ; -100.00		21 (20/1)	-45.78 (130.13)	-100.00	-100.00 ; -34.86	-100.00 ; -100.00		21 (21/0)	-82.44 (32.63)	-96.61	-100.00 ; -80.65	-100.00 ; -100.00		4 (3/1)	-84.03 (13.10)	-82.50	-100.00 ; -94.57	-100.00 ; -100.00	
Week 11	23 (22/1)	-48.53 (61.08)	-64.49	-100.00 ; -15.12	-100.00 ; -100.00		24 (21/3)	-46.90 (68.16)	-50.17	-100.00 ; -31.94	-100.00 ; -100.00		21 (20/1)	-45.78 (130.13)	-100.00	-100.00 ; -34.86	-100.00 ; -100.00		21 (21/0)	-82.44 (32.63)	-96.61	-100.00 ; -80.65	-100.00 ; -100.00		4 (3/1)	-84.03 (13.10)	-82.50	-100.00 ; -94.57	-100.00 ; -100.00	
Week 11	23 (22/1)	-48.53 (61.08)	-64.49	-100.00 ; -15.12	-100.00 ; -100.00		24 (21/3)	-46.90 (68.16)	-50.17	-100.00 ; -31.94	-100.00 ; -100.00		21 (20/1)	-45.78 (130.13)	-100.00	-100.00 ; -34.86	-100.00 ; -100.00		21 (21/0)	-82.44 (32.63)	-96.61	-100.00 ; -80.65	-100.00 ; -100.00		4 (3/1)	-84.03 (13.10)	-82.50	-100.00 ; -94.57	-100.00 ; -100.00	
Week 11	23 (22/1)	-48.53 (61.08)	-64.49	-100.00 ; -15.12	-100.00 ; -100.00		24 (21/3)	-46.90 (68.16)	-50.17	-100.00 ; -31.94	-100.00 ; -100.00		21 (20/1)	-45.78 (130.13)	-100.00	-100.00 ; -34.86	-100.00 ; -100.00		21 (21/0)	-82.44 (32.63)	-96.61	-100.00 ; -80.65	-100.00 ; -100.00		4 (3/1)	-84.03 (13.10)	-82.50	-100.00 ; -94.57	-100.00 ; -100.00	
Week 11	23 (22/1)	-48.53 (61.08)	-64.49	-100.00 ; -15.12	-100.00 ; -100.00		24 (21/3)	-46.90 (68.16)	-50.17	-100.00 ; -31.94	-100.00																			

AAS7	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
	Number (observed/imputed)	22 (21/1)	21 (18/3)	20 (18/2)	20 (19/1)	3 (2/1)	1 (1/0)	2 (1/1)
	Mean (SD)	-36.77 (31.45)	-29.03 (28.74)	-35.73 (26.59)	-37.55 (25.86)	-71.67 (34.96)	-63.00 (NC)	-39.50 (3.54)
	Median	-40.00	-28.00	-37.00	-31.00	-85.00	-63.00	-39.50
	Q1 ; Q3	-59.00 ; -8.00	-56.00 ; -8.00	-49.60 ; -15.00	-57.00 ; -16.00	-98.00 ; -32.00	-63.00 ; -63.00	-42.00 ; -37.00
	Min ; Max	-91.0 ; 11.8	-75.0 ; 42.8	-92.0 ; 7.0	-91.0 ; -3.0	-98.0 ; -32.0	-63.0 ; -63.0	-42.0 ; -37.0
Percent change from baseline	Number (observed/imputed)	22 (21/1)	21 (18/3)	20 (18/2)	20 (19/1)	3 (2/1)	1 (1/0)	2 (2/0)
	Mean (SD)	-56.70 (50.79)	-48.34 (71.54)	-76.62 (36.34)	-82.72 (30.20)	-87.83 (14.97)	-92.65 (NC)	-100.00 (0.00)
	Median	-68.13	-59.34	-100.00	-100.00	-92.39	-92.65	-100.00
	Q1 ; Q3	-100.00 ; -32.79	-100.00 ; -25.12	-100.00 ; -62.99	-100.00 ; -66.28	-100.00 ; -71.11	-92.65 ; -92.65	-100.00 ; -100.00
	Min ; Max	-100.0 ; 64.7	-100.0 ; 225.4	-100.0 ; 30.4	-100.0 ; -7.7	-100.0 ; -71.1	-92.6 ; -92.6	-100.0 ; -100.0
End of Study	Number (observed/imputed)	4 (2/2)	4 (1/3)	3 (1/2)	4 (3/1)	0 (0/0)	0 (0/0)	0 (0/0)
	Mean (SD)	33.50 (31.96)	17.46 (29.82)	27.33 (24.01)	26.75 (33.68)			30.42 (14.73)
	Median	28.50	4.00	37.00	16.00			30.42
	Q1 ; Q3	14.00 ; 53.00	0.00 ; 34.92	0.00 ; 45.00	4.00 ; 49.50			20.00 ; 40.83
	Min ; Max	0.0 ; 77.0	0.0 ; 61.8	0.0 ; 45.0	0.0 ; 75.0			20.0 ; 40.8
Change from baseline	Number (observed/imputed)	4 (2/2)	4 (1/3)	3 (1/2)	4 (3/1)	0 (0/0)	0 (0/0)	2 (0/2)
	Mean (SD)	-23.75 (27.40)	-4.04 (35.07)	-38.33 (25.03)	-21.25 (14.29)			1.50 (2.12)
	Median	-22.00	-8.50	-37.00	-27.00			1.50
	Q1 ; Q3	-44.00 ; -3.50	-26.50 ; 18.42	-64.00 ; -14.00	-29.00 ; -13.50			0.00 ; 3.00
	Min ; Max	-58.0 ; 7.0	-42.0 ; 42.8	-64.0 ; -14.0	-31.0 ; 0.0			0.0 ; 3.0
Percent change from baseline	Number (observed/imputed)	4 (2/2)	4 (1/3)	3 (1/2)	4 (3/1)	0 (0/0)	0 (0/0)	2 (0/2)
	Mean (SD)	-37.75 (58.01)	-14.64 (160.23)	-57.91 (38.75)	-58.11 (43.26)			8.82 (12.48)
	Median	-41.41	-92.00	-50.00	-66.21			8.82
	Q1 ; Q3	-83.72 ; 8.22	-100.00 ; 70.72	-100.00 ; -23.73	-89.74 ; -26.47			0.00 ; 17.65
	Min ; Max	-100.0 ; 31.8	-100.0 ; 225.4	-100.0 ; -23.7	-100.0 ; 0.0			0.0 ; 17.6

Table 41. Change and Percent Change from Baseline in AAS7 over Time up to Week 12 in Participants with Angioedema at Baseline (ITT Population)

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo		% Change difference for rilzabrutinib vs. placebo ^a		
					LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Week 1									
Rilzabrutinib 400mg TID (N=41)	26	45.99 (22.33)	17.50 (22.29)	-29.55 (4.16)	-15.05 (-28.44, - 1.67)	0.0085	-54.51 (9.77)	-34.55 (-66.00, - 3.09)	0.0101
Rilzabrutinib 400mg BID (N=41)	28	46.08 (25.73)	23.35 (30.86)	-24.34 (4.19)	-9.84 (-22.84, 3.16)	0.0737	-60.34 (9.85)	-40.37 (-70.92, - 9.83)	0.0021
Rilzabrutinib 400mg QPM (N=38)	28	54.00 (25.23)	34.57 (21.50)	-19.68 (3.99)	-5.18 (-18.04, 7.67)	0.3380	-32.14 (9.37)	-12.18 (-42.38, 18.02)	0.3380
Placebo (N=40)	30	59.70 (27.08)	42.73 (29.16)	-14.50 (4.14)			-19.96 (9.73)		
Week 2									
Rilzabrutinib 400mg TID (N=41)	26	45.99 (22.33)	15.52 (20.15)	-32.35 (4.37)	-11.45 (-23.02, 0.12)	0.0524	-60.12 (12.38)	-18.75 (-51.54, 14.04)	0.2625
Rilzabrutinib 400mg BID (N=41)	27	46.08 (25.73)	22.75 (28.74)	-26.86 (4.43)	-5.96 (-17.22, 5.30)	0.2996	-49.52 (12.60)	-8.15 (-40.12, 23.82)	0.6173
Rilzabrutinib 400mg QPM (N=38)	28	54.00 (25.23)	32.95 (23.02)	-21.54 (4.19)	-0.63 (-11.74, 10.48)	0.9109	-37.11 (11.87)	4.26 (-27.23, 35.76)	0.7908
Placebo (N=40)	29	59.70 (27.08)	35.80 (30.53)	-20.90 (4.36)			-41.37 (12.36)		
Week 3									
Rilzabrutinib 400mg TID (N=41)	26	45.99 (22.33)	13.26 (21.30)	-36.15 (4.48)	-12.00 (-23.87, - 0.13)	0.0476	-73.45 (15.58)	-24.93 (-66.27, 16.41)	0.2373
Rilzabrutinib 400mg BID (N=41)	28	46.08 (25.73)	14.81 (20.54)	-35.57 (4.51)	-11.42 (-22.95, 0.12)	0.0524	-55.85 (15.71)	-7.33 (-47.50, 32.83)	0.7205
Rilzabrutinib 400mg QPM (N=38)	28	54.00 (25.23)	32.48 (20.51)	-21.82 (4.29)	2.33 (-9.09, 13.74)	0.6895	-33.35 (14.94)	15.17 (-24.59, 54.94)	0.4545
Placebo (N=40)	29	59.70 (27.08)	31.90 (31.01)	-24.15 (4.48)			-48.52 (15.62)		
Week 4									
Rilzabrutinib 400mg TID (N=41)	26	45.99 (22.33)	11.20 (15.95)	-38.27 (4.30)	-15.67 (-27.11, - 4.22)	0.0073	-78.35 (13.78)	-41.77 (-78.55, - 4.98)	0.0260
Rilzabrutinib 400mg BID (N=41)	27	46.08 (25.73)	13.70 (17.64)	-35.34 (4.34)	-12.73 (-23.88, - 1.58)	0.0252	-60.60 (13.93)	-24.02 (-59.85, 11.81)	0.1889
Rilzabrutinib 400mg QPM (N=38)	28	54.00 (25.23)	29.42 (20.30)	-25.28 (4.12)	-2.68 (-13.70, 8.35)	0.6344	-49.47 (13.21)	-12.88 (-48.34, 22.58)	0.4765
Placebo (N=40)	28	59.70 (27.08)	33.19 (34.22)	-22.60 (4.34)			-36.59 (13.98)		

					Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
					Change from baseline	LS Mean	p-value ^a	% Change from baseline	LS Mean	p-value ^a
					LS Mean (SE) ^a	(95% CI) ^a		LS Mean (SE) ^a	(95% CI) ^a	
Week 5										
Rilzabrutinib 400mg TID	26	45.99 (22.33)	11.12 (14.82)	-38.91 (4.22)	-9.32 (-20.56, 1.93)	0.1043	-69.87 (9.90)	-16.05 (-42.45, 10.36)	0.2337	
(N=41)										
Rilzabrutinib 400mg BID	27	46.08 (25.73)	12.95 (20.09)	-36.13 (4.29)	-6.53 (-17.51, 4.44)	0.2432	-68.19 (10.08)	-14.36 (-40.13, 11.41)	0.2747	
(N=41)										
Rilzabrutinib 400mg QPM	27	54.00 (25.23)	25.01 (22.48)	-28.04 (4.08)	1.56 (-9.31, 12.42)	0.7787	-54.71 (9.56)	-0.88 (-26.37, 24.61)	0.9461	
(N=38)										
Placebo (N=40)	27	59.70 (27.08)	22.68 (25.39)	-29.59 (4.26)			-53.83 (10.03)			
Week 6										
Rilzabrutinib 400mg TID	24	45.99 (22.33)	12.73 (19.47)	-38.03 (4.48)	-11.42 (-23.52, 0.68)	0.0644	-64.66 (10.25)	-17.35 (-45.04, 10.34)	0.2194	
(N=41)										
Rilzabrutinib 400mg BID	27	46.08 (25.73)	12.28 (18.70)	-36.76 (4.50)	-10.15 (-21.84, 1.54)	0.0887	-70.86 (10.33)	-23.55 (-50.40, 3.31)	0.0857	
(N=41)										
Rilzabrutinib 400mg QPM	25	54.00 (25.23)	27.97 (22.56)	-25.61 (4.32)	1.00 (-10.55, 12.54)	0.8656	-46.12 (9.92)	1.19 (-25.36, 27.75)	0.9297	
(N=38)										
Placebo (N=40)	26	59.70 (27.08)	26.41 (26.26)	-26.61 (4.62)			-47.31 (10.61)			
Week 7										
Rilzabrutinib 400mg TID	23	45.99 (22.33)	12.07 (15.62)	-37.16 (4.45)	-9.86 (-21.60, 1.88)	0.0996	-68.52 (11.69)	-22.57 (-53.40, 8.26)	0.1513	
(N=41)										
Rilzabrutinib 400mg BID	27	46.08 (25.73)	13.39 (19.19)	-37.72 (4.37)	-10.42 (-21.71, 0.87)	0.0705	-71.37 (11.45)	-25.42 (-54.97, 4.13)	0.0918	
(N=41)										
Rilzabrutinib 400mg QPM	24	54.00 (25.23)	31.05 (21.43)	-22.95 (4.29)	4.35 (-7.06, 15.76)	0.4545	-29.64 (11.30)	16.32 (-13.52, 46.16)	0.2838	
(N=38)										
Placebo (N=40)	27	59.70 (27.08)	24.84 (26.78)	-27.30 (4.43)			-45.95 (11.59)			
Week 8										
Rilzabrutinib 400mg TID	22	45.99 (22.33)	11.17 (12.56)	-39.35 (4.28)	-11.02 (-22.54, 0.50)	0.0608	-74.30 (11.67)	-22.25 (-53.63, 9.12)	0.1645	
(N=41)										
Rilzabrutinib 400mg BID	26	46.08 (25.73)	9.20 (16.24)	-41.63 (4.21)	-13.31 (-24.25, -2.37)	0.0171	-81.40 (11.62)	-29.34 (-59.45, 0.76)	0.0560	
(N=41)										
Rilzabrutinib 400mg QPM	24	54.00 (25.23)	24.69 (22.82)	-30.07 (4.07)	-1.74 (-12.55, 9.06)	0.7517	-54.56 (11.16)	-2.51 (-32.23, 27.22)	0.8687	
(N=38)										
Placebo (N=40)	27	59.70 (27.08)	25.86 (25.97)	-28.33 (4.29)			-52.05 (11.75)			

