TREATMENT OF MODERATE-TO-SEVERE ASTHMA BY ADMINISTERING RILZABRUTINIB

[0001] Disclosed herein are methods for treating moderate-to-severe asthma. BTK inhibitors and pharmaceutical compositions comprising the same are also disclosed.

[0002] Asthma is a chronic inflammatory disease of the airways characterized by airway hyperresponsiveness, acute and chronic bronchoconstriction, airway edema and mucus plugging. The inflammation component of asthma is thought to involve many cell types including epithelial cells, T lymphocytes, eosinophils, mast cells, neutrophils, innate lymphoid cells type 2 (ILC2) and their biological products. Patients with asthma most often present with symptoms of wheezing, shortness of breath, cough, and chest tightness (Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, Updated 2019, Updated 2020, Updated 2021).

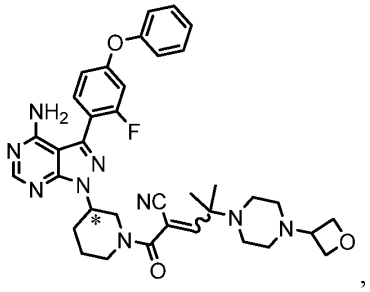
[0003] Despite current treatment options, uncontrolled asthma continues to carry a significant burden, with more than 1 million moderate-to-severe asthmatic adolescent and adults in the U.S. having uncontrolled symptoms on inhaled corticosteroids (ICS) combined with a second controller or systemic corticosteroid therapy (Chung KF et al., 2014; Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, Updated 2019, Updated 2020, Updated 2021). These patients are prone to severe exacerbations and contribute disproportionately to the overall morbidity in this condition, including more hospital days, emergency room visits, and lost work/school days than matched controls with good asthma control. Additionally, they are likely to experience co-morbidities such as anxiety, depression, and insomnia (Bahadori K et al., 2009; To T et al., 2012). Furthermore, systemic corticosteroids, while clinically effective, are associated with significant side effects, such as fluid retention and swelling, glaucoma, increased blood pressure, increased risk of infections, diabetes, osteoporosis, and impaired growth in children (McCracken JL et al., 2016).

[0004] For severe uncontrolled asthma patients, there are several currently approved biologics (Pelaia C et al., 2020). In the severe, corticosteroid-refractory allergy-induced asthma population, the anti-immunoglobulin E (IgE) agent omalizumab (Xolair®) has shown efficacy. Xolair is associated with a black box warning of potential for anaphylaxis. In the severe population with an eosinophilic phenotype, the two currently approved anti-interleukin

(IL)-5 agents, mepolizumab (Nucala®) and reslizumab (Cinqair®), and the anti-IL5 receptor benralizumab (Fasenra™) have shown efficacy as well. These anti-IL5 agents now provide additional therapeutic options with important limitations though. Even in the high eosinophilic group, 36% of patients on mepolizumab had no decrease in oral corticosteroid (OCS) dose or had a lack of asthma control (Bel EH et al., 2014), suggesting that targeting a single cytokine in a heterogenous disease such as asthma is not sufficient. Despite the advent of biologics in the past decade, there remains a significant unmet need for effective asthma treatments. In support of this, up to 60% of patients remain uncontrolled despite treatment with ICS/LABA.

[0005] The main objectives for new therapies are to improve asthma symptoms, lung function, and prevent exacerbations, while optimizing adherence to the treatment. As noted above, one of the reasons for the poor response to medication in some patients with severe asthma may be the heterogeneity of the disease, namely the mixed eosinophilic and neutrophilic inflammation, only partly responding to the current targeted therapies. Underlying deficiencies in innate immunity and evidence of a synergism between viral infection and allergic mechanisms in increasing risk of exacerbations are all important mechanisms to target with novel treatments (Custovic A et al., 2013). Thus, there is an important need for new therapeutic options for patients with asthma.

[0006] Compound (**I**) is a BTK inhibitor of the following structure:



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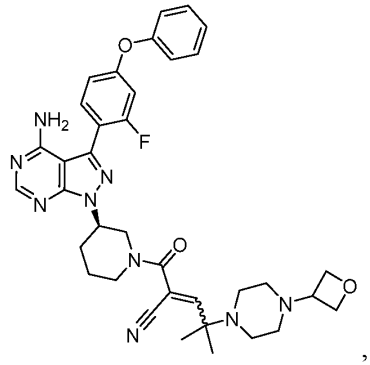
wherein *C is a stereochemical center. *See* PCT Publication No. WO 2014/039899, which is incorporated herein by reference, e.g., Example 31.

[0007] (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:



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is also known as PRN1008 and 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.

[0008] 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).

[0009] 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 μM rilzabrutinib achieved >90% inhibition of just 6 of 251 kinases sharing a common cysteine in their active site. By contrast, 1 μM 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.

[0010] 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).

[0011] 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).

[0012] 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).

[0013] 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.

[0014] Accordingly, disclosed herein are methods of treating asthma 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.

[0015] Further disclosed herein are methods of treating asthma 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 asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and a long-acting β2 adrenergic agonist (LABA).

[0016] 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 asthma 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 asthma in a human patient in need thereof, wherein the human patient in need thereof has asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA).

[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 in the manufacture of a medicament for treating asthma in a human patient in need thereof.

[0019] 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 asthma in a human patient in need

thereof, wherein the human patient in need thereof has asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA).

[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 treating asthma in a human patient in need thereof.

[0021] 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 asthma in a human patient in need thereof, wherein the human patient in need thereof has asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA).

[0022] 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 asthma in a human patient in need thereof.

[0023] 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 asthma in a human patient in need thereof, wherein the human patient in need thereof has asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA).

BRIEF DESCRIPTION OF DRAWINGS

[0024] **Fig. 1** shows a graphical representation of the study design for the 400 mg BID cohort.

[0025] **Fig. 2** shows a graphical representation of the study design for the 400 mg TID cohort.

[0026] **Figs. 3A** and **B** show a Kaplan-Meier plot of time to LOAC post-randomization for the 400 mg BID (A) and 400 mg TID (B) cohorts (mITT population).

[0027] **Figs. 4A** and **B** show a plot of mean change from baseline in pre-bronchodilator FEV1 (L) over time for the 400 mg BID (A) and 400 mg TID (B) cohorts (on-site conventional spirometry, as observed; mITT population).

[0028] **Figs. 5A** and **B** show a plot of LS mean change from baseline in pre-bronchodilator FEV1 over time, reduced model, for the 400 mg BID (A) and 400 mg TID (B) cohorts (mITT population).

[0029] **Figs. 6A** and **B** show a plot of LS mean change from baseline in pre-bronchodilator percent predicted FEV1 (L) over time, reduced model, for the 400 mg BID (A) and 400 mg TID (B) cohorts (mITT population).

[0030] **Fig. 7** shows a plot of LS mean change from inhalations/day of albuterol or levalbuterol for symptom relief over time for the 400 mg BID cohort (mITT population).

[0031] **Fig. 8** shows a plot of LS mean change from inhalations/day of albuterol or levalbuterol for symptom relief over time, reduced model, for the 400 mg BID cohort (mITT population).

[0032] **Figs. 9A** and **B** show a plot of LS mean change from ACQ-5 over time for the 400 mg BID (A) and 400 mg TID (B) cohorts (mITT population).

[0033] **Fig. 10** shows a plot of the proportion of participants with ACQ-5 score less than 0.75 over time for the 400 mg BID cohort (ITT population).

[0034] **Figs. 11A** and **B** show a plot of LS mean change from baseline in ACQ-5 frequency of awakening by asthma over time for the 400 mg BID (A) and 400 mg TID (B) cohorts (mITT population).

[0035] **Figs. 12A** and **B** show a plot of LS mean change from baseline in ACQ-5 asthma symptoms when woke up over time for the 400 mg BID (A) and 400 mg TID (B) cohorts (mITT population).

[0036] **Figs. 13A** and **B** show a plot of LS mean change from baseline in ACQ-5 limitation of activities by asthma over time for the 400 mg BID (A) and 400 mg TID (B) cohorts (mITT population).

[0037] **Figs. 14A** and **B** show a plot of LS mean change from baseline in ACQ-5 shortness of breath experienced over time for the 400 mg BID (A) and 400 mg TID (B) cohorts (mITT population).

[0038] **Figs. 15A** and **B** show a plot of LS mean change from baseline in ACQ-5 wheeze over time for the 400 mg BID (A) and the 400 mg TID (B) cohorts (mITT population).

[0039] **Figs. 16A** and **B** show a plot of LS mean change from AQLQ global score over time for the 400 mg BID (A) and 400 mg TID (B) cohorts (mITT population).

Definitions:

[0040] 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.

[0041] 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.

[0042] 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.

[0043] As used herein, the term "active pharmaceutical ingredient" or "therapeutic agent" ("API") refers to a biologically active compound.

[0044] As used herein, the term "approved treatment" refers to a medication that has received regulatory authorization, in any country, for its intended use.

[0045] 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.

[0046] As used herein, the term "baseline" refers to a measurement obtained within four weeks prior to initiating rilzabrutinib treatment.

[0047] As used herein, "BID" and "bid" are used interchangeably to refer to twice a day. As used herein, 400 mg BID refers to a total dose of 800 mg per day.

[0048] 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.

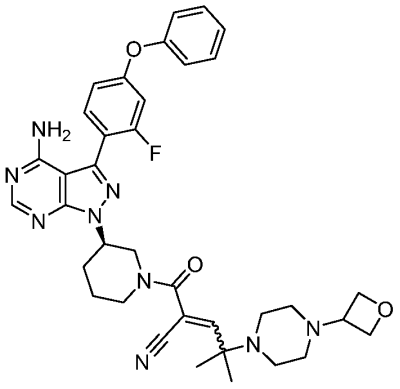
[0049] As used herein, an amount expressed in terms of "mg of [X]" refers to the total amount in milligrams of [X], i.e., the free base. In some embodiments, rilzabrutinib may be administered as a pharmaceutically acceptable salt of rilzabrutinib, in which case an amount expressed in terms of "mg of 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.

[0050] 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.

[0051] 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,

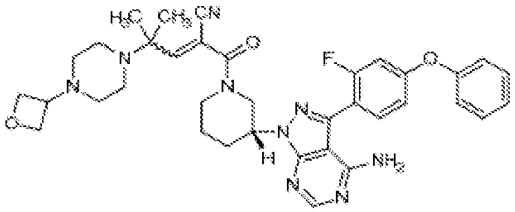
salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, and the like; or formed with organic acids such as formic acid, acetic acid, propionic acid, hexanoic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric 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.

[0052] As used herein, the terms "PRN1008," "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:



(I),

which is also referred to as 2-[(3R)-2-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperdine-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) 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.

[0053] An 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."

[0054] 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 asthma or a symptom of asthma, or lessening the severity of asthma or a symptom of asthma). 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).

[0055] As used herein, "TID" and "tid" are used interchangeably to refer to three times a day. As used herein, 400 mg TID refers to a total dose of 1200 mg per day.

[0056] 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.

[0057] The present disclosure provides methods of treating asthma 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.

[0058] In some embodiments, the human patient has mild asthma. In some embodiments, the human patient has moderate-to-severe asthma. In some embodiments, the human patient has moderate asthma. In some embodiments, the human patient has severe asthma. In some embodiments, the human patient has asthma that is not well controlled. In some embodiments, the human patient has asthma that is not well controlled for one or more symptoms. In some embodiments, the one or more symptoms is selected from frequency of awakening by asthma, asthma symptoms when woke up, limitation of activities by asthma, shortness of breath, and wheeze. In some embodiments, the one or more symptom is frequency of awakening by asthma. In some embodiments, the one or more symptom is asthma symptoms when woke up. In some embodiments, the one or more symptom is limitation of activities by asthma. In some embodiments, the one or more symptom is shortness of breath. In some embodiments, the one or more symptom is wheeze. In some embodiments, the human patient is receiving treatment with step 3, 4, or 5 of the Global Initiative for Asthma (GINA). In some embodiments, the human patient is receiving treatment with step 3 of GINA. In some embodiments, the human patient is receiving treatment with step 4 of GINA. In some embodiments, the human patient is receiving treatment with step 5 of GINA. In some embodiments, the human patient has asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA). In some embodiments, the human patient has asthma that is not well controlled by treatment with an ICS. In some embodiments, the human patient has asthma that is not well controlled by treatment with an LABA.

[0059] In some embodiments, the human patient is withdrawn from ICS/LABA therapy. In some embodiments, the human patient is not withdrawn from ICS/LABA therapy.

[0060] In some embodiments, the human patient does not experience a ≥30% reduction from baseline in morning PEF.

[0061] In some embodiments, the human patient does not require ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol within a 24-hour period for two consecutive 24-hour periods. In some embodiments, the human patient does not

require ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol within a 24-hour period. In some embodiments, the human patient does not require ≥5 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol within a 24-hour period. In some embodiments, the human patient does not require ≥4 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol within a 24-hour period. In some embodiments, the human patient does not require ≥3 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol within a 24-hour period. In some embodiments, the human patient does not require ≥2 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol within a 24-hour period.

[0062] In some embodiments, the human patient does not require an increase in ICS ≥4 times the last prescribed ICS dose. In some embodiments, the human patient does not require an increase in ICS ≥3 times the last prescribed ICS dose. In some embodiments, the human patient does not require an increase in ICS ≥2 times the last prescribed ICS dose. In some embodiments, the human patient does not require an increase in ICS ≥50% of the last prescribed ICS dose. In some embodiments, the human patient does not require an increase in ICS dose. In some embodiments, the human patient achieves a decrease in ICS dose.

[0063] In some embodiments, the human patient does not require the use of systemic steroid treatment, optionally wherein the systemic steroid treatment comprises oral or parenteral treatment.

[0064] In some embodiments, the human patient does not require hospitalization or an emergency room visit for asthma exacerbation.

[0065] In some embodiments, the human patient achieves an increase in pre-bronchodilator FEV1 relative to baseline pre-bronchodilator FEV1. In some embodiments, the human patient achieves an increase in the percent predicted pre-bronchodilator FEV1 prior to baseline pre-bronchodilator FEV1.

[0066] In some embodiments, the human patient achieves a reduction in Asthma Control Questionnaire-5 (ACQ-5) score relative to a baseline ACQ-5 score. In some embodiments, the human patient achieves a reduction in ACQ-5 of ≥0.5 relative to baseline ACQ-5. In some embodiments, the human patient achieves an ACQ-5 score of ≤0.75.

[0067] In some embodiments, the human patient achieves an increase in Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ(S)) relative to baseline AQLQ(S).

[0068] In some embodiments, the human patient achieves a reduction in asthma daytime symptom diary (ADSD) relative to baseline ADSD. In some embodiments, the human patient achieves a reduction in asthma nighttime symptom diary (ANSD) relative to baseline ANSD. In some embodiments, wherein the human patient achieves a reduction in ADSD relative to baseline ADSD and/or a reduction in ANSD relative to baseline ANSD, the patient receives concomitant treatment with ICS and/or LABA.

[0069] In some embodiments, the human patient achieves a reduction in inhalations/day of albuterol or levalbuterol for symptom relief relative to baseline inhalations/day. In some embodiments, wherein the human patient achieves a reduction in inhalations/day of albuterol or levalbuterol for symptom relief relative to baseline inhalations/day, the patient receives concomitant treatment with ICS/LABA.

[0070] In some embodiments, the human patient achieves a reduction in Patient Global Impression of Severity (PGIS) relative to baseline PGIS. In some embodiments, the human patient achieves an improvement in Patient Global Impression of Change (PGIC).

[0071] In some embodiments, the human patient has had asthma for at least 12 months.

[0072] In some embodiments, the human patient is being treated with a moderate to high dose of ICS therapy in combination with LABA. In some embodiments, the human patient is being treated with a moderate dose of ICS therapy in combination with LABA. In some embodiments, the human patient is being treated with a high dose of ICS therapy in combination with LABA. In some embodiments, the ICS is fluticasone propionate and the human patient is being treated with ≥250 μg of fluticasone propionate BID or comparable ICS daily dosage to a maximum of 2000 μg/day of fluticasone propionate or clinically comparable ICS. In some embodiments, the human patient has received treatment with the ICS for at least 3 months. In some embodiments, the human patient has received treatment with a stable dose of the ICS for at least 1 month.

[0073] In some embodiments, the human patient has a baseline reversibility of at least 12% and 200 mL in FEV1 15 to 30 minutes after administration of 200-400 μg of albuterol/salbutamol or levalbuterol/levosalbutamol. In some embodiments, the human patient has a history reversibility of at least 12% and 200 mL in FEV1 15 to 30 minutes after administration of 200-400 μg of albuterol/salbutamol or levalbuterol/levosalbutamol within the 5 years prior to initiation rilzabrutinib treatment. In some embodiments, the human patient has a history of positive response to methacholine challenge within the 5 years prior

to initiation rilzabrutinib treatment. In some embodiments, the human patient has a history of one or more of the following within the 2 years prior to initiation of rilzabrutinib treatment: (a) treatment with a systemic steroid for worsening asthma, optionally wherein the systemic steroid treatment comprises oral or parenteral treatment; and (b) hospitalization or an emergency room visit for asthma exacerbation.

[0074] In some embodiments, the treatment period is at least 12 weeks.

[0075] 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.

[0076] In some embodiments, the methods comprise administering rilzabrutinib to the human patient twice a day. In some embodiments, the methods comprise administering to the human patient 400 mg of rilzabrutinib twice a day. In some embodiments, the methods comprise administering rilzabrutinib to the human patient three times a day. In some embodiments, the methods comprise administering to the human patient 400 mg of rilzabrutinib three times a day.

[0077] 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.

[0078] 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.

[0079] In some embodiments, the at least one compound is rilzabrutinib.

[0080] 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

asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA)

[0081] 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 asthma in a human patient in need thereof.

[0082] 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 asthma in a human patient in need thereof, wherein the human patient in need thereof has asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA).

[0083] 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 asthma in a human patient in need thereof.

[0084] 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 asthma in a human patient in need thereof, wherein the human patient in need thereof has asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA).

[0085] 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 asthma in a human patient in need thereof.

[0086] 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 asthma in a human patient in need thereof, wherein the human patient in need thereof has asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA).

[0087] 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 asthma in a human patient in need thereof.

[0088] 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 asthma in a human patient in need thereof, wherein the human patient in need thereof has asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA).

Pharmaceutical Compositions:

[0089] 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.

[0090] In some embodiments of the present disclosure, rilzabrutinib is orally 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.

[0091] In some embodiments, rilzabrutinib is administered in the form of a film-coated tablet.

[0092] 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.

[0093] In some embodiments, rilzabrutinib is administered with a glass of water.

[0094] 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.

[0095] 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.

[0096] 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

[0097] The following example is intended to be illustrative and is not meant in any way to limit the scope of the disclosure.

Abbreviations:

ACQ-5	Asthma Control Questionnaire-5
AD	Atopic dermatitis
ADSD	Asthma daytime symptom diary
AE	Adverse event
AESI	Adverse event of special interest
ANSD	Asthma nighttime symptom diary
AQLQ(S)	Asthma Quality of Life Questionnaire with Standardized Activities
ATC	Anatomical therapeutic chemical
BD	Bronchodilator
BDR	Bronchodilator response
BID	Twice daily
BTK	Bruton's tyrosine kinase
CI	Confidence interval
CS	Corticosteroid
CSICF	Core study informed consent form
CYP	Cytochrome P450
DPI	Dry powder inhaler
ECG	Electrocardiogram
EOT	End of treatment
ETD	Early treatment discontinuation
FcγR	Fc-gamma receptor
FcεR	Fc-epsilon receptor
FEF	Forced expiratory flow
FVC	Forced vital capacity
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRT	Hormonal replacement therapy
ICS	Inhaled corticosteroid
IgG4-RD	Immunoglobin G4-related disease
IL	Interleukin
ILC2	Innate lymphoid cells type 2
IMP	Investigational medicinal product
IRT	Interactive response technology
ITP	Immune thrombocytopenia
ITT	Intent-to-treat
LABA	Long-acting β2 adrenergic agonist
LAR	Legally authorized representative
LOAC	Loss of asthma control
LOCF	Last observation carried forward
LS	Least squared
MCID	Minimal clinically important difference

MDI	Metered dose inhaler
µg	micrograms
mg	milligrams
OCS	Oral corticosteroid
PBMC	Peripheral blood mononuclear cell
PCSA	Potentially clinically significant abnormality
PD	Pharmacodynamics
PEF	Peak exploratory flow
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PK	Pharmacokinetics
PO	Orally
RD	Risk difference
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TBI	Tuberculosis infection
TEAE	Treatment-emergent adverse event
TID	Three times a day
V	Visit
wAIHA	Warm autoimmune hemolytic anemia
Wk	Week
WOCBP	Woman of childbearing potential
WONCBP	Woman of non-childbearing potential

Example 1: A randomized, double-blind, placebo-controlled, parallel-group, 12-week proof-of-concept (PoC) study to assess the efficacy, safety, and tolerability of rilzabrutinib in patients with moderate-to-severe asthma who are not well controlled on inhaled corticosteroid (ICS) plus long-acting β2 adrenergic agonist (LABA) therapy

Study Design

[0098] This is a global, multicenter, Phase 2, double-blind, 2 arm, parallel treatment, placebo-controlled randomized, proof-of-concept (PoC) study with 2 staggered cohorts (2 arms in each cohort) evaluating the efficacy and safety of rilzabrutinib in adult participants (aged 18-70 years, inclusive) with moderate-to-severe asthma who are not well controlled on inhaled corticosteroid (ICS) plus long-acting β2 adrenergic agonist (LABA) therapy.

[0099] Approximately 192 adult participants meeting the inclusion/exclusion criteria were to be stratified by IgE levels at screening (IgE < 100 IU/mL versus IgE ≥100 IU/mL) and by region and were to be randomized in a 1:1 allocation ratio to either rilzabrutinib or matching placebo. An enrollment cap was to ensure that at least 60% of the participants have IgE ≥ 100 IU/mL at screening.

[0100] Participants were to be enrolled into 2 staggered dose regimen cohorts: a 400 mg BID cohort and a 400 mg TID cohort, starting with the 400 mg BID cohort. These 2 dosing regimen cohorts were to be evaluated with the same double-blind fashion and planned assessments in this study. Participants could only be enrolled in one cohort and were not to be allowed to participate in the 400 mg TID cohort if they had already enrolled in the 400 mg BID cohort.

[0101] Study treatment was to include IMP (rilzabrutinib or placebo) added-on to a background therapy of ICS/LABA (fluticasone/salmeterol (non-investigational medicinal product), standardized at screening). Background therapy of ICS/LABA was to be withdrawn during the 12-week randomized treatment period and resumed at the end of the IMP treatment period, as outlined below:

- Screening period (4 weeks (D-28-D-1))
- Randomized IMP treatment period (12 weeks ± 3 days)
    - Background therapy stabilization phase (4 weeks)
    - Background therapy withdrawal phase (4-5 weeks)
    - No background therapy phase (3-4 weeks)
- Post IMP treatment safety follow-up period (4 weeks ± 3 days)

[0102] At screening, participants must have been using at least moderate to high doses of ICS therapy (≥250 µg of fluticasone propionate BID or comparable ICS daily dosage (1) to a maximum of 2000 µg/day of fluticasone propionate or clinically comparable) in combination with a LABA for at least 3 months with a stable dose ≥1 month prior to Screening Visit 1.

[0103] During the Screening period, participants were to be:

- Trained on using electronic questionnaires (e-diary) at the Screening visit (Visit 1) and will record ANSD (Asthma Nighttime Symptom Diary) and ADSD (Asthma Daytime Symptom Diary), compliance with background treatment starting after the screening visit and continuing through the study period using this e-diary. Clinical site staff were to check patient data collected on the e-diary at each visit.
- Trained on the use of the electronic home PEF meter/spirometry device. Clinical site staff were to check patient data collected on the home PEF meter/spirometry device at each visit.
- Queried on personal history of comorbid atopic conditions as well as history of allergy (including aeroallergens, dust mites, and molds). Results of historical skin

testing specifying the technique (prick/puncture (percutaneous) or intradermal (intracutaneous) or RAST) was to be collected.

[0104] After completion of screening procedures, all eligible participants were to be switched to clinically comparable doses of the study-specific ICS/LABA combination therapy with fluticasone/salmeterol, as approved by local Health Authority:

- Fluticasone/salmeterol – DPI:
  - 1 inhalation of 250/50 µg BID or
  - 1 inhalation of 500/50 µg BID

  OR
- Fluticasone/salmeterol – MDI:
  - 2 inhalations of 115/21 µg (230/42 µg) BID or
  - 2 inhalations of 230/21 µg (460/42 µg) BID

  OR
- Fluticasone/salmeterol – MDI:
  - 2 inhalations of 125/25 µg (250/50 µg) BID or
  - 2 inhalations of 250/25 µg (500/50 µg) BID

[0105] Participants who satisfied the inclusion and exclusion criteria were to be randomized (1:1 ratio) to either rilzabrutinib (400 mg) or matching placebo, administered orally BID for 12 weeks.

Background therapy (ICS/LABA) withdrawal phase

[0106] At Week 4 (Visit 6), the LABA component (salmeterol) was to be withdrawn, and participants were to be switched from their BID fluticasone/salmeterol combination therapy to a clinically comparable ICS dose of fluticasone BID monotherapy, as approved by local Health Authority:

- Fluticasone (DPI formulation):
  - 1 inhalation of 250 µg BID or
  - 2 inhalations of 250 µg (500 µg) BID,

  OR
- Fluticasone (MDI formulation):
  - 2 inhalations of 110 µg (220 µg) BID or
  - 2 inhalations of 220 µg (440 µg) BID

  OR

- Fluticasone (MDI formulation):
    - 2 inhalations of 125 µg (250 µg) BID or
    - 2 inhalations of 250 µg (500 µg) BID

[0107] The ICS component (fluticasone) was to be withdrawn by a stepwise dose reduction starting at Week 6 (Visit 8) and was to continue at each Week 7 (Visit 9), Week 8 (Visit 10), and, in those being tapered from high dose ICS, Week 9 (Visit 11), provided that participants did not experience an LOAC event (**Table 1**).

[0108] **Table 1. Withdrawal of fluticasone – downward titration doses (administered twice a day).**

	Wk 4/V 6	**Wk 6/ V8**	**Wk 7/V 9**	**Wk 8/V 10**	**Wk 9/V 11**
Fluticasone DPI Dose (µg) administered BID	250	100	50	0	0
	500	250	100	50	0
Fluticasone MDI Dose (µg) administered BID	220	110	44	0	0
	440	220	110	44	0
	250	125	50	0	0
	500	250	125	50	0

[0109] Participants were to use the same inhaler type (either DPI or MDI) throughout the study.

[0110] Participants that met the criteria for a LOAC, at any time during the randomized IMP treatment phase, were to (be):

- Discontinue early from IMP treatment,
- Evaluated and receive treatment by the Investigator with standard of care according to standard medical practice. If practicable and safe, the participant was to undergo EOT Visit (Visit 14) assessment prior to the administration of rescue medications.
- Resume their individual prescreening ICS/LABA background therapy and,
- Followed for safety during a 4-week Post IMP Treatment Period.

Early treatment discontinuation (ETD) follow-up

[0111] Participants who discontinued IMP treatment prior to completing the 12-week IMP treatment (due to LOAC or due to early treatment discontinuation), were to be evaluated as soon as possible at the individual participant's EOT Visit and using procedures as planned for the EOT Visit at Week 12 (Visit 14). At their EOT visit, participants were to resume their

prescreening ICS/LABA background therapy or appropriate therapy as needed per treating physician were to be resumed after the EOT study assessments had been performed and entered the 4-week safety follow-up period/Post IMP Treatment Period, concluding with the EOS Visit (Visit 16).

Post IMP treatment follow-up

[0112] Participants who completed the 12-week randomized IMP treatment period at Week 12 (Visit 14) EOT visit, as per protocol, were to resume their prescreening ICS/LABA therapy and enter the 4-week safety follow-up period/Post IMP Treatment Period concluding with the EOS Visit (Visit 16).

[0113] At EOT visit, if a participant's asthma could be adequately controlled by the prescreening ICS/LABA therapy, additional controller therapies may also have been prescribed based on the Investigator's clinical judgement.

Objectives and Endpoints

[0114] Objectives and endpoints for this study are described in **Table 2** below.

[0115] Table 2. Objectives and endpoints.

Objectives	Endpoints
Primary	
Evaluate the effects of rilzabrutinib compared to placebo on reducing the incidence of "loss of asthma control" (LOAC) events	Proportion of participants with an LOAC event during the treatment period, defined as any one of the following: (1) a 30% or greater reduction from baseline in morning peak expiratory flow (PEF) on 2 consecutive days; (2) ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared to baseline) on 2 consecutive days; (3) increase in ICS ≥4 times the last prescribed ICS dose (or ≥50% of the prescribed ICS dose at V2 if background therapy withdrawal completed); (4) requiring use of systemic (oral and/or parenteral) steroid treatment; (5) requiring hospitalization or emergency room visit for asthma exacerbation
Secondary	
Evaluate the effects of rilzabrutinib compared to placebo on lung function as measured by FEV1	Pre-bronchodilator FEV1 change from baseline at EOT (key secondary endpoint)
	Post-bronchodilator FEV1 change from baseline at EOT

	The absolute change in the percent predicted FEV1 from baseline to EOT (pre- and post-bronchodilator)
Assess the effects of rilzabrutinib on other elements of spirometric lung function	Change from baseline in pre- and post-bronchodilator FEV1 and other lung function measurements (PEF, forced vital capacity (FVC), and forced expiratory flow (FEV) 25-75%) at each spirometry endpoint
Assess the effect of rilzabrutinib on patient reported outcomes	Asthma Control Questionnaire-5 (ACQ-5) score change from baseline at EOT and at each assessment time point
	Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ(S) Self-administered score change from baseline at EOT and at each assessment time point
Assess the effects of rilzabrutinib on asthma symptoms	Change from baseline at EOT and change from baseline at each week for Asthma Daytime Symptom Diary (ADSD) and Asthma Nighttime Symptom Diary (ANSD) scores.
Assess the plasma pharmacokinetics (PK) of rilzabrutinib in participants with asthma	Plasma PK concentrations of rilzabrutinib in participants with asthma
Assess the safety of rilzabrutinib in participants with asthma	Adverse events (AEs), vital signs, labs
Assess the use of rilzabrutinib on bronchodilator therapy	Change from baseline and at EOT and change from baseline at each week in numbers of inhalations/day of albuterol or levalbuterol for symptom relief
Exploratory	
Assess the effect of rilzabrutinib based on baseline blood IgE levels	Primary and secondary outcomes in subgroups of participants with baseline blood IgE levels of ≥100 or <100 IU/uL
Assess the effects of rilzabrutinib on fraction of exhaled nitric oxide (FENO)	Change in FENO from baseline to EOT
Assess the effects of rilzabrutinib on allergic phenotype	Skin prick test (SPT) to be administered in participants with documented previously positive allergy testing at baseline and EOT
Assess the effects of rilzabrutinib on oscillatory lung mechanics	Change from baseline in forced oscillatory technique (FOT)
Assess the effects of rilzabrutinib on biomarkers in participants with asthma	Patient Global Impression of Severity (PGIS) change from baseline to EOT and at each assessment time point
	Patient Global Impression of Change (PGIC) from baseline to EOT and at each assessment time point

Appropriateness of Measurements

[0116] The assessments used in this study are all standard endpoints in evaluation of disease activity and response to therapy in asthma.

[0117] The general construct of this 12-week Loss of Asthma Control (LOAC) study consisted of a 4-week standardized ICS/LABA background therapy stabilization phase, a 4-

or 5-week background therapy withdrawal phase and a 3- or 4-week no background therapy phase, followed by a 4-week post IMP treatment safety follow-up period at the beginning of which, pre-screening asthma controller medications are restarted. Participants had access to short-acting β-agonist (SABA) reliever medication at all times during the protocol. The primary endpoint of this study is defined as the proportion of participants with an LOAC event during the treatment period, which consists of any of the following: 1) A 30% or greater reduction from baseline in morning PEF on 2 consecutive days; 2) 6 or more additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared to baseline) on 2 consecutive days; 3) Increase in ICS ≥4 times the last prescribed ICS dose (or ≥50% of the prescribed ICS dose at V2 if background therapy withdrawal completed); 4) Requiring use of systemic (oral and/or parenteral) steroid treatment; or 5) Requiring hospitalization or emergency room visit for asthma exacerbation.

[0118] This approach allowed for a relatively brief study capable of rapidly identifying the loss of asthma control and minimizing the duration of patient exposure to loss of controller therapy.

[0119] Spirometry is a standard test to measure patients' lung function. It was to be performed in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (Graham BL et al., 2019).

[0120] The ACQ-5 was designed to measure both the adequacy of asthma control and change in asthma control which may have occurred either spontaneously or as a result of treatment. Measurement properties such as reliability and ability to detect change have been documented in the literature (Juniper et al. 2005).

[0121] The AQLQ(S) is a self-administered patient reported outcome to measure the functional impairments that are most troublesome to adolescents and adults≥12 years of age as a result of their asthma. The instrument has been used in many clinical trials, and it has been shown to be reliable, valid (patient interviews), and sensitive to change. The MCID for AQLQ(S) is 0.5 (Juniper et al. 1994).

[0122] ADSD and ANSD are PRO measures developed by the PRO Consortium' Asthma Working Group. Both instruments have been designed to measure asthma symptoms in adult and adolescent (12 years of age and older) patients diagnosed with mild to severe asthma. ADSD and ANSD assess asthma severity based on patient self-report of asthma core symptoms. They have demonstrated adequate evidence of content validity and cross-sectional

measurement properties (*i.e.*, internal consistency reliability, test-retest reliability, convergent validity, and known-groups validity) to measure symptoms of asthma (Gater et al. 2016).

[0123] In terms of safety, TEAEs, SAEs, adverse events of special interest (AESIs), vital signs, and laboratory analyses were to be reported.

Study Population

[0124] Inclusion criteria are summarized in **Table 3**. Participants were eligible to be included in the study only if all of the criteria applied.

[0125] **Table 3. Inclusion Criteria.**

Age	Participants must have been from 18 to 70 years of age at the time of signing the informed consent
Type of participant and disease characteristics	A physician diagnosis of asthma for at least 12 months based on the Global Initiative for Asthma (GINA) 2019, 202, or 2021 Guidelines (Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, Updated 2019, Updated 2020, Updated 2021)
	Participants with existing treatment with at least moderate to high doses of ICS therapy (≥250 μg of fluticasone propionate BID or comparable ICS daily dosage (1) to a maximum of 2000 μg/day of fluticasone propionate or clinically comparable) in combination with a LABA as a second controller for at least 3 months with a stable dose ≥1 month prior to V 1. The lower limit of allowed ICS dose (500 μg of fluticasone propionate daily) corresponds to upper limit of medium dose defined by GINA guidelines. Patients receiving medium ICS dose <500 μg daily were not eligible.
	Participants with prebronchodilator FEV >40% of predicted normal at V 1screening. Prebronchodilator FEV1 ≥50% of predicted normal at V 2/baseline.
	Participants with reversibility of at least 12% and 200 mL in FEV1 15 to 30 minutes after administration of 2 to 4 puffs (200-400 μg) of albuterol/salbutamol or levalbuterol/levosalbutamol during screening or documented history of a reversibility test that met this criterion within 5 years prior to V 1 or documented positive response to methacholine challenge (a decrease in FEV1 by 20% (PC_{20}) of <8 mg/mL) within 5 years prior to V 1/screening

	were considered acceptable to meet this inclusion criterion.
	Participants must have experienced, within 2 years prior to V 1, any of the following asthma exacerbation events at least once: (1) treatment with a systemic steroid (oral or parenteral) for worsening asthma; and (2) hospitalization or emergency medical care visit for worsening asthma.
Weight	Body mass index (BMI) ≥17.5 and ≤40 kg/m^2
Sex, contraceptive/barrier method, and pregnancy testing requirements	All contraceptive use by men and women should have been consistent with local regulations regarding the methods of contraception for those participating in clinical studies
	Male participants were eligible to participate if they 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; AND • (1) Abstain from heterosexual intercourse as their preferred and usual lifestyle (*i.e.,* be abstinent on a long term and persistent basis) and agree to remain abstinent; OR (2) agree to use contraception/barrier[1]
	Female participants were eligible to participate if they were not pregnant or breastfeeding, and one of the following conditions applied: • She was a woman of non-childbearing potential (WONCBP); OR • She was a woman of childbearing potential (WOCBP)[2] and agreed to use a contraceptive method that is highly effective (with a failure rate of <1%), preferably with low user dependency, during the study intervention period (to be effective before starting the intervention) and for at least 4 weeks after the last administration of study

[1] A male condom and an additional highly effective contraceptive method when having sexual intercourse with a woman of childbearing potential who is not currently pregnant; or a male condom when engaging in any activity that allows for passage of ejaculate to another person.

[2] A WOCBP must have had a negative highly sensitive pregnancy test ((urine or serum) as required by local regulations) within 28 days before the first administration of study intervention. If a urine test could not be confirmed as negative (*e.g.,* an ambiguous result), a serum pregnancy test was to be required. In such cases, the participant must have been excluded from participation if the serum pregnancy result was positive.

	intervention and agreed not to donate or cryopreserve eggs (ova, oocytes) for the purpose of reproduction during this period.
Informed consent	Capable of giving signed informed consent, which included compliance with the requirements listed in the informed consent form (ICF) and in this protocol. In countries where legal age of majority is above 18 years, a specific ICF must also have been signed by the participant's legally authorized representative (LAR).
COVID-19 vaccination	Participants must have completed COVID-19 vaccination per current regional health authority recommendations prior to screening.

[0126] Exclusion criteria are summarized in **Table 4**. Participants were excluded from the study if any of the criteria applied.

[0127] **Table 4. Exclusion criteria.**

Medical conditions	History of serious infections requiring intravenous therapy with the potential for recurrence (as judged by the Site Investigator, with less than 4 weeks' interval between resolution of serious infection and first dose of study drug, or currently active moderate-to-sever infection at screening (Grade 2 or higher).
	Chronic lung disease (for example, chronic obstructive pulmonary disease (COPD), or idiopathic pulmonary fibrosis (IPF)) which may impair lung function, or another diagnosed pulmonary or systemic disease associated with elevated peripheral eosinophil counts, for *e.g.*, eosinophilic granulomatosis with polyangiitis.
	History of life-threatening asthma (*i.e.*, severe exacerbation that requires intubation).
	Participants with any of the following events within the 4 weeks prior to their screening V 1 or during the screening period: (1) treatment with 1 or more systemic (oral and/or parenteral) steroid bursts for worsening asthma; and (2) hospitalization or emergency medical care visit for worsening asthma.
	Asthma Control Questionnaire 5-question version (ACQ-5) score <1.25 or >3.0 at V 2/randomization. During the screening period, an ACQ-5 of up to ≤4 was acceptable.
	Current smoker or cessation of smoking within the 6 months prior to V 1.

	Previous smoker with a smoking history of >10 pack-years.
	Current or chronic history of liver disease. This included but was not limited to hepatitis virus infections, drug- or alcohol-related liver disease, non-alcoholic steatohepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, primary biliary cholangitis, primary sclerosing cholangitis, or any other liver disease considered clinically significant by the Investigator.
	Symptomatic herpes zoster within 3 months prior to screening.
	Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate rilzabrutinib/placebo absorption.
	Conditions that may have predisposed the participant to excessive bleeding: • A bleeding disorder or known platelet dysfunction at any time prior to the screening visit. • The participant had major surgery within 4 weeks prior to the screening visit, which could affect the participant's safety or affect immune response (as judged by the Investigator) or had planned any elective major surgery during the study. • A history of significant bleeding event within 6 months prior to screening, according to the Investigator's judgment such as, but not limited to, cerebral or gastrointestinal bleeding.
	History of solid organ transplant
	A history of malignancy of any type within 5 years before D 1, other than surgically excised non-melanoma skin cancers or in situ cervical cancers
	Was not up-to-date with recommended vaccinations per local guidelines.
Prior/concomitant therapy	Anti-immunoglobulin E (IgE) therapy (*e.g.,* omalizumab (Xolair®) within 130 days prior to V 1 or any other biologic therapy (including anti-IL4/4R or IL-5/5R monoclonal antibodies (mAb) or systemic immunosuppressant (*e.g.,* methotrexate) to treat inflammatory disease or autoimmune disease (*e.g.,* rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis) and other diseases, within 2 months or 5 half-lives prior to V 1, whichever is longer.

	Use of inhalers other than ICSs, LABAs, and short-acting beta agonists (no LAMAs or mucolytics) and leukotriene receptor antagonists (montelukast, zafirkulast) during the study period.
	Participants who had received bronchial thermoplasty within 2 years prior to V 1 or plan to begin therapy during the screening period or the randomized treatment period.
	Use of proton pump inhibitor drugs such as omeprazole and esomeprazole within 3 days of D 1 (it was acceptable to change patient to H2 receptor blocking drugs prior to D 1)
	Use of known systemic strong-to-moderate inducers[3] or inhibitors[4] of CYP3A within 14 days or 5 half-lives (whichever is longer) of study D 1 and until the end of the active treatment period.
	Live vaccine except Bacille Calmette Guerin vaccination within 28 days prior to D 1 or plans to receive one during the trial; Calmette Guerin vaccination within 12 months prior to screening.
	COVID-19 vaccine within 14 days prior to study D 1
Prior/concurrent clinical study experience	Previous use of a BTK inhibitor
	Had received any investigational drug (or is currently using an investigational device) within the 30 days before D 1, or at least 5 times the respective elimination half-life time (whichever is longer).
Diagnostic assessments	Any of the following laboratory abnormalities at the screening visit (identified by the central laboratory): • Absolute neutrophil count $<1.5 \times 10^9$/L

[3] Strong CYP3A inducers include apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, and St. John's wort. Moderate CYP3A inducers include Bosentan, efavirenz, etravirine, phenobarbital, and primidone. Source: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, U.S. Food and Drug Administration..

[4] Strong CYP3A inhibitors include 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, and voriconazole. Moderate CYP3A inhibitors include aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, and verapamil. Source: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, U.S. Food and Drug Administration.

	• Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 upper limit of normal (ULN) • Total bilirubin >1.5 ULN (isolated bilirubin >1.5 x ULN is acceptable if total bilirubin is fractionated and direct bilirubin <35%) • IgG <500 mg/dL • Abnormal international normalized ratio (INR) test and activated partial thromboplastin time (aPTT) judged by the Investigator to be clinically significant • A platelet count <150,000/μL[5]
	Positive for human immunodeficiency virus (HIV) at screening
	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 first administration of study intervention.
	Positive hepatitis C antibody test result at screening or within 3 months prior to starting study intervention[6].
	Exclusion related to tuberculosis infection (TBI): • Active TBI or a history of incompletely treated TBI regardless of screening Quantiferon (QFT) result. • QFT positive patients (no active disease) are excluded from the study unless the following conditions were met: (1) patients with a history of prior documented completed chemoprophylaxis for latent TBI (*e.g.*, acceptable treatments would be 9 months of isoniazid 300 mg oral daily or equivalent proven regimen per local guidelines) or treatment of active TBI who had obtained consultation with a specialist to rule out active TBI or treat active TBI; (2) consultation with and prior approval from the Sponsor were required in either of the aforementioned scenarios. **Otherwise**, a documented negative screening for TB via a negative QFT within 3 months prior to screening

[5] A one-time retest value at screening may have been performed by the Investigator if abnormal laboratory test values are found.

[6] Participants with positive hepatitis C antibody due to prior resolved disease could be enrolled, only if a confirmatory negative Hepatitis C RNA test was obtained.

	(and if required per local standard of care, a chest X-ray), was sufficient and no further screening with QFT was required; if clinically indicated, the test may have been repeated based on clinical judgment, borderline results, or clinical suspicion of TBI. • Clinically significant abnormality consistent with prior/active TBI based upon chest radiograph with at least posterior-anterior view (radiograph must have been taken within 12 weeks prior to screening visit or during the screening period). Additional lateral view was recommended but not required. • Suspected extrapulmonary TBI regardless of screening QFT result. • Patients at high risk of contracting TB, such as close contact with individuals with active or latent TBI.
	Electrocardiogram (ECG) findings of QT corrected for heart rate (QTc) >450 msec (males) or >470 msec (females), poorly controlled atrial fibrillation (*i.e.*, symptomatic patients or a ventricular rate above 100 beats/min on ECG), or other clinically significant cardiovascular abnormalities.
	Active COVID-19 infection as documented by a positive COVID-19 molecular test

Lifestyle Considerations

[0128] Participants were to refrain from consumption of grapefruit or grapefruit juice, from 7 days before the start of study intervention until the completion of the final dose.

[0129] No restriction of caffeine or activity was required. Smoking was not permitted during the trial and current smokers were excluded from participation.

Retesting: Laboratory Inclusion/Exclusion Criteria

[0130] If a participant did not meet certain laboratory inclusion/exclusion criteria at Screening due to the following laboratory results, the Investigator may have repeated one or more of these tests once during the screening period:

- ALT or AST > 1.5 x ULN (may have been repeated if 1.5 to 3 x ULN)
- Total bilirubin > 1.5 x ULN (may have been repeated if 1.5 to 3 x ULN)

- Absolute neutrophils count <1.5 x 10^9/L (may have been repeated if 1.2 to 1.5 x 10^9/L)
- A platelet count <150,000/µL (may have been repeated if 120,000/µL to 150,000/µL)
- Positive result for SARS-CoV-2 infection

[0131] If the participant met the laboratory eligibility criteria on the second assessment, he or she was to be permitted to enter the study. It was not to be considered a retesting if blood samples had to be redrawn because of sample handling problems, breakage, sample integrity, or laboratory error.

[0132] If a hematology/chemistry lab value fell outside the normal range and was judged by the Investigator to be clinically significant and was NOT one of explicit exclusionary laboratory testing, it may have been repeated once and if the repeat value was no longer considered clinically significant then that specific laboratory testing result should not have disqualified a participant from the study.

Study Intervention(s) and Concomitant Therapy

[0133] 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 5-6**).

[0134] Rilzabrutinib and placebo tablets were supplied ready for use; no preparation was needed. Participants were to use study medication directly from the dispensed bottles.

[0135] Participants were to administer rilzabrutinib or placebo by mouth twice daily (400 mg BID cohort) or three times daily (400 mg TID cohort). Consecutive doses should ideally have been administered approximately 12 hours apart (and not less than 8 hours apart) for 400 mg BID dosing, and ideally approximately 6 hours apart (and not less than 4 hours apart) for 400 mg TID dosing. Tablets should not have been broken or crushed.

[0136] Study intervention was to be dispensed at the study visits. The study intervention to be taken by a participant was to be allocated using an IRT. The site was to contact the IRT prior to the start of study intervention administration for each participant. The site was to record the intervention assignment on the applicable case report form, if required.

[0137] Table 5. Overview of study interventions administered.

Intervention label	Rilzabrutinib	Placebo
Intervention name	Rilzabrutinib	Placebo
Type	Drug	Drug
Dose formulation	Tablets (modified-capsule shaped tablets)	Tablets (modified-capsule shaped tablets)
Unit dose strength(s)	400 mg	0 mg
Dosage level(s)	400 mg (1 tablet) BID or TID	1 tablet BID or TID
Route of administration	Oral	Oral
Use	Experimental	Placebo
IMP or NIMP	IMP	IMP
Packaging and labeling	Rilzabrutinib tablets were to be supplied in white plastic bottles with child-resistant induction-sealed caps. The bottles were to be labeled as required per country requirement	Placebo tablets were to be supplied in white plastic bottles with child-resistant induction-sealed caps. The bottles were to be labeled as required per country requirement
Current/former name(s) or alias(es)	Rilzabrutinib	Not applicable

[0138] Table 6. Arms and associated interventions.

Arm name	**Rilzabrutinib 400 mg BID**	**Placebo BID**	**Rilzabrutinib 400 mg TID**	**Placebo TID**
Associated interventions (intervention label(s))	Rilzabrutinib and ICS/LABA	Placebo and ICS/LABA	Rilzabrutinib and ICS/LABA	Placebo and ICS/LABA

[0139] Participants were to continue their background therapy of ICS/LABA (fluticasone/salmeterol (non-investigational medicinal product), standardized at screening). Background therapy of ICS/LABA was to be withdrawn during the 12-week randomized treatment period and resumed at the end of the IMP treatment period (**Figures 1-2** and **Table 7**).

[0140] Table 7. Background therapy.

Intervention label	ICS/LABA stabilization phase V2 Week 0 to V6 Week 4	ICS/LABA withdrawal phase V6 Week 4 to V10 Week 8 (V11 Week 9 in those tapering from high dose ICS)
Intervention name	Fluticasone/Salmeterol combination therapy	Fluticasone monotherapy
Type	Drug	
Dose formulation	Dry powder inhaler (DPI) or metered dose inhaler (MDI)	
Unit dose strength(s)	DPI: 1 inhalation of 250/50 µg BID or 1 inhalation of 500/50 µg BID OR MDI: 2 inhalations of 115/21 µg BID or 2 inhalations 230/21 µg BID OR MDI: 2 inhalations of 125/25 µg BID or 2 inhalations of 250/25 µg BID	DPI: 1 inhalation of 250 µg BID or 2 inhalations of 250 µg BID OR MDI: 2 inhalations of 110 µg BID or 2 inhalations of 220 µg BID OR MDI: 2 inhalations of 125 µg BID or 2 inhalations of 250 µg BID
Dosage level(s)		
Route of administration	Inhalation	
Use	Background therapy	
IMP or NIMP	NIMP	
Packaging and labelling	Not applicable	
Current/former name(s) or alias(es)	Not applicable	

[0141] Participants were to use the same inhaler type (either DPI or MDI) throughout the study.

Dose Modification

[0142] Rilzabrutinib dose modification was not allowed.

Concomitant Therapy

[0143] Any medication or vaccine (including over-the-counter or prescription medicines, 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:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and

[0144] The Medical Monitor should have been contacted if there were any questions regarding concomitant or prior therapy.

[0145] Participants were to have abstained from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is 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.

[0146] Medications that were not listed as exclusion criteria were permitted for use during the trial.

[0147] These include the following:

- Oral corticosteroid rinses (mouth washes) were allowed, as are ocular, intranasal, and topical corticosteroids.
- Clinically relevant drugs that are substrates of cytochrome P450 (CYP)3A, including those considered to be sensitive CYP3A substrates[7] 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 should also have been given to avoidance of high doses, dose reduction, or replacement of sensitive and narrow therapeutic index CYP3A substrate drugs. Systemic moderate or strong inhibitors (including foods such as grapefruit juice) and inducers of CYP3A should have been avoided.
- Histamine 2 (H2) receptor blocking drugs were permitted provided they could have been given 2-3 hours after administration of rilzabrutinib or placebo. For patients receiving the IMP three times a day, H2-receptor blockers must have been taken once daily only, 2-3 hours after the evening dose of rilzabrutinib or placebo.

[7] Sensitive CYP3A substrates include Alfentanil, avanafil, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, ibrutinib, indinavir, lomitapide, lovastatin, lurasidone, maraviroc, midazolam, naloxegol, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, ticagrelor, tolvaptan, tipranavir, triazolam, and vardenafil. Source: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, U.S. Food and Drug Administration. This list is not intended to be exhaustive and may be out of date. For updated information, please refer to https://www.fda.gov/drugs/drug-interactionslabeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers or product labeling.

- Antacids were permitted provided they were given 2 hours or more apart from rilzabrutinib or placebo.
- Previously initiated immunotherapy was to be allowed to continue during the study.

[0148] The following concomitant treatments were not permitted during the screening or treatment phases:

- Any inhaled steroid other than the standardized fluticasone/salmeterol or fluticasone
- background therapy administered as per protocol
- Systemic steroids (except systemic steroids to treat asthma exacerbations)
- LABA other than the salmeterol component of the fixed dose combination administered per protocol
- Ipratropium bromide or other inhaled anti-cholinergic agents (tiotropium)*
- Methylxanthines (theophylline, aminophyllines)*
- Inhaled mucolytic*
- Leukotriene receptor antagonists or leukotriene synthesis inhibitors*
- Lipoxygenase inhibitors
- Cromones
- Anti-IL4R mAb (eg, dupilumab (Dupixent®))
- Anti-IL5 or IL-5R mAb (eg, benralizumab (Fasenra®), mepolizumab (Nucala®), or reslizumab (Cinqair®))
- Anti-IgE mAb (eg, omalizumab (Xolair®))
- Anti-TSLP mAb (eg, tezepelumab)
- Systemic immunosuppressant (*e.g.*, methotrexate, any anti-TNF mAbs, B and/or T cell targeted immunosuppressive therapies)
- Bronchial thermoplasty
- Intravenous Ig (IVIG) therapy
- Live Attenuated Vaccines[8]
- Beta-adrenergic receptor blockers (except for a selective beta-1 adrenergic receptor blocker used with stable dose at least 1 month prior to Visit 1)

[8] Live (attenuated) vaccines include Chickenpox (Varicella), Intranasal influenza, Measles (Rubeola), Measles-mumps-rubella (MMR) combination, Mumps, Oral polio (Sabin), Oral typhoid, Rubella, Smallpox (Vaccinia), Shingles (Herpes zoster), Bacille Calmette-Guerin, Yellow fever. Note: Shingrix is allowed for Shingles as a non-live Varicella vaccine.

