

**RILZABRUTINIB FOR USE IN THE TREATMENT OF ITCH ASSOCIATED
WITH ATOPIC DERMATITIS AND/OR PRURIGO NODULARIS**

[001] Disclosed herein are methods for treating itch associated with atopic dermatitis and/or prurigo nodularis using BTK inhibitors and pharmaceutical compositions comprising the same.

[002] Atopic dermatitis (AD) is a common, chronic, relapsing, pruritic, inflammatory skin disease. It is characterized by xerosis and acute (erythematous papules, vesicles, edema, exudation, crusting), subacute and chronic (scaly, erythematous papules and plaques, lichenification, excoriations, fissuring) eczematous skin lesions (Bieber T 2010, Eichenfield LF et al. 2014a, Bieber T et al. 2017, Boguniewicz M et al. 2017, Silverberg JI 2017). Itch is the central and debilitating manifestation, aggravated by mechanical injury inflicted by uncontrolled scratching and leading to bacterial, fungal, and viral infections, particularly *Staphylococcus aureus* and herpes simplex type 1 (Moyle M et al. 2019). Intense pruritus has a considerable negative impact on quality of life (QOL), sleep, and possible mental health disorders, including anxiety and depression.

[003] Typically, AD presents with an age-related morphology and distribution (Eichenfield LF et al. 2014a, Bieber T et al. 2017). The global prevalence of AD is estimated to be approximately 2-10% in adults. The incidence has increased by 2- to 3-fold during the past 3 decades in industrialized countries. The proportion of adult patients with childhood-onset and adult-onset AD is approximately 4 to 1. Patients having suffered from AD since childhood commonly present with comorbidities, including food allergy, asthma, and allergic rhinitis, while those with adult-onset AD are at risk for systemic complications, including rheumatoid arthritis and inflammatory bowel disease (Schmitt J et al. 2016).

[004] The pathogenesis of AD is multifactorial and includes abnormalities of the skin barrier, defects in the innate and adaptive immune response and alterations in the resident skin microflora (Boguniewicz M et al. 2017).

[005] Prurigo Nodularis (PN), also known as chronic nodular prurigo, is a chronic disease characterized by intensely pruritic, raised, nodular lesions. It is often characterized by an inflammatory skin disease characterized by the presence of chronic pruritus for ≥ 6 weeks, a history and/or signs of repeated scratching, picking, or rubbing of the skin, and the presence of firm, nodular skin lesions, which are usually symmetrically distributed on areas of the trunk and extremities (Elmariah S. et al. 2020). The itch in PN is characteristically intense,

causing people to scratch themselves and leading to the development of an itch-scratch cycle, which exacerbates the cellular damage in skin lesions, facilitates secondary infections and impairs quality of life (Mullins et al. 2022; Whang 2022).

[006] In the United States, PN has an estimated prevalence of 72 per 100,000 individuals in adults 18 to 64 years of age (Huang et al. 2020). A recent European study in a German population found an incidence rate of PN of 111 per 100,000 person-years (Ständer S 2020). Approximately 20-60% of patients have either past or current history of atopic dermatitis (AD) or other atopic disorders (Huang AH 2020; Iking A et al. 2013; Tanaka M et al. 1995; Fukushima S et al. 2011; Miyachi Y et al. 1980).

[007] Dysregulation of the innate immune system include changes in antimicrobial peptide (AMP) levels, reduced toll-like receptor (TLR) function, increased mast cells in the skin, increased levels of serum IgE, IgE-mediated degranulation and cytokine production, increased thymic stromal lymphopoietin (TSLP) by keratinocytes, increase in eosinophil infiltrates, dermal dendritic cell involvement, and basophil recruitment and activation (Boguniewicz M et al. 2017, Werfel et al. 2016, Weidinger S et al. 2018).

[008] Abnormalities of the adaptive immune system include an increase in TH2 lymphocytes, increased TH2 cytokine activity A (interleukin-4 (IL-4) and IL-13) which initiates B-cell IgE class switching, increase in TH1, TH17, and TH22 cells and their related cytokine and chemokine production (Weidinger S et al. 2018). Levels of thymus and activation-regulated chemokine (TARC/CCL17), a member of the T-helper 2 chemokine family, are associated with disease activity and sensitively reflect short-term changes in skin conditions (Kataoka Y 2014).

[009] Topical treatments (*e.g.*, emollients, corticosteroids, calcineurin or phosphodiesterase 4 inhibitors) reduce inflammation and pruritus and are useful in controlling acute flares and are therefore the mainstay of AD and PN therapy. However, the long-term use of topical corticosteroids should be avoided, as it may lead to cutaneous side effects such as skin atrophy, purpura, telangiectasis, and dyspigmentation (Weidinger S et al. 2018). Long-term use of corticosteroids, especially high- to very high-potency agents, may also lead to systemic side effects. Topical calcineurin inhibitors (TCIs) like tacrolimus and pimecrolimus are mostly used as second line therapy, either alone or in combination with topical corticosteroids (TCSs), and may incur side effects ranging from localized burning and stinging to an increased risk of lymphoma (Ahmed A et al. 2018). In addition to these known side effects, repeated application of any topical therapy over a long period of time or too large surface areas may lead to reduced patient compliance.

[0010] Systemic drugs are used in more severe forms of AD, when QOL is substantially impacted, and/or for treating PN. First generation antihistamines, which are widely prescribed for acute symptomatic treatment of pruritus, have limited efficacy and may have a sedating effect. Systemic glucocorticoids are associated with side effects such as diabetes, hypertension, and osteoporosis, thus limiting their use to short courses and/or intermittent therapy exposing patients to a risk of rebound after steroid discontinuation. First generation of oral immunosuppressants such as cyclosporine, methotrexate, mycophenolate mofetil, and azathioprine or leukotriene or calcineurin inhibitors have also been used in atopic dermatitis; however they are not devoid of adverse events. More recently, the Janus kinase (JAK) inhibitors such as baricitinib or upadacitinib have been approved for atopic dermatitis but they may carry an increased risk of serious infection, malignancies such as lymphomas and lung cancers, higher rate of all-cause mortality and MACE (defined as cardiovascular death, myocardial infarction, and stroke), pulmonary embolism, venous and arterial thrombosis. Dupilumab (anti-IL-4/IL-13) is also approved for AD and PN, and it needs to be given subcutaneously. Thus, there is an unmet need for a safe, effective, and easy-to-use oral drug in the field.

[0011] Bruton's agammaglobulinemia tyrosine kinase (BTK), an essential signaling element in B cells and innate immune cells, is expressed downstream of the B cell receptor (BCR), Fc-gamma receptor (FcγR), and Fc-epsilon receptor (FcεR) and serves a direct regulator of the NLRP3 inflammasome. BTK is a non-receptor tyrosine kinase and a member of the TEC family of kinases. BTK is essential to B cell differentiation, development, and antibody production. Illustratively, inhibition of BTK activity produces phenotypic changes consistent with blockade of the BCR, including the down-regulation of cell proliferation, differentiation, maturation, and survival, as well as the up-regulation of apoptosis.

[0012] Rather than acting in an "on/off switch" manner, BTK may be best viewed as an immune function "modulator" (Crofford LJ et al., 2016; Pal Singh S et al., 2018). Important insights into BTK function come from loss of function analyses in humans and mice. Individuals with loss of function mutations in the BTK gene develop X-linked agammaglobulinemia (XLA), characterized by a complete absence of circulating B cells and plasma cells, and very low levels of immunoglobulins of all classes (Tsukada 1993, Vetrie 1993). This indicates the potential for BTK inhibition to suppress production of autoantibodies thought to be important in the development of autoimmune diseases.

[0013] BTK also regulates the activation of other hematopoietic cells, such as mast cells, basophils, macrophages, and neutrophils primarily through Fc receptor signaling (Rip J et al. 2018). BTK integrates BCR signaling to regulate B cell development. IgE antibodies bind FcεR on mast cells and basophils to trigger degranulation and acute inflammation, whereas IgG binds FcγR on macrophages, plasmacytoid dendritic cells (pDCs) and natural killer cells to promote cellular activation or phagocytosis. BTK positively regulates FcεR signaling in mast cells and basophils and FcγR signaling in macrophages or pDCs to internalize and deliver immune complexes to initiate and perpetuate overactive skin immune responses (Zarrin AA et al. 2021).

[0014] While BTK is not expressed in T cells, natural killer cells, or plasma cells and has no traceable direct functions in T cells or plasma cells (Sideras and Smith 1995; Mohamed et al., 2009), the enzyme regulates the activation of other hematopoietic cells, such as B cells, monocytes, basophils, mast cells, macrophages, neutrophils, and platelets. For example, BTK plays a role in the activation of neutrophils, which are key players in the inflammatory response that contributes to wound healing but may also cause tissue damage (Volmering S et al., 2016).

[0015] BTK inhibition results in the down regulation of various immune cell activities including cell proliferation, differentiation, maturation, survival, cytokine production and the induction of apoptosis. Inhibition of BTK activity in B cells produces phenotypic changes consistent with blockade of the BCR, preventing activation, maturation, and antibody production. Inhibition of BTK in FcγR and FcεR expressing cells (such as macrophages or mast cells) blocks the inflammatory cytokine cascade driven by antibody cross-linking to the surface receptors (Chang BY et al. 2011, Xu D et al. 2012). Deficiency or inhibition of BTK has been shown to reduce disease in several immune-mediated rodent models. Pertinent to the treatment of patients with immune-mediated diseases, inhibitors of BTK have been shown to be anti-inflammatory in several rodent models of arthritis (Chang BY et al. 2011, Xu D et al. 2012, Di Paolo JA et al. 2011, Honigberg LA et al. 2010, Kim KH et al. 2011), and lupus (Honigberg LA et al. 2010, Crofford LJ et al. 2016, Hutcheson J et al. 2012) with inhibition of proteinuria, kidney histopathology, nephritis, and cutaneous endpoints. BTK inhibitors also inhibit acute skin inflammation and vasculitis in antibody induced arthritis reaction model and murine passive cutaneous anaphylaxis models (Chang BY et al. 2011).

[0016] AD is a Th2 inflammatory disease with multiple BTK innate dependent mechanisms (eosinophils infiltration, basophil recruitment and activation, mast cells increase and activation (IgE mediated degranulation and cytokine production), dermal dendritic cells

involvement through IgE/FcεR mechanisms). Accordingly, a selective BTK inhibitor has the potential to target multiple pathways involved in AD, including, but not limited to: blocking BCR signaling; inhibiting plasma cell differentiation and antibody production; blocking IgG-mediated FcγR activation, phagocytosis, and inflammatory mediators in monocytes or macrophages; blocking IgE-mediated FcεR activation and degranulation in mast cells or basophils; and inhibiting activation, adhesion, recruitment, and oxidative burst in neutrophils. Based on these effects, a selective BTK inhibitor may slow the progression or mitigate the symptoms of AD. Although individuals with loss of function mutations in the BTK gene have decreased humoral immunity and are susceptible to pyogenic bacterial and enterovirus infections, requiring treatment with intravenous immunoglobulin, inhibition of BTK in individuals with an intact immune system is not predicted to produce similar susceptibility to infection.

[0017] BTK appears as a possible attractive drug target in reducing the inflammation of AD by inhibiting the dysregulated signaling and activation of these pathogenic cells.