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
					LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	
Rilzabrutinib 400mg TID (N=41)	23	45.99 (22.33)	7.98 (11.59)	-42.57 (4.09)	-13.12 (-23.93, - 2.31)	0.0174	-84.57 (11.49)	-34.54 (-64.85, - 4.23)	0.0255	
Rilzabrutinib 400mg BID (N=41)	25	46.08 (25.73)	10.00 (17.78)	-40.70 (4.08)	-11.25 (-21.79, - 0.72)	0.0363	-76.91 (11.50)	-26.88 (-56.35, - 2.58)	0.0738	
Rilzabrutinib 400mg QPM (N=38)	25	54.00 (25.23)	27.24 (21.46)	-26.47 (3.93)	2.98 (-7.44, 13.40)	0.5753	-48.50 (10.95)	1.53 (-27.52, 30.59)	0.9177	
Placebo (N=40)	26	59.70 (27.08)	24.79 (23.80)	-29.45 (4.07)			-50.03 (11.36)			
Week 10										
Rilzabrutinib 400mg TID (N=41)	24	45.99 (22.33)	7.10 (9.58)	-43.40 (4.49)	-13.07 (-24.96, - 1.18)	0.0313	-87.33 (15.54)	-38.35 (-79.56, - 2.86)	0.0682	
Rilzabrutinib 400mg BID (N=41)	23	46.08 (25.73)	12.72 (19.89)	-39.12 (4.47)	-8.79 (-20.40, 2.82)	0.1378	-64.07 (15.65)	-15.09 (-55.38, - 25.21)	0.4631	
Rilzabrutinib 400mg QPM (N=38)	25	54.00 (25.23)	26.59 (23.15)	-27.81 (4.28)	2.53 (-8.76, 13.81)	0.6608	-50.13 (14.94)	-1.14 (-41.08, - 38.79)	0.9553	
Placebo (N=40)	27	59.70 (27.08)	23.41 (26.52)	-30.33 (4.43)			-48.99 (15.58)			
Week 11										
Rilzabrutinib 400mg TID (N=41)	24	45.99 (22.33)	9.40 (13.36)	-40.74 (4.34)	-6.88 (-18.42, 4.67)	0.2430	-76.91 (10.59)	-15.53 (-43.68, - 12.62)	0.2796	
Rilzabrutinib 400mg BID (N=41)	23	46.08 (25.73)	10.31 (18.47)	-42.03 (4.41)	-8.17 (-19.55, 3.20)	0.1591	-84.81 (10.85)	-23.43 (-51.36, - 4.50)	0.1002	
Rilzabrutinib 400mg QPM (N=38)	25	54.00 (25.23)	26.34 (24.19)	-28.68 (4.16)	5.18 (-6.05, 16.41)	0.3656	-53.78 (10.24)	7.61 (-19.90, 35.12)	0.5877	
Placebo (N=40)	27	59.70 (27.08)	19.70 (24.82)	-33.86 (4.39)			-61.39 (10.72)			
Week 12										
Rilzabrutinib 400mg TID (N=41)	22	45.99 (22.33)	7.37 (12.64)	-43.36 (4.14)	-8.06 (-19.05, 2.94)	0.1511	-82.82 (10.03)	-19.84 (-46.44, - 6.76)	0.1438	
Rilzabrutinib 400mg BID (N=41)	22	46.08 (25.73)	10.67 (17.53)	-42.38 (4.13)	-7.07 (-17.69, 3.54)	0.1916	-87.51 (10.12)	-24.53 (-50.33, - 1.27)	0.0624	
Rilzabrutinib 400mg QPM (N=38)	22	54.00 (25.23)	24.92 (22.92)	-28.63 (4.01)	6.68 (-4.00, 17.35)	0.2200	-54.80 (9.75)	8.18 (-17.80, 34.16)	0.5371	
Placebo (N=40)	25	59.70 (27.08)	20.12 (23.69)	-35.31 (4.14)			-62.98 (10.04)			

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

Table 42. Change and Percent Change from Baseline in AAS7 over Time up to Week 12 in Participants with Angioedema at Baseline (Omalizumab-Naïve Population)

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo		% Change difference for rilzabrutinib vs. placebo		
					LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Week 1									
Rilzabrutinib 400mg TID (N=35)	23	47.91 (22.78)	18.96 (23.24)	-29.80 (4.48)	-16.03 (-30.69, -1.38)	0.0105	-53.40 (10.59)	-36.35 (-71.01, -1.69)	0.0140
Rilzabrutinib 400mg BID (N=35)	26	46.58 (26.66)	25.15 (31.33)	-23.46 (4.42)	-9.69 (-23.74, 4.37)	0.1032	-59.22 (10.46)	-42.17 (-75.41, -8.93)	0.0032
Rilzabrutinib 400mg QPM (N=37)	27	53.48 (25.55)	34.85 (21.86)	-19.33 (4.16)	-5.57 (-19.34, 8.21)	0.3371	-31.74 (9.84)	-14.70 (-47.27, 17.88)	0.2843
Placebo (N=36)	26	58.73 (26.52)	43.46 (28.75)	-13.77 (4.48)			-17.04 (10.60)		
Week 2									
Rilzabrutinib 400mg TID (N=35)	23	47.91 (22.78)	17.03 (20.90)	-32.47 (4.53)	-13.79 (-25.99, -1.60)	0.0266	-59.25 (13.33)	-22.03 (-57.92, 13.85)	0.2288
Rilzabrutinib 400mg BID (N=35)	25	46.58 (26.66)	24.57 (29.12)	-26.11 (4.50)	-7.43 (-19.15, 4.29)	0.2138	-46.69 (13.31)	-9.47 (-44.02, 25.08)	0.5912
Rilzabrutinib 400mg QPM (N=37)	27	53.48 (25.55)	33.25 (23.40)	-21.21 (4.21)	-2.53 (-13.99, 8.94)	0.6656	-36.33 (12.38)	0.88 (-32.86, 34.63)	0.9590
Placebo (N=36)	25	58.73 (26.52)	38.14 (29.33)	-18.68 (4.55)			-37.22 (13.40)		
Week 3									
Rilzabrutinib 400mg TID (N=35)	23	47.91 (22.78)	14.08 (22.48)	-36.16 (4.71)	-13.01 (-25.71, -0.30)	0.0449	-72.78 (16.93)	-25.10 (-70.77, 20.57)	0.2814
Rilzabrutinib 400mg BID (N=35)	26	46.58 (26.66)	15.95 (20.90)	-35.08 (4.66)	-11.92 (-24.12, 0.27)	0.0553	-52.68 (16.72)	-5.01 (-48.85, 38.83)	0.8229
Rilzabrutinib 400mg QPM (N=37)	27	53.48 (25.55)	32.60 (20.89)	-21.85 (4.38)	1.31 (-10.66, 13.27)	0.8306	-33.23 (15.73)	14.44 (-28.58, 57.46)	0.5105
Placebo (N=36)	25	58.73 (26.52)	33.14 (30.73)	-23.16 (4.75)			-47.68 (17.09)		
Week 4									
Rilzabrutinib 400mg TID (N=35)	23	47.91 (22.78)	11.73 (16.82)	-38.89 (4.51)	-19.05 (-31.29, -6.81)	0.0023	-79.54 (14.89)	-49.61 (-90.06, -9.16)	0.0162
Rilzabrutinib 400mg BID (N=35)	25	46.58 (26.66)	14.79 (17.89)	-34.90 (4.47)	-15.05 (-26.84, -3.27)	0.0123	-58.12 (14.75)	-28.19 (-67.14, 10.77)	0.1561

				Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Rilzabrutinib 400mg QPM (N=37)	27	53.48 (25.55)	29.55 (20.68)	-25.16 (4.19)	-5.31 (-16.86, 6.24)	0.3674	-49.19 (13.84)	-19.26 (-57.48, 18.97)	0.3234
Placebo (N=36)	24	58.73 (26.52)	36.02 (34.33)	-19.84 (4.60)			-29.93 (15.25)		
Week 5									
Rilzabrutinib 400mg TID (N=35)	23	47.91 (22.78)	10.83 (15.39)	-39.59 (4.46)	-8.94 (-21.03, 3.15)	0.1474	-72.25 (10.51)	-17.62 (-46.15, 10.90)	0.2259
Rilzabrutinib 400mg BID (N=35)	25	46.58 (26.66)	13.98 (20.55)	-35.28 (4.45)	-4.63 (-16.28, 7.02)	0.4358	-65.60 (10.49)	-10.97 (-38.45, 16.50)	0.4339
Rilzabrutinib 400mg QPM (N=37)	26	53.48 (25.55)	24.55 (22.80)	-28.57 (4.18)	2.08 (-9.37, 13.52)	0.7221	-55.66 (9.83)	-1.04 (-28.01, 25.93)	0.9399
Placebo (N=36)	23	58.73 (26.52)	21.08 (24.61)	-30.65 (4.54)			-54.63 (10.73)		
Week 6									
Rilzabrutinib 400mg TID (N=35)	21	47.91 (22.78)	13.55 (20.58)	-38.09 (4.88)	-10.77 (-24.18, 2.64)	0.1154	-64.16 (11.13)	-15.46 (-46.06, 15.15)	0.3222
Rilzabrutinib 400mg BID (N=35)	25	46.58 (26.66)	13.26 (19.12)	-36.17 (4.80)	-8.84 (-21.64, 3.95)	0.1753	-69.32 (10.99)	-20.62 (-49.95, 8.72)	0.1683
Rilzabrutinib 400mg QPM (N=37)	24	53.48 (25.55)	28.26 (23.00)	-25.45 (4.55)	1.87 (-10.66, 14.40)	0.7699	-46.08 (10.42)	2.62 (-26.14, 31.38)	0.8582
Placebo (N=36)	22	58.73 (26.52)	25.43 (27.48)	-27.32 (5.07)			-48.70 (11.62)		
Week 7									
Rilzabrutinib 400mg TID (N=35)	20	47.91 (22.78)	12.43 (15.87)	-37.68 (4.70)	-8.96 (-21.57, 3.65)	0.1636	-67.11 (12.58)	-20.11 (-53.85, 13.63)	0.2427
Rilzabrutinib 400mg BID (N=35)	25	46.58 (26.66)	14.38 (19.63)	-37.12 (4.53)	-8.40 (-20.39, 3.59)	0.1698	-70.13 (12.07)	-23.13 (-55.14, 8.88)	0.1567
Rilzabrutinib 400mg QPM (N=37)	23	53.48 (25.55)	31.88 (21.51)	-22.00 (4.38)	6.71 (-5.27, 18.69)	0.2720	-27.39 (11.77)	19.61 (-12.44, 51.65)	0.2304
Placebo (N=36)	23	58.73 (26.52)	22.56 (25.96)	-28.72 (4.72)			-47.00 (12.61)		
Week 8									
Rilzabrutinib 400mg TID (N=35)	19	47.91 (22.78)	12.20 (13.05)	-39.04 (4.68)	-11.12 (-23.92, 1.69)	0.0888	-73.05 (12.72)	-23.05 (-57.86, 11.76)	0.1943
Rilzabrutinib 400mg BID (N=35)	24	46.58 (26.66)	9.97 (16.69)	-41.30 (4.49)	-13.38 (-25.33, -1.44)	0.0281	-80.38 (12.36)	-30.39 (-63.25, 2.47)	0.0699

				Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Rilzabrutinib 400mg QPM (N=37)	23	53.48 (25.55)	24.98 (23.29)	-29.76 (4.29)	-1.84 (-13.56, 9.89)	0.7587	-54.13 (11.75)	-4.14 (-36.36, 28.09)	0.8014
Placebo (N=36)	23	58.73 (26.52)	25.96 (27.00)	-27.92 (4.70)			-50.00 (12.91)		
Week 9									
Rilzabrutinib 400mg TID (N=35)	20	47.91 (22.78)	8.52 (12.19)	-42.94 (4.44)	-15.14 (-27.06, -3.23)	0.0127	-84.73 (12.57)	-37.56 (-71.28, -3.83)	0.0291
Rilzabrutinib 400mg BID (N=35)	23	46.58 (26.66)	10.87 (18.30)	-40.15 (4.33)	-12.36 (-23.79, -0.92)	0.0342	-74.80 (12.27)	-27.62 (-59.82, 4.58)	0.0927
Rilzabrutinib 400mg QPM (N=37)	24	53.48 (25.55)	27.96 (21.62)	-25.79 (4.12)	2.00 (-9.20, 13.21)	0.7262	-47.25 (11.58)	-0.07 (-31.59, 31.45)	0.9964
Placebo (N=36)	22	58.73 (26.52)	26.38 (25.55)	-27.79 (4.43)			-47.18 (12.47)		
Week 10									
Rilzabrutinib 400mg TID (N=35)	21	47.91 (22.78)	6.83 (9.73)	-44.63 (4.75)	-17.05 (-29.81, -4.29)	0.0088	-89.99 (16.85)	-46.10 (-91.54, -0.67)	0.0467
Rilzabrutinib 400mg BID (N=35)	21	46.58 (26.66)	13.93 (20.43)	-38.01 (4.62)	-10.43 (-22.69, 1.83)	0.0953	-60.11 (16.65)	-16.22 (-60.13, 27.69)	0.4690
Rilzabrutinib 400mg QPM (N=37)	24	53.48 (25.55)	27.70 (22.96)	-26.74 (4.35)	0.84 (-10.97, 12.66)	0.8887	-48.11 (15.70)	-4.23 (-47.40, 38.95)	0.8478
Placebo (N=36)	23	58.73 (26.52)	26.17 (27.80)	-27.58 (4.71)			-43.89 (17.02)		
Week 11									
Rilzabrutinib 400mg TID (N=35)	21	47.91 (22.78)	9.80 (13.81)	-41.34 (4.63)	-9.39 (-21.92, 3.13)	0.1414	-78.48 (11.38)	-20.16 (-50.91, 10.58)	0.1986
Rilzabrutinib 400mg BID (N=35)	21	46.58 (26.66)	11.30 (19.07)	-41.52 (4.63)	-9.58 (-21.83, 2.67)	0.1255	-83.14 (11.48)	-24.83 (-55.17, 5.52)	0.1088
Rilzabrutinib 400mg QPM (N=37)	24	53.48 (25.55)	27.44 (24.07)	-27.59 (4.31)	4.36 (-7.60, 16.33)	0.4749	-52.05 (10.68)	6.27 (-23.29, 35.83)	0.6775
Placebo (N=36)	23	58.73 (26.52)	21.57 (26.48)	-31.95 (4.74)			-58.32 (11.64)		
Week 12									
Rilzabrutinib 400mg TID (N=35)	20	47.91 (22.78)	7.10 (12.86)	-44.04 (4.42)	-10.65 (-22.56, 1.26)	0.0797	-84.63 (10.83)	-23.26 (-52.37, 5.85)	0.1173
Rilzabrutinib 400mg BID (N=35)	20	46.58 (26.66)	11.73 (18.07)	-41.53 (4.39)	-8.14 (-19.74, 3.45)	0.1685	-86.30 (10.67)	-24.94 (-53.17, 3.29)	0.0834

		Change difference for rilzabrutinib vs. placebo			% Change difference for rilzabrutinib vs. placebo		
		LS Mean (95% CI) ^a	Change from baseline LS Mean (SE) ^a	p-value ^a	LS Mean (95% CI) ^a	% Change from baseline LS Mean (SE) ^a	p-value ^a
n	Baseline Mean (SD)	Post-baseline Mean (SD)					
Rilzabrutinib 400mg QPM (N=37)	53.48 (25.55)	25.87 (23.04)	-26.98 (4.16)	6.41 (-5.00, 17.81)	0.2708	-52.66 (10.25)	8.71 (-19.46, 36.88)
Placebo (N=36)	58.73 (26.52)	21.96 (24.66)	-33.39 (4.44)			-61.36 (10.86)	0.5444

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

[00256] A substantial percentage of patients receiving 400 mg BID or TID rilzabrutinib achieved angioedema scores of 0 (see **Figures 33-34** and **Tables 43-44**. Notably, in the omalizumab-naïve population, 42.3% of patients in the 400 mg BID arm and 30.4% of patients in the 400 mg TID arm achieved scores of 0 within one week of initiating treatment. Further, at Week 12, 42.3% of omalizumab-naïve patients in the 400 mg BID arm and 60.9% of omalizumab-naïve patients in the 400 mg TID arm had scores of 0, indicating that the improvements were sustained over the course of the study.