- Asthma relievers other than salbutamol/albuterol or levosalbutamol/levalbuterol: their use was not recommended during the study period. In case of use in exceptional circumstances (*e.g.*, prescribed by a physician not participating in the study), their use was to be documented in the patient's file and reported in the eCRF.
- Initiation of immunotherapy
- Other investigational drugs
- Use of proton-pump inhibitor drugs such as omeprazole and esomeprazole (allowed during screening provided they were stopped within 3 days of Day 1).
- Use of known systemic strong-to-moderate inducers or inhibitors of CYP3A (allowed during screening provided they were stopped days within 14 days or 5 half-lives (whichever is longer) of Day 1).

[0149] * The third controller was not allowed to be used for an additional 2 weeks prior to screening visit (V1).

Rescue Medicine

[0150] If medically necessary, participants may have received rescue therapy for asthma at the discretion of the Investigator as an LOAC event. If practicable and safe, the participant should have undergone EOT Visit (Visit 14) assessment prior to the administration of rescue medications. Participants who discontinued IMP treatment prior to completing the 12-week IMP treatment (due to LOAC or due to other early treatment discontinuation), were to be evaluated as soon as possible at the individual participants' EOT Visit, using procedures as planned for the EOT Visit at Week 12 (Visit 14). At their EOT visit, participants were to resume their prescreening ICS/LABA background therapy and enter the 4-week safety follow-up period/Post IMP Treatment Period. If a participant's asthma could not be consistently controlled on his/her original ICS/LABA therapy, and there was a safety concern, additional controller therapies may have been prescribed based on the Investigator's clinical judgement.

Efficacy Assessments

[0151] The following efficacy parameters were to be analyzed for assessing the primary and secondary endpoints.

[0152] The primary endpoint was the proportion of patients with LOAC. The key secondary endpoint for the study was change in pre-bronchodilator FEV1 from baseline at EOT.

[0153] Other efficacy endpoints included:

- Change from baseline in pre- and post-bronchodilator FEV1 and other lung function measurement (peak expiratory flow (PEF), forced vital capacity (FVC), forced expiratory flow (FEF) 25-75%) at each spirometry endpoint.
- Asthma Control Questionnaire-5 (ACQ-5) score change from baseline at EOT and at each assessment time point.
- Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ(S)) Self-Administered score change from baseline at EOT and at each assessment time point.
- Change from baseline at EOT and change from baseline at each week for asthma symptom scores in the morning and evening (ADSD and ANSD). Questionnaire was to be administered daily and score averaged weekly for analysis.
- Change from baseline at EOT and change from baseline at each week in number of inhalations/day of albuterol or levalbuterol for symptom relief.

Disease-Specific Efficacy Measures

Spirometry

[0154] Spirometry was to be performed in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (Graham et al. 2019) and prior to administration of IMP at the planned time point. For prebronchodilator measured parameters, including FEV1, PEF, FVC and FEF 25%-75%, spirometry was to be performed after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours.

[0155] Reversibility is defined as an increase of the absolute FEV1 after administration of bronchodilator and is measured by spirometry as postbronchodilator increase in FEV1 in percent of the prebronchodilator FEV1. After spirometry for measuring prebronchodilator FEV1, participants were to receive 2-4 puffs of albuterol/salbutamol or levalbuterol/levosalbutamol from a primed MDI. The postbronchodilator spirometry may have been repeated several times within 30 minutes after administration of bronchodilator. Alternatively, and only if it was consistent with usual office practice (to be documented),

reversibility may have been performed using inhalation of nebulized albuterol/salbutamol or levalbuterol/levosalbutamol.

ACQ-5 (Asthma Control Questionnaire, 5-Question Version)

[0156] The ACQ-5 is a questionnaire that measures the adequacy of asthma control and any changes in asthma control that may occur spontaneously or as a result of treatment. The ACQ-5 has five questions on the asthma symptoms and patients are asked to recall how their asthma has been during the previous week and to respond on a 7-point scale for each question (0 = no impairment, 6 = maximum impairment). The ACQ-5 score is the mean of the 5 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). A high score indicates low asthma control. Participants with a score below 1.0 reflected adequately controlled asthma and participants with scores above 1.0 reflected inadequately controlled asthma. On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 is the smallest change that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

[0157] Measurement properties such as reliability and ability to detect change have been documented in the literature (Juniper et al. 2005). Participants were to complete the questionnaire in an electronic diary during onsite visits.

Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ(S)) self-administered (≥12 years)

[0158] The AQLQ(S) was designed as a self-administered patient reported outcome to measure the functional impairments that are most troublesome to adolescents and adults ≥12 years of age as a result of their asthma. The instrument is comprised of 32 items, each rated on a 7-point Likert scales from 1 to 7. The AQLQ(S) has 4 domains. The domains and the number of items in each domain are as follows:

- Symptoms (12 items)
- Activity limitation (11 items)
- Emotional function (5 items)
- Environmental stimuli (4 items)

[0159] A global score is calculated ranging from 1 to 7 and a score by domain. Higher scores indicate better quality of life. The instrument has been used in many clinical trials, and it has been shown to be reliable, valid (patient interviews), and sensitive to change. The

MCID for AQLQ(S) is 0.5 (Juniper et al. 1994). Patients were to complete the questionnaire in an electronic diary during on-site visits.

Asthma Daytime Symptom Diary (ADSD) and Asthma Nighttime Symptom Diary (ANSD)

[0160] The ADSD and ANSD are PRO measures developed by the PRO Consortium' Asthma Working Group. Both instruments have been designed to measure asthma symptoms in adult and adolescent (12 years of age and older) patients diagnosed with mild to severe asthma. ADSD and ANSD assess asthma severity based on patient self-report of asthma core symptoms, *i.e.*, difficulty of breathing; wheezing; shortness of breath; chest tightness; chest pain; and cough. Patients were asked to complete the ADSD every night before they went to bed, thinking about their asthma symptoms on that day, from when they got up this morning until then; the ANSD when getting up, thinking about their asthma symptoms from the previous night from when they went to bed until then. They have demonstrated adequate evidence of content validity and cross-sectional measurement properties (*i.e.*, internal consistency reliability, test-retest reliability, convergent validity, and known-groups validity) to measure symptoms of asthma.

[0161] Both the ADSD and ANSD are composed of 6 items rated using an 11-point NRS that ranges from 0 = None to 10 = As bad as you can imagine (Gater et al. 2016). The participants were to record their daytime and nighttime asthma symptoms in an electronic diary, once in the evening and once in the morning, respectively. The participants were to complete the ADSD and the ANSD.

Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC)

[0162] The Patient Global Impression of Severity (PGIS) is a 1-item questionnaire that asks participants to provide a self-assessment of their overall asthma severity for the past week on a 4-point scale. Response choices are: "None", "Mild", "Moderate" and "Severe".

[0163] The Patient Global Impression of Change (PGIC) is a 1-item questionnaire that asks the participant to provide a self-assessment of overall change in their asthma 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."

[0164] Participants were to complete the 2 items in an electronic diary during on-site visits.

Electronic diary/PEF meter

[0165] The electronic diary/PEF meter was to be dispensed at Visit 1 and recorded information was to be downloaded from this device on the other indicated days. The electronic diary/PEF meter was to be used for daily recording of salbutamol/albuterol or levosalbutamol/levalbuterol use, asthma controller drug use, ADSD/ANSD, and AM and PM PEF.

[0166] On a daily basis throughout the study, the participant was to use an electronic diary/PEF meter to:

- Measure morning and evening PEF.
- Respond to the morning and evening asthma symptom score ADSD/ANSD questions.
- Indicate the number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief.
- Record the number of inhalations/day of ICS/LABA or ICS background therapy.

[0167] At screening (Visit 1), participants were to be issued an electronic diary and PEF meter. Participants were to be instructed on the use of the devices, and written instructions on the use of the electronic PEF meter were to be provided to the participants. In addition, the Investigator was to instruct the participants on how to record the following variables in the electronic PEF meter:

- AM PEF performed within 15 minutes after arising (between 5:30 AM and 12 PM).
- PM PEF performed in the evening (between 5:30 PM and 12 AM).
- Participants were to try to withhold albuterol or levalbuterol for at least 6 hours prior to measuring their PEF.
- Three PEF efforts were to be performed by the participants; all 3 values were to be recorded by the electronic PEF meter, and the highest value was to be used for evaluation.

[0168] Baseline AM PEF was to be the mean AM measurement recorded for the 7 days prior to the first dose of IMP, and baseline PM PEF was to be the mean PM measurement recorded for the 7 days prior to the first dose of IMP. Period stability limit is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Day 1. There should have been at least 4 days of measurements for setting up the stability limit, and the first dosing visit may have been rescheduled until data for 4 days are available.

[0169] The following efficacy parameters (described in more detail below) were to be analyzed for assessing exploratory endpoints: fractional exhaled nitric oxide (FeNo) and oscillometry.

Fractional exhaled nitric oxide (FeNO)

[0170] FeNO levels (ppb) were to be collected on site with a dedicated medical device such as a commercially available hand worn device (NIOX VERO®). Participants were to inhale to total lung capacity through the device and then exhale for 10 seconds at 50 mL/sec.

Oscillometry

[0171] Oscillometry is a complementary technique to spirometry determining the physiological behavior of the lung in asthmatics. Oscillometry was to be conducted during tidal breathing using the tremoflo® device (Thorasys, Montreal, Canada) according to ERS recommended guidelines (Oostveen et al. 2003). A minimum of 3 recordings that achieve coefficient of variation of ≤15% were required for quality control (Peters et al. 2016). Only these data were to be used for the data analysis. The individual measurements could have been reviewed manually to confirm that a quality measurement was indeed performed.

Safety Assessments

[0172] Safety assessments included physical examinations, measurements of vital signs, electrocardiograms, clinical safety laboratory assessments, and pregnancy testing.

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

AE definition

[0173] An AE is 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 intervention. An AE could therefore have been any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

SAE definition

[0174] An SAE is defined as any adverse event that, at any dose:

- Resulted in death
- Was life-threatening
- Required inpatient hospitalization or prolongation of existing hospitalization.
- Resulted in persistent or significant disability/incapacity.
- Was a congenital anomaly/birth defect.
- Other situations such as significant medical events that may have jeopardized the participant or may have required medical or surgical intervention to prevent one of the other outcomes listed in the above definition (*e.g.*, 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).

AESI definition

[0175] An adverse event of special interest (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 was required. Such events may have required further investigation in order to characterize and understand them. Adverse events of special interest may have been added, modified or removed during a study by protocol amendment. AESIs include the following:

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP.
- Symptomatic overdose (serious or nonserious) with IMP.
- Other project-specific AESI(s), including: severe infections including opportunistic infections; tuberculosis or initiation of medications for suspected tuberculosis; active COVID-19 infection as documented by a positive COVID-19 molecular test; major hemorrhagic events, including symptomatic bleeding in a critical area or organ such as the CNS, or intraocular bleeding, resulting in an SAE; serious adverse events (or non-serious adverse events with a severity level consistent with Grade 3 CTCAE of cytopenia; and atrial fibrillation.

Populations for Analyses

[0176] The populations for analyses are defined in **Table 8**.

[0177] **Table 8. 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.
Modified ITT (mITT)	All participants from ITT population who received at least one dose of investigational product analyzed according to the treatment group allocated by randomization. Randomized participants for whom it was unclear whether they took the study medication were included in the mITT population.
Safety	All randomized participants who took at least 1 dose of study intervention. Participants were analyzed according to the intervention they actually received.
Pharmacokinetic (PK)	All randomized and treated participants (safety population) with at least one post-baseline PK sample with adequate documentation of dosing and sampling dates and times. Participants were analyzed according to the intervention they actually received.

[0178] Participants exposed to study intervention before or without being randomized were not to be considered randomized and were not to be included in any analysis population. The safety experience of these participants was to be reported separately.

[0179] Randomized participants for whom it was unclear whether they took the study intervention were not to be considered as exposed and were to be included in the safety population as randomized.

[0180] For any participant randomized more than once, only the data associated with the first randomization was to be used in any analysis population. The safety experience associated with any later randomization was to be reported separately.

Statistical Analyses

[0181] This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

General considerations

[0182] The baseline value is defined as the last available value before the first dose of double-blind IMP. For participants randomized but not treated, the baseline value is defined as the last available value before randomization.

[0183] Unless otherwise specified, analyses were to be performed by intervention group (and overall for baseline and demographics characteristics).

[0184] Continuous data were to be summarized using the number of available data, mean, standard deviation (SD), median, Q1, Q3, minimum and maximum for each intervention group. Categorical and ordinal data were to be summarized using the number and percentage of patients in each intervention group.

[0185] The observation period was to be divided into 3 segments:

- The pre-treatment period is defined as the period up to the first IMP administration.
- The on-treatment period is defined as the period from the first IMP administration to the last IMP administration + 1 day.
- The post-treatment period is defined as the period from the end of the on-treatment period up to the follow-up visit.

[0186] The treatment-emergent period consisted of on-treatment period and post-treatment period.

Primary endpoint(s)

[0187] The primary endpoint was proportion of participants with LOAC during the 12-week treatment period.

[0188] The incidence of LOAC was to be analyzed between rilzabrutinib and placebo. The primary analysis was to be performed using a logistic regression model with treatment (Cramer 2002), baseline IgE strata, region (pooled country), and number of asthma exacerbation events (as defined in I 06) within 2 years prior to screening as the covariates. Note that if the number of participants in some regions was too low, these regions may have been pooled with other regions. This strategy also applied to all the rest of the analyses where region was one of the covariates.

[0189] The following comparisons were to be tested without control for type I error:

- Rilzabrutinib 400 mg TID versus its matching placebo.
- Rilzabrutinib 400 mg BID versus its matching placebo.

[0190] Comparison may also have been done on the pooled 400 mg BID and 400 mg TID dose level groups of rilzabrutinib versus placebo.

[0191] The odds ratio, 95% confidence interval (CI) and nominal p-value for each comparison was to be estimated from this model.

Sensitivity analysis

[0192] Sensitivity analyses using all observed values were also to be conducted.

Supportive analyses

[0193] Time to LOAC post-randomization was to be analyzed using a Cox regression model with treatment (Cox 1972), baseline IgE strata, and region (pooled country) as covariates. The Kaplan-Meier (KM) method was to be used to estimate the probabilities of the event at specific time points for each treatment group (Kaplan and Meier 1958). Nominal p-value from log-rank test stratified by baseline IgE strata and region was also to be provided.

Subgroup analysis

[0194] To assess the consistency in treatment effects across different subgroup levels, subgroup analyses were to be performed for the primary efficacy endpoint with respect to age group, gender, region, and other factors.

Secondary endpoint(s)

[0195] A summary of the primary estimand for key secondary endpoints is shown in **Table 9** below.

[0196] **Table 9. Summary of primary estimand for key secondary endpoints.**

Endpoint category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event(s) handling strategy	Population-level summary (analysis and missing data handling)
Secondary objective: To evaluate the effects of rilzabrutinib compared to placebo on lung function as measured by pre-BD FEV1.				
Key secondary endpoint	Pre-bronchodilator FEV1 change from baseline at EOT	miTT	Occurrence of LOAC. For LOAC with rescue medication, data collected after LOAC was to be set to missing, and missing data was to	The missing values at after discontinuation of study intervention due to other reasons or after occurrence of LOAC without rescue

			be imputed with LOCF (hypothetical policy). For LOAC without rescue medication, all observed values after LOAC were to be included (treatment policy). If study intervention was discontinued due to lack of efficacy or AE related to asthma worsening, data were to be imputed with LOCF (hypothetical policy). If study intervention was discontinued for other reasons, all observed data after discontinuation of study intervention were to be included (treatment policy). If OCS were used without LOAC, data collected after start of OCS were to be set to missing and missing data were to be imputed with LOCF (hypothetical policy).	medication were to be imputed using multiple imputation (MI). Mean difference of pre-BD FEV1 at EOT between intervention groups was to be estimated form analysis of covariance (ANCOVA). Statistical inference obtained from each imputed data was to be combined using Rubin's rule. Least squared (LS) means, differences in LS means, the corresponding 95% CI and p-value was to be presented.

Secondary efficacy endpoints

[0197] Secondary efficacy endpoints included:

- Post-bronchodilator FEV1 change from baseline at EOT.
- The absolute change in the percent predicted FEV1 from baseline to EOT (pre-and postbronchodilator).
- Change from baseline in pre- and post-bronchodilator FEV1 and in other lung function measurement (peak expiratory flow (PEF), forced vital capacity (FVC), forced expiratory flow (FEF) 25-75%) at each spirometry endpoint.
- Asthma Control Questionnaire-5 (ACQ-5) score change from baseline at EOT and at each assessment time point.
- Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ(S)) Self-administered score change from baseline at EOT and at each assessment time point.

- Change from baseline at EOT and change from baseline at each week for asthma daytime symptom diary and asthma nighttime symptom diary scores.
- Change from baseline at EOT and change from baseline at each week in numbers of inhalations/day of albuterol or levalbuterol for symptom relief.

[0198] Other secondary efficacy endpoints (*e.g.*, FEV1, FVC, PEF, ACQ-5 score, AQLQ, asthma symptom scores) were to be analyzed using the same approach as for the key secondary endpoint, except for that age, gender and height were to be only included in the models for spirometry variables as response variable.

Multiplicity considerations

[0199] No adjustments for multiplicity across secondary efficacy endpoints were planned for this Phase 2 study. Nominal p-values were to be reported.

Other safety analysis

[0200] The safety variables, including AEs, vital signs, physical examination, and laboratory values were to be summarized using descriptive statistics in each treatment group in the safety population.

[0201] The summary of safety results were to be presented by treatment group. All safety analyses were to be performed on the safety population. The baseline value is defined generally as the last available value before the first dose of IMP.

Adverse events

[0202] In general, AEs were to be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened, or became serious during the pre-treatment period.
- TEAEs: AEs that developed, worsened, or became serious during the treatment-emergent period.
- Post-treatment AEs: AEs that developed, worsened, or became serious during the post-treatment period.

Example 2: Rilzabrutinib in Asthma

[0203] A study was initiated to evaluate the effect of rilzabrutinib treatment in N=196 patients with moderate-to-severe asthma uncontrolled by ICS/LABA. Over the course of this 12-week PoC withdrawal study, N=64 patients were administered 400 mg BID rilzabrutinib or a placebo, while N=132 patients were administered 400 mg TID rilzabrutinib or placebo.

[0204] The primary endpoint for this study was the proportion of participants with an LOAC event during the treatment period. Secondary endpoints included pre-bronchodilator FEV1 change from baseline at EOT, ACQ-5 score change from baseline, and AQLQ score change from baseline. Other secondary and exploratory endpoints are described in **Table 2.**

[0205] Compared to patients who received the placebo, patients who received 400 mg BID or 400 mg TID rilzabrutinib exhibited a marked and meaningful improvement in symptoms despite ICS/LABA withdrawal (**Table 10)**. Rilzabrutinib-treated patients experienced a numerical reduction in LOAC events, a significant and meaningful improvement in asthma symptoms (ACQ-5), and an improvement in quality of life as measured by AQLQ. Furthermore, patients did not exhibit any change in FEV1 following ICS/LABA withdrawal.

[0206] Additionally, rilzabrutinib was generally safe, with no evidence of new safety concerns.

[0207] Table 10. Summary of the primary and key secondary endpoints (mITT population).

Parameter	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Difference vs. placebo (95% CI)	P-value	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)	Difference vs. placebo (95% CI)	P-value
Primary endpoint								
Odds ratio incidence of LOAC	16 (50.0%)	12 (37.5%)	0.570 (0.202, 1.608)	0.2880	20 (29.4%)	12 (18.8%)	0.584 (0.253, 1.349)	0.2083
Key secondary endpoint								
LS Mean change from baseline in pre-bronchodilator FEV1 (L) at Week 12	-0.08 (0.08)	-0.07 (0.08)	0.01 (-0.17, 0.19)	0.9466	-0.04 (0.05)	-0.13 (0.05)	-0.09 (-0.21, 0.03)	0.1523

Patient Demographics

[0208] The 132 and 64 patients enrolled in the 400 mg TID and 400 mg BID cohorts, respectively, were characterized by the demographic information provided in **Tables 11-19**. The median age of enrolled patients in the 400 mg TID cohort was 50 years, while the median age of enrolled patients in the 400 mg BID cohort was 52 years. For all patients in the 400 mg TID cohort, the median time since first diagnosis of asthma was 17.96 years. For all patients in the 400 mg BID cohort, the median time since first diagnosis of asthma was 20.79 years.

[0209] **Table 11. Analysis population.**

n (%)	400 mg BID cohort			400 mg TID cohort		
	Placebo BID	Rilzabrutinib 400 mg BID	All BID	Placebo TID	Rilzabrutinib 400 mg TID	All TID
Randomized population	32 (100)	32 (100)	64 (100)	68 (100)	64 (100)	132 (100)
Efficacy population						
Modified intent-to-treat (mITT)	32 (100)	32 (100)	64 (100)	68 (100)	64 (100)	132 (100)
Safety population	32	32	64	68	64	132
Pharmacokinetic (PK) population	0	31 (96.9)	31 (48.4)	0	64 (100)	64 (48.5)

[0210] **Table 12. Participant disposition.**

n (%)	400 mg BID cohort			400 mg TID cohort		
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	All (N=64)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)	All (N=132)
Exposed but not randomized	0	0	0	0	0	0
Randomized and not exposed	0	0	0	0	0	0
Randomized and exposed	32 (100)	32 (100)	64 (100)	68 (100)	64 (100)	132 (100)
Still on study intervention or missing EOT page	0	0	0	0	0	0

	400 mg BID cohort			400 mg TID cohort		
n (%)	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	All (N=64)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)	All (N=132)
Completed the study intervention period	18 (56.3)	18 (56.3)	36 (56.3)	45 (66.2)	44 (68.8)	89 (67.4)
Did not complete the study intervention period	14 (43.8)	14 (43.8)	28 (43.8)	23 (33.8)	20 (31.3)	43 (32.6)
Reason for permanent study intervention discontinuation						
Adverse event	2 (6.3)	2 (6.3)	4 (6.3)	2 (2.9)	5 (7.8)	7 (5.3)
Related to COVID-19	2 (6.3)	0	2 (3.1)	1 (1.5)	3 (4.7)	4 (3.0)
Not related to COVID-19	0	2 (6.3)	2 (3.1)	1 (1.5)	2 (3.1)	3 (2.3)
Lack of efficacy	0	0	0	1 (1.5)	1 (1.6)	2 (1.5)
Poor compliance to protocol	1 (3.1)	1 (3.1)	2 (3.1)	0	1 (1.6)	1 (0.8)
Withdrawal by subject	0	1 (3.1)	1 (1.6)	1 (1.5)	3 (4.7)	4 (3.0)
Loss of asthma control (LOAC)	10 (31.3)	8 (25.0)	18 (28.1)	18 (26.5)	10 (15.6)	28 (21.2)
Other	1 (3.1)	2 (6.3)	3 (4.7)	1 (1.5)	0	1 (0.8)
Related to COVID-19	0	0	0	0	0	0
Not related to COVID-19	1 (3.1)	2 (6.3)	3 (4.7)	1 (1.5)	0	1 (0.8)
Reason for study intervention withdrawal by subject						
Adverse event	0	1 (3.1)	1 (1.6)	0	2 (3.1)	2 (1.5)
Study procedure	0	0	0	0	0	0
Inconvenience of device use	0	0	0	0	0	0
Other	0	0	0	0	0	0
Related to COVID-19	0	0	0	0	0	0
Not related to COVID-19	0	0	0	0	0	0

	400 mg BID cohort			400 mg TID cohort		
n (%)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**All (N=64)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**	**All (N=132)**
Completed the study period	31 (96.9)	30 (93.8)	61 (95.3)	67 (98.5)	60 (93.8)	127 (96.2)
Did not complete the study period	1 (3.1)	2 (6.3)	3 (4.7)	1 (1.5)	4 (6.3)	5 (3.8)
Reason for study discontinuation						
Adverse event	0	1 (3.1)	1 (1.6)	0	0	0
Related to COVID-19	0	0	0	0	0	0
Not related to COVID-19	0	1 (3.1)	1 (1.6)	0	0	0
Poor compliance to protocol	1 (3.1)	0	1 (1.6)	0	0	0
Withdrawal by subject	0	0	0	1 (1.5)	4 (6.3)	5 (3.8)
Site terminated by sponsor	0	0	0	0	0	0
Study terminated by sponsor	0	1 (3.1)	1 (1.6)	0	0	0
Other	0	0	0	0	0	0
Related to COVID-19	0	0	0	0	0	0
Not related to COVID-19	0	0	0	0	0	0
Status at last contact	32 (100)	31 (96.9)	63 (98.4)	68 (100)	64 (100)	132 (100)
Alive	32 (100)	31 (96.9)	63 (98.4)	68 (100)	64 (100)	132 (100)
Dead	0	0	0	0	0	0

[0211] Table 13. Demographic and participant characteristics at baseline (randomized population).

	400 mg BID cohort			400 mg TID cohort		
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**All (N=64)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**	**All (N=132)**
Age (years)						
Number	32	32	64	68	64	132
Mean (SD)	50.8 (12.3)	48.0 (13.4)	49.4 (12.8)	48.6 (13.7)	48.8 (13.3)	48.7 (13.5)
Median	53.5	51.5	52.0	48.5	50.0	50.0
Min ; Max	28 ; 70	21 ; 70	21 ; 70	18 ; 70	18 ; 68	18 ; 70
Age group 1 (years) [n (%)]						
Number	32	32	64	68	64	132
< 45	10 (31.3)	12 (37.5)	22 (34.4)	29 (42.6)	25 (39.1)	54 (40.9)
≥ 45	22 (68.8)	20 (62.5)	42 (65.6)	39 (57.4)	39 (60.9)	78 (59.1)
Age group 2 (years) [n (%)]						
Number	32	32	64	68	64	132
< 65	28 (87.5)	29 (90.6)	57 (89.1)	57 (83.8)	56 (87.5)	113 (85.6)
≥ 65	4 (12.5)	3 (9.4)	7 (10.9)	11 (16.2)	8 (12.5)	19 (14.4)
Sex [n (%)]						
Number	32	32	64	68	64	132
Male	8 (25.0)	14 (43.8)	22 (34.4)	27 (39.7)	25 (39.1)	52 (39.4)
Female	24 (75.0)	18 (56.3)	42 (65.6)	41 (60.3)	39 (60.9)	80 (60.6)
Height (cm)						
Number	32	32	64	68	64	132
Mean (SD)	164.9 (10.2)	166.0 (8.8)	165.4 (9.5)	167.9 (11.8)	169.5 (11.9)	168.6 (11.8)
Median	165.0	164.5	165.0	169.5	169.0	169.0
Min ; Max	148 ; 185	150 ; 184	148 ; 185	140 ; 194	146 ; 194	140 ; 194
Weight (kg)						
Number	32	32	64	68	64	132
Mean (SD)	77.0 (13.1)	78.0 (15.2)	77.5 (14.0)	77.2 (14.1)	83.2 (12.4)	80.1 (13.6)
Median	76.5	75.5	76.0	78.0	83.7	81.9
Min ; Max	50 ; 117	54 ; 126	50 ; 126	48 ; 104	54 ; 112	48 ; 112
Weight by category (kg) [n (%)]						
Number	32	32	64	68	64	132
< 60	4 (12.5)	3 (9.4)	7 (10.9)	12 (17.6)	2 (3.1)	14 (10.6)
≥ 60 - < 90	25 (78.1)	23 (71.9)	48 (75.0)	40 (58.8)	41 (64.1)	81 (61.4)
≥ 90	3 (9.4)	6 (18.8)	9 (14.1)	16 (23.5)	21 (32.8)	37 (28.0)
BMI (kg/m^2)						
Number	32	32	64	68	64	132
Mean (SD)	28.39 (4.79)	28.18 (4.01)	28.29 (4.38)	27.46 (4.75)	29.08 (4.29)	28.24 (4.59)

	400 mg BID cohort			400 mg TID cohort		
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	All (N=64)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)	All (N=132)
Median	27.60	27.75	27.65	26.75	28.90	27.55
Min ; Max	20.5 ; 40.1	21.8 ; 38.2	20.5 ; 40.1	19.6 ; 38.3	21.6 ; 38.7	19.6 ; 38.7
BMI by category (kg/m^2) [n (%)]						
Number	32	32	64	68	64	132
< 25	6 (18.8)	8 (25.0)	14 (21.9)	22 (32.4)	12 (18.8)	34 (25.8)
≥ 25 - < 30	17 (53.1)	16 (50.0)	33 (51.6)	27 (39.7)	29 (45.3)	56 (42.4)
≥ 30	9 (28.1)	8 (25.0)	17 (26.6)	19 (27.9)	23 (35.9)	42 (31.8)
Region [n (%)]						
Number	32	32	64	68	64	132
Eastern Europe	4 (12.5)	3 (9.4)	7 (10.9)	45 (66.2)	43 (67.2)	88 (66.7)
Latin America	25 (78.1)	25 (78.1)	50 (78.1)	19 (27.9)	19 (29.7)	38 (28.8)
Western Countries	1 (3.1)	2 (6.3)	3 (4.7)	2 (2.9)	2 (3.1)	4 (3.0)
Asia and Pacific Region	2 (6.3)	2 (6.3)	4 (6.3)	2 (2.9)	0	2 (1.5)

[0212] Table 14. Asthma history characteristics at baseline (randomized population).

	400 mg BID cohort			400 mg TID cohort		
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	All (N=64)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)	All (N=132)
Age of onset of asthma (years)						
Number	32	32	64	68	64	132
Mean (SD)	28.1 (16.6)	24.2 (16.4)	26.1 (16.5)	28.5 (18.0)	28.7 (16.5)	28.6 (17.2)
Median	29.5	26.5	27.5	28.0	30.0	29.5
Q1 ; Q3	15.0 ; 40.0	9.5 ; 36.0	11.5 ; 37.0	13.0 ; 44.5	13.5 ; 40.5	13.0 ; 41.5
Min ; Max	0 ; 65	0 ; 60	0 ; 65	0 ; 63	1 ; 61	0 ; 63
Age of onset of asthma group 1 (years) [n (%)]						
Number	32	32	64	68	64	132
< 12	7 (21.9)	9 (28.1)	16 (25.0)	15 (22.1)	14 (21.9)	29 (22.0)
≥ 12 - < 18	2 (6.3)	5 (15.6)	7 (10.9)	5 (7.4)	5 (7.8)	10 (7.6)
≥ 18 - < 40	15 (46.9)	14 (43.8)	29 (45.3)	28 (41.2)	27 (42.2)	55 (41.7)
≥ 40	8 (25.0)	4 (12.5)	12 (18.8)	20 (29.4)	18 (28.1)	38 (28.8)
Age of onset of asthma group 2 (years) [n (%)]						
Number	32	32	64	68	64	132
< 18	9 (28.1)	14 (43.8)	23 (35.9)	20 (29.4)	19 (29.7)	39 (29.5)

	400 mg BID cohort			400 mg TID cohort		
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**All (N=64)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**	**All (N=132)**
≥ 18	23 (71.9)	18 (56.3)	41 (64.1)	48 (70.6)	45 (70.3)	93 (70.5)
Time since first diagnosis of asthma (years)						
Number	32	32	64	68	64	132
Mean (SD)	23.47 (13.87)	24.89 (14.90)	24.18 (14.30)	20.93 (14.00)	21.02 (13.28)	20.97 (13.61)
Median	21.58	20.50	20.79	17.29	20.04	17.96
Q1 ; Q3	12.63 ; 33.54	14.96 ; 34.92	13.71 ; 33.54	11.08 ; 32.21	9.67 ; 29.08	10.38 ; 30.00
Min ; Max	1.3 ; 54.0	3.8 ; 56.5	1.3 ; 56.5	1.1 ; 55.8	1.8 ; 62.2	1.1 ; 62.2
With history of atopic medical conditions [n (%)]						
Number	32	32	64	68	64	132
Yes	17 (53.1)	20 (62.5)	37 (57.8)	24 (35.3)	21 (32.8)	45 (34.1)
Ongoing	16 (50.0)	19 (59.4)	35 (54.7)	24 (35.3)	21 (32.8)	45 (34.1)
Smoking history [n (%)]						
Number	32	32	64	68	64	132
Former	8 (25.0)	4 (12.5)	12 (18.8)	6 (8.8)	6 (9.4)	12 (9.1)
Never	24 (75.0)	28 (87.5)	52 (81.3)	62 (91.2)	58 (90.6)	120 (90.9)
Time since cessation (years)						
Number	8	4	12	6	6	12
Mean (SD)	19.74 (15.64)	19.46 (10.13)	19.65 (13.55)	21.82 (17.53)	20.63 (11.86)	21.22 (14.28)
Median	21.21	20.67	21.21	17.25	20.63	20.63
Q1 ; Q3	3.92 ; 32.17	12.29 ; 26.63	6.33 ; 31.21	9.33 ; 41.17	15.58 ; 25.42	9.33 ; 32.00
Min ; Max	0.8 ; 42.6	6.2 ; 30.3	0.8 ; 42.6	2.5 ; 43.4	2.9 ; 38.6	2.5 ; 43.4
Pack-year						
Number	8	4	12	6	6	12
Mean (SD)	1.402 (1.139)	4.500 (1.291)	2.434 (1.899)	5.183 (2.669)	3.092 (2.288)	4.138 (2.610)
Median	1.300	4.500	2.400	4.500	3.000	4.000
Q1 ; Q3	0.400 ; 2.400	3.500 ; 5.500	0.900 ; 3.500	4.000 ; 7.500	1.000 ; 4.650	2.050 ; 5.750
Min ; Max	0.01 ; 3.00	3.00 ; 6.00	0.01 ; 6.00	1.60 ; 9.00	0.40 ; 6.50	0.40 ; 9.00
E-cigarette history [n (%)]						
Number	32	32	64	68	64	132
Former	0	0	0	0	0	0
Never	32 (100)	32 (100)	64 (100)	68 (100)	64 (100)	132 (100)

[0213] Table 15. Asthma severity and control at baseline (randomized population).

	400 mg BID cohort			400 mg TID cohort		
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	All (N=64)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)	All (N=132)
ICS/LABA dose level [n (%)]						
Number	32	32	64	68	64	132
High	29 (90.6)	27 (84.4)	56 (87.5)	33 (48.5)	35 (54.7)	68 (51.5)
Medium	3 (9.4)	5 (15.6)	8 (12.5)	35 (51.5)	29 (45.3)	64 (48.5)
ICS/LABA total dose (ug)						
Number	32	32	64	68	64	132
Mean (SD)	953.1 (148.1)	953.1 (265.2)	953.1 (213.0)	742.6 (251.7)	773.4 (250.9)	757.6 (250.8)
Median	1000.0	1000.0	1000.0	500.0	1000.0	1000.0
Q1 ; Q3	1000.0 ; 1000.0	1000.0 ; 1000.0	1000.0 ; 1000.0	500.0 ; 1000.0	500.0 ; 1000.0	500.0 ; 1000.0
Min ; Max	500 ; 1000	500 ; 2000	500 ; 2000	500 ; 1000	500 ; 1000	500 ; 1000
LABA total daily dose (ug)						
Number	32	32	64	68	64	132
Mean (SD)	98.4 (8.8)	100.0 (22.0)	99.2 (16.6)	97.8 (18.2)	96.1 (13.5)	97.0 (16.1)
Median	100.0	100.0	100.0	100.0	100.0	100.0
Q1 ; Q3	100.0 ; 100.0	100.0 ; 100.0	100.0 ; 100.0	100.0 ; 100.0	100.0 ; 100.0	100.0 ; 100.0
Min ; Max	50 ; 100	50 ; 200	50 ; 200	50 ; 200	50 ; 100	50 ; 200
Number of prescribed salbutamol/albuterol or levosalbutamol/levalbuterol (puffs)						
Number	19	23	42	53	47	100
Mean (SD)	1.5 (0.5)	2.4 (2.3)	2.0 (1.8)	2.3 (2.9)	2.0 (1.8)	2.2 (2.4)
Median	2.0	2.0	2.0	1.0	1.0	1.0
Q1 ; Q3	1.0 ; 2.0	1.0 ; 2.0	1.0 ; 2.0	1.0 ; 2.0	1.0 ; 2.0	1.0 ; 2.0
Min ; Max	1 ; 2	0 ; 8	0 ; 8	1 ; 20	1 ; 8	1 ; 20
Time since last asthma exacerbation (months)						
Number	32	32	64	68	64	132
Mean (SD)	6.94 (3.73)	7.69 (4.83)	7.31 (4.30)	8.51 (4.55)	9.64 (4.90)	9.06 (4.74)
Median	6.00	7.00	6.00	8.00	9.00	8.00
Q1 ; Q3	4.00 ; 8.50	4.00 ; 10.00	4.00 ; 9.00	6.00 ; 11.00	6.00 ; 12.50	6.00 ; 11.50
Min ; Max	2.0 ; 15.0	2.0 ; 23.0	2.0 ; 23.0	1.0 ; 24.0	2.0 ; 24.0	1.0 ; 24.0

	400 mg BID cohort			400 mg TID cohort		
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	All (N=64)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)	All (N=132)
Number of asthma exacerbations experienced 2 years before the screening visit						
Number	32	32	64	68	64	132
Mean (SD)	2.3 (1.5)	1.9 (1.0)	2.1 (1.2)	1.3 (0.7)	1.5 (0.8)	1.4 (0.7)
Median	2.0	2.0	2.0	1.0	1.0	1.0
Q1 ; Q3	1.0 ; 2.5	1.0 ; 2.5	1.0 ; 2.5	1.0 ; 1.5	1.0 ; 2.0	1.0 ; 2.0
Min ; Max	1 ; 8	1 ; 5	1 ; 8	1 ; 6	1 ; 5	1 ; 6
Number of asthma exacerbations experienced 2 years before the screening visit [n (%)]						
Number	32	32	64	68	64	132
1	9 (28.1)	13 (40.6)	22 (34.4)	51 (75.0)	36 (56.3)	87 (65.9)
2	15 (46.9)	11 (34.4)	26 (40.6)	16 (23.5)	23 (35.9)	39 (29.5)
3	3 (9.4)	7 (21.9)	10 (15.6)	0	4 (6.3)	4 (3.0)
≥ 4	5 (15.6)	1 (3.1)	6 (9.4)	1 (1.5)	1 (1.6)	2 (1.5)
Number of asthma exacerbations experienced 1 year before the screening visit						
Number	32	32	64	68	64	132
Mean (SD)	1.6 (0.9)	1.4 (0.8)	1.5 (0.8)	0.8 (0.6)	0.8 (0.8)	0.8 (0.7)
Median	2.0	1.0	1.0	1.0	1.0	1.0
Q1 ; Q3	1.0 ; 2.0	1.0 ; 2.0	1.0 ; 2.0	0.0 ; 1.0	0.0 ; 1.0	0.0 ; 1.0
Min ; Max	0 ; 4	0 ; 3	0 ; 4	0 ; 3	0 ; 4	0 ; 4
Number of asthma exacerbations experienced 1 year before the screening visit [n (%)]						
Number	32	32	64	68	64	132
0	2 (6.3)	2 (6.3)	4 (6.3)	19 (27.9)	23 (35.9)	42 (31.8)
1	13 (40.6)	19 (59.4)	32 (50.0)	43 (63.2)	31 (48.4)	74 (56.1)
2	13 (40.6)	8 (25.0)	21 (32.8)	5 (7.4)	9 (14.1)	14 (10.6)
3	3 (9.4)	3 (9.4)	6 (9.4)	1 (1.5)	0	1 (0.8)
≥ 4	1 (3.1)	0	1 (1.6)	0	1 (1.6)	1 (0.8)
Number of asthma exacerbations experienced 1 year before the screening visit group 2 [n (%)]						
Number	32	32	64	68	64	132
0	2 (6.3)	2 (6.3)	4 (6.3)	19 (27.9)	23 (35.9)	42 (31.8)
≥ 1	30 (93.8)	30 (93.8)	60 (93.8)	49 (72.1)	41 (64.1)	90 (68.2)

	400 mg BID cohort			400 mg TID cohort		
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**All (N=64)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**	**All (N=132)**
Number of asthma exacerbations required hospitalization or emergency medical care within 2 years before the screening visit						
Number	32	32	64	68	64	132
Mean (SD)	0.5 (1.3)	0.1 (0.3)	0.3 (1.0)	0.3 (0.6)	0.2 (0.5)	0.2 (0.5)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Q1 ; Q3	0.0 ; 0.5	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0
Min ; Max	0 ; 7	0 ; 1	0 ; 7	0 ; 2	0 ; 2	0 ; 2
Number of asthma exacerbations required hospitalization or emergency medical care within 2 years before the screening visit group [n (%)]						
Number	32	32	64	68	64	132
0	24 (75.0)	29 (90.6)	53 (82.8)	54 (79.4)	55 (85.9)	109 (82.6)
1	4 (12.5)	3 (9.4)	7 (10.9)	10 (14.7)	6 (9.4)	16 (12.1)
2	3 (9.4)	0	3 (4.7)	4 (5.9)	3 (4.7)	7 (5.3)
3	0	0	0	0	0	0
≥ 4	1 (3.1)	0	1 (1.6)	0	0	0
Number of asthma exacerbations required hospitalization or emergency medical care within 1 year before the screening visit						
Number	32	32	64	68	64	132
Mean (SD)	0.3 (0.6)	0.1 (0.3)	0.2 (0.5)	0.2 (0.4)	0.1 (0.4)	0.2 (0.4)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Q1 ; Q3	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0
Min ; Max	0 ; 3	0 ; 1	0 ; 3	0 ; 1	0 ; 2	0 ; 2
Number of asthma exacerbations required hospitalization or emergency medical care within 1 year before the screening visit group [n (%)]						
Number	32	32	64	68	64	132
0	26 (81.3)	29 (90.6)	55 (85.9)	55 (80.9)	58 (90.6)	113 (85.6)
1	5 (15.6)	3 (9.4)	8 (12.5)	13 (19.1)	5 (7.8)	18 (13.6)
2	0	0	0	0	1 (1.6)	1 (0.8)
3	1 (3.1)	0	1 (1.6)	0	0	0
≥ 4	0	0	0	0	0	0
Pre-bronchodilator FEV1 (L)						
Number	32	31	63	67	63	130

	400 mg BID cohort			400 mg TID cohort		
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**All (N=64)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**	**All (N=132)**
Mean (SD)	2.16 (0.77)	2.11 (0.67)	2.13 (0.72)	2.42 (0.90)	2.50 (0.95)	2.46 (0.92)
Median	2.10	1.94	2.02	2.15	2.36	2.20
Q1 ; Q3	1.47 ; 2.50	1.59 ; 2.52	1.59 ; 2.52	1.77 ; 2.98	1.73 ; 3.10	1.75 ; 3.03
Min ; Max	1.2 ; 3.9	1.0 ; 3.8	1.0 ; 3.9	1.0 ; 5.0	1.1 ; 5.3	1.0 ; 5.3
Pre-bronchodilator FEV1 percent predicted (%)						
Number	32	31	63	68	63	131
Mean (SD)	71.7 (12.7)	66.4 (10.4)	69.1 (11.8)	76.0 (16.7)	75.7 (16.2)	75.9 (16.4)
Median	72.5	64.0	68.0	74.5	78.0	77.0
Q1 ; Q3	61.5 ; 79.5	58.0 ; 75.0	59.0 ; 78.0	62.5 ; 87.0	65.0 ; 85.0	64.0 ; 86.0
Min ; Max	54 ; 115	50 ; 87	50 ; 115	50 ; 115	35 ; 118	35 ; 118
Pre-bronchodilator FEV1 percent predicted group (%) [n (%)]						
Number	32	31	63	68	63	131
< 80	24 (75.0)	26 (83.9)	50 (79.4)	41 (60.3)	37 (58.7)	78 (59.5)
≥ 80	8 (25.0)	5 (16.1)	13 (20.6)	27 (39.7)	26 (41.3)	53 (40.5)
Post-bronchodilator FEV1 (L)						
Number	32	32	64	63	59	122
Mean (SD)	2.39 (0.77)	2.40 (0.75)	2.40 (0.76)	2.60 (0.91)	2.66 (0.98)	2.63 (0.94)
Median	2.30	2.21	2.26	2.35	2.51	2.42
Q1 ; Q3	1.77 ; 2.86	1.96 ; 2.79	1.88 ; 2.85	1.94 ; 3.03	1.83 ; 3.27	1.91 ; 3.08
Min ; Max	1.3 ; 4.3	1.2 ; 4.3	1.2 ; 4.3	1.1 ; 5.1	1.3 ; 5.3	1.1 ; 5.3
Post-bronchodilator FEV1 percent predicted (%)						
Number	32	32	64	67	62	129
Mean (SD)	79.3 (12.9)	75.7 (14.9)	77.5 (13.9)	82.0 (16.2)	81.9 (14.9)	82.0 (15.5)
Median	80.0	75.0	77.0	82.0	81.0	81.0
Q1 ; Q3	70.5 ; 87.0	64.0 ; 85.5	67.5 ; 86.5	68.0 ; 93.0	71.0 ; 91.0	70.0 ; 91.0
Min ; Max	53 ; 111	50 ; 126	50 ; 126	50 ; 117	51 ; 122	50 ; 122
FEV1 reversibility at screening (%)						
Number	30	32	62	67	64	131
Mean (SD)	22.901 (10.238)	25.238 (12.189)	24.107 (11.257)	21.265 (14.469)	23.026 (10.145)	22.125 (12.527)
Median	20.000	21.600	20.000	18.000	19.750	19.000

	400 mg BID cohort			400 mg TID cohort		
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**All (N=64)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**	**All (N=132)**
Q1 ; Q3	14.000 ; 29.000	15.500 ; 35.500	15.000 ; 30.600	14.000 ; 26.000	15.700 ; 28.825	15.000 ; 27.000
Min ; Max	12.00 ; 46.00	10.00 ; 55.00	10.00 ; 55.00	-1.00 ; 105.00	12.20 ; 55.00	-1.00 ; 105.00
FEV1 reversibility (%)						
Number	30	29	59	60	56	116
Mean (SD)	11.364 (13.206)	12.927 (9.681)	12.132 (11.535)	7.142 (8.179)	7.932 (10.140)	7.523 (9.146)
Median	8.329	13.632	9.396	4.708	5.539	5.239
Q1 ; Q3	4.079 ; 13.434	5.722 ; 18.199	4.977 ; 16.887	2.062 ; 10.190	1.105 ; 11.469	1.634 ; 10.658
Min ; Max	-2.84 ; 67.78	-1.82 ; 33.42	-2.84 ; 67.78	-4.56 ; 33.53	-6.78 ; 53.68	-6.78 ; 53.68
Baseline FEV1 reversibility group (%) [n (%)]						
Number	30	29	59	60	56	116
< 12	21 (70.0)	14 (48.3)	35 (59.3)	48 (80.0)	43 (76.8)	91 (78.4)
≥ 12	9 (30.0)	15 (51.7)	24 (40.7)	12 (20.0)	13 (23.2)	25 (21.6)
AM PEF (L/min)						
Number	32	32	64	68	63	131
Mean (SD)	319.66 (130.75)	307.34 (123.27)	313.50 (126.21)	304.13 (121.76)	323.69 (107.13)	313.54 (114.94)
Median	297.19	305.07	302.07	277.79	307.86	289.71
Q1 ; Q3	214.29 ; 391.83	211.46 ; 352.59	211.46 ; 383.18	212.10 ; 371.07	245.14 ; 387.43	227.43 ; 382.43
Min ; Max	148.6 ; 632.4	116.0 ; 611.1	116.0 ; 632.4	96.5 ; 631.3	144.8 ; 567.3	96.5 ; 631.3
PM PEF (L/min)						
Number	32	32	64	67	62	129
Mean (SD)	322.39 (127.71)	320.15 (117.16)	321.27 (121.57)	308.20 (118.90)	330.75 (104.19)	319.04 (112.21)
Median	298.29	317.78	306.91	283.43	319.36	306.29
Q1 ; Q3	221.95 ; 387.43	220.92 ; 378.00	220.92 ; 378.93	218.33 ; 380.57	260.43 ; 409.43	234.29 ; 383.71
Min ; Max	153.4 ; 651.6	135.6 ; 622.6	135.6 ; 651.6	99.7 ; 596.2	146.0 ; 557.6	99.7 ; 596.2
ACQ-5 score						
Number	32	32	64	68	64	132
Mean (SD)	2.19 (0.40)	2.04 (0.37)	2.12 (0.38)	2.18 (0.40)	2.24 (0.48)	2.21 (0.44)
Median	2.20	2.00	2.00	2.20	2.20	2.20
Q1 ; Q3	2.00 ; 2.40	1.80 ; 2.20	1.80 ; 2.30	1.80 ; 2.40	2.00 ; 2.60	2.00 ; 2.60
Min ; Max	1.4 ; 3.2	1.4 ; 2.8	1.4 ; 3.2	1.2 ; 3.2	1.4 ; 4.0	1.2 ; 4.0

	400 mg BID cohort			400 mg TID cohort		
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**All (N=64)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**	**All (N=132)**
ACQ-5 score group [n (%)]						
Number	32	32	64	68	64	132
≤ 2	15 (46.9)	19 (59.4)	34 (53.1)	29 (42.6)	24 (37.5)	53 (40.2)
> 2	17 (53.1)	13 (40.6)	30 (46.9)	39 (57.4)	40 (62.5)	79 (59.8)
AQLQ global score						
Number	31	32	63	67	62	129
Mean (SD)	4.67 (1.07)	4.91 (1.04)	4.79 (1.06)	4.68 (0.83)	4.96 (0.71)	4.82 (0.79)
Median	4.69	5.19	4.88	4.56	4.94	4.81
Q1 ; Q3	4.13 ; 5.59	4.31 ; 5.64	4.13 ; 5.59	4.00 ; 5.41	4.38 ; 5.44	4.22 ; 5.41
Min ; Max	2.1 ; 6.2	2.4 ; 6.4	2.1 ; 6.4	2.8 ; 6.3	3.7 ; 6.6	2.8 ; 6.6
PGIS score						
Number	31	32	63	67	62	129
Mean (SD)	1.6 (0.5)	1.3 (0.6)	1.5 (0.6)	1.7 (0.6)	1.6 (0.6)	1.7 (0.6)
Median	2.0	1.0	1.0	2.0	2.0	2.0
Q1 ; Q3	1.0 ; 2.0	1.0 ; 2.0	1.0 ; 2.0	1.0 ; 2.0	1.0 ; 2.0	1.0 ; 2.0
Min ; Max	1 ; 2	0 ; 3	0 ; 3	0 ; 3	0 ; 2	0 ; 3
Number of inhalations of salbutamol/albuterol or levosalbutamol/levalbuterol /24 hours (puffs)						
Number	32	32	64	67	62	129
Mean (SD)	2.52 (3.02)	1.57 (1.98)	2.04 (2.58)	0.94 (2.13)	0.82 (1.50)	0.88 (1.85)
Median	1.29	0.62	0.85	0.00	0.00	0.00
Q1 ; Q3	0.00 ; 4.71	0.00 ; 2.93	0.00 ; 4.00	0.00 ; 1.14	0.00 ; 1.00	0.00 ; 1.00
Min ; Max	0.0 ; 12.3	0.0 ; 7.4	0.0 ; 12.3	0.0 ; 12.5	0.0 ; 7.3	0.0 ; 12.5

[0214] **Table 16. Summary of baseline biomarkers (randomized population).**

	400 mg BID cohort			400 mg TID cohort		
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	All (N=64)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)	All (N=132)
Blood eosinophils (10^9/L)						
Number	32	32	64	68	64	132
Mean (SD)	0.326 (0.242)	0.381 (0.334)	0.354 (0.290)	0.267 (0.290)	0.248 (0.215)	0.257 (0.256)
Median	0.285	0.275	0.280	0.170	0.165	0.170
Q1 ; Q3	0.160 ; 0.420	0.140 ; 0.495	0.150 ; 0.470	0.100 ; 0.315	0.100 ; 0.325	0.100 ; 0.320
Min ; Max	0.02 ; 1.18	0.03 ; 1.59	0.02 ; 1.59	0.02 ; 1.51	0.04 ; 1.06	0.02 ; 1.51
Blood eosinophils group [n (%)]						
Number	32	31	64	68	64	132
< 0.15	6 (18.8)	8 (25.8)	14 (21.9)	29 (42.6)	28 (43.8)	57 (43.2)
≥ 0.15 - < 0.3	13 (40.6)	10 (31.3)	23 (35.9)	20 (29.4)	18 (28.1)	38 (28.8)
≥ 0.3	13 (40.6)	14 (43.8)	27 (42.2)	19 (27.9)	18 (28.1)	37 (28.0)
FeNO (ppb)						
Number	31	32	63	64	62	126
Mean (SD)	36.5 (34.4)	37.4 (39.3)	37.0 (36.7)	24.4 (22.2)	23.0 (17.5)	23.7 (19.9)
Median	26.0	27.0	26.0	17.5	17.0	17.5
Q1 ; Q3	13.0 ; 46.0	18.5 ; 39.5	15.0 ; 42.0	11.5 ; 31.0	11.0 ; 32.0	11.0 ; 32.0
Min ; Max	8 ; 161	11 ; 231	8 ; 231	5 ; 147	5 ; 85	5 ; 147
FeNO group 1 [n (%)]						
Number	31	32	63	64	62	126
< 25	15 (48.4)	12 (37.5)	27 (42.9)	42 (65.6)	42 (67.7)	84 (66.7)
≥ 25 - < 50	10 (32.3)	15 (46.9)	25 (39.7)	18 (28.1)	16 (25.8)	34 (27.0)
≥ 50	6 (19.4)	5 (15.6)	11 (17.5)	4 (6.3)	4 (6.5)	8 (6.3)
FeNO group 2 [n (%)]						
Number	31	32	63	64	62	126
< 35	19 (61.3)	21 (65.6)	40 (63.5)	50 (78.1)	47 (75.8)	97 (77.0)
≥ 35	12 (38.7)	11 (34.4)	23 (36.5)	14 (21.9)	15 (24.2)	29 (23.0)
Total IgE (IU/mL)						
Number	32	32	64	68	64	132
Mean (SD)	526.43 (630.53)	509.28 (815.43)	517.85 (723.11)	386.70 (724.05)	517.94 (924.94)	450.33 (826.98)
Median	281.05	178.40	210.80	119.65	132.65	121.85
Q1 ; Q3	88.70 ; 718.35	95.55 ; 682.20	93.30 ; 708.25	64.35 ; 366.40	40.00 ; 466.70	60.85 ; 410.25
Min ; Max	10.9 ; 2413.0	7.9 ; 4030.0	7.9 ; 4030.0	2.9 ; 3630.0	0.2 ; 4015.0	0.2 ; 4015.0
Total IgE level (IU/mL) [n (%)]						

	400 mg BID cohort			400 mg TID cohort		
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	All (N=64)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)	All (N=132)
Number	32	32	64	68	64	132
< 100	11 (34.4)	8 (25.0)	19 (29.7)	27 (39.7)	23 (35.9)	50 (37.9)
≥ 100	21 (65.6)	24 (75.0)	45 (70.3)	41 (60.3)	41 (64.1)	82 (62.1)
Total IgG (IU/mL)						
Number	32	32	64	68	64	132
Mean (SD)	12.325 (2.582)	11.941 (2.805)	12.133 (2.681)	11.546 (2.590)	11.643 (2.601)	11.593 (2.586)
Median	12.210	11.645	12.020	10.985	11.385	11.205
Q1 ; Q3	10.640 ; 13.490	9.705 ; 14.055	10.160 ; 13.615	9.630 ; 12.920	9.830 ; 13.120	9.650 ; 13.100
Min ; Max	6.90 ; 20.46	7.59 ; 17.90	6.90 ; 20.46	6.63 ; 19.75	6.28 ; 19.80	6.28 ; 19.80
Total IgA (IU/mL)						
Number	32	32	64	68	64	132
Mean (SD)	2543.4 (1226.2)	2785.9 (1299.6)	2664.7 (1259.3)	2510.1 (1108.5)	2540.5 (1349.0)	2524.8 (1226.3)
Median	2665.0	2440.0	2600.0	2190.0	2175.0	2190.0
Q1 ; Q3	1570.0 ; 3295.0	1785.0 ; 3525.0	1695.0 ; 3470.0	1585.0 ; 3340.0	1650.0 ; 2990.0	1640.0 ; 3240.0
Min ; Max	360 ; 5640	890 ; 6690	360 ; 6690	730 ; 5100	930 ; 8950	730 ; 8950
Total IgM (IU/mL)						
Number	32	32	64			
Mean (SD)	1.030 (0.525)	1.075 (0.579)	1.053 (0.549)	1.189 (0.683)	1.121 (0.718)	1.156 (0.698)
Median	0.955	1.025	0.990	1.005	0.895	0.950
Q1 ; Q3	0.645 ; 1.285	0.610 ; 1.365	0.610 ; 1.330	0.800 ; 1.310	0.670 ; 1.360	0.730 ; 1.330
Min ; Max	0.29 ; 2.40	0.26 ; 2.93	0.26 ; 2.93	0.25 ; 3.66	0.30 ; 3.88	0.25 ; 3.88

[0215] Table 17. Atopic comorbidity history (randomized population).