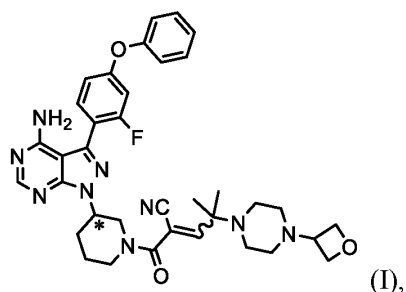
[0018] Like AD, PN is an inflammatory disease with multiple immune innate dependent mechanisms implicating several immune cells and cytokines. Further, 20-60% of patients have either past or current history of atopic dermatitis or other atopic disorders. Accordingly, a selective BTK inhibitor has the potential to target multiple pathways involved in PN by, for example, inhibiting basophile and mast cell activation.

[0019] Several orally administered BTK inhibitors (BTKi), including ibrutinib (PCI-32765) and spebrutinib (CC-292), are currently marketed or in clinical development for a range of indications (Lee A et al., 2017). For example, ibrutinib has provided further clinical validation of the BTK target and was recently approved for human use in mantle cell lymphoma, Waldenström's macroglobulinemia, and chronic lymphocytic leukemia by the U.S. Food and Drug Administration (FDA). Ibrutinib has also demonstrated activity in other hematological malignancies (Wang 2013; Byrd 2013; Imbruvica Package Insert, 2015). In addition, CC-292 has been reported to be well tolerated in a healthy volunteer population at doses which provide 100% occupancy of the BTK enzyme (Evans 2013). Furthermore, evobrutinib recently demonstrated efficacy for multiple sclerosis in a Phase 2 trial (Montalban X et al., 2019). Other BTKi compounds are in clinical development for various immune-mediated disorders, such as rheumatoid arthritis (NCT03823378, NCT03682705, NCT03233230), and asthma (NCT03944707) (Montalban X et al., 2019; Norman P 2016;

Tam CS et al., 2018; Crawford JJ et al., 2018; Min TK et al., 2019; Gillooly KM 2017; Nadeem A et al., 2019).

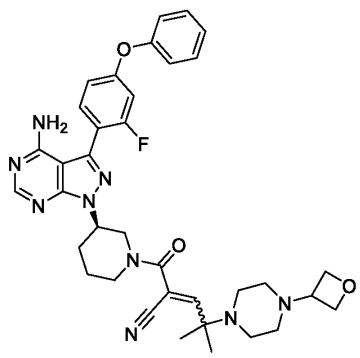
[0020] While covalent BTKi, such as ibrutinib and acalabrutinib, improved on the selectivity issues that plagued many first-generation kinase inhibitors, these inhibitors are typically irreversible, causing permanent modification of both on- and off-target kinases and side effects such as thrombocytopenia, anemia, platelet aggregation, and hepatotoxicity (RITUXAN Prescribing Information, 2018; Drug Record Kinase Inhibitors, 2019; Khan Y et al., 2019; Paydas S, 2019; IMBRUVICA, 2013; Rigg RA et al., 2016; Tang CPS et al., 2018). Thus, there is a need for treatment modalities for immune-mediated diseases such as AD and PN, based on BTKi with reduced side effects.

[0021] Compound (I) is a BTK inhibitor of the following structure:



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

[0022] (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-enitrile, having the following structure:



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

[0023] 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 PN, rilzabrutinib has the potential to (1) reduce the release of pruritogens from eosinophils, basophils, and mast cells, thereby reducing immune-mediated itch; (2) reduce the release of mediators that promote itch induction from eosinophils, basophils, and mast cells, thereby reducing sensitization and nerve fiber growth; (3) downregulate pathways involved in neurogenic inflammation; (4) and reduce the release of VEGF from eosinophils, basophils, and mast cells, thereby reducing hypervascularization (Hashimoto T et al., 2021; Kim B et al., 2023; Kolkhir P et al., 2023; Mukai K et al., 2018).

[0024] Rilzabrutinib functions as a reversible covalent BTK inhibitor and forms both a non-covalent and a covalent bond with 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.

[0025] 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).

[0026] 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).

[0027] 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).

[0028] Accordingly, disclosed herein are methods of treating itch associated with atopic dermatitis (AD) in a human patient in need thereof, including 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.

[0029] Also disclosed herein are methods of treating itch associated with prurigo nodularis (PN) in a human patient in need thereof, including 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.

[0030] Further disclosed herein are methods of treating itch associated with atopic dermatitis (AD) in a human patient in need thereof, including administering to the 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 patient has at least one of an inadequate response to topical corticosteroids (TCS); and an intolerance to TCS.

[0031] Further disclosed herein are methods of treating itch associated with prurigo nodularis (PN) in a human patient in need thereof, including administering to the 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 patient has at least one of an inadequate response to topical corticosteroids (TCS); and an intolerance to TCS.

[0032] 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof.

[0033] 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof.

[0034] 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof.

[0035] 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof.

[0036] 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof, wherein the patient

has at least one of an inadequate response to topical corticosteroids (TCS); and an intolerance to TCS.

[0037] 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof, wherein the patient has at least one of an inadequate response to topical corticosteroids (TCS); and an intolerance to TCS.

[0038] 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof, wherein the patient has at least one of an inadequate response to topical corticosteroids (TCS); and an intolerance to TCS.

[0039] 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof, wherein the patient has at least one of an inadequate response to topical corticosteroids (TCS); and an intolerance to TCS.

BRIEF DESCRIPTION OF DRAWINGS

[0040] **Fig. 1** shows a graphical representation of the main study design. R* indicates that the randomization of the TID cohort started after the enrollment of the BID cohort.

[0041] **Fig. 2** shows a graphical representation of the optional sub-study design.

[0042] **Fig. 3** shows the proportion of participants with a reduction of weekly average of PP-NRS ≥ 4 points at Week 16 (ITT population).

[0043] **Figs. 4A and B** show the proportion of participants in (A) the 400 mg rilzabrutinib BID cohort and (B) the 400 mg rilzabrutinib TID cohort with a reduction of weekly average of PP-NRS ≥ 4 points from baseline over time up to Week 16 (ITT population). Note: Participants who received any rescue medication or phototherapy before each timepoint were

considered as non-responders up to Week 16, and missing data at each timepoint were considered as non-responders up to Week 16.

[0044] **Fig. 5** shows the LS mean change from baseline in weekly average of PP-NRS at Week 16 (ITT population).

[0045] **Figs. 6A and B** show the LS mean change from baseline in weekly average of PP-NRS over time up to Week 16 for participants in **(A)** the 400 mg rilzabrutinib BID cohort and **(B)** the 400 mg rilzabrutinib TID cohort (ITT population).

[0046] **Fig. 7** shows the LS mean percent change from baseline in weekly average of PP-NRS over time at Week 16 (ITT population).

[0047] **Figs. 8A and B** show the LS mean percent change from baseline in weekly average of PP-NRS over time up to Week 16 for participants in **(A)** the 400 mg rilzabrutinib BID cohort and **(B)** the 400 mg rilzabrutinib TID cohort (ITT population).

[0048] **Figs. 9A and B** show a Kaplan-Meier curve of time to first PP-NRS reduction from baseline ≥ 4 points during 16-week intervention period for participants in **(A)** the 400 mg rilzabrutinib BID cohort and **(B)** the 400 mg rilzabrutinib TID cohort (ITT population).

[0049] **Figs. 10A and B** shows the cumulative distribution function curves of change in weekly average of PP-NRS from baseline to Week 16 for participants in **(A)** the 400 mg rilzabrutinib BID cohort and **(B)** the 400 mg rilzabrutinib TID cohort (ITT population). Note: data collected after study intervention discontinuation were included. Data post the use of any rescue medication or phototherapy were set to missing and imputed by WOCF. Missing data after study intervention discontinuation due to lack of efficacy were imputed by WOCF.

[0050] **Fig. 11** shows the median percent change from baseline in serum levels of thymus and activation regulated chemokine (TARC) over time up to Week 16.

[0051] **Fig. 12** shows the normalized enrichment score for gene pathways enriched in lesional skin tape strip samples collected at baseline and Week 16.

Definitions:

[0052] 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.

[0053] 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.

[0054] 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.

[0055] As used herein, the term “active pharmaceutical ingredient” or “therapeutic agent” (“API”) refers to a biologically active compound.

[0056] As used herein, the term “approved treatment” refers to a medication that has received regulatory authorization, in any country, for its intended use.

[0057] 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.

[0058] As used herein, the term “baseline” or “baseline value” is defined as a measurement or an average of measurements taken on or before day 1 (D1) of initiating rilzabrutinib treatment. By way of non-limiting example, baseline can be determined for, e.g., PP-NRS.

[0059] As used herein, the term “inadequate response,” when referring to topical corticosteroid (TCS) treatment, comprises failure to achieve and maintain remission or low disease activity (e.g., IGA 0 = clear to 2 = mild) despite treatment with TCS of medium to high potency ($\pm$ topical calcineurin inhibitor as appropriate), applied daily for at least 28 days or for the maximum duration recommended by the product prescribing information (e.g., 14 days for superpotent TCS), whichever was shorter. Patients who failed systemic therapies intended to treat AD within 6 months preceding screening, such as cyclosporine, methotrexate, azathioprine, and mycophenolate will be also considered as surrogates for having inadequate response to topical therapy.

[0060] 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.

[0061] As used herein, the term “intolerance,” when referring to TCS treatment, means that a patient has experienced important side effects or safety risks defined as those that outweighed the potential treatment benefits (*e.g.*, hypersensitivity reactions, significant skin atrophy, systemic effects, *etc.*... or imminence thereof), assessed by the investigator or treating physician.

[0062] 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.

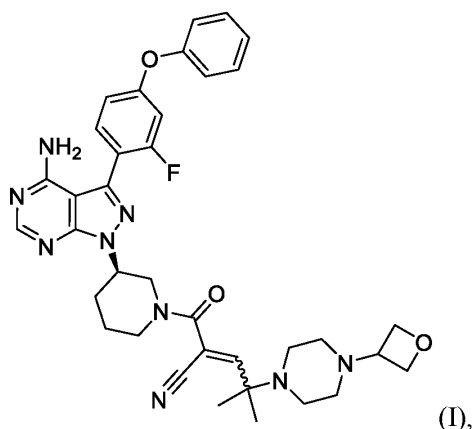
[0063] As used herein, the term “moderate-to-severe” encompasses patients with either “moderate” or “severe” disease, such as moderate AD or severe AD.

[0064] 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.

[0065] 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.

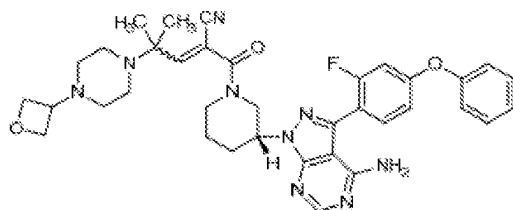
[0066] As used herein, the terms “rilzabrutinib,” “(R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile;” “the compound of Formula (I);” and “2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]-pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile” are used interchangeably to refer to a compound having the structure:



which is also referred to as 2-[(3R)-2-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-(E and Z)-pent-2-enenitrile; (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile; 1-piperidinepropanenitrile, 3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-α-[2-methyl-2-[4-(3-oxetanyl)-1-piperazinyl]propylidene]-β-oxo-, (3R)-; (EZ)-2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile; and also by the International Nonproprietary Names for Pharmaceutical Substances (INN) as published by the World Health Organization

(<https://cdn.who.int/media/docs/default-source/international-nonproprietary-names->

(inn)/pl121.pdf?sfvrsn=69617906_15&download=true) 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.