Table 43. Proportion of Participants with AAS7 =0 over Time up to Week 12 (Participants with Angioedema at Baseline in Omalizumab-Naïve Population)

	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b
Baseline						
Rilzabrutinib 400mg TID (N=23)	0	23 (100)	0			
Rilzabrutinib 400mg BID (N=26)	0	26 (100)	0			
Rilzabrutinib 400mg QPM (N=27)	0	27 (100)	0			
Placebo (N=26)	0	26 (100)	0			
Week 1						
Rilzabrutinib 400mg TID (N=23)	7 (30.4)	16 (69.6)	0	21.8 (1.41, 42.21)	9.250 (0.901, 94.977)	0.0399
Rilzabrutinib 400mg BID (N=26)	11 (42.3)	15 (57.7)	0	35.1 (14.62, 55.52)	20.850 (2.026, 214.582)	0.0019
Rilzabrutinib 400mg QPM (N=27)	3 (11.1)	24 (88.9)	0	9.1 (-5.96, 24.23)	3.545 (0.387, 32.487)	0.2210
Placebo (N=26)	1 (3.8)	25 (96.2)	0			
Week 2						
Rilzabrutinib 400mg TID (N=23)	9 (39.1)	14 (60.9)	0	12.9 (-13.45, 39.17)	1.922 (0.506, 7.307)	0.3449
Rilzabrutinib 400mg BID (N=26)	9 (34.6)	17 (65.4)	1 (3.8)	14.6 (-10.55, 39.70)	2.012 (0.587, 6.895)	0.2526
Rilzabrutinib 400mg QPM (N=27)	3 (11.1)	24 (88.9)	0	-9.2 (-29.54, 11.20)	0.514 (0.114, 2.332)	0.3750
Placebo (N=26)	5 (19.2)	21 (80.8)	1 (3.8)			
Week 3						
Rilzabrutinib 400mg TID (N=23)	12 (52.2)	11 (47.8)	0	22.5 (-4.30, 49.32)	3.063 (0.815, 11.508)	0.0959
Rilzabrutinib 400mg BID (N=26)	11 (42.3)	15 (57.7)	0	20.8 (-4.36, 45.88)	2.703 (0.776, 9.417)	0.1107
Rilzabrutinib 400mg QPM (N=27)	4 (14.8)	23 (85.2)	0	-5.0 (-25.05, 14.97)	0.686 (0.153, 3.070)	0.6344
Placebo (N=26)	5 (19.2)	21 (80.8)	1 (3.8)			
Week 4						

	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b
Rilzabrutinib 400mg TID (N=23)	9 (39.1)	14 (60.9)	0	7.3 (-17.51, 32.12)	1.519 (0.372, 6.200)	0.5701
Rilzabrutinib 400mg BID (N=26)	11 (42.3)	15 (57.7)	1 (3.8)	16.8 (-9.25, 42.82)	2.118 (0.633, 7.081)	0.2174
Rilzabrutinib 400mg QPM (N=27)	6 (22.2)	21 (77.8)	1 (3.7)	-2.4 (-24.90, 20.12)	0.869 (0.230, 3.275)	0.8394
Placebo (N=26)	6 (23.1)	20 (76.9)	2 (7.7)			
Week 5						
Rilzabrutinib 400mg TID (N=23)	10 (43.5)	13 (56.5)	0	9.8 (-18.19, 37.86)	1.550 (0.448, 5.366)	0.4959
Rilzabrutinib 400mg BID (N=26)	13 (50.0)	13 (50.0)	2 (7.7)	22.3 (-5.17, 49.87)	2.390 (0.769, 7.427)	0.1186
Rilzabrutinib 400mg QPM (N=27)	8 (29.6)	19 (70.4)	2 (7.4)	1.6 (-23.44, 26.63)	1.079 (0.327, 3.558)	0.9006
Placebo (N=26)	7 (26.9)	19 (73.1)	3 (11.5)			
Week 6						
Rilzabrutinib 400mg TID (N=23)	11 (47.8)	12 (52.2)	2 (8.7)	13.5 (-13.95, 41.01)	1.874 (0.528, 6.650)	0.3486
Rilzabrutinib 400mg BID (N=26)	11 (42.3)	15 (57.7)	2 (7.7)	13.6 (-12.56, 39.77)	1.828 (0.565, 5.910)	0.3156
Rilzabrutinib 400mg QPM (N=27)	4 (14.8)	23 (85.2)	4 (14.8)	-13.0 (-34.72, 8.69)	0.437 (0.106, 1.796)	0.2620
Placebo (N=26)	7 (26.9)	19 (73.1)	5 (19.2)			
Week 7						
Rilzabrutinib 400mg TID (N=23)	10 (43.5)	13 (56.5)	3 (13.0)	7.2 (-21.57, 35.92)	1.351 (0.407, 4.489)	0.6220
Rilzabrutinib 400mg BID (N=26)	11 (42.3)	15 (57.7)	2 (7.7)	10.5 (-17.21, 38.23)	1.515 (0.499, 4.599)	0.4586
Rilzabrutinib 400mg QPM (N=27)	3 (11.1)	24 (88.9)	6 (22.2)	-23.0 (-43.69, -2.37)	0.200 (0.039, 1.034)	0.0441
Placebo (N=26)	8 (30.8)	18 (69.2)	4 (15.4)			
Week 8						
Rilzabrutinib 400mg TID (N=23)	6 (26.1)	17 (73.9)	4 (17.4)	-6.2 (-29.94, 17.56)	0.690 (0.160, 2.969)	0.6203
Rilzabrutinib 400mg BID (N=26)	13 (50.0)	13 (50.0)	3 (11.5)	26.4 (-0.77, 53.60)	2.829 (0.886, 9.031)	0.0626
Rilzabrutinib 400mg QPM (N=27)	7 (25.9)	20 (74.1)	7 (25.9)	-1.3 (-24.15, 21.56)	0.929 (0.251, 3.430)	0.9119
Placebo (N=26)	6 (23.1)	20 (76.9)	4 (15.4)			
Week 9						
Rilzabrutinib 400mg TID (N=23)	10 (43.5)	13 (56.5)	3 (13.0)	6.9 (-21.07, 34.92)	1.358 (0.394, 4.681)	0.6178
Rilzabrutinib 400mg BID (N=26)	12 (46.2)	14 (53.8)	4 (15.4)	14.5 (-12.95, 41.93)	1.787 (0.578, 5.519)	0.3088
Rilzabrutinib 400mg QPM (N=27)	5 (18.5)	22 (81.5)	6 (22.2)	-15.5 (-38.66, 7.74)	0.431 (0.116, 1.602)	0.2062
Placebo (N=26)	8 (30.8)	18 (69.2)	5 (19.2)			
Week 10						

	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b
Rilzabrutinib 400mg TID (N=23)	10 (43.5)	13 (56.5)	2 (8.7)	11.0 (-16.84, 38.85)	1.627 (0.465, 5.690)	0.4184
Rilzabrutinib 400mg BID (N=26)	11 (42.3)	15 (57.7)	6 (23.1)	13.1 (-13.64, 39.79)	1.734 (0.544, 5.526)	0.3524
Rilzabrutinib 400mg QPM (N=27)	7 (25.9)	20 (74.1)	6 (22.2)	-9.2 (-32.92, 14.48)	0.616 (0.174, 2.186)	0.4559
Placebo (N=26)	8 (30.8)	18 (69.2)	4 (15.4)			
Week 11						
Rilzabrutinib 400mg TID (N=23)	10 (43.5)	13 (56.5)	2 (8.7)	3.1 (-23.73, 29.88)	1.160 (0.319, 4.214)	0.8269
Rilzabrutinib 400mg BID (N=26)	13 (50.0)	13 (50.0)	6 (23.1)	17.8 (-9.70, 45.21)	2.010 (0.651, 6.204)	0.2207
Rilzabrutinib 400mg QPM (N=27)	8 (29.6)	19 (70.4)	6 (22.2)	-8.6 (-32.83, 15.69)	0.650 (0.189, 2.239)	0.5103
Placebo (N=26)	9 (34.6)	17 (65.4)	4 (15.4)			
Week 12						
Rilzabrutinib 400mg TID (N=23)	14 (60.9)	9 (39.1)	4 (17.4)	29.7 (0.65, 58.69)	3.085 (0.945, 10.074)	0.0526
Rilzabrutinib 400mg BID (N=26)	11 (42.3)	15 (57.7)	8 (30.8)	11.3 (-15.22, 37.83)	1.627 (0.513, 5.167)	0.4132
Rilzabrutinib 400mg QPM (N=27)	6 (22.2)	21 (77.8)	9 (33.3)	-11.2 (-35.56, 13.12)	0.571 (0.165, 1.976)	0.3734
Placebo (N=26)	8 (30.8)	18 (69.2)	5 (19.2)			

CMH: Cochran-Mantel Haenzel

^a OR: odds ratio; RRD: response rate difference; derived from the Mantel-Haenszel estimator**Table 44. Proportion of Participants with AAS7 =0 over Time up to Week 12 (Omalizumab-Naïve Population with Outlier Removed from Analysis)**

	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b
Baseline						
Rilzabrutinib 400mg TID (N=34)	11 (32.4)	23 (67.6)	0			
Rilzabrutinib 400mg BID (N=35)	9 (25.7)	26 (74.3)	0			
Rilzabrutinib 400mg QPM (N=37)	10 (27.0)	27 (73.0)	0			
Placebo (N=36)	10 (27.8)	26 (72.2)	0			
Week 1						
Rilzabrutinib 400mg TID (N=34)	18 (52.9)	16 (47.1)	0	21.8 (-0.83, 44.41)	2.576 (0.940, 7.060)	0.0644
Rilzabrutinib 400mg BID (N=35)	19 (54.3)	16 (45.7)	0	23.4 (1.75, 45.01)	2.944 (1.046, 8.292)	0.0408
Rilzabrutinib 400mg QPM (N=37)	13 (35.1)	24 (64.9)	0	8.1 (-13.79, 30.07)	1.428 (0.543, 3.758)	0.4649
Placebo (N=36)	10 (27.8)	26 (72.2)	0			
Week 2						

	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b
Rilzabrutinib 400mg TID (N=34)	18 (52.9)	16 (47.1)	0	10.2 (-12.61, 33.08)	1.556 (0.579, 4.185)	0.3883
Rilzabrutinib 400mg BID (N=35)	17 (48.6)	18 (51.4)	1 (2.9)	8.2 (-15.79, 32.29)	1.366 (0.549, 3.395)	0.4941
Rilzabrutinib 400mg QPM (N=37)	13 (35.1)	24 (64.9)	0	-3.3 (-26.15, 19.57)	0.875 (0.347, 2.209)	0.7761
Placebo (N=36)	14 (38.9)	22 (61.1)	1 (2.8)			
Week 3						
Rilzabrutinib 400mg TID (N=34)	22 (64.7)	12 (35.3)	0	26.5 (3.50, 49.54)	3.010 (1.126, 8.044)	0.0228
Rilzabrutinib 400mg BID (N=35)	20 (57.1)	15 (42.9)	0	21.6 (-1.62, 44.84)	2.357 (0.913, 6.082)	0.0679
Rilzabrutinib 400mg QPM (N=37)	12 (32.4)	25 (67.6)	0	0.9 (-20.42, 22.15)	1.041 (0.385, 2.817)	0.9362
Placebo (N=36)	12 (33.3)	24 (66.7)	1 (2.8)			
Week 4						
Rilzabrutinib 400mg TID (N=34)	16 (47.1)	18 (52.9)	2 (5.9)	1.1 (-21.36, 23.50)	1.049 (0.384, 2.863)	0.9267
Rilzabrutinib 400mg BID (N=35)	18 (51.4)	17 (48.6)	2 (5.7)	7.4 (-15.53, 30.33)	1.361 (0.523, 3.539)	0.5317
Rilzabrutinib 400mg QPM (N=37)	14 (37.8)	23 (62.2)	1 (2.7)	-3.0 (-24.84, 18.78)	0.874 (0.331, 2.307)	0.7907
Placebo (N=36)	15 (41.7)	21 (58.3)	2 (5.6)			
Week 5						
Rilzabrutinib 400mg TID (N=34)	20 (58.8)	14 (41.2)	1 (2.9)	7.5 (-15.98, 30.99)	1.359 (0.520, 3.550)	0.5302
Rilzabrutinib 400mg BID (N=35)	21 (60.0)	14 (40.0)	2 (5.7)	11.1 (-11.98, 34.23)	1.574 (0.610, 4.061)	0.3477
Rilzabrutinib 400mg QPM (N=37)	16 (43.2)	21 (56.8)	2 (5.4)	-3.4 (-26.11, 19.41)	0.872 (0.344, 2.211)	0.7714
Placebo (N=36)	17 (47.2)	19 (52.8)	3 (8.3)			
Week 6						
Rilzabrutinib 400mg TID (N=34)	20 (58.8)	14 (41.2)	3 (8.8)	6.5 (-16.05, 28.96)	1.334 (0.490, 3.635)	0.5811
Rilzabrutinib 400mg BID (N=35)	18 (51.4)	17 (48.6)	2 (5.7)	2.9 (-20.98, 26.81)	1.118 (0.447, 2.795)	0.8106
Rilzabrutinib 400mg QPM (N=37)	13 (35.1)	24 (64.9)	4 (10.8)	-11.4 (-33.39, 10.50)	0.606 (0.231, 1.594)	0.3192
Placebo (N=36)	17 (47.2)	19 (52.8)	5 (13.9)			
Week 7						
Rilzabrutinib 400mg TID (N=34)	19 (55.9)	15 (44.1)	4 (11.8)	6.5 (-17.94, 30.95)	1.277 (0.509, 3.205)	0.5961
Rilzabrutinib 400mg BID (N=35)	17 (48.6)	18 (51.4)	2 (5.7)	0.6 (-23.63, 24.78)	1.022 (0.414, 2.525)	0.9620
Rilzabrutinib 400mg QPM (N=37)	13 (35.1)	24 (64.9)	6 (16.2)	-11.8 (-34.27, 10.63)	0.611 (0.238, 1.570)	0.3105
Placebo (N=36)	17 (47.2)	19 (52.8)	4 (11.1)			
Week 8						