	400 mg BID cohort			400 mg TID cohort		
n (%)	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	All (N=64)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)	All (N=132)
Any comorbidity history						
Number	32	32	64	68	64	132
Yes	29 (90.6)	29 (90.6)	58 (90.6)	48 (70.6)	44 (68.8)	92 (69.7)
Ongoing condition	29 (90.6)	28 (87.5)	57 (89.1)	48 (70.6)	44 (68.8)	92 (69.7)
Atopic diseases						
Number	32	32	64	68	64	132
Yes	17 (53.1)	20 (62.5)	37 (57.8)	24 (35.3)	21 (32.8)	45 (34.1)

	400 mg BID cohort			400 mg TID cohort		
n (%)	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	All (N=64)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)	All (N=132)
Ongoing condition	16 (50.0)	19 (59.4)	35 (54.7)	24 (35.3)	21 (32.8)	45 (34.1)
Atopy and type 2 diseases						
Number	32	32	64	68	64	132
Yes	29 (90.6)	29 (90.6)	58 (90.6)	48 (70.6)	44 (68.8)	92 (69.7)
Ongoing condition	29 (90.6)	28 (87.5)	57 (89.1)	48 (70.6)	44 (68.8)	92 (69.7)
Atopic dermatitis history						
Number	32	32	64	68	64	132
Yes	2 (6.3)	2 (6.3)	4 (6.3)	2 (2.9)	0	2 (1.5)
Ongoing condition	2 (6.3)	2 (6.3)	4 (6.3)	2 (2.9)	0	2 (1.5)
Allergic conjunctivitis and allergic rhinitis history						
Number	32	32	64	68	64	132
Yes	4 (12.5)	3 (9.4)	7 (10.9)	2 (2.9)	2 (3.1)	4 (3.0)
Ongoing condition	4 (12.5)	3 (9.4)	7 (10.9)	2 (2.9)	2 (3.1)	4 (3.0)
Allergic conjunctivitis history						
Number	32	32	64	68	64	132
Yes	4 (12.5)	3 (9.4)	7 (10.9)	2 (2.9)	2 (3.1)	4 (3.0)
Ongoing condition	4 (12.5)	3 (9.4)	7 (10.9)	2 (2.9)	2 (3.1)	4 (3.0)
Allergic rhinitis history						
Number	32	32	64	68	64	132
Yes	16 (50.0)	18 (56.3)	34 (53.1)	21 (30.9)	20 (31.3)	41 (31.1)
Ongoing condition	15 (46.9)	17 (53.1)	32 (50.0)	21 (30.9)	20 (31.3)	41 (31.1)
Chronic rhinosinusitis history						
Number	32	32	64	68	64	132
Yes	6 (18.8)	5 (15.6)	11 (17.2)	3 (4.4)	4 (6.3)	7 (5.3)
Ongoing condition	6 (18.8)	5 (15.6)	11 (17.2)	3 (4.4)	4 (6.3)	7 (5.3)

	400 mg BID cohort			400 mg TID cohort		
n (%)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**All (N=64)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**	**All (N=132)**
Nasal polyposis history						
Number	32	32	64	68	64	132
Yes	1 (3.1)	2 (6.3)	3 (4.7)	0	1 (1.6)	1 (0.8)
Ongoing condition	1 (3.1)	2 (6.3)	3 (4.7)	0	1 (1.6)	1 (0.8)
Hypersensitivity to aspirin or other NSAID						
Number	32	32	64	68	64	132
Yes	2 (6.3)	1 (3.1)	3 (4.7)	0	2 (3.1)	2 (1.5)
Ongoing condition	2 (6.3)	1 (3.1)	3 (4.7)	0	2 (3.1)	2 (1.5)
Eosinophilic esophagitis history						
Number	32	32	64	68	64	132
Yes	0	0	0	0	0	0
Ongoing condition	0	0	0	0	0	0
Food allergy history						
Number	32	32	64	68	64	132
Yes	0	0	0	2 (2.9)	1 (1.6)	3 (2.3)
Ongoing condition	0	0	0	2 (2.9)	1 (1.6)	3 (2.3)
Hives history						
Number	32	32	64	68	64	132
Yes	1 (3.1)	2 (6.3)	3 (4.7)	0	1 (1.6)	1 (0.8)
Ongoing condition	1 (3.1)	2 (6.3)	3 (4.7)	0	0	0
Rubber sensitivity						
Number	32	32	64	68	64	132
Yes	1 (3.1)	0	1 (1.6)	0	0	0
Ongoing condition	1 (3.1)	0	1 (1.6)	0	0	0

[0216] **Table 18. Prior medications for asthma - number of participants by predefined categories and standardized medication name (randomized population)**

	400 mg BID cohort			400 mg TID cohort		
Predefined categories Standardized Medication Name n (%)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**All (N=64)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**	**All (N=132)**
Any prior medications	32 (100)	32 (100)	64 (100)	68 (100)	64 (100)	132 (100)
Pre-screening background therapy	32 (100)	32 (100)	64 (100)	68 (100)	64 (100)	132 (100)
Salmeterol	15 (46.9)	9 (28.1)	24 (37.5)	10 (14.7)	8 (12.5)	18 (13.6)
Fluticasone	15 (46.9)	6 (18.8)	21 (32.8)	8 (11.8)	4 (6.3)	12 (9.1)
Fluticasone propionate;salmeterol xinafoate	5 (15.6)	11 (34.4)	16 (25.0)	26 (38.2)	30 (46.9)	56 (42.4)
Fluticasone;salmeterol	4 (12.5)	6 (18.8)	10 (15.6)	1 (1.5)	3 (4.7)	4 (3.0)
Budesonide;formoterol fumarate	4 (12.5)	3 (9.4)	7 (10.9)	8 (11.8)	8 (12.5)	16 (12.1)
Beclometasone dipropionate;formoterol fumarate	2 (6.3)	2 (6.3)	4 (6.3)	14 (20.6)	7 (10.9)	21 (15.9)
Budesonide	2 (6.3)	2 (6.3)	4 (6.3)	3 (4.4)	2 (3.1)	5 (3.8)
Fluticasone propionate	1 (3.1)	3 (9.4)	4 (6.3)	3 (4.4)	4 (6.3)	7 (5.3)
Formoterol	2 (6.3)	1 (3.1)	3 (4.7)	3 (4.4)	1 (1.6)	4 (3.0)
Fluticasone furoate;vilanterol trifenatate	1 (3.1)	1 (3.1)	2 (3.1)	1 (1.5)	3 (4.7)	4 (3.0)
Beclometasone dipropionate	0	0	0	2 (2.9)	0	2 (1.5)
Beclometasone;formoterol	0	0	0	2 (2.9)	2 (3.1)	4 (3.0)
Budesonide;formoterol	0	0	0	2 (2.9)	2 (3.1)	4 (3.0)
Formoterol fumarate	0	0	0	2 (2.9)	0	2 (1.5)
Glycopyrronium bromide;indacaterol acetate;mometasone furoate	0	0	0	1 (1.5)	0	1 (0.8)
Systemic steroids	3 (9.4)	1 (3.1)	4 (6.3)	3 (4.4)	2 (3.1)	5 (3.8)
Meprednisone	1 (3.1)	1 (3.1)	2 (3.1)	1 (1.5)	1 (1.6)	2 (1.5)
Prednisone	2 (6.3)	0	2 (3.1)	2 (2.9)	0	2 (1.5)
Methylprednisolone	0	0	0	0	1 (1.6)	1 (0.8)
Asthma reliever	29 (90.6)	31 (96.9)	60 (93.8)	66 (97.1)	61 (95.3)	127 (96.2)
Salbutamol	29 (90.6)	31 (96.9)	60 (93.8)	66 (97.1)	60 (93.8)	126 (95.5)
Salbutamol sulfate	0	0	0	0	1 (1.6)	1 (0.8)
Antihistamines	3 (9.4)	2 (6.3)	5 (7.8)	1 (1.5)	0	1 (0.8)

	400 mg BID cohort			400 mg TID cohort		
Predefined categories Standardized Medication Name n (%)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**All (N=64)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**	**All (N=132)**
Fexofenadine hydrochloride	1 (3.1)	1 (3.1)	2 (3.1)	0	0	0
Levocetirizine	2 (6.3)	0	2 (3.1)	0	0	0
Azelastine	0	1 (3.1)	1 (1.6)	0	0	0
Desloratadine	0	1 (3.1)	1 (1.6)	0	0	0
Levocetirizine dihydrochloride	0	0	0	1 (1.5)	0	1 (0.8)
Mucolytics	0	2 (6.3)	2 (3.1)	0	0	0
Carbocisteine	0	1 (3.1)	1 (1.6)	0	0	0
Erdosteine	0	1 (3.1)	1 (1.6)	0	0	0
Leukotriene receptor antagonists or leukotriene synthesis inhibitors	1 (3.1)	1 (3.1)	2 (3.1)	0	2 (3.1)	2 (1.5)
Montelukast sodium	1 (3.1)	1 (3.1)	2 (3.1)	0	0	0
Azelastine	0	1 (3.1)	1 (1.6)	0	0	0
Montelukast	0	0	0	0	2 (3.1)	2 (1.5)
Anticholinergic bronchodilators	0	0	0	1 (1.5)	0	1 (0.8)
Ipratropium bromide	0	0	0	1 (1.5)	0	1 (0.8)
Other	1 (3.1)	0	1 (1.6)	0	0	0
Doxofylline	1 (3.1)	0	1 (1.6)	0	0	0
Hedera helix extract	1 (3.1)	0	1 (1.6)	0	0	0

[0217] Table 19. Concomitant medications for asthma - number of participants by predefined categories and standardized medication name (randomized population).

	400 mg BID cohort		400 mg TID cohort	
Predefined categories Standardized Medication Name n (%)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Any concomitant medications	32 (100)	32 (100)	68 (100)	64 (100)
Controller	32 (100)	32 (100)	68 (100)	64 (100)
Fluticasone	32 (100)	32 (100)	68 (100)	64 (100)
Salmeterol	32 (100)	32 (100)	68 (100)	64 (100)
Formoterol	0	0	1 (1.5)	0
Antibiotics	0	3 (9.4)	0	0
Azithromycin	0	3 (9.4)	0	0
Leukotriene receptor antagonists or leukotriene synthesis inhibitors	0	0	0	0

	400 mg BID cohort		400 mg TID cohort	
Predefined categories Standardized Medication Name n (%)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Anticholinergic bronchodilators	0	0	1 (1.5)	0
Ipratropium bromide	0	0	1 (1.5)	0
Antihistamines and antiallergics	3 (9.4)	1 (3.1)	0	0
Fexofenadine hydrochloride	1 (3.1)	1 (3.1)	0	0
Levocetirizine	2 (6.3)	0	0	0
Systemic steroid	4 (12.5)	5 (15.6)	2 (2.9)	1 (1.6)
Prednisone	1 (3.1)	3 (9.4)	0	0
Betamethasone dipropionate	0	1 (3.1)	0	0
Meprednisone	2 (6.3)	1 (3.1)	1 (1.5)	1 (1.6)
Methylprednisolone	1 (3.1)	1 (3.1)	1 (1.5)	0
Asthma reliever	29 (90.6)	31 (96.9)	65 (95.6)	60 (93.8)
Salbutamol	29 (90.6)	31 (96.9)	65 (95.6)	59 (92.2)
Salbutamol sulfate	0	0	0	1 (1.6)
Mucolytics	0	2 (6.3)	0	0
Carbocisteine	0	1 (3.1)	0	0
Erdosteine	0	1 (3.1)	0	0
Xanthines	0	0	1 (1.5)	0
Theophylline	0	0	1 (1.5)	0
PPI	0	0	0	0

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

LOAC

[0218] Treatment with rilzabrutinib yielded a numerical reduction in LOAC events relative to treatment with the placebo for patients in both the 400 mg BID and 400 mg TID cohorts (**Figure 3** and **Tables 20-28**). Although 50% of placebo-treated patients in the 400 mg BID cohort experienced LOAC during the treatment period, only 37.5% of rilzabrutinib-treated patients in the 400 mg BID cohort experienced LOAC (**Table 20**). Similar results were observed for the 400 mg TID cohort, in which 29.4% of placebo-treated patients and 18.8% of rilzabrutinib-treated patients experienced LOAC (**Table 20**). This represents a relative risk reduction of 25% and 36%, for the 400 mg BID and 400 mg TID cohorts, respectively.

[0219] Subgroup analysis further supports the efficacy of rilzabrutinib treatment in both cohorts. In general, patients receiving 400 mg BID or 400 mg TID rilzabrutinib exhibited a numerical improvement in the incidence of LOAC events regardless of baseline demographic characteristics, disease characteristics, ICS/LABA dose level, biomarker levels, eosinophil count, and FeNO (ppb) (**Tables 24-28**).

[0220] **Table 20. Primary analysis: incidence of LOAC (mITT population).**

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Number of participants with LOAC				
Number	32	32	68	64
No	16 (50.0)	20 (62.5)	48 (70.6)	52 (81.3)
Yes	16 (50.0)	12 (37.5)	20 (29.4)	12 (18.8)
Crude RRR vs. placebo		25.0		36.1
OR vs. placebo (95% CI)		0.570 (0.202, 1.608)		0.584 (0.253, 1.349)
P-value vs. placebo		0.2880		0.2083
RD vs. Placebo (95% CI)		-0.123 (-0.361, 0.115)		-0.088 (-0.238, 0.061)
RR vs. placebo (95% CI)		0.756 (0.433, 1.319)		0.653 (0.348, 1.226)
RRR vs. placebo (%)		24.4		34.7

LOAC: Loss of asthma control, OR: Odds ratio, RD: Risk difference, LATAM: Latin America, ROW: Rest of the world

[0221] **Table 21. Critical or major protocol deviations potentially impact on the primary endpoint (randomized population).**

	400 mg BID cohort		400 mg TID cohort	
Deviation category Deviation term n (%)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Any critical or major protocol deviation with potential impact on the primary endpoint	2 (6.3)	1 (3.1)	2 (2.9)	3 (4.7)
Inclusion/exclusion criteria	0	0	1 (1.5)	1 (1.6)

	400 mg BID cohort		400 mg TID cohort	
Deviation category **Deviation term** **n (%)**	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Asthma Control Questionnaire 5-question version (ACQ-5) score of >4 during the screening period or <1.25 or >3.0 at V2.	0	0	1 (1.5)	0
Participants with prebronchodilator FEV1 > 40% of predicted normal at V1. Prebronchodilator FEV1 >= 50% but <= 85% of predicted normal at V2.	0	0	0	1 (1.6)
Concomitant medications/ therapy	2 (6.3)	1 (3.1)	1 (1.5)	2 (3.1)
NIMP administered but not as per protocol	2 (6.3)	1 (3.1)	1 (1.5)	2 (3.1)

[0222] Table 22. Summary of LOAC events (mITT population).

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Number of participants with LOAC				
Number	32	32	68	64
No	16 (50.0)	20 (62.5)	48 (70.6)	52 (81.3)
Yes	16 (50.0)	12 (37.5)	20 (29.4)	12 (18.8)
Triggered by use of rescue medication	8 (25.0)	6 (18.8)	9 (13.2)	1 (1.6)
Number of participants with ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24 hour period (compared with baseline) on 2 consecutive days	4 (12.5)	2 (6.3)	7 (10.3)	0
Number of participants with increase in ICS ≥4 times the last prescribed ICS dose (or ≥50% of the prescribed ICS dose at baseline if background therapy withdrawal completed)	0	1 (3.1)	0	0
Number of participants requiring use of systemic (oral and/or parenteral) steroid treatment	4 (12.5)	4 (12.5)	2 (2.9)	1 (1.6)
Not triggered by use of rescue medication	8 (25.0)	6 (18.8)	10 (14.7)	10 (15.6)

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)
Number of participants with ≥30% reduction from baseline in AM PEF on 2 consecutive days	8 (25.0)	6 (18.8)	10 (14.7)	10 (15.6)
Number of participants requiring hospitalization or emergency room visit	0	0	0	0
Intervention discontinuation due to lack of efficacy or an AE related to asthma worsening	0	0	1 (1.5)	1 (1.6)

[0223] Table 23. Supportive analysis: time to LOAC post-randomization (mITT population).

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)
Number of participants with LOAC	16 (50.0)	12 (37.5)	20 (29.4)	12 (18.8)
Number of participants censored	16 (50.0)	20 (62.5)	48 (70.6)	52 (81.3)
Q1 of time to LOAC (days) (95% CI)	50.0 (14.0, 72.0)	55.0 (19.0, 84.0)	78.0 (52.0, NC)	NC (44.0, NC)
Median time to LOAC (days) (95% CI)	74.0 (64.0, NC)	NC (73.0, NC)	NC (87.0, NC)	NC (NC, NC)
Q3 of time to LOAC (days) (95% CI)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)
Probability of LOAC (95% CI) at				
Week 4	0.129 (0.041, 0.270)	0.161 (0.059, 0.309)	0.045 (0.012, 0.115)	0.017 (0.001, 0.080)
Week 9	0.330 (0.173, 0.496)	0.265 (0.125, 0.429)	0.168 (0.089, 0.267)	0.156 (0.077, 0.261)
Week 12	0.531 (0.341, 0.689)	0.432 (0.243, 0.607)	0.295 (0.189, 0.408)	0.211 (0.117, 0.325)
HR vs. Placebo (95% CI)		0.750 (0.352, 1.595)		0.679 (0.327, 1.408)
P-value vs. placebo		0.4543		0.2980

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)
P-value vs. placebo		0.3948		0.2794

NE: Not able to estimate, LATAM: Latin America, ROW: Rest of the world

[0224] Table 24. Subgroup analysis: incidence of LOAC by demographics subgroups (mITT population).

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)
Age group 1 (years)				
< 45				
Number	10	12	29	25
LOAC	3 (30.0)	6 (50.0)	11 (37.9)	2 (8.0)
OR vs. placebo (95% CI)		2.489 (0.342, 18.129)		0.142 (0.028, 0.725)
P-value vs. placebo		0.3680		0.0189
RD vs. Placebo (95% CI)		0.184 (-0.266, 0.634)		-0.299 (-0.505, -0.093)
≥ 45				
Number	22	20	39	39
LOAC	13 (59.1)	6 (30.0)	9 (23.1)	10 (25.6)
OR vs. placebo (95% CI)		0.266 (0.069, 1.023)		1.149 (0.408, 3.236)
P-value vs. placebo		0.0540		0.7920
RD vs. Placebo (95% CI)		-0.295 (-0.583, -0.007)		0.026 (-0.165, 0.216)
Overall p-value for interaction		0.0738		0.0298
Gender				
Male				
Number	8	14	27	25
LOAC	2 (25.0)	5 (35.7)	7 (25.9)	4 (16.0)
OR vs. placebo (95% CI)		2.062 (0.173, 24.590)		0.423 (0.091, 1.966)
P-value vs. placebo		0.5671		0.2721
RD vs. Placebo (95% CI)		0.256 (-0.420, 0.931)		-0.111 (-0.461, 0.238)
Female				
Number	24	18	41	39
LOAC	14 (58.3)	7 (38.9)	13 (31.7)	8 (20.5)
OR vs. placebo (95% CI)		0.311 (0.076, 1.263)		0.640 (0.224, 1.828)
P-value vs. placebo		0.1023		0.4042

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
RD vs. Placebo (95% CI)		-0.258 (-0.560, 0.045)		-0.084 (-0.291, 0.123)
Overall p-value for interaction		0.1040		0.9230
Baseline weight group (kg)				
< 60				
Number	4	3	12	2
LOAC	4 (100)	0	3 (25.0)	1 (50.0)
OR vs. placebo (95% CI)		NC (NC, NC)		3.000 (0.140, 64.262)
P-value vs. placebo		NC		0.4823
RD vs. Placebo (95% CI)		NC (NC, NC)		0.250 (-0.485, 0.985)
≥ 60 - < 90				
Number	25	23	40	41
LOAC	10 (40.0)	10 (43.5)	13 (32.5)	8 (19.5)
OR vs. placebo (95% CI)		1.154 (0.366, 3.640)		0.503 (0.182, 1.392)
P-value vs. placebo		0.8071		0.1860
RD vs. Placebo (95% CI)		0.035 (-0.244, 0.314)		-0.130 (-0.319, 0.059)
≥ 90				
Number	3	6	16	21
LOAC	2 (66.7)	2 (33.3)	4 (25.0)	3 (14.3)
OR vs. placebo (95% CI)		0.250 (0.013, 4.729)		0.500 (0.095, 2.645)
P-value vs. placebo		0.3554		0.4147
RD vs. Placebo (95% CI)		-0.333 (-0.987, 0.320)		-0.107 (-0.367, 0.153)
Overall p-value for interaction		0.0116		0.4929
Baseline BMI group (kg/m^2)				
< 25				
Number	6	8	22	12
LOAC	4 (66.7)	3 (37.5)	8 (36.4)	3 (25.0)
OR vs. placebo (95% CI)		0.300 (0.033, 2.763)		0.583 (0.121, 2.801)
P-value vs. placebo		0.2879		0.5008
RD vs. Placebo (95% CI)		-0.292 (-0.796, 0.213)		-0.114 (-0.431, 0.203)
≥ 25 - < 30				

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Number	17	16	27	29
LOAC	8 (47.1)	6 (37.5)	8 (29.6)	3 (10.3)
OR vs. placebo (95% CI)		0.675 (0.168, 2.709)		0.274 (0.064, 1.172)
P-value vs. placebo		0.5794		0.0807
RD vs. Placebo (95% CI)		-0.096 (-0.431, 0.240)		-0.193 (-0.398, 0.012)
≥ 30				
Number	9	8	19	23
LOAC	4 (44.4)	3 (37.5)	4 (21.1)	6 (26.1)
OR vs. placebo (95% CI)		0.750 (0.107, 5.238)		1.324 (0.313, 5.604)
P-value vs. placebo		0.7717		0.7034
RD vs. Placebo (95% CI)		-0.069 (-0.536, 0.397)		0.050 (-0.206, 0.307)
P-value vs. placebo		0.7706		0.2506
Region				
Eastern Europe				
Number	4	3	45	43
LOAC	2 (50.0)	1 (33.3)	14 (31.1)	8 (18.6)
OR vs. placebo (95% CI)		0.500 (0.023, 11.088)		0.506 (0.187, 1.368)
P-value vs. placebo		0.6611		0.1794
RD vs. Placebo (95% CI)		-0.167 (-0.891, 0.558)		-0.125 (-0.303, 0.053)
Latin America				
Number	25	25	19	19
LOAC	11 (44.0)	9 (36.0)	5 (26.3)	4 (21.1)
OR vs. placebo (95% CI)		0.716 (0.230, 2.230)		0.747 (0.166, 3.357)
P-value vs. placebo		0.5642		0.7032
RD vs. Placebo (95% CI)		-0.080 (-0.351, 0.191)		-0.053 (-0.322, 0.217)
Western Countries				
Number	1	2	2	2
LOAC	1 (100)	0	1 (50.0)	0
OR vs. placebo (95% CI)		NC (NC, NC)		NC (NC, NC)
P-value vs. placebo		NC		NC
RD vs. Placebo (95% CI)		NC (NC, NC)		NC (NC, NC)
APAC				
Number	2	2	2	0
LOAC	2 (100)	2 (100)	0	0

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)
OR vs. placebo (95% CI)		NC (NC, NC)		NC (NC, NC)
P-value vs. placebo		NC		NC
RD vs. Placebo (95% CI)		NC (NC, NC)		NC (NC, NC)
Overall p-value for interaction		NC		NC

LATAM: Latin America, ROW: Rest of the world

[0225] Table 25. Subgroup analysis: incidence of LOAC by disease and other characteristics subgroups (mITT population).

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)
Age at onset of asthma (years)				
< 12				
Number	7	9	15	14
LOAC	2 (28.6)	4 (44.4)	6 (40.0)	2 (14.3)
OR vs. placebo (95% CI)		2.000 (0.244, 16.362)		0.250 (0.041, 1.541)
P-value vs. placebo		0.5180		0.1352
RD vs. Placebo (95% CI)		0.159 (-0.308, 0.625)		-0.257 (-0.565, 0.051)
≥ 12 - < 18				
Number	2	5	5	5
LOAC	1 (50.0)	1 (20.0)	1 (20.0)	0
OR vs. placebo (95% CI)		0.250 (0.007, 8.560)		NC (NC, NC)
P-value vs. placebo		0.4419		NC
RD vs. Placebo (95% CI)		-0.300 (-1.077, 0.477)		NC (NC, NC)
≥ 18 - < 40				
Number	15	14	28	27
LOAC	9 (60.0)	4 (28.6)	10 (35.7)	6 (22.2)
OR vs. placebo (95% CI)		0.267 (0.056, 1.260)		0.514 (0.156, 1.694)
P-value vs. placebo		0.0953		0.2742
RD vs. Placebo (95% CI)		-0.314 (-0.657, 0.028)		-0.135 (-0.372, 0.102)
≥ 40				
Number	8	4	20	18
LOAC	4 (50.0)	3 (75.0)	3 (15.0)	4 (22.2)

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
OR vs. placebo (95% CI)		3.000 (0.211, 42.624)		1.619 (0.309, 8.478)
P-value vs. placebo		0.4171		0.5684
RD vs. Placebo (95% CI)		0.250 (-0.298, 0.798)		0.072 (-0.176, 0.320)
Overall p-value for interaction		0.1351		0.3189
Age at onset of asthma (years)				
< 18				
Number	9	14	20	19
LOAC	3 (33.3)	5 (35.7)	7 (35.0)	2 (10.5)
OR vs. placebo (95% CI)		1.402 (0.206, 9.530)		0.218 (0.039, 1.232)
P-value vs. placebo		0.7295		0.0847
RD vs. Placebo (95% CI)		0.126 (-0.346, 0.597)		-0.245 (-0.495, 0.006)
≥ 18				
Number	23	18	48	45
LOAC	13 (56.5)	7 (38.9)	13 (27.1)	10 (22.2)
OR vs. placebo (95% CI)		0.323 (0.079, 1.322)		0.769 (0.298, 1.986)
P-value vs. placebo		0.1160		0.5876
RD vs. Placebo (95% CI)		-0.258 (-0.560, 0.045)		-0.049 (-0.223, 0.126)
Overall p-value for interaction		0.2794		0.1729
Number of asthma exacerbations within 2 years before screening visit				
1				
Number	9	13	51	36
LOAC	3 (33.3)	5 (38.5)	17 (33.3)	5 (13.9)
OR vs. placebo (95% CI)		1.218 (0.176, 8.423)		0.323 (0.106, 0.978)
P-value vs. placebo		0.8416		0.0457
RD vs. Placebo (95% CI)		0.059 (-0.390, 0.508)		-0.194 (-0.366, -0.023)
2				
Number	15	11	16	23
LOAC	9 (60.0)	4 (36.4)	3 (18.8)	7 (30.4)
OR vs. placebo (95% CI)		0.471 (0.084, 2.634)		1.896 (0.407, 8.824)
P-value vs. placebo		0.3917		0.4149

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
RD vs. Placebo (95% CI)		-0.199 (-0.617, 0.219)		0.117 (-0.151, 0.385)
> 2				
Number	8	8	1	5
LOAC	4 (50.0)	3 (37.5)	0	0
OR vs. placebo (95% CI)		0.508 (0.044, 5.914)		NC (NC, NC)
P-value vs. placebo		0.5890		NC
RD vs. Placebo (95% CI)		-0.115 (-0.780, 0.551)		NC (NC, NC)
Overall p-value for interaction		0.8727		NC
Atopic medical conditions				
Yes				
Number	17	20	24	21
LOAC	8 (47.1)	8 (40.0)	6 (25.0)	4 (19.0)
OR vs. placebo (95% CI)		0.681 (0.174, 2.666)		0.821 (0.175, 3.846)
P-value vs. placebo		0.5815		0.8026
RD vs. Placebo (95% CI)		-0.069 (-0.384, 0.246)		-0.031 (-0.320, 0.257)
No				
Number	15	12	44	43
LOAC	8 (53.3)	4 (33.3)	14 (31.8)	8 (18.6)
OR vs. placebo (95% CI)		0.380 (0.065, 2.206)		0.493 (0.180, 1.353)
P-value vs. placebo		0.2809		0.1700
RD vs. Placebo (95% CI)		-0.204 (-0.557, 0.149)		-0.130 (-0.311, 0.051)
Overall p-value for interaction		0.6695		0.6159
Background ICS dose level at randomization (400 mg TID only)				
Medium				
Number			35	29
LOAC			14 (40.0)	6 (20.7)
OR vs. placebo (95% CI)				0.421 (0.125, 1.414)
P-value vs. placebo				0.1615
RD vs. placebo (95% CI)				-0.173 (-0.407, 0.061)
High				

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)
Number			33	35
LOAC			6 (18.2)	6 (17.1)
OR vs. placebo (95% CI)				0.911 (0.253, 3.276)
P-value vs. placebo				0.8867
RD vs. placebo (95% CI)				-0.011 (-0.218, 0.195)
Overall p-value for interaction				0.3913
Smoking history				
Former				
Number	8	4	6	6
LOAC	4 (50.0)	3 (75.0)	3 (50.0)	2 (33.3)
OR vs. placebo (95% CI)		3.000 (0.211, 42.624)		0.500 (0.049, 5.154)
P-value vs. placebo		0.4171		0.5603
RD vs. Placebo (95% CI)		0.250 (-0.298, 0.798)		-0.167 (-0.717, 0.383)
Never				
Number	24	28	62	58
LOAC	12 (50.0)	9 (32.1)	17 (27.4)	10 (17.2)
OR vs. placebo (95% CI)		0.474 (0.154, 1.461)		0.551 (0.229, 1.330)
P-value vs. placebo		0.1936		0.1853
RD vs. Placebo (95% CI)		-0.179 (-0.443, 0.086)		-0.102 (-0.249, 0.046)
Overall p-value for interaction		0.2175		0.7814
Baseline pre-bronchodilator FEV1 (L) (400 mg BID only)				
< Median (2.022)				
Number	14	17		
LOAC	7 (50.0)	7 (41.2)		
OR vs. placebo (95% CI)		0.700 (0.168, 2.910)		
P-value vs. placebo		0.6237		
RD vs. Placebo (95% CI)		-0.088 (-0.439, 0.263)		
P-value vs. placebo		0.6224		
≥ Median (2.022)				
Number	18	14		
LOAC	9 (50.0)	5 (35.7)		
OR vs. placebo (95% CI)		0.556 (0.133, 2.325)		

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
P-value vs. placebo		0.4209		
RD vs. Placebo (95% CI)		-0.143 (-0.484, 0.198)		
P-value vs. placebo		0.4117		
Overall p-value for interaction		0.7743		
Baseline pre-bronchodilator percent predicted FEV1 (%) (400 mg BID only)				
< Median (68)				
Number	12	17		
LOAC	6 (50.0)	7 (41.2)		
OR vs. placebo (95% CI)		0.700 (0.158, 3.099)		
P-value vs. placebo		0.6384		
RD vs. Placebo (95% CI)		-0.088 (-0.455, 0.279)		
P-value vs. placebo		0.6376		
≥ Median (68)				
Number	20	14		
LOAC	10 (50.0)	5 (35.7)		
OR vs. placebo (95% CI)		0.556 (0.137, 2.256)		
P-value vs. placebo		0.4110		
RD vs. Placebo (95% CI)		-0.143 (-0.476, 0.190)		
P-value vs. placebo		0.4007		
Overall p-value for interaction		0.5557		
Baseline pre-bronchodilator FEV1 (L) (400 mg TID only)				
< Median (2.1955)				
Number			36	29
LOAC			10 (27.8)	7 (24.1)
OR vs. placebo (95% CI)				0.827 (0.270, 2.536)
P-value vs. placebo				0.7401
RD vs. placebo (95% CI)				-0.036 (-0.250, 0.177)
≥ Median (2.1955)				
Number			31	34
LOAC			10 (32.3)	5 (14.7)

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
OR vs. placebo (95% CI)				0.362 (0.108, 1.216)
P-value vs. placebo				0.1003
RD vs. placebo (95% CI)				-0.176 (-0.379, 0.028)
Overall p-value for interaction				0.3196
Baseline pre-bronchodilator percent predicted FEV1 group 1 (%) (400 mg TID only)				
< Median (77)				
Number			36	29
LOAC			9 (25.0)	4 (13.8)
OR vs. placebo (95% CI)				0.452 (0.118, 1.730)
P-value vs. placebo				0.2464
RD vs. placebo (95% CI)				-0.129 (-0.394, 0.135)
≥ Median (77)				
Number			32	34
LOAC			11 (34.4)	8 (23.5)
OR vs. placebo (95% CI)				0.599 (0.185, 1.937)
P-value vs. placebo				0.3916
RD vs. placebo (95% CI)				-0.078 (-0.320, 0.165)
Overall p-value for interaction				0.6831
Baseline pre-bronchodilator percent predicted FEV1 group 2 (%) (400 mg TID only)				
< 80				
Number			41	37
LOAC			10 (24.4)	7 (18.9)
OR vs. placebo (95% CI)				0.736 (0.243, 2.229)
P-value vs. placebo				0.5884
RD vs. placebo (95% CI)				-0.047 (-0.244, 0.149)
≥ 80				
Number			27	26
LOAC			10 (37.0)	5 (19.2)

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
OR vs. placebo (95% CI)				0.429 (0.112, 1.648)
P-value vs. placebo				0.2176
RD vs. placebo (95% CI)				-0.139 (-0.406, 0.128)
Overall p-value for interaction				0.5675
Baseline FEV1 reversibility (%)				
< 12				
Number	21	14	48	43
LOAC	10 (47.6)	5 (35.7)	14 (29.2)	9 (20.9)
OR vs. placebo (95% CI)		0.611 (0.152, 2.450)		0.643 (0.245, 1.684)
P-value vs. placebo		0.4870		0.3685
RD vs. Placebo (95% CI)		-0.119 (-0.449, 0.211)		-0.082 (-0.259, 0.095)
≥ 12				
Number	9	15	12	13
LOAC	5 (55.6)	6 (40.0)	2 (16.7)	1 (7.7)
OR vs. placebo (95% CI)		0.533 (0.100, 2.839)		0.417 (0.033, 5.299)
P-value vs. placebo		0.4612		0.4998
RD vs. Placebo (95% CI)		-0.156 (-0.564, 0.253)		-0.090 (-0.346, 0.166)
Overall p-value for interaction		0.8792		0.7503
Baseline ACQ-5 score				
≤ 2				
Number	15	19	29	24
LOAC	7 (46.7)	7 (36.8)	7 (24.1)	6 (25.0)
OR vs. placebo (95% CI)		0.651 (0.153, 2.769)		1.162 (0.297, 4.543)
P-value vs. placebo		0.5608		0.8289
RD vs. Placebo (95% CI)		-0.098 (-0.429, 0.233)		0.025 (-0.209, 0.259)
> 2				
Number	17	13	39	40
LOAC	9 (52.9)	5 (38.5)	13 (33.3)	6 (15.0)
OR vs. placebo (95% CI)		0.475 (0.090, 2.502)		0.346 (0.113, 1.060)
P-value vs. placebo		0.3800		0.0632
RD vs. Placebo (95% CI)		-0.125 (-0.473, 0.224)		-0.181 (-0.379, 0.018)

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)
Overall p-value for interaction		0.7235		0.1501

LATAM: Latin America, ROW: Rest of the world

[0226] Table 26. Subgroup analysis: incidence of LOAC by baseline ICS/LABA dose level subgroups (mITT population).

	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
Background ICS/LABA dose level at randomization		
Medium		
Number	3	5
LOAC	2 (66.7)	1 (20.0)
OR vs. placebo (95% CI)		0.125 (0.005, 3.225)
P-value vs. placebo		0.2099
RD vs. Placebo (95% CI)		-0.467 (-1.105, 0.172)
P-value vs. placebo		0.1519
High		
Number	29	27
LOAC	14 (48.3)	11 (40.7)
OR vs. placebo (95% CI)		0.737 (0.256, 2.122)
P-value vs. placebo		0.5713
RD vs. Placebo (95% CI)		-0.075 (-0.335, 0.184)
P-value vs. placebo		0.5695
Overall p-value for interaction		0.3273

LATAM: Latin America, ROW: Rest of the world

[0227] Table 27. Subgroup analysis: incidence of LOAC by baseline biomarker subgroups (mITT population).

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)
Baseline IgE level (IU/mL)				
< 100				
Number	11	8	27	23
LOAC	5 (45.5)	2 (25.0)	7 (25.9)	4 (17.4)
OR vs. placebo (95% CI)		0.412 (0.053, 3.217)		0.602 (0.151, 2.390)
P-value vs. placebo		0.3977		0.4702

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
RD vs. Placebo (95% CI)		-0.220 (-0.676, 0.236)		-0.085 (-0.312, 0.141)
≥ 100				
Number	21	24	41	41
LOAC	11 (52.4)	10 (41.7)	13 (31.7)	8 (19.5)
OR vs. placebo (95% CI)		0.652 (0.192, 2.222)		0.522 (0.189, 1.440)
P-value vs. placebo		0.4946		0.2093
RD vs. Placebo (95% CI)		-0.092 (-0.376, 0.192)		-0.122 (-0.309, 0.065)
Overall p-value for interaction		0.6260		0.9272
Baseline median IgE level (IU/mL) (400 mg BID only)				
< Median (210.8)				
Number	13	19		
LOAC	5 (38.5)	6 (31.6)		
OR vs. placebo (95% CI)		0.744 (0.161, 3.434)		
P-value vs. placebo		0.7042		
RD vs. Placebo (95% CI)		-0.053 (-0.393, 0.286)		
P-value vs. placebo		0.7585		
≥ Median (210.8)				
Number	19	13		
LOAC	11 (57.9)	6 (46.2)		
OR vs. placebo (95% CI)		0.604 (0.136, 2.679)		
P-value vs. placebo		0.5067		
RD vs. Placebo (95% CI)		-0.124 (-0.482, 0.233)		
P-value vs. placebo		0.4960		
Overall p-value for interaction		0.9289		
Baseline median IgA level (IU/mL) (400 mg BID only)				
< Median (2600)				
Number	15	17		
LOAC	9 (60.0)	4 (23.5)		
OR vs. placebo (95% CI)		0.205 (0.045, 0.942)		
P-value vs. placebo		0.0416		
RD vs. Placebo (95% CI)		-0.365 (-0.684, -0.045)		

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
P-value vs. placebo		0.0253		
≥ Median (2600)				
Number	17	15		
LOAC	7 (41.2)	8 (53.3)		
OR vs. placebo (95% CI)		1.633 (0.402, 6.625)		
P-value vs. placebo		0.4927		
RD vs. Placebo (95% CI)		0.122 (-0.223, 0.466)		
P-value vs. placebo		0.4888		
Overall p-value for interaction		0.0553		
Baseline median IgE level (IU/mL) (400 mg TID only)				
< Median (121.85)				
Number			34	32
LOAC			9 (26.5)	6 (18.8)
OR vs. placebo (95% CI)				0.681 (0.209, 2.219)
P-value vs. placebo				0.5236
RD vs. placebo (95% CI)				-0.070 (-0.274, 0.135)
≥ Median (121.85)				
Number			34	32
LOAC			11 (32.4)	6 (18.8)
OR vs. placebo (95% CI)				0.510 (0.156, 1.672)
P-value vs. placebo				0.2663
RD vs. placebo (95% CI)				-0.122 (-0.356, 0.112)
Overall p-value for interaction				0.7981
Baseline median IgA level (mg/L) (400 mg TID only)				
< Median (2190)				
Number			34	32
LOAC			9 (26.5)	6 (18.8)
OR vs. placebo (95% CI)				0.774 (0.217, 2.765)
P-value vs. placebo				0.6933
RD vs. placebo (95% CI)				-0.011 (-0.239, 0.218)
≥ Median (2190)				

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Number			34	32
LOAC			11 (32.4)	6 (18.8)
OR vs. placebo (95% CI)				0.514 (0.160, 1.646)
P-value vs. placebo				0.2622
RD vs. placebo (95% CI)				-0.120 (-0.347, 0.107)
Overall p-value for interaction				0.6801
Baseline blood eosinophil level 1 (10^9/L)				
< 0.15				
Number	6	8	29	28
LOAC	3 (50.0)	2 (25.0)	8 (27.6)	6 (21.4)
OR vs. placebo (95% CI)		0.527 (0.017, 16.019)		0.716 (0.212, 2.415)
P-value vs. placebo		0.7133		0.5900
RD vs. Placebo (95% CI)		-0.135 (-0.945, 0.675)		-0.062 (-0.284, 0.161)
P-value vs. placebo		0.7433		
≥ 0.15 (400 mg BID only)				
Number	26	23		
LOAC	13 (50.0)	10 (43.5)		
OR vs. placebo (95% CI)		0.737 (0.221, 2.453)		
P-value vs. placebo		0.6186		
RD vs. Placebo (95% CI)		-0.077 (-0.361, 0.207)		
P-value vs. placebo		0.5938		
Overall p-value for interaction		0.4802		
≥ 0.15 - < 0.3 (400 mg TID only)				
Number			20	18
LOAC			3 (15.0)	4 (22.2)
OR vs. placebo (95% CI)				1.619 (0.309, 8.478)
P-value vs. placebo				0.5684
RD vs. placebo (95% CI)				0.072 (-0.176, 0.320)
≥ 0.3 (400 mg TID only)				
Number			19	18
LOAC			9 (47.4)	2 (11.1)

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
OR vs. placebo (95% CI)				0.139 (0.025, 0.779)
P-value vs. placebo				0.0248
RD vs. placebo (95% CI)				-0.363 (-0.630, -0.095)
Overall p-value for interaction				0.1249
Baseline blood eosinophil level 2 (10^9/L)				
< 0.3				
Number	19	17	49	46
LOAC	10 (52.6)	5 (29.4)	11 (22.4)	10 (21.7)
OR vs. placebo (95% CI)		0.231 (0.042, 1.283)		1.019 (0.376, 2.763)
P-value vs. placebo		0.0939		0.9711
RD vs. Placebo (95% CI)		-0.197 (-0.567, 0.174)		0.047 (-0.153, 0.247)
≥ 0.3				
Number	13	14	19	18
LOAC	6 (46.2)	7 (50.0)	9 (47.4)	2 (11.1)
OR vs. placebo (95% CI)		0.951 (0.192, 4.710)		0.146 (0.025, 0.844)
P-value vs. placebo		0.9511		0.0316
RD vs. Placebo (95% CI)		-0.013 (-0.398, 0.372)		-0.350 (-0.653, -0.047)
Overall p-value for interaction		0.2298		0.0574
Baseline FeNO level 1 (ppb)				
< 25				
Number	15	12	42	42
LOAC	8 (53.3)	3 (25.0)	14 (33.3)	9 (21.4)
OR vs. placebo (95% CI)		0.261 (0.044, 1.567)		0.567 (0.208, 1.548)
P-value vs. placebo		0.1420		0.2682
RD vs. Placebo (95% CI)		-0.227 (-0.621, 0.166)		-0.065 (-0.275, 0.145)
≥ 25				
Number	16	20	22	20
LOAC	8 (50.0)	9 (45.0)	4 (18.2)	3 (15.0)
OR vs. placebo (95% CI)		0.946 (0.233, 3.843)		0.798 (0.151, 4.218)
P-value vs. placebo		0.9383		0.7903
RD vs. Placebo (95% CI)		-0.007 (-0.333, 0.320)		-0.053 (-0.313, 0.207)

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Overall p-value for interaction		0.2742		0.6308
Baseline FeNO level 2 (ppb)				
< 35				
Number	19	21	50	47
LOAC	11 (57.9)	8 (38.1)	14 (28.0)	9 (19.1)
OR vs. placebo (95% CI)		0.448 (0.126, 1.589)		0.655 (0.246, 1.743)
P-value vs. placebo		0.2136		0.3965
RD vs. Placebo (95% CI)		-0.198 (-0.502, 0.106)		-0.029 (-0.221, 0.162)
≥ 35				
Number	12	11	14	15
LOAC	5 (41.7)	4 (36.4)	4 (28.6)	3 (20.0)
OR vs. placebo (95% CI)		0.800 (0.149, 4.297)		0.628 (0.108, 3.647)
P-value vs. placebo		0.7947		0.6038
RD vs. Placebo (95% CI)		-0.053 (-0.451, 0.345)		-0.094 (-0.398, 0.210)
Overall p-value for interaction		0.1981		0.9120

LATAM: Latin America, ROW: Rest of the world

[0228] Table 28. Subgroup analysis: incidence of LOAC in the baseline low EOS and low FeNO subgroup (mITT population).

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Baseline blood eosinophil (10^9/L) and FeNO (ppb)				
Low EOS (< 0.15) and low FeNO (< 25)				
Number	4	3	23	21
LOAC	3 (75.0)	0	8 (34.8)	4 (19.0)
OR vs. placebo (95% CI)		NC (NC, NC)		0.441 (0.110, 1.765)
P-value vs. placebo		NC		0.2474
RD vs. Placebo (95% CI)		NC (NC, NC)		-0.157 (-0.414, 0.100)
All others				
Number	27	28	41	41
LOAC	13 (48.1)	12 (42.9)	10 (24.4)	8 (19.5)

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)
OR vs. placebo (95% CI)		0.808 (0.279, 2.338)		0.752 (0.263, 2.150)
P-value vs. placebo		0.6938		0.5942
RD vs. Placebo (95% CI)		-0.053 (-0.316, 0.210)		-0.049 (-0.228, 0.130)
P-value vs. placebo		0.6933		0.4970

LATAM: Latin America, ROW: Rest of the world

FEV1

[0229] Rilzabrutinib treatment was not associated with an improvement in FEV1 values relative to treatment with the placebo (**Figures 4-6** and **Tables 29-38**).

[0230] Table 29. Key secondary analysis: change from baseline in pre-bronchodilator FEV1 (L) at Week 12, reduced model (mITT population).

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Baseline				
Number	32	31		
Mean (SD)	2.16 (0.77)	2.11 (0.67)	67	63
Median	2.10	1.94	2.42 (0.90)	2.50 (0.95)
Q1 ; Q3	1.47 ; 2.50	1.59 ; 2.52	2.15	2.36
Min ; Max	1.2 ; 3.9	1.0 ; 3.8	1.77 ; 2.98	1.73 ; 3.10
			1.0 ; 5.0	1.1 ; 5.3
Week 12				
Number (observed/LOCF imputed)	25 (16/9)	26 (21/5)		
Mean (SD)	2.00 (0.72)	2.02 (0.77)	55 (45/10)	49 (46/3)
Median	1.82	1.88	2.47 (0.90)	2.43 (0.83)
Q1 ; Q3	1.44 ; 2.33	1.57 ; 2.57	2.39	2.39
Min ; Max	1.0 ; 3.6	0.6 ; 3.8	1.76 ; 3.10	1.86 ; 2.80
			0.9 ; 5.0	1.1 ; 4.5
Change from baseline				
Number (observed/LOCF imputed)	25 (16/9)	25 (20/5)	54 (44/10)	48 (45/3)
Mean (SD)	-0.06 (0.22)	-0.04 (0.39)	-0.06 (0.31)	-0.15 (0.27)
Median	-0.06	-0.02	-0.07	-0.12
Q1 ; Q3	-0.18 ; 0.10	-0.21 ; 0.12	-0.21 ; 0.06	-0.28 ; 0.05
Min ; Max	-0.6 ; 0.3	-1.0 ; 0.7	-0.7 ; 1.2	-1.1 ; 0.4
LS Mean (SE)	-0.08 (0.08)	-0.07 (0.08)	-0.04 (0.05)	-0.13 (0.05)

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
LS Mean Diff vs. placebo (95% CI)		0.01 (-0.17, 0.19)		
P-value vs. placebo		0.9466		-0.09 (-0.21, 0.03)

LATAM: Latin America, ROW: Rest of the world

[0231] Table 30. Supplementary analysis (MMRM): change from baseline in pre-bronchodilator FEV1 (L) at EOT (Week 12; mITT population).