[0067] A dose of the (E) isomer of rilzabrutinib may contain the corresponding (Z) isomer as an impurity in less than about 1% by weight; a dose of the (Z) isomer of rilzabrutinib may contain the corresponding (E) isomer as an impurity in less than about 1% by weight. When rilzabrutinib is denoted as a mixture of (E) and (Z) isomers of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enitrile, it means that the amount of (E) or (Z) isomer in the mixture is greater than about 2% 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.”

[0068] As used herein, “QD” and “qd” are used interchangeably to refer to once a day.

[0069] 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 AD or a symptom of AD, or lessening the severity of AD or a symptom of AD, or improvement in PN or a symptom of PN, or lessening the severity of PN or a symptom of PN). 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*).

[0070] 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.

[0071] The present disclosure provides methods of treating itch associated with atopic dermatitis (AD) in a human patient in need thereof. The present disclosure provides methods of treating itch associated with prurigo nodularis (PN) in a human patient in need thereof. In

some embodiments, the methods include 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.

[0072] In some embodiments, the methods include 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 has at least one of an inadequate response to topical corticosteroids (TCS), and an intolerance to TCS. In at least one embodiment, the methods include administering to the human patient in need thereof a therapeutically effective amount of rilzabrutinib.

[0073] In some embodiments, the disclosed methods of treating itch associated with atopic dermatitis (AD) are provided to a patient having moderate-to-severe AD. In some embodiments, the disclosed methods of treating itch associated with prurigo nodularis (PN) are provided to a patient having AD. In some embodiments, the disclosed methods are provided to a patient having moderate AD. In some embodiments, the disclosed methods are provided to a patient having severe AD. In some embodiments, the disclosed methods are provided to a patient that has an inadequate response to topical corticosteroids (TCS). In some embodiment, the disclosed methods are provided to a patient that has an intolerance to TCS.

[0074] The disclosed methods, in some embodiments, are provided to a patient having at least two, for example, at least three, at least four, at least five, at least six, or all of the following characteristics:

- (a) a history of atopic dermatitis (AD) for at least 12 months;
- (b) an Eczema Area and Severity Index (EASI) score ≥ 12 ;
- (c) an Investigator's Global Assessment (IGA) score ≥ 3 on the 0 to 4 IGA scale;
- (d) a body surface area (BSA) of AD involvement score ≥ 10 ;
- (e) an inadequate response or intolerance to topical corticosteroids (TCS) within 6 months prior to treatment;
- (f) an inadequate response to one or more of cyclosporine, methotrexate, azathioprine, and mycophenolate; and

(g) a baseline Peak Pruritis Numerical Rating Scale (PP-NRS) score for maximum itch intensity of ≥ 4 .

[0075] In some embodiments, the disclosed methods are provided to a patient that has at least three of the above-listed characteristics. In some embodiments, the patient has at least four of the above-listed characteristics. In some embodiments, the patient has at least five of the above-listed characteristics. In some embodiments, the patient has at least six of the above-listed characteristics. In some embodiments, the patient has two of the above-listed characteristics. In some embodiments, the patient has three of the above-listed characteristics. In some embodiments, the patient has four of the above-listed characteristics. In some embodiments, the patient has five of the above-listed characteristics. In some embodiments, the patient has six of the above-listed characteristics. In some embodiments, the patient has no more than two of the above-listed characteristics. In some embodiments, the patient has no more than three of the above-listed characteristics. In some embodiments, the patient has no more than four of the above-listed characteristics. In some embodiments, the patient has no more than five of the above-listed characteristics. In some embodiments, the patient has no more than six of the above-listed characteristics.

[0076] In some embodiments, the disclosed methods of treating itch associated with atopic dermatitis (AD) and/or prurigo nodularis (PN) are provided to a human patient achieving a Peak Pruritis Numerical Rating Scale (PP-NRS) score that is lower than baseline PP-NRS. For example, in some embodiments, the patient achieves a PP-NRS score that is at least four points lower than baseline PP-NRS. In some embodiments, the patient achieves a PP-NRS score that is lower than baseline PP-NRS within three weeks of treatment. In some embodiments, the patient achieves a PP-NRS score that is at least four points lower than baseline PP-NRS within three weeks of treatment. In some embodiments, the patient achieves a PP-NRS score that is lower than baseline PP-NRS within two weeks of treatment. In some embodiments, the patient achieves a PP-NRS score that is lower than baseline PP-NRS within one week of treatment. In some embodiments, the patient achieves a PP-NRS score that is at least four points lower than baseline PP-NRS within one week of treatment.

[0077] In some embodiments, the disclosed methods of treating itch associated with atopic dermatitis (AD) and/or prurigo nodularis (PN) are provided to a patient having baseline IgE levels of <300 UI/mL. In at least one embodiment, the patient has baseline IgE levels ≥ 300 UI/mL.

[0078] In some embodiments, the disclosed methods of treating itch associated with atopic dermatitis (AD) and/or prurigo nodularis (PN) are provided to a patient receiving at least one

concomitant treatment chosen from: low-to-medium potency TCS, topical crisaborole, and topical calcineurin inhibitors. In some embodiments, the patient is receiving at least two concomitant treatments chosen from: low-to-medium potency TCS, topical crisaborole, and topical calcineurin inhibitors. In some embodiments, the patient is receiving at least three concomitant treatments chosen from: low-to-medium potency TCS, topical crisaborole, and topical calcineurin inhibitors. In some embodiments, the patient is receiving no more than one concomitant treatment chosen from: low-to-medium potency TCS, topical crisaborole, and topical calcineurin inhibitors. In some embodiments, the patient is receiving no more than two concomitant treatments chosen from: low-to-medium potency TCS, topical crisaborole, and topical calcineurin inhibitors. In some embodiments, the patient is receiving no more than three concomitant treatments chosen from: low-to-medium potency TCS, topical crisaborole, and topical calcineurin inhibitors.

[0079] In some embodiments, the present disclosure provides methods of treating itch associated with atopic dermatitis (AD) and/or prurigo nodularis (PN) during a specific treatment period. In at least one embodiment, the treatment period is at least 16 weeks.

[0080] In some embodiments, the present disclosure provides methods of treating itch associated with atopic dermatitis (AD) and/or prurigo nodularis (PN) with a specific amount of at least one compound chosen from rilzabrutinib and pharmaceutically acceptable salts thereof. For example, in at least one embodiment, the methods include administering to the patient about 400 mg of at least one compound chosen from rilzabrutinib and pharmaceutically acceptable salts thereof. In some embodiments, the methods include administering to the patient 400 mg of at least one compound chosen from rilzabrutinib and pharmaceutically acceptable salts thereof.

[0081] In some embodiments, the present disclosure provides methods of treating itch associated with atopic dermatitis (AD) and/or prurigo nodularis (PN) in a patient in need thereof by administering at least one compound chosen from the (E) isomer of rilzabrutinib and pharmaceutically acceptable salts thereof. In some embodiments, at least one compound consisting of at least one compound chosen from the (Z) isomer of rilzabrutinib and pharmaceutically acceptable salts thereof is administered to the patient. In some embodiments, at least one compound consisting of a mixture of (E) and (Z) isomers of rilzabrutinib or a pharmaceutically acceptable salt of the foregoing, is administered to the patient. In at least one embodiment, the at least one compound is the (E) isomer of rilzabrutinib. In at least one embodiment, the at least one compound is the (Z) isomer of

rilzabrutinib. In at least one embodiment, the at least one compound consists of a mixture of (E) and (Z) isomers of rilzabrutinib.

[0082] The disclosed methods, in some embodiments, include treating itch associated with atopic dermatitis (AD) and/or prurigo nodularis (PN) in a patient in need thereof by administering to the patient the at least one compound via oral administration.

[0083] In some embodiments, the present disclosure provides methods of treating itch associated with atopic dermatitis (AD) and/or prurigo nodularis (PN) in a patient in need thereof by administering to the human patient rilzabrutinib twice or thrice a day. In some embodiments, the methods include administering to the human patient rilzabrutinib twice a day. In some embodiments, the methods include administering to the human patient rilzabrutinib thrice a day.

[0084] In some embodiments, the present disclosure provides methods of treating itch associated with atopic dermatitis (AD) and/or prurigo nodularis (PN) in a patient in need thereof by administering to the patient about 400 mg of at least one compound chosen from rilzabrutinib and pharmaceutically acceptable salts thereof, twice or thrice a day. In some embodiments, the present disclosure provides methods of treating itch associated with atopic dermatitis (AD) and/or prurigo nodularis (PN) in a patient in need thereof by administering to the patient 400 mg of at least one compound chosen from rilzabrutinib and pharmaceutically acceptable salts thereof, twice or thrice a day. In some embodiments, the methods include administering to the patient about 400 mg of rilzabrutinib twice a day. In some embodiments, the methods include administering to the patient 400 mg of rilzabrutinib twice a day. In some embodiments, the methods include administering to the patient about 400 mg of rilzabrutinib thrice a day. In some embodiments, the methods include administering to the patient 400 mg of rilzabrutinib thrice a day.

[0085] In some embodiments, the disclosed methods of treating itch associated with atopic dermatitis (AD) and/or prurigo nodularis (PN) in a patient in need thereof include treatment with at least one compound that is administered to the patient in the form of at least one tablet. In some embodiments, the patient is administered the at least one compound in the form of one tablet. In some embodiments, the patient is administered the at least one compound with water.

[0086] In some embodiments, the at least one compound is rilzabrutinib.

[0087] In some embodiments, the method further comprises administering at least one topical corticosteroid (TCS). In some embodiments, the patient is administered the TCS prior to administration of the at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-

phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof. In some embodiments, the patient is administered the TCS after administration of the at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof. In some embodiments, the patient is administered both the TCS and the 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 on the same day or days.

[0088] In some embodiments, the only therapeutic agent administered is the 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.

[0089] In some embodiments, the human patient achieves a reduction in serum levels of TARC or IL-31. In some embodiments, the human patient achieves a reduction in serum levels of TARC. In some embodiments, the human patient achieves at least a 5%, 10%, 15%, 20%, 25%, 30%, or 35% reduction in serum levels of TARC. In some embodiments, the human patient achieves at least a 10% reduction in serum levels of TARC. In some embodiments, the human patient achieves at least a 20% reduction in serum levels of TARC. In some embodiments, the human patient achieves at least a 30% reduction in serum levels of TARC. In some embodiments, the human patient achieves a reduction in serum levels of IL-31.

[0090] In some embodiments, the human patient achieves a reduction in the expression of one or more of NGF-TrkA, TPH1, IL-31, NMBR, Alox5AP, and TPS1 in lesional skin. In some embodiments, the human patient achieves a reduction in the expression of NGF-TrkA. In some embodiments, the human patient achieves a reduction in the expression of TPH1. In some embodiments, the human patient achieves a reduction in the expression of IL-31. In some embodiments, the human patient achieves a reduction in the expression of NMBR. In some embodiments, the human patient achieves a reduction in the expression of Alox5AP. In some embodiments, the human patient achieves a reduction in the expression of TPS1.

[0091] In some embodiments, the present disclosure provides for the use of a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-

phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof for treating itch associated with prurigo nodularis (PN) in a human patient in need thereof.