	Responder n (%)	Non- responder n (%)	Imputed non- responder n (%)	RRD (%) for rilzabrutinib vs. placebo (95% CI) ^a	OR (95% CI) for rilzabrutinib vs. placebo ^a	P-value vs. placebo ^b
Rilzabrutinib 400mg TID (N=34)	15 (44.1)	19 (55.9)	6 (17.6)	-0.9 (-24.66, 22.82)	0.964 (0.373, 2.489)	0.9387
Rilzabrutinib 400mg BID (N=35)	21 (60.0)	14 (40.0)	3 (8.6)	17.0 (-6.09, 40.01)	1.991 (0.768, 5.157)	0.1565
Rilzabrutinib 400mg QPM (N=37)	17 (45.9)	20 (54.1)	7 (18.9)	4.2 (-18.73, 27.17)	1.185 (0.471, 2.982)	0.7177
Placebo (N=36)	15 (41.7)	21 (58.3)	4 (11.1)			
Week 9						
Rilzabrutinib 400mg TID (N=34)	19 (55.9)	15 (44.1)	5 (14.7)	3.6 (-20.13, 27.35)	1.155 (0.448, 2.981)	0.7579
Rilzabrutinib 400mg BID (N=35)	17 (48.6)	18 (51.4)	7 (20.0)	-2.1 (-25.67, 21.40)	0.919 (0.363, 2.330)	0.8577
Rilzabrutinib 400mg QPM (N=37)	13 (35.1)	24 (64.9)	6 (16.2)	-15.0 (-36.92, 6.90)	0.520 (0.197, 1.373)	0.1891
Placebo (N=36)	18 (50.0)	18 (50.0)	5 (13.9)			
Week 10						
Rilzabrutinib 400mg TID (N=34)	18 (52.9)	16 (47.1)	4 (11.8)	6.0 (-18.63, 30.54)	1.247 (0.499, 3.119)	0.6201
Rilzabrutinib 400mg BID (N=35)	16 (45.7)	19 (54.3)	8 (22.9)	-1.4 (-24.86, 22.01)	0.945 (0.371, 2.404)	0.9055
Rilzabrutinib 400mg QPM (N=37)	17 (45.9)	20 (54.1)	6 (16.2)	-1.9 (-25.10, 21.27)	0.927 (0.372, 2.311)	0.8717
Placebo (N=36)	17 (47.2)	19 (52.8)	4 (11.1)			
Week 11						
Rilzabrutinib 400mg TID (N=34)	19 (55.9)	15 (44.1)	3 (8.8)	3.1 (-19.84, 26.01)	1.142 (0.427, 3.049)	0.7922
Rilzabrutinib 400mg BID (N=35)	21 (60.0)	14 (40.0)	7 (20.0)	10.4 (-12.89, 33.65)	1.516 (0.592, 3.884)	0.3828
Rilzabrutinib 400mg QPM (N=37)	17 (45.9)	20 (54.1)	7 (18.9)	-4.7 (-26.95, 17.57)	0.819 (0.316, 2.121)	0.6860
Placebo (N=36)	18 (50.0)	18 (50.0)	4 (11.1)			
Week 12						
Rilzabrutinib 400mg TID (N=34)	22 (64.7)	12 (35.3)	7 (20.6)	13.0 (-10.57, 36.55)	1.685 (0.646, 4.396)	0.2803
Rilzabrutinib 400mg BID (N=35)	17 (48.6)	18 (51.4)	11 (31.4)	-1.9 (-25.26, 21.39)	0.925 (0.362, 2.365)	0.8730
Rilzabrutinib 400mg QPM (N=37)	13 (35.1)	24 (64.9)	10 (27.0)	-15.0 (-36.78, 6.76)	0.516 (0.194, 1.370)	0.1891
Placebo (N=36)	18 (50.0)	18 (50.0)	5 (13.9)			

^a OR: odds ratio; RRD: response rate difference; derived from the Mantel-Haenszel estimator

UCT

[00257] Overall, patients in the 400 mg TID cohort experienced a mild increase in UCT over baseline, with >20% of patients achieving a UCT ≥ 12 over time up to Week 12 (see **Figures 35-37** and **Tables 45-47**).

Table 45. Summary of UCT by Visit in the Double-Blind Period

UCT	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders			
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
Baseline								
Number	34	35	35	34	1	1	6	6
Mean (SD)	4.29 (3.08)	4.00 (2.18)	4.51 (3.21)	4.47 (3.54)	0.00 (NC)	5.00 (NC)	2.67 (1.03)	4.83 (3.60)
Median	4.00	4.00	4.00	4.00	0.00	5.00	3.00	4.00
Q1 ; Q3	2.00 ; 6.00	2.00 ; 6.00	2.00 ; 7.00	2.00 ; 6.00	0.00 ; 0.00	5.00 ; 5.00	2.00 ; 3.00	3.00 ; 8.00
Min ; Max	0.0 ; 12.0	0.0 ; 9.0	0.0 ; 13.0	0.0 ; 15.0	0.0 ; 0.0	5.0 ; 5.0	1.0 ; 4.0	0.0 ; 10.0
Week 4								
Number (observed/imputed)	30 (30/0)	34 (33/1)	33 (33/0)	30 (30/0)	3 (3/0)	1 (1/0)	6 (5/1)	5 (5/0)
Mean (SD)	7.47 (4.07)	6.35 (3.14)	8.85 (4.53)	9.77 (4.17)	4.33 (3.51)	8.00 (NC)	7.00 (7.18)	11.60 (4.51)
Median	8.00	6.00	9.00	10.50	4.00	8.00	5.50	13.00
Q1 ; Q3	4.00 ; 11.00	4.00 ; 8.00	6.00 ; 12.00	7.00 ; 12.00	1.00 ; 8.00	8.00 ; 8.00	1.00 ; 15.00	12.00 ; 13.00
Min ; Max	0.0 ; 16.0	1.0 ; 14.0	1.0 ; 16.0	1.0 ; 16.0	1.0 ; 8.0	8.0 ; 8.0	0.0 ; 15.0	4.0 ; 16.0
Change from baseline								
Number (observed/imputed)	30 (30/0)	33 (32/1)	33 (33/0)	30 (30/0)	1 (1/0)	1 (1/0)	6 (5/1)	5 (5/0)
Mean (SD)	2.80 (3.51)	2.27 (3.07)	4.21 (4.97)	5.63 (4.70)	8.00 (NC)	3.00 (NC)	4.33 (6.77)	7.80 (5.89)
Median	3.00	2.00	4.00	6.50	8.00	3.00	4.00	9.00
Q1 ; Q3	1.00 ; 6.00	0.00 ; 5.00	1.00 ; 7.00	2.00 ; 9.00	8.00 ; 8.00	3.00 ; 3.00	-2.00 ; 11.00	5.00 ; 9.00
Min ; Max	-6.0 ; 9.0	-3.0 ; 8.0	-6.0 ; 15.0	-3.0 ; 15.0	8.0 ; 8.0	3.0 ; 3.0	-3.0 ; 12.0	0.0 ; 16.0
Percent change from baseline								
Number (observed/imputed)	27 (27/0)	32 (31/1)	31 (31/0)	26 (26/0)	0 (0/0)	1 (1/0)	6 (5/1)	4 (4/0)
Mean (SD)	76.17 (117.81)	102.47 (169.77)	220.19 (390.12)	254.30 (370.78)	NC (NC)	60.00 (NC)	151.39 (233.48)	146.88 (139.33)
Median	50.00	45.00	75.00	100.00	NC	60.00	137.50	143.75
Q1 ; Q3	0.00 ; 120.00	0.00 ; 135.00	20.00 ; 166.67	33.33 ; 275.00	NC ; NC	60.00 ; 60.00	-66.67 ; 400.00	31.25 ; 262.50
Min ; Max	-100.0 ; 450.0	-42.9 ; 600.0	-80.0 ; 1500.0	-37.5 ; 1500.0	NC ; NC	60.0 ; 60.0	-100.0 ; 400.0	0.0 ; 300.0
Week 8								
Number (observed/imputed)	31 (30/1)	32 (29/3)	33 (32/1)	30 (30/0)	3 (3/0)	1 (1/0)	5 (4/1)	6 (5/1)
Mean (SD)	8.65 (4.36)	6.84 (3.84)	10.12 (4.20)	9.80 (3.86)	6.00 (2.00)	11.00 (NC)	9.20 (7.98)	11.00 (4.00)
Median	10.00	7.00	11.00	9.50	6.00	11.00	14.00	11.50
Q1 ; Q3	5.00 ; 12.00	4.00 ; 10.00	7.00 ; 14.00	8.00 ; 13.00	4.00 ; 8.00	11.00 ; 11.00	1.00 ; 15.00	10.00 ; 13.00
Min ; Max	0.0 ; 16.0	0.0 ; 16.0	1.0 ; 16.0	2.0 ; 16.0	4.0 ; 8.0	11.0 ; 11.0	0.0 ; 16.0	4.0 ; 16.0
Change from baseline								
Number (observed/imputed)	31 (30/1)	32 (29/3)	33 (32/1)	30 (30/0)	1 (1/0)	1 (1/0)	5 (4/1)	6 (5/1)

UCT	Omalizumab-Naïve Population					Patients with Prior Omalizumab Use, Including Omalizumab-Incomplete Responders											
	Placebo (N=36)		Rilzabrutinib 400mg QPM (N=37)		Rilzabrutinib 400mg BID (N=35)		Rilzabrutinib 400mg TID (N=35)		Placebo (N=4)		Rilzabrutinib 400mg QPM (N=1)		Rilzabrutinib 400mg BID (N=6)		Rilzabrutinib 400mg TID (N=6)		
Percent change from baseline Number (observed/imputed)	Mean (SD)	4.16 (3.60)	3.09 (3.84)	5.70 (5.00)	6.20 (3.99)	6.50	4.00 (NC)	6.00 (NC)	6.00 (NC)	6.00 (NC)	6.00 (NC)	6.00 (NC)	6.00 (NC)	6.00 (NC)	6.17 (6.01)	5.00	
	Median	3.00	2.00	5.00	6.50	6.50	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	11.00	5.00	
	Q1 ; Q3	1.00 ; 8.00	0.00 ; 6.00	2.00 ; 9.00	3.00 ; 9.00	3.00 ; 9.00	4.00 ; 4.00	4.00 ; 4.00	4.00 ; 4.00	4.00 ; 4.00	4.00 ; 4.00	4.00 ; 4.00	4.00 ; 4.00	4.00 ; 4.00	0.00 ; 11.00	2.00 ; 9.00	
	Min ; Max	-1.0 ; 11.0	-3.0 ; 11.0	-6.0 ; 15.0	-3.0 ; 14.0	-3.0 ; 14.0	4.0 ; 4.0	4.0 ; 4.0	4.0 ; 4.0	4.0 ; 4.0	4.0 ; 4.0	4.0 ; 4.0	4.0 ; 4.0	4.0 ; 4.0	-3.0 ; 14.0	0.0 ; 16.0	
Week 12	Percent change from baseline Number (observed/imputed)	Mean (SD)	27 (26/1)	31 (28/3)	30 (29/1)	26 (26/0)	0 (0/0)	1 (1/0)	5 (4/1)	5 (4/1)	5 (4/1)	5 (4/1)	5 (4/1)	5 (4/1)	5 (4/1)	5 (4/1)	
		Median	100.69 (122.18)	138.85 (261.15)	290.62 (401.91)	277.48 (345.91)	NC (NC)	120.00 (NC)	248.33 (316.91)	107.33 (127.63)	120.00 (NC)	275.00	25.00	25.00	25.00	25.00	25.00
		Q1 ; Q3	33.33 ; 133.33	0.00 ; 150.00	40.00 ; 400.00	75.00 ; 300.00	NC ; NC	120.00 ; 120.00	0.00 ; 366.67	20.00 ; 225.00	120.00 ; 120.00	0.00 ; 366.67	20.00 ; 225.00	20.00 ; 225.00	20.00 ; 225.00	20.00 ; 225.00	20.00 ; 225.00
		Min ; Max	-100.0 ; 400.0	-100.0 ; 1000.0	-46.2 ; 1500.0	-50.0 ; 1200.0	NC ; NC	120.0 ; 120.0	-100.0 ; 700.0	0.0 ; 266.7	120.0 ; 120.0	-100.0 ; 700.0	0.0 ; 266.7	0.0 ; 266.7	0.0 ; 266.7	0.0 ; 266.7	0.0 ; 266.7
Change from baseline	Number (observed/imputed)	Mean (SD)	30 (29/1)	33 (30/3)	31 (29/2)	30 (29/1)	3 (2/1)	1 (1/0)	5 (4/1)	5 (4/1)	5 (4/1)	5 (4/1)	5 (4/1)	5 (4/1)	5 (4/1)	5 (4/1)	
		Median	8.73 (4.23)	6.88 (3.86)	10.03 (4.29)	10.50 (4.23)	7.67 (3.51)	10.00 (NC)	9.20 (7.33)	11.80 (4.71)	10.00 (NC)	11.00	12.00	12.00	12.00	12.00	12.00
		Q1 ; Q3	9.00 ; 6.00	7.00 ; 4.00	11.00 ; 12.00	8.00 ; 13.00	4.00 ; 11.00	10.00 ; 10.00	2.00 ; 16.00	4.00 ; 15.00	10.00 ; 10.00	2.00 ; 16.00	4.00 ; 15.00	4.00 ; 15.00	4.00 ; 15.00	4.00 ; 15.00	4.00 ; 15.00
		Min ; Max	0.0 ; 16.0	0.0 ; 13.0	0.0 ; 16.0	1.0 ; 16.0	4.0 ; 11.0	10.0 ; 10.0	1.0 ; 16.0	4.0 ; 16.0	10.0 ; 10.0	1.0 ; 16.0	4.0 ; 16.0	4.0 ; 16.0	4.0 ; 16.0	4.0 ; 16.0	4.0 ; 16.0
Percent change from baseline Number (observed/imputed)	Number (observed/imputed)	Mean (SD)	30 (29/1)	31 (28/3)	31 (29/2)	30 (29/1)	1 (1/0)	1 (1/0)	5 (4/1)	5 (4/1)	5 (4/1)	5 (4/1)	5 (4/1)	5 (4/1)	5 (4/1)	5 (4/1)	
		Median	4.43 (3.48)	3.13 (3.69)	5.65 (5.32)	6.67 (4.92)	8.00 (NC)	5.00 (NC)	6.60 (6.84)	8.00 (6.20)	5.00 (NC)	8.00	9.00	9.00	9.00	9.00	9.00
		Q1 ; Q3	4.00 ; 3.00	2.00 ; 6.00	4.00 ; 11.00	3.00 ; 11.00	8.00 ; 8.00	5.00 ; 5.00	0.00 ; 12.00	4.00 ; 11.00	5.00 ; 5.00	0.00 ; 12.00	4.00 ; 11.00	4.00 ; 11.00	4.00 ; 11.00	4.00 ; 11.00	4.00 ; 11.00
		Min ; Max	-3.0 ; 11.0	-4.0 ; 11.0	-6.0 ; 14.0	-2.0 ; 16.0	8.0 ; 8.0	5.0 ; 5.0	-1.0 ; 14.0	0.0 ; 16.0	5.0 ; 5.0	-1.0 ; 14.0	0.0 ; 16.0	0.0 ; 16.0	0.0 ; 16.0	0.0 ; 16.0	0.0 ; 16.0
End of study	Percent change from baseline Number (observed/imputed)	Mean (SD)	26 (25/1)	30 (27/3)	28 (26/2)	26 (26/0)	0 (0/0)	1 (1/0)	5 (4/1)	5 (4/1)	5 (4/1)	5 (4/1)	5 (4/1)	5 (4/1)	5 (4/1)	5 (4/1)	
		Median	131.15 (177.29)	121.74 (233.08)	301.53 (394.02)	311.71 (436.58)	NC (NC)	100.00 (NC)	246.67 (294.96)	156.25 (153.26)	100.00 (NC)	266.67	162.50	162.50	162.50	162.50	162.50
		Q1 ; Q3	33.33 ; 220.00	0.00 ; 140.00	28.33 ; 416.67	60.00 ; 300.00	NC ; NC	100.00 ; 100.00	0.00 ; 300.00	25.00 ; 287.50	100.00 ; 100.00	0.00 ; 300.00	25.00 ; 287.50	25.00 ; 287.50	25.00 ; 287.50	25.00 ; 287.50	25.00 ; 287.50
		Min ; Max	-100.0 ; 800.0	-100.0 ; 1100.0	-46.2 ; 1400.0	-66.7 ; 1500.0	NC ; NC	100.0 ; 100.0	-33.3 ; 700.0	0.0 ; 300.0	100.0 ; 100.0	-33.3 ; 700.0	0.0 ; 300.0	0.0 ; 300.0	0.0 ; 300.0	0.0 ; 300.0	0.0 ; 300.0
End of study	Number (observed/imputed)	Mean (SD)	5 (4/1)	2 (2/0)	3 (3/0)	3 (3/0)	1	1	6	6	6	6	6	6	6	6	
		Median															