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Baseline				
Number	32	31	67	63
Mean (SD)	2.16 (0.77)	2.11 (0.67)	2.42 (0.90)	2.50 (0.95)
Median	2.10	1.94	2.15	2.36
Q1 ; Q3	1.47 ; 2.50	1.59 ; 2.52	1.77 ; 2.98	1.73 ; 3.10
Min ; Max	1.2 ; 3.9	1.0 ; 3.8	1.0 ; 5.0	1.1 ; 5.3
Week 12				
Number	16	21	45	46
Mean (SD)	2.03 (0.69)	2.01 (0.83)	2.37 (0.83)	2.46 (0.81)
Median	1.78	1.88	2.22	2.40
Q1 ; Q3	1.61 ; 2.40	1.57 ; 2.30	1.76 ; 2.82	1.89 ; 2.80
Min ; Max	1.0 ; 3.3	0.6 ; 3.8	0.9 ; 4.1	1.1 ; 4.5
Change from baseline				
Number	16	20	44	45
Mean (SD)	-0.03 (0.21)	-0.02 (0.41)	-0.07 (0.34)	-0.14 (0.27)
Median	-0.06	-0.04	-0.06	-0.09
Q1 ; Q3	-0.16 ; 0.17	-0.22 ; 0.32	-0.27 ; 0.06	-0.28 ; 0.05
Min ; Max	-0.4 ; 0.3	-1.0 ; 0.7	-0.7 ; 1.2	-1.1 ; 0.4
LS Mean (SE)	0.00 (0.08)	-0.01 (0.08)	-0.08 (0.05)	-0.16 (0.05)
LS Mean diff vs. placebo (95% CI)		0.00 (-0.21, 0.21)		-0.08 (-0.21, 0.05)
P-value vs. placebo		0.9747		0.2225

LATAM: Latin America, ROW: Rest of the world

[0232] Table 31. Summary of pre-bronchodilator FEV1 (L) over time (on-site conventional spirometry before LOAC and OCS use as observed; mITT population).

Pre-bronchodilator FEV1 (L)	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
Baseline		
Number	32	31
Mean (SD)	2.16 (0.77)	2.11 (0.67)
Median	2.10	1.94
Q1 ; Q3	1.47 ; 2.50	1.59 ; 2.52
Min ; Max	1.2 ; 3.9	1.0 ; 3.8
Week 2		
Number	28	27
Mean (SD)	2.23 (0.77)	2.20 (0.68)
Median	2.15	2.08
Q1 ; Q3	1.68 ; 2.63	1.79 ; 2.64
Min ; Max	1.2 ; 4.0	1.0 ; 4.0
Change from baseline		
Number	28	26
Mean (SD)	0.07 (0.29)	0.08 (0.29)
Median	0.05	0.04
Q1 ; Q3	-0.05 ; 0.18	-0.08 ; 0.22
Min ; Max	-0.7 ; 0.8	-0.6 ; 0.6
Percent change from baseline		
Number	28	26
Mean (SD)	4.24 (15.23)	4.47 (12.91)
Median	1.71	2.02
Q1 ; Q3	-2.49 ; 9.97	-2.56 ; 11.40
Min ; Max	-29.8 ; 45.4	-19.9 ; 38.3
Week 4		
Number	24	25
Mean (SD)	2.24 (0.75)	2.05 (0.62)
Median	2.11	1.96
Q1 ; Q3	1.73 ; 2.73	1.70 ; 2.36
Min ; Max	1.0 ; 3.9	1.0 ; 3.3
Change from baseline		
Number	24	25
Mean (SD)	0.08 (0.29)	0.07 (0.24)
Median	0.02	0.02
Q1 ; Q3	-0.08 ; 0.19	-0.07 ; 0.17
Min ; Max	-0.4 ; 0.9	-0.3 ; 0.6
Percent change from baseline		
Number	24	25
Mean (SD)	4.31 (16.19)	3.72 (12.19)
Median	0.51	0.55
Q1 ; Q3	-5.00 ; 8.08	-4.02 ; 11.68

Pre-bronchodilator FEV1 (L)	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
Min ; Max	-17.9 ; 54.0	-16.7 ; 30.7
Week 6		
Number	27	23
Mean (SD)	2.08 (0.67)	2.24 (0.79)
Median	2.19	2.01
Q1 ; Q3	1.46 ; 2.53	1.56 ; 2.71
Min ; Max	1.0 ; 3.5	1.0 ; 3.9
Change from baseline		
Number	27	22
Mean (SD)	0.05 (0.33)	0.09 (0.39)
Median	0.07	0.07
Q1 ; Q3	-0.13 ; 0.18	-0.11 ; 0.25
Min ; Max	-0.7 ; 0.9	-0.7 ; 1.2
Percent change from baseline		
Number	27	22
Mean (SD)	3.38 (17.82)	3.99 (17.73)
Median	2.56	3.66
Q1 ; Q3	-5.05 ; 12.12	-4.84 ; 11.59
Min ; Max	-35.5 ; 53.4	-27.7 ; 44.3
Week 8		
Number	24	20
Mean (SD)	2.05 (0.68)	2.10 (0.85)
Median	2.03	1.83
Q1 ; Q3	1.49 ; 2.45	1.51 ; 2.51
Min ; Max	0.9 ; 3.6	0.9 ; 3.9
Change from baseline		
Number	24	19
Mean (SD)	0.04 (0.24)	0.08 (0.41)
Median	-0.01	0.11
Q1 ; Q3	-0.12 ; 0.19	-0.07 ; 0.28
Min ; Max	-0.3 ; 0.7	-1.1 ; 0.7
Percent change from baseline		
Number	24	19
Mean (SD)	2.52 (14.71)	3.28 (18.63)
Median	-0.52	3.73
Q1 ; Q3	-5.85 ; 7.52	-4.40 ; 17.61
Min ; Max	-25.8 ; 41.1	-42.2 ; 27.5
Week 10		
Number	21	17
Mean (SD)	2.03 (0.75)	2.29 (0.76)
Median	1.99	1.93
Q1 ; Q3	1.57 ; 2.40	1.78 ; 2.57
Min ; Max	0.8 ; 3.8	1.6 ; 4.2

Pre-bronchodilator FEV1 (L)	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
Change from baseline		
Number	21	16
Mean (SD)	0.03 (0.29)	0.21 (0.29)
Median	-0.05	0.12
Q1 ; Q3	-0.17 ; 0.23	-0.01 ; 0.42
Min ; Max	-0.4 ; 0.8	-0.2 ; 0.7
Percent change from baseline		
Number	21	16
Mean (SD)	1.05 (15.30)	10.71 (16.43)
Median	-1.77	4.52
Q1 ; Q3	-8.09 ; 13.55	-0.45 ; 24.37
Min ; Max	-28.7 ; 28.2	-11.9 ; 45.6
Week 12		
Number	16	21
Mean (SD)	2.03 (0.69)	2.01 (0.83)
Median	1.78	1.88
Q1 ; Q3	1.61 ; 2.40	1.57 ; 2.30
Min ; Max	1.0 ; 3.3	0.6 ; 3.8
Change from baseline		
Number	16	20
Mean (SD)	-0.03 (0.21)	-0.02 (0.41)
Median	-0.06	-0.04
Q1 ; Q3	-0.16 ; 0.17	-0.22 ; 0.32
Min ; Max	-0.4 ; 0.3	-1.0 ; 0.7
Percent change from baseline		
Number	16	20
Mean (SD)	-0.55 (11.79)	-2.63 (21.27)
Median	-2.60	-2.04
Q1 ; Q3	-10.10 ; 9.07	-11.09 ; 12.57
Min ; Max	-18.0 ; 23.4	-54.6 ; 32.7
Week 16		
Number	19	19
Mean (SD)	2.21 (0.80)	2.30 (0.84)
Median	2.09	2.01
Q1 ; Q3	1.48 ; 2.66	1.80 ; 2.67
Min ; Max	1.0 ; 3.8	0.9 ; 4.2
Change from baseline		
Number	19	18
Mean (SD)	0.06 (0.29)	0.29 (0.37)
Median	0.12	0.28
Q1 ; Q3	-0.12 ; 0.28	-0.03 ; 0.44
Min ; Max	-0.7 ; 0.6	-0.3 ; 1.1

Pre-bronchodilator FEV1 (L)	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
Percent change from baseline		
Number	19	18
Mean (SD)	2.89 (15.39)	13.96 (17.98)
Median	4.48	15.23
Q1 ; Q3	-5.52 ; 9.15	-1.39 ; 22.70
Min ; Max	-33.5 ; 34.5	-12.4 ; 57.3

[0233] Table 32. Summary of pre-bronchodilator FEV1 (L) over time (on-site conventional spirometry as observed; mITT population).

Pre-bronchodilator FEV1 (L)	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
Baseline		
Number	32	31
Mean (SD)	2.16 (0.77)	2.11 (0.67)
Median	2.10	1.94
Q1 ; Q3	1.47 ; 2.50	1.59 ; 2.52
Min ; Max	1.2 ; 3.9	1.0 ; 3.8
Week 2		
Number	29	27
Mean (SD)	2.20 (0.77)	2.20 (0.68)
Median	2.13	2.08
Q1 ; Q3	1.66 ; 2.55	1.79 ; 2.64
Min ; Max	1.2 ; 4.0	1.0 ; 4.0
Change from baseline		
Number	29	26
Mean (SD)	0.07 (0.29)	0.08 (0.29)
Median	0.03	0.04
Q1 ; Q3	-0.04 ; 0.17	-0.08 ; 0.22
Min ; Max	-0.7 ; 0.8	-0.6 ; 0.6
Percent change from baseline		
Number	29	26
Mean (SD)	4.12 (14.97)	4.47 (12.91)
Median	1.16	2.02
Q1 ; Q3	-2.46 ; 8.38	-2.56 ; 11.40
Min ; Max	-29.8 ; 45.4	-19.9 ; 38.3
Week 4		
Number	25	25
Mean (SD)	2.29 (0.79)	2.05 (0.62)
Median	2.12	1.96
Q1 ; Q3	1.79 ; 2.75	1.70 ; 2.36
Min ; Max	1.0 ; 3.9	1.0 ; 3.3
Change from baseline		
Number	25	25

Pre-bronchodilator FEV1 (L)	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
Mean (SD)	0.09 (0.28)	0.07 (0.24)
Median	0.03	0.02
Q1 ; Q3	-0.08 ; 0.19	-0.07 ; 0.17
Min ; Max	-0.4 ; 0.9	-0.3 ; 0.6
Percent change from baseline		
Number	25	25
Mean (SD)	4.36 (15.85)	3.72 (12.19)
Median	0.66	0.55
Q1 ; Q3	-4.25 ; 7.82	-4.02 ; 11.68
Min ; Max	-17.9 ; 54.0	-16.7 ; 30.7
Week 6		
Number	29	24
Mean (SD)	2.11 (0.70)	2.24 (0.78)
Median	2.19	2.06
Q1 ; Q3	1.51 ; 2.53	1.63 ; 2.64
Min ; Max	1.0 ; 3.5	1.0 ; 3.9
Change from baseline		
Number	29	23
Mean (SD)	0.07 (0.33)	0.10 (0.39)
Median	0.07	0.07
Q1 ; Q3	-0.06 ; 0.18	-0.11 ; 0.33
Min ; Max	-0.7 ; 0.9	-0.7 ; 1.2
Percent change from baseline		
Number	29	23
Mean (SD)	4.36 (18.18)	4.61 (17.58)
Median	2.56	5.14
Q1 ; Q3	-4.60 ; 12.12	-4.84 ; 13.93
Min ; Max	-35.5 ; 53.4	-27.7 ; 44.3
Week 8		
Number	24	21
Mean (SD)	2.05 (0.68)	2.08 (0.83)
Median	2.03	1.86
Q1 ; Q3	1.49 ; 2.45	1.52 ; 2.45
Min ; Max	0.9 ; 3.6	0.9 ; 3.9
Change from baseline		
Number	24	20
Mean (SD)	0.04 (0.24)	0.08 (0.40)
Median	-0.01	0.09
Q1 ; Q3	-0.12 ; 0.19	-0.06 ; 0.25
Min ; Max	-0.3 ; 0.7	-1.1 ; 0.7
Percent change from baseline		
Number	24	20

Pre-bronchodilator FEV1 (L)	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
Mean (SD)	2.52 (14.71)	3.30 (18.14)
Median	-0.52	3.64
Q1 ; Q3	-5.85 ; 7.52	-4.06 ; 14.97
Min ; Max	-25.8 ; 41.1	-42.2 ; 27.5
Week 10		
Number	24	17
Mean (SD)	1.96 (0.74)	2.29 (0.76)
Median	1.97	1.93
Q1 ; Q3	1.40 ; 2.33	1.78 ; 2.57
Min ; Max	0.8 ; 3.8	1.6 ; 4.2
Change from baseline		
Number	24	16
Mean (SD)	-0.02 (0.30)	0.21 (0.29)
Median	-0.10	0.12
Q1 ; Q3	-0.18 ; 0.20	-0.01 ; 0.42
Min ; Max	-0.5 ; 0.8	-0.2 ; 0.7
Percent change from baseline		
Number	24	16
Mean (SD)	-1.48 (16.21)	10.71 (16.43)
Median	-5.47	4.52
Q1 ; Q3	-9.15 ; 13.20	-0.45 ; 24.37
Min ; Max	-30.1 ; 28.2	-11.9 ; 45.6
Week 12		
Number	19	23
Mean (SD)	2.13 (0.71)	1.97 (0.81)
Median	2.04	1.82
Q1 ; Q3	1.67 ; 2.47	1.43 ; 2.30
Min ; Max	1.0 ; 3.5	0.6 ; 3.8
Change from baseline		
Number	19	22
Mean (SD)	-0.04 (0.20)	-0.03 (0.40)
Median	-0.08	-0.05
Q1 ; Q3	-0.19 ; 0.14	-0.23 ; 0.31
Min ; Max	-0.4 ; 0.3	-1.0 ; 0.7
Percent change from baseline		
Number	19	22
Mean (SD)	-1.25 (11.01)	-3.27 (20.46)
Median	-2.79	-2.70
Q1 ; Q3	-8.91 ; 8.26	-11.12 ; 9.91
Min ; Max	-18.0 ; 23.4	-54.6 ; 32.7
Week 16		
Number	19	19
Mean (SD)	2.21 (0.80)	2.30 (0.84)

Pre-bronchodilator FEV1 (L)	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
Median	2.09	2.01
Q1 ; Q3	1.48 ; 2.66	1.80 ; 2.67
Min ; Max	1.0 ; 3.8	0.9 ; 4.2
Change from baseline		
Number	19	18
Mean (SD)	0.06 (0.29)	0.29 (0.37)
Median	0.12	0.28
Q1 ; Q3	-0.12 ; 0.28	-0.03 ; 0.44
Min ; Max	-0.7 ; 0.6	-0.3 ; 1.1
Percent change from baseline		
Number	19	18
Mean (SD)	2.89 (15.39)	13.96 (17.98)
Median	4.48	15.23
Q1 ; Q3	-5.52 ; 9.15	-1.39 ; 22.70
Min ; Max	-33.5 ; 34.5	-12.4 ; 57.3

All data were summarized as observed.

[0234] Table 33. Change from baseline in pre-bronchodilator FEV1 (L) over time (mITT population).

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Baseline				
Number	32	31	67	63
Mean (SD)	2.16 (0.77)	2.11 (0.67)	2.42 (0.90)	2.50 (0.95)
Median	2.10	1.94	2.15	2.36
Q1 ; Q3	1.47 ; 2.50	1.59 ; 2.52	1.77 ; 2.98	1.73 ; 3.10
Min ; Max	1.2 ; 3.9	1.0 ; 3.8	1.0 ; 5.0	1.1 ; 5.3
Week 2				
Number (observed/LOCF imputed)	29 (28/1)	27 (27/0)	64 (63/1)	56 (56/0)
Mean (SD)	2.20 (0.77)	2.20 (0.68)	2.48 (0.94)	2.47 (0.80)
Median	2.13	2.08	2.25	2.37
Q1 ; Q3	1.66 ; 2.55	1.79 ; 2.64	1.75 ; 3.07	1.76 ; 3.06
Min ; Max	1.2 ; 4.0	1.0 ; 4.0	1.0 ; 5.2	1.1 ; 4.1
Change from baseline				
Number (observed/LOCF imputed)	29 (28/1)	26 (26/0)	63 (62/1)	55 (55/0)
Mean (SD)	0.07 (0.29)	0.08 (0.29)	0.01 (0.20)	-0.04 (0.25)
Median	0.03	0.04	0.02	-0.02
Q1 ; Q3	-0.04 ; 0.17	-0.08 ; 0.22	-0.12 ; 0.15	-0.17 ; 0.10

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Min ; Max	-0.7 ; 0.8	-0.6 ; 0.6	-0.6 ; 0.6	-0.7 ; 0.7
LS Mean (SE)	0.05 (0.06)	0.06 (0.06)	-0.01 (0.03)	-0.05 (0.03)
LS Mean Diff vs. placebo (95% CI)		0.00 (-0.15, 0.15)		-0.04 (-0.12, 0.04)
P-value vs. placebo		0.9752		0.3401
Week 4				
Number (observed/LOCF imputed)	26 (24/2)	26 (25/1)	56 (55/1)	51 (51/0)
Mean (SD)	2.25 (0.79)	2.07 (0.62)	2.47 (0.92)	2.58 (0.86)
Median	2.11	1.96	2.30	2.50
Q1 ; Q3	1.66 ; 2.75	1.70 ; 2.56	1.75 ; 3.12	1.82 ; 3.14
Min ; Max	1.0 ; 3.9	1.0 ; 3.3	1.0 ; 5.3	1.2 ; 4.8
Change from baseline				
Number (observed/LOCF imputed)	26 (24/2)	26 (25/1)	55 (54/1)	51 (51/0)
Mean (SD)	0.08 (0.28)	0.07 (0.24)	-0.04 (0.30)	0.02 (0.22)
Median	0.02	0.02	-0.05	-0.01
Q1 ; Q3	-0.08 ; 0.18	-0.07 ; 0.17	-0.17 ; 0.13	-0.13 ; 0.13
Min ; Max	-0.4 ; 0.9	-0.3 ; 0.6	-0.9 ; 0.8	-0.5 ; 0.6
LS Mean (SE)	0.09 (0.05)	0.08 (0.05)	-0.07 (0.04)	-0.01 (0.04)
LS Mean Diff vs. placebo (95% CI)		-0.01 (-0.14, 0.12)		0.05 (-0.05, 0.15)
P-value vs. placebo		0.8701		0.3010
Week 6				
Number (observed/LOCF imputed)	29 (27/2)	25 (23/2)	58 (56/2)	54 (52/2)
Mean (SD)	2.10 (0.72)	2.24 (0.77)	2.35 (0.88)	2.52 (0.87)
Median	2.19	2.01	2.23	2.37
Q1 ; Q3	1.46 ; 2.53	1.70 ; 2.64	1.65 ; 2.97	1.84 ; 3.17
Min ; Max	1.0 ; 3.6	1.0 ; 3.9	1.0 ; 5.0	1.0 ; 4.8
Change from baseline				
Number (observed/LOCF imputed)	29 (27/2)	24 (22/2)	57 (55/2)	53 (51/2)
Mean (SD)	0.05 (0.32)	0.09 (0.38)	-0.08 (0.24)	-0.07 (0.34)
Median	0.07	0.07	-0.05	-0.09
Q1 ; Q3	-0.06 ; 0.18	-0.10 ; 0.22	-0.22 ; 0.08	-0.23 ; 0.08
Min ; Max	-0.7 ; 0.9	-0.7 ; 1.2	-0.6 ; 0.4	-1.3 ; 0.9
LS Mean (SE)	-0.00 (0.08)	-0.03 (0.08)	-0.11 (0.04)	-0.07 (0.04)

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
LS Mean Diff vs. placebo (95% CI)		-0.03 (-0.22, 0.17)		0.04 (-0.07, 0.15)
P-value vs. placebo		0.7797		0.4831
Week 8				
Number (observed/LOCF imputed)	27 (24/3)	24 (20/4)	56 (53/3)	45 (42/3)
Mean (SD)	2.05 (0.74)	2.09 (0.81)	2.36 (0.89)	2.41 (0.82)
Median	2.00	1.83	2.23	2.38
Q1 ; Q3	1.44 ; 2.48	1.51 ; 2.58	1.60 ; 3.03	1.81 ; 2.96
Min ; Max	0.9 ; 3.6	0.9 ; 3.9	0.7 ; 5.0	1.1 ; 4.3
Change from baseline				
Number (observed/LOCF imputed)	27 (24/3)	23 (19/4)	55 (52/3)	44 (41/3)
Mean (SD)	0.02 (0.26)	0.04 (0.41)	-0.11 (0.22)	-0.12 (0.40)
Median	0.00	0.05	-0.08	-0.10
Q1 ; Q3	-0.12 ; 0.13	-0.09 ; 0.23	-0.26 ; 0.04	-0.21 ; 0.08
Min ; Max	-0.6 ; 0.7	-1.1 ; 0.7	-0.6 ; 0.4	-2.3 ; 0.6
LS Mean (SE)	-0.03 (0.07)	-0.00 (0.07)	-0.10 (0.05)	-0.07 (0.05)
LS Mean Diff vs. placebo (95% CI)		0.02 (-0.14, 0.19)		0.03 (-0.10, 0.15)
P-value vs. placebo		0.7849		0.6679
Week 10				
Number (observed/LOCF imputed)	27 (21/6)	21 (17/4)	54 (50/4)	50 (47/3)
Mean (SD)	2.02 (0.77)	2.24 (0.73)	2.32 (0.88)	2.53 (0.88)
Median	1.99	1.93	2.15	2.50
Q1 ; Q3	1.38 ; 2.40	1.76 ; 2.57	1.62 ; 2.98	1.78 ; 3.15
Min ; Max	0.8 ; 3.8	1.3 ; 4.2	0.9 ; 5.0	1.1 ; 4.4
Change from baseline				
Number (observed/LOCF imputed)	27 (21/6)	20 (16/4)	53 (49/4)	50 (47/3)
Mean (SD)	0.00 (0.28)	0.13 (0.33)	-0.10 (0.28)	-0.10 (0.27)
Median	-0.05	0.09	-0.07	-0.09
Q1 ; Q3	-0.17 ; 0.18	-0.05 ; 0.36	-0.25 ; 0.05	-0.26 ; 0.09
Min ; Max	-0.6 ; 0.8	-0.7 ; 0.7	-1.0 ; 0.6	-1.0 ; 0.4
LS Mean (SE)	-0.05 (0.08)	0.02 (0.09)	-0.10 (0.04)	-0.09 (0.04)
LS Mean Diff vs. placebo (95% CI)		0.06 (-0.13, 0.26)		0.00 (-0.10, 0.11)

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
P-value vs. placebo		0.5282		0.9509
Week 12				
Number (observed/LOCF imputed)	25 (16/9)	26 (21/5)	55 (45/10)	49 (46/3)
Mean (SD)	2.00 (0.72)	2.02 (0.77)	2.47 (0.90)	2.43 (0.83)
Median	1.82	1.88	2.39	2.39
Q1 ; Q3	1.44 ; 2.33	1.57 ; 2.57	1.76 ; 3.10	1.86 ; 2.80
Min ; Max	1.0 ; 3.6	0.6 ; 3.8	0.9 ; 5.0	1.1 ; 4.5
Change from baseline				
Number (observed/LOCF imputed)	25 (16/9)	25 (20/5)	54 (44/10)	48 (45/3)
Mean (SD)	-0.06 (0.22)	-0.04 (0.39)	-0.06 (0.31)	-0.15 (0.27)
Median	-0.06	-0.02	-0.07	-0.12
Q1 ; Q3	-0.18 ; 0.10	-0.21 ; 0.12	-0.21 ; 0.06	-0.28 ; 0.05
Min ; Max	-0.6 ; 0.3	-1.0 ; 0.7	-0.7 ; 1.2	-1.1 ; 0.4
LS Mean (SE)	-0.08 (0.08)	-0.07 (0.08)	-0.04 (0.05)	-0.13 (0.05)
LS Mean Diff vs. placebo (95% CI)		0.01 (-0.17, 0.19)		-0.09 (-0.21, 0.03)
P-value vs. placebo		0.9466		0.1523

LATAM: Latin America, ROW: Rest of the world

[0235] Table 34. Subgroup analysis: change from baseline in pre-bronchodilator FEV1 (L) at EOT (Week 12) by demographics subgroups (mITT population).

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Age group 1 (years)				
< 45				
Number	8	9	26	22
Mean (SD)	-0.06 (0.21)	-0.05 (0.52)	-0.07 (0.24)	-0.24 (0.34)
LS Mean (SE)	-0.01 (0.19)	-0.13 (0.19)	-0.06 (0.08)	-0.24 (0.08)
LS Mean Diff vs. placebo (95% CI)		-0.13 (-0.60, 0.35)		-0.18 (-0.38, 0.02)
P-value vs. placebo		0.6056		0.0756
≥ 45				
Number	17	16	28	26
Mean (SD)	-0.06 (0.23)	-0.03 (0.32)	-0.06 (0.38)	-0.08 (0.17)
LS Mean (SE)	-0.16 (0.10)	-0.14 (0.10)	-0.03 (0.05)	-0.04 (0.06)

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
LS Mean Diff vs. placebo (95% CI)		0.02 (-0.19, 0.23)		-0.01 (-0.17, 0.14)
P-value vs. placebo		0.8611		0.8854
Overall p-value for interaction		0.9627		0.1988
Gender				
Male				
Number	6	11	22	21
Mean (SD)	-0.12 (0.31)	-0.08 (0.53)	-0.07 (0.36)	-0.16 (0.29)
LS Mean (SE)	-0.07 (0.19)	-0.23 (0.19)	-0.05 (0.08)	-0.15 (0.08)
LS Mean Diff vs. placebo (95% CI)		-0.16 (-0.72, 0.41)		-0.09 (-0.31, 0.12)
P-value vs. placebo		0.5836		0.3923
Female				
Number	19	14	32	27
Mean (SD)	-0.04 (0.18)	-0.01 (0.26)	-0.06 (0.28)	-0.14 (0.25)
LS Mean (SE)	-0.03 (0.10)	0.00 (0.09)	-0.02 (0.05)	-0.11 (0.06)
LS Mean Diff vs. placebo (95% CI)		0.04 (-0.17, 0.24)		-0.09 (-0.24, 0.05)
P-value vs. placebo		0.7294		0.2138
Overall p-value for interaction		0.7567		0.9813
Baseline weight group (kg)				
< 60				
Number	4	3	3	0
Mean (SD)	-0.10 (0.08)	-0.02 (0.04)	0.11 (0.31)	NC (NC)
LS Mean (SE)	NC (NC)	NC (NC)	NC (NC)	NC (NC)
LS Mean Diff vs. placebo (95% CI)		NC (NC, NC)		NC (NC, NC)
P-value vs. placebo		NC		NC
≥ 60 - < 90				
Number	18	18	29	28
Mean (SD)	-0.06 (0.25)	-0.01 (0.43)	-0.08 (0.37)	-0.15 (0.31)
LS Mean (SE)	-0.12 (0.12)	-0.09 (0.11)	-0.05 (0.07)	-0.13 (0.07)
LS Mean Diff vs. placebo (95% CI)		0.03 (-0.23, 0.28)		-0.07 (-0.25, 0.10)
P-value vs. placebo		0.8258		0.4062
≥ 90				
Number	3	4	15	18
Mean (SD)	-0.00 (0.10)	-0.17 (0.42)	-0.15 (0.21)	-0.17 (0.20)
LS Mean (SE)	0.12 (0.23)	-0.25 (0.37)	-0.10 (0.06)	-0.15 (0.06)
LS Mean Diff vs. placebo (95% CI)		-0.37 (-1.14, 0.40)		-0.05 (-0.21, 0.11)
P-value vs. placebo		0.3471		0.5184

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Overall p-value for interaction		0.8383		0.9293
Baseline BMI group (kg/m^2)				
< 25				
Number	5	7	19	8
Mean (SD)	-0.10 (0.07)	0.02 (0.51)	-0.04 (0.41)	-0.21 (0.45)
LS Mean (SE)	-0.24 (0.33)	-0.09 (0.32)	-0.03 (0.10)	-0.19 (0.15)
LS Mean Diff vs. placebo (95% CI)		0.15 (-0.48, 0.78)		-0.16 (-0.48, 0.16)
P-value vs. placebo		0.6436		0.3337
≥ 25 - < 30				
Number	14	12	20	25
Mean (SD)	-0.08 (0.25)	-0.00 (0.36)	-0.06 (0.27)	-0.14 (0.23)
LS Mean (SE)	-0.12 (0.12)	-0.06 (0.12)	-0.06 (0.06)	-0.11 (0.06)
LS Mean Diff vs. placebo (95% CI)		0.06 (-0.25, 0.37)		-0.05 (-0.22, 0.11)
P-value vs. placebo		0.7084		0.5147
≥ 30				
Number	6	6	15	15
Mean (SD)	0.03 (0.23)	-0.18 (0.33)	-0.09 (0.25)	-0.14 (0.22)
LS Mean (SE)	0.09 (0.27)	-0.04 (0.25)	-0.04 (0.07)	-0.11 (0.07)
LS Mean Diff vs. placebo (95% CI)		-0.13 (-0.63, 0.37)		-0.07 (-0.27, 0.13)
P-value vs. placebo		0.6158		0.5078
Overall p-value for interaction		0.7816		0.6728
Region				
Eastern Europe				
Number	4	1	38	32
Mean (SD)	-0.24 (0.31)	-0.21 (NC)	-0.10 (0.26)	-0.18 (0.28)
LS Mean (SE)	NC (NC)	NC (NC)	-0.10 (0.05)	-0.18 (0.05)
LS Mean Diff vs. placebo (95% CI)		NC (NC, NC)		-0.08 (-0.22, 0.06)
P-value vs. placebo		NC		0.2618
Latin America				
Number	19	21	14	14
Mean (SD)	-0.02 (0.19)	-0.05 (0.39)	0.03 (0.44)	-0.08 (0.27)
LS Mean (SE)	-0.06 (0.10)	-0.07 (0.08)	0.04 (0.12)	-0.08 (0.11)
LS Mean Diff vs. placebo (95% CI)		-0.01 (-0.25, 0.22)		-0.12 (-0.37, 0.12)
P-value vs. placebo		0.9056		0.3256
Western Countries				
Number	1	2	1	2
Mean (SD)	-0.05 (NC)	0.24 (0.67)	-0.14 (NC)	-0.18 (0.06)
LS Mean (SE)	NC (NC)	NC (NC)	NC (NC)	NC (NC)

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
LS Mean Diff vs. placebo (95% CI)		NC (NC, NC)		NC (NC, NC)
P-value vs. placebo		NC		NC
APAC				
Number	1	1	1	0
Mean (SD)	-0.07 (NC)	-0.09 (NC)	0.02 (NC)	NC (NC)
LS Mean (SE)	NC (NC)	NC (NC)	NC (NC)	NC (NC)
LS Mean Diff vs. placebo (95% CI)		NC (NC, NC)		NC (NC, NC)
P-value vs. placebo		NC		NC
Overall p-value for interaction		0.8887		0.8187

LATAM: Latin America, ROW: Rest of the world

[0236] Table 35. Subgroup analysis: change from baseline in pre-bronchodilator FEV1 (L) at EOT (Week 12) by disease and other characteristics subgroups (mITT population).

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Age at onset of asthma (years)				
< 12				
Number	7	8	12	11
Mean (SD)	-0.08 (0.21)	0.00 (0.48)	-0.07 (0.25)	-0.25 (0.38)
LS Mean (SE)	-0.06 (0.25)	0.12 (0.32)	-0.05 (0.10)	-0.34 (0.11)
LS Mean Diff vs. placebo (95% CI)		0.18 (-0.43, 0.80)		-0.28 (-0.58, 0.01)
P-value vs. placebo		0.5568		0.0576
≥ 12 - < 18				
Number	1	4	5	4
Mean (SD)	-0.01 (NC)	0.12 (0.29)	0.31 (0.56)	-0.01 (0.38)
LS Mean (SE)	NC (NC)	NC (NC)	0.45 (0.42)	0.05 (0.41)
LS Mean Diff vs. placebo (95% CI)		NC (NC, NC)		-0.40 (-1.36, 0.57)
P-value vs. placebo		NC		0.4199
≥ 18 - < 40				
Number	11	11	23	21
Mean (SD)	-0.06 (0.28)	-0.08 (0.36)	-0.13 (0.30)	-0.17 (0.23)
LS Mean (SE)	-0.14 (0.13)	-0.14 (0.13)	-0.10 (0.06)	-0.18 (0.07)
LS Mean Diff vs. placebo (95% CI)		0.00 (-0.29, 0.29)		-0.08 (-0.24, 0.09)
P-value vs. placebo		0.9979		0.3506

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
≥ 40				
Number	6	2	14	12
Mean (SD)	-0.03 (0.12)	-0.31 (0.55)	-0.09 (0.19)	-0.07 (0.14)
LS Mean (SE)	-0.07 (0.27)	0.00 (0.63)	-0.05 (0.07)	0.01 (0.08)
LS Mean Diff vs. placebo (95% CI)		0.07 (-0.91, 1.05)		0.06 (-0.13, 0.25)
P-value vs. placebo		0.8887		0.5330
Overall p-value for interaction		0.9178		0.2462
Age at onset of asthma (years)				
< 18				
Number	8	12	17	15
Mean (SD)	-0.07 (0.19)	0.04 (0.41)	0.04 (0.39)	-0.18 (0.38)
LS Mean (SE)	-0.09 (0.18)	-0.00 (0.18)	0.02 (0.10)	-0.25 (0.11)
LS Mean Diff vs. placebo (95% CI)		0.08 (-0.30, 0.47)		-0.27 (-0.55, -0.00)
P-value vs. placebo		0.6639		0.0498
≥ 18				
Number	17	13	37	33
Mean (SD)	-0.05 (0.23)	-0.11 (0.37)	-0.11 (0.26)	-0.14 (0.20)
LS Mean (SE)	-0.13 (0.11)	-0.17 (0.11)	-0.07 (0.05)	-0.10 (0.05)
LS Mean Diff vs. placebo (95% CI)		-0.03 (-0.27, 0.21)		-0.02 (-0.16, 0.11)
P-value vs. placebo		0.7986		0.7110
Overall p-value for interaction		0.4111		0.0777
Number of asthma exacerbations within 2 years before screening visit				
1				
Number	5	10	40	31
Mean (SD)	-0.02 (0.19)	0.05 (0.51)	-0.03 (0.30)	-0.16 (0.29)
LS Mean (SE)	-0.03 (0.22)	-0.08 (0.17)	-0.01 (0.05)	-0.14 (0.06)
LS Mean Diff vs. placebo (95% CI)		-0.05 (-0.57, 0.47)		-0.13 (-0.27, 0.01)
P-value vs. placebo		0.8488		0.0625
2				
Number	14	9	14	14
Mean (SD)	-0.07 (0.27)	-0.06 (0.28)	-0.17 (0.34)	-0.16 (0.24)
LS Mean (SE)	-0.11 (0.12)	-0.01 (0.16)	-0.14 (0.09)	-0.08 (0.09)
LS Mean Diff vs. placebo (95% CI)		0.10 (-0.22, 0.41)		0.06 (-0.18, 0.30)
P-value vs. placebo		0.5439		0.6174
> 2				
Number	6	6	0	3
Mean (SD)	-0.05 (0.10)	-0.15 (0.34)	NC (NC)	0.01 (0.06)

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
LS Mean (SE)	-0.20 (0.18)	-0.36 (0.14)	NC (NC)	NC (NC)
LS Mean Diff vs. placebo (95% CI)		-0.16 (-0.52, 0.20)		NC (NC, NC)
P-value vs. placebo		0.3826		NC
Overall p-value for interaction		0.7653		0.4094
Atopic medical conditions				
Yes				
Number	15	16	16	16
Mean (SD)	0.02 (0.18)	0.03 (0.25)	-0.07 (0.25)	-0.09 (0.25)
LS Mean (SE)	0.05 (0.09)	0.02 (0.08)	-0.07 (0.07)	-0.12 (0.07)
LS Mean Diff vs. placebo (95% CI)		-0.03 (-0.19, 0.12)		-0.04 (-0.23, 0.14)
P-value vs. placebo		0.6793		0.6505
No				
Number	10	9	38	32
Mean (SD)	-0.17 (0.23)	-0.16 (0.56)	-0.06 (0.34)	-0.18 (0.28)
LS Mean (SE)	-0.25 (0.16)	-0.15 (0.19)	-0.04 (0.07)	-0.15 (0.07)
LS Mean Diff vs. placebo (95% CI)		0.10 (-0.39, 0.60)		-0.11 (-0.26, 0.04)
P-value vs. placebo		0.6862		0.1594
Overall p-value for interaction		0.8948		0.6133
Background ICS dose level at randomization (400 mg TID only)				
Medium				
Number			29	21
Mean (SD)			-0.06 (0.26)	-0.18 (0.28)
LS Mean (SE)			-0.05 (0.06)	-0.15 (0.07)
LS Mean Diff vs. placebo (95% CI)				-0.10 (-0.25, 0.05)
P-value vs. placebo				0.1837
High				
Number			25	27
Mean (SD)			-0.07 (0.37)	-0.13 (0.27)
LS Mean (SE)			-0.07 (0.07)	-0.13 (0.07)
LS Mean Diff vs. placebo (95% CI)				-0.07 (-0.25, 0.11)
P-value vs. placebo				0.4593
Overall p-value for interaction				0.7498
Smoking history				
Former				
Number	7	4	3	3
Mean (SD)	-0.07 (0.28)	-0.36 (0.39)	-0.06 (0.09)	-0.21 (0.28)

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
LS Mean (SE)	-0.36 (0.22)	-0.57 (0.43)	-0.07 (0.16)	-0.12 (0.16)
LS Mean Diff vs. placebo (95% CI)		-0.21 (-0.96, 0.55)		-0.05 (-0.46, 0.37)
P-value vs. placebo		0.5908		0.8328
Never				
Number	18	21	51	45
Mean (SD)	-0.05 (0.19)	0.02 (0.37)	-0.06 (0.32)	-0.15 (0.27)
LS Mean (SE)	-0.08 (0.11)	-0.05 (0.10)	-0.04 (0.05)	-0.13 (0.05)
LS Mean Diff vs. placebo (95% CI)		0.03 (-0.18, 0.24)		-0.09 (-0.21, 0.04)
P-value vs. placebo		0.7800		0.1745
Overall p-value for interaction		0.1306		0.9511
Baseline pre-bronchodilator FEV1 (L) (400 mg BID only)				
< Median (2.022)				
Number	12	13		
Mean (SD)	-0.08 (0.25)	-0.06 (0.27)		
LS Mean (SE)	-0.12 (0.13)	-0.08 (0.14)		
LS Mean Diff vs. placebo (95% CI)		0.04 (-0.19, 0.27)		
P-value vs. placebo		0.7330		
≥ Median (2.022)				
Number	13	12		
Mean (SD)	-0.04 (0.19)	-0.02 (0.50)		
LS Mean (SE)	-0.07 (0.13)	-0.09 (0.14)		
LS Mean Diff vs. placebo (95% CI)		-0.03 (-0.38, 0.32)		
P-value vs. placebo		0.8705		
Overall p-value for interaction		0.8540		
Baseline pre-bronchodilator percent predicted FEV1 (%) (400 mg BID only)				
< Median (68)				
Number	11	16		
Mean (SD)	-0.08 (0.26)	-0.05 (0.41)		
LS Mean (SE)	-0.24 (0.16)	-0.21 (0.16)		
LS Mean Diff vs. placebo (95% CI)		0.03 (-0.27, 0.34)		
P-value vs. placebo		0.8283		
≥ Median (68)				
Number	14	9		
Mean (SD)	-0.04 (0.18)	-0.02 (0.39)		
LS Mean (SE)	-0.06 (0.13)	-0.07 (0.13)		

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
LS Mean Diff vs. placebo (95% CI)		-0.01 (-0.28, 0.26)		
P-value vs. placebo		0.9404		
Overall p-value for interaction		0.7813		
Baseline pre-bronchodilator FEV1 (L) (400 mg TID only)				
< Median (2.1955)				
Number			24	18
Mean (SD)			0.05 (0.35)	-0.05 (0.23)
LS Mean (SE)			0.05 (0.07)	-0.03 (0.08)
LS Mean Diff vs. placebo (95% CI)				-0.09 (-0.28, 0.10)
P-value vs. placebo				0.3726
≥ Median (2.1955)				
Number			30	30
Mean (SD)			-0.15 (0.26)	-0.21 (0.28)
LS Mean (SE)			-0.13 (0.06)	-0.22 (0.06)
LS Mean Diff vs. placebo (95% CI)				-0.09 (-0.24, 0.07)
P-value vs. placebo				0.2881
Overall p-value for interaction				0.9725
Baseline pre-bronchodilator percent predicted FEV1 group 1 (%) (400 mg TID only)				
< Median (77)				
Number			28	21
Mean (SD)			-0.01 (0.37)	-0.10 (0.25)
LS Mean (SE)			0.01 (0.07)	-0.03 (0.08)
LS Mean Diff vs. placebo (95% CI)				-0.04 (-0.24, 0.15)
P-value vs. placebo				0.6453
≥ Median (77)				
Number			26	27
Mean (SD)			-0.12 (0.24)	-0.19 (0.28)
LS Mean (SE)			-0.09 (0.06)	-0.21 (0.06)
LS Mean Diff vs. placebo (95% CI)				-0.13 (-0.28, 0.03)
P-value vs. placebo				0.1033
Overall p-value for interaction				0.4854
Baseline pre-bronchodilator percent predicted FEV1 group 2 (%) (400 mg TID only)				

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
< 80				
Number			33	26
Mean (SD)			-0.03 (0.35)	-0.13 (0.30)
LS Mean (SE)			-0.01 (0.06)	-0.09 (0.07)
LS Mean Diff vs. placebo (95% CI)				-0.08 (-0.25, 0.08)
P-value vs. placebo				0.3269
≥ 80				
Number			21	22
Mean (SD)			-0.12 (0.25)	-0.17 (0.24)
LS Mean (SE)			-0.09 (0.06)	-0.20 (0.06)
LS Mean Diff vs. placebo (95% CI)				-0.11 (-0.28, 0.06)
P-value vs. placebo				0.2034
Overall p-value for interaction				0.8177
Baseline FEV1 reversibility (%)				
< 12				
Number	14	10	40	35
Mean (SD)	-0.16 (0.20)	-0.24 (0.47)	-0.06 (0.33)	-0.18 (0.25)
LS Mean (SE)	-0.23 (0.10)	-0.23 (0.12)	-0.04 (0.05)	-0.16 (0.05)
LS Mean Diff vs. placebo (95% CI)		-0.00 (-0.26, 0.26)		-0.12 (-0.25, 0.02)
P-value vs. placebo		0.9928		0.0828
≥ 12				
Number	9	14	9	10
Mean (SD)	0.04 (0.15)	0.08 (0.27)	0.01 (0.30)	0.00 (0.27)
LS Mean (SE)	0.12 (0.12)	0.07 (0.11)	0.02 (0.13)	-0.01 (0.12)
LS Mean Diff vs. placebo (95% CI)		-0.05 (-0.26, 0.16)		-0.02 (-0.34, 0.29)
P-value vs. placebo		0.6636		0.8822
Overall p-value for interaction		0.4867		0.4422
Baseline ACQ-5 score				
≤ 2				
Number	12	14	20	12
Mean (SD)	0.00 (0.20)	0.00 (0.47)	-0.20 (0.24)	-0.10 (0.19)
LS Mean (SE)	-0.15 (0.16)	-0.12 (0.13)	-0.11 (0.06)	-0.12 (0.08)
LS Mean Diff vs. placebo (95% CI)		0.04 (-0.28, 0.35)		-0.01 (-0.20, 0.19)
P-value vs. placebo		0.8203		0.9587
> 2				
Number	13	11	34	36
Mean (SD)	-0.11 (0.22)	-0.09 (0.29)	0.01 (0.33)	-0.17 (0.29)
LS Mean (SE)	-0.08 (0.10)	-0.12 (0.12)	0.00 (0.06)	-0.15 (0.06)

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
LS Mean Diff vs. placebo (95% CI)		-0.04 (-0.29, 0.20)		-0.16 (-0.31, 0.00)
P-value vs. placebo		0.7321		0.0511
Overall p-value for interaction		0.9187		0.2088

LATAM: Latin America, ROW: Rest of the world

[0237] Table 36. Subgroup analysis: change from baseline in pre-bronchodilator FEV1 (L) at EOT (Week 12) by baseline ICS/LABA dose level (mITT population).

Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**
Background ICS/LABA dose level at randomization		
Medium		
Number	2	2
Mean (SD)	-0.07 (0.00)	0.04 (0.47)
LS Mean (SE)	NC (NC)	NC (NC)
LS Mean Diff vs. placebo (95% CI)		NC (NC, NC)
P-value vs. placebo		NC
High		
Number	23	23
Mean (SD)	-0.06 (0.23)	-0.05 (0.40)
LS Mean (SE)	-0.12 (0.09)	-0.11 (0.09)
LS Mean Diff vs. placebo (95% CI)		0.02 (-0.19, 0.23)
P-value vs. placebo		0.8815
Overall p-value for interaction		0.8062

LATAM: Latin America, ROW: Rest of the world

[0238] Table 37. Subgroup analysis: change from baseline in pre-bronchodilator FEV1 (L) at EOT (Week 12) by baseline biomarker subgroups (mITT population).

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Baseline IgE level (IU/mL)				
< 100				
Number	7	7	22	18
Mean (SD)	-0.10 (0.30)	-0.09 (0.52)	-0.08 (0.21)	-0.20 (0.31)
LS Mean (SE)	-0.07 (0.27)	-0.11 (0.26)	0.02 (0.12)	-0.10 (0.13)
LS Mean Diff vs. placebo (95% CI)		-0.03 (-0.56, 0.50)		-0.11 (-0.27, 0.05)
P-value vs. placebo		0.8986		0.1765
≥ 100				

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Number	18	18	32	30
Mean (SD)	-0.04 (0.19)	-0.02 (0.35)	-0.05 (0.37)	-0.12 (0.24)
LS Mean (SE)	-0.06 (0.20)	-0.04 (0.18)	-0.06 (0.09)	-0.13 (0.09)
LS Mean Diff vs. placebo (95% CI)		0.02 (-0.20, 0.23)		-0.07 (-0.24, 0.10)
P-value vs. placebo		0.8821		0.4002
Overall p-value for interaction		0.5502		0.6890
Baseline median IgE level (IU/mL) (400 mg BID only)				
< Median (210.8)				
Number	8	17		
Mean (SD)	-0.11 (0.28)	-0.02 (0.37)		
LS Mean (SE)	-0.13 (0.15)	-0.11 (0.13)		
LS Mean Diff vs. placebo (95% CI)		0.01 (-0.34, 0.37)		
P-value vs. placebo		0.9444		
≥ Median (210.8)				
Number	17	8		
Mean (SD)	-0.03 (0.19)	-0.08 (0.45)		
LS Mean (SE	-0.04 (0.11)	-0.02 (0.14)		
LS Mean Diff vs. placebo (95% CI)		0.01 (-0.29, 0.31)		
P-value vs. placebo		0.9284		
Overall p-value for interaction		0.8938		
Baseline median IgE level (IU/mL) (400 mg TID only)				
< Median (121.85)				
Number			28	24
Mean (SD)			-0.10 (0.23)	-0.17 (0.29)
LS Mean (SE)			-0.08 (0.07)	-0.16 (0.07)
LS Mean Diff vs. placebo (95% CI)				-0.08 (-0.23, 0.07)
P-value vs. placebo				0.3135
≥ Median (121.85)				
Number			26	24
Mean (SD)			-0.03 (0.39)	-0.13 (0.25)
LS Mean (SE)			-0.22 (0.22)	-0.33 (0.23)
LS Mean Diff vs. placebo (95% CI)				-0.11 (-0.30, 0.07)
P-value vs. placebo				0.2365
Overall p-value for interaction				0.8457

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Baseline median IgA level (mg/L) (400 mg TID only)				
< Median (2190)				
Number			29	21
Mean (SD)			-0.04 (0.23)	-0.12 (0.26)
LS Mean (SE)			-0.03 (0.06)	-0.12 (0.07)
LS Mean Diff vs. placebo (95% CI)				-0.09 (-0.25, 0.07)
P-value vs. placebo				0.2572
≥ Median (2190)				
Number			25	27
Mean (SD)			-0.09 (0.39)	-0.17 (0.28)
LS Mean (SE)			-0.06 (0.07)	-0.15 (0.07)
LS Mean Diff vs. placebo (95% CI)				-0.09 (-0.27, 0.09)
P-value vs. placebo				0.3176
Overall p-value for interaction				0.9795
Baseline blood eosinophil level 1 (10^9/L)				
< 0.15				
Number	5	8	22	22
Mean (SD)	0.03 (0.18)	-0.10 (0.49)	-0.15 (0.27)	-0.17 (0.32)
LS Mean (SE)	-0.04 (0.26)	-0.08 (0.16)	-0.13 (0.07)	-0.17 (0.07)
LS Mean Diff vs. placebo (95% CI)		-0.04 (-0.65, 0.57)		-0.05 (-0.23, 0.14)
P-value vs. placebo		0.8932		0.6211
≥ 0.15 (400 mg BID only)				
Number	20	17		
Mean (SD)	-0.08 (0.22)	-0.01 (0.35)		
LS Mean (SE)	-0.10 (0.10)	-0.03 (0.11)		
LS Mean Diff vs. placebo (95% CI)		0.07 (-0.15, 0.28)		
P-value vs. placebo		0.5498		
Overall p-value for interaction		0.3640		
Baseline blood eosinophil level 2 (10^9/L) (400 mg BID only)				
< 0.3				
Number	14	14		
Mean (SD)	-0.01 (0.25)	-0.10 (0.42)		
LS Mean (SE)	-0.08 (0.11)	-0.15 (0.12)		
LS Mean Diff vs. placebo (95% CI)		-0.07 (-0.35, 0.20)		
P-value vs. placebo		0.6075		

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
≥ 0.3				
Number	11	11		
Mean (SD)	-0.11 (0.16)	0.04 (0.36)		
LS Mean (SE)	-0.07 (0.17)	0.00 (0.14)		
LS Mean Diff vs. placebo (95% CI)		0.07 (-0.21, 0.35)		
P-value vs. placebo		0.6310		
Overall p-value for interaction		0.2578		
Baseline blood eosinophil level 1 (10^9/L) (400 mg TID only)				
< 0.15				
Number			22	22
Mean (SD)			-0.15 (0.27)	-0.17 (0.32)
LS Mean (SE)			-0.13 (0.07)	-0.17 (0.07)
LS Mean Diff vs. placebo (95% CI)				-0.05 (-0.23, 0.14)
P-value vs. placebo				0.6211
≥ 0.15 - < 0.3				
Number			18	13
Mean (SD)			-0.04 (0.25)	-0.10 (0.16)
LS Mean (SE)			-0.00 (0.08)	-0.04 (0.09)
LS Mean Diff vs. placebo (95% CI)				-0.04 (-0.24, 0.17)
P-value vs. placebo				0.7282
≥ 0.3				
Number			14	13
Mean (SD)			0.04 (0.42)	-0.16 (0.27)
LS Mean (SE)			0.04 (0.12)	-0.16 (0.11)
LS Mean Diff vs. placebo (95% CI)				-0.20 (-0.45, 0.05)
P-value vs. placebo				0.1159
Overall p-value for interaction				0.5643
Baseline blood eosinophil level 2 (10^9/L) (400 mg TID only)				
< 0.3				
Number			40	35
Mean (SD)			-0.10 (0.27)	-0.15 (0.27)
LS Mean (SE)			-0.08 (0.05)	-0.13 (0.05)
LS Mean Diff vs. placebo (95% CI)				-0.05 (-0.19, 0.09)
P-value vs. placebo				0.4664
≥ 0.3				
Number			14	13

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Mean (SD)			0.04 (0.42)	-0.16 (0.27)
LS Mean (SE)			0.04 (0.12)	-0.16 (0.11)
LS Mean Diff vs. placebo (95% CI)				-0.20 (-0.45, 0.05)
P-value vs. placebo				0.1159
Overall p-value for interaction				0.3072
Baseline FeNO level 1 (ppb)				
< 25				
Number	11	9	31	32
Mean (SD)	-0.04 (0.26)	-0.12 (0.51)	-0.06 (0.25)	-0.19 (0.28)
LS Mean (SE)	-0.18 (0.15)	-0.16 (0.14)	-0.04 (0.05)	-0.16 (0.05)
LS Mean Diff vs. placebo (95% CI)		0.03 (-0.32, 0.37)		-0.12 (-0.26, 0.02)
P-value vs. placebo		0.8792		0.0953
≥ 25				
Number	14	16	19	14
Mean (SD)	-0.07 (0.19)	0.01 (0.32)	-0.06 (0.41)	-0.09 (0.25)
LS Mean (SE)	0.01 (0.11)	-0.00 (0.11)	-0.04 (0.10)	-0.09 (0.11)
LS Mean Diff vs. placebo (95% CI)		-0.01 (-0.23, 0.22)		-0.04 (-0.32, 0.23)
P-value vs. placebo		0.9359		0.7523
Overall p-value for interaction		0.6767		0.5841
Baseline FeNO level 2 (ppb)				
< 35				
Number	14	17	38	36
Mean (SD)	-0.03 (0.25)	-0.10 (0.43)	-0.09 (0.27)	-0.18 (0.27)
LS Mean (SE)	-0.15 (0.13)	-0.19 (0.11)	-0.06 (0.05)	-0.14 (0.05)
LS Mean Diff vs. placebo (95% CI)		-0.04 (-0.30, 0.21)		-0.09 (-0.22, 0.04)
P-value vs. placebo		0.7398		0.1794
≥ 35				
Number	11	8	12	10
Mean (SD)	-0.09 (0.17)	0.08 (0.29)	0.02 (0.44)	-0.07 (0.27)
LS Mean (SE)	-0.01 (0.12)	0.05 (0.14)	0.04 (0.17)	-0.07 (0.16)
LS Mean Diff vs. placebo (95% CI)		0.06 (-0.26, 0.38)		-0.12 (-0.49, 0.26)
P-value vs. placebo		0.7100		0.5388
Overall p-value for interaction		0.2631		0.8679

LATAM: Latin America, ROW: Rest of the world

[0239] Table 38. Subgroup analysis: change from baseline in pre-bronchodilator FEV1 (L) at EOT (Week 12) in the baseline low EOS and low FeNO subgroup (mITT population).