[0092] In some embodiments, the present disclosure provides for the use of a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof in the manufacture of a medicament for treating itch associated with prurigo nodularis (PN) in a human patient in need thereof.

[0093] In some embodiments, the present disclosure provides for a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for use in treating itch associated with prurigo nodularis (PN) in a human patient in need thereof.

[0094] In some embodiments, the present disclosure provides for a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof, for use in the manufacture of a medicament for treating itch associated with prurigo nodularis (PN) in a human patient in need thereof.

[0095] In some embodiments, the present disclosure provides for the use of a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof for treating itch associated with prurigo nodularis (PN) in a human patient in need thereof, wherein the patient has at least one of an inadequate response to topical corticosteroids (TCS); and an intolerance to TCS.

[0096] In some embodiments, the present disclosure provides for the use of a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof in the manufacture of a medicament for treating itch associated with prurigo

nodularis (PN) in a human patient in need thereof, wherein the patient has at least one of an inadequate response to topical corticosteroids (TCS); and an intolerance to TCS.

[0097] In some embodiments, the present disclosure provides for a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof for use in treating itch associated with prurigo nodularis (PN) in a human patient in need thereof, wherein the patient has at least one of an inadequate response to topical corticosteroids (TCS); and an intolerance to TCS.

[0098] In some embodiments, the present disclosure provides for a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (rilzabrutinib) and pharmaceutically acceptable salts thereof for use in the manufacture of a medicament for treating itch associated with prurigo nodularis (PN) in a human patient in need thereof, wherein the patient has at least one of an inadequate response to topical corticosteroids (TCS); and an intolerance to TCS.

Pharmaceutical Compositions:

[0099] 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.

[00100] 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.

[00101] In some embodiments, rilzabrutinib is administered in the form of a film-coated tablet.

[00102] 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.

[00103] In some embodiments, rilzabrutinib is administered with a glass of water.

[00104] 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.

[00105] 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.

[00106] Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D.B. Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York also discloses additional non-limiting examples of pharmaceutically acceptable excipients, as well as known techniques for preparing and using the same.

[00107] 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

[00108] The following example is intended to be illustrative and is not meant in any way to limit the scope of the disclosure.

Abbreviations:

AD	Atopic dermatitis
AE	Adverse event
AESI	Adverse event of special interest
Alox5AP	Arachidonate 5-lipoxygenase activating protein
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMP	Antimicrobial peptide
ANCOVA	Analysis of covariance)
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BHRA	Basophil histamine release assay
BID	Twice a day
BSA	Body surface area
BTK	Bruton's tyrosine kinase
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel test
COVID-19	Coronavirus disease 2019
CPK	Creatine kinase
CRF	Case report form
CYP	Cytochrome P450
D	Day
DTP	Direct to patient
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eCRF	Electronic case report form

ED	Early discontinuation
e-diary	Electronic diary
EOS	End of study
EOT	End of treatment
FcεR	Fc-epsilon receptor
FDA	Food and Drug Administration
H2	Histamine 2
HBV	Hepatitis B virus (Hep B)
HCV	Hepatitis C virus (Hep C)
HCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
hS-CRP	High-sensitivity C-reactive protein
ICF	Informed consent form
IEC	Independent ethics committee
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgG4-RD	Immunoglobulin G4-related disease
IL	Interleukin
IL-31	Interleukin 31
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent-to-treat
ITP	Immune thrombocytopenia
JAK	Janus kinase
LDH	Lactate dehydrogenase
LAR	Legally authorized representative
LDH	Lactate dehydrogenase

LS	Least square
MI	Multiple imputation
NGF	Nerve growth factor
NIMP	Non-investigative medicinal product
NMBR	Neuromedin B receptor
NRS	Numerical rating scale
PK	Pharmacokinetic
PBMC	Peripheral blood mononuclear cell
PCSA	Potentially clinically significant abnormality
PP-NRS	Peak pruritis numerical rating scale
QD	Once per day
QFT	QuantiFERON test
qRT-PCR	Quantitative reverse transcription polymerase chain reaction
QOL	Quality of life
RAST	Radioallergosorbent test
RBC	Red blood cell
SAE	Serious adverse event
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reaction
TARC	Thymus and activation regulated chemokine
TB	Tuberculosis
TBNK	T, B, and natural killer cells
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroids
TEAE	Treatment emergent adverse event
TID	Three times a day
TPH1	Tryptophan hydroxylase 1
TPS1	Tryptase alpha
TrkA	Tropomyosin receptor kinase A

ULN	Upper limit of normal
wAIHA	Warm autoimmune hemolytic anemia
WBC	White blood cell
WOCBP	Woman of childbearing potential
WOCF	Worst observation carried forward
WONCBP	Woman of non-childbearing potential
V	Visit
Wk	Week

Example 1: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multicenter Proof-of-Concept Study Evaluating Efficacy and Safety of Rilzabrutinib in Adult Patients with Moderate-to-Severe Atopic Dermatitis Who are Inadequate Responders or Intolerant to Topical Corticosteroids.

Rationale:

[00109] Rilzabrutinib, a selective Bruton's tyrosine kinase (BTK) inhibitor, is an investigational drug being developed as an oral agent for the treatment of immune-mediated dermatological diseases. This study explored the efficacy and safety of rilzabrutinib in participants with moderate-to-severe atopic dermatitis (AD).

Study overview:

[00110] This was a parallel treatment, Phase 2, double-blind, 2-arm, placebo-controlled study with 2 staggered cohorts (2 arms in each cohort) in adult participants (aged at least 18 years) with moderate-to-severe AD and intolerance or inadequate response to topical corticosteroids (TCS).

[00111] Participants were enrolled into 2 staggered dose regimen cohort. The first cohort received 400 mg rilzabrutinib twice a day (BID), while the second cohort received 400 mg rilzabrutinib three times a day (TID) (**Figure 1**). These 2 dose regimen cohorts were evaluated using the same double-blind approach and assessments.

[00112] Adult participants who met the inclusion/exclusion criteria were stratified by immunoglobulin E (IgE) levels ($<$ or ≥ 300 UI/mL) at screening and were randomized in a 3:2 allocation ratio to receive either rilzabrutinib or matching placebo on Day 1 (Week 0, Visit 2). The total study duration per participant was approximately 21 weeks, including up to 4 weeks for Screening, 16 weeks on-treatment double-blind period, and 1-week post-treatment follow-up.

[00113] An optional sub-study was proposed to participants for skin tape strip samples to be taken at baseline and Week 16 for exploratory biomarkers analysis.

Objectives and endpoints:

[00114] The objectives and endpoints for the study are shown in **Table 1**.

Table 1. Objectives and Endpoints.

Objectives	Endpoints
Primary	
Assess the efficacy of rilzabrutinib in participants with atopic dermatitis (AD)	Percent change from baseline to Week 16 in Eczema Area and Severity Index (EASI) score
Secondary	
Assess the efficacy of rilzabrutinib at different time points	• Proportion of participants with Investigator's Global Assessment (IGA) of 0 or 1 (disease free or almost disease free) compared to placebo at Week 16 • Proportion of participants achieving EASI-75 (reduction of EASI score by $\geq 75\%$ from baseline) at Week 16 • Proportion of participants with reduction of weekly average of daily peak pruritis Numerical Rating Scale (PP-NRS) of ≥ 4 points from baseline at Week 16 • Time to onset of effect on pruritis (≥ 4 points reduction of weekly average of daily PP-NRS from baseline during the 16-week treatment period) • Absolute change from baseline to Week 16 in EASI score • Proportion of participants achieving EASI-50/90 (reduction of EASI score by $\geq 50\%$ or $\geq 90\%$ from baseline) at Week 16 • Change from baseline to Week 16 in percent body surface areas (BSA) of EASI • Change (absolute and percentage change) on weekly average of daily PP-NRS based on daily participant assessments documented in their electronic diary (e-diary) from baseline to Week 16 • Proportion of participants achieving IGA*BSA-50/75/90 (reduction of IGA*BSA by $\geq 50\%$ or 75% or 90% from baseline) at Week 16
Assess the safety of rilzabrutinib.	• Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) from baseline to Week 16

	Incidence of study investigational medicinal product (IMP) discontinuation and withdrawals due to TEAEs from baseline to Week 16
Exploratory	
Assess the plasma pharmacokinetics (PK) of rilzabrutinib, and Bruton's tyrosine kinase (BTK) occupancy in peripheral blood mononuclear cells (PBMCs)	- Plasma PK concentrations of rilzabrutinib - BTK occupancy in PBMCs
Assess the effect of rilzabrutinib on biomarkers	Change from baseline in total immunoglobulin E (IgE), total immunoglobulin G (IgG), total immunoglobulin M (IgM), cytokines/chemokines profiling including thymus and activation-regulated chemokine (TARC), and histamine release factors including functional autoantibodies against FcεRI
Assess the effect of rilzabrutinib based on IgE Screening levels	EASI and PP-NRS in subgroups of participants with Screening IgE level < or ≥300 UI/mL
Optional sub-study: elucidate the effects of rilzabrutinib on tissue resident immune cells using a skin tape strip and comparison with blood test results	Optional sub-study: Skin tape strip at baseline and Week 16 for exploratory biomarkers analysis (such as, but not limited to, ribonucleic acid (RNA) sequencing and quantitative reverse transcription polymerase chain reaction (qRT-PCR) of immune and barrier biomarkers)

Appropriateness of measurements:

[00115] Efficacy was assessed using EASI, IGA, and PP-NRS. EASI was assessed by the investigator to measure severity and extent of AD. IGA is a static measure of disease severity used by the investigator. PP-NRS is a tool that patients use to report the intensity of their itch during a daily recall period using an electronic diary (e-diary). EASI, IGA and PP-NRS are validated scales and can be used reliably in clinical trials.

[00116] In terms of safety, TEAEs, SAEs, adverse events of special interest (AESIs), vital signs, electrocardiograms (ECGs), and laboratory analyses were to be reported.

[00117] Since this study was primarily aimed at assessing efficacy and safety, PK and PD were assessed as exploratory endpoints.

[00118] **Overall design:**

[00119] This study was 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 at least 18 years) with moderate-to-severe AD and intolerance or inadequate response to TCS.

[00120] Participants were enrolled into 2 staggered dose regimen cohorts: a BID cohort and a TID cohort, starting with the BID cohort. These 2 dose regimen cohorts were evaluated in the same double-blind fashion and using the same assessments.

[00121] An optional sub-study was proposed to participants for skin tape strip samples to be taken at baseline and Week 16 for exploratory biomarkers analysis.

Number of participants:

[00122] The total number of participants in this study was to be approximately 136.

[00123] For the main study, approximately 120 adult participants who met the inclusion/exclusion criteria were to be stratified by immunoglobulin E (IgE) levels ($<$ or $\geq$ 300 UI/mL) at Screening and were to be randomized in a 3:2 allocation ratio to receive either rilzabrutinib or matching placebo on Day 1 (Week 0, Visit 2). In the BID cohort, approximately 50 participants were to receive either rilzabrutinib ($n = 30$) or matching placebo ($n = 20$) twice a day, and in the TID cohort, approximately 70 participants were to receive either rilzabrutinib ($n = 42$) or matching placebo ($n = 28$) three times a day.