UCT	Omalizumab-Naïve Population				Patients with Prior Omalizumab Use, Including Omalizumab-Naïve			
	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)	Placebo (N=4)	Rilzabrutinib 400mg QPM (N=1)	Rilzabrutinib 400mg BID (N=6)	Rilzabrutinib 400mg TID (N=6)
Change from baseline Number (observed/imputed)	Mean (SD)	8.40 (3.44)	11.50 (0.71)	6.67 (8.14)	0.00 (NC)	5.00 (NC)	2.67 (1.03)	4.83 (3.60)
	Median	7.00	11.50	3.00	0.00	5.00	3.00	4.00
	Q1 ; Q3	6.00 ; 11.00	11.00 ; 12.00	1.00 ; 16.00	0.00 ; 0.00	5.00 ; 5.00	2.00 ; 3.00	3.00 ; 8.00
	Min ; Max	5.0 ; 13.0	11.0 ; 12.0	1.0 ; 16.0	0.0 ; 0.0	5.0 ; 5.0	1.0 ; 4.0	0.0 ; 10.0
Change from baseline Number (observed/imputed)	Mean (SD)	5 (4/1)	2 (2/0)	3 (3/0)	3 (3/0)	1 (1/0)	6 (5/1)	5 (5/0)
	Median	4.60 (2.70)	8.50 (0.71)	0.00 (5.29)	4.33 (3.51)	8.00 (NC)	7.00 (7.18)	11.60 (4.51)
	Q1 ; Q3	5.00	8.50	-2.00	4.00	8.00	5.50	13.00
	Min ; Max	3.00 ; 6.00	8.00 ; 9.00	-4.00 ; 6.00	2.00 ; 6.00	8.00 ; 8.00	1.00 ; 15.00	12.00 ; 13.00
Percent change from baseline Number (observed/imputed)	Mean (SD)	1.0 ; 8.0	8.0 ; 9.0	-4.0 ; 6.0	1.0 ; 8.0	8.0 ; 8.0	0.0 ; 15.0	4.0 ; 16.0
	Median	4 (3/1)	2 (2/0)	3 (3/0)	1 (1/0)	1 (1/0)	6 (5/1)	5 (5/0)
	Q1 ; Q3	217.50 (262.35)	283.33 (23.57)	-21.27 (70.54)	41.03 (36.26)	8.00 (NC)	4.33 (6.77)	7.80 (5.89)
	Min ; Max	130.00	283.33	-57.14	41.03	8.00	3.00	9.00
Percent change from baseline Number (observed/imputed)	Mean (SD)	55.00 ; 380.00	266.67 ; 300.00	-66.67 ; 60.00	15.38 ; 66.67	8.00 ; 8.00	-2.00 ; 11.00	5.00 ; 9.00
	Median	10.0 ; 600.0	266.7 ; 300.0	-66.7 ; 60.0	15.4 ; 66.7	8.0 ; 8.0	3.0 ; 3.0	0.0 ; 16.0
	Q1 ; Q3	10.0 ; 600.0	266.7 ; 300.0	-66.7 ; 60.0	15.4 ; 66.7	8.0 ; 8.0	3.0 ; 3.0	0.0 ; 16.0
	Min ; Max	10.0 ; 600.0	266.7 ; 300.0	-66.7 ; 60.0	15.4 ; 66.7	8.0 ; 8.0	3.0 ; 3.0	0.0 ; 16.0

Table 46. Change and Percent Change from Baseline in UCT over Time up to Week 12 (ITT Population)

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo		% Change difference for rilzabrutinib vs. placebo		
					LS Mean (95% CI) ^a	p-value ^a	LS Mean (95% CI) ^a	p-value ^a	
									% Change from baseline LS Mean (SE) ^a
Week 4									
Rilzabrutinib 400mg TID (N=41)	35	4.53 (3.50)	10.03 (4.20)	5.68 (0.68)	2.34 (0.46, 4.22)	0.0146	262.11 (48.72)	122.56 (-10.01, 255.13)	0.0699
Rilzabrutinib 400mg BID (N=41)	39	4.24 (3.06)	8.56 (4.95)	4.27 (0.65)	0.94 (-0.87, 2.75)	0.3089	236.29 (42.88)	96.74 (-24.75, 218.23)	0.1185
Rilzabrutinib 400mg QPM (N=38)	35	4.03 (2.16)	6.40 (3.11)	2.44 (0.68)	-0.89 (-2.79, 1.00)	0.3558	95.52 (42.85)	-44.03 (-169.40, 81.34)	0.4908
Placebo (N=40)	33	4.17 (3.12)	7.18 (4.07)	3.33 (0.71)			139.55 (48.25)		

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo		% Change difference for rilzabrutinib vs. placebo		
					LS Mean (95% CI) ^a	p-value ^a	LS Mean (95% CI) ^a	p-value ^a	
Rilzabrutinib 400mg T1D (N=41)	36	4.53 (3.50)	10.00 (3.85)	5.80 (0.69)	1.43 (-0.50, 3.37)	0.1471	272.85 (43.60)	108.30 (-18.30, 234.90)	0.0935
Rilzabrutinib 400mg BID (N=41)	38	4.24 (3.06)	10.00 (4.71)	5.38 (0.68)	1.01 (-0.90, 2.92)	0.3016	304.12 (43.11)	139.58 (18.06, 261.09)	0.0244
Rilzabrutinib 400mg QPM (N=38)	33	4.03 (2.16)	6.97 (3.84)	3.16 (0.71)	-1.21 (-3.16, 0.74)	0.2226	126.71 (44.63)	-37.84 (-167.44, 91.76)	0.5667
Placebo (N=40)	34	4.17 (3.12)	8.41 (4.25)	4.37 (0.74)			164.55 (48.15)		
Week 12									
Rilzabrutinib 400mg T1D (N=41)	35	4.53 (3.50)	10.69 (4.25)	6.53 (0.70)	1.80 (-0.20, 3.79)	0.0771	322.21 (47.00)	122.43 (-16.89, 261.74)	0.0849
Rilzabrutinib 400mg BID (N=41)	36	4.24 (3.06)	9.92 (4.69)	5.44 (0.71)	0.71 (-1.27, 2.68)	0.4839	309.12 (47.68)	109.34 (-24.34, 243.02)	0.1088
Rilzabrutinib 400mg QPM (N=38)	34	4.03 (2.16)	6.97 (3.84)	2.92 (0.76)	-1.82 (-3.87, 0.23)	0.0812	99.76 (47.53)	-100.02 (-238.68, 38.64)	0.1572
Placebo (N=40)	33	4.17 (3.12)	8.64 (4.14)	4.74 (0.76)			199.78 (53.12)		

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

Table 47. Change and Percent Change from Baseline in UCT over Time up to Week 12 (Omalizumab-Naïve Population)

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo		% Change difference for rilzabrutinib vs. placebo		
					LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
Week 4									
Rilzabrutinib 400mg T1D (N=35)	30	4.47 (3.54)	9.77 (4.17)	5.47 (0.70)	2.23 (0.33, 4.13)	0.0216	267.24 (49.68)	124.43 (-9.74, 258.61)	0.0691
Rilzabrutinib 400mg BID (N=35)	33	4.51 (3.21)	8.85 (4.53)	4.51 (0.66)	1.27 (-0.56, 3.11)	0.1736	263.00 (44.80)	120.19 (-1.20, 241.59)	0.0523
Rilzabrutinib 400mg QPM (N=37)	34	4.00 (2.18)	6.35 (3.14)	2.36 (0.66)	-0.88 (-2.74, 0.99)	0.3559	94.30 (43.68)	-48.50 (-174.55, 77.55)	0.4504
Placebo (N=36)	30	4.29 (3.08)	7.47 (4.07)	3.24 (0.70)			142.81 (47.73)		

				Change difference for rilzabrutinib vs. placebo		% Change difference for rilzabrutinib vs. placebo		
				LS Mean (95% CI) ^a	p-value ^a	% Change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	p-value ^a
n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a					
Week 8								
Rilzabrutinib 400mg TID (N=35)	4.47 (3.54)	9.80 (3.86)	5.66 (0.71)	1.19 (-0.75, 3.12)	0.2295	272.13 (49.40)	102.55 (-31.38, 236.49)	0.1332
Rilzabrutinib 400mg BID (N=35)	4.51 (3.21)	10.12 (4.20)	5.61 (0.69)	1.14 (-0.74, 3.02)	0.2334	328.12 (46.96)	158.55 (28.05, 289.04)	0.0173
Rilzabrutinib 400mg QPM (N=37)	4.00 (2.18)	6.84 (3.84)	2.98 (0.71)	-1.49 (-3.43, 0.45)	0.1318	121.09 (44.66)	-48.49 (-177.78, 80.81)	0.4620
Placebo (N=36)	4.29 (3.08)	8.65 (4.36)	4.47 (0.72)			169.58 (49.20)		
Week 12								
Rilzabrutinib 400mg TID (N=35)	4.47 (3.54)	10.50 (4.23)	6.31 (0.76)	1.58 (-0.47, 3.63)	0.1307	329.00 (51.79)	131.76 (-18.16, 281.68)	0.0848
Rilzabrutinib 400mg BID (N=35)	4.51 (3.21)	10.03 (4.29)	5.52 (0.74)	0.80 (-1.21, 2.81)	0.4374	344.03 (53.11)	146.79 (5.56, 288.02)	0.0417
Rilzabrutinib 400mg QPM (N=37)	4.00 (2.18)	6.88 (3.86)	2.77 (0.75)	-1.96 (-3.99, 0.08)	0.0595	91.29 (48.06)	-105.95 (-247.17, 35.27)	0.1412
Placebo (N=36)	4.29 (3.08)	8.73 (4.23)	4.73 (0.75)			197.24 (53.74)		

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

Quality of Life

[00258] Patients receiving 400 mg TID rilzabrutinib experienced an improvement in quality of life as measured by PGIS and PGIC (see **Figures 38-39** and **Tables 48-52**).

Table 48. Summary of PGIS by Visit in the Double-Blind Period (Omalizumab-Naïve Population)

PGIS	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Baseline				
Number	36	37	35	34
Mean (SD)	2.39 (0.60)	2.51 (0.61)	2.20 (0.63)	2.32 (0.68)
Median	2.00	3.00	2.00	2.00
Q1 ; Q3	2.00 ; 3.00	2.00 ; 3.00	2.00 ; 3.00	2.00 ; 3.00
Min ; Max	1.0 ; 3.0	1.0 ; 3.0	1.0 ; 3.0	0.0 ; 3.0
Week 2				
Number (observed/imputed)	30 (30/0)	33 (33/0)	31 (31/0)	34 (34/0)
Mean (SD)	1.90 (0.71)	2.00 (0.71)	1.55 (0.93)	1.38 (0.85)
Median	2.00	2.00	2.00	1.00
Q1 ; Q3	1.00 ; 2.00	2.00 ; 2.00	1.00 ; 2.00	1.00 ; 2.00
Min ; Max	1.0 ; 3.0	1.0 ; 3.0	0.0 ; 3.0	0.0 ; 3.0
Change from baseline				
Number (observed/imputed)	30 (30/0)	33 (33/0)	31 (31/0)	34 (34/0)
Mean (SD)	-0.43 (0.63)	-0.48 (0.67)	-0.65 (1.02)	-0.94 (1.01)
Median	0.00	0.00	0.00	-1.00
Q1 ; Q3	-1.00 ; 0.00	-1.00 ; 0.00	-2.00 ; 0.00	-2.00 ; 0.00
Min ; Max	-2.0 ; 1.0	-2.0 ; 1.0	-3.0 ; 1.0	-3.0 ; 2.0
Percent change from baseline				
Number (observed/imputed)	30 (30/0)	33 (33/0)	31 (31/0)	33 (33/0)
Mean (SD)	-17.22 (26.07)	-17.68 (25.66)	-23.12 (50.49)	-41.92 (35.63)
Median	0.00	0.00	0.00	-50.00
Q1 ; Q3	-33.33 ; 0.00	-33.33 ; 0.00	-66.67 ; 0.00	-66.67 ; 0.00
Min ; Max	-66.7 ; 50.0	-66.7 ; 50.0	-100.0 ; 100.0	-100.0 ; 50.0
Week 4				
Number (observed/imputed)	30 (30/0)	34 (33/1)	33 (33/0)	29 (29/0)
Mean (SD)	1.63 (0.76)	1.88 (0.81)	1.48 (0.87)	1.34 (0.77)
Median	2.00	2.00	2.00	1.00
Q1 ; Q3	1.00 ; 2.00	1.00 ; 2.00	1.00 ; 2.00	1.00 ; 2.00
Min ; Max	0.0 ; 3.0	0.0 ; 3.0	0.0 ; 3.0	0.0 ; 3.0
Change from baseline				
Number (observed/imputed)	30 (30/0)	34 (33/1)	33 (33/0)	29 (29/0)
Mean (SD)	-0.67 (0.76)	-0.65 (0.73)	-0.70 (0.92)	-1.07 (0.80)
Median	-1.00	-0.50	0.00	-1.00
Q1 ; Q3	-1.00 ; 0.00	-1.00 ; 0.00	-1.00 ; 0.00	-2.00 ; -1.00
Min ; Max	-2.0 ; 1.0	-2.0 ; 0.0	-3.0 ; 1.0	-3.0 ; 0.0
Percent change from baseline				
Number (observed/imputed)	30 (30/0)	34 (33/1)	33 (33/0)	29 (29/0)
Mean (SD)	-27.22 (31.71)	-25.49 (29.08)	-27.78 (43.43)	-43.10 (30.71)
Median	-33.33	-16.67	0.00	-50.00