	400 mg BID cohort		400 mg TID cohort	
Pre-bronchodilator FEV1 (L)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Baseline blood eosinophil (10^9/L) and FeNO (ppb)				
Low EOS (< 0.15) and low FeNO (< 25)				
Number	3	3	16	16
Mean (SD)	0.02 (0.17)	-0.17 (0.85)	-0.08 (0.23)	-0.24 (0.35)
LS Mean (SE)	NC (NC)	NC (NC)	-0.06 (0.07)	-0.20 (0.07)
LS Mean Diff vs. placebo (95% CI)		NC (NC, NC)		-0.14 (-0.33, 0.06)
P-value vs. placebo		NC		0.1770
All others				
Number	22	22	34	30
Mean (SD)	-0.07 (0.22)	-0.02 (0.32)	-0.05 (0.35)	-0.11 (0.22)
LS Mean (SE)	-0.08 (0.09)	-0.05 (0.09)	-0.02 (0.06)	-0.09 (0.06)
LS Mean Diff vs. placebo (95% CI)		0.03 (-0.16, 0.21)		-0.07 (-0.23, 0.09)
P-value vs. placebo		0.7753		0.3909
Overall p-value for interaction		0.3586		0.6290

FLATAM: Latin America, ROW: Rest of the world

Bronchodilator Therapy

[0240] When used in combination with ICS/LABA, treatment with 400 mg BID rilzabrutinib led to a reduction in the number of inhalations/day relative to treatment with the placebo (**Figures 7-8** and **Tables 39-40A**).

[0241] An analysis was performed on the number of participants with ≥2, ≥3, ≥4, and ≥5 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol compared with baseline on 2 consecutive days during the treatment period, to assess increase in reliever medication during 12-week treatment period. In both cohorts, number of participants with ≥2 to 5 additional reliever puffs compared to baseline was lower in the rilzabrutinib arms compared to the placebo arms (**Table 40B**).

[0242] Table 39. Change from baseline in inhalations/day of albuterol or levalbuterol for symptom relief over time (mITT population).

Albuterol or levalbuterol for symptom relief	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
Baseline		
Number	32	32
Mean (SD)	2.52 (3.02)	1.57 (1.98)
Median	1.29	0.62
Q1 ; Q3	0.00 ; 4.71	0.00 ; 2.93
Min ; Max	0.0 ; 12.3	0.0 ; 7.4
Week 1		
Number (observed/LOCF imputed)	32 (32/0)	32 (32/0)
Mean (SD)	2.02 (2.56)	1.15 (1.78)
Median	0.59	0.21
Q1 ; Q3	0.00 ; 3.50	0.00 ; 1.93
Min ; Max	0.0 ; 10.3	0.0 ; 7.4
Change from baseline		
Number (observed/LOCF imputed)	32 (32/0)	32 (32/0)
Mean (SD)	-0.50 (1.03)	-0.41 (1.03)
Median	0.00	0.00
Q1 ; Q3	-0.69 ; 0.00	-0.62 ; 0.00
Min ; Max	-3.5 ; 0.7	-5.3 ; 1.0
LS Mean (SE)	-0.23 (0.20)	-0.39 (0.19)
LS Mean Diff vs. placebo (95% CI)		-0.16 (-0.64, 0.32)
P-value vs. placebo		0.5052
Week 2		
Number (observed/LOCF imputed)	32 (31/1)	31 (31/0)
Mean (SD)	1.91 (2.63)	0.94 (1.76)
Median	0.37	0.14
Q1 ; Q3	0.00 ; 3.21	0.00 ; 0.80
Min ; Max	0.0 ; 9.5	0.0 ; 7.4
Change from baseline		
Number (observed/LOCF imputed)	32 (31/1)	31 (31/0)
Mean (SD)	-0.61 (1.34)	-0.68 (1.24)
Median	0.00	0.00
Q1 ; Q3	-1.50 ; 0.00	-1.14 ; 0.00
Min ; Max	-4.0 ; 2.9	-5.3 ; 0.3
LS Mean (SE)	-0.31 (0.27)	-0.61 (0.26)
LS Mean Diff vs. placebo (95% CI)		-0.31 (-0.91, 0.30)
P-value vs. placebo		0.3228
Week 3		

Albuterol or levalbuterol for symptom relief	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
Number (observed/LOCF imputed)	31 (30/1)	31 (31/0)
Mean (SD)	1.96 (2.75)	0.79 (1.48)
Median	0.29	0.00
Q1 ; Q3	0.00 ; 4.00	0.00 ; 0.67
Min ; Max	0.0 ; 9.0	0.0 ; 5.3
Change from baseline		
Number (observed/LOCF imputed)	31 (30/1)	31 (31/0)
Mean (SD)	-0.24 (1.98)	-0.83 (1.48)
Median	0.00	0.00
Q1 ; Q3	-0.67 ; 0.00	-1.33 ; 0.00
Min ; Max	-5.4 ; 6.3	-5.0 ; 1.3
LS Mean (SE)	0.32 (0.37)	-0.49 (0.35)
LS Mean Diff vs. placebo (95% CI)		-0.81 (-1.64, 0.01)
P-value vs. placebo		0.0539
Week 4		
Number (observed/LOCF imputed)	31 (29/2)	30 (29/1)
Mean (SD)	1.92 (2.71)	0.86 (1.72)
Median	0.29	0.00
Q1 ; Q3	0.00 ; 3.43	0.00 ; 0.50
Min ; Max	0.0 ; 9.0	0.0 ; 6.0
Change from baseline		
Number (observed/LOCF imputed)	31 (29/2)	30 (29/1)
Mean (SD)	-0.28 (2.14)	-0.81 (1.41)
Median	0.00	-0.29
Q1 ; Q3	-1.29 ; 0.00	-1.71 ; 0.00
Min ; Max	-5.4 ; 6.3	-5.5 ; 2.0
LS Mean (SE)	0.31 (0.37)	-0.51 (0.36)
LS Mean Diff vs. placebo (95% CI)		-0.82 (-1.67, 0.03)
P-value vs. placebo		0.0573
Week 5		
Number (observed/LOCF imputed)	30 (28/2)	31 (29/2)
Mean (SD)	1.89 (2.65)	1.11 (1.80)
Median	0.25	0.00
Q1 ; Q3	0.00 ; 4.00	0.00 ; 2.50
Min ; Max	0.0 ; 9.0	0.0 ; 5.7
Change from baseline		
Number (observed/LOCF imputed)	30 (28/2)	31 (29/2)
Mean (SD)	-0.39 (1.97)	-0.51 (1.14)
Median	0.00	0.00

Albuterol or levalbuterol for symptom relief	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
Q1 ; Q3	-1.29 ; 0.00	-0.83 ; 0.00
Min ; Max	-4.9 ; 6.3	-3.5 ; 1.0
LS Mean (SE)	0.13 (0.33)	-0.20 (0.32)
LS Mean Diff vs. placebo (95% CI)		-0.33 (-1.08, 0.41)
P-value vs. placebo		0.3824
Week 6		
Number (observed/LOCF imputed)	30 (28/2)	31 (29/2)
Mean (SD)	2.13 (2.77)	1.00 (1.92)
Median	1.14	0.00
Q1 ; Q3	0.00 ; 3.14	0.00 ; 0.50
Min ; Max	0.0 ; 9.0	0.0 ; 7.3
Change from baseline		
Number (observed/LOCF imputed)	30 (28/2)	31 (29/2)
Mean (SD)	-0.15 (1.94)	-0.61 (1.44)
Median	0.00	0.00
Q1 ; Q3	-0.83 ; 0.00	-1.00 ; 0.05
Min ; Max	-4.9 ; 6.3	-5.0 ; 1.3
LS Mean (SE)	0.39 (0.36)	-0.40 (0.35)
LS Mean Diff vs. placebo (95% CI)		-0.79 (-1.61, 0.03)
P-value vs. placebo		0.0589
Week 7		
Number (observed/LOCF imputed)	30 (27/3)	31 (29/2)
Mean (SD)	1.64 (2.52)	1.61 (3.82)
Median	0.57	0.00
Q1 ; Q3	0.00 ; 2.00	0.00 ; 0.86
Min ; Max	0.0 ; 9.0	0.0 ; 19.4
Change from baseline		
Number (observed/LOCF imputed)	30 (27/3)	31 (29/2)
Mean (SD)	-0.63 (2.16)	-0.00 (3.35)
Median	-0.05	0.00
Q1 ; Q3	-1.43 ; 0.00	-1.00 ; 0.00
Min ; Max	-4.9 ; 6.3	-4.3 ; 16.8
LS Mean (SE)	-0.28 (0.67)	-0.07 (0.64)
LS Mean Diff vs. placebo (95% CI)		0.21 (-1.27, 1.70)
P-value vs. placebo		0.7812
Week 8		
Number (observed/LOCF imputed)	30 (27/3)	30 (27/3)
Mean (SD)	1.59 (2.52)	1.66 (3.98)
Median	0.21	0.00

Albuterol or levalbuterol for symptom relief	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
Q1 ; Q3	0.00 ; 3.00	0.00 ; 1.14
Min ; Max	0.0 ; 9.0	0.0 ; 19.4
Change from baseline		
Number (observed/LOCF imputed)	30 (27/3)	30 (27/3)
Mean (SD)	-0.68 (2.34)	-0.01 (3.76)
Median	0.00	0.00
Q1 ; Q3	-1.86 ; 0.00	-1.00 ; 0.00
Min ; Max	-5.9 ; 6.3	-5.5 ; 16.8
LS Mean (SE)	-0.36 (0.71)	-0.08 (0.68)
LS Mean Diff vs. placebo (95% CI)		0.28 (-1.32, 1.87)
P-value vs. placebo		0.7344
Week 9		
Number (observed/LOCF imputed)	30 (27/3)	29 (25/4)
Mean (SD)	1.70 (2.55)	1.66 (3.98)
Median	0.29	0.00
Q1 ; Q3	0.00 ; 2.29	0.00 ; 1.00
Min ; Max	0.0 ; 9.0	0.0 ; 19.4
Change from baseline		
Number (observed/LOCF imputed)	30 (27/3)	29 (25/4)
Mean (SD)	-0.57 (2.40)	-0.07 (3.96)
Median	0.00	-0.29
Q1 ; Q3	-1.86 ; 0.00	-1.14 ; 0.00
Min ; Max	-5.9 ; 6.3	-5.5 ; 16.8
LS Mean (SE)	-0.10 (0.69)	-0.11 (0.66)
LS Mean Diff vs. placebo (95% CI)		-0.01 (-1.58, 1.56)
P-value vs. placebo		0.9891
Week 10		
Number (observed/LOCF imputed)	29 (25/4)	29 (25/4)
Mean (SD)	1.90 (2.72)	1.49 (3.98)
Median	0.00	0.00
Q1 ; Q3	0.00 ; 3.29	0.00 ; 0.57
Min ; Max	0.0 ; 9.0	0.0 ; 19.4
Change from baseline		
Number (observed/LOCF imputed)	29 (25/4)	29 (25/4)
Mean (SD)	-0.25 (2.97)	-0.23 (3.88)
Median	0.00	-0.29
Q1 ; Q3	-1.86 ; 0.33	-1.86 ; 0.00
Min ; Max	-6.9 ; 6.3	-5.5 ; 16.8
LS Mean (SE)	-0.13 (0.73)	-0.68 (0.70)

Albuterol or levalbuterol for symptom relief	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
LS Mean Diff vs. placebo (95% CI)		-0.55 (-2.20, 1.11)
P-value vs. placebo		0.5185
Week 11		
Number (observed/LOCF imputed)	30 (24/6)	27 (23/4)
Mean (SD)	2.37 (3.30)	1.61 (4.24)
Median	0.33	0.00
Q1 ; Q3	0.00 ; 5.00	0.00 ; 0.67
Min ; Max	0.0 ; 11.0	0.0 ; 19.4
Change from baseline		
Number (observed/LOCF imputed)	30 (24/6)	27 (23/4)
Mean (SD)	0.09 (3.30)	-0.10 (3.99)
Median	0.00	-0.40
Q1 ; Q3	-1.71 ; 0.50	-1.43 ; 0.00
Min ; Max	-6.5 ; 7.2	-5.5 ; 16.8
LS Mean (SE)	0.28 (0.82)	-0.29 (0.79)
LS Mean Diff vs. placebo (95% CI)		-0.57 (-2.39, 1.25)
P-value vs. placebo		0.5406
Week 12		
Number (observed/LOCF imputed)	28 (19/9)	26 (21/5)
Mean (SD)	2.57 (3.34)	1.97 (4.32)
Median	1.14	0.00
Q1 ; Q3	0.00 ; 4.60	0.00 ; 2.00
Min ; Max	0.0 ; 11.0	0.0 ; 19.4
Change from baseline		
Number (observed/LOCF imputed)	28 (19/9)	26 (21/5)
Mean (SD)	0.16 (3.31)	0.26 (3.85)
Median	0.00	-0.19
Q1 ; Q3	-2.41 ; 1.00	-1.00 ; 0.00
Min ; Max	-5.3 ; 7.2	-4.3 ; 16.8
LS Mean (SE)	0.19 (0.77)	0.07 (0.76)
LS Mean Diff vs. placebo (95% CI)		-0.12 (-1.90, 1.66)
P-value vs. placebo		0.8932

LATAM: Latin America, ROW: Rest of the world

[0243] Table 40A. Change from baseline in inhalations/day of albuterol or levalbuterol for symptom relief over time, reduced model (mITT population).

Albuterol or levalbuterol for symptom relief	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
Baseline		
Number	32	32
Mean (SD)	2.52 (3.02)	1.57 (1.98)
Median	1.29	0.62
Q1 ; Q3	0.00 ; 4.71	0.00 ; 2.93
Min ; Max	0.0 ; 12.3	0.0 ; 7.4
Week 1		
Number (observed/LOCF imputed)	32 (32/0)	32 (32/0)
Mean (SD)	2.02 (2.56)	1.15 (1.78)
Median	0.59	0.21
Q1 ; Q3	0.00 ; 3.50	0.00 ; 1.93
Min ; Max	0.0 ; 10.3	0.0 ; 7.4
Change from baseline		
Number (observed/LOCF imputed)	32 (32/0)	32 (32/0)
Mean (SD)	-0.50 (1.03)	-0.41 (1.03)
Median	0.00	0.00
Q1 ; Q3	-0.69 ; 0.00	-0.62 ; 0.00
Min ; Max	-3.5 ; 0.7	-5.3 ; 1.0
LS Mean (SE)	-0.34 (0.18)	-0.44 (0.19)
LS Mean Diff vs. placebo (95% CI)		-0.10 (-0.56, 0.36)
P-value vs. placebo		0.6691
Week 2		
Number (observed/LOCF imputed)	32 (31/1)	31 (31/0)
Mean (SD)	1.91 (2.63)	0.94 (1.76)
Median	0.37	0.14
Q1 ; Q3	0.00 ; 3.21	0.00 ; 0.80
Min ; Max	0.0 ; 9.5	0.0 ; 7.4
Change from baseline		
Number (observed/LOCF imputed)	32 (31/1)	31 (31/0)
Mean (SD)	-0.61 (1.34)	-0.68 (1.24)
Median	0.00	0.00
Q1 ; Q3	-1.50 ; 0.00	-1.14 ; 0.00
Min ; Max	-4.0 ; 2.9	-5.3 ; 0.3
LS Mean (SE)	-0.42 (0.23)	-0.67 (0.24)
LS Mean Diff vs. placebo (95% CI)		-0.25 (-0.82, 0.32)
P-value vs. placebo		0.3848
Week 3		
Number (observed/LOCF imputed)	31 (30/1)	31 (31/0)
Mean (SD)	1.96 (2.75)	0.79 (1.48)
Median	0.29	0.00
Q1 ; Q3	0.00 ; 4.00	0.00 ; 0.67
Min ; Max	0.0 ; 9.0	0.0 ; 5.3

Albuterol or levalbuterol for symptom relief	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
Change from baseline		
Number (observed/LOCF imputed)	31 (30/1)	31 (31/0)
Mean (SD)	-0.24 (1.98)	-0.83 (1.48)
Median	0.00	0.00
Q1 ; Q3	-0.67 ; 0.00	-1.33 ; 0.00
Min ; Max	-5.4 ; 6.3	-5.0 ; 1.3
LS Mean (SE)	0.11 (0.32)	-0.59 (0.34)
LS Mean Diff vs. placebo (95% CI)		-0.70 (-1.49, 0.09)
P-value vs. placebo		0.0826
Week 4		
Number (observed/LOCF imputed)	31 (29/2)	30 (29/1)
Mean (SD)	1.92 (2.71)	0.86 (1.72)
Median	0.29	0.00
Q1 ; Q3	0.00 ; 3.43	0.00 ; 0.50
Min ; Max	0.0 ; 9.0	0.0 ; 6.0
Change from baseline		
Number (observed/LOCF imputed)	31 (29/2)	30 (29/1)
Mean (SD)	-0.28 (2.14)	-0.81 (1.41)
Median	0.00	-0.29
Q1 ; Q3	-1.29 ; 0.00	-1.71 ; 0.00
Min ; Max	-5.4 ; 6.3	-5.5 ; 2.0
LS Mean (SE)	-0.01 (0.33)	-0.65 (0.35)
LS Mean Diff vs. placebo (95% CI)		-0.64 (-1.46, 0.18)
P-value vs. placebo		0.1245
Week 5		
Number (observed/LOCF imputed)	30 (28/2)	31 (29/2)
Mean (SD)	1.89 (2.65)	1.11 (1.80)
Median	0.25	0.00
Q1 ; Q3	0.00 ; 4.00	0.00 ; 2.50
Min ; Max	0.0 ; 9.0	0.0 ; 5.7
Change from baseline		
Number (observed/LOCF imputed)	30 (28/2)	31 (29/2)
Mean (SD)	-0.39 (1.97)	-0.51 (1.14)
Median	0.00	0.00
Q1 ; Q3	-1.29 ; 0.00	-0.83 ; 0.00
Min ; Max	-4.9 ; 6.3	-3.5 ; 1.0
LS Mean (SE)	-0.11 (0.30)	-0.35 (0.32)
LS Mean Diff vs. placebo (95% CI)		-0.23 (-0.97, 0.50)
P-value vs. placebo		0.5339
Week 6		
Number (observed/LOCF imputed)	30 (28/2)	31 (29/2)
Mean (SD)	2.13 (2.77)	1.00 (1.92)
Median	1.14	0.00
Q1 ; Q3	0.00 ; 3.14	0.00 ; 0.50
Min ; Max	0.0 ; 9.0	0.0 ; 7.3

Albuterol or levalbuterol for symptom relief	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
Change from baseline		
Number (observed/LOCF imputed)	30 (28/2)	31 (29/2)
Mean (SD)	-0.15 (1.94)	-0.61 (1.44)
Median	0.00	0.00
Q1 ; Q3	-0.83 ; 0.00	-1.00 ; 0.05
Min ; Max	-4.9 ; 6.3	-5.0 ; 1.3
LS Mean (SE)	-0.03 (0.34)	-0.60 (0.35)
LS Mean Diff vs. placebo (95% CI)		-0.57 (-1.40, 0.25)
P-value vs. placebo		0.1706
Week 7		
Number (observed/LOCF imputed)	30 (27/3)	31 (29/2)
Mean (SD)	1.64 (2.52)	1.61 (3.82)
Median	0.57	0.00
Q1 ; Q3	0.00 ; 2.00	0.00 ; 0.86
Min ; Max	0.0 ; 9.0	0.0 ; 19.4
Change from baseline		
Number (observed/LOCF imputed)	30 (27/3)	31 (29/2)
Mean (SD)	-0.63 (2.16)	-0.00 (3.35)
Median	-0.05	0.00
Q1 ; Q3	-1.43 ; 0.00	-1.00 ; 0.00
Min ; Max	-4.9 ; 6.3	-4.3 ; 16.8
LS Mean (SE)	-0.59 (0.59)	-0.14 (0.62)
LS Mean Diff vs. placebo (95% CI)		0.45 (-0.98, 1.87)
P-value vs. placebo		0.5396
Week 8		
Number (observed/LOCF imputed)	30 (27/3)	30 (27/3)
Mean (SD)	1.59 (2.52)	1.66 (3.98)
Median	0.21	0.00
Q1 ; Q3	0.00 ; 3.00	0.00 ; 1.14
Min ; Max	0.0 ; 9.0	0.0 ; 19.4
Change from baseline		
Number (observed/LOCF imputed)	30 (27/3)	30 (27/3)
Mean (SD)	-0.68 (2.34)	-0.01 (3.76)
Median	0.00	0.00
Q1 ; Q3	-1.86 ; 0.00	-1.00 ; 0.00
Min ; Max	-5.9 ; 6.3	-5.5 ; 16.8
LS Mean (SE)	-0.56 (0.62)	-0.07 (0.65)
LS Mean Diff vs. placebo (95% CI)		0.49 (-1.03, 2.00)
P-value vs. placebo		0.5291
Week 9		
Number (observed/LOCF imputed)	30 (27/3)	29 (25/4)
Mean (SD)	1.70 (2.55)	1.66 (3.98)
Median	0.29	0.00
Q1 ; Q3	0.00 ; 2.29	0.00 ; 1.00
Min ; Max	0.0 ; 9.0	0.0 ; 19.4

Albuterol or levalbuterol for symptom relief	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
Change from baseline		
Number (observed/LOCF imputed)	30 (27/3)	29 (25/4)
Mean (SD)	-0.57 (2.40)	-0.07 (3.96)
Median	0.00	-0.29
Q1 ; Q3	-1.86 ; 0.00	-1.14 ; 0.00
Min ; Max	-5.9 ; 6.3	-5.5 ; 16.8
LS Mean (SE)	-0.48 (0.61)	-0.23 (0.64)
LS Mean Diff vs. placebo (95% CI)		0.24 (-1.27, 1.76)
P-value vs. placebo		0.7514
Week 10		
Number (observed/LOCF imputed)	29 (25/4)	29 (25/4)
Mean (SD)	1.90 (2.72)	1.49 (3.98)
Median	0.00	0.00
Q1 ; Q3	0.00 ; 3.29	0.00 ; 0.57
Min ; Max	0.0 ; 9.0	0.0 ; 19.4
Change from baseline		
Number (observed/LOCF imputed)	29 (25/4)	29 (25/4)
Mean (SD)	-0.25 (2.97)	-0.23 (3.88)
Median	0.00	-0.29
Q1 ; Q3	-1.86 ; 0.33	-1.86 ; 0.00
Min ; Max	-6.9 ; 6.3	-5.5 ; 16.8
LS Mean (SE)	-0.45 (0.64)	-0.77 (0.68)
LS Mean Diff vs. placebo (95% CI)		-0.33 (-1.91, 1.25)
P-value vs. placebo		0.6832
Week 11		
Number (observed/LOCF imputed)	30 (24/6)	27 (23/4)
Mean (SD)	2.37 (3.30)	1.61 (4.24)
Median	0.33	0.00
Q1 ; Q3	0.00 ; 5.00	0.00 ; 0.67
Min ; Max	0.0 ; 11.0	0.0 ; 19.4
Change from baseline		
Number (observed/LOCF imputed)	30 (24/6)	27 (23/4)
Mean (SD)	0.09 (3.30)	-0.10 (3.99)
Median	0.00	-0.40
Q1 ; Q3	-1.71 ; 0.50	-1.43 ; 0.00
Min ; Max	-6.5 ; 7.2	-5.5 ; 16.8
LS Mean (SE)	-0.01 (0.71)	-0.36 (0.75)
LS Mean Diff vs. placebo (95% CI)		-0.36 (-2.08, 1.37)
P-value vs. placebo		0.6865
Week 12		
Number (observed/LOCF imputed)	28 (19/9)	26 (21/5)
Mean (SD)	2.57 (3.34)	1.97 (4.32)
Median	1.14	0.00
Q1 ; Q3	0.00 ; 4.60	0.00 ; 2.00
Min ; Max	0.0 ; 11.0	0.0 ; 19.4

Albuterol or levalbuterol for symptom relief	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
Change from baseline		
Number (observed/LOCF imputed)	28 (19/9)	26 (21/5)
Mean (SD)	0.16 (3.31)	0.26 (3.85)
Median	0.00	-0.19
Q1 ; Q3	-2.41 ; 1.00	-1.00 ; 0.00
Min ; Max	-5.3 ; 7.2	-4.3 ; 16.8
LS Mean (SE)	0.06 (0.68)	-0.01 (0.72)
LS Mean Diff vs. placebo (95% CI)		-0.07 (-1.75, 1.60)
P-value vs. placebo		0.9303

LATAM: Latin America, ROW: Rest of the world

Table 40B. Number of participants requiring ≥2, ≥3, ≥4, or ≥5 reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol

	BID cohort		TID cohort	
	Placebo BID (N=32)	Rilzabrutinib 400mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400mg TID (N=64)
Number of participants with ≥ 2 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol compared with baseline on 2 consecutive days during the treatment period	11 (34.4)	6 (18.8)	24 (35.3)	11 (17.2)
Number of participants with ≥ 3 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol compared with baseline on 2 consecutive days during the treatment period	7 (21.9)	3 (9.4)	16 (23.5)	4 (6.3)
Number of participants with ≥ 4 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol compared with baseline on 2 consecutive days during the treatment period,	6 (18.8)	2 (6.3)	12 (17.6)	3 (4.7)

		BID cohort		TID cohort
	Placebo BID (N=32)	**Rilzabrutinib 400mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400mg TID (N=64)**
Number of participants with ≥ 5 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol compared with baseline on 2 consecutive days during the treatment period	4 (12.5)	2 (6.3)	10 (14.7)	1 (1.6)

ACQ-5

[0244] In both the 400 mg BID and 400 mg TID rilzabrutinib cohorts, patients experienced significant and clinically meaningful changes in ACQ-5 relative to patients who received the placebo (**Figures 9-15)** and **Tables 41-50**). The 400 mg BID rilzabrutinib cohort and placebo cohort exhibited LS mean (SE) values of -0.70 and -0.12 (p=0.0184), respectively, at Week 12 (**Table 41**). Meanwhile, the 400 mg TID rilzabrutinib cohort and placebo cohort exhibited LS mean (SE) values of -0.85 and -0.31 (p=0.0013), respectively, at Week 12 (**Table 41**). The overall ACQ-5 reduction observed in both of the rilzabrutinib cohorts therefore exceeded the minimal clinically important (MCID) difference of -0.5.

[0245] Consistent with this, a significant percentage of rilzabrutinib-treated patients also achieved ACQ-5 reductions in excess of -0.5. 67.9% of rilzabrutinib-treated patients in the 400 mg BID cohort showed ACQ-5 score reductions of at least -0.05 from baseline at Week 12. Meanwhile, only 35.7% of placebo-treated patients had equivalent reductions in ACQ-5 scores (p=0.0100) (**Table 43**). Meanwhile, 63.3% of patients in the 400 mg TID cohort showed ACQ-5 score reductions of at least -0.05 from baseline at Week 12, as compared to 40.0% of patients in the placebo group (p=0.0297) (**Table 43**). Additionally, at Week 12, 40.6% and 15.6% of rilzabrutinib-treated patients in the 400 mg BID and 400 mg TID cohorts, respectively, achieved an ACQ-5 below 0.75, while only 9.4% and 13.2% of placebo-treated patients in the 400 mg BID and 400 mg TID cohorts, respectively, achieved a similar reduction in score (p=0.0092 for the 400 mg BID cohort and 0.6286 for the 400 mg TID cohort) (**Table 44**).

[0246] Patients treated with rilzabrutinib also experienced a rapid decrease in ACQ-5. Significant (p<0.05) differences between rilzabrutinib- and placebo-treated patients in the

two cohorts were observed as early as Week 2 and were largely sustained over the course of the treatment period. Moreover, in the 400 mg TID rilzabrutinib cohort, the difference between rilzabrutinib- and placebo-treated patients continued to increase throughout the treatment period.

[0247] Additionally, 34.4% of rilzabrutinib-treated patients in the 400 mg BID cohort achieved an ACQ-5 score below 0.75 as early as Week 4, as compared to 6.3% of placebo-treated patients in the 400 mg BID cohort (p=0.0133) (**Table 44**). Similarly, 17.2% of rilzabrutinib-treated patients in the 400 mg TID cohort achieved an ACQ-5 score below 0.75 by Week 4, as compared to 7.4% of placebo-treated patients in the 400 mg TID cohort (p=0.0919) (**Table 44**).

[0248] Rilzabrutinib was efficacious across patients with different baseline demographics, disease characteristics, with or without exacerbations in the previous year, ICS/LABA dose levels, biomarker levels, eosinophil counts, or FeNO (ppb) (**Tables 46-50**).

[0249] Table 41. Change from baseline in ACQ-5 over time (mITT population).

	400 mg BID cohort		**400 mg TID cohort**	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Baseline				
Number	32	32	68	64
Mean (SD)	2.19 (0.40)	2.04 (0.37)	2.18 (0.40)	2.24 (0.48)
Median	2.20	2.00	2.20	2.20
Q1 ; Q3	2.00 ; 2.40	1.80 ; 2.20	1.80 ; 2.40	2.00 ; 2.60
Min ; Max	1.4 ; 3.2	1.4 ; 2.8	1.2 ; 3.2	1.4 ; 4.0
Week 2				
Number (observed/LOCF imputed)	30 (29/1)	30 (30/0)	63 (62/1)	61 (61/0)
Mean (SD)	1.91 (0.74)	1.30 (0.64)	2.00 (0.69)	1.87 (0.88)
Median	1.80	1.20	2.00	2.20
Q1 ; Q3	1.60 ; 2.20	0.80 ; 1.80	1.60 ; 2.40	1.20 ; 2.60
Min ; Max	0.4 ; 3.8	0.4 ; 2.6	0.4 ; 3.4	0.0 ; 3.4
Change from baseline				
Number (observed/LOCF imputed)	30 (29/1)	30 (30/0)	63 (62/1)	61 (61/0)
Mean (SD)	-0.25 (0.78)	-0.74 (0.62)	-0.17 (0.62)	-0.37 (0.79)
Median	-0.20	-1.00	0.00	-0.20

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Q1 ; Q3	-0.80 ; 0.00	-1.20 ; -0.20	-0.60 ; 0.20	-0.80 ; 0.20
Min ; Max	-1.8 ; 1.6	-1.8 ; 0.4	-1.8 ; 1.6	-2.0 ; 1.2
LS Mean (SE)	-0.20 (0.14)	-0.74 (0.15)	-0.19 (0.09)	-0.47 (0.10)
LS Mean Diff vs. placebo (95% CI)		-0.54 (-0.89, -0.19)		-0.27 (-0.53, -0.02)
P-value vs. placebo		0.0026		0.0335
Week 4				
Number (observed/LOCF imputed)	30 (28/2)	31 (30/1)	62 (61/1)	59 (59/0)
Mean (SD)	1.77 (0.82)	1.10 (0.78)	1.93 (0.84)	1.66 (0.86)
Median	1.80	1.00	2.00	1.80
Q1 ; Q3	1.20 ; 2.20	0.40 ; 1.80	1.40 ; 2.60	1.00 ; 2.40
Min ; Max	0.0 ; 3.4	0.0 ; 2.6	0.0 ; 4.0	0.0 ; 3.4
Change from baseline				
Number (observed/LOCF imputed)	30 (28/2)	31 (30/1)	62 (61/1)	59 (59/0)
Mean (SD)	-0.40 (0.96)	-0.94 (0.64)	-0.23 (0.79)	-0.57 (0.77)
Median	-0.30	-0.80	-0.20	-0.40
Q1 ; Q3	-0.80 ; 0.20	-1.60 ; -0.40	-0.60 ; 0.20	-1.00 ; 0.00
Min ; Max	-2.6 ; 1.6	-2.0 ; 0.4	-2.2 ; 2.0	-2.4 ; 1.0
LS Mean (SE)	-0.29 (0.16)	-0.84 (0.17)	-0.29 (0.10)	-0.66 (0.11)
LS Mean Diff vs. placebo (95% CI)		-0.55 (-0.95, -0.14)		-0.37 (-0.64, -0.09)
P-value vs. placebo		0.0085		0.0088
Week 6				
Number (observed/LOCF imputed)	28 (26/2)	30 (28/2)	60 (58/2)	57 (56/1)
Mean (SD)	1.91 (0.92)	1.10 (0.80)	1.79 (0.80)	1.68 (0.92)
Median	2.00	1.00	1.60	2.00
Q1 ; Q3	1.20 ; 2.50	0.40 ; 1.60	1.20 ; 2.20	0.80 ; 2.40
Min ; Max	0.4 ; 4.0	0.0 ; 3.2	0.0 ; 3.2	0.0 ; 3.2
Change from baseline				

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Number (observed/LOCF imputed)	28 (26/2)	30 (28/2)	60 (58/2)	57 (56/1)
Mean (SD)	-0.26 (0.99)	-0.97 (0.74)	-0.38 (0.75)	-0.57 (0.83)
Median	-0.10	-1.20	-0.40	-0.60
Q1 ; Q3	-1.00 ; 0.40	-1.60 ; -0.60	-1.00 ; 0.20	-1.00 ; 0.00
Min ; Max	-2.4 ; 1.4	-1.8 ; 1.0	-2.0 ; 0.8	-2.8 ; 1.2
LS Mean (SE)	-0.16 (0.18)	-0.89 (0.19)	-0.30 (0.12)	-0.62 (0.12)
LS Mean Diff vs. placebo (95% CI)		-0.72 (-1.16, -0.28)		-0.32 (-0.62, -0.01)
P-value vs. placebo		0.0013		0.0412
Week 8				
Number (observed/LOCF imputed)	30 (27/3)	28 (24/4)	63 (60/3)	52 (49/3)
Mean (SD)	1.61 (0.97)	1.12 (0.90)	1.95 (0.99)	1.54 (0.77)
Median	1.80	0.80	1.80	1.80
Q1 ; Q3	0.80 ; 2.20	0.60 ; 1.40	1.20 ; 2.40	1.00 ; 2.00
Min ; Max	0.0 ; 4.0	0.0 ; 3.6	0.0 ; 5.2	0.0 ; 3.2
Change from baseline				
Number (observed/LOCF imputed)	30 (27/3)	28 (24/4)	63 (60/3)	52 (49/3)
Mean (SD)	-0.56 (1.04)	-0.91 (0.80)	-0.19 (0.94)	-0.72 (0.73)
Median	-0.40	-1.20	-0.40	-0.60
Q1 ; Q3	-1.20 ; 0.00	-1.40 ; -0.80	-1.00 ; 0.40	-1.20 ; -0.20
Min ; Max	-3.2 ; 1.4	-2.2 ; 1.0	-2.0 ; 3.0	-2.6 ; 1.0
LS Mean (SE)	-0.40 (0.19)	-0.80 (0.22)	-0.29 (0.11)	-0.75 (0.12)
LS Mean Diff vs. placebo (95% CI)		-0.40 (-0.87, 0.07)		-0.46 (-0.76, -0.17)
P-value vs. placebo		0.0968		0.0023
Week 10				
Number (observed/LOCF imputed)	28 (22/6)	27 (23/4)	55 (51/4)	56 (53/3)
Mean (SD)	1.73 (1.03)	1.15 (0.90)	1.80 (1.02)	1.49 (0.84)
Median	1.70	1.00	1.80	1.60

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Q1 ; Q3	0.90 ; 2.50	0.40 ; 1.60	1.00 ; 2.60	0.90 ; 2.00
Min ; Max	0.0 ; 4.0	0.0 ; 3.2	0.0 ; 4.0	0.0 ; 3.2
Change from baseline				
Number (observed/LOCF imputed)	28 (22/6)	27 (23/4)	55 (51/4)	56 (53/3)
Mean (SD)	-0.42 (1.11)	-0.92 (0.89)	-0.33 (0.90)	-0.75 (0.81)
Median	-0.40	-1.00	-0.40	-0.70
Q1 ; Q3	-1.20 ; 0.40	-1.60 ; -0.40	-1.00 ; 0.40	-1.40 ; -0.20
Min ; Max	-2.6 ; 1.6	-2.4 ; 1.0	-2.2 ; 1.4	-2.6 ; 1.2
LS Mean (SE)	-0.15 (0.18)	-0.73 (0.19)	-0.33 (0.13)	-0.84 (0.13)
LS Mean Diff vs. placebo (95% CI)		-0.59 (-1.03, -0.14)		-0.51 (-0.84, -0.18)
P-value vs. placebo		0.0095		0.0022
Week 12				
Number (observed/LOCF imputed)	28 (19/9)	28 (23/5)	60 (50/10)	49 (46/3)
Mean (SD)	1.83 (0.98)	1.16 (0.94)	1.93 (1.12)	1.46 (0.75)
Median	2.00	1.00	1.80	1.60
Q1 ; Q3	1.10 ; 2.20	0.40 ; 2.00	1.10 ; 2.50	1.00 ; 2.00
Min ; Max	0.0 ; 4.0	0.0 ; 3.2	0.0 ; 5.4	0.0 ; 3.2
Change from baseline				
Number (observed/LOCF imputed)	28 (19/9)	28 (23/5)	60 (50/10)	49 (46/3)
Mean (SD)	-0.34 (1.02)	-0.89 (0.93)	-0.22 (1.03)	-0.82 (0.72)
Median	-0.10	-1.30	-0.40	-0.80
Q1 ; Q3	-1.00 ; 0.10	-1.60 ; -0.20	-1.00 ; 0.40	-1.40 ; -0.20
Min ; Max	-3.0 ; 1.6	-2.4 ; 1.0	-1.8 ; 3.2	-2.2 ; 0.4
LS Mean (SE)	-0.12 (0.20)	-0.70 (0.22)	-0.31 (0.12)	-0.85 (0.13)
LS Mean Diff vs. placebo (95% CI)		-0.59 (-1.07, -0.10)		-0.54 (-0.86, -0.21)
P-value vs. placebo		0.0184		0.0013

LATAM: Latin America, ROW: Rest of the world

[0250] **Table 42. Summary of ACQ-5 over time (mITT population).**

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Mean score				
Baseline				
Number	32	32	68	64
Mean (SD)	2.19 (0.40)	2.04 (0.37)	2.18 (0.40)	2.24 (0.48)
Median	2.20	2.00	2.20	2.20
Q1 ; Q3	2.00 ; 2.40	1.80 ; 2.20	1.80 ; 2.40	2.00 ; 2.60
Min ; Max	1.4 ; 3.2	1.4 ; 2.8	1.2 ; 3.2	1.4 ; 4.0
Week 2				
Number (observed/LOCF imputed)	30 (29/1)	30 (30/0)	63 (62/1)	61 (61/0)
Mean (SD)	1.91 (0.74)	1.30 (0.64)	2.00 (0.69)	1.87 (0.88)
Median	1.80	1.20	2.00	2.20
Q1 ; Q3	1.60 ; 2.20	0.80 ; 1.80	1.60 ; 2.40	1.20 ; 2.60
Min ; Max	0.4 ; 3.8	0.4 ; 2.6	0.4 ; 3.4	0.0 ; 3.4
Change from baseline				
Number (observed/LOCF imputed)	30 (29/1)	30 (30/0)	63 (62/1)	61 (61/0)
Mean (SD)	-0.25 (0.78)	-0.74 (0.62)	-0.17 (0.62)	-0.37 (0.79)
Median	-0.20	-1.00	0.00	-0.20
Q1 ; Q3	-0.80 ; 0.00	-1.20 ; -0.20	-0.60 ; 0.20	-0.80 ; 0.20
Min ; Max	-1.8 ; 1.6	-1.8 ; 0.4	-1.8 ; 1.6	-2.0 ; 1.2
LS Mean (SE)	-0.20 (0.14)	-0.74 (0.15)	-0.19 (0.09)	-0.47 (0.10)
LS Mean Diff vs. placebo (95% CI)		-0.54 (-0.89, -0.19)		-0.27 (-0.53, -0.02)
P-value vs. placebo		0.0026		0.0335
Week 4				
Number (observed/LOCF imputed)	30 (28/2)	31 (30/1)	62 (61/1)	59 (59/0)
Mean (SD)	1.77 (0.82)	1.10 (0.78)	1.93 (0.84)	1.66 (0.86)
Median	1.80	1.00	2.00	1.80
Q1 ; Q3	1.20 ; 2.20	0.40 ; 1.80	1.40 ; 2.60	1.00 ; 2.40
Min ; Max	0.0 ; 3.4	0.0 ; 2.6	0.0 ; 4.0	0.0 ; 3.4
Change from baseline				
Number (observed/LOCF imputed)	30 (28/2)	31 (30/1)	62 (61/1)	59 (59/0)
Mean (SD)	-0.40 (0.96)	-0.94 (0.64)	-0.23 (0.79)	-0.57 (0.77)
Median	-0.30	-0.80	-0.20	-0.40
Q1 ; Q3	-0.80 ; 0.20	-1.60 ; -0.40	-0.60 ; 0.20	-1.00 ; 0.00

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Min ; Max	-2.6 ; 1.6	-2.0 ; 0.4	-2.2 ; 2.0	-2.4 ; 1.0
LS Mean (SE)	-0.29 (0.16)	-0.84 (0.17)	-0.29 (0.10)	-0.66 (0.11)
LS Mean Diff vs. placebo (95% CI)		-0.55 (-0.95, -0.14)		-0.37 (-0.64, -0.09)
P-value vs. placebo		0.0085		0.0088
Week 6				
Number (observed/LOCF imputed)	28 (26/2)	30 (28/2)	60 (58/2)	57 (56/1)
Mean (SD)	1.91 (0.92)	1.10 (0.80)	1.79 (0.80)	1.68 (0.92)
Median	2.00	1.00	1.60	2.00
Q1 ; Q3	1.20 ; 2.50	0.40 ; 1.60	1.20 ; 2.20	0.80 ; 2.40
Min ; Max	0.4 ; 4.0	0.0 ; 3.2	0.0 ; 3.2	0.0 ; 3.2
Change from baseline				
Number (observed/LOCF imputed)	28 (26/2)	30 (28/2)	60 (58/2)	57 (56/1)
Mean (SD)	-0.26 (0.99)	-0.97 (0.74)	-0.38 (0.75)	-0.57 (0.83)
Median	-0.10	-1.20	-0.40	-0.60
Q1 ; Q3	-1.00 ; 0.40	-1.60 ; -0.60	-1.00 ; 0.20	-1.00 ; 0.00
Min ; Max	-2.4 ; 1.4	-1.8 ; 1.0	-2.0 ; 0.8	-2.8 ; 1.2
LS Mean (SE)	-0.16 (0.18)	-0.89 (0.19)	-0.30 (0.12)	-0.62 (0.12)
LS Mean Diff vs. placebo (95% CI)		-0.72 (-1.16, -0.28)		-0.32 (-0.62, -0.01)
P-value vs. placebo		0.0013		0.0412
Week 8				
Number (observed/LOCF imputed)	30 (27/3)	28 (24/4)	63 (60/3)	52 (49/3)
Mean (SD)	1.61 (0.97)	1.12 (0.90)	1.95 (0.99)	1.54 (0.77)
Median	1.80	0.80	1.80	1.80
Q1 ; Q3	0.80 ; 2.20	0.60 ; 1.40	1.20 ; 2.40	1.00 ; 2.00
Min ; Max	0.0 ; 4.0	0.0 ; 3.6	0.0 ; 5.2	0.0 ; 3.2
Change from baseline				
Number (observed/LOCF imputed)	30 (27/3)	28 (24/4)	63 (60/3)	52 (49/3)
Mean (SD)	-0.56 (1.04)	-0.91 (0.80)	-0.19 (0.94)	-0.72 (0.73)
Median	-0.40	-1.20	-0.40	-0.60
Q1 ; Q3	-1.20 ; 0.00	-1.40 ; -0.80	-1.00 ; 0.40	-1.20 ; -0.20
Min ; Max	-3.2 ; 1.4	-2.2 ; 1.0	-2.0 ; 3.0	-2.6 ; 1.0
LS Mean (SE)	-0.40 (0.19)	-0.80 (0.22)	-0.29 (0.11)	-0.75 (0.12)
LS Mean Diff vs. placebo (95% CI)		-0.40 (-0.87, 0.07)		-0.46 (-0.76, -0.17)

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
P-value vs. placebo		0.0968		0.0023
Week 10				
Number (observed/LOCF imputed)	28 (22/6)	27 (23/4)	55 (51/4)	56 (53/3)
Mean (SD)	1.73 (1.03)	1.15 (0.90)	1.80 (1.02)	1.49 (0.84)
Median	1.70	1.00	1.80	1.60
Q1 ; Q3	0.90 ; 2.50	0.40 ; 1.60	1.00 ; 2.60	0.90 ; 2.00
Min ; Max	0.0 ; 4.0	0.0 ; 3.2	0.0 ; 4.0	0.0 ; 3.2
Change from baseline				
Number (observed/LOCF imputed)	28 (22/6)	27 (23/4)	55 (51/4)	56 (53/3)
Mean (SD)	-0.42 (1.11)	-0.92 (0.89)	-0.33 (0.90)	-0.75 (0.81)
Median	-0.40	-1.00	-0.40	-0.70
Q1 ; Q3	-1.20 ; 0.40	-1.60 ; -0.40	-1.00 ; 0.40	-1.40 ; -0.20
Min ; Max	-2.6 ; 1.6	-2.4 ; 1.0	-2.2 ; 1.4	-2.6 ; 1.2
LS Mean (SE)	-0.15 (0.18)	-0.73 (0.19)	-0.33 (0.13)	-0.84 (0.13)
LS Mean Diff vs. placebo (95% CI)		-0.59 (-1.03, -0.14)		-0.51 (-0.84, -0.18)
P-value vs. placebo		0.0095		0.0022
Week 12				
Number (observed/LOCF imputed)	28 (19/9)	28 (23/5)	60 (50/10)	49 (46/3)
Mean (SD)	1.83 (0.98)	1.16 (0.94)	1.93 (1.12)	1.46 (0.75)
Median	2.00	1.00	1.80	1.60
Q1 ; Q3	1.10 ; 2.20	0.40 ; 2.00	1.10 ; 2.50	1.00 ; 2.00
Min ; Max	0.0 ; 4.0	0.0 ; 3.2	0.0 ; 5.4	0.0 ; 3.2
Change from baseline				
Number (observed/LOCF imputed)	28 (19/9)	28 (23/5)	60 (50/10)	49 (46/3)
Mean (SD)	-0.34 (1.02)	-0.89 (0.93)	-0.22 (1.03)	-0.82 (0.72)
Median	-0.10	-1.30	-0.40	-0.80
Q1 ; Q3	-1.00 ; 0.10	-1.60 ; -0.20	-1.00 ; 0.40	-1.40 ; -0.20
Min ; Max	-3.0 ; 1.6	-2.4 ; 1.0	-1.8 ; 3.2	-2.2 ; 0.4
LS Mean (SE)	-0.12 (0.20)	-0.70 (0.22)	-0.31 (0.12)	-0.85 (0.13)
LS Mean Diff vs. placebo (95% CI)		-0.59 (-1.07, -0.10)		-0.54 (-0.86, -0.21)
P-value vs. placebo		0.0184		0.0013
Frequency of awakening by asthma				

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Baseline				
Number	32	32	68	64
Mean (SD)	1.91 (0.64)	1.63 (0.66)	1.91 (0.69)	1.89 (0.72)
Median	2.00	2.00	2.00	2.00
Q1 ; Q3	2.00 ; 2.00	1.00 ; 2.00	2.00 ; 2.00	2.00 ; 2.00
Min ; Max	0.0 ; 3.0	0.0 ; 3.0	0.0 ; 3.0	0.0 ; 4.0
Week 2				
Number (observed/LOCF imputed)	30 (29/1)	30 (30/0)	63 (62/1)	61 (61/0)
Mean (SD)	1.70 (1.12)	1.03 (0.81)	1.67 (1.05)	1.72 (1.05)
Median	2.00	1.00	2.00	2.00
Q1 ; Q3	1.00 ; 2.00	0.00 ; 2.00	1.00 ; 2.00	1.00 ; 2.00
Min ; Max	0.0 ; 4.0	0.0 ; 2.0	0.0 ; 5.0	0.0 ; 4.0
Change from baseline				
Number (observed/LOCF imputed)	30 (29/1)	30 (30/0)	63 (62/1)	61 (61/0)
Mean (SD)	-0.17 (1.15)	-0.57 (0.82)	-0.24 (1.07)	-0.18 (1.09)
Median	0.00	-0.50	0.00	0.00
Q1 ; Q3	-1.00 ; 0.00	-1.00 ; 0.00	-1.00 ; 0.00	-1.00 ; 0.00
Min ; Max	-3.0 ; 2.0	-2.0 ; 1.0	-3.0 ; 2.0	-2.0 ; 2.0
LS Mean (SE)	-0.06 (0.20)	-0.58 (0.21)	-0.19 (0.14)	-0.23 (0.14)
LS Mean Diff vs. placebo (95% CI)		-0.53 (-1.01, -0.04)		-0.03 (-0.39, 0.32)
P-value vs. placebo		0.0349		0.8553
Week 4				
Number (observed/LOCF imputed)	30 (28/2)	31 (30/1)	62 (61/1)	59 (59/0)
Mean (SD)	1.40 (1.04)	0.90 (0.98)	1.65 (1.03)	1.39 (0.93)
Median	2.00	1.00	2.00	2.00
Q1 ; Q3	0.00 ; 2.00	0.00 ; 2.00	1.00 ; 2.00	1.00 ; 2.00
Min ; Max	0.0 ; 3.0	0.0 ; 3.0	0.0 ; 4.0	0.0 ; 3.0
Change from baseline				
Number (observed/LOCF imputed)	30 (28/2)	31 (30/1)	62 (61/1)	59 (59/0)
Mean (SD)	-0.47 (1.04)	-0.71 (1.07)	-0.24 (1.10)	-0.51 (1.06)
Median	0.00	-1.00	0.00	0.00
Q1 ; Q3	-1.00 ; 0.00	-2.00 ; 0.00	-1.00 ; 0.00	-1.00 ; 0.00
Min ; Max	-3.0 ; 1.0	-2.0 ; 2.0	-3.0 ; 3.0	-2.0 ; 2.0
LS Mean (SE)	-0.39 (0.21)	-0.76 (0.22)	-0.23 (0.14)	-0.52 (0.14)