Intervention groups and duration:

[00124] The duration of the study for a participant was expected to be approximately 21 weeks and was to include a screening period of up to 4 weeks; a double-blind IMP treatment period of 16 weeks $\pm$ 3 days; and a post-treatment safety follow-up period of 1 week $\pm$ 3 days. The End of Treatment (EOT) visit was planned on Week 16 after the last dose of IMP (morning of Week 16 visit). The End of Study (EOS) visit was to be 7 days after the last dose of IMP.

[00125] For the main study, an interim analysis was to be performed before the final database lock.

Screening period

[00126] Participants were to be trained on using electronic questionnaires (e-diary) at the Screening visit (Visit 1). They were to have recorded pruritus NRS scores daily during the screening period for training purposes. Nevertheless, clinical site staff were only to review pruritus NRS scores collected on the e-diary beginning 7 days preceding the baseline visit (Visit 2) and the data that were not reviewed by clinical site staff (between D-28 and D-7) were not to be transferred to the Sponsor. Baseline PP-NRS score for maximum itch intensity were to be determined based on the average of daily NRS scores for maximum itch intensity during the 7 days immediately preceding randomization. A minimum of 4 daily scores out of the 7 days was required to calculate the baseline average score. For participants who did not have at least 4 daily scores reported during the 7 days immediately preceding the planned randomization date, randomization was to be postponed until this requirement is met, but without exceeding the 28-day maximum duration for Screening.

[00127] Participants were to be queried on personal and family history of allergies (aeroallergens, dust mites, cats, and mold). Results of historical skin testing (prick/puncture (percutaneous) or intradermal (intracutaneous) or RAST) were to be collected. At sites able to conduct RAST testing or skin prick testing, participants who did not have a past history of skin testing were to undergo RAST testing or skin prick testing at Screening and results were to be collected in the corresponding electronic case report form (eCRF) page.

[00128] Intervention period

[00129] Participants were to record pruritus NRS scores, rilzabrutinib dosing times, compliance with rilzabrutinib and background topical treatment (*i.e.*, moisturizers/emollients) every day during the intervention period of the study using e-diary.

[00130] Participants were to be assessed for efficacy (at on-site visits: baseline, Week 2, 4, 8, 12 and 16, and at unscheduled visits (if unscheduled visits occurred)), safety (continuous assessment throughout the course of the study), PD and PK at different timepoints. As much as possible, morning visits were preferable to permit collection of pre-dose PK samples. On visit days, the participants were to be invited to take their morning dose at the clinic, after predose PK samples have been collected. Unless permanently discontinued from the study, all participants were to complete the scheduled study visits and assessments

whether or not they complete study intervention treatment and whether or not they receive rescue treatment for AD.

[00131] Participants may have received rescue therapy for AD at the discretion of the Investigator at any time during the study, if judged medically necessary. The participants were to continue study intervention if rescue consisted of the following medications: low to medium potency TCS, topical crisaborole, or TCIs. Topical calcineurin inhibitors may have been used for rescue but should have been reserved for problem areas only (*e.g.*, face, neck, intertriginous and genital areas, etc.). If a participant received rescue treatment with high potency TCS, systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.), study intervention was to have been immediately discontinued. After the treatment with these medications was completed, study intervention may have been resumed if deemed appropriate by the Investigator and the medical monitor, but not sooner than 5 half-lives after the last dose of the rescue medication. Investigators were to make every attempt to conduct efficacy and safety assessments (*e.g.*, disease severity scores, safety labs) immediately before administering any rescue treatment with high potency TCS or systemic medications. An unscheduled visit may have been used for this purpose if necessary. For the purpose of efficacy analysis, participants who received high potency TCS or systemic medications during the study intervention period were to be considered treatment failures.

End of study definition

[00132] The end of the study is defined as the date of the last visit/last contact of the last participant in the study. A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure.

Study population

[00133] Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, was not permitted.

Inclusion criteria

[00134] Participants were eligible to be included in the study only if all of the following criteria apply:

[00135] *Age*: Participants must have been 18 years of age, inclusive, or older at the time of signing the informed consent.

[00136] *Type of participants and disease characteristics*: Patients were required to have each of the following criteria: AD as defined by the American Academy of Dermatology Consensus Criteria (Eichenfield LF et al. 2014a); a history of AD for at least 12 months prior to baseline as determined by the Investigator through patient interview; Eczema Area and Severity Index (EASI) score ≥ 12 during screening¹ and at baseline; IGA score ≥ 3 (on the 0 to 4 IGA scale) at baseline; BSA² of AD involvement $\geq 10\%$ at baseline; documented³ inadequate response⁴ or intolerance⁵ to TCS within 6 months prior to baseline visit; documented⁶ inadequate response⁷ or intolerance⁸ to TCS within 6 months prior to

¹ Patients with EASI score between 10 to 12 may have been re-tested once during the screening phase if, per investigator's judgement, the results may have evolved up to ≥ 12 during screening.

² BSA was estimated by assessing each section of the body (the highest possible score for each region is: head and neck (10%), trunk including genitalia (30%), upper limbs (20%), lower limbs (40%)) and was to be reported as a percentage of all major body sections combined.

³ Acceptable documentation included contemporaneous chart notes that recorded TCS prescription and treatment outcome, or Investigator documentation based on communication with the patient's treating physician, the patient's pharmacist, or the patient.

⁴ Failure to achieve and maintain remission or low disease activity (*e.g.*, IGA 0 = clear to 2 = mild) despite treatment with TCS of medium to high potency ($\pm$ topical calcineurin inhibitor as appropriate), applied daily for at least 28 days or for the maximum duration recommended by the product prescribing information (*e.g.*, 14 days for superpotent TCS), whichever was shorter. Patients who failed systemic therapies intended to treat AD within 6 months preceding screening, such as cyclosporine, methotrexate, azathioprine, and mycophenolate were also to be considered as surrogate for having inadequate response to topical therapy.

⁵ Important side effects or safety risks defined as those that outweighed the potential treatment benefits (*e.g.*, hypersensitivity reactions, significant skin atrophy, systemic effects, etc.... or imminence thereof), assessed by the investigator or treating physician.

⁶ Acceptable documentation included contemporaneous chart notes that recorded TCS prescription and treatment outcome, or Investigator documentation based on communication with the patient's treating physician, the patient's pharmacist, or the patient.

⁷ Failure to achieve and maintain remission or low disease activity (*e.g.*, IGA 0 = clear to 2 = mild) despite treatment with TCS of medium to high potency ($\pm$ topical calcineurin inhibitor as appropriate), applied daily for at least 28 days or for the maximum duration recommended by the product prescribing information (*e.g.*, 14 days for superpotent TCS), whichever was shorter. Patients who failed systemic therapies intended to treat AD within 6 months preceding screening, such as cyclosporine, methotrexate, azathioprine, and mycophenolate were also to be considered as surrogate for having inadequate response to topical therapy.

⁸ Important side effects or safety risks defined as those that outweighed the potential treatment benefits (*e.g.*, hypersensitivity reactions, significant skin atrophy, systemic effects, etc.... or imminence thereof), assessed by the investigator or treating physician.

baseline visit; and baseline PP-NRS score for maximum itch intensity $\geq 4^9$.

[00137] *Weight*: Not applicable.

[00138] *Sex, contraceptive/barrier method and pregnancy testing requirements*: All contraceptive use by men and women was to be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

[00139] *Male participants*: Male participants were eligible to participate if they agreed to refrain from donating or cryopreserving sperm during the study intervention period and for at least 13 weeks after the last administration of study intervention. Additionally, they must have either (1) been abstinent (from heterosexual or homosexual intercourse) as their preferred and usual lifestyle (*i.e.*, been abstinent on a long term and persistent basis) and agreed to remain abstinent or (2) agreed to use contraception/barrier¹⁰.

[00140] *Female participants*: A female participant was eligible to participate if she was not pregnant or breastfeeding, and one of the following conditions applied:

[00141] The participant was (1) a woman of nonchildbearing potential (WONCBP) or (2) a WOCBP and agreed to use a contraceptive method that is highly effective (with a failure rate of $< 1\%$ per year), 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 intervention and agreed not to donate or cryopreserve eggs (ova, oocytes) for the purpose of reproduction during this period.

[00142] A WOCBP must have had a negative highly sensitive pregnancy test (serum as required by local regulations) within 28 days before the first administration of study

⁹ Baseline PP-NRS score for maximum itch intensity was to be determined based on the average of daily NRS scores for maximum itch intensity (the daily score ranges from 0 to 10) during the 7 days immediately preceding randomization. A minimum of 4 daily scores out of the 7 days was required to calculate the baseline average score. For patients who did not have at least 4 daily scores reported during the 7 days immediately preceding the planned randomization date, randomization was to be postponed until this requirement is met, but without exceeding the 28-day maximum duration for screening.

¹⁰ *I.e.*, a male condom and an additional highly effective contraceptive method when having sexual intercourse with a woman of childbearing potential (WOCBP) who was not currently pregnant or a male condom when engaging in any activity that allows for passage of ejaculate to another person.

intervention. If a urine test could not be confirmed as negative (*e.g.*, an ambiguous result), a serum pregnancy test was required. In such cases, the participant must have been excluded from participation if the serum pregnancy result was positive.

Other inclusions:

Sub-study: Participants must have been willing to have 2 tape strips for comparison of baseline and treatment response and capable of giving signed informed consent specific to the sub-study.

Exclusion criteria

[00143] Participants were excluded from the study if any of the following criteria applied:

[00144] *Medical conditions:*

[00145] Skin comorbidities that may have interfered with study assessments such as psoriasis, tinea corporis, lupus erythematosus.

[00146] Any other clinically significant disease, condition, or medical history that, in the opinion of the Investigator, would have interfered with participant safety, trial evaluations, and/or trial procedures. Examples included, but were not limited to participants with short life expectancy, participants with uncontrolled diabetes (hemoglobin A1c $\geq 9\%$), participants with cardiovascular conditions (*e.g.*, Class III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (*e.g.*, participants on dialysis), neurological conditions (*e.g.*, demyelinating diseases), hepato-biliary conditions such as 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, moderate or severe hepatic impairment (Child Pugh B or C) or any other liver disease considered clinically significant by the Investigator, active major autoimmune diseases (*e.g.*, lupus, inflammatory bowel disease, rheumatoid arthritis, etc.), other severe endocrinological, gastrointestinal, metabolic, pulmonary, or lymphatic diseases.

[00147] Any of the following laboratory abnormalities at the screening visit (identified by the central laboratory)¹¹: an absolute neutrophil count $< 1.5 \times 10^9/L$; an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $> 1.5 \times$ upper limit of normal (ULN); total bilirubin $> 1.5 \times$ ULN, (isolated bilirubin $> 1.5 \times$ ULN was acceptable if total bilirubin was fractionated and direct bilirubin $< 35\%$); IgG < 500 mg/dL; and an abnormal international normalized ratio (INR) test and activated partial thromboplastin time (aPTT) judged by the Investigator to be clinically significant; a platelet count $< 150\,000/\mu L$.

[00148] 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 severe infection at Screening (Grade 2 or higher), including active coronavirus disease 2019 (COVID-19).

[00149] Live vaccine (except Bacille Calmette Guerin-vaccination) within 28 days prior to Day 1 or plan to receive one during the trial; Bacille Calmette Guerin-vaccination within 12 months prior to Screening.

[00150] COVID-19 vaccine within 14 days prior to Study Day 1.