PGIS	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Q1 ; Q3	-50.00 ; 0.00	-50.00 ; 0.00	-50.00 ; 0.00	-66.67 ; -33.33
Min ; Max	-100.0 ; 50.0	-100.0 ; 0.0	-100.0 ; 100.0	-100.0 ; 0.0
Week 8				
Number (observed/imputed)	31 (30/1)	33 (30/3)	33 (32/1)	30 (30/0)
Mean (SD)	1.52 (0.89)	1.88 (0.82)	1.18 (0.98)	1.33 (0.96)
Median	1.00	2.00	1.00	1.00
Q1 ; Q3	1.00 ; 2.00	1.00 ; 2.00	0.00 ; 2.00	1.00 ; 2.00
Min ; Max	0.0 ; 3.0	0.0 ; 3.0	0.0 ; 3.0	0.0 ; 3.0
Change from baseline				
Number (observed/imputed)	31 (30/1)	33 (30/3)	33 (32/1)	30 (30/0)
Mean (SD)	-0.81 (0.91)	-0.67 (0.74)	-1.00 (0.97)	-1.13 (0.86)
Median	-1.00	-1.00	-1.00	-1.00
Q1 ; Q3	-1.00 ; 0.00	-1.00 ; 0.00	-2.00 ; 0.00	-2.00 ; -1.00
Min ; Max	-3.0 ; 1.0	-2.0 ; 1.0	-3.0 ; 1.0	-3.0 ; 0.0
Percent change from baseline				
Number (observed/imputed)	31 (30/1)	33 (30/3)	33 (32/1)	30 (30/0)
Mean (SD)	-32.80 (36.64)	-25.25 (35.63)	-44.95 (43.60)	-47.22 (34.49)
Median	-33.33	-33.33	-50.00	-50.00
Q1 ; Q3	-50.00 ; 0.00	-50.00 ; 0.00	-100.00 ; 0.00	-66.67 ; -33.33
Min ; Max	-100.0 ; 50.0	-100.0 ; 100.0	-100.0 ; 50.0	-100.0 ; 0.0
Week 12				
Number (observed/imputed)	31 (30/1)	34 (31/3)	31 (29/2)	30 (29/1)
Mean (SD)	1.58 (0.92)	1.88 (0.81)	1.13 (1.06)	1.27 (0.91)
Median	1.00	2.00	1.00	1.00
Q1 ; Q3	1.00 ; 2.00	1.00 ; 2.00	0.00 ; 2.00	1.00 ; 2.00
Min ; Max	0.0 ; 3.0	0.0 ; 3.0	0.0 ; 3.0	0.0 ; 3.0
Change from baseline				
Number (observed/imputed)	31 (30/1)	34 (31/3)	31 (29/2)	30 (29/1)
Mean (SD)	-0.81 (0.95)	-0.68 (0.64)	-1.03 (1.17)	-1.17 (0.91)
Median	-1.00	-1.00	-1.00	-1.00
Q1 ; Q3	-2.00 ; 0.00	-1.00 ; 0.00	-2.00 ; 0.00	-2.00 ; 0.00
Min ; Max	-2.0 ; 1.0	-2.0 ; 0.0	-3.0 ; 1.0	-3.0 ; 0.0
Percent change from baseline				
Number (observed/imputed)	31 (30/1)	34 (31/3)	31 (29/2)	30 (29/1)
Mean (SD)	-32.26 (39.89)	-27.45 (26.87)	-43.55 (55.56)	-47.22 (35.85)
Median	-33.33	-33.33	-50.00	-50.00
Q1 ; Q3	-66.67 ; 0.00	-50.00 ; 0.00	-100.00 ; 0.00	-66.67 ; 0.00
Min ; Max	-100.0 ; 50.0	-100.0 ; 0.0	-100.0 ; 100.0	-100.0 ; 0.0

Table 49. Change and Percent Change from Baseline in PGIS over Time up to Week 12 (Omalizumab-Naïve Population)

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for rilzabrutinib vs. placebo		% Change difference for rilzabrutinib vs. placebo			
					LS Mean (95% CI) ^a	p-value ^a	LS Mean (95% CI) ^a	p-value ^a		
Week 2										
Rilzabrutinib 400mg TID (N=35)	34	2.32 (0.68)	1.38 (0.85)	-0.96 (0.13)	-0.46 (-0.83, -0.09)	0.0148	-40.66 (6.06)	-22.00 (-38.77, -5.22)	0.0102	
Rilzabrutinib 400mg BID (N=35)	31	2.20 (0.63)	1.55 (0.93)	-0.76 (0.14)	-0.26 (-0.63, 0.11)	0.1666	-26.23 (6.28)	-7.56 (-24.17, 9.05)	0.3723	
Rilzabrutinib 400mg QPM (N=37)	33	2.51 (0.61)	2.00 (0.71)	-0.47 (0.14)	0.03 (-0.34, 0.41)	0.8643	-17.80 (6.05)	0.86 (-15.86, 17.59)	0.9195	
Placebo (N=36)	30	2.39 (0.60)	1.90 (0.71)	-0.50 (0.14)			-18.67 (6.28)			
Week 4										
Rilzabrutinib 400mg TID (N=35)	29	2.32 (0.68)	1.34 (0.77)	-0.96 (0.13)	-0.27 (-0.62, 0.09)	0.1413	-41.04 (6.24)	-12.52 (-29.03, 4.00)	0.1374	
Rilzabrutinib 400mg BID (N=35)	33	2.20 (0.63)	1.48 (0.87)	-0.81 (0.13)	-0.12 (-0.48, 0.25)	0.5305	-29.83 (5.99)	-1.31 (-17.26, 14.65)	0.8725	
Rilzabrutinib 400mg QPM (N=37)	34	2.51 (0.61)	1.88 (0.81)	-0.61 (0.13)	0.09 (-0.27, 0.44)	0.6363	-25.46 (5.77)	3.06 (-12.83, 18.95)	0.7058	
Placebo (N=36)	30	2.39 (0.60)	1.63 (0.76)	-0.70 (0.14)			-28.52 (5.99)			
Week 8										
Rilzabrutinib 400mg TID (N=35)	30	2.32 (0.68)	1.33 (0.96)	-1.02 (0.15)	-0.17 (-0.58, 0.25)	0.4296	-45.65 (7.05)	-11.39 (-30.26, 7.48)	0.2367	
Rilzabrutinib 400mg BID (N=35)	33	2.20 (0.63)	1.18 (0.98)	-1.11 (0.15)	-0.25 (-0.67, 0.16)	0.2338	-46.44 (6.74)	-12.18 (-30.63, 6.27)	0.1958	
Rilzabrutinib 400mg QPM (N=37)	33	2.51 (0.61)	1.88 (0.82)	-0.61 (0.15)	0.24 (-0.17, 0.65)	0.2464	-24.99 (6.69)	9.27 (-9.09, 27.62)	0.3223	
Placebo (N=36)	31	2.39 (0.60)	1.52 (0.89)	-0.85 (0.16)			-34.26 (7.00)			
Week 12										
Rilzabrutinib 400mg TID (N=35)	30	2.32 (0.68)	1.27 (0.91)	-1.04 (0.16)	-0.24 (-0.67, 0.19)	0.2700	-44.96 (7.44)	-12.67 (-32.97, 7.63)	0.2211	
Rilzabrutinib 400mg BID (N=35)	31	2.20 (0.63)	1.13 (1.06)	-1.14 (0.16)	-0.34 (-0.77, 0.10)	0.1301	-45.76 (7.46)	-13.46 (-33.69, 6.76)	0.1919	
Rilzabrutinib 400mg QPM (N=37)	34	2.51 (0.61)	1.88 (0.81)	-0.59 (0.15)	0.21 (-0.22, 0.63)	0.3380	-26.42 (7.16)	5.87 (-13.65, 25.38)	0.5555	
Placebo (N=36)	31	2.39 (0.60)	1.58 (0.92)	-0.80 (0.16)			-32.29 (7.54)			

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

Table 50. Categorical Summary of PGIS by Visit up to Week 12 (Omalizumab-Naïve Population)

PGIS	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Baseline				
Number	36	37	35	34
None	0	0	0	1 (2.9)
Mild	2 (5.6)	2 (5.4)	4 (11.4)	1 (2.9)
Moderate	18 (50.0)	14 (37.8)	20 (57.1)	18 (52.9)
Severe	16 (44.4)	21 (56.8)	11 (31.4)	14 (41.2)
Week 2				
Number (observed/imputed)	30 (30/0)	33 (33/0)	31 (31/0)	34 (34/0)
None	0	0	5 (16.1)	4 (11.8)
Mild	9 (30.0)	8 (24.2)	8 (25.8)	17 (50.0)
Moderate	15 (50.0)	17 (51.5)	14 (45.2)	9 (26.5)
Severe	6 (20.0)	8 (24.2)	4 (12.9)	4 (11.8)
Week 4				
Number (observed/imputed)	30 (30/0)	34 (33/1)	33 (33/0)	29 (29/0)
None	1 (3.3)	1 (2.9)	5 (15.2)	3 (10.3)
Mild	13 (43.3)	10 (29.4)	10 (30.3)	15 (51.7)
Moderate	12 (40.0)	15 (44.1)	15 (45.5)	9 (31.0)
Severe	4 (13.3)	8 (23.5)	3 (9.1)	2 (6.9)
Week 8				
Number (observed/imputed)	31 (30/1)	33 (30/3)	33 (32/1)	30 (30/0)
None	3 (9.7)	1 (3.0)	9 (27.3)	6 (20.0)
Mild	14 (45.2)	10 (30.3)	13 (39.4)	12 (40.0)
Moderate	9 (29.0)	14 (42.4)	7 (21.2)	8 (26.7)
Severe	5 (16.1)	8 (24.2)	4 (12.1)	4 (13.3)
Week 12				
Number (observed/imputed)	31 (30/1)	34 (31/3)	31 (29/2)	30 (29/1)
None	3 (9.7)	1 (2.9)	12 (38.7)	6 (20.0)
Mild	13 (41.9)	10 (29.4)	6 (19.4)	13 (43.3)
Moderate	9 (29.0)	15 (44.1)	10 (32.3)	8 (26.7)
Severe	6 (19.4)	8 (23.5)	3 (9.7)	3 (10.0)

Table 51. Summary of PGIC by Visit in the Double-Blind Period (Omalizumab-Naïve Population)

PGIC	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Week 2				
Number (observed/imputed)	30 (30/0)	33 (33/0)	31 (31/0)	33 (33/0)
Mean (SD)	2.50 (1.25)	2.33 (1.24)	1.61 (1.63)	1.42 (1.52)
Median	3.00	3.00	1.00	1.00
Q1 ; Q3	2.00 ; 3.00	2.00 ; 3.00	0.00 ; 3.00	0.00 ; 2.00
Min ; Max	0.0 ; 6.0	0.0 ; 6.0	0.0 ; 6.0	0.0 ; 6.0
LS Mean (SE) ^a	2.34 (0.25)	2.12 (0.24)	1.53 (0.25)	1.43 (0.24)
LS Mean Diff vs. placebo (95% CI) ^a		-0.22 (-0.89, 0.45)	-0.81 (-1.47, -0.15)	-0.91 (-1.59, -0.23)
P-value vs. placebo ^a		0.5204	0.0166	0.0085
Week 4				
Number (observed/imputed)	30 (30/0)	34 (33/1)	33 (33/0)	29 (29/0)
Mean (SD)	2.13 (1.31)	2.24 (1.54)	1.67 (1.49)	1.14 (1.25)
Median	2.00	2.00	1.00	1.00
Q1 ; Q3	1.00 ; 3.00	1.00 ; 3.00	0.00 ; 3.00	0.00 ; 2.00
Min ; Max	0.0 ; 5.0	0.0 ; 6.0	0.0 ; 6.0	0.0 ; 4.0
LS Mean (SE) ^a	2.09 (0.25)	2.06 (0.24)	1.59 (0.24)	1.18 (0.25)

PGIC	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
LS Mean Diff vs. placebo (95% CI) ^a		-0.02 (-0.67, 0.62)	-0.49 (-1.15, 0.16)	-0.90 (-1.58, - 0.22)
P-value vs. placebo ^a		0.9433	0.1411	0.0092
Week 8				
Number (observed/imputed)	31 (30/1)	33 (30/3)	33 (32/1)	30 (30/0)
Mean (SD)	1.84 (1.07)	2.21 (1.41)	1.42 (1.62)	0.90 (1.12)
Median	2.00	2.00	1.00	1.00
Q1 ; Q3	1.00 ; 3.00	1.00 ; 3.00	0.00 ; 3.00	0.00 ; 1.00
Min ; Max	0.0 ; 4.0	0.0 ; 6.0	0.0 ; 6.0	0.0 ; 4.0
LS Mean (SE) ^a	1.84 (0.24)	2.10 (0.23)	1.43 (0.24)	0.98 (0.24)
LS Mean Diff vs. placebo (95% CI) ^a		0.27 (-0.37, 0.90)	-0.41 (-1.05, 0.23)	-0.86 (-1.50, - 0.21)
P-value vs. placebo ^a		0.4112	0.2098	0.0093
Week 12				
Number (observed/imputed)	31 (30/1)	34 (31/3)	30 (28/2)	31 (29/2)
Mean (SD)	1.58 (1.15)	2.12 (1.49)	1.03 (1.40)	0.97 (1.30)
Median	2.00	2.00	0.50	0.00
Q1 ; Q3	0.00 ; 3.00	1.00 ; 3.00	0.00 ; 1.00	0.00 ; 2.00
Min ; Max	0.0 ; 3.0	0.0 ; 6.0	0.0 ; 5.0	0.0 ; 4.0
LS Mean (SE) ^a	1.62 (0.26)	2.00 (0.25)	1.17 (0.25)	0.98 (0.25)
LS Mean Diff vs. placebo (95% CI) ^a		0.38 (-0.30, 1.05)	-0.46 (-1.14, 0.23)	-0.64 (-1.34, 0.05)
P-value vs. placebo ^a		0.2716	0.1904	0.0703

^a Data were analyzed by fitting an ANCOVA model with the intervention group and regions as covariates.

Table 52. Categorical Summary of PGIC by Visit up to Week 12 (Omalizumab-Naïve Population)

PGIC	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Week 2				
Number (observed/imputed)	30 (30/0)	33 (33/0)	31 (31/0)	33 (33/0)
Very much better	3 (10.0)	3 (9.1)	11 (35.5)	12 (36.4)
Moderately better	1 (3.3)	5 (15.2)	5 (16.1)	7 (21.2)
A little better	9 (30.0)	7 (21.2)	6 (19.4)	7 (21.2)
No change	15 (50.0)	16 (48.5)	6 (19.4)	5 (15.2)
A little worse	0	1 (3.0)	1 (3.2)	0
Moderately worse	1 (3.3)	0	1 (3.2)	1 (3.0)
Very much worse	1 (3.3)	1 (3.0)	1 (3.2)	1 (3.0)
Week 4				
Number (observed/imputed)	30 (30/0)	34 (33/1)	33 (33/0)	29 (29/0)
Very much better	4 (13.3)	6 (17.6)	9 (27.3)	13 (44.8)
Moderately better	5 (16.7)	4 (11.8)	8 (24.2)	5 (17.2)
A little better	8 (26.7)	10 (29.4)	6 (18.2)	6 (20.7)
No change	11 (36.7)	7 (20.6)	7 (21.2)	4 (13.8)
A little worse	0	5 (14.7)	2 (6.1)	1 (3.4)
Moderately worse	2 (6.7)	1 (2.9)	0	0
Very much worse	0	1 (2.9)	1 (3.0)	0
Week 8				
Number (observed/imputed)	31 (30/1)	33 (30/3)	33 (32/1)	30 (30/0)
Very much better	4 (12.9)	4 (12.1)	13 (39.4)	14 (46.7)
Moderately better	7 (22.6)	6 (18.2)	8 (24.2)	10 (33.3)
A little better	11 (35.5)	9 (27.3)	3 (9.1)	2 (6.7)
No change	8 (25.8)	10 (30.3)	6 (18.2)	3 (10.0)
A little worse	1 (3.2)	2 (6.1)	1 (3.0)	1 (3.3)
Moderately worse	0	1 (3.0)	1 (3.0)	0

PGIC	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
Very much worse	0	1 (3.0)	1 (3.0)	0
Week 12				
Number (observed/imputed)	31 (30/1)	34 (31/3)	30 (28/2)	31 (29/2)
Very much better	8 (25.8)	6 (17.6)	15 (50.0)	17 (54.8)
Moderately better	5 (16.1)	6 (17.6)	8 (26.7)	5 (16.1)
A little better	10 (32.3)	7 (20.6)	1 (3.3)	4 (12.9)
No change	8 (25.8)	11 (32.4)	4 (13.3)	3 (9.7)
A little worse	0	2 (5.9)	1 (3.3)	2 (6.5)
Moderately worse	0	1 (2.9)	1 (3.3)	0
Very much worse	0	1 (2.9)	0	0

Biomarkers

[00259] Changes in disease-relevant biomarkers were assessed over the course of the 12-Week double-blind phase (see **Figure 40**). Biomarkers included sMRGPRX2, IgE anti-TPO, IgG anti-FCεRI, IL-31, IgM, IgE, IgG, IgG anti-IgE, and white blood cell levels. Consistent with the effects of rilzabrutinib on other aspects of CSU, patients receiving rilzabrutinib achieved a reduction in levels of sMRGPRX2 (a mast cell receptor associated with disease activity in CSU), IgE anti-TPO (a marker of Type IIb autoimmune CSU), IgG anti-FCεRI (a marker of Type IIb autoimmune CSU), IL-31 (an itch mediator secreted by mast cells and basophils), and eosinophils (an indirect mediator of mast cell activation) at Week 12 relative to patients receiving the placebo (see **Table 53**).