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
LS Mean Diff vs. placebo (95% CI)		-0.36 (-0.88, 0.15)		-0.29 (-0.64, 0.07)
P-value vs. placebo		0.1702		0.1165
Week 6				
Number (observed/LOCF imputed)	28 (26/2)	30 (28/2)	60 (58/2)	57 (56/1)
Mean (SD)	1.46 (0.96)	0.93 (0.83)	1.50 (1.10)	1.56 (0.91)
Median	2.00	1.00	1.00	2.00
Q1 ; Q3	1.00 ; 2.00	0.00 ; 1.00	1.00 ; 2.00	1.00 ; 2.00
Min ; Max	0.0 ; 3.0	0.0 ; 3.0	0.0 ; 4.0	0.0 ; 4.0
Change from baseline				
Number (observed/LOCF imputed)	28 (26/2)	30 (28/2)	60 (58/2)	57 (56/1)
Mean (SD)	-0.39 (0.96)	-0.67 (0.88)	-0.40 (1.06)	-0.33 (0.87)
Median	0.00	-1.00	0.00	0.00
Q1 ; Q3	-1.00 ; 0.00	-1.00 ; 0.00	-1.00 ; 0.00	-1.00 ; 0.00
Min ; Max	-3.0 ; 1.0	-2.0 ; 1.0	-3.0 ; 2.0	-2.0 ; 1.0
LS Mean (SE)	-0.30 (0.18)	-0.70 (0.19)	-0.31 (0.14)	-0.39 (0.14)
LS Mean Diff vs. placebo (95% CI)		-0.40 (-0.85, 0.05)		-0.08 (-0.42, 0.27)
P-value vs. placebo		0.0792		0.6678
Week 8				
Number (observed/LOCF imputed)	30 (27/3)	28 (24/4)	63 (60/3)	52 (49/3)
Mean (SD)	1.23 (0.97)	0.93 (1.05)	1.70 (1.16)	1.46 (0.87)
Median	1.00	1.00	2.00	1.50
Q1 ; Q3	0.00 ; 2.00	0.00 ; 1.50	1.00 ; 3.00	1.00 ; 2.00
Min ; Max	0.0 ; 3.0	0.0 ; 4.0	0.0 ; 5.0	0.0 ; 4.0
Change from baseline				
Number (observed/LOCF imputed)	30 (27/3)	28 (24/4)	63 (60/3)	52 (49/3)
Mean (SD)	-0.63 (0.93)	-0.64 (1.10)	-0.16 (1.12)	-0.42 (1.02)
Median	-0.50	-1.00	0.00	0.00
Q1 ; Q3	-1.00 ; 0.00	-1.50 ; 0.00	-1.00 ; 1.00	-1.00 ; 0.00
Min ; Max	-3.0 ; 1.0	-2.0 ; 2.0	-3.0 ; 3.0	-3.0 ; 2.0
LS Mean (SE)	-0.47 (0.21)	-0.64 (0.23)	-0.20 (0.14)	-0.47 (0.15)
LS Mean Diff vs. placebo (95% CI)		-0.17 (-0.69, 0.35)		-0.28 (-0.64, 0.09)
P-value vs. placebo		0.5311		0.1389

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Week 10				
Number (observed/LOCF imputed)	28 (22/6)	27 (23/4)	55 (51/4)	56 (53/3)
Mean (SD)	1.29 (1.05)	0.89 (0.89)	1.45 (1.05)	1.32 (1.11)
Median	1.00	1.00	1.00	1.00
Q1 ; Q3	0.00 ; 2.00	0.00 ; 1.00	1.00 ; 2.00	1.00 ; 2.00
Min ; Max	0.0 ; 3.0	0.0 ; 3.0	0.0 ; 4.0	0.0 ; 5.0
Change from baseline				
Number (observed/LOCF imputed)	28 (22/6)	27 (23/4)	55 (51/4)	56 (53/3)
Mean (SD)	-0.57 (1.10)	-0.67 (1.07)	-0.42 (1.08)	-0.55 (1.14)
Median	0.00	-1.00	0.00	-1.00
Q1 ; Q3	-1.00 ; 0.00	-1.00 ; 0.00	-1.00 ; 0.00	-1.00 ; 0.00
Min ; Max	-3.0 ; 1.0	-3.0 ; 1.0	-3.0 ; 2.0	-2.0 ; 3.0
LS Mean (SE)	-0.26 (0.20)	-0.65 (0.21)	-0.44 (0.15)	-0.68 (0.15)
LS Mean Diff vs. placebo (95% CI)		-0.38 (-0.88, 0.11)		-0.24 (-0.62, 0.14)
P-value vs. placebo		0.1272		0.2171
Week 12				
Number (observed/LOCF imputed)	28 (19/9)	28 (23/5)	60 (50/10)	49 (46/3)
Mean (SD)	1.39 (1.10)	0.89 (1.07)	1.63 (1.16)	1.31 (0.89)
Median	1.00	1.00	2.00	1.00
Q1 ; Q3	0.50 ; 2.00	0.00 ; 1.50	1.00 ; 2.00	1.00 ; 2.00
Min ; Max	0.0 ; 4.0	0.0 ; 4.0	0.0 ; 5.0	0.0 ; 3.0
Change from baseline				
Number (observed/LOCF imputed)	28 (19/9)	28 (23/5)	60 (50/10)	49 (46/3)
Mean (SD)	-0.46 (1.00)	-0.71 (1.24)	-0.23 (1.17)	-0.61 (1.02)
Median	0.00	-1.00	0.00	-1.00
Q1 ; Q3	-1.00 ; 0.00	-1.50 ; 0.00	-1.00 ; 0.50	-1.00 ; 0.00
Min ; Max	-2.0 ; 2.0	-3.0 ; 2.0	-3.0 ; 3.0	-3.0 ; 1.0
LS Mean (SE)	-0.21 (0.23)	-0.60 (0.25)	-0.27 (0.14)	-0.63 (0.15)
LS Mean Diff vs. placebo (95% CI)		-0.39 (-0.95, 0.18)		-0.36 (-0.73, 0.01)
P-value vs. placebo		0.1778		0.0598
Asthma symptoms when woke up				
Baseline				
Number	32	32	68	64
Mean (SD)	2.25 (0.62)	2.16 (0.51)	2.34 (0.61)	2.52 (0.67)

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Median	2.00	2.00	2.00	3.00
Q1 ; Q3	2.00 ; 3.00	2.00 ; 2.00	2.00 ; 3.00	2.00 ; 3.00
Min ; Max	1.0 ; 4.0	1.0 ; 3.0	1.0 ; 4.0	1.0 ; 4.0
Week 2				
Number (observed/LOCF imputed)	30 (29/1)	30 (30/0)	63 (62/1)	61 (61/0)
Mean (SD)	1.90 (0.88)	1.60 (0.81)	2.11 (0.76)	1.93 (1.05)
Median	2.00	2.00	2.00	2.00
Q1 ; Q3	1.00 ; 2.00	1.00 ; 2.00	2.00 ; 3.00	1.00 ; 3.00
Min ; Max	0.0 ; 4.0	0.0 ; 3.0	0.0 ; 3.0	0.0 ; 3.0
Change from baseline				
Number (observed/LOCF imputed)	30 (29/1)	30 (30/0)	63 (62/1)	61 (61/0)
Mean (SD)	-0.33 (0.92)	-0.57 (1.01)	-0.21 (0.79)	-0.57 (1.09)
Median	0.00	-1.00	0.00	0.00
Q1 ; Q3	-1.00 ; 0.00	-1.00 ; 0.00	-1.00 ; 0.00	-1.00 ; 0.00
Min ; Max	-2.0 ; 1.0	-3.0 ; 1.0	-2.0 ; 2.0	-3.0 ; 1.0
LS Mean (SE)	-0.28 (0.18)	-0.57 (0.19)	-0.33 (0.11)	-0.66 (0.12)
LS Mean Diff vs. placebo (95% CI)		-0.28 (-0.72, 0.15)		-0.33 (-0.63, -0.03)
P-value vs. placebo		0.2021		0.0333
Week 4				
Number (observed/LOCF imputed)	30 (28/2)	31 (30/1)	62 (61/1)	59 (59/0)
Mean (SD)	1.77 (1.14)	1.13 (0.92)	2.08 (0.89)	1.83 (1.10)
Median	2.00	1.00	2.00	2.00
Q1 ; Q3	1.00 ; 3.00	0.00 ; 2.00	2.00 ; 3.00	1.00 ; 3.00
Min ; Max	0.0 ; 4.0	0.0 ; 3.0	0.0 ; 4.0	0.0 ; 4.0
Change from baseline				
Number (observed/LOCF imputed)	30 (28/2)	31 (30/1)	62 (61/1)	59 (59/0)
Mean (SD)	-0.47 (1.41)	-1.03 (1.05)	-0.24 (0.97)	-0.66 (1.08)
Median	0.00	-1.00	0.00	0.00
Q1 ; Q3	-1.00 ; 0.00	-2.00 ; 0.00	-1.00 ; 0.00	-2.00 ; 0.00
Min ; Max	-3.0 ; 3.0	-3.0 ; 1.0	-3.0 ; 2.0	-3.0 ; 1.0
LS Mean (SE)	-0.16 (0.20)	-0.71 (0.22)	-0.44 (0.12)	-0.81 (0.12)
LS Mean Diff vs. placebo (95% CI)		-0.55 (-1.05, -0.05)		-0.37 (-0.69, -0.05)
P-value vs. placebo		0.0324		0.0252

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Week 6				
Number (observed/LOCF imputed)	28 (26/2)	30 (28/2)	60 (58/2)	57 (56/1)
Mean (SD)	2.00 (1.02)	1.30 (0.95)	1.92 (0.89)	1.86 (1.04)
Median	2.00	1.00	2.00	2.00
Q1 ; Q3	1.00 ; 3.00	1.00 ; 2.00	1.00 ; 3.00	1.00 ; 3.00
Min ; Max	0.0 ; 4.0	0.0 ; 3.0	0.0 ; 4.0	0.0 ; 3.0
Change from baseline				
Number (observed/LOCF imputed)	28 (26/2)	30 (28/2)	60 (58/2)	57 (56/1)
Mean (SD)	-0.25 (1.14)	-0.87 (1.04)	-0.45 (0.91)	-0.61 (0.98)
Median	0.00	-1.00	0.00	-1.00
Q1 ; Q3	-1.00 ; 1.00	-2.00 ; 0.00	-1.00 ; 0.00	-1.00 ; 0.00
Min ; Max	-2.0 ; 2.0	-3.0 ; 1.0	-3.0 ; 1.0	-3.0 ; 1.0
LS Mean (SE)	-0.12 (0.20)	-0.76 (0.22)	-0.44 (0.13)	-0.73 (0.13)
LS Mean Diff vs. placebo (95% CI)		-0.64 (-1.13, -0.15)		-0.29 (-0.62, 0.05)
P-value vs. placebo		0.0107		0.0947
Week 8				
Number (observed/LOCF imputed)	30 (27/3)	28 (24/4)	63 (60/3)	52 (49/3)
Mean (SD)	1.60 (1.10)	1.25 (1.11)	2.00 (1.03)	1.73 (0.95)
Median	2.00	1.00	2.00	2.00
Q1 ; Q3	1.00 ; 2.00	1.00 ; 2.00	1.00 ; 3.00	1.00 ; 2.50
Min ; Max	0.0 ; 4.0	0.0 ; 5.0	0.0 ; 5.0	0.0 ; 3.0
Change from baseline				
Number (observed/LOCF imputed)	30 (27/3)	28 (24/4)	63 (60/3)	52 (49/3)
Mean (SD)	-0.63 (1.33)	-0.96 (1.00)	-0.30 (1.07)	-0.83 (1.00)
Median	-1.00	-1.00	0.00	-1.00
Q1 ; Q3	-1.00 ; 0.00	-2.00 ; 0.00	-1.00 ; 0.00	-2.00 ; 0.00
Min ; Max	-3.0 ; 2.0	-3.0 ; 2.0	-3.0 ; 3.0	-3.0 ; 1.0
LS Mean (SE)	-0.40 (0.23)	-0.71 (0.26)	-0.48 (0.13)	-0.82 (0.14)
LS Mean Diff vs. placebo (95% CI)		-0.32 (-0.87, 0.24)		-0.34 (-0.69, 0.01)
P-value vs. placebo		0.2646		0.0540
Week 10				
Number (observed/LOCF imputed)	28 (22/6)	27 (23/4)	55 (51/4)	56 (53/3)
Mean (SD)	1.79 (1.32)	1.30 (0.99)	1.93 (1.00)	1.64 (1.02)

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Median	2.00	1.00	2.00	2.00
Q1 ; Q3	1.00 ; 3.00	1.00 ; 2.00	1.00 ; 3.00	1.00 ; 2.00
Min ; Max	0.0 ; 4.0	0.0 ; 3.0	0.0 ; 4.0	0.0 ; 3.0
Change from baseline				
Number (observed/LOCF imputed)	28 (22/6)	27 (23/4)	55 (51/4)	56 (53/3)
Mean (SD)	-0.43 (1.37)	-0.89 (0.97)	-0.35 (0.87)	-0.86 (1.02)
Median	0.00	-1.00	0.00	-1.00
Q1 ; Q3	-1.50 ; 0.50	-2.00 ; 0.00	-1.00 ; 0.00	-2.00 ; 0.00
Min ; Max	-3.0 ; 2.0	-2.0 ; 1.0	-2.0 ; 1.0	-3.0 ; 1.0
LS Mean (SE)	-0.15 (0.22)	-0.63 (0.24)	-0.46 (0.13)	-0.95 (0.13)
LS Mean Diff vs. placebo (95% CI)		-0.47 (-1.02, 0.07)		-0.49 (-0.83, -0.15)
P-value vs. placebo		0.0874		0.0050
Week 12				
Number (observed/LOCF imputed)	28 (19/9)	28 (23/5)	60 (50/10)	49 (46/3)
Mean (SD)	2.00 (1.15)	1.25 (1.08)	2.00 (1.25)	1.67 (0.97)
Median	2.00	1.00	2.00	2.00
Q1 ; Q3	1.00 ; 3.00	0.00 ; 2.00	1.00 ; 3.00	1.00 ; 2.00
Min ; Max	0.0 ; 4.0	0.0 ; 3.0	0.0 ; 6.0	0.0 ; 3.0
Change from baseline				
Number (observed/LOCF imputed)	28 (19/9)	28 (23/5)	60 (50/10)	49 (46/3)
Mean (SD)	-0.18 (1.25)	-0.89 (1.10)	-0.32 (1.24)	-0.84 (0.99)
Median	0.00	-1.00	0.00	-1.00
Q1 ; Q3	-1.00 ; 1.00	-2.00 ; 0.00	-1.00 ; 0.00	-1.00 ; 0.00
Min ; Max	-3.0 ; 2.0	-3.0 ; 1.0	-3.0 ; 4.0	-3.0 ; 1.0
LS Mean (SE)	0.03 (0.25)	-0.66 (0.28)	-0.49 (0.15)	-0.89 (0.15)
LS Mean Diff vs. placebo (95% CI)		-0.70 (-1.28, -0.11)		-0.40 (-0.79, -0.00)
P-value vs. placebo		0.0192		0.0494
Limitation activities by asthma				
Baseline				
Number	32	32	68	64
Mean (SD)	2.34 (0.87)	2.06 (0.56)	2.13 (0.64)	2.17 (0.52)
Median	2.00	2.00	2.00	2.00
Q1 ; Q3	2.00 ; 3.00	2.00 ; 2.00	2.00 ; 3.00	2.00 ; 2.00
Min ; Max	0.0 ; 4.0	1.0 ; 3.0	1.0 ; 3.0	1.0 ; 4.0

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Week 2				
Number (observed/LOCF imputed)	30 (29/1)	30 (30/0)	63 (62/1)	61 (61/0)
Mean (SD)	1.93 (0.98)	1.27 (0.94)	2.03 (0.98)	1.75 (0.99)
Median	2.00	1.00	2.00	2.00
Q1 ; Q3	1.00 ; 3.00	1.00 ; 2.00	2.00 ; 3.00	1.00 ; 3.00
Min ; Max	0.0 ; 4.0	0.0 ; 3.0	0.0 ; 4.0	0.0 ; 3.0
Change from baseline				
Number (observed/LOCF imputed)	30 (29/1)	30 (30/0)	63 (62/1)	61 (61/0)
Mean (SD)	-0.37 (1.16)	-0.80 (1.03)	-0.13 (0.89)	-0.39 (1.04)
Median	0.00	-1.00	0.00	0.00
Q1 ; Q3	-1.00 ; 0.00	-2.00 ; 0.00	-1.00 ; 0.00	-1.00 ; 0.00
Min ; Max	-3.0 ; 3.0	-2.0 ; 2.0	-2.0 ; 2.0	-3.0 ; 2.0
LS Mean (SE)	-0.31 (0.20)	-0.90 (0.22)	-0.11 (0.13)	-0.48 (0.13)
LS Mean Diff vs. placebo (95% CI)		-0.59 (-1.08, -0.09)		-0.37 (-0.71, -0.03)
P-value vs. placebo		0.0203		0.0323
Week 4				
Number (observed/LOCF imputed)	30 (28/2)	31 (30/1)	62 (61/1)	59 (59/0)
Mean (SD)	1.93 (1.01)	0.94 (1.00)	1.95 (1.00)	1.56 (0.95)
Median	2.00	1.00	2.00	2.00
Q1 ; Q3	1.00 ; 3.00	0.00 ; 2.00	2.00 ; 2.00	1.00 ; 2.00
Min ; Max	0.0 ; 4.0	0.0 ; 3.0	0.0 ; 4.0	0.0 ; 3.0
Change from baseline				
Number (observed/LOCF imputed)	30 (28/2)	31 (30/1)	62 (61/1)	59 (59/0)
Mean (SD)	-0.37 (1.27)	-1.13 (0.96)	-0.16 (0.96)	-0.58 (1.05)
Median	0.00	-1.00	0.00	0.00
Q1 ; Q3	-1.00 ; 0.00	-2.00 ; 0.00	-1.00 ; 1.00	-1.00 ; 0.00
Min ; Max	-3.0 ; 2.0	-3.0 ; 1.0	-2.0 ; 2.0	-3.0 ; 1.0
LS Mean (SE)	-0.27 (0.21)	-1.15 (0.22)	-0.23 (0.13)	-0.70 (0.13)
LS Mean Diff vs. placebo (95% CI)		-0.88 (-1.40, -0.37)		-0.47 (-0.80, -0.13)
P-value vs. placebo		0.0007		0.0064
Week 6				
Number (observed/LOCF imputed)	28 (26/2)	30 (28/2)	60 (58/2)	57 (56/1)

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Mean (SD)	2.04 (1.17)	0.97 (1.07)	1.82 (1.03)	1.46 (1.05)
Median	2.00	1.00	2.00	1.00
Q1 ; Q3	1.00 ; 3.00	0.00 ; 2.00	1.00 ; 2.00	1.00 ; 2.00
Min ; Max	0.0 ; 4.0	0.0 ; 3.0	0.0 ; 4.0	0.0 ; 4.0
Change from baseline				
Number (observed/LOCF imputed)	28 (26/2)	30 (28/2)	60 (58/2)	57 (56/1)
Mean (SD)	-0.29 (1.08)	-1.13 (1.04)	-0.32 (1.08)	-0.72 (1.15)
Median	0.00	-1.00	0.00	-1.00
Q1 ; Q3	-1.00 ; 0.50	-2.00 ; 0.00	-1.00 ; 1.00	-2.00 ; 0.00
Min ; Max	-3.0 ; 1.0	-3.0 ; 1.0	-3.0 ; 2.0	-3.0 ; 2.0
LS Mean (SE)	-0.07 (0.22)	-0.95 (0.23)	-0.25 (0.15)	-0.76 (0.15)
LS Mean Diff vs. placebo (95% CI)		-0.89 (-1.42, -0.35)		-0.51 (-0.89, -0.13)
P-value vs. placebo		0.0012		0.0090
Week 8				
Number (observed/LOCF imputed)	30 (27/3)	28 (24/4)	63 (60/3)	52 (49/3)
Mean (SD)	1.73 (1.17)	1.00 (0.98)	1.94 (1.15)	1.31 (0.88)
Median	2.00	1.00	2.00	1.00
Q1 ; Q3	1.00 ; 3.00	0.00 ; 1.50	1.00 ; 2.00	1.00 ; 2.00
Min ; Max	0.0 ; 4.0	0.0 ; 3.0	0.0 ; 5.0	0.0 ; 3.0
Change from baseline				
Number (observed/LOCF imputed)	30 (27/3)	28 (24/4)	63 (60/3)	52 (49/3)
Mean (SD)	-0.60 (1.28)	-1.07 (1.09)	-0.16 (1.21)	-0.87 (0.95)
Median	0.00	-1.00	0.00	-1.00
Q1 ; Q3	-2.00 ; 0.00	-2.00 ; 0.00	-1.00 ; 1.00	-1.00 ; 0.00
Min ; Max	-3.0 ; 1.0	-3.0 ; 1.0	-3.0 ; 4.0	-3.0 ; 1.0
LS Mean (SE)	-0.30 (0.21)	-0.85 (0.25)	-0.27 (0.14)	-0.91 (0.14)
LS Mean Diff vs. placebo (95% CI)		-0.55 (-1.08, -0.02)		-0.64 (-1.00, -0.28)
P-value vs. placebo		0.0432		0.0005
Week 10				
Number (observed/LOCF imputed)	28 (22/6)	27 (23/4)	55 (51/4)	56 (53/3)
Mean (SD)	1.79 (1.45)	1.11 (1.19)	1.76 (1.14)	1.36 (0.98)
Median	1.50	1.00	2.00	1.00
Q1 ; Q3	1.00 ; 3.00	0.00 ; 2.00	1.00 ; 3.00	1.00 ; 2.00
Min ; Max	0.0 ; 5.0	0.0 ; 3.0	0.0 ; 4.0	0.0 ; 3.0

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Change from baseline				
Number (observed/LOCF imputed)	28 (22/6)	27 (23/4)	55 (51/4)	56 (53/3)
Mean (SD)	-0.54 (1.48)	-0.96 (1.16)	-0.35 (1.11)	-0.80 (1.05)
Median	0.00	-1.00	0.00	-1.00
Q1 ; Q3	-2.00 ; 0.50	-2.00 ; 0.00	-1.00 ; 1.00	-1.00 ; 0.00
Min ; Max	-3.0 ; 3.0	-2.0 ; 1.0	-2.0 ; 2.0	-3.0 ; 1.0
LS Mean (SE)	-0.10 (0.24)	-0.67 (0.26)	-0.34 (0.15)	-0.91 (0.15)
LS Mean Diff vs. placebo (95% CI)		-0.58 (-1.17, 0.02)		-0.57 (-0.96, -0.19)
P-value vs. placebo		0.0570		0.0035
Week 12				
Number (observed/LOCF imputed)	28 (19/9)	28 (23/5)	60 (50/10)	49 (46/3)
Mean (SD)	1.93 (1.27)	1.18 (1.12)	1.78 (1.12)	1.20 (0.96)
Median	2.00	1.00	2.00	1.00
Q1 ; Q3	1.00 ; 3.00	0.00 ; 2.00	1.00 ; 3.00	0.00 ; 2.00
Min ; Max	0.0 ; 5.0	0.0 ; 3.0	0.0 ; 5.0	0.0 ; 4.0
Change from baseline				
Number (observed/LOCF imputed)	28 (19/9)	28 (23/5)	60 (50/10)	49 (46/3)
Mean (SD)	-0.39 (1.31)	-0.89 (1.03)	-0.30 (1.25)	-0.98 (1.03)
Median	0.00	-1.00	0.00	-1.00
Q1 ; Q3	-1.00 ; 0.50	-2.00 ; 0.00	-1.00 ; 1.00	-2.00 ; 0.00
Min ; Max	-3.0 ; 3.0	-2.0 ; 1.0	-3.0 ; 4.0	-3.0 ; 2.0
LS Mean (SE)	-0.08 (0.23)	-0.67 (0.25)	-0.42 (0.14)	-1.02 (0.15)
LS Mean Diff vs. placebo (95% CI)		-0.58 (-1.13, -0.03)		-0.60 (-0.97, -0.22)
P-value vs. placebo		0.0391		0.0020
Shortness of breath experienced				
Baseline				
Number	32	32	68	64
Mean (SD)	2.50 (0.62)	2.31 (0.69)	2.37 (0.62)	2.41 (0.71)
Median	2.00	2.00	2.00	2.00
Q1 ; Q3	2.00 ; 3.00	2.00 ; 3.00	2.00 ; 3.00	2.00 ; 3.00
Min ; Max	2.0 ; 4.0	1.0 ; 4.0	1.0 ; 4.0	0.0 ; 4.0
Week 2				
Number (observed/LOCF imputed)	30 (29/1)	30 (30/0)	63 (62/1)	61 (61/0)

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Mean (SD)	2.23 (0.90)	1.60 (0.77)	2.29 (0.87)	2.05 (1.07)
Median	2.00	1.50	2.00	2.00
Q1 ; Q3	2.00 ; 3.00	1.00 ; 2.00	2.00 ; 3.00	1.00 ; 3.00
Min ; Max	0.0 ; 4.0	0.0 ; 3.0	0.0 ; 4.0	0.0 ; 4.0
Change from baseline				
Number (observed/LOCF imputed)	30 (29/1)	30 (30/0)	63 (62/1)	61 (61/0)
Mean (SD)	-0.23 (0.94)	-0.70 (0.84)	-0.06 (0.90)	-0.38 (1.11)
Median	0.00	-1.00	0.00	0.00
Q1 ; Q3	-1.00 ; 0.00	-1.00 ; 0.00	-1.00 ; 0.00	-1.00 ; 0.00
Min ; Max	-2.0 ; 2.0	-2.0 ; 1.0	-3.0 ; 2.0	-3.0 ; 2.0
LS Mean (SE)	-0.12 (0.17)	-0.66 (0.18)	-0.09 (0.13)	-0.44 (0.13)
LS Mean Diff vs. placebo (95% CI)		-0.55 (-0.96, -0.13)		-0.35 (-0.68, -0.01)
P-value vs. placebo		0.0099		0.0409
Week 4				
Number (observed/LOCF imputed)	30 (28/2)	31 (30/1)	62 (61/1)	59 (59/0)
Mean (SD)	2.13 (1.04)	1.29 (0.94)	2.11 (1.09)	1.73 (1.05)
Median	2.00	1.00	2.00	2.00
Q1 ; Q3	2.00 ; 3.00	1.00 ; 2.00	2.00 ; 3.00	1.00 ; 3.00
Min ; Max	0.0 ; 4.0	0.0 ; 3.0	0.0 ; 5.0	0.0 ; 3.0
Change from baseline				
Number (observed/LOCF imputed)	30 (28/2)	31 (30/1)	62 (61/1)	59 (59/0)
Mean (SD)	-0.33 (1.21)	-1.03 (0.87)	-0.24 (1.07)	-0.66 (1.06)
Median	0.00	-1.00	0.00	-1.00
Q1 ; Q3	-1.00 ; 0.00	-2.00 ; 0.00	-1.00 ; 0.00	-1.00 ; 0.00
Min ; Max	-3.0 ; 2.0	-3.0 ; 0.0	-3.0 ; 3.0	-3.0 ; 1.0
LS Mean (SE)	-0.17 (0.20)	-0.88 (0.21)	-0.27 (0.14)	-0.73 (0.15)
LS Mean Diff vs. placebo (95% CI)		-0.71 (-1.21, -0.21)		-0.47 (-0.84, -0.09)
P-value vs. placebo		0.0053		0.0147
Week 6				
Number (observed/LOCF imputed)	28 (26/2)	30 (28/2)	60 (58/2)	57 (56/1)
Mean (SD)	2.32 (1.16)	1.33 (1.03)	2.05 (0.89)	1.81 (1.09)
Median	2.00	1.00	2.00	2.00
Q1 ; Q3	1.50 ; 3.00	1.00 ; 2.00	2.00 ; 3.00	1.00 ; 3.00
Min ; Max	0.0 ; 5.0	0.0 ; 4.0	0.0 ; 4.0	0.0 ; 4.0

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Change from baseline				
Number (observed/LOCF imputed)	28 (26/2)	30 (28/2)	60 (58/2)	57 (56/1)
Mean (SD)	-0.14 (1.27)	-1.03 (1.03)	-0.30 (0.83)	-0.61 (1.18)
Median	0.00	-1.00	0.00	0.00
Q1 ; Q3	-1.00 ; 1.00	-2.00 ; -1.00	-1.00 ; 0.00	-1.00 ; 0.00
Min ; Max	-3.0 ; 2.0	-3.0 ; 2.0	-3.0 ; 1.0	-4.0 ; 2.0
LS Mean (SE)	-0.00 (0.24)	-0.90 (0.25)	-0.25 (0.14)	-0.64 (0.14)
LS Mean Diff vs. placebo (95% CI)		-0.90 (-1.47, -0.33)		-0.39 (-0.74, -0.04)
P-value vs. placebo		0.0019		0.0310
Week 8				
Number (observed/LOCF imputed)	30 (27/3)	28 (24/4)	63 (60/3)	52 (49/3)
Mean (SD)	1.80 (1.06)	1.32 (1.19)	2.16 (1.25)	1.63 (1.01)
Median	2.00	1.00	2.00	2.00
Q1 ; Q3	1.00 ; 3.00	1.00 ; 2.00	1.00 ; 3.00	1.00 ; 2.00
Min ; Max	0.0 ; 4.0	0.0 ; 5.0	0.0 ; 6.0	0.0 ; 3.0
Change from baseline				
Number (observed/LOCF imputed)	30 (27/3)	28 (24/4)	63 (60/3)	52 (49/3)
Mean (SD)	-0.67 (1.21)	-0.93 (1.25)	-0.21 (1.12)	-0.77 (1.08)
Median	0.00	-1.00	0.00	-1.00
Q1 ; Q3	-1.00 ; 0.00	-2.00 ; -1.00	-1.00 ; 0.00	-1.00 ; 0.00
Min ; Max	-4.0 ; 1.0	-3.0 ; 3.0	-2.0 ; 3.0	-3.0 ; 1.0
LS Mean (SE)	-0.44 (0.24)	-0.83 (0.27)	-0.29 (0.14)	-0.87 (0.15)
LS Mean Diff vs. placebo (95% CI)		-0.39 (-0.97, 0.19)		-0.58 (-0.96, -0.20)
P-value vs. placebo		0.1848		0.0026
Week 10				
Number (observed/LOCF imputed)	28 (22/6)	27 (23/4)	55 (51/4)	56 (53/3)
Mean (SD)	1.86 (1.18)	1.26 (1.10)	2.02 (1.28)	1.63 (0.98)
Median	2.00	1.00	2.00	2.00
Q1 ; Q3	1.00 ; 3.00	0.00 ; 2.00	1.00 ; 3.00	1.00 ; 2.00
Min ; Max	0.0 ; 4.0	0.0 ; 4.0	0.0 ; 5.0	0.0 ; 3.0
Change from baseline				
Number (observed/LOCF imputed)	28 (22/6)	27 (23/4)	55 (51/4)	56 (53/3)

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Mean (SD)	-0.57 (1.37)	-1.15 (1.17)	-0.31 (1.22)	-0.79 (1.16)
Median	0.00	-1.00	0.00	-1.00
Q1 ; Q3	-2.00 ; 0.50	-2.00 ; 0.00	-1.00 ; 1.00	-1.00 ; 0.00
Min ; Max	-4.0 ; 1.0	-3.0 ; 2.0	-3.0 ; 2.0	-3.0 ; 2.0
LS Mean (SE)	-0.19 (0.21)	-0.74 (0.23)	-0.24 (0.16)	-0.81 (0.17)
LS Mean Diff vs. placebo (95% CI)		-0.54 (-1.07, -0.01)		-0.57 (-0.99, -0.15)
P-value vs. placebo		0.0442		0.0080
Week 12				
Number (observed/LOCF imputed)	28 (19/9)	28 (23/5)	60 (50/10)	49 (46/3)
Mean (SD)	1.96 (0.96)	1.29 (1.05)	2.17 (1.33)	1.63 (0.97)
Median	2.00	1.00	2.00	2.00
Q1 ; Q3	1.00 ; 3.00	0.50 ; 2.00	1.00 ; 3.00	1.00 ; 2.00
Min ; Max	0.0 ; 4.0	0.0 ; 4.0	0.0 ; 6.0	0.0 ; 3.0
Change from baseline				
Number (observed/LOCF imputed)	28 (19/9)	28 (23/5)	60 (50/10)	49 (46/3)
Mean (SD)	-0.50 (1.17)	-1.07 (1.18)	-0.22 (1.22)	-0.86 (1.02)
Median	0.00	-1.00	0.00	-1.00
Q1 ; Q3	-1.00 ; 0.00	-2.00 ; -1.00	-1.00 ; 1.00	-2.00 ; 0.00
Min ; Max	-4.0 ; 1.0	-3.0 ; 2.0	-3.0 ; 3.0	-3.0 ; 1.0
LS Mean (SE)	-0.20 (0.21)	-0.87 (0.23)	-0.25 (0.15)	-0.84 (0.15)
LS Mean Diff vs. placebo (95% CI)		-0.66 (-1.18, -0.15)		-0.59 (-0.99, -0.19)
P-value vs. placebo		0.0116		0.0039
Wheeze				
Baseline				
Number	32	32	68	64
Mean (SD)	1.97 (0.82)	2.06 (0.72)	2.13 (0.83)	2.23 (0.79)
Median	2.00	2.00	2.00	2.00
Q1 ; Q3	1.00 ; 2.00	2.00 ; 2.00	2.00 ; 3.00	2.00 ; 3.00
Min ; Max	1.0 ; 4.0	1.0 ; 4.0	0.0 ; 5.0	1.0 ; 4.0
Week 2				
Number (observed/LOCF imputed)	30 (29/1)	30 (30/0)	63 (62/1)	61 (61/0)
Mean (SD)	1.80 (1.19)	1.00 (0.87)	1.90 (0.93)	1.89 (1.05)
Median	2.00	1.00	2.00	2.00
Q1 ; Q3	1.00 ; 2.00	0.00 ; 2.00	1.00 ; 3.00	1.00 ; 3.00

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Min ; Max	0.0 ; 6.0	0.0 ; 3.0	0.0 ; 4.0	0.0 ; 5.0
Change from baseline				
Number (observed/LOCF imputed)	30 (29/1)	30 (30/0)	63 (62/1)	61 (61/0)
Mean (SD)	-0.17 (1.05)	-1.07 (0.94)	-0.21 (1.09)	-0.34 (1.00)
Median	0.00	-1.00	0.00	0.00
Q1 ; Q3	-1.00 ; 0.00	-2.00 ; 0.00	-1.00 ; 0.00	-1.00 ; 0.00
Min ; Max	-2.0 ; 3.0	-3.0 ; 1.0	-4.0 ; 2.0	-2.0 ; 3.0
LS Mean (SE)	-0.25 (0.19)	-1.08 (0.20)	-0.29 (0.12)	-0.44 (0.12)
LS Mean Diff vs. placebo (95% CI)		-0.83 (-1.29, -0.36)		-0.15 (-0.47, 0.17)
P-value vs. placebo		0.0005		0.3687
Week 4				
Number (observed/LOCF imputed)	30 (28/2)	31 (30/1)	62 (61/1)	59 (59/0)
Mean (SD)	1.60 (1.04)	1.26 (1.12)	1.84 (1.09)	1.81 (1.12)
Median	1.50	1.00	2.00	2.00
Q1 ; Q3	1.00 ; 2.00	0.00 ; 2.00	1.00 ; 3.00	1.00 ; 3.00
Min ; Max	0.0 ; 4.0	0.0 ; 5.0	0.0 ; 4.0	0.0 ; 5.0
Change from baseline				
Number (observed/LOCF imputed)	30 (28/2)	31 (30/1)	62 (61/1)	59 (59/0)
Mean (SD)	-0.37 (1.10)	-0.81 (1.01)	-0.26 (1.23)	-0.42 (1.02)
Median	0.00	-1.00	0.00	0.00
Q1 ; Q3	-1.00 ; 0.00	-1.00 ; 0.00	-1.00 ; 0.00	-1.00 ; 0.00
Min ; Max	-3.0 ; 2.0	-3.0 ; 2.0	-5.0 ; 2.0	-2.0 ; 3.0
LS Mean (SE)	-0.45 (0.21)	-0.83 (0.22)	-0.43 (0.14)	-0.50 (0.14)
LS Mean Diff vs. placebo (95% CI)		-0.38 (-0.89, 0.14)		-0.07 (-0.44, 0.30)
P-value vs. placebo		0.1498		0.7130
Week 6				
Number (observed/LOCF imputed)	28 (26/2)	30 (28/2)	60 (58/2)	57 (56/1)
Mean (SD)	1.75 (1.46)	0.97 (0.93)	1.67 (1.13)	1.70 (1.05)
Median	2.00	1.00	2.00	2.00
Q1 ; Q3	1.00 ; 2.00	0.00 ; 2.00	1.00 ; 2.00	1.00 ; 2.00
Min ; Max	0.0 ; 6.0	0.0 ; 3.0	0.0 ; 4.0	0.0 ; 4.0
Change from baseline				

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Number (observed/LOCF imputed)	28 (26/2)	30 (28/2)	60 (58/2)	57 (56/1)
Mean (SD)	-0.21 (1.55)	-1.13 (1.04)	-0.45 (1.21)	-0.58 (0.96)
Median	0.00	-1.00	0.00	-1.00
Q1 ; Q3	-1.00 ; 0.00	-2.00 ; 0.00	-1.00 ; 0.00	-1.00 ; 0.00
Min ; Max	-3.0 ; 3.0	-3.0 ; 1.0	-5.0 ; 2.0	-3.0 ; 2.0
LS Mean (SE)	-0.27 (0.24)	-1.08 (0.26)	-0.45 (0.14)	-0.61 (0.14)
LS Mean Diff vs. placebo (95% CI)		-0.81 (-1.40, -0.22)		-0.16 (-0.52, 0.20)
P-value vs. placebo		0.0076		0.3907
Week 8				
Number (observed/LOCF imputed)	30 (27/3)	28 (24/4)	63 (60/3)	52 (49/3)
Mean (SD)	1.70 (1.44)	1.11 (1.07)	1.94 (1.32)	1.58 (0.98)
Median	2.00	1.00	2.00	2.00
Q1 ; Q3	1.00 ; 2.00	0.00 ; 2.00	1.00 ; 3.00	1.00 ; 2.00
Min ; Max	0.0 ; 5.0	0.0 ; 3.0	0.0 ; 5.0	0.0 ; 4.0
Change from baseline				
Number (observed/LOCF imputed)	30 (27/3)	28 (24/4)	63 (60/3)	52 (49/3)
Mean (SD)	-0.27 (1.44)	-0.96 (1.07)	-0.13 (1.41)	-0.69 (0.98)
Median	0.00	-1.00	0.00	-1.00
Q1 ; Q3	-1.00 ; 0.00	-2.00 ; 0.00	-1.00 ; 1.00	-1.00 ; 0.00
Min ; Max	-4.0 ; 3.0	-3.0 ; 1.0	-5.0 ; 3.0	-3.0 ; 1.0
LS Mean (SE)	-0.32 (0.25)	-0.99 (0.27)	-0.31 (0.15)	-0.69 (0.16)
LS Mean Diff vs. placebo (95% CI)		-0.67 (-1.27, -0.06)		-0.37 (-0.77, 0.03)
P-value vs. placebo		0.0315		0.0669
Week 10				
Number (observed/LOCF imputed)	28 (22/6)	27 (23/4)	55 (51/4)	56 (53/3)
Mean (SD)	1.93 (1.27)	1.19 (0.96)	1.85 (1.38)	1.52 (1.03)
Median	2.00	1.00	2.00	1.00
Q1 ; Q3	1.00 ; 2.50	0.00 ; 2.00	1.00 ; 3.00	1.00 ; 2.00
Min ; Max	0.0 ; 5.0	0.0 ; 3.0	0.0 ; 5.0	0.0 ; 4.0
Change from baseline				
Number (observed/LOCF imputed)	28 (22/6)	27 (23/4)	55 (51/4)	56 (53/3)
Mean (SD)	0.00 (1.44)	-0.93 (1.14)	-0.25 (1.49)	-0.73 (1.12)
Median	0.00	-1.00	0.00	-1.00

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Q1 ; Q3	-1.00 ; 1.00	-2.00 ; 0.00	-1.00 ; 1.00	-1.00 ; 0.00
Min ; Max	-3.0 ; 2.0	-4.0 ; 1.0	-5.0 ; 3.0	-3.0 ; 2.0
LS Mean (SE)	-0.00 (0.21)	-0.83 (0.23)	-0.36 (0.16)	-0.79 (0.17)
LS Mean Diff vs. placebo (95% CI)		-0.82 (-1.35, -0.30)		-0.43 (-0.85, -0.01)
P-value vs. placebo		0.0021		0.0450
Week 12				
Number (observed/LOCF imputed)	28 (19/9)	28 (23/5)	60 (50/10)	49 (46/3)
Mean (SD)	1.86 (1.35)	1.21 (1.10)	2.05 (1.53)	1.49 (0.84)
Median	2.00	1.00	2.00	2.00
Q1 ; Q3	1.00 ; 2.00	0.00 ; 2.00	1.00 ; 3.50	1.00 ; 2.00
Min ; Max	0.0 ; 5.0	0.0 ; 3.0	0.0 ; 5.0	0.0 ; 3.0
Change from baseline				
Number (observed/LOCF imputed)	28 (19/9)	28 (23/5)	60 (50/10)	49 (46/3)
Mean (SD)	-0.14 (1.58)	-0.86 (1.11)	-0.05 (1.41)	-0.80 (1.00)
Median	0.00	-1.00	0.00	-1.00
Q1 ; Q3	-1.00 ; 1.00	-2.00 ; 0.00	-1.00 ; 1.00	-1.00 ; 0.00
Min ; Max	-4.0 ; 2.0	-2.0 ; 1.0	-3.0 ; 3.0	-3.0 ; 1.0
LS Mean (SE)	-0.03 (0.25)	-0.63 (0.28)	-0.22 (0.16)	-0.80 (0.17)
LS Mean Diff vs. placebo (95% CI)		-0.60 (-1.21, 0.00)		-0.58 (-1.00, -0.15)
P-value vs. placebo		0.0500		0.0078

ACQ-5: Asthma control questionnaire, 5-question version, LOAC: Loss of asthma control, LOCF: Last observation carried forward, LATAM: Latin America, EASTEU: Eastern Europe, ROW: Rest of the world

[0251] Table 43. Responder analysis for change from baseline in ACQ-5 score at Week 12 (mITT population).

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Week 12				
Number (observed/LOCF imputed)	28 (19/9)	28 (23/5)	60 (50/10)	49 (46/3)
Responder (observed/LOCF imputed)	10 (35.7) (9/1)	19 (67.9) (17/2)	24 (40.0) (23/1)	31 (63.3) (31/0)
Non-responder (observed/LOCF imputed)	18 (64.3) (10/8)	9 (32.1) (6/3)	36 (60.0) (27/9)	18 (36.7) (15/3)

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)
Responder (including multiply imputed)	11.5 (35.9)	21.2 (66.1)	26.8 (39.4)	38.3 (59.8)
OR vs. placebo (95% CI)		5.18 (1.48, 18.15)		2.38 (1.09, 5.18)
P-value vs. placebo		0.0100		0.0297

LATAM: Latin America, ROW: Rest of the world

[0252] Table 44. Responder analysis for ACQ-5 score less than 0.75 over time (mITT population).

	BID cohort		TID cohort	
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)
Baseline				
Number (observed/NR imputed)	32 (32/0)	32 (32/0)	68 (68/0)	64 (64/0)
Responder (observed)	0	0	0	0
Non-responder (observed/NR imputed)	32 (100) (32/0)	32 (100) (32/0)	68 (100) (68/0)	64 (100) (64/0)
Week 2				
Number (observed/LOCF imputed/NR imputed)	32 (29/1/2)	32 (30/0/2)	68 (62/1/5)	64 (61/0/3)
Responder (observed/LOCF imputed)	1 (3.1) (1/0)	6 (18.8) (6/0)	4 (5.9) (4/0)	10 (15.6) (10/0)
Non-responder (observed/LOCF imputed/NR imputed)	31 (96.9) (28/1/2)	26 (81.3) (24/0/2)	64 (94.1) (58/1/5)	54 (84.4) (51/0/3)
OR vs. placebo (95% CI)		5.66 (0.61, 52.11)		3.39 (0.95, 12.05)
P-value vs. placebo		0.1262		0.0590
Week 4				
Number (observed/LOCF imputed/NR imputed)	32 (28/2/2)	32 (30/1/1)	68 (61/1/6)	64 (59/0/5)
Responder (observed/LOCF imputed)	2 (6.3) (2/0)	11 (34.4) (11/0)	5 (7.4) (5/0)	10 (15.6) (10/0)
Non-responder (observed/LOCF imputed/NR imputed)	30 (93.8) (26/2/2)	21 (65.6) (19/1/1)	63 (92.6) (56/1/6)	54 (84.4) (49/0/5)
OR vs. placebo (95% CI)		8.34 (1.55, 44.69)		2.78 (0.82, 9.38)
P-value vs. placebo		0.0133		0.1003
Week 6				
Number (observed/LOCF imputed/NR imputed)	32 (26/2/4)	32 (28/2/2)	68 (58/2/8)	64 (56/1/7)
Responder (observed/LOCF imputed)	3 (9.4) (3/0)	11 (34.4) (11/0)	5 (7.4) (5/0)	11 (17.2) (11/0)
Non-responder (observed/LOCF imputed/NR imputed)	29 (90.6) (23/2/4)	21 (65.6) (17/2/2)	63 (92.6) (53/2/8)	53 (82.8) (45/1/7)

	BID cohort		TID cohort	
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
OR vs. placebo (95% CI)		4.74 (1.12, 20.02)		3.22 (0.96, 10.79)
P-value vs. placebo		0.0344		0.0575
Week 8				
Number (observed/LOCF imputed/NR imputed)	32 (27/3/2)	32 (24/4/4)	68 (60/3/5)	64 (49/3/12)
Responder (observed/LOCF imputed)	6 (18.8) (6/0)	9 (28.1) (9/0)	4 (5.9) (4/0)	9 (14.1) (9/0)
Non-responder (observed/LOCF imputed/NR imputed)	26 (81.3) (21/3/2)	23 (71.9) (15/4/4)	64 (94.1) (56/3/5)	55 (85.9) (40/3/12)
OR vs. placebo (95% CI)		1.51 (0.45, 5.09)		3.03 (0.83, 11.04)
P-value vs. placebo		0.5033		0.0919
Week 10				
Number (observed/LOCF imputed/NR imputed)	32 (22/6/4)	32 (23/4/5)	68 (51/4/13)	64 (53/3/8)
Responder (observed/LOCF imputed)	5 (15.6) (5/0)	11 (34.4) (11/0)	7 (10.3) (7/0)	12 (18.8) (12/0)
Non-responder (observed/LOCF imputed/NR imputed)	27 (84.4) (17/6/4)	21 (65.6) (12/4/5)	61 (89.7) (44/4/13)	52 (81.3) (41/3/8)
OR vs. placebo (95% CI)		3.58 (0.95, 13.55)		2.45 (0.80, 7.47)
P-value vs. placebo		0.0599		0.1146
Week 12				
Number (observed/LOCF imputed/NR imputed)	32 (19/9/4)	32 (23/5/4)	68 (50/10/8)	64 (46/3/15)
Responder (observed/LOCF imputed)	3 (9.4) (3/0)	13 (40.6) (12/1)	9 (13.2) (9/0)	10 (15.6) (10/0)
Non-responder (observed/LOCF imputed/NR imputed)	29 (90.6) (16/9/4)	19 (59.4) (11/4/4)	59 (86.8) (41/10/8)	54 (84.4) (36/3/15)
OR vs. placebo (95% CI)		6.79 (1.61, 28.67)		1.29 (0.46, 3.64)
P-value vs. placebo		0.0092		0.6286

LATAM: Latin America, ROW: Rest of the world, NR: non-responder

[0253] Table 45. Number and proportion of participants remained as ACQ-5 less than 0.75 responders since Week 4 over time (mITT population).

	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**
Week 4		
Number (observed/LOCF imputed/NR imputed)	32 (28/2/2)	32 (30/1/1)
Responder (observed/LOCF imputed)	2 (6.3) (2/0)	11 (34.4) (11/0)

	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
Non-responder (observed/LOCF imputed/NR imputed)	30 (93.8) (26/2/2)	21 (65.6) (19/1/1)
Week 6		
Number (observed/LOCF imputed)	2 (2/0)	11 (10/0)
Responder (observed/LOCF imputed)	1 (50.0) (1/0)	7 (63.6) (7/0)
OR vs. placebo (95% CI)		0.81 (0.01, 126.85)
P-value vs. placebo		0.9356
Week 8		
Number (observed/LOCF imputed)	2 (2/0)	11 (10/1)
Responder (observed/LOCF imputed)	1 (50.0) (1/0)	5 (45.5) (5/0)
OR vs. placebo (95% CI)		0.26 (0.00, 28.99)
P-value vs. placebo		0.5729
Week 10		
Number (observed/LOCF imputed)	2 (2/0)	11 (8/1)
Responder (observed/LOCF imputed)	1 (50.0) (1/0)	4 (36.4) (4/0)
OR vs. placebo (95% CI)		0.12 (0.00, 16.67)
P-value vs. placebo		0.3991
Week 12		
Number (observed/LOCF imputed)	2 (1/1)	11 (8/2)
Responder (observed/LOCF imputed)	0	3 (27.3) (2/1)
OR vs. placebo (95% CI)		NC (NC, NC)
P-value vs. placebo		NC

LATAM: Latin America, ROW: Rest of the world, NR: non-responder

[0254] Table 46. Subgroup analysis: change from baseline in ACQ-5 score at EOT (Week 12) by demographics subgroups (mITT population).