[00151] Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would have precluded adequate rilzabrutinib/placebo absorption.

[00152] Donation of a unit or more of blood or blood products within 4 weeks prior to Day 1.

[00153] History of solid organ transplant.

[00154] A history of malignancy of any type within 5 years before Day 1, other than surgically excised non-melanoma skin cancers or in situ cervical cancer.

[00155] Conditions that may have predisposed the patient to excessive bleeding:

[00156] A bleeding disorder or known platelet dysfunction at any time prior to the Screening Visit.

[00157] Major surgery within 4 weeks prior to the Screening Visit, which could have affected the participant's safety or affect immune response (as judged by the Investigator) or any elective major surgery during the study.

¹¹ A one-time retest at screening may have been performed by the Investigator if abnormal laboratory test values were found.

[00158] 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.

[00159] *Prior/concomitant therapy:*

[00160] Initiation of prescription moisturizers (with or without additives such as ceramide, hyaluronic acid, urea, or filaggrin), topical anesthetics or antihistamines during the screening period¹².

[00161] Use of TCS, topical calcineurin (tacrolimus, and/or pimecrolimus) or topical phosphodiesterase 4 inhibitor within 1 week prior to baseline and as concomitant medication

[00162] Use of systemic corticosteroids within 4 weeks prior to baseline and as concomitant medication.

[00163] Phototherapy for AD or regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks prior to baseline or likely to be required as concomitant procedure during the study.

[00164] Use of mycophenolate mofetil, azathioprine, methotrexate, cyclosporine, dapsone, intravenous immunoglobulin (IVIG), Kineret (anakinra), Enbrel (etanercept), or any other immunosuppressant not mentioned in this exclusion criterion within 4 weeks prior to baseline.

[00165] Use of infliximab, adalimumab, golimumab, abatacept, tocilizumab, certolizumab, secukinumab, IFN- γ , JAK inhibitors, dupilumab, and any other biologic or targeted synthetic disease modifier drug not mentioned in the exclusion criteria, as well as plasmapheresis within 12 weeks prior to baseline.

[00166] Use of anti-CD20 drugs such as rituximab, ofatumumab, other long-acting biologics within 6 months prior to baseline (or shorter if there is documented B cell reconstitution for anti-CD20 drugs).

[00167] Use of proton pump inhibitor drugs such as omeprazole and esomeprazole within 3 days of baseline (it is acceptable to change participant to H2 receptor blocking drugs prior to baseline).

[00168] Concomitant use of known systemic strong-to-moderate inhibitors and inducers of cytochrome P450 3A (CYP3A) within 14 days or 5 half-lives (whichever is

¹² Participants may have continued using stable doses of such drugs if initiated before the screening visit.

longer) prior to baseline (see **Tables 2** and **3**).

Table 2. CYP3A Inhibitors and Inducers.

	Strong	Moderate
CYP3A inducers	Apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort	Bosentan, efavirenz, etravirine, phenobarbital, primidone
CYP3A inhibitors	Boceprevir, clarithromycin, cobicistat, danoprevir/ritonavir, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, paritaprevir/ritonavir and ombitasvir and/or dasabuvir, posaconazole, ritonavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole	Aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil

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.

Table 3. Sensitive CYP3A substrates.

Sensitive CYP3A substrates
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, tolcapten, tipranavir, triazolam, 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.

Prior/concurrent clinical study experience:

[00169] (1) Previous use of a BTK inhibitor or (2) receipt of any investigational drug (or current use of an investigational device) within the 30 days before baseline, or at least 5 times the drug's elimination half-life time (whichever is longer).

Diagnostic assessments:

[00170] Positive for human immunodeficiency virus (HIV) at Screening.

- [00171] Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) with positive DNA test result at Screening or within 3 months prior to the Screening visit.
- [00172] Positive hepatitis C antibody test result at Screening or within 3 months prior to the Screening visit¹³.
- [00173] Exclusion related to tuberculosis (TB):
- [00174] Active TB or a history of incompletely treated TB regardless of screening Quantiferon test (QFT) result.
- [00175] Quantiferon positive patients (no active disease) unless the following conditions were met.
- [00176] Patients with a history of prior documented completed chemoprophylaxis for latent tuberculosis infection (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.
- [00177] Consultation with and prior approval from sponsor were required in either of the aforementioned scenarios.
- [00178] Otherwise documented negative screening for TB via a negative QFT within 3 months prior to screening (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 TB infection.
- [00179] Clinically significant abnormality consistent with prior/active TB infection 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.
- [00180] Suspected extrapulmonary TB infection regardless of screening Quantiferon result.
- [00181] Patients at high risk of contracting TB, such as close contact with individuals with active or latent TB.

¹³ Participants with positive hepatitis C antibody due to prior resolved disease could have been enrolled only if a confirmatory negative Hepatitis C ribonucleic acid (RNA) test was obtained.

[00182] Electrocardiogram (ECG) findings of QT corrected for heart rate (QTc) >450 msec (males) or >470 msec (females), poorly controlled atrial fibrillation (*i.e.*, symptomatic participants or a ventricular rate above 100 beats/min on ECG), or other clinically significant cardiovascular abnormalities.

Study intervention(s) and concomitant therapy

[00183] 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. Study interventions are outlined in **Tables 4** and **5**.

[00184] Rilzabrutinib tablets were supplied ready for use; no preparation was needed. Participants were to use study medication directly from the dispensed bottles.

[00185] Participants were to administer rilzabrutinib by mouth twice or three times a day starting on Day 1. Consecutive doses were ideally to be administered 12 hours apart (and not less than 8 hours apart) for BID dosing, and ideally at least 6 hours apart (and not less than 4 hours apart) for TID dosing. Tablets should not have been broken or crushed.

[00186] Study intervention was to be dispensed at the study visits.

Table 4. Study Intervention(s) Administered.

Intervention label	Rilzabrutinib	Placebo
Intervention name	Rilzabrutinib	Placebo
Type	Drug	Drug
Dose formulation	Tablets (modified-capsule shaped tables/caplets)	Tablets (modified-capsule shaped tables/caplets)
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-comparator
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 labelled 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 labelled as required per country requirement.
Current/former name(s) or alias(es)	Rilzabrutinib	Placebo

Table 5. Arms and Associated Interventions

Arm name	Rilzabrutinib BID	Placebo BID	Rilzabrutinib TID	Placebo TID
Associated interventions (intervention label(s))	Rilzabrutinib	Placebo	Rilzabrutinib	Placebo

[00187] **Dose modification**

[00188] Dose modification was not allowed.

Continued access to intervention after the end of the study

[00189] Continued access to study intervention after the end of study was not planned for this study.

Concomitant therapy

Prohibited medications/procedures:

[00190] The following medications/procedures were prohibited during the study:

[00191] Immunosuppressive or immunomodulating drugs

[00192] Live vaccines (see **Table 6**)

[00193] Phototherapy or regular use (more than 2 visits per week) of a tanning booth/parlor

[00194] Proton Pump inhibitors (Esomeprazole was shown to reduce the exposure of rilzabrutinib by approximately 50%, presumably due to a lack of an acidic environment on tablet dissolution. Participants who were on proton pump inhibitors were to be changed to histamine (H2) receptor blocking drugs, if possible, or not be enrolled in the study.)

[00195] Known systemic strong-to-moderate inducers or inhibitors of CYP3A (see **Table 2**)

[00196] A non-exhaustive list of prohibited medications and therapies is provided in **Table 7**. All medications that are not listed as prohibited therapies were allowed during the study.

[00197] 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 receives during the study were to be recorded along with the reason for use, dates of administration (including the start and end dates), and dosage information (including

dosage and frequency). The Medical Monitor was to be contacted if there were any questions regarding concomitant or prior therapy.

[00198] Participants were to abstain 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.

[00199] Medications that are not listed as exclusion criteria were permitted for use during the trial. These include the following:

[00200] Prescription moisturizers (with or without additives such as ceramide, hyaluronic acid, urea, or filaggrin), topical anesthetics or antihistamines that had been initiated prior to the screening period were allowed to be continued if the doses were stable.

[00201] Oral corticosteroid rinses (mouth washes), ocular or inhaled corticosteroids were allowed.

[00202] Clinically relevant drugs that are substrates of CYP3A, including those considered to be sensitive CYP3A substrates (see **Table 3**) were permitted. Appropriate caution was to be used when co-administering sensitive CYP3A substrates with rilzabrutinib and a benefit-risk assessment was to be conducted for each medication. Consideration was also to be given to avoidance of high doses, dose reduction, or replacement of sensitive and narrow therapeutic index CYP3A substrate drugs. Systemic strong or moderate inhibitors and inducers of CYP3A should be avoided.

[00203] Histamine 2 (H2) receptor blocking drugs were permitted provided they could be given 2-3 hours after administration of rilzabrutinib or placebo. For participants receiving the IMP three times a day, H2-receptor blockers were to be taken once daily only, 2-3 hours after the evening dose of rilzabrutinib or placebo.

[00204] Antacids were permitted provided they were given 2 hours or more apart from rilzabrutinib or placebo.

[00205] COVID-19 vaccines: To allow for an optimal immune response as well as protection against COVID-19, it was strongly recommended that study participants receive their COVID vaccine (per local requirements) a minimum of 14 days prior to receiving the first dose of study medication. The safety profile and effectiveness of COVID-19 vaccines on people with compromised immune systems or therapies (such as rilzabrutinib) that modify or suppress their immune response, is not yet established. While vaccination with an approved COVID-19 vaccine was widely recommended (American College of Rheumatology 2021),

this decision should only have been made by the participant, after discussing with his/her physician as well as the investigator to assess the benefits and risks of receiving a COVID-19 vaccination during this study. If the vaccine was authorized, available, and recommended by the local regulatory health authority, it may have been administered during the study and should have been administered according to the label or local health authority recommendations.

Table 6. List of live (attenuated) vaccines.

Live (attenuated) vaccines
Chickenpox (Varicella ^a), 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: this list is indicative and not exhaustive

^a Shingrix was allowed for Shingles as a non-live Varicella vaccine.

Table 7. Non-exhaustive list of prohibited medications and therapies.

Drug category	Non-exhaustive list of drugs
Immunosuppressive or immunomodulating drugs	Immunosuppressant drugs: mycophenolate mofetil, azathioprine, methotrexate, cyclosporine, dapsone, Intravenous immunoglobulin (IVIG), anakinra (Kineret), etanercept (Enbrel), other immunosuppressant drugs Biologic or targeted-synthetic disease modifier drugs: infliximab, adalimumab, golimumab, abatacept, tocilizumab, certolizumab, secukinumab, IFN- γ , JAK inhibitors, Dupilumab, other biologic or targeted-synthetic disease modifiers Anti-CD20 drugs or long-acting biologics: rituximab, ofatumumab, other anti-CD20 drugs or long-acting biologics
Live vaccines	See Table 6
Phototherapy or regular use of tanning booth/parlor	Phototherapy or regular use (more than 2 visits per week) of a tanning booth/parlor
Proton pump inhibitors	Omeprazole, esomeprazole, lansoprazole, pantoprazole, or other proton pump inhibitors
Known strong-to-moderate inducers or inhibitors of CYP3A	See Table 2 .

This table provides a list of the most common medications within the classes of prohibited concomitant drugs. It is not exhaustive, and Site Investigators were to contact the Medical Monitor if they were unsure about a specific medication that is not listed in this table.