[00260] Patients treated with 400 mg TID rilzabrutinib exhibited a 22.8% and 8.1% reduction from baseline median sMRGPRX2 and IL-31 levels, respectively while patients treated with the placebo experienced a 4.5% reduction in sMRGPRX2 levels and an increase of 15.4% in IL-31 levels.

Additionally, patients receiving 400 mg TID rilzabrutinib achieved a 46.7% and 38.7% reduction from baseline for IgG anti-TPO and IgG anti-FCεRI, respectively, while patients receiving the placebo achieved only a 7.0% decrease in IgG anti-TPO and a 14.2% increase in IgG anti-FCεRI. The reduction in IgG anti-FCεRI following inhibition of BTK signaling with rilzabrutinib may result in a reduction in mast-cell and basophil activation.

[00261] Patients receiving 400 mg TID rilzabrutinib also exhibited a 29.0% reduction in eosinophil levels, while patients receiving the placebo experienced a 3.6% increase in eosinophil levels.

[00262] Treatment with rilzabrutinib was not associated with a change in total serum IgE or IgG levels.

Table 53. Summary of Change in Biomarkers from Baseline to Week 12

Median Percent Change from Baseline (Q1; Q3 range)	Placebo (N=36)	Rilzabrutinib 400mg QPM (N=37)	Rilzabrutinib 400mg BID (N=35)	Rilzabrutinib 400mg TID (N=35)
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)

Safety

[00263] Rilzabrutinib was generally safe, with no evidence of new safety concerns or dose-related AEs (see **Table 54**). Consistent with this, vital signs and ECG results were similar across all groups.

[00264] Participants receiving 400 mg BID or TID rilzabrutinib experienced more TEAEs than patients receiving 400 mg QD rilzabrutinib or the placebo. The majority of TEAEs in patients receiving 400 mg TID and BID rilzabrutinib were reported as mild, with the most frequently occurring TEAEs being diarrhea, nausea, and headaches. Skin-related AEs were more frequent in participants receiving the placebo or 400 mg QD rilzabrutinib than in patients receiving 400 mg BID or TID rilzabrutinib.

[00265] Throughout the study, there were 3 treatment-emergent SAEs and no deaths. SAEs occurred at the same incidence rate across all rilzabrutinib dosing groups. There were no severe/serious infections or opportunistic infections. Additionally, there were no drug-induced liver injuries (including Hy's law). ALT increases >3 x ULN, which meet the criteria for an AESI, were observed in 2 patients in the QPM cohort, 1 patient in the BID cohort, and 1 patient in the TID cohort. Of these patients, 3 recovered while continuing rilzabrutinib treatment. Notably, no TEAEs observed in clinical trials of other BTK inhibitors were observed in this study, further attesting to the safety of rilzabrutinib.

Table 54. Overview of Adverse Event Profile: Treatment-Emergent Adverse Events in the Double-Blind Period (Safety Population)

n (%)	Placebo (N=40)	Rilzabrutinib 400mg QPM (N=38)	Rilzabrutinib 400mg BID (N=41)	Rilzabrutinib 400mg TID (N=41)
Participants with any TEAE	23 (57.5)	23 (60.5)	30 (73.2)	31 (75.6)
Participants with any severe TEAE	1 (2.5)	1 (2.6)	1 (2.4)	1 (2.4)
Participants with any treatment-emergent SAE	1 (2.5)	0	0	2 (4.9)
Participants with any TEAE leading to death	0	0	0	0
Participants with any TEAE leading to permanent study intervention discontinuation	0	0	1 (2.4)	1 (2.4)
Participants with any treatment-emergent AESI	2 (5.0)	4 (10.5)	4 (9.8)	3 (7.3)
Participants with any TEAE related to IMP	8 (20.0)	9 (23.7)	22 (53.7)	22 (53.7)

TEAE: Treatment-emergent adverse event, SAE: Serious adverse event, AESI: Adverse event of special interest

n (%) = number and percentage of participants with at least one TEAE.

Embodiments:

Non-limiting embodiments of the disclosure include:

1. A method of treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, comprising administering to the human patient in need thereof a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof.
2. The method of Embodiment 1, wherein the human patient has moderate-to-severe CSU.
3. The method of Embodiment 1 or 2, wherein the human patient has moderate CSU.
4. The method of Embodiment 1 or 2, wherein the human patient has severe CSU.
5. The method of any one of the preceding Embodiments, wherein the human patient has CSU refractory to H1 antihistamine (H1-AH) treatment.
6. The method of any one of Embodiments 1-5, wherein the human patient has Type I autoimmune CSU.

7. The method of any one of Embodiments 1-5, wherein the human patient has Type IIb autoimmune CSU.
8. The method of any one of the preceding Embodiments, wherein the human patient has angioedema.
9. The method of any one of the preceding Embodiments, wherein the human patient achieves a Urticaria Activity Score (UAS7) that is lower than baseline UAS7.
10. The method of any one of the preceding Embodiments, wherein the human patient achieves a UAS7 that is lower than baseline UAS7 within 52 weeks of initiating rilzabrutinib treatment.
11. The method of any one of the preceding Embodiments, wherein the human patient achieves a UAS7 that is lower than baseline UAS7 within 24 weeks of initiating rilzabrutinib treatment.
12. The method of any one of the preceding Embodiments, wherein the human patient achieves a UAS7 that is lower than baseline UAS7 within 12 weeks of initiating rilzabrutinib treatment.
13. The method of any one of the preceding Embodiments, wherein the human patient achieves a UAS7 that is lower than baseline UAS7 within 4 weeks of initiating rilzabrutinib treatment.
14. The method of any one of the preceding Embodiments, wherein the human patient achieves a UAS7 ≤ 6 .
15. The method of any one of the preceding Embodiments, wherein the human patient achieves a UAS7 ≤ 6 within 12 weeks of initiating rilzabrutinib treatment.

16. The method of any one of the preceding Embodiments, wherein the human patient achieves a UAS7 of 0.
17. The method of any one of the preceding Embodiments, wherein the human patient achieves a UAS7 of 0 within 12 weeks of initiating rilzabrutinib treatment.
18. The method of any one of the preceding Embodiments, wherein the human patient achieves a UAS7 that is at least 10 points lower than baseline UAS7.
19. The method of any one of the preceding Embodiments, wherein the human patient achieves an Itch Severity Score (ISS7) that is lower than baseline ISS7.
20. The method of any one of the preceding Embodiments, wherein the human patient achieves an ISS7 that is lower than baseline ISS7 within 52 weeks of initiating rilzabrutinib treatment.
21. The method of any one of the preceding Embodiments, wherein the human patient achieves an ISS7 that is lower than baseline ISS7 within 24 weeks of initiating rilzabrutinib treatment.
22. The method of any one of the preceding Embodiments, wherein the human patient achieves an ISS7 that is lower than baseline ISS7 within 12 weeks of initiating rilzabrutinib treatment.
23. The method of any one of the preceding Embodiments, wherein the human patient achieves an ISS7 that is at least 5 points lower than baseline ISS7.
24. The method of any one of the preceding Embodiments, wherein the human patient achieves a Hives Severity Score (HSS7) that is lower than baseline HSS7.
25. The method of any one of the preceding Embodiments, wherein the human patient achieves a HSS7 that is lower than baseline HSS7 within 52 weeks of initiating

rilzabrutinib treatment.

26. The method of any one of the preceding Embodiments, wherein the human patient achieves a HSS7 that is lower than baseline HSS7 within 24 weeks of initiating rilzabrutinib treatment.
27. The method of any one of the preceding Embodiments, wherein the human patient achieves a HSS7 that is lower than baseline HSS7 within 12 weeks of initiating rilzabrutinib treatment.
28. The method of any one of the preceding Embodiments, wherein the human patient achieves an Angioedema Activity Score (AAS7) that is lower than baseline AAS7.
29. The method of any one of the preceding Embodiments, wherein the human patient achieves an AAS7 that is lower than baseline AAS7 within 52 weeks of initiating rilzabrutinib treatment.
30. The method of any one of the preceding Embodiments, wherein the human patient achieves an AAS7 that is lower than baseline AAS7 within 24 weeks of initiating rilzabrutinib treatment.
31. The method of any one of the preceding Embodiments, wherein the human patient achieves an AAS7 that is lower than baseline AAS7 within 12 weeks of initiating rilzabrutinib treatment.
32. The method of any one of the preceding Embodiments, wherein the human patient achieves a Urticaria Control Test (UCT) score that is higher than baseline UCT score.
33. The method of any one of the preceding Embodiments, wherein the human patient achieves a UCT score that is higher than baseline UCT score within 52 weeks of initiating rilzabrutinib treatment.

34. The method of any one of the preceding Embodiments, wherein the human patient achieves a UCT score that is higher than baseline UCT score within 24 weeks of initiating rilzabrutinib treatment.
35. The method of any one of the preceding Embodiments, wherein the human patient achieves a UCT score that is higher than baseline UCT score within 12 weeks of initiating rilzabrutinib treatment.
36. The method of any one of the preceding Embodiments, wherein the human patient achieves a UCT score that is higher than baseline UCT score within 8 weeks of initiating rilzabrutinib treatment.
37. The method of any one of the preceding Embodiments, wherein the human patient achieves a UCT score that is higher than baseline UCT score within 4 weeks of initiating rilzabrutinib treatment.
38. The method of any one of the preceding Embodiments, wherein the human patient achieves a UCT score ≥ 12 .
39. The method of any one of the preceding Embodiments, wherein the human patient achieves a UCT score ≥ 12 within 12 weeks of initiating rilzabrutinib treatment.
40. The method of any one of the preceding Embodiments, wherein the human patient achieves a UCT score ≥ 12 within 8 weeks of initiating rilzabrutinib treatment.
41. The method of any one of the preceding Embodiments, wherein the human patient achieves a UCT score ≥ 12 within 4 weeks of initiating rilzabrutinib treatment.
42. The method of any one of the preceding Embodiments, wherein the human patient achieves a change from baseline in health-related quality-of-life (HRQoL).

43. The method of any one of the preceding Embodiments, wherein the human patient achieves a change from baseline in HRQoL as measured by the Patient Global Impression of Severity (PGIS).
44. The method of any one of the preceding Embodiments, wherein the human patient achieves a change from baseline in HRQoL as measured by the PGIS within 12 weeks of initiating rilzabrutinib treatment.
45. The method of any one of the preceding Embodiments, wherein the human patient achieves a change from baseline in HRQoL as measured by the PGIS within 8 weeks of initiating rilzabrutinib treatment.
46. The method of any one of the preceding Embodiments, wherein the human patient achieves a change from baseline in HRQoL as measured by the PGIS within 4 weeks of initiating rilzabrutinib treatment.
47. The method of any one of the preceding Embodiments, wherein the human patient achieves a change from baseline in HRQoL as measured by the PGIS within 2 weeks of initiating rilzabrutinib treatment.
48. The method of any one of the preceding Embodiments, wherein the human patient achieves a change from baseline in HRQoL as measured by the PGIC.
49. The method of any one of the preceding Embodiments, wherein the human patient achieves a change from baseline in HRQoL as measured by the PGIC within 12 weeks of initiating rilzabrutinib treatment.
50. The method of any one of the preceding Embodiments, wherein the human patient achieves a change from baseline in HRQoL as measured by the PGIC within 8 weeks of initiating rilzabrutinib treatment.

51. The method of any one of the preceding Embodiments, wherein the human patient achieves a change from baseline in HRQoL as measured by the PGIC within 4 weeks of initiating rilzabrutinib treatment.
52. The method of any one of the preceding Embodiments, wherein the human patient achieves a change from baseline in HRQoL as measured by the PGIC within 2 weeks of initiating rilzabrutinib treatment.
53. The method of any one of the preceding Embodiments, wherein the human patient requires rescue therapy.
54. The method of Embodiment 53, wherein the total number of days for which the human patient requires rescue therapy is lower than the total number of days for which the human patient required rescue therapy during a baseline time period of the same length.
55. The method of any one of the preceding claims, wherein the human patient has a history of taking omalizumab prior to the start of the treatment period.
56. The method of any one of the preceding Embodiments, wherein the human patient has had an incomplete response to omalizumab.
57. The method of any one of Embodiments 1-54, wherein the human patient is omalizumab naïve.
58. The method of any one of the preceding Embodiments, wherein the human patient has a positive basophil histamine release assay (BHRA) status.
59. The method of any one of the preceding Embodiments, wherein the human patient receives concomitant treatment with an H1-AH.

60. The method of any one of the preceding Embodiments, wherein the human patient has previously been identified as having increased sMRGPRX2 serum levels.
61. The method of any one of the preceding Embodiments, wherein the human patient has previously been identified as having increased mast cell MRGPRX2 expression.
62. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in sMRGPRX2 serum levels.
63. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in sMRGPRX2 serum levels within 12 weeks of initiating rilzabrutinib treatment.
64. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in sMRGPRX2 serum levels within 8 weeks of initiating rilzabrutinib treatment.
65. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in sMRGPRX2 serum levels within 4 weeks of initiating rilzabrutinib treatment.
66. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in sMRGPRX2 serum levels within 2 weeks of initiating rilzabrutinib treatment.
67. The method of any one of the preceding Embodiments, wherein the human patient has previously been identified as having increased IL-31 serum levels.
68. The method of any one of the preceding Embodiments, wherein the human patient has previously been identified as having increased IL-31 serum levels as a result of increased mast cell or basophil activation.

69. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in IL-31 serum levels.
70. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in IL-31 serum levels within 12 weeks of initiating rilzabrutinib treatment.
71. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in IL-31 serum levels within 8 weeks of initiating rilzabrutinib treatment.
72. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in IL-31 serum levels within 4 weeks of initiating rilzabrutinib treatment.
73. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in IL-31 serum levels within 2 weeks of initiating rilzabrutinib treatment.
74. The method of any one of the preceding Embodiments, wherein the human patient has previously been identified as having increased IgG anti-TPO serum levels.
75. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in IgG anti-TPO serum levels.
76. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in IgG anti-TPO serum levels within 12 weeks of initiating rilzabrutinib treatment.
77. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in IgG anti-TPO serum levels within 8 weeks of

initiating rilzabrutinib treatment.

78. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in IgG anti-TPO serum levels within 4 weeks of initiating rilzabrutinib treatment.
79. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in IgG anti-TPO serum levels within 2 weeks of initiating rilzabrutinib treatment.
80. The method of any one of the preceding Embodiments, wherein the human patient has previously been identified as having increased IgG anti-FC ϵ RI serum levels.
81. The method of any one of the preceding Embodiments, wherein the human patient has previously been identified as having increased mast cell or basophil activation as a result of increased IgG anti-FC ϵ RI levels serum levels.
82. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in IgG anti-FC ϵ RI serum levels.
83. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in IgG anti-FC ϵ RI serum levels within 12 weeks of initiating rilzabrutinib treatment.
84. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in IgG anti-FC ϵ RI serum levels within 8 weeks of initiating rilzabrutinib treatment.
85. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in IgG anti-FC ϵ RI serum levels within 4 weeks of initiating rilzabrutinib treatment.

86. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in IgG anti-FCεRI serum levels within 2 weeks of initiating rilzabrutinib treatment.
87. The method of any one of the preceding Embodiments, wherein the human patient has previously been identified as having increased eosinophil levels.
88. The method of any one of the preceding Embodiments, wherein the human patient has previously been identified as having increased mast cell activation as a result of increased eosinophil levels.
89. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in eosinophil levels.
90. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in eosinophil levels within 12 weeks of initiating rilzabrutinib treatment.
91. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in eosinophil levels within 8 weeks of initiating rilzabrutinib treatment.
92. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in eosinophil levels within 4 weeks of initiating rilzabrutinib treatment.
93. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction from baseline in eosinophil levels within 2 weeks of initiating rilzabrutinib treatment.

94. The method of any one of the preceding Embodiments, wherein the human patient does not achieve a reduction in total serum IgG or IgE levels.
95. A method for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, comprising administering to the human patient a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, wherein the human patient in need thereof has CSU refractory to H1 antihistamines (H1-AH) treatment.
96. The method of any one of the preceding Embodiments, wherein the treatment period is at least 12 weeks.
97. The method of any one of the preceding Embodiments, wherein the treatment period is at least 52 weeks.
98. The method of any one of the preceding Embodiments, wherein the at least one compound consists of at least one compound chosen from the (E) isomer of rilzabrutinib and pharmaceutically acceptable salts thereof.
99. The method of any one of Embodiments 1-97, wherein the at least one compound consists of at least one compound chosen from the (Z) isomer of rilzabrutinib and pharmaceutically acceptable salts thereof.
100. The method of any one of Embodiments 1-97, wherein the at least one compound consists of a mixture of (E) and (Z) isomers of rilzabrutinib or a pharmaceutically acceptable salt of the foregoing.
101. The method of any one of the preceding Embodiments, comprising administering to the human patient rilzabrutinib once, twice, or thrice a day.

102. The method of any one of the preceding Embodiments, comprising administering to the human patient 400 mg of rilzabrutinib once, twice, or thrice a day.
103. The method of any one of the preceding Embodiments, comprising administering to the human patient 400 mg of rilzabrutinib once a day.
104. The method of any one of Embodiments 1-102, comprising administering to the human patient 400 mg of rilzabrutinib twice a day.
105. The method of any one of Embodiments 1-102, comprising administering to the human patient 400 mg of rilzabrutinib thrice a day.
106. The method of any one of Embodiments 1-98 and 101-105 wherein the at least one compound is the (E) isomer of rilzabrutinib.
107. The method of any one of Embodiments 1-97, 99, and 101-105, wherein the at least one compound is the (Z) isomer of rilzabrutinib.
108. The method of any one of Embodiments 1-97 and 100-105, wherein the at least one compound consists of a mixture of (E) and (Z) isomers of rilzabrutinib.
109. The method of any one of the preceding Embodiments, wherein the at least one compound is orally administered to the human patient.
110. The method of any one of the preceding Embodiments, wherein the at least one compound is administered to the human patient in the form of at least one tablet.
111. The method of any one of the preceding Embodiments, wherein the at least one compound is administered with water.

112. The method of any one of Embodiments 1-100 and 109-111, wherein the at least one compound is rilzabrutinib.
113. A therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for use in treating chronic spontaneous urticaria (CSU) in a human patient in need thereof.
114. A therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for use in the manufacture of a medicament for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof.
115. Use of a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof.
116. Use of a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for the manufacture of a medicament for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof.
117. A therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile

(rilzabrutinib) and pharmaceutically acceptable salts thereof, for use in treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, wherein the human patient in need thereof has CSU refractory to H1 antihistamines (H1-AH) treatment.

118. A therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for use in the manufacture of a medicament for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, wherein the human patient in need thereof has CSU refractory to H1 antihistamines (H1-AH) treatment.

119. Use of a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, wherein the human patient in need thereof has CSU refractory to H1 antihistamines (H1-AH) treatment.

120. Use of a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, wherein the human patient in need thereof has CSU refractory to H1 antihistamines (H1-AH) treatment.

[00266] Claims or descriptions that include “or” or “and/or” between at least one members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The disclosure

includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The disclosure includes embodiments in which more than one, or all the group members are present in, employed in, or otherwise relevant to a given product or process.

[00267] Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[00268] The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the disclosure should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

What is claimed is:

1. A method of treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, comprising administering to the human patient in need thereof a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof.
2. The method of claim 1, wherein the human patient has moderate-to-severe CSU.
3. The method of claim 1 or 2, wherein the human patient has moderate CSU.
4. The method of claim 1 or 2, wherein the human patient has severe CSU.
5. The method of any one of the preceding claims, wherein the human patient has CSU refractory to H1 antihistamine (H1-AH) treatment.
6. The method of any one of claims 1-5, wherein the human patient has Type I autoimmune CSU.
7. The method of any one of claims 1-5, wherein the human patient has Type IIb autoimmune CSU.
8. The method of any one of the preceding claims, wherein the human patient has angioedema.
9. The method of any one of the preceding claims, wherein the human patient achieves a Urticaria Activity Score (UAS7) that is lower than baseline UAS7.
10. The method of any one of the preceding claims, wherein the human patient achieves a UAS7 that is lower than baseline UAS7 within 52 weeks of initiating rilzabrutinib

treatment.

11. The method of any one of the preceding claims, wherein the human patient achieves a UAS7 that is lower than baseline UAS7 within 24 weeks of initiating rilzabrutinib treatment.
12. The method of any one of the preceding claims, wherein the human patient achieves a UAS7 that is lower than baseline UAS7 within 12 weeks of initiating rilzabrutinib treatment.
13. The method of any one of the preceding claims, wherein the human patient achieves a UAS7 that is lower than baseline UAS7 within 4 weeks of initiating rilzabrutinib treatment.
14. The method of any one of the preceding claims, wherein the human patient achieves a $UAS7 \leq 6$.
15. The method of any one of the preceding claims, wherein the human patient achieves a $UAS7 \leq 6$ within 12 weeks of initiating rilzabrutinib treatment.
16. The method of any one of the preceding claims, wherein the human patient achieves a UAS7 of 0.
17. The method of any one of the preceding claims, wherein the human patient achieves a UAS7 of 0 within 12 weeks of initiating rilzabrutinib treatment.
18. The method of any one of the preceding claims, wherein the human patient achieves a UAS7 that is at least 10 points lower than baseline UAS7.
19. The method of any one of the preceding claims, wherein the human patient achieves an Itch Severity Score (ISS7) that is lower than baseline ISS7.

20. The method of any one of the preceding claims, wherein the human patient achieves an ISS7 that is lower than baseline ISS7 within 52 weeks of initiating rilzabrutinib treatment.
21. The method of any one of the preceding claims, wherein the human patient achieves an ISS7 that is lower than baseline ISS7 within 24 weeks of initiating rilzabrutinib treatment.
22. The method of any one of the preceding claims, wherein the human patient achieves an ISS7 that is lower than baseline ISS7 within 12 weeks of initiating rilzabrutinib treatment.
23. The method of any one of the preceding claims, wherein the human patient achieves an ISS7 that is at least 5 points lower than baseline ISS7.
24. The method of any one of the preceding claims, wherein the human patient achieves a Hives Severity Score (HSS7) that is lower than baseline HSS7.
25. The method of any one of the preceding claims, wherein the human patient achieves a HSS7 that is lower than baseline HSS7 within 52 weeks of initiating rilzabrutinib treatment.
26. The method of any one of the preceding claims, wherein the human patient achieves a HSS7 that is lower than baseline HSS7 within 24 weeks of initiating rilzabrutinib treatment.
27. The method of any one of the preceding claims, wherein the human patient achieves a HSS7 that is lower than baseline HSS7 within 12 weeks of initiating rilzabrutinib treatment.

28. The method of any one of the preceding claims, wherein the human patient achieves an Angioedema Activity Score (AAS7) that is lower than baseline AAS7.
29. The method of any one of the preceding claims, wherein the human patient achieves an AAS7 that is lower than baseline AAS7 within 52 weeks of initiating rilzabrutinib treatment.
30. The method of any one of the preceding claims, wherein the human patient achieves an AAS7 that is lower than baseline AAS7 within 24 weeks of initiating rilzabrutinib treatment.
31. The method of any one of the preceding claims, wherein the human patient achieves an AAS7 that is lower than baseline AAS7 within 12 weeks of initiating rilzabrutinib treatment.
32. The method of any one of the preceding claims, wherein the human patient achieves a Urticaria Control Test (UCT) score that is higher than baseline UCT score.
33. The method of any one of the preceding claims, wherein the human patient achieves a UCT score that is higher than baseline UCT score within 52 weeks of initiating rilzabrutinib treatment.
34. The method of any one of the preceding claims, wherein the human patient achieves a UCT score that is higher than baseline UCT score within 24 weeks of initiating rilzabrutinib treatment.
35. The method of any one of the preceding claims, wherein the human patient achieves a UCT score that is higher than baseline UCT score within 12 weeks of initiating rilzabrutinib treatment.
36. The method of any one of the preceding claims, wherein the human patient achieves a UCT score that is higher than baseline UCT score within 8 weeks of initiating

rilzabrutinib treatment.

37. The method of any one of the preceding claims, wherein the human patient achieves a UCT score that is higher than baseline UCT score within 4 weeks of initiating rilzabrutinib treatment.
38. The method of any one of the preceding claims, wherein the human patient achieves a UCT score ≥ 12 .
39. The method of any one of the preceding claims, wherein the human patient achieves a UCT score ≥ 12 within 12 weeks of initiating rilzabrutinib treatment.
40. The method of any one of the preceding claims, wherein the human patient achieves a UCT score ≥ 12 within 8 weeks of initiating rilzabrutinib treatment.
41. The method of any one of the preceding claims, wherein the human patient achieves a UCT score ≥ 12 within 4 weeks of initiating rilzabrutinib treatment.
42. The method of any one of the preceding claims, wherein the human patient achieves a change from baseline in health-related quality-of-life (HRQoL).
43. The method of any one of the preceding claims, wherein the human patient achieves a change from baseline in HRQoL as measured by the Patient Global Impression of Severity (PGIS).
44. The method of any one of the preceding claims, wherein the human patient achieves a change from baseline in HRQoL as measured by the PGIS within 12 weeks of initiating rilzabrutinib treatment.
45. The method of any one of the preceding claims, wherein the human patient achieves a change from baseline in HRQoL as measured by the PGIS within 8 weeks of initiating rilzabrutinib treatment.

46. The method of any one of the preceding claims, wherein the human patient achieves a change from baseline in HRQoL as measured by the PGIS within 4 weeks of initiating rilzabrutinib treatment.
47. The method of any one of the preceding claims, wherein the human patient achieves a change from baseline in HRQoL as measured by the PGIS within 2 weeks of initiating rilzabrutinib treatment.
48. The method of any one of the preceding claims, wherein the human patient achieves a change from baseline in HRQoL as measured by the PGIC.
49. The method of any one of the preceding claims, wherein the human patient achieves a change from baseline in HRQoL as measured by the PGIC within 12 weeks of initiating rilzabrutinib treatment.
50. The method of any one of the preceding claims, wherein the human patient achieves a change from baseline in HRQoL as measured by the PGIC within 8 weeks of initiating rilzabrutinib treatment.
51. The method of any one of the preceding claims, wherein the human patient achieves a change from baseline in HRQoL as measured by the PGIC within 4 weeks of initiating rilzabrutinib treatment.
52. The method of any one of the preceding claims, wherein the human patient achieves a change from baseline in HRQoL as measured by the PGIC within 2 weeks of initiating rilzabrutinib treatment.
53. The method of any one of the preceding claims, wherein the human patient requires rescue therapy.

54. The method of claim 53, wherein the total number of days for which the human patient requires rescue therapy is lower than the total number of days for which the human patient required rescue therapy during a baseline time period of the same length.
55. The method of any one of the preceding claims, wherein the human patient has a history of taking omalizumab prior to the start of the treatment period.
56. The method of any one of the preceding claims, wherein the human patient has had an incomplete response to omalizumab.
57. The method of any one of claims 1-55, wherein the human patient is omalizumab naïve.
58. The method of any one of the preceding claims, wherein the human patient has a positive basophil histamine release assay (BHRA) status.
59. The method of any one of the preceding claims, wherein the human patient receives concomitant treatment with an H1-AH.
60. A method of treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, comprising administering to the human patient a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, wherein the human patient in need thereof has CSU refractory to H1 antihistamines (H1-AH) treatment.
61. The method of any one of the preceding claims, wherein the treatment period is at least 12 weeks.

62. The method of any one of the preceding claims, wherein the treatment period is at least 52 weeks.
63. The method of any one of the preceding claims, wherein the at least one compound consists of at least one compound chosen from the (E) isomer of rilzabrutinib and pharmaceutically acceptable salts thereof.
64. The method of any one of claims 1-62, wherein the at least one compound consists of at least one compound chosen from the (Z) isomer of rilzabrutinib and pharmaceutically acceptable salts thereof.
65. The method of any one of claims 1-62, wherein the at least one compound consists of a mixture of (E) and (Z) isomers of rilzabrutinib or a pharmaceutically acceptable salt of the foregoing.
66. The method of any one of the preceding claims, comprising administering to the human patient rilzabrutinib once, twice, or thrice a day.
67. The method of any one of the preceding claims, comprising administering to the human patient 400 mg of rilzabrutinib once, twice, or thrice a day.
68. The method of any one of the preceding claims, comprising administering to the human patient 400 mg of rilzabrutinib once a day.
69. The method of any one of claims 1-67, comprising administering to the human patient 400 mg of rilzabrutinib twice a day.
70. The method of any one of claims 1-67, comprising administering to the human patient 400 mg of rilzabrutinib thrice a day.
71. The method of any one of claims 1-63 and 66-70 wherein the at least one compound is the (E) isomer of rilzabrutinib.

72. The method of any one of claims 1-62, 64, and 66-70, wherein the at least one compound is the (Z) isomer of rilzabrutinib.
73. The method of any one of claims 1-62 and 65-70, wherein the at least one compound consists of a mixture of (E) and (Z) isomers of rilzabrutinib.
74. The method of any one of the preceding claims, wherein the at least one compound is orally administered to the human patient.
75. The method of any one of the preceding claims, wherein the at least one compound is administered to the human patient in the form of at least one tablet.
76. The method of any one of the preceding claims, wherein the at least one compound is administered with water.
77. The method of any one of claims 1-65 and 74-76, wherein the at least one compound is rilzabrutinib.
78. A therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for use in treating chronic spontaneous urticaria (CSU) in a human patient in need thereof.
79. A therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for use in the manufacture of a medicament for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof.

80. Use of a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof.
81. Use of a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for the manufacture of a medicament for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof.
82. A therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for use in treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, wherein the human patient in need thereof has CSU refractory to H1 antihistamines (H1-AH) treatment.
83. A therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for use in the manufacture of a medicament for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, wherein the human patient in need thereof has CSU refractory to H1 antihistamines (H1-AH) treatment.
84. Use of a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for treating chronic

spontaneous urticaria (CSU) in a human patient in need thereof, wherein the human patient in need thereof has CSU refractory to H1 antihistamines (H1-AH) treatment.

85. Use of a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for treating chronic spontaneous urticaria (CSU) in a human patient in need thereof, wherein the human patient in need thereof has CSU refractory to H1 antihistamines (H1-AH) treatment.