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Age group 1 (years)				
< 45				
Number	10	9	28	23
Mean (SD)	-0.70 (0.91)	-0.49 (0.94)	-0.05 (1.02)	-0.84 (0.62)
LS Mean (SE)	-0.70 (0.31)	-0.68 (0.34)	-0.25 (0.17)	-0.95 (0.17)
LS Mean Diff vs. placebo (95% CI)		0.02 (-0.76, 0.79)		-0.70 (-1.15, -0.25)
P-value vs. placebo		0.9616		0.0024
≥ 45				
Number	18	19	32	26
Mean (SD)	-0.13 (1.05)	-1.07 (0.88)	-0.38 (1.04)	-0.79 (0.81)
LS Mean (SE)	0.14 (0.23)	-0.78 (0.25)	-0.35 (0.17)	-0.79 (0.18)
LS Mean Diff vs. placebo (95% CI)		-0.92 (-1.50, -0.35)		-0.43 (-0.90, 0.03)

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
P-value vs. placebo		0.0016		0.0643
Overall p-value for interaction		0.0568		0.5311
Gender				
Male				
Number	7	12	26	22
Mean (SD)	-0.31 (0.98)	-1.08 (0.79)	-0.22 (0.82)	-0.65 (0.65)
LS Mean (SE)	-0.32 (0.36)	-0.82 (0.42)	-0.31 (0.17)	-0.64 (0.17)
LS Mean Diff vs. placebo (95% CI)		-0.50 (-1.67, 0.67)		-0.34 (-0.78, 0.11)
P-value vs. placebo		0.4019		0.1396
Female				
Number	21	16	34	27
Mean (SD)	-0.34 (1.06)	-0.74 (1.02)	-0.22 (1.18)	-0.96 (0.76)
LS Mean (SE)	-0.02 (0.27)	-0.58 (0.27)	-0.31 (0.17)	-0.96 (0.18)
LS Mean Diff vs. placebo (95% CI)		-0.56 (-1.19, 0.06)		-0.65 (-1.11, -0.19)
P-value vs. placebo		0.0747		0.0056
Overall p-value for interaction		0.9599		0.3680
Baseline weight group (kg)				
< 60				
Number	4	3	10	2
Mean (SD)	0.35 (0.47)	-1.13 (0.83)	-0.54 (1.12)	-1.90 (0.42)
LS Mean (SE)	0.32 (0.47)	-1.71 (0.99)	-0.18 (0.41)	-1.72 (0.80)
LS Mean Diff vs. placebo (95% CI)		-2.03 (-5.03, 0.98)		-1.54 (-3.28, 0.21)
P-value vs. placebo		0.1010		0.0847
≥ 60 - < 90				
Number	21	20	35	29
Mean (SD)	-0.52 (1.00)	-0.80 (0.89)	-0.15 (1.07)	-0.74 (0.68)
LS Mean (SE)	-0.27 (0.25)	-0.63 (0.25)	-0.25 (0.16)	-0.80 (0.17)
LS Mean Diff vs. placebo (95% CI)		-0.35 (-0.93, 0.22)		-0.54 (-0.97, -0.11)
P-value vs. placebo		0.2295		0.0130
≥ 90				
Number	3	5	15	18
Mean (SD)	0.07 (1.50)	-1.08 (1.25)	-0.17 (0.91)	-0.81 (0.74)
LS Mean (SE)	-0.68 (0.45)	-1.96 (0.57)	-0.34 (0.23)	-0.86 (0.19)
LS Mean Diff vs. placebo (95% CI)		-1.27 (-2.46, -0.09)		-0.51 (-1.08, 0.05)
P-value vs. placebo		0.0353		0.0737
Overall p-value for interaction		0.4298		0.4325

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Baseline BMI group (kg/m^2)				
< 25				
Number	6	8	20	8
Mean (SD)	0.00 (0.79)	-0.90 (0.81)	-0.33 (1.02)	-1.03 (0.82)
LS Mean (SE)	0.65 (0.54)	0.03 (0.68)	-0.40 (0.25)	-1.06 (0.37)
LS Mean Diff vs. placebo (95% CI)		-0.61 (-1.75, 0.53)		-0.66 (-1.45, 0.14)
P-value vs. placebo		0.2545		0.1043
≥ 25 - < 30				
Number	15	13	23	26
Mean (SD)	-0.53 (1.16)	-0.69 (0.94)	-0.22 (0.98)	-0.86 (0.73)
LS Mean (SE)	-0.40 (0.29)	-0.67 (0.33)	-0.42 (0.18)	-1.01 (0.17)
LS Mean Diff vs. placebo (95% CI)		-0.27 (-1.10, 0.56)		-0.59 (-1.04, -0.14)
P-value vs. placebo		0.5253		0.0101
≥ 30				
Number	7	7	17	15
Mean (SD)	-0.20 (0.92)	-1.23 (1.06)	-0.11 (1.16)	-0.63 (0.65)
LS Mean (SE)	0.50 (0.37)	-0.67 (0.37)	-0.13 (0.24)	-0.66 (0.23)
LS Mean Diff vs. placebo (95% CI)		-1.17 (-1.91, -0.42)		-0.53 (-1.17, 0.11)
P-value vs. placebo		0.0021		0.1017
Overall p-value for interaction		0.3782		0.9246
Region				
Eastern Europe				
Number	4	1	43	32
Mean (SD)	-0.05 (1.17)	1.00 (NC)	-0.04 (0.88)	-0.72 (0.66)
LS Mean (SE)	-0.48 (0.69)	0.40 (0.94)	-0.06 (0.13)	-0.59 (0.14)
LS Mean Diff vs. placebo (95% CI)		0.88 (-1.58, 3.35)		-0.53 (-0.90, -0.15)
P-value vs. placebo		0.4823		0.0059
Latin America				
Number	22	24	15	15
Mean (SD)	-0.54 (0.91)	-1.02 (0.85)	-0.93 (0.81)	-0.87 (0.77)
LS Mean (SE)	-0.54 (0.21)	-1.12 (0.20)	-0.91 (0.26)	-1.04 (0.25)
LS Mean Diff vs. placebo (95% CI)		-0.58 (-1.11, -0.05)		-0.14 (-0.70, 0.43)
P-value vs. placebo		0.0315		0.6394
Western Countries				
Number	1	2	1	2
Mean (SD)	1.60 (NC)	-0.60 (1.41)	3.20 (NC)	-2.00 (0.00)
LS Mean (SE)	NC (NC)	NC (NC)	NC (NC)	NC (NC)
LS Mean Diff vs. placebo (95% CI)		NC (NC, NC)		NC (NC, NC)

ACQ-5	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)
P-value vs. placebo		NC		NC
APAC				
Number	1	1	1	0
Mean (SD)	1.00 (NC)	-0.20 (NC)	-0.80 (NC)	NC (NC)
LS Mean (SE)	NC (NC)	NC (NC)	NC (NC)	NC (NC)
LS Mean Diff vs. placebo (95% CI)		NC (NC, NC)		NC (NC, NC)
P-value vs. placebo		NC		NC
Overall p-value for interaction		0.6608		0.0007

LATAM: Latin America, ROW: Rest of the world

[0255] Table 47. Subgroup analysis: change from baseline in ACQ-5 score at EOT (Week 12) by disease and other characteristics subgroups (mITT population).

ACQ-5	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)
Age at onset of asthma (years)				
< 12				
Number	7	8	14	12
Mean (SD)	-0.49 (0.80)	-0.68 (1.13)	0.09 (0.93)	-0.58 (0.67)
LS Mean (SE)	-0.70 (0.42)	-0.71 (0.55)	-0.02 (0.22)	-0.63 (0.24)
LS Mean Diff vs. placebo (95% CI)		-0.01 (-1.21, 1.18)		-0.61 (-1.24, 0.02)
P-value vs. placebo		0.9822		0.0595
≥ 12 - < 18				
Number	2	4	5	5
Mean (SD)	-0.40 (0.57)	-1.30 (0.20)	-0.76 (1.18)	-1.04 (0.65)
LS Mean (SE)	-0.14 (0.88)	-0.96 (0.54)	-1.10 (0.84)	-1.08 (0.64)
LS Mean Diff vs. placebo (95% CI)		-0.82 (-3.23, 1.59)		0.01 (-1.86, 1.89)
P-value vs. placebo		0.2812		0.9849
≥ 18 - < 40				
Number	13	13	24	20
Mean (SD)	-0.25 (1.06)	-0.97 (0.98)	-0.11 (1.24)	-0.87 (0.69)
LS Mean (SE)	0.15 (0.27)	-0.71 (0.27)	-0.20 (0.23)	-0.77 (0.24)
LS Mean Diff vs. placebo (95% CI)		-0.85 (-1.52, -0.19)		-0.57 (-1.15, 0.01)
P-value vs. placebo		0.0119		0.0537
≥ 40				
Number	6	3	17	12
Mean (SD)	-0.33 (1.44)	-0.53 (0.81)	-0.48 (0.64)	-0.87 (0.86)
LS Mean (SE)	-0.08 (0.49)	-0.87 (0.83)	-0.39 (0.20)	-0.90 (0.22)

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
LS Mean Diff vs. placebo (95% CI)		-0.78 (-2.44, 0.88)		-0.51 (-1.06, 0.03)
P-value vs. placebo		0.3555		0.0660
Overall p-value for interaction		0.5580		0.8917
Age at onset of asthma (years)				
< 18				
Number	9	12	19	17
Mean (SD)	-0.47 (0.72)	-0.88 (0.96)	-0.14 (1.04)	-0.72 (0.68)
LS Mean (SE)	-0.67 (0.34)	-0.91 (0.39)	-0.22 (0.20)	-0.66 (0.21)
LS Mean Diff vs. placebo (95% CI)		-0.24 (-1.08, 0.59)		-0.44 (-0.99, 0.12)
P-value vs. placebo		0.5658		0.1215
≥ 18				
Number	19	16	41	32
Mean (SD)	-0.27 (1.15)	-0.89 (0.94)	-0.26 (1.04)	-0.87 (0.75)
LS Mean (SE)	0.05 (0.23)	-0.70 (0.26)	-0.30 (0.15)	-0.84 (0.17)
LS Mean Diff vs. placebo (95% CI)		-0.76 (-1.35, -0.16)		-0.54 (-0.94, -0.14)
P-value vs. placebo		0.0136		0.0089
Overall p-value for interaction		0.4014		0.8634
Number of asthma exacerbations within 2 years before screening visit				
1				
Number	8	10	45	31
Mean (SD)	-0.63 (0.92)	-1.06 (1.05)	-0.23 (0.99)	-0.95 (0.74)
LS Mean (SE)	-0.37 (0.37)	-1.12 (0.35)	-0.39 (0.15)	-1.04 (0.16)
LS Mean Diff vs. placebo (95% CI)		-0.76 (-1.61, 0.09)		-0.66 (-1.07, -0.25)
P-value vs. placebo		0.0811		0.0016
2				
Number	14	10	15	15
Mean (SD)	-0.39 (1.18)	-0.88 (0.97)	-0.21 (1.20)	-0.64 (0.69)
LS Mean (SE)	0.13 (0.33)	-0.11 (0.48)	-0.26 (0.26)	-0.70 (0.24)
LS Mean Diff vs. placebo (95% CI)		-0.23 (-1.17, 0.70)		-0.45 (-1.07, 0.17)
P-value vs. placebo		0.6244		0.1584
> 2				
Number	6	8	0	3
Mean (SD)	0.17 (0.61)	-0.68 (0.78)	NC (NC)	-0.33 (0.31)
LS Mean (SE)	0.18 (0.30)	-0.53 (0.25)	NC (NC)	NC (NC)
LS Mean Diff vs. placebo (95% CI)		-0.70 (-1.38, -0.03)		NC (NC, NC)
P-value vs. placebo		0.0417		NC

ACQ-5	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)
Overall p-value for interaction		0.8549		0.4193
Atopic medical conditions				
Yes				
Number	16	19	19	16
Mean (SD)	-0.75 (1.04)	-0.89 (0.92)	-0.38 (0.97)	-0.80 (0.83)
LS Mean (SE)	-0.41 (0.29)	-0.71 (0.28)	-0.23 (0.21)	-0.79 (0.24)
LS Mean Diff vs. placebo (95% CI)		-0.30 (-0.92, 0.32)		-0.56 (-1.15, 0.03)
P-value vs. placebo		0.3393		0.0640
No				
Number	12	9	41	33
Mean (SD)	0.22 (0.71)	-0.87 (1.00)	-0.15 (1.06)	-0.82 (0.67)
LS Mean (SE)	0.27 (0.28)	-0.69 (0.33)	-0.36 (0.17)	-0.87 (0.17)
LS Mean Diff vs. placebo (95% CI)		-0.96 (-1.71, -0.21)		-0.51 (-0.92, -0.10)
P-value vs. placebo		0.0118		0.0149
Overall p-value for interaction		0.1288		0.8698
Background ICS dose level at randomization (400 mg TID only)				
Medium				
Number			32	19
Mean (SD)			-0.11 (0.96)	-0.72 (0.72)
LS Mean (SE)			-0.29 (0.19)	-0.76 (0.20)
LS Mean Diff vs. placebo (95% CI)				-0.46 (-0.93, 0.00)
P-value vs. placebo				0.0518
High				
Number			28	30
Mean (SD)			-0.36 (1.11)	-0.88 (0.73)
LS Mean (SE)			-0.32 (0.18)	-0.92 (0.18)
LS Mean Diff vs. placebo (95% CI)				-0.60 (-1.08, -0.11)
P-value vs. placebo				0.0167
Overall p-value for interaction				0.6694
Smoking history				
Former				
Number	7	4	3	3
Mean (SD)	-0.03 (0.88)	-1.20 (1.07)	0.33 (0.42)	0.07 (0.42)
LS Mean (SE)	0.75 (0.48)	-0.50 (0.62)	0.27 (0.44)	-0.56 (0.47)
LS Mean Diff vs. placebo (95% CI)		-1.25 (-2.44, -0.06)		-0.83 (-1.97, 0.31)
P-value vs. placebo		0.0396		0.1522

ACQ-5	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)
Never				
Number	21	24	57	46
Mean (SD)	-0.44 (1.07)	-0.83 (0.92)	-0.25 (1.05)	-0.87 (0.70)
LS Mean (SE)	-0.25 (0.23)	-0.69 (0.23)	-0.40 (0.13)	-0.92 (0.13)
LS Mean Diff vs. placebo (95% CI)		-0.44 (-0.98, 0.10)		-0.52 (-0.86, -0.18)
P-value vs. placebo		0.1102		0.0025
Overall p-value for interaction		0.2052		0.7507
Baseline pre-bronchodilator FEV1 (L) (400 mg BID only)				
< Median (2.022)				
Number	13	15		
Mean (SD)	-0.31 (1.08)	-0.88 (0.81)		
LS Mean (SE)	0.04 (0.28)	-0.42 (0.30)		
LS Mean Diff vs. placebo (95% CI)		-0.45 (-1.09, 0.19)		
P-value vs. placebo		0.1647		
≥ Median (2.022)				
Number	15	12		
Mean (SD)	-0.36 (1.01)	-0.83 (1.11)		
LS Mean (SE)	-0.24 (0.29)	-0.89 (0.34)		
LS Mean Diff vs. placebo (95% CI)		-0.66 (-1.46, 0.14)		
P-value vs. placebo		0.1073		
Overall p-value for interaction		0.7510		
Baseline pre-bronchodilator percent predicted FEV1 (%) (400 mg BID only)				
< Median (68)				
Number	12	16		
Mean (SD)	-0.32 (1.13)	-0.98 (0.85)		
LS Mean (SE)	0.27 (0.32)	-0.23 (0.32)		
LS Mean Diff vs. placebo (95% CI)		-0.50 (-1.15, 0.16)		
P-value vs. placebo		0.1359		
≥ Median (68)				
Number	16	11		
Mean (SD)	-0.35 (0.97)	-0.69 (1.07)		
LS Mean (SE)	-0.26 (0.25)	-0.79 (0.33)		
LS Mean Diff vs. placebo (95% CI)		-0.53 (-1.28, 0.22)		
P-value vs. placebo		0.1642		

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Overall p-value for interaction		0.9232		
Baseline pre-bronchodilator FEV1 (L) (400 mg TID only)				
< Median (2.1955)				
Number			28	19
Mean (SD)			-0.24 (1.11)	-0.91 (0.74)
LS Mean (SE)			-0.23 (0.18)	-0.89 (0.21)
LS Mean Diff vs. placebo (95% CI)				-0.66 (-1.18, -0.15)
P-value vs. placebo				0.0120
≥ Median (2.1955)				
Number			31	29
Mean (SD)			-0.21 (0.99)	-0.76 (0.72)
LS Mean (SE)			-0.39 (0.17)	-0.83 (0.16)
LS Mean Diff vs. placebo (95% CI)				-0.44 (-0.88, -0.01)
P-value vs. placebo				0.0467
Overall p-value for interaction				0.4527
Baseline pre-bronchodilator percent predicted FEV1 group 1 (%) (400 mg TID only)				
< Median (77)				
Number			31	21
Mean (SD)			-0.14 (1.04)	-0.72 (0.70)
LS Mean (SE)			-0.23 (0.18)	-0.74 (0.22)
LS Mean Diff vs. placebo (95% CI)				-0.52 (-1.01, -0.03)
P-value vs. placebo				0.0393
≥ Median (77)				
Number			29	27
Mean (SD)			-0.32 (1.03)	-0.89 (0.75)
LS Mean (SE)			-0.38 (0.17)	-0.90 (0.16)
LS Mean Diff vs. placebo (95% CI)				-0.52 (-0.98, -0.05)
P-value vs. placebo				0.0286
Overall p-value for interaction				0.9797
Baseline pre-bronchodilator percent predicted FEV1 group 2 (%) (400 mg TID only)				
< 80				
Number			36	26
Mean (SD)			-0.13 (1.03)	-0.75 (0.73)
LS Mean (SE)			-0.21 (0.17)	-0.75 (0.19)

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
LS Mean Diff vs. placebo (95% CI)				-0.54 (-0.98, -0.10)
P-value vs. placebo				0.0165
≥ 80				
Number			24	22
Mean (SD)			-0.36 (1.04)	-0.89 (0.73)
LS Mean (SE)			-0.38 (0.18)	-0.95 (0.19)
LS Mean Diff vs. placebo (95% CI)				-0.57 (-1.08, -0.06)
P-value vs. placebo				0.0295
Overall p-value for interaction				0.9237
Baseline FEV1 reversibility (%)				
< 12				
Number	17	12	43	33
Mean (SD)	-0.14 (0.82)	-0.65 (0.88)	-0.33 (1.11)	-0.79 (0.75)
LS Mean (SE)	-0.15 (0.23)	-0.61 (0.28)	-0.41 (0.15)	-0.85 (0.17)
LS Mean Diff vs. placebo (95% CI)		-0.46 (-1.10, 0.18)		-0.45 (-0.87, -0.03)
P-value vs. placebo		0.1609		0.0375
≥ 12				
Number	9	14	10	10
Mean (SD)	-0.31 (1.06)	-1.03 (1.01)	-0.20 (0.72)	-0.94 (0.68)
LS Mean (SE)	0.12 (0.33)	-0.29 (0.35)	-0.22 (0.30)	-0.85 (0.32)
LS Mean Diff vs. placebo (95% CI)		-0.41 (-1.10, 0.28)		-0.63 (-1.36, 0.10)
P-value vs. placebo		0.2413		0.0907
Overall p-value for interaction		0.9399		0.6991
Baseline ACQ-5 score				
≤ 2				
Number	13	16	25	14
Mean (SD)	-0.15 (0.83)	-0.76 (0.96)	-0.29 (0.80)	-0.91 (0.89)
LS Mean (SE)	0.12 (0.28)	-0.60 (0.27)	-0.27 (0.18)	-0.81 (0.21)
LS Mean Diff vs. placebo (95% CI)		-0.72 (-1.32, -0.12)		-0.54 (-1.06, -0.02)
P-value vs. placebo		0.0197		0.0426
> 2				
Number	15	12	35	35
Mean (SD)	-0.49 (1.17)	-1.05 (0.89)	-0.18 (1.18)	-0.78 (0.65)
LS Mean (SE)	-0.20 (0.34)	-0.78 (0.39)	-0.34 (0.17)	-0.89 (0.17)
LS Mean Diff vs. placebo (95% CI)		-0.58 (-1.39, 0.23)		-0.55 (-0.98, -0.12)
P-value vs. placebo		0.1633		0.0118

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Overall p-value for interaction		0.8615		0.9369

LATAM: Latin America, ROW: Rest of the world

[0256] Table 48. Subgroup analysis: change from baseline in ACQ-5 score at EOT (Week 12) by baseline ICS/LABA dose level (mITT population).

ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**
Background ICS/LABA dose level at randomization		
Medium		
Number	3	3
Mean (SD)	0.00 (1.00)	-1.07 (0.70)
LS Mean (SE)	0.02 (0.94)	-0.79 (0.75)
LS Mean Diff vs. placebo (95% CI)		-0.80 (-2.49, 0.88)
P-value vs. placebo		0.3496
High		
Number	25	25
Mean (SD)	-0.38 (1.04)	-0.86 (0.96)
LS Mean (SE)	-0.12 (0.22)	-0.70 (0.23)
LS Mean Diff vs. placebo (95% CI)		-0.57 (-1.12, -0.03)
P-value vs. placebo		0.0372
Overall p-value for interaction		0.9013

LATAM: Latin America, ROW: Rest of the world

[0257] Table 49. Subgroup analysis: change from baseline in ACQ-5 score at EOT (Week 12) by baseline biomarker subgroups (mITT population).

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo BID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Baseline IgE level (IU/mL)				
< 100				
Number	8	7	24	18
Mean (SD)	-0.50 (1.22)	-0.83 (0.76)	-0.20 (0.93)	-0.93 (0.66)
LS Mean (SE)	-0.35 (0.50)	-0.63 (0.50)	-0.40 (0.37)	-1.08 (0.40)
LS Mean Diff vs. placebo (95% CI)		-0.28 (-1.44, 0.88)		-0.67 (-1.19, -0.16)
P-value vs. placebo		0.6362		0.0107
≥ 100				
Number	20	21	36	31
Mean (SD)	-0.27 (0.96)	-0.90 (1.00)	-0.24 (1.11)	-0.75 (0.76)
LS Mean (SE)	-0.24 (0.51)	-0.83 (0.48)	-0.18 (0.22)	-0.64 (0.24)

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo BID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
LS Mean Diff vs. placebo (95% CI)		-0.59 (-1.14, -0.04)		-0.46 (-0.89, -0.03)
P-value vs. placebo		0.0358		0.0366
Overall p-value for interaction		0.8951		0.5332
Baseline median IgE level (IU/mL) (400 mg BID only)				
< Median (210.8)				
Number	10	18		
Mean (SD)	-0.44 (1.09)	-0.76 (0.94)		
LS Mean (SE)	-0.14 (0.33)	-0.60 (0.26)		
LS Mean Diff vs. placebo (95% CI)		-0.46 (-1.24, 0.32)		
P-value vs. placebo		0.2488		
≥ Median (210.8)				
Number	18	10		
Mean (SD)	-0.28 (1.01)	-1.12 (0.90)		
LS Mean (SE)	-0.08 (0.24)	-0.87 (0.36)		
LS Mean Diff vs. placebo (95% CI)		-0.79 (-1.49, -0.08)		
P-value vs. placebo		0.0282		
Overall p-value for interaction		0.5416		
Baseline median IgE level (IU/mL) (400 mg TID only)				
< Median (121.85)				
Number			30	23
Mean (SD)			0.01 (1.11)	-0.95 (0.63)
LS Mean (SE)			0.02 (0.23)	-0.79 (0.23)
LS Mean Diff vs. placebo (95% CI)				-0.81 (-1.30, -0.32)
P-value vs. placebo				0.0011
≥ Median (121.85)				
Number			30	26
Mean (SD)			-0.46 (0.91)	-0.70 (0.79)
LS Mean (SE)			-0.71 (0.43)	-0.99 (0.46)
LS Mean Diff vs. placebo (95% CI)				-0.27 (-0.71, 0.16)
P-value vs. placebo				0.2121
Overall p-value for interaction				0.0955
Baseline median IgA level (mg/L) (400 mg TID only)				
< Median (2190)				
Number			32	23

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo BID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Mean (SD)			-0.06 (1.02)	-0.86 (0.68)
LS Mean (SE)			-0.23 (0.17)	-0.90 (0.19)
LS Mean Diff vs. placebo (95% CI)				-0.67 (-1.14, -0.19)
P-value vs. placebo				0.0060
≥ Median (2190)				
Number			28	26
Mean (SD)			-0.41 (1.03)	-0.78 (0.77)
LS Mean (SE)			-0.38 (0.18)	-0.80 (0.18)
LS Mean Diff vs. placebo (95% CI)				-0.41 (-0.89, 0.07)
P-value vs. placebo				0.0925
Overall p-value for interaction				0.4742
Baseline blood eosinophil level 1 (10^9/L) (400 mg BID only)				
< 0.15				
Number	6	8		
Mean (SD)	-0.80 (1.40)	-0.50 (0.99)		
LS Mean (SE)	-0.34 (0.65)	-0.57 (0.45)		
LS Mean Diff vs. placebo (95% CI)		-0.23 (-2.01, 1.56)		
P-value vs. placebo		0.7785		
≥ 0.15				
Number	22	20		
Mean (SD)	-0.21 (0.90)	-1.04 (0.88)		
LS Mean (SE)	-0.07 (0.21)	-0.85 (0.26)		
LS Mean Diff vs. placebo (95% CI)		-0.78 (-1.31, -0.24)		
P-value vs. placebo		0.0044		
Overall p-value for interaction		0.1355		
Baseline blood eosinophil level 2 (10^9/L) (400 mg BID only)				
< 0.3				
Number	17	16		
Mean (SD)	-0.52 (1.21)	-1.04 (0.92)		
LS Mean (SE)	-0.13 (0.24)	-0.81 (0.27)		
LS Mean Diff vs. placebo (95% CI)		-0.68 (-1.33, -0.03)		
P-value vs. placebo		0.0399		
≥ 0.3				
Number	11	12		
Mean (SD)	-0.05 (0.57)	-0.68 (0.94)		
LS Mean (SE)	-0.16 (0.35)	-0.72 (0.35)		

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo BID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
LS Mean Diff vs. placebo (95% CI)		-0.55 (-1.22, 0.12)		
P-value vs. placebo		0.1049		
Overall p-value for interaction		0.8601		
Baseline blood eosinophil level 1 (10^9/L) (400 mg TID only)				
< 0.15				
Number			27	21
Mean (SD)			-0.38 (0.84)	-0.85 (0.80)
LS Mean (SE)			-0.49 (0.16)	-0.84 (0.17)
LS Mean Diff vs. placebo (95% CI)				-0.35 (-0.79, 0.09)
P-value vs. placebo				0.1217
≥ 0.15 - < 0.3				
Number			18	13
Mean (SD)			-0.02 (1.32)	-0.78 (0.66)
LS Mean (SE)			0.03 (0.27)	-0.81 (0.29)
LS Mean Diff vs. placebo (95% CI)				-0.83 (-1.55, -0.12)
P-value vs. placebo				0.0229
≥ 0.3				
Number			15	15
Mean (SD)			-0.19 (0.98)	-0.80 (0.70)
LS Mean (SE)			-0.26 (0.30)	-0.91 (0.27)
LS Mean Diff vs. placebo (95% CI)				-0.65 (-1.29, -0.01)
P-value vs. placebo				0.0451
Overall p-value for interaction				0.5667
Baseline blood eosinophil level 2 (10^9/L) (400 mg TID only)				
< 0.3				
Number			45	34
Mean (SD)			-0.24 (1.06)	-0.82 (0.74)
LS Mean (SE)			-0.34 (0.15)	-0.86 (0.15)
LS Mean Diff vs. placebo (95% CI)				-0.52 (-0.92, -0.12)
P-value vs. placebo				0.0104
≥ 0.3				
Number			15	15
Mean (SD)			-0.19 (0.98)	-0.80 (0.70)
LS Mean (SE)			-0.26 (0.30)	-0.91 (0.27)
LS Mean Diff vs. placebo (95% CI)				-0.65 (-1.29, -0.01)

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo BID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
P-value vs. placebo				0.0451
Overall p-value for interaction				0.7504
Baseline FeNO level 1 (ppb)				
< 25				
Number	14	11	37	30
Mean (SD)	-0.39 (1.12)	-1.02 (0.80)	-0.26 (0.97)	-0.84 (0.71)
LS Mean (SE)	-0.01 (0.32)	-0.81 (0.32)	-0.43 (0.15)	-0.93 (0.15)
LS Mean Diff vs. placebo (95% CI)		-0.80 (-1.53, -0.06)		-0.51 (-0.89, -0.12)
P-value vs. placebo		0.0344		0.0101
≥ 25				
Number	14	17	19	17
Mean (SD)	-0.29 (0.95)	-0.80 (1.02)	-0.31 (1.18)	-0.84 (0.78)
LS Mean (SE)	-0.15 (0.26)	-0.62 (0.30)	-0.29 (0.27)	-0.82 (0.26)
LS Mean Diff vs. placebo (95% CI)		-0.47 (-1.15, 0.22)		-0.53 (-1.19, 0.13)
P-value vs. placebo		0.1826		0.1127
Overall p-value for interaction		0.5887		0.9211
Baseline FeNO level 2 (ppb)				
< 35				
Number	17	20	44	35
Mean (SD)	-0.36 (1.05)	-0.91 (0.86)	-0.25 (1.08)	-0.81 (0.72)
LS Mean (SE)	0.11 (0.27)	-0.64 (0.24)	-0.36 (0.15)	-0.85 (0.15)
LS Mean Diff vs. placebo (95% CI)		-0.75 (-1.32, -0.19)		-0.49 (-0.89, -0.10)
P-value vs. placebo		0.0089		0.0141
≥ 35				
Number	11	8	12	12
Mean (SD)	-0.29 (1.02)	-0.83 (1.15)	-0.37 (0.90)	-0.92 (0.77)
LS Mean (SE)	-0.26 (0.32)	-0.67 (0.46)	-0.38 (0.36)	-0.89 (0.32)
LS Mean Diff vs. placebo (95% CI)		-0.41 (-1.47, 0.66)		-0.51 (-1.24, 0.23)
P-value vs. placebo		0.4551		0.1744
Overall p-value for interaction		0.4819		0.8970

LATAM: Latin America, ROW: Rest of the world

[0258] Table 50. Subgroup analysis: change from baseline in ACQ-5 score at EOT (Week 12) in the baseline low EOS and low FeNO subgroup (mITT population).

	400 mg BID cohort		400 mg TID cohort	
ACQ-5	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo BID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Baseline blood eosinophil (10^9/L) and FeNO (ppb)				
Low EOS (< 0.15) and low FeNO (< 25)				
Number	4	3	21	14
Mean (SD)	-0.50 (1.70)	-0.60 (1.00)	-0.30 (0.86)	-1.04 (0.80)
LS Mean (SE)	0.83 (1.42)	-1.61 (1.12)	-0.41 (0.18)	-1.02 (0.21)
LS Mean Diff vs. placebo (95% CI)		-2.44 (-11.51, 6.64)		-0.61 (-1.13, -0.09)
P-value vs. placebo		0.3675		0.0214
All others				
Number	24	25	35	33
Mean (SD)	-0.31 (0.92)	-0.92 (0.94)	-0.27 (1.14)	-0.75 (0.68)
LS Mean (SE)	-0.09 (0.20)	-0.68 (0.23)	-0.26 (0.17)	-0.76 (0.17)
LS Mean Diff vs. placebo (95% CI)		-0.59 (-1.08, -0.11)		-0.50 (-0.95, -0.06)
P-value vs. placebo		0.0172		0.0267
Overall p-value for interaction		0.9709		0.8721

LATAM: Latin America, ROW: Rest of the world

AQLQ and AQLQ(S)

[0259] Rilzabrutinib treatment led to significant improvements in AQLQ and AQLQ(S) (**Figure 16** and **Tables 51-57**). Notably, 51.7% of participants in the 400 mg rilzabrutinib BID cohort and 54.7% of participants in the 400 mg rilzabrutinib TID cohort—but only 34.5% of participants in the placebo BID cohort and 40.3% of participants in the placebo TID cohort—achieved a response, defined as an improvement of at least 0.5 from baseline at Week 12 (p=0.0281 and p=0.0456, respectively). Clinically important results were observed as early as Week 4 and sustained through Week 12 (**Tables 51** and **52**).

[0260] Table 51. Responder analysis for change from baseline in AQLQ global score at Week 12 (mITT population).

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Week 12				
Number (observed/LOCF imputed)	29 (20/9)	29 (24/5)	62 (52/10)	53 (50/3)

	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Responder (observed/LOCF imputed)	10 (34.5) (7/3)	15 (51.7) (14/1)	25 (40.3) (24/1)	29 (54.7) (28/1)
Non-responder (observed/LOCF imputed)	19 (65.5) (13/6)	14 (48.3) (10/4)	37 (59.7) (28/9)	24 (45.3) (22/2)
Responder (including multiply imputed)	10.6 (33.0)	16.6 (51.7)	26.9 (39.6)	32.9 (51.4)
OR vs. placebo (95% CI)		4.89 (1.19, 20.17)		2.23 (1.02, 4.89)
P-value vs. placebo		0.0281		0.0456

LATAM: Latin America, ROW: Rest of the world

[0261] Table 52. Change from baseline in AQLQ(S) over time (mITT population).

	400 mg BID cohort		400 mg TID cohort	
AQLQ(S)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Global score				
Baseline				
Number	31	32	67	62
Mean (SD)	4.67 (1.07)	4.91 (1.04)	4.68 (0.83)	4.96 (0.71)
Median	4.69	5.19	4.56	4.94
Q1 ; Q3	4.13 ; 5.59	4.31 ; 5.64	4.00 ; 5.41	4.38 ; 5.44
Min ; Max	2.1 ; 6.2	2.4 ; 6.4	2.8 ; 6.3	3.7 ; 6.6
Week 4				
Number (observed/LOCF imputed)	30 (28/2)	31 (30/1)	65 (64/1)	61 (61/0)
Mean (SD)	4.67 (1.17)	5.63 (0.82)	4.90 (0.91)	5.16 (0.97)
Median	4.69	5.69	4.84	5.03
Q1 ; Q3	4.03 ; 5.50	5.34 ; 6.28	4.22 ; 5.59	4.44 ; 6.03
Min ; Max	1.9 ; 6.7	3.1 ; 6.7	2.2 ; 6.7	2.5 ; 6.9
Change from baseline				
Number (observed/LOCF imputed)	29 (27/2)	31 (30/1)	65 (64/1)	60 (60/0)
Mean (SD)	-0.03 (1.35)	0.73 (0.93)	0.19 (0.72)	0.19 (0.89)
Median	0.00	0.69	0.28	0.13
Q1 ; Q3	-0.50 ; 0.63	0.09 ; 1.09	-0.19 ; 0.59	-0.25 ; 0.67
Min ; Max	-3.7 ; 2.2	-0.8 ; 3.2	-1.9 ; 1.7	-2.2 ; 2.7
LS Mean (SE)	-0.04 (0.21)	0.80 (0.21)	0.24 (0.10)	0.33 (0.11)
LS Mean Diff vs. placebo (95% CI)		0.84 (0.34, 1.34)		0.09 (-0.18, 0.36)
P-value vs. placebo		0.0010		0.4929
Week 8				

AQLQ(S)	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)
Number (observed/LOCF imputed)	31 (28/3)	31 (27/4)	65 (62/3)	59 (56/3)
Mean (SD)	4.94 (1.14)	5.79 (0.75)	5.02 (0.98)	5.27 (0.88)
Median	5.06	5.88	5.13	5.06
Q1 ; Q3	3.88 ; 6.00	5.53 ; 6.28	4.06 ; 5.81	4.59 ; 6.16
Min ; Max	2.8 ; 6.8	4.0 ; 7.0	2.6 ; 7.0	3.5 ; 6.9
Change from baseline				
Number (observed/LOCF imputed)	30 (27/3)	31 (27/4)	65 (62/3)	58 (55/3)
Mean (SD)	0.22 (1.06)	0.90 (0.85)	0.30 (0.86)	0.29 (0.74)
Median	0.33	0.63	0.34	0.34
Q1 ; Q3	-0.19 ; 0.88	0.22 ; 1.31	-0.25 ; 1.00	-0.09 ; 0.75
Min ; Max	-3.0 ; 1.9	-0.4 ; 2.8	-1.6 ; 2.6	-1.3 ; 2.0
LS Mean (SE)	0.13 (0.16)	0.92 (0.17)	0.32 (0.10)	0.42 (0.11)
LS Mean Diff vs. placebo (95% CI)		0.79 (0.39, 1.20)		0.10 (-0.18, 0.37)
P-value vs. placebo		0.0001		0.4993
Week 12				
Number (observed/LOCF imputed)	30 (21/9)	29 (24/5)	62 (52/10)	54 (51/3)
Mean (SD)	4.99 (1.17)	5.75 (0.84)	4.99 (1.06)	5.41 (0.88)
Median	5.05	5.72	5.06	5.23
Q1 ; Q3	3.88 ; 5.97	5.41 ; 6.34	4.13 ; 5.88	4.91 ; 6.13
Min ; Max	2.9 ; 7.0	4.0 ; 7.0	1.4 ; 6.7	3.1 ; 7.0
Change from baseline				
Number (observed/LOCF imputed)	29 (20/9)	29 (24/5)	62 (52/10)	53 (50/3)
Mean (SD)	0.29 (1.15)	0.84 (0.99)	0.26 (0.90)	0.46 (0.86)
Median	0.22	0.69	0.30	0.53
Q1 ; Q3	-0.13 ; 1.25	0.16 ; 1.38	-0.41 ; 0.78	0.00 ; 1.00
Min ; Max	-2.5 ; 2.3	-0.7 ; 3.1	-1.7 ; 3.1	-1.9 ; 2.6
LS Mean (SE)	0.10 (0.18)	0.82 (0.20)	0.28 (0.12)	0.57 (0.12)
LS Mean Diff vs. placebo (95% CI)		0.72 (0.25, 1.18)		0.29 (-0.01, 0.60)
P-value vs. placebo		0.0025		0.0620
Symptoms score				
Baseline				
Number	31	32	67	62
Mean (SD)	4.59 (1.05)	5.05 (1.05)	4.70 (0.80)	4.97 (0.73)
Median	4.75	5.21	4.75	4.83
Q1 ; Q3	4.25 ; 5.25	4.42 ; 5.83	4.08 ; 5.33	4.33 ; 5.42
Min ; Max	1.7 ; 6.0	2.6 ; 6.6	3.0 ; 6.8	3.8 ; 6.6
Week 4				
Number (observed/LOCF imputed)	30 (28/2)	31 (30/1)	65 (64/1)	61 (61/0)

	400 mg BID cohort		400 mg TID cohort	
AQLQ(S)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Mean (SD)	4.82 (1.09)	5.83 (0.72)	4.92 (0.90)	5.19 (1.00)
Median	4.88	6.00	4.92	5.08
Q1 ; Q3	4.00 ; 5.50	5.50 ; 6.33	4.42 ; 5.58	4.42 ; 6.00
Min ; Max	1.8 ; 6.8	3.7 ; 6.7	2.2 ; 6.6	2.4 ; 7.0
Change from baseline				
Number (observed/LOCF imputed)	29 (27/2)	31 (30/1)	65 (64/1)	60 (60/0)
Mean (SD)	0.15 (1.27)	0.80 (0.90)	0.19 (0.77)	0.22 (0.98)
Median	0.08	0.75	0.25	0.25
Q1 ; Q3	-0.25 ; 0.75	0.08 ; 1.25	-0.25 ; 0.67	-0.29 ; 0.67
Min ; Max	-3.2 ; 2.4	-0.8 ; 3.3	-1.8 ; 1.7	-2.3 ; 2.8
LS Mean (SE)	0.06 (0.18)	0.92 (0.19)	0.22 (0.11)	0.38 (0.11)
LS Mean Diff vs. placebo (95% CI)		0.86 (0.41, 1.32)		0.15 (-0.14, 0.44)
P-value vs. placebo		0.0002		0.3018
Week 8				
Number (observed/LOCF imputed)	31 (28/3)	31 (27/4)	65 (62/3)	59 (56/3)
Mean (SD)	5.05 (1.06)	5.93 (0.79)	5.02 (1.03)	5.29 (0.84)
Median	5.08	6.00	5.25	5.17
Q1 ; Q3	4.25 ; 5.83	5.67 ; 6.50	4.17 ; 5.75	4.58 ; 6.08
Min ; Max	2.3 ; 6.9	3.5 ; 6.9	2.6 ; 7.0	3.7 ; 7.0
Change from baseline				
Number (observed/LOCF imputed)	30 (27/3)	31 (27/4)	65 (62/3)	58 (55/3)
Mean (SD)	0.38 (1.06)	0.91 (0.94)	0.29 (0.96)	0.29 (0.77)
Median	0.13	0.83	0.17	0.38
Q1 ; Q3	-0.08 ; 0.83	0.25 ; 1.25	-0.42 ; 1.08	-0.08 ; 0.75
Min ; Max	-1.8 ; 2.6	-0.6 ; 3.0	-1.6 ; 2.3	-1.8 ; 2.0
LS Mean (SE)	0.23 (0.17)	0.99 (0.18)	0.31 (0.11)	0.44 (0.12)
LS Mean Diff vs. placebo (95% CI)		0.76 (0.35, 1.18)		0.13 (-0.16, 0.43)
P-value vs. placebo		0.0003		0.3792
Week 12				
Number (observed/LOCF imputed)	30 (21/9)	29 (24/5)	62 (52/10)	54 (51/3)
Mean (SD)	5.13 (1.05)	5.87 (0.85)	4.97 (1.19)	5.41 (0.83)
Median	5.08	5.92	5.00	5.25
Q1 ; Q3	4.67 ; 5.83	5.50 ; 6.50	4.42 ; 5.92	4.83 ; 6.08
Min ; Max	3.0 ; 7.0	3.8 ; 7.0	1.0 ; 6.8	3.7 ; 7.0
Change from baseline				
Number (observed/LOCF imputed)	29 (20/9)	29 (24/5)	62 (52/10)	53 (50/3)
Mean (SD)	0.47 (1.07)	0.87 (1.12)	0.21 (1.08)	0.44 (0.92)
Median	0.33	0.83	0.08	0.58

	400 mg BID cohort		400 mg TID cohort	
AQLQ(S)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Q1 ; Q3	-0.08 ; 1.17	0.08 ; 1.58	-0.58 ; 0.92	0.00 ; 0.92
Min ; Max	-1.8 ; 2.6	-1.3 ; 3.3	-2.3 ; 3.2	-2.0 ; 2.8
LS Mean (SE)	0.17 (0.18)	0.84 (0.19)	0.26 (0.13)	0.59 (0.14)
LS Mean Diff vs. placebo (95% CI)		0.67 (0.22, 1.11)		0.34 (-0.01, 0.68)
P-value vs. placebo		0.0032		0.0542
Activity limitation score				
Baseline				
Number	31	32	67	62
Mean (SD)	4.74 (1.13)	4.78 (1.12)	4.70 (0.83)	4.99 (0.78)
Median	4.73	5.00	4.64	4.91
Q1 ; Q3	4.09 ; 5.73	4.09 ; 5.55	4.00 ; 5.36	4.45 ; 5.45
Min ; Max	2.4 ; 6.6	1.9 ; 6.5	3.0 ; 6.6	3.4 ; 6.7
Week 4				
Number (observed/LOCF imputed)	30 (28/2)	31 (30/1)	65 (64/1)	61 (61/0)
Mean (SD)	4.70 (1.24)	5.48 (0.88)	4.93 (0.97)	5.15 (0.95)
Median	4.68	5.55	5.00	5.18
Q1 ; Q3	4.00 ; 5.45	5.09 ; 6.18	4.27 ; 5.64	4.45 ; 6.00
Min ; Max	2.5 ; 7.0	3.2 ; 7.0	2.5 ; 6.7	2.6 ; 6.9
Change from baseline				
Number (observed/LOCF imputed)	29 (27/2)	31 (30/1)	65 (64/1)	60 (60/0)
Mean (SD)	-0.07 (1.21)	0.73 (0.98)	0.20 (0.80)	0.16 (0.89)
Median	0.00	0.55	0.27	0.09
Q1 ; Q3	-0.64 ; 0.55	0.00 ; 1.18	-0.18 ; 0.64	-0.41 ; 0.59
Min ; Max	-3.2 ; 2.1	-1.1 ; 3.0	-2.2 ; 1.9	-2.0 ; 2.9
LS Mean (SE)	-0.03 (0.20)	0.72 (0.21)	0.26 (0.10)	0.34 (0.11)
LS Mean Diff vs. placebo (95% CI)		0.75 (0.26, 1.24)		0.08 (-0.20, 0.35)
P-value vs. placebo		0.0029		0.5846
Week 8				
Number (observed/LOCF imputed)	31 (28/3)	31 (27/4)	65 (62/3)	59 (56/3)
Mean (SD)	4.96 (1.22)	5.72 (0.81)	5.05 (0.94)	5.28 (0.90)
Median	5.09	5.91	5.09	5.27
Q1 ; Q3	3.91 ; 6.27	5.09 ; 6.18	4.18 ; 5.82	4.64 ; 6.00
Min ; Max	2.6 ; 6.9	3.9 ; 7.0	3.0 ; 7.0	3.5 ; 6.9
Change from baseline				
Number (observed/LOCF imputed)	30 (27/3)	31 (27/4)	65 (62/3)	58 (55/3)
Mean (SD)	0.17 (0.97)	0.96 (0.92)	0.30 (0.86)	0.29 (0.83)
Median	0.18	0.82	0.36	0.36
Q1 ; Q3	-0.18 ; 0.73	0.18 ; 1.55	-0.18 ; 0.91	-0.27 ; 0.91
Min ; Max	-3.1 ; 1.5	-0.4 ; 2.8	-1.8 ; 2.9	-1.4 ; 2.2

	400 mg BID cohort		400 mg TID cohort	
AQLQ(S)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
LS Mean (SE)	0.09 (0.17)	0.89 (0.17)	0.32 (0.11)	0.42 (0.11)
LS Mean Diff vs. placebo (95% CI)		0.80 (0.39, 1.21)		0.10 (-0.18, 0.38)
P-value vs. placebo		0.0001		0.4877
Week 12				
Number (observed/LOCF imputed)	30 (21/9)	29 (24/5)	62 (52/10)	54 (51/3)
Mean (SD)	4.90 (1.31)	5.66 (0.96)	5.03 (1.00)	5.45 (0.86)
Median	4.95	5.82	4.95	5.36
Q1 ; Q3	3.82 ; 6.00	5.18 ; 6.36	4.18 ; 5.82	4.91 ; 6.18
Min ; Max	2.7 ; 7.0	3.8 ; 7.0	2.1 ; 6.6	3.1 ; 7.0
Change from baseline				
Number (observed/LOCF imputed)	29 (20/9)	29 (24/5)	62 (52/10)	53 (50/3)
Mean (SD)	0.14 (1.14)	0.85 (0.96)	0.29 (0.82)	0.50 (0.86)
Median	0.00	0.45	0.27	0.55
Q1 ; Q3	-0.18 ; 0.91	0.18 ; 1.27	-0.27 ; 0.91	-0.18 ; 1.09
Min ; Max	-3.0 ; 2.3	-0.7 ; 2.9	-1.8 ; 2.8	-1.3 ; 2.8
LS Mean (SE)	-0.01 (0.20)	0.77 (0.22)	0.31 (0.11)	0.62 (0.11)
LS Mean Diff vs. placebo (95% CI)		0.78 (0.28, 1.28)		0.31 (0.02, 0.60)
P-value vs. placebo		0.0023		0.0339
Emotional function score				
Baseline				
Number	31	32	67	62
Mean (SD)	4.70 (1.71)	5.21 (1.26)	4.87 (1.14)	5.15 (1.14)
Median	5.40	5.30	4.80	5.20
Q1 ; Q3	3.80 ; 5.80	4.10 ; 6.50	4.20 ; 5.60	4.40 ; 6.00
Min ; Max	1.2 ; 7.0	2.0 ; 7.0	1.8 ; 6.8	1.2 ; 7.0
Week 4				
Number (observed/LOCF imputed)	30 (28/2)	31 (30/1)	65 (64/1)	61 (61/0)
Mean (SD)	4.51 (1.71)	5.85 (1.36)	5.02 (1.12)	5.37 (1.23)
Median	4.70	6.40	5.00	5.40
Q1 ; Q3	3.60 ; 5.80	5.00 ; 7.00	4.40 ; 5.80	4.80 ; 6.40
Min ; Max	1.0 ; 7.0	1.6 ; 7.0	2.0 ; 7.0	1.2 ; 7.0
Change from baseline				
Number (observed/LOCF imputed)	29 (27/2)	31 (30/1)	65 (64/1)	60 (60/0)
Mean (SD)	-0.23 (1.80)	0.61 (1.24)	0.10 (0.99)	0.22 (1.08)
Median	0.20	0.40	0.20	0.20
Q1 ; Q3	-0.60 ; 0.60	-0.40 ; 1.60	-0.40 ; 0.80	-0.40 ; 0.80
Min ; Max	-5.2 ; 2.8	-2.4 ; 3.0	-2.4 ; 3.0	-2.6 ; 2.8
LS Mean (SE)	-0.25 (0.29)	0.77 (0.31)	0.14 (0.13)	0.35 (0.13)

	400 mg BID cohort		400 mg TID cohort	
AQLQ(S)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
LS Mean Diff vs. placebo (95% CI)		1.02 (0.30, 1.74)		0.21 (-0.12, 0.54)
P-value vs. placebo		0.0058		0.2202
Week 8				
Number (observed/LOCF imputed)	31 (28/3)	31 (27/4)	65 (62/3)	59 (56/3)
Mean (SD)	4.92 (1.63)	6.12 (1.01)	5.25 (1.21)	5.52 (1.11)
Median	5.20	6.20	5.60	5.40
Q1 ; Q3	3.40 ; 6.20	5.80 ; 7.00	4.40 ; 6.20	4.80 ; 6.60
Min ; Max	1.0 ; 7.0	2.8 ; 7.0	2.0 ; 7.0	1.2 ; 7.0
Change from baseline				
Number (observed/LOCF imputed)	30 (27/3)	31 (27/4)	65 (62/3)	58 (55/3)
Mean (SD)	0.15 (1.34)	0.87 (1.17)	0.33 (1.09)	0.37 (0.87)
Median	0.20	0.60	0.20	0.40
Q1 ; Q3	-0.40 ; 1.00	0.00 ; 1.40	-0.60 ; 1.20	0.00 ; 0.80
Min ; Max	-3.8 ; 2.2	-1.2 ; 4.2	-1.8 ; 3.0	-1.8 ; 2.6
LS Mean (SE)	0.08 (0.23)	1.06 (0.24)	0.38 (0.12)	0.51 (0.13)
LS Mean Diff vs. placebo (95% CI)		0.98 (0.42, 1.54)		0.13 (-0.20, 0.45)
P-value vs. placebo		0.0006		0.4378
Week 12				
Number (observed/LOCF imputed)	30 (21/9)	29 (24/5)	62 (52/10)	54 (51/3)
Mean (SD)	5.14 (1.55)	5.96 (1.16)	5.12 (1.42)	5.57 (1.28)
Median	5.40	6.20	5.10	5.60
Q1 ; Q3	4.00 ; 6.20	5.20 ; 7.00	4.40 ; 6.40	5.20 ; 6.60
Min ; Max	1.0 ; 7.0	3.2 ; 7.0	1.0 ; 7.0	1.2 ; 7.0
Change from baseline				
Number (observed/LOCF imputed)	29 (20/9)	29 (24/5)	62 (52/10)	53 (50/3)
Mean (SD)	0.37 (1.62)	0.72 (1.14)	0.19 (1.20)	0.43 (1.04)
Median	0.40	0.40	0.20	0.40
Q1 ; Q3	0.00 ; 1.20	0.00 ; 1.40	-0.40 ; 1.00	0.00 ; 1.00
Min ; Max	-3.8 ; 4.8	-0.8 ; 3.4	-3.8 ; 3.4	-2.4 ; 2.8
LS Mean (SE)	0.23 (0.24)	0.97 (0.27)	0.21 (0.15)	0.53 (0.16)
LS Mean Diff vs. placebo (95% CI)		0.74 (0.12, 1.36)		0.32 (-0.08, 0.72)
P-value vs. placebo		0.0195		0.1134
Environmental stimuli score				
Baseline				
Number	31	32	67	62
Mean (SD)	4.62 (1.46)	4.43 (1.64)	4.31 (1.16)	4.64 (1.06)
Median	4.75	4.75	4.25	4.75
Q1 ; Q3	3.75 ; 5.75	3.63 ; 5.75	3.50 ; 5.25	4.00 ; 5.25

AQLQ(S)	400 mg BID cohort		400 mg TID cohort	
	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)
Min ; Max	1.8 ; 7.0	1.0 ; 7.0	1.0 ; 7.0	1.0 ; 7.0
Week 4				
Number (observed/LOCF imputed)	30 (28/2)	31 (30/1)	65 (64/1)	61 (61/0)
Mean (SD)	4.37 (1.62)	5.13 (1.26)	4.62 (1.25)	4.78 (1.20)
Median	4.88	5.25	4.75	4.75
Q1 ; Q3	3.00 ; 5.75	4.25 ; 6.00	3.75 ; 5.50	4.00 ; 5.75
Min ; Max	1.3 ; 6.5	2.0 ; 7.0	1.0 ; 7.0	1.8 ; 7.0
Change from baseline				
Number (observed/LOCF imputed)	29 (27/2)	31 (30/1)	65 (64/1)	60 (60/0)
Mean (SD)	-0.22 (2.04)	0.67 (1.52)	0.28 (0.97)	0.12 (1.09)
Median	0.00	0.50	0.00	0.25
Q1 ; Q3	-0.50 ; 1.25	-0.75 ; 1.75	-0.25 ; 0.75	-0.50 ; 0.63
Min ; Max	-5.8 ; 2.5	-2.3 ; 4.8	-2.5 ; 2.8	-2.5 ; 2.3
LS Mean (SE)	-0.15 (0.30)	0.60 (0.31)	0.33 (0.12)	0.30 (0.13)
LS Mean Diff vs. placebo (95% CI)		0.76 (0.02, 1.49)		-0.03 (-0.37, 0.30)
P-value vs. placebo		0.0432		0.8468
Week 8				
Number (observed/LOCF imputed)	31 (28/3)	31 (27/4)	65 (62/3)	59 (56/3)
Mean (SD)	4.60 (1.53)	5.19 (1.24)	4.66 (1.34)	4.90 (1.29)
Median	5.25	5.25	5.00	4.75
Q1 ; Q3	3.75 ; 5.75	4.50 ; 6.00	3.75 ; 5.75	4.00 ; 6.00
Min ; Max	1.3 ; 6.8	2.0 ; 7.0	1.0 ; 7.0	2.0 ; 7.0
Change from baseline				
Number (observed/LOCF imputed)	30 (27/3)	31 (27/4)	65 (62/3)	58 (55/3)
Mean (SD)	0.01 (1.65)	0.73 (1.57)	0.33 (1.21)	0.24 (1.15)
Median	0.25	0.50	0.00	0.25
Q1 ; Q3	-0.50 ; 1.25	-0.25 ; 1.25	-0.25 ; 1.00	-0.50 ; 1.00
Min ; Max	-5.8 ; 2.0	-1.8 ; 4.8	-2.8 ; 3.8	-2.8 ; 2.8
LS Mean (SE)	-0.02 (0.27)	0.66 (0.28)	0.29 (0.15)	0.36 (0.16)
LS Mean Diff vs. placebo (95% CI)		0.68 (0.03, 1.33)		0.06 (-0.34, 0.47)
P-value vs. placebo		0.0394		0.7524
Week 12				
Number (observed/LOCF imputed)	30 (21/9)	29 (24/5)	62 (52/10)	54 (51/3)
Mean (SD)	4.66 (1.66)	5.34 (1.20)	4.76 (1.35)	5.08 (1.27)
Median	4.88	5.25	5.00	5.00
Q1 ; Q3	3.75 ; 6.00	5.00 ; 6.25	3.75 ; 5.75	4.50 ; 5.75
Min ; Max	1.0 ; 7.0	2.0 ; 7.0	1.0 ; 7.0	1.0 ; 7.0

	400 mg BID cohort		400 mg TID cohort	
AQLQ(S)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Change from baseline				
Number (observed/LOCF imputed)	29 (20/9)	29 (24/5)	62 (52/10)	53 (50/3)
Mean (SD)	0.09 (1.71)	0.87 (1.65)	0.40 (1.10)	0.46 (1.18)
Median	0.25	0.50	0.25	0.50
Q1 ; Q3	-0.50 ; 1.25	0.00 ; 1.75	-0.25 ; 1.00	0.00 ; 1.25
Min ; Max	-5.5 ; 2.3	-2.0 ; 5.3	-2.0 ; 3.0	-3.3 ; 2.5
LS Mean (SE)	-0.08 (0.28)	0.70 (0.31)	0.37 (0.15)	0.54 (0.16)
LS Mean Diff vs. placebo (95% CI)		0.78 (0.06, 1.49)		0.17 (-0.23, 0.57)
P-value vs. placebo		0.0331		0.4016

[0262] Table 53. Subgroup analysis: change from baseline in AQLQ global score at EOT (Week 12) by demographics subgroups (mITT population).