Rescue medicine:

[00206] If medically necessary (*i.e.*, to control intolerable AD symptoms), rescue treatment for AD was to be provided to study participants at the discretion of the Investigator.

[00207] If possible, Investigators were to attempt to limit the first step of rescue therapy topical medications with: (1) low-to-medium potency TCS (see **Table 8**), (2) crisaborole (cAMP-specific phosphodiesterase-4 inhibitor), and (3) calcineurin inhibitors (which should be reserved for problem areas only, *e.g.*, face, neck, intertriginous and genital areas). Participants were to continue study intervention if rescue consists of these topical medications.

Table 8. Relative potencies of topical corticosteroids

	Drug	Dosage form(s)	Strength (%)
I. Very high potency	Augmented betamethasone dipropionate	Ointment	0.05
	Clobetasol propionate	Cream, foam, ointment	0.05
	Diflorasone diacetate	Ointment	0.05
	Halobetasol propionate	Cream, ointment	0.05
II. High potency	Amcinonide	Cream, lotion, ointment	0.1
	Augmented betamethasone dipropionate	Cream	0.05
	Betamethasone dipropionate	Cream, foam, ointment, solution	0.05
	Desoximetasone		0.25
	Desoximetasone	Cream, ointment	0.05
	Desoximetasone	Gel	0.05
	Diflorasone diacetate	Cream	0.05
	Fluocinonide	Cream, gel, ointment, solution	0.1
	Halcinonide		0.1
	Mometasone furoate	Cream, ointment	0.5
	Triamcinolone acetonide	Ointment	
III-IV. Medium potency		Cream, ointment	
	Betamethasone valerate	Cream, foam, lotion, ointment	0.1
	Clocortolone pivalate		0.1
	Desoximetasone	Cream	0.05
	Fluocinolone acetonide	Cream	0.025
	Flurandrenolide	Cream, ointment	0.05
	Fluticasone propionate	Cream, ointment	0.05
	Fluticasone propionate	Cream	0.005
	Mometasone furoate	Ointment	0.1
	Triamcinolone acetonide	Cream	0.1
V. Lower-medium potency		Cream, ointment	
	Hydrocortisone butyrate	Cream, ointment, solution	0.1
	Hydrocortisone probutate	Cream	0.1
	Hydrocortisone valerate	Cream, ointment	0.2
	Prednicarbate	Cream	0.1

VI. Low potency	Alclometasone dipropionate	Cream, ointment	0.05
	Desonide	Cream, gel, foam, ointment	0.05
	Fluocinolone acetonide	Cream, solution	0.01
VII. Lowest potency	Dexamethasone	Cream	0.1
	Hydrocortisone	Cream, lotion, ointment, solution	0.25, 0.5, 1
	Hydrocortisone acetate	Cream, ointment	0.5-1

Includes representative examples and not all available agents. This table is sourced from literature (Paller AS and Mancini AJ 2011, Eichenfield LF et al. 2014b).

[00208] Efficacy assessments: The following efficacy parameters were to be analyzed for assessing the primary and secondary efficacy endpoints.

[00209] *Eczema Area and Skin Severity Index (EASI)*: The EASI index is a validated Investigator-administered scoring system used to measure the severity of clinical signs in AD (Hanifin JM et al. 2001). The EASI is a composite index with scores ranging from 0 to 72. Four AD disease characteristics (erythema, thickness (induration, papulation, edema), scratching (excoriation), and lichenification) were each to be assessed for severity by the investigator or designee on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement was to be assessed as a percentage by body area of head, trunk, upper limbs, and lower limbs, and converted to a score of 0 to 6. In each body region, the area was to be expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%).

[00210] *Estimation of body surface area (BSA) of EASI*: Body surface area (BSA) affected by AD was to be assessed for each section of the body (the possible highest score for each region is: head and neck (10%), trunk including genitalia (30%), upper limbs (20%), lower limbs (40%)) and will be reported as a percentage of all major body sections combined.

[00211] *Pruritis numeric rating scale (NRS)*: The Pruritus NRS is a simple assessment tool that patients used to report the intensity of their pruritus (itch) during a daily recall period. This tool has been used in clinical studies of AD (Yosipovitch G et al. 2019).

[00212] Patients were to be instructed on using the e-diary to complete the pruritus categorical scale daily. Clinical sites were to receive alerts when patients did not complete e-diary items. Sites were expected to contact patients who missed 2 consecutive e-diary entries to encourage patient compliance. The questions asked to patients are the following:

[00213] For average itch intensity: “On a scale of 0 to 10, with 0 being ‘no itch’ and 10 being the ‘worst itch imaginable’, how would you rate your itch overall (on average) during the previous 24 hours?”

[00214] For maximum itch intensity: “On a scale of 0 to 10, with 0 being ‘no itch’ and 10 being the ‘worst itch imaginable’, how would you rate your itch at the worst moment during the previous 24 hours?”

[00215] *Investigator global assessment (IGA) of disease activity*: Investigator Global Assessment (IGA) is a static 5-point measure of disease severity based on an overall assessment of the skin lesions on a 5-point scale (0 = clear, 1 = almost clear, 2 = mild disease, 3 = moderate disease, 4 = severe disease).

[00216] *Atopic dermatitis area photographs*: At selected study sites and in participants who consented, photographs may have been taken of representative area(s) of AD involvement (*e.g.*, one or some of the lesional areas) used for EASI assessments on Day 1 / baseline (pre-dose). Area chosen for photographs was not to comprise participant’s direct identifier (such as participant’s face, tattoos, identifiable jewelry, *etc.*). Subsequent photographs of the same areas were to be taken at Week 16 (EOT) and Week 17 (EOS).

[00217] Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting: AEs were to be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant’s LAR).

[00218] Optional Sub-study: Lesional and non-lesional skin samples for exploratory biomarker analysis (He H et al. 2021), including RNA sequencing and quantitative reverse transcription polymerase chain reaction (qRT-PCR) validation of immune and barrier biomarkers, were to be obtained using a tape stripping procedure at Day 1/baseline (Visit 2, predose) and at Week 16 (Visit 7, EOT) from participants who chose to participate in this optional sub-study and provided consent for participating in this optional sub-study.

[00219] Skin tape strip samples for RNA isolation were to be collected from all participants who consented to participate in the sub-study. Participants who did not wish to participate in the genomic/genetic research could not participate in this sub-study.

Statistical Considerations

[00220] Populations for Analysis: The populations for analyses in the main study are defined in **Table 9**.

Table 9. Populations for Analyses.

Population	Description
Screened	All participants who signed the ICF
Randomized	All participants from screened population who were allocated to a randomized intervention by IRT regardless of whether the intervention was received.
Intent-to-treat (ITT)	All randomized participants. Participants were analyzed according to the intervention allocated by randomization.
Safety	All randomized participants who took at least 1 dose of study intervention. Participants were analyzed according to the intervention they actually received.
Pharmacokinetics	All randomized and treated participants (safety population), with at least one postbaseline PK sample with adequate documentation of dosing and sampling dates and times. Participants in the placebo group were not part of the PK population. Participants were to be analyzed according to the intervention they actually received.

[00221] Participants exposed to study intervention before or without being randomized are not considered randomized and were not to be included in any analysis population. The safety experience of these participants was to be reported separately.

[00222] Randomized participants for whom it was unclear whether they took the study intervention are to be considered as exposed and were to be included in the safety population as randomized.

[00223] 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.

[00224] The efficacy of rilzabrutinib was to be based on the posterior probability that the mean percent change in EASI score from baseline to Week 16 of rilzabrutinib group

would be greater than that of the placebo group. A posterior probability of at least 95% is to be considered significant.

- [00225] *Secondary Endpoints:* The main secondary endpoints included:
- [00226] Proportion of participants with IGA of 0 or 1 (disease free or almost disease free) compared to placebo at Week 16
- [00227] Proportion of participants achieving EASI-75 (reduction of EASI score by $\geq 75\%$ from baseline) at Week 16
- [00228] Proportion of participants with reduction of weekly average of daily PP-NRS of ≥ 4 points from baseline at Week 16
- [00229] The binary endpoints at Week 16 were to be analyzed using the CMH test adjusted by randomization stratification of Screening IgE level ($<$ or ≥ 300 UI/mL) in the ITT population.
- [00230] Account for the impact of selected rescue medications on the efficacy effect:
- [00231] For the binary efficacy endpoints, if high potency TCS or systemic medications were used, the participant was to be specified as a non-responder from the time the rescue was used.
- [00232] If a participant withdrew from the study, this participant was to be counted as a non-responder for endpoints after withdrawal.
- [00233] *Other Secondary Endpoints:* Other secondary endpoints included:
- [00234] Time to onsite of effect on pruritus (≥ 4 points reduction of weekly average of daily PP-NRS from baseline during the 16-week treatment period).
- [00235] Absolute change from baseline to Week 16 in EASI score
- [00236] Proportion of participants achieving EASI-50/90 (reduction of EASI score by $\geq 50\%$ or $\geq 90\%$ from baseline) at Week 16
- [00237] Change from baseline to Week 16 in percent BSA of EASI
- [00238] Absolute and percent change on weekly average of daily PP-NRS based on daily participant assessments documented in their e-diary from baseline to Week 16
- [00239] Proportion of participants achieving IGA*BSA-50/75/90 (reduction of IGA*BSA by $\geq 50\%$ or 75% or 90% from baseline) at Week 16
- [00240] Time to onsite of the effect on pruritus (≥ 4 points reduction of weekly average of daily PP-NRS from baseline during the 16-week treatment period) was to be analyzed using the Cox proportional hazard model with time to event as the dependent

variable, and treatment, randomization stratification of Screening IgE level ($<$ or ≥ 300 UI/mL) as covariates. The estimates of the hazard ratio and corresponding 90% CI and p-values were to be provided for the rilzabrutinib versus the placebo group.

[00241] The continuous efficacy endpoints were to be analyzed using the same analysis approach as for the primary endpoint.

[00242] The binary efficacy endpoints were to be analyzed using the CMH test in the same fashion as for the main secondary endpoints.

[00243] *Multiplicity Considerations:* No adjustments for multiplicity were planned for this Phase 2 study. More specifically, no adjustments were to be made in comparing the treatment groups based on the secondary efficacy endpoints and no adjustments were to be made for the subgroup analyses. Reported p-values for the secondary endpoints were to be nominal p-values.

[00244] *Safety Analysis:* All safety analyses were to be performed using the safety population according to the intervention group to which the participants were exposed.

[00245] Adverse events: In general, AEs were to be analyzed in the following two categories: pre-treatment AEs (AEs that developed, worsened, or became serious during the pre-treatment period; and TEAEs (AEs that developed, worsened, or became serious during the treatment-emergent period. Similarly, the deaths were to be analyzed in the pre-treatment, emergent, and post-treatment periods.

Definitions and procedures for recording, evaluating, follow-up, and reporting

Definition of AE

[00246] 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 can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of SAE

[00247] An SAE is defined as any adverse event that, at any dose: (1) results in death; (2) is life-threatening; (3) requires inpatient hospitalization or prolongation of existing hospitalization; (4) results in persistent or significant disability/incapacity; (5) is a congenital

anomaly/birth defect; and/or (6) 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., examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that did not result in hospitalization, or development of drug dependency or drug abuse).