	400 mg BID cohort		400 mg TID cohort	
AQLQ global score	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Age group 1 (years)				
< 45				
Number	10	10	29	23
Mean (SD)	0.80 (0.76)	0.62 (0.82)	0.12 (1.03)	0.53 (0.64)
LS Mean (SE)	0.66 (0.23)	0.86 (0.26)	0.26 (0.16)	0.69 (0.17)
LS Mean Diff vs. placebo (95% CI)		0.20 (-0.36, 0.76)		0.43 (0.00, 0.85)
P-value vs. placebo		0.4823		0.0494
≥ 45				
Number	19	19	33	30
Mean (SD)	0.03 (1.25)	0.95 (1.07)	0.37 (0.76)	0.41 (1.01)
LS Mean (SE)	-0.16 (0.22)	0.89 (0.25)	0.32 (0.16)	0.47 (0.18)
LS Mean Diff vs. placebo (95% CI)		1.04 (0.47, 1.62)		0.15 (-0.29, 0.59)
P-value vs. placebo		0.0004		0.5139
Overall p-value for interaction		0.0607		0.5248
Gender				
Male				
Number	7	13	27	23
Mean (SD)	0.31 (0.58)	0.97 (0.88)	0.17 (0.82)	0.40 (0.92)
LS Mean (SE)	0.32 (0.28)	0.73 (0.30)	0.26 (0.17)	0.41 (0.18)
LS Mean Diff vs. placebo (95% CI)		0.41 (-0.46, 1.28)		0.15 (-0.31, 0.60)
P-value vs. placebo		0.3547		0.5238
Female				
Number	22	16	35	30

	400 mg BID cohort		400 mg TID cohort	
AQLQ global score	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Mean (SD)	0.29 (1.30)	0.74 (1.09)	0.32 (0.96)	0.51 (0.83)
LS Mean (SE)	0.02 (0.27)	0.74 (0.27)	0.33 (0.16)	0.66 (0.17)
LS Mean Diff vs. placebo (95% CI)		0.73 (0.11, 1.35)		0.32 (-0.11, 0.75)
P-value vs. placebo		0.0220		0.1394
Overall p-value for interaction		0.6030		0.5902
Baseline weight group (kg)				
< 60				
Number	4	3	10	2
Mean (SD)	-0.12 (1.31)	0.95 (1.45)	0.58 (0.79)	0.78 (0.40)
LS Mean (SE)	-0.81 (0.11)	0.82 (0.16)	0.67 (0.29)	0.59 (0.63)
LS Mean Diff vs. placebo (95% CI)		1.63 (0.98, 2.28)		-0.08 (-1.53, 1.37)
P-value vs. placebo		0.0084		0.9112
≥ 60 - < 90				
Number	22	20	37	32
Mean (SD)	0.26 (1.17)	0.87 (0.91)	0.23 (0.98)	0.56 (0.86)
LS Mean (SE)	0.06 (0.22)	0.77 (0.24)	0.25 (0.16)	0.66 (0.17)
LS Mean Diff vs. placebo (95% CI)		0.70 (0.17, 1.23)		0.41 (-0.02, 0.84)
P-value vs. placebo		0.0092		0.0612
≥ 90				
Number	3	6	15	19
Mean (SD)	1.09 (0.62)	0.70 (1.21)	0.11 (0.73)	0.26 (0.89)
LS Mean (SE)	1.06 (0.70)	0.80 (1.03)	0.15 (0.21)	0.32 (0.18)
LS Mean Diff vs. placebo (95% CI)		-0.26 (-3.62, 3.10)		0.17 (-0.34, 0.68)
P-value vs. placebo		0.8398		0.5090
Overall p-value for interaction		0.4319		0.7466
Baseline BMI group (kg/m^2)				
< 25				
Number	6	8	20	8
Mean (SD)	0.09 (1.08)	1.12 (0.99)	0.24 (0.88)	0.65 (0.74)
LS Mean (SE)	-0.45 (0.56)	0.55 (0.62)	0.42 (0.19)	0.98 (0.29)
LS Mean Diff vs. placebo (95% CI)		1.00 (-0.23, 2.22)		0.56 (-0.07, 1.18)
P-value vs. placebo		0.0991		0.0813
≥ 25 - < 30				
Number	15	13	25	26
Mean (SD)	0.13 (1.24)	0.61 (0.73)	0.25 (1.05)	0.75 (0.71)
LS Mean (SE)	0.02 (0.25)	0.69 (0.29)	0.48 (0.16)	0.96 (0.16)
LS Mean Diff vs. placebo (95% CI)		0.67 (-0.05, 1.39)		0.47 (0.07, 0.87)

	400 mg BID cohort		400 mg TID cohort	
AQLQ global score	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
P-value vs. placebo		0.0679		0.0210
≥ 30				
Number	8	8	17	19
Mean (SD)	0.75 (1.03)	0.93 (1.36)	0.28 (0.70)	0.00 (0.94)
LS Mean (SE)	0.56 (0.46)	1.30 (0.45)	0.20 (0.21)	0.19 (0.20)
LS Mean Diff vs. placebo (95% CI)		0.73 (-0.21, 1.68)		-0.01 (-0.58, 0.56)
P-value vs. placebo		0.1287		0.9701
Overall p-value for interaction		0.9298		0.3404
Region				
Eastern Europe				
Number	4	2	44	35
Mean (SD)	-0.04 (0.34)	-0.19 (0.66)	0.08 (0.91)	0.46 (0.68)
LS Mean (SE)	-0.03 (0.30)	0.04 (0.53)	0.06 (0.11)	0.48 (0.12)
LS Mean Diff vs. placebo (95% CI)		0.08 (-1.12, 1.28)		0.43 (0.10, 0.76)
P-value vs. placebo		0.9007		0.0111
Latin America				
Number	22	24	16	16
Mean (SD)	0.35 (1.29)	0.98 (0.96)	0.83 (0.51)	0.44 (1.22)
LS Mean (SE)	0.30 (0.20)	1.16 (0.20)	0.74 (0.28)	0.52 (0.28)
LS Mean Diff vs. placebo (95% CI)		0.87 (0.36, 1.38)		-0.22 (-0.83, 0.39)
P-value vs. placebo		0.0009		0.4745
Western Countries				
Number	1	2	1	2
Mean (SD)	1.25 (NC)	0.44 (1.64)	-1.44 (NC)	0.78 (0.75)
LS Mean (SE)	NC (NC)	NC (NC)	NC (NC)	NC (NC)
LS Mean Diff vs. placebo (95% CI)		NC (NC, NC)		NC (NC, NC)
P-value vs. placebo		NC		NC
APAC				
Number	2	1	1	0
Mean (SD)	-0.11 (0.60)	0.22 (NC)	0.72 (NC)	NC (NC)
LS Mean (SE)	NC (NC)	NC (NC)	NC (NC)	NC (NC)
LS Mean Diff vs. placebo (95% CI)		NC (NC, NC)		NC (NC, NC)
P-value vs. placebo		NC		NC
Overall p-value for interaction		0.4777		0.0019

LATAM: Latin America, ROW: Rest of the world

[0263] Table 54. Subgroup analysis: change from baseline in AQLQ global score at EOT (Week 12) by disease and other characteristics subgroups (mITT population).

	400 mg BID cohort		400 mg TID cohort	
AQLQ global score	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo BID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Age at onset of asthma (years)				
< 12				
Number	7	8	14	12
Mean (SD)	0.58 (0.91)	0.89 (0.71)	-0.04 (0.87)	0.51 (0.94)
LS Mean (SE)	0.61 (0.29)	0.95 (0.38)	0.03 (0.23)	0.49 (0.26)
LS Mean Diff vs. placebo (95% CI)		0.34 (-0.43, 1.11)		0.46 (-0.19, 1.12)
P-value vs. placebo		0.3884		0.1645
≥ 12 - < 18				
Number	2	5	5	5
Mean (SD)	0.44 (0.57)	0.91 (1.28)	0.34 (0.67)	0.53 (1.61)
LS Mean (SE)	-3.05 (5.06)	-0.56 (2.39)	0.77 (0.98)	0.40 (0.73)
LS Mean Diff vs. placebo (95% CI)		2.49 (-9.16, 14.14)		-0.37 (-2.70, 1.96)
P-value vs. placebo		0.4551		0.7001
≥ 18 - < 40				
Number	14	13	26	22
Mean (SD)	0.51 (1.05)	0.86 (1.12)	0.13 (0.95)	0.34 (0.74)
LS Mean (SE)	0.20 (0.30)	0.77 (0.31)	0.23 (0.18)	0.48 (0.19)
LS Mean Diff vs. placebo (95% CI)		0.57 (-0.18, 1.32)		0.25 (-0.23, 0.72)
P-value vs. placebo		0.1339		0.3043
≥ 40				
Number	6	3	17	14
Mean (SD)	-0.59 (1.53)	0.48 (0.97)	0.67 (0.81)	0.60 (0.71)
LS Mean (SE)	-0.70 (0.46)	0.23 (0.73)	0.41 (0.22)	0.71 (0.25)
LS Mean Diff vs. placebo (95% CI)		0.93 (-0.59, 2.46)		0.29 (-0.34, 0.92)
P-value vs. placebo		0.2299		0.3596
Overall p-value for interaction		0.8090		0.8443
Age at onset of asthma (years)				
< 18				
Number	9	13	19	17
Mean (SD)	0.55 (0.81)	0.90 (0.92)	0.06 (0.82)	0.52 (1.12)
LS Mean (SE)	0.60 (0.23)	1.03 (0.23)	0.15 (0.22)	0.45 (0.23)
LS Mean Diff vs. placebo (95% CI)		0.43 (-0.08, 0.95)		0.31 (-0.27, 0.89)
P-value vs. placebo		0.0978		0.2994
≥ 18				
Number	20	16	43	36

	400 mg BID cohort		400 mg TID cohort	
AQLQ global score	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo BID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Mean (SD)	0.18 (1.28)	0.79 (1.07)	0.34 (0.93)	0.44 (0.73)
LS Mean (SE)	-0.07 (0.25)	0.68 (0.29)	0.34 (0.14)	0.57 (0.15)
LS Mean Diff vs. placebo (95% CI)		0.75 (0.08, 1.43)		0.24 (-0.14, 0.61)
P-value vs. placebo		0.0286		0.2154
Overall p-value for interaction		0.5227		0.7855
Number of asthma exacerbations within 2 years before screening visit				
1				
Number	9	11	47	31
Mean (SD)	0.84 (0.91)	1.05 (0.99)	0.30 (0.86)	0.57 (0.88)
LS Mean (SE)	0.42 (0.34)	1.16 (0.37)	0.39 (0.13)	0.68 (0.16)
LS Mean Diff vs. placebo (95% CI)		0.75 (-0.16, 1.65)		0.29 (-0.08, 0.66)
P-value vs. placebo		0.1070		0.1248
2				
Number	13	10	15	19
Mean (SD)	0.35 (0.98)	0.76 (0.86)	0.12 (1.01)	0.34 (0.89)
LS Mean (SE)	0.15 (0.27)	0.76 (0.37)	0.14 (0.24)	0.41 (0.22)
LS Mean Diff vs. placebo (95% CI)		0.61 (-0.11, 1.33)		0.27 (-0.33, 0.87)
P-value vs. placebo		0.0972		0.3775
> 2				
Number	7	8	0	3
Mean (SD)	-0.51 (1.41)	0.66 (1.20)	NC (NC)	0.14 (0.53)
LS Mean (SE)	-0.64 (0.36)	0.54 (0.33)	NC (NC)	NC (NC)
LS Mean Diff vs. placebo (95% CI)		1.18 (0.30, 2.07)		NC (NC, NC)
P-value vs. placebo		0.0089		NC
Overall p-value for interaction		0.4656		0.2099
Atopic medical conditions				
Yes				
Number	16	20	20	18
Mean (SD)	0.28 (1.35)	0.81 (0.98)	0.52 (0.92)	0.48 (0.84)
LS Mean (SE)	0.14 (0.28)	0.66 (0.26)	0.43 (0.21)	0.56 (0.23)
LS Mean Diff vs. placebo (95% CI)		0.52 (-0.09, 1.13)		0.13 (-0.45, 0.71)
P-value vs. placebo		0.0945		0.6600
No				
Number	13	9	42	35
Mean (SD)	0.31 (0.91)	0.91 (1.06)	0.13 (0.87)	0.46 (0.89)
LS Mean (SE)	-0.10 (0.27)	0.99 (0.32)	0.27 (0.16)	0.64 (0.16)

	400 mg BID cohort		400 mg TID cohort	
AQLQ global score	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo BID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
LS Mean Diff vs. placebo (95% CI)		1.08 (0.29, 1.87)		0.37 (0.00, 0.73)
P-value vs. placebo		0.0074		0.0477
Overall p-value for interaction		0.2340		0.6262
Background ICS dose level at randomization (400 mg TID only)				
Medium				
Number			34	22
Mean (SD)			0.15 (0.85)	0.41 (0.73)
LS Mean (SE)			0.23 (0.17)	0.53 (0.19)
LS Mean Diff vs. placebo (95% CI)				0.31 (-0.11, 0.72)
P-value vs. placebo				0.1446
High				
Number			28	31
Mean (SD)			0.38 (0.95)	0.50 (0.96)
LS Mean (SE)			0.33 (0.18)	0.59 (0.19)
LS Mean Diff vs. placebo (95% CI)				0.26 (-0.22, 0.74)
P-value vs. placebo				0.2872
Overall p-value for interaction				0.8865
Smoking history				
Former				
Number	7	4	4	4
Mean (SD)	0.43 (1.52)	0.73 (1.45)	0.23 (0.26)	-0.55 (1.82)
LS Mean (SE)	-0.16 (0.46)	1.74 (0.68)	-0.09 (0.79)	-0.11 (0.84)
LS Mean Diff vs. placebo (95% CI)		1.89 (0.62, 3.16)		-0.02 (-1.90, 1.86)
P-value vs. placebo		0.0035		0.9823
Never				
Number	22	25	58	49
Mean (SD)	0.25 (1.05)	0.86 (0.94)	0.26 (0.93)	0.55 (0.71)
LS Mean (SE)	0.09 (0.21)	0.74 (0.21)	0.34 (0.11)	0.68 (0.12)
LS Mean Diff vs. placebo (95% CI)		0.65 (0.15, 1.15)		0.34 (0.04, 0.63)
P-value vs. placebo		0.0106		0.0266
Overall p-value for interaction		0.5532		0.5469
Baseline pre-bronchodilator FEV1 (L) (400 mg BID only)				
< Median (2.022)				
Number	13	15		
Mean (SD)	0.04 (1.27)	0.89 (0.98)		

	400 mg BID cohort		400 mg TID cohort	
AQLQ global score	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo BID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
LS Mean (SE)	-0.30 (0.26)	0.59 (0.28)		
LS Mean Diff vs. placebo (95% CI)		0.89 (0.28, 1.51)		
P-value vs. placebo		0.0046		
≥ Median (2.022)				
Number	16	13		
Mean (SD)	0.50 (1.04)	0.74 (1.06)		
LS Mean (SE)	0.40 (0.26)	0.94 (0.29)		
LS Mean Diff vs. placebo (95% CI)		0.54 (-0.14, 1.21)		
P-value vs. placebo		0.1187		
Overall p-value for interaction		0.3692		
Baseline pre-bronchodilator percent predicted FEV1 (%) (400 mg BID only)				
< Median (68)				
Number	11	16		
Mean (SD)	0.24 (1.11)	1.00 (1.01)		
LS Mean (SE)	-0.22 (0.30)	0.69 (0.30)		
LS Mean Diff vs. placebo (95% CI)		0.92 (0.29, 1.55)		
P-value vs. placebo		0.0044		
≥ Median (68)				
Number	18	12		
Mean (SD)	0.32 (1.21)	0.58 (0.98)		
LS Mean (SE)	0.20 (0.25)	0.67 (0.31)		
LS Mean Diff vs. placebo (95% CI)		0.47 (-0.26, 1.20)		
P-value vs. placebo		0.2058		
Overall p-value for interaction		0.3643		
Baseline pre-bronchodilator FEV1 (L) (400 mg TID only)				
< Median (2.1955)				
Number			30	23
Mean (SD)			0.26 (0.84)	0.48 (0.93)
LS Mean (SE)			0.25 (0.17)	0.53 (0.20)
LS Mean Diff vs. placebo (95% CI)				0.28 (-0.19, 0.76)
P-value vs. placebo				0.2414
≥ Median (2.1955)				
Number			31	29
Mean (SD)			0.22 (0.96)	0.47 (0.84)
LS Mean (SE)			0.32 (0.16)	0.59 (0.16)

	400 mg BID cohort		400 mg TID cohort	
AQLQ global score	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo BID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
LS Mean Diff vs. placebo (95% CI)				0.27 (-0.15, 0.69)
P-value vs. placebo				0.2026
Overall p-value for interaction				0.7803
Baseline pre-bronchodilator percent predicted FEV1 group 1 (%) (400 mg TID only)				
< Median (77)				
Number			32	23
Mean (SD)			0.05 (0.87)	0.49 (0.92)
LS Mean (SE)			0.13 (0.18)	0.55 (0.21)
LS Mean Diff vs. placebo (95% CI)				0.42 (-0.05, 0.88)
P-value vs. placebo				0.0787
≥ Median (77)				
Number			30	29
Mean (SD)			0.48 (0.89)	0.47 (0.84)
LS Mean (SE)			0.43 (0.16)	0.60 (0.16)
LS Mean Diff vs. placebo (95% CI)				0.16 (-0.26, 0.58)
P-value vs. placebo				0.4566
Overall p-value for interaction				0.2958
Baseline pre-bronchodilator percent predicted FEV1 group 2 (%) (400 mg TID only)				
< 80				
Number			37	30
Mean (SD)			0.10 (0.82)	0.41 (0.94)
LS Mean (SE)			0.16 (0.16)	0.50 (0.18)
LS Mean Diff vs. placebo (95% CI)				0.35 (-0.06, 0.76)
P-value vs. placebo				0.0977
≥ 80				
Number			25	22
Mean (SD)			0.49 (0.97)	0.57 (0.77)
LS Mean (SE)			0.43 (0.17)	0.70 (0.18)
LS Mean Diff vs. placebo (95% CI)				0.27 (-0.20, 0.74)
P-value vs. placebo				0.2629
Overall p-value for interaction				0.5797
Baseline FEV1 reversibility (%)				
< 12				

	400 mg BID cohort		400 mg TID cohort	
AQLQ global score	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo BID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Number	19	13	45	36
Mean (SD)	0.11 (1.26)	0.61 (0.72)	0.33 (0.86)	0.42 (0.85)
LS Mean (SE)	-0.03 (0.23)	0.71 (0.28)	0.36 (0.13)	0.48 (0.15)
LS Mean Diff vs. placebo (95% CI)		0.73 (0.07, 1.40)		0.12 (-0.24, 0.48)
P-value vs. placebo		0.0303		0.5068
≥ 12				
Number	9	14	10	10
Mean (SD)	0.57 (0.88)	0.97 (1.23)	0.39 (0.79)	0.56 (0.72)
LS Mean (SE)	0.47 (0.33)	0.76 (0.33)	0.30 (0.32)	0.63 (0.41)
LS Mean Diff vs. placebo (95% CI)		0.29 (-0.39, 0.97)		0.32 (-0.63, 1.28)
P-value vs. placebo		0.4038		0.5035
Overall p-value for interaction		0.3793		0.3913
Baseline ACQ-5 score				
≤ 2				
Number	14	17	26	18
Mean (SD)	0.47 (0.92)	0.50 (0.80)	0.46 (0.94)	0.53 (1.02)
LS Mean (SE)	0.17 (0.27)	0.60 (0.24)	0.35 (0.19)	0.64 (0.22)
LS Mean Diff vs. placebo (95% CI)		0.43 (-0.16, 1.02)		0.29 (-0.26, 0.85)
P-value vs. placebo		0.1568		0.2966
> 2				
Number	15	12	36	35
Mean (SD)	0.13 (1.35)	1.32 (1.06)	0.11 (0.85)	0.43 (0.78)
LS Mean (SE)	0.10 (0.33)	1.05 (0.40)	0.22 (0.14)	0.60 (0.15)
LS Mean Diff vs. placebo (95% CI)		0.95 (0.11, 1.79)		0.38 (0.01, 0.75)
P-value vs. placebo		0.0267		0.0447
Overall p-value for interaction		0.3060		0.6263

LATAM: Latin America, ROW: Rest of the world

[0264] Table 55. Subgroup analysis: change from baseline in AQLQ global score at EOT (Week 12) by baseline ICS/LABA dose level (mITT population).

AQLQ global score	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**
Background ICS/LABA dose level at randomization		
Medium		
Number	3	4
Mean (SD)	0.02 (0.48)	1.07 (0.57)
LS Mean (SE)	-0.08 (0.50)	0.84 (0.50)
LS Mean Diff vs. placebo (95% CI)		0.93 (0.72, 1.13)

AQLQ global score	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)
P-value vs. placebo		0.0007
High		
Number	26	25
Mean (SD)	0.32 (1.21)	0.80 (1.04)
LS Mean (SE)	0.10 (0.20)	0.83 (0.22)
LS Mean Diff vs. placebo (95% CI)		0.73 (0.21, 1.24)
P-value vs. placebo		0.0057
Overall p-value for interaction		0.8629

LATAM: Latin America, ROW: Rest of the world

[0265] Table 56. Subgroup analysis: change from baseline in AQLQ global score at EOT (Week 12) by baseline biomarker subgroups (mITT population).

	400 mg BID cohort		400 mg TID cohort	
AQLQ global score	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)
Baseline IgE level (IU/mL)				
< 100				
Number	10	7	24	18
Mean (SD)	0.00 (1.71)	1.01 (1.21)	0.13 (0.98)	0.55 (0.59)
LS Mean (SE)	-0.25 (0.58)	0.64 (0.61)	0.23 (0.30)	0.69 (0.36)
LS Mean Diff vs. placebo (95% CI)		0.90 (-0.36, 2.16)		0.46 (0.01, 0.91)
P-value vs. placebo		0.1622		0.0448
≥ 100				
Number	19	22	38	35
Mean (SD)	0.45 (0.74)	0.78 (0.94)	0.34 (0.85)	0.42 (0.98)
LS Mean (SE)	0.15 (0.41)	0.74 (0.39)	0.32 (0.22)	0.49 (0.23)
LS Mean Diff vs. placebo (95% CI)		0.59 (0.14, 1.04)		0.16 (-0.25, 0.58)
P-value vs. placebo		0.0095		0.4392
Overall p-value for interaction		0.6080		0.4953
Baseline median IgE level (IU/mL) (400 mg BID only)				
< Median (210.8)				
Number	12	18		
Mean (SD)	-0.03 (1.56)	0.73 (0.89)		
LS Mean (SE)	-0.34 (0.34)	0.68 (0.27)		
LS Mean Diff vs. placebo (95% CI)		1.03 (0.21, 1.84)		
P-value vs. placebo		0.0141		
≥ Median (210.8)				
Number	17	11		

	400 mg BID cohort		400 mg TID cohort	
AQLQ global score	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Mean (SD)	0.52 (0.72)	1.01 (1.15)		
LS Mean (SE)	0.26 (0.20)	0.94 (0.26)		
LS Mean Diff vs. placebo (95% CI)		0.67 (0.12, 1.22)		
P-value vs. placebo		0.0161		
Overall p-value for interaction		0.7770		
Baseline median IgE level (IU/mL) (400 mg TID only)				
< Median (121.85)				
Number			31	25
Mean (SD)			0.03 (1.00)	0.64 (0.61)
LS Mean (SE)			0.10 (0.19)	0.71 (0.20)
LS Mean Diff vs. placebo (95% CI)				0.60 (0.19, 1.02)
P-value vs. placebo				0.0044
≥ Median (121.85)				
Number			31	28
Mean (SD)			0.48 (0.73)	0.31 (1.03)
LS Mean (SE)			0.76 (0.45)	0.74 (0.48)
LS Mean Diff vs. placebo (95% CI)				-0.02 (-0.48, 0.44)
P-value vs. placebo				0.9314
Overall p-value for interaction				0.0564
Baseline median IgA level (mg/L) (400 mg TID only)				
< Median (2190)				
Number			33	26
Mean (SD)			0.14 (0.93)	0.69 (0.74)
LS Mean (SE)			0.27 (0.16)	0.77 (0.17)
LS Mean Diff vs. placebo (95% CI)				0.50 (0.09, 0.92)
P-value vs. placebo				0.0162
≥ Median (2190)				
Number			29	27
Mean (SD)			0.39 (0.85)	0.25 (0.94)
LS Mean (SE)			0.33 (0.17)	0.41 (0.18)
LS Mean Diff vs. placebo (95% CI)				0.08 (-0.39, 0.55)
P-value vs. placebo				0.7400
Overall p-value for interaction				0.1785
Baseline blood eosinophil level 1 (10^9/L) (400 mg BID only)				

	400 mg BID cohort		400 mg TID cohort	
AQLQ global score	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
< 0.15				
Number	5	8		
Mean (SD)	-0.01 (1.38)	0.82 (1.24)		
LS Mean (SE)	0.07 (0.59)	0.69 (0.40)		
LS Mean Diff vs. placebo (95% CI)		0.62 (-0.95, 2.19)		
P-value vs. placebo		0.3897		
≥ 0.15				
Number	24	21		
Mean (SD)	0.36 (1.12)	0.85 (0.91)		
LS Mean (SE)	0.14 (0.20)	0.83 (0.26)		
LS Mean Diff vs. placebo (95% CI)		0.69 (0.15, 1.23)		
P-value vs. placebo		0.0128		
Overall p-value for interaction		0.9910		
Baseline blood eosinophil level 2 (10^9/L) (400 mg BID only)				
< 0.3				
Number	17	16		
Mean (SD)	0.33 (1.18)	0.90 (1.18)		
LS Mean (SE)	0.10 (0.26)	0.89 (0.29)		
LS Mean Diff vs. placebo (95% CI)		0.79 (0.09, 1.49)		
P-value vs. placebo		0.0267		
≥ 0.3				
Number	12	13		
Mean (SD)	0.23 (1.16)	0.77 (0.73)		
LS Mean (SE)	-0.11 (0.32)	0.56 (0.30)		
LS Mean Diff vs. placebo (95% CI)		0.67 (0.10, 1.25)		
P-value vs. placebo		0.0221		
Overall p-value for interaction		0.9184		
Baseline blood eosinophil level 1 (10^9/L) (400 mg TID only)				
< 0.15				
Number			28	21
Mean (SD)			0.40 (0.76)	0.41 (0.58)
LS Mean (SE)			0.47 (0.13)	0.54 (0.15)
LS Mean Diff vs. placebo (95% CI)				0.07 (-0.29, 0.44)
P-value vs. placebo				0.6928
≥ 0.15 - < 0.3				
Number			19	15

	400 mg BID cohort		400 mg TID cohort	
AQLQ global score	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Mean (SD)			0.16 (1.13)	0.43 (0.93)
LS Mean (SE)			0.07 (0.27)	0.39 (0.29)
LS Mean Diff vs. placebo (95% CI)				0.32 (-0.36, 1.01)
P-value vs. placebo				0.3579
≥ 0.3				
Number			15	17
Mean (SD)			0.12 (0.83)	0.57 (1.11)
LS Mean (SE)			0.02 (0.31)	0.72 (0.28)
LS Mean Diff vs. placebo (95% CI)				0.70 (0.04, 1.36)
P-value vs. placebo				0.0378
Overall p-value for interaction				0.3666
Baseline blood eosinophil level 2 (10^9/L) (400 mg TID only)				
< 0.3				
Number			47	36
Mean (SD)			0.30 (0.92)	0.42 (0.73)
LS Mean (SE)			0.33 (0.13)	0.50 (0.14)
LS Mean Diff vs. placebo (95% CI)				0.17 (-0.18, 0.52)
P-value vs. placebo				0.3450
≥ 0.3				
Number			15	17
Mean (SD)			0.12 (0.83)	0.57 (1.11)
LS Mean (SE)			0.02 (0.31)	0.72 (0.28)
LS Mean Diff vs. placebo (95% CI)				0.70 (0.04, 1.36)
P-value vs. placebo				0.0378
Overall p-value for interaction				0.2659
Baseline FeNO level 1 (ppb)				
< 25				
Number	13	12	39	32
Mean (SD)	0.41 (1.26)	0.92 (0.93)	0.33 (0.91)	0.40 (0.88)
LS Mean (SE)	0.18 (0.28)	1.16 (0.28)	0.38 (0.14)	0.53 (0.16)
LS Mean Diff vs. placebo (95% CI)		0.98 (0.31, 1.66)		0.15 (-0.24, 0.54)
P-value vs. placebo		0.0044		0.4375
≥ 25				
Number	16	17	19	19
Mean (SD)	0.20 (1.10)	0.78 (1.05)	0.29 (0.80)	0.61 (0.86)
LS Mean (SE)	0.08 (0.25)	0.59 (0.29)	0.26 (0.22)	0.70 (0.22)

	400 mg BID cohort		400 mg TID cohort	
AQLQ global score	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
LS Mean Diff vs. placebo (95% CI)		0.51 (-0.15, 1.17)		0.44 (-0.12, 1.00)
P-value vs. placebo		0.1276		0.1229
Overall p-value for interaction		0.4272		0.2955
Baseline FeNO level 2 (ppb)				
< 35				
Number	17	21	46	37
Mean (SD)	0.40 (1.25)	0.74 (0.99)	0.28 (0.91)	0.41 (0.84)
LS Mean (SE)	0.01 (0.25)	0.85 (0.23)	0.30 (0.13)	0.48 (0.15)
LS Mean Diff vs. placebo (95% CI)		0.84 (0.28, 1.40)		0.18 (-0.19, 0.54)
P-value vs. placebo		0.0032		0.3422
≥ 35				
Number	12	8	12	14
Mean (SD)	0.15 (1.03)	1.09 (1.01)	0.47 (0.70)	0.65 (0.97)
LS Mean (SE)	0.08 (0.30)	0.85 (0.40)	0.23 (0.34)	0.68 (0.30)
LS Mean Diff vs. placebo (95% CI)		0.77 (-0.16, 1.70)		0.45 (-0.24, 1.14)
P-value vs. placebo		0.1046		0.2020
Overall p-value for interaction		0.8943		0.5672

AQLQ(S): Asthma quality of life questionnaire with standardized activities, LOAC: Loss of asthma control, LOCF: Last observation carried forward, LATAM: Latin America, ROW: Rest of the world

[0266] Table 57. Subgroup analysis: change from baseline in AQLQ global score at EOT (Week 12) in the baseline low EOS and low FeNO subgroup (mITT population).

	400 mg BID		400 mg TID	
AQLQ global score	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo BID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
Baseline blood eosinophil (10^9/L) and FeNO (ppb)				
Low EOS (< 0.15) and low FeNO (< 25)				
Number	3	3	22	14
Mean (SD)	-0.49 (1.63)	0.71 (1.25)	0.41 (0.72)	0.41 (0.64)
LS Mean (SE)	-1.16 (0.91)	1.28 (0.65)	0.45 (0.15)	0.55 (0.19)
LS Mean Diff vs. placebo (95% CI)		2.45 (-13.85, 18.75)		0.10 (-0.36, 0.56)
P-value vs. placebo		0.3072		0.6810
All others				
Number	26	26	36	37
Mean (SD)	0.38 (1.09)	0.85 (0.99)	0.26 (0.95)	0.51 (0.95)
LS Mean (SE)	0.16 (0.19)	0.77 (0.22)	0.21 (0.17)	0.56 (0.16)

	400 mg BID		400 mg TID	
AQLQ global score	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo BID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**
LS Mean Diff vs. placebo (95% CI)		0.61 (0.13, 1.09)		0.35 (-0.07, 0.77)
P-value vs. placebo		0.0135		0.1044
Overall p-value for interaction		0.1818		0.4365

LATAM: Latin America, ROW: Rest of the world

Safety

[0267] Rilzabrutinib was generally safe, with no evidence of new safety concerns (**Table 58**). Participants receiving 400 mg BID or 400 mg TID rilzabrutinib experienced fewer TEAEs than patients receiving the placebo, further attesting to the safety of rilzabrutinib.

[0268] Table 58. Overview of adverse event profile: treatment-emergent adverse events (safety population).

	400 mg BID cohort		400 mg TID cohort		Combined	
n (%)	**Placebo BID (N=32)**	**Rilzabrutinib 400 mg BID (N=32)**	**Placebo TID (N=68)**	**Rilzabrutinib 400 mg TID (N=64)**	**Placebo (N=100)**	**Rilzabrutinib (N=96)**
Participants with any TEAE	20 (62.5)	14 (43.8)	18 (26.5)	26 (40.6)	38 (38.0)	40 (41.7)
Participants with any severe TEAE	0	0	0	1 (1.6)	0	1 (1.0)
Participants with any treatment emergent SAE	0	2 (6.3)	0	0	0	2 (2.1)
Participants with any TEAE leading to death	0	0	0	0	0	0
Participants with any TEAE leading to permanent study intervention discontinuation	2 (6.3)	4 (12.5)	3 (4.4)	7 (10.9)	5 (5.0)	11 (11.5)
Participants with any treatment emergent AESI	2 (6.3)	1 (3.1)	4 (5.9)	3 (4.7)	6 (6.0)	4 (4.2)
Participants with any TEAE related to IMP	1 (3.1)	5 (15.6)	7 (10.3)	10 (15.6)	8 (8.0)	15 (15.6)

	400 mg BID cohort		400 mg TID cohort		Combined	
n (%)	Placebo BID (N=32)	Rilzabrutinib 400 mg BID (N=32)	Placebo TID (N=68)	Rilzabrutinib 400 mg TID (N=64)	Placebo (N=100)	Rilzabrutinib (N=96)

TEAE: Treatment-emergent adverse event, SAE: Serious adverse event, AESI: Adverse event of special interest, IMP: Investigational medicinal product
n (%) = number and percentage of participants with at least one TEAE

Change from baseline at EOT and change from baseline at each week for Asthma Daytime Symptom Diary (ADSD) and Asthma Nighttime Symptom Diary (ANSD) scores

[0269] In both cohorts, patients treated with rilzabrutinib showed an improvement in ADSD and ANSD symptom score as indicated by a reduction from baseline in ADSD and ANSD symptom score at Week 12 relative to patients treated with the placebo. The improvement has been observed across all ADSD and ANSD components, including difficulty breathing, wheezing, shortness of breath, chest tightness, chest pain, and cough.

[0270] Patients in the rilzabrutinib 400 mg BID arm exhibited a reduction in daytime and nighttime asthma symptom score as measured by change from baseline at Week 12 (LS mean ADSD: -0.27, LS mean ANSD: -0.35) that was greater than that observed in patients in the placebo BID arm (LS mean ADSD: 0.12, ANSD: 0.33); the LS mean difference versus placebo was -0.39 [95% CI: -1.03, 0.26, nominal p-value=0.2377] for ADSD symptom score and -0.68 [95% CI: -1.33, -0.03, nominal p-value=0.0390] for ANSD symptom score. The improvement has been observed across all ADSD and ANSD components.

[0271] Patients in the rilzabrutinib 400 mg TID arm also exhibited a reduction in daytime and nighttime asthma symptom score as measured by change from baseline at Week 12 (LS mean ADSD: -0.43, LS mean ANSD: -0.48) that was greater than that observed in patients in the placebo TID arm (LS mean ADSD: 0.08, ANSD: 0.06), the LS mean difference versus placebo was -0.50 [95% CI: -1.15, 0.14, nominal p-value=0.1276] for ADSD symptom score and -0.54 [95% CI: -1.13, 0.06, nominal p-value=0.0758] for ANSD symptom score. The improvement has been observed across all ADSD and ANSD components.

Embodiments:

Non-limiting embodiments of the disclosure include:

1. A method of treating asthma 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 mild asthma.

3. The method of Embodiment 1, wherein the human patient has moderate-to-severe asthma.

4. The method of Embodiment 1 or 3, wherein the human patient has moderate asthma.

5. The method of Embodiment 1 or 3, wherein the human patient has severe asthma.

6. The method of any one of Embodiments 1-5, wherein the human patient has asthma that is not well controlled.

7. The method of any one of the preceding Embodiments, wherein the human patient has asthma that is not well controlled for one or more symptoms.

8. The method of Embodiment 7, wherein the one or more symptoms is selected from frequency of awakening by asthma, asthma symptoms when woke up, limitation of activities by asthma, shortness of breath, and wheeze.

9. The method of any one of the preceding Embodiments, wherein the human patient is receiving treatment with step 3, 4, or 5 of the Global Initiative for Asthma (GINA).

10. The method of any one of the preceding Embodiments, wherein the human patient has asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA).

11. The method of any one of the preceding Embodiments, wherein the human patient is withdrawn from ICS/LABA therapy.

12. The method of any one of the preceding Embodiments, wherein the human patient does not experience a ≥30% reduction from baseline in morning peak expiratory flow (PEF) on at least 2 consecutive days.

13. The method of any one of the preceding Embodiments, wherein the human patient does not experience a ≥30% reduction from baseline in morning PEF.

14. The method of any one of the preceding Embodiments, wherein the human patient does not require ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol within a 24-hour period for two consecutive 24-hour periods.

15. The method of any one of the preceding Embodiments, wherein the human patient does not require ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol within a 24-hour period.

16. The method of any one of the preceding Embodiments, wherein the human patient does not require ≥5 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol within a 24-hour period.

17. The method of any one of the preceding Embodiments, wherein the human patient does not require ≥4 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol within a 24-hour period.

18. The method of any one of the preceding Embodiments, wherein the human patient does not require ≥3 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol within a 24-hour period.

19. The method of any one of the preceding Embodiments, wherein the human patient does not require ≥2 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol within a 24-hour period.

20. The method of any one of the preceding Embodiments, wherein the human patient does not require an increase in ICS ≥4 times the last prescribed ICS dose.

21. The method of any one of the preceding Embodiments, wherein the human patient does not require an increase in ICS ≥50% of the last prescribed ICS dose.

22. The method of any one of the preceding Embodiments, wherein the human patient does not require the use of systemic steroid treatment, optionally wherein the systemic steroid treatment comprises oral or parenteral treatment.

23. The method of any one of the preceding Embodiments, wherein the human patient does not require hospitalization or an emergency room visit for asthma exacerbation.

24. The method of any one of the preceding Embodiments, wherein the human patient achieves an increase in pre-bronchodilator FEV1 relative to baseline pre-bronchodilator FEV1.

25. The method of any one of the preceding Embodiments, wherein the human patient achieves an increase in the percent predicted pre-bronchodilator FEV1 prior to baseline pre-bronchodilator FEV1.

26. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction in Asthma Control Questionnaire-5 (ACQ-5) score relative to a baseline ACQ-5 score.

27. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction in ACQ-5 of ≥0.5 relative to baseline ACQ-5.

28. The method of any one of the preceding Embodiments, wherein the human patient achieves an ACQ-5 score of ≤0.75.

29. The method of any one of the preceding Embodiments, wherein the human patient achieves an increase in Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ(S)) relative to baseline AQLQ(S).

30. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction in asthma daytime symptom diary (ADSD) relative to baseline ADSD.

31. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction in asthma nighttime symptom diary (ANSD) relative to baseline ANSD.

32. The method of any one of Embodiments 1-10 or 12-31, wherein the human patient achieves a reduction in inhalations/day of albuterol or levalbuterol for symptom relief relative to baseline inhalations/day.

33. The method of any one of Embodiments 1-10 or 12-32, wherein the human patient achieves a reduction in inhalations/day of albuterol or levalbuterol for symptom relief relative to baseline inhalations/day, further wherein the patient receives concomitant treatment with ICS and/or LABA.

34. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction in Patient Global Impression of Severity (PGIS) relative to baseline PGIS.

35. The method of any one of the preceding Embodiments, wherein the human patient achieves an improvement in Patient Global Impression of Change (PGIC).

36. The method of any one of the preceding Embodiments, wherein the human patient has had asthma for at least 12 months.

37. The method of any one of the preceding Embodiments, wherein the human patient is being treated with a moderate to high dose of ICS therapy in combination with LABA.

38. The method of Embodiment 37, wherein the ICS is fluticasone propionate and the human patient is being treated with ≥250 µg of fluticasone propionate BID or comparable ICS daily dosage to a maximum of 2000 µg/day of fluticasone propionate or clinically comparable ICS.

39. The method of Embodiment 37 or 38, wherein the human patient has received treatment with the ICS for at least 3 months.

40. The method of any one of the preceding Embodiments, wherein the human patient has a baseline reversibility of at least 12% and 200 mL in FEV1 15 to 30 minutes after administration of 200-400 μg of albuterol/salbutamol or levalbuterol/levosalbutamol.

41. The method of any one of the preceding Embodiments, wherein the human patient has a history reversibility of at least 12% and 200 mL in FEV1 15 to 30 minutes after administration of 200-400 μg of albuterol/salbutamol or levalbuterol/levosalbutamol within the 5 years prior to initiation rilzabrutinib treatment.

42. The method of any one of the preceding Embodiments, wherein the human patient has a history of positive response to methacholine challenge within the 5 years prior to initiation rilzabrutinib treatment.

43. The method of any one of the preceding Embodiments, wherein the human patient has a history of one or more of the following within the 2 years prior to initiation of rilzabrutinib treatment:
    a. treatment with a systemic steroid for worsening asthma, optionally wherein the systemic steroid treatment comprises oral or parenteral treatment; and
    b. hospitalization or an emergency room visit for asthma exacerbation.

44. The method of any one of the preceding Embodiments, wherein the treatment period is at least 12 weeks.

45. 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.

46. The method of any one of Embodiments 1-44, wherein the at least one compound consists of at least one compound chosen from the (Z) isomer of rilzabrutinib and pharmaceutically acceptable salts thereof.

47. The method of any one of Embodiments 1-44, 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.

48. The method of any one of Embodiments 1-47, comprising administering rilzabrutinib to the human patient twice a day.

49. The method of any one of Embodiments 1-48, comprising administering to the human patient 400 mg of rilzabrutinib twice a day.

50. The method of any one of Embodiments 1-47, comprising administering rilzabrutinib to the human patient rilzabrutinib three times a day.

51. The method of any one of Embodiments 1-47 or 50, comprising administering to the human patient 400 mg of rilzabrutinib three times a day.

52. The method of any one of Embodiments 1-45 or 48-51 wherein the at least one compound is the (E) isomer of rilzabrutinib.

53. The method of any one of Embodiments 1-44, 46, or 48-51, wherein the at least one compound is the (Z) isomer of rilzabrutinib.

54. The method of any one of Embodiments 1-44 or 47-51, wherein the at least one compound consists of a mixture of (E) and (Z) isomers of rilzabrutinib.

55. The method of any one of the preceding Embodiments, wherein the at least one compound is orally administered to the human patient.

56. 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.

57. The method of any one of the preceding Embodiments, wherein the at least one compound is administered with water.

58. The method of any one of Embodiments 1-44 and 55-57, wherein the at least one compound is rilzabrutinib.

59. A method of treating asthma 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 asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA).

60. 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 asthma in a human patient in need thereof.

61. 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 asthma in a

human patient in need thereof, wherein the human patient in need thereof has asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA).

62. 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 asthma in a human patient in need thereof.

63. 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 asthma in a human patient in need thereof, wherein the human patient in need thereof has asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA).

64. 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 asthma in a human patient in need thereof.

65. 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 asthma in a human patient in need thereof, wherein the human patient in need thereof has asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA).

66. 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 asthma in a human patient in need thereof.

67. 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 asthma in a human patient in need thereof, wherein the human patient in need thereof has asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA)

[0272] 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.

[0273] 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.

[0274] 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 asthma 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 mild asthma.

3. The method of claim 1, wherein the human patient has moderate-to-severe asthma.

4. The method of claim 1 or 3, wherein the human patient has moderate asthma.

5. The method of claim 1 or 3, wherein the human patient has severe asthma.

6. The method of any one of claims 1-5, wherein the human patient has asthma that is not well controlled.

7. The method of any one of the preceding claims, wherein the human patient has asthma that is not well controlled for one or more symptoms.

8. The method of claim 7, wherein the one or more symptoms is selected from frequency of awakening by asthma, asthma symptoms when woke up, limitation of activities by asthma, shortness of breath, and wheeze.

9. The method of any one of the preceding claims, wherein the human patient is receiving treatment with step 3, 4, or 5 of the Global Initiative for Asthma (GINA).

10. The method of any one of the preceding claims, wherein the human patient has asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA).

11. The method of any one of the preceding claims, wherein the human patient is withdrawn from ICS/LABA therapy.

12. The method of any one of the preceding claims, wherein the human patient does not experience a ≥30% reduction from baseline in morning peak expiratory flow (PEF) on at least 2 consecutive days.

13. The method of any one of the preceding claims, wherein the human patient does not experience a ≥30% reduction from baseline in morning PEF.

14. The method of any one of the preceding claims, wherein the human patient does not require ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol within a 24-hour period for two consecutive 24-hour periods.

15. The method of any one of the preceding claims, wherein the human patient does not require ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol within a 24-hour period.

16. The method of any one of the preceding claims, wherein the human patient does not require an increase in ICS ≥4 times the last prescribed ICS dose.

17. The method of any one of the preceding claims, wherein the human patient does not require an increase in ICS ≥50% of the last prescribed ICS dose.

18. The method of any one of the preceding claims, wherein the human patient does not require the use of systemic steroid treatment, optionally wherein the systemic steroid treatment comprises oral or parenteral treatment.

19. The method of any one of the preceding claims, wherein the human patient does not require hospitalization or an emergency room visit for asthma exacerbation.

20. The method of any one of the preceding claims, wherein the human patient achieves an increase in pre-bronchodilator FEV1 relative to baseline pre-bronchodilator FEV1.

21. The method of any one of the preceding claims, wherein the human patient achieves an increase in the percent predicted pre-bronchodilator FEV1 prior to baseline pre-bronchodilator FEV1.

22. The method of any one of the preceding claims, wherein the human patient achieves a reduction in Asthma Control Questionnaire-5 (ACQ-5) score relative to a baseline ACQ-5 score.

23. The method of any one of the preceding claims, wherein the human patient achieves a reduction in ACQ-5 of $\geq$0.5 relative to baseline ACQ-5.

24. The method of any one of the preceding claims, wherein the human patient achieves an ACQ-5 score of $\leq$0.75.

25. The method of any one of the preceding claims, wherein the human patient achieves an increase in Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ(S)) relative to baseline AQLQ(S).

26. The method of any one of the preceding claims, wherein the human patient achieves a reduction in asthma daytime symptom diary (ADSD) relative to baseline ADSD.

27. The method of any one of the preceding claims, wherein the human patient achieves a reduction in asthma nighttime symptom diary (ANSD) relative to baseline ANSD.

28. The method of any one of claims 1-10 or 12-27, wherein the human patient achieves a reduction in inhalations/day of albuterol or levalbuterol for symptom relief relative to baseline inhalations/day.

29. The method of any one of claims 1-10 or 12-28, wherein the human patient achieves a reduction in inhalations/day of albuterol or levalbuterol for symptom relief relative to

baseline inhalations/day, further wherein the patient receives concomitant treatment with ICS and/or LABA.

30. The method of any one of the preceding claims, wherein the human patient achieves a reduction in Patient Global Impression of Severity (PGIS) relative to baseline PGIS.

31. The method of any one of the preceding claims, wherein the human patient achieves an improvement in Patient Global Impression of Change (PGIC).

32. The method of any one of the preceding claims, wherein the human patient has had asthma for at least 12 months.

33. The method of any one of the preceding claims, wherein the human patient is being treated with a moderate to high dose of ICS therapy in combination with LABA.

34. The method of claim 33, wherein the ICS is fluticasone propionate and the human patient is being treated with ≥250 μg of fluticasone propionate BID or comparable ICS daily dosage to a maximum of 2000 μg/day of fluticasone propionate or clinically comparable ICS.

35. The method of claim 33 or 34, wherein the human patient has received treatment with the ICS for at least 3 months.

36. The method of any one of the preceding claims, wherein the human patient has a baseline reversibility of at least 12% and 200 mL in FEV1 15 to 30 minutes after administration of 200-400 μg of albuterol/salbutamol or levalbuterol/levosalbutamol.

37. The method of any one of the preceding claims, wherein the human patient has a history reversibility of at least 12% and 200 mL in FEV1 15 to 30 minutes after administration of 200-400 μg of albuterol/salbutamol or levalbuterol/levosalbutamol within the 5 years prior to initiation rilzabrutinib treatment.

38. The method of any one of the preceding claims, wherein the human patient has a history of positive response to methacholine challenge within the 5 years prior to initiation rilzabrutinib treatment.

39. The method of any one of the preceding claims, wherein the human patient has a history of one or more of the following within the 2 years prior to initiation of rilzabrutinib treatment:
    a. treatment with a systemic steroid for worsening asthma, optionally wherein the systemic steroid treatment comprises oral or parenteral treatment; and
    b. hospitalization or an emergency room visit for asthma exacerbation.

40. The method of any one of the preceding claims, wherein the treatment period is at least 12 weeks.

41. 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.

42. The method of any one of claims 1-40, wherein the at least one compound consists of at least one compound chosen from the (Z) isomer of rilzabrutinib and pharmaceutically acceptable salts thereof.

43. The method of any one of claims 1-40, 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.

44. The method of any one of claims 1-43, comprising administering rilzabrutinib to the human patient twice a day.

45. The method of any one of claims 1-44, comprising administering to the human patient 400 mg of rilzabrutinib twice a day.

46. The method of any one of claims 1-43, comprising administering rilzabrutinib to the human patient three times a day.

47. The method of any one of claims 1-43 or 46, comprising administering to the human patient 400 mg of rilzabrutinib three times a day.

48. The method of any one of claims 1-41 or 44-47 wherein the at least one compound is the (E) isomer of rilzabrutinib.

49. The method of any one of claims 1-40, 42, or 44-47, wherein the at least one compound is the (Z) isomer of rilzabrutinib.

50. The method of any one of claims 1-40 or 43-47, wherein the at least one compound consists of a mixture of (E) and (Z) isomers of rilzabrutinib.

51. The method of any one of the preceding claims, wherein the at least one compound is orally administered to the human patient.

52. 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.

53. The method of any one of the preceding claims, wherein the at least one compound is administered with water.

54. The method of any one of claims 1-40 and 51-53, wherein the at least one compound is rilzabrutinib.

55. A method of treating asthma 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 asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA).

56. 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 asthma in a human patient in need thereof.

57. 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 asthma in a human patient in need thereof, wherein the human patient in need thereof has asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA).

58. 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 asthma in a human patient in need thereof.

59. 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 asthma in a human patient in need thereof, wherein the human patient in need thereof has asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA).

60. 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 asthma in a human patient in need thereof.

61. 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 asthma in a human patient in need thereof, wherein the human patient in need thereof has asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA).

62. 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 asthma in a human patient in need thereof.

63. 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 asthma in a human patient in need thereof, wherein the human patient in need thereof has asthma that is not well controlled by treatment with an inhaled corticosteroid (ICS) and/or a long-acting β2 adrenergic agonist (LABA).