[00248] *Overall design:*

[00249] This is a double-blind, Phase 2, parallel treatment, 3-arms, placebo controlled sub-study to assess the efficacy and safety of rilzabrutinib in adult participants (aged at least 18 years) with moderate-to-severe AD and intolerance or inadequate response to TCS.

[00250] Adult participants who met the inclusion/exclusion criteria are to be stratified by immunoglobulin E (IgE) levels ($<$ or ≥ 300 UI/mL) at Screening and are to be randomized in a 3:3:2 allocation ratio to receive rilzabrutinib 400 mg BID (morning and evening) + matching placebo QD (midday) or rilzabrutinib 400 mg TID or matching placebo TID on Day 1 (Week 0, Visit 2), as shown in **Fig. 2**. The total study duration per participant is expected to be approximately 21 weeks: including up to 4 weeks for screening, 16 weeks on-treatment double-blind period, and 1-week post-treatment follow-up. Visits during the on-treatment period are to be at Week 0, 2, 4, 8, 12 and 16.

[00251] The study duration, end of study definition, study population, and the corresponding details and procedure are the same as the main study.

[00252] Common definitions of baseline: 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.

[00253] *General methods:*

[00254] Descriptive analyses include summarization of quantitative variables (using n, mean, standard deviation, inter quartile range, median, minimum, and maximum) and qualitative data (by reporting absolute and relative frequencies).

[00255] Unless otherwise specified, analyses are performed by intervention group (and overall for baseline and demographics characteristics).

[00256] The observation period is divided into 3 segments: the treatment period, which is defined as the period up to the first IMP administration; the on-treatment period, which is

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

[00257] Treatment emergent (TE) period includes both on-treatment period and post-treatment period.

[00258] Primary, secondary, and exploratory endpoints are the same as for the main study. These endpoints are analyzed with descriptive statistics.

[00259] Multiplicity considerations are the same as for the main study.

[00260] Safety analysis and other analyses are the same as for the main study.

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

[00261] A Phase 2 proof-of-concept trial was initiated to evaluate the efficacy and safety of rilzabrutinib in adults with moderate-to-severe atopic dermatitis (AD) and an inadequate response or intolerance to topical corticosteroids (TCS). Over the course of this 16-week, double-blind, placebo-controlled study, N=124 patients were administered a placebo, 400 mg BID rilzabrutinib, or 400 mg TID rilzabrutinib.

[00262] The primary endpoint for this study was the percent change from baseline to Week 16 in Eczema Area and Severity Index (EASI) score. Secondary and exploratory endpoints are described in **Table 1**.

[00263] The study did not meet the primary or secondary endpoints for either treatment arm (see **Table 10**). However, rilzabrutinib treatment led to a numerically favorable percent change in EASI score at Week 16 for patients treated with both doses of rilzabrutinib. Moreover, treatment with both doses of rilzabrutinib led to a rapid and sustained improvement in itch.

Table 10. Summary of the Primary and Key Secondary Endpoints and Other Endpoints (ITT Population)

Parameter	BID cohort				TID cohort			
	Placebo ^a (N=18)	Rilzabrutinib 400mg BID ^a (N=27)	Difference (95% CI) ^b for Rilzabrutinib 400mg BID vs Placebo	P- value ^c	Placebo ^a (N=31)	Rilzabrutinib 400mg TID ^a (N=48)	Difference (95% CI) ^b for Rilzabrutinib 400mg TID vs Placebo	P- value ^c
Primary endpoint								
Percent change in EASI score from baseline to Week 16	-47.33 (9.77)	-53.57 (8.25)	-6.25 (-31.26, 18.77)	0.6246	-43.33 (6.99)	-47.21 (6.26)	-3.88 (-21.97, 14.21)	0.6740
Key secondary endpoints								
Proportion of participants with IGA 0 to 1 (on a 5-point scale) at Week 16	4 (22.2)	2 (7.4)	-14.9 (-36.82, 6.95)	0.1585	4 (12.9)	7 (14.6)	1.7 (-13.82, 17.18)	0.8353
Odds ratio			0.3 (0.05, 1.73)				1.2 (0.31, 4.30)	

Parameter	BID cohort				TID cohort			
	Placebo ^a (N=18)	Rilzabrutinib 400mg BID ^a (N=27)	Difference (95% CI) ^b for Rilzabrutinib 400mg BID vs Placebo	P- value ^c	Placebo ^a (N=31)	Rilzabrutinib 400mg TID ^a (N=48)	Difference (95% CI) ^b for Rilzabrutinib 400mg TID vs Placebo	P- value ^c
Proportion of participants with EASI-75 response (reduction of EASI score $\geq$ 75% from baseline) at Week 16	5 (27.8)	8 (29.6)	3.1 (-23.86, 30.15)	0.8193	9 (29.0)	9 (18.8)	-10.3 (-29.18, 8.64)	0.2818
Odds ratio			1.2 (0.31, 4.36)				0.5 (0.18, 1.63)	
Proportion of participants with reduction of weekly average of peak daily Pruritus NRS $\geq$ 4 from baseline to Week 16	2 (11.1)	5 (18.5)	8.2 (-11.83, 28.32)	0.4599	4 (12.9)	10 (20.8)	7.9 (-8.70, 24.56)	0.3725
Odds ratio			2.0 (0.32, 12.70)				1.8 (0.50, 6.11)	
Other secondary endpoints								
Time to onset of effect on pruritus ($\geq$ 4 points reduction of weekly average of daily PP-NRS from baseline during the 16-week treatment period)	2 (11.1)	7 (25.9)	2.837 (0.589, 13.676)	0.1937	4 (12.9)	13 (27.1)	2.762 (0.898, 8.501)	0.0765
Change from baseline to Week 16 in EASI score	-12.83 (2.31)	-14.00 (1.94)	-1.18 (-7.06, 4.71)	0.6946	-10.37 (2.48)	-11.34 (2.20)	-0.97 (-7.36, 5.43)	0.7669
Proportion of participants achieving EASI-50 (reduction of EASI score $\geq$ 50% from baseline) at Week 16	10 (55.6)	12 (44.4)	-7.8 (-32.67, 17.06)	0.5390	12 (38.7)	14 (29.2)	-9.5 (-30.46, 11.40)	0.3741
Odds ratio			0.6 (0.15, 2.68)				0.6 (0.24, 1.70)	

Parameter	BID cohort				TID cohort			
	Placebo ^a (N=18)	Rilzabrutinib 400mg BID ^a (N=27)	Difference (95% CI) ^b for Rilzabrutinib 400mg BID vs Placebo	P- value ^c	Placebo ^a (N=31)	Rilzabrutinib 400mg TID ^a (N=48)	Difference (95% CI) ^b for Rilzabrutinib 400mg TID vs Placebo	P- value ^c
Proportion of participants achieving EASI-90 (reduction of EASI score $\geq$ 90% from baseline) at Week 16	3 (16.7)	3 (11.1)	-6.2 (-27.31, 14.94)	0.5522	4 (12.9)	4 (8.3)	-4.6 (-18.65, 9.52)	0.5150
Odds ratio			0.6 (0.11, 3.29)				0.6 (0.14, 2.67)	
Change from baseline to Week 16 in percent BSA of AD	-10.45 (4.37)	-15.30 (3.61)	-4.85 (-15.94, 6.24)	0.3915	-7.35 (3.38)	-11.80 (3.08)	-4.44 (-13.43, 4.54)	0.3321
Change on weekly average of daily PP-NRS from baseline to Week 16	-1.60 (0.66)	-3.11 (0.52)	-1.51 (-3.14, 0.13)	0.0703	-0.83 (0.51)	-2.07 (0.43)	-1.24 (-2.51, 0.04)	0.0568
Percent change on weekly average of daily PP-NRS from baseline to Week 16	-21.55 (8.37)	-43.53 (6.80)	-21.98 (-43.09, -0.87)	0.0413	-10.36 (7.19)	-30.13 (6.08)	-19.77 (-37.82, -1.71)	0.0319

^a Values presented are LS mean % change or change from baseline with standard error for continuous variables and number and percent of responders for binary variables.

^b Difference is LS mean difference for continuous variables and CMH response rate difference and odds ratio for binary variables.

^c Nominal p-values for all other endpoints except primary endpoint.

Participant Demographics

[00264] The 124 patients enrolled in the Phase 2 study were characterized by the demographic information provided in **Tables 11** and **12**. The median age of enrolled patients was 30.0 years. At enrollment, patients had AD for a median duration of 22 years.

[00265] **Table 11. Demographics and Participant Characteristics at Baseline**
(Randomized Population)

	BID cohort			TID cohort		
	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)	All (N=45)	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)	All (N=79)
Age (years)						
Number	18	27	45	31	48	79
Mean (SD)	33.9 (13.0)	38.3 (16.1)	36.6 (14.9)	33.1 (12.4)	36.1 (14.1)	34.9 (13.5)
Median	32.5	32.0	32.0	30.0	31.5	30.0
Q1 ; Q3	22.0 ; 45.0	24.0 ; 54.0	24.0 ; 50.0	24.0 ; 40.0	26.0 ; 43.5	26.0 ; 41.0
Min ; Max	18 ; 54	18 ; 65	18 ; 65	18 ; 67	18 ; 70	18 ; 70
Age group [n (%)]						
Number	18	27	45	31	48	79
≥18 - <40	12 (66.7)	15 (55.6)	27 (60.0)	23 (74.2)	31 (64.6)	54 (68.4)
≥40 - <65	6 (33.3)	10 (37.0)	16 (35.6)	6 (19.4)	16 (33.3)	22 (27.8)
≥65	0	2 (7.4)	2 (4.4)	2 (6.5)	1 (2.1)	3 (3.8)
Sex [n (%)]						
Number	18	27	45	31	48	79
Male	8 (44.4)	12 (44.4)	20 (44.4)	16 (51.6)	17 (35.4)	33 (41.8)
Female	10 (55.6)	15 (55.6)	25 (55.6)	15 (48.4)	31 (64.6)	46 (58.2)
Race [n (%)]						
Number	18	27	45	31	48	79
White	16 (88.9)	23 (85.2)	39 (86.7)	25 (80.6)	38 (79.2)	63 (79.7)
Black or African American	0	1 (3.7)	1 (2.2)	2 (6.5)	4 (8.3)	6 (7.6)
Asian	2 (11.1)	2 (7.4)	4 (8.9)	4 (12.9)	6 (12.5)	10 (12.7)
Japanese	0	0	0	1 (3.2)	0	1 (1.3)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
American Indian or Alaska Native	0	0	0	0	0	0
Multiple	0	1 (3.7)	1 (2.2)	0	0	0
Unknown	0	0	0	0	0	0
Not Reported	0	0	0	0	0	0
Ethnicity [n (%)]						
Number	18	27	45	31	48	79
Hispanic or Latino	4 (22.2)	5 (18.5)	9 (20.0)	10 (32.3)	21 (43.8)	31 (39.2)
Not Hispanic or Latino	13 (72.2)	21 (77.8)	34 (75.6)	21 (67.7)	27 (56.3)	48 (60.8)
Not Reported	1 (5.6)	0	1 (2.2)	0	0	0
Unknown	0	1 (3.7)	1 (2.2)	0	0	0
Country						
Number	18	27	45	31	48	79
Canada	2 (11.1)	5 (18.5)	7 (15.6)	5 (16.1)	11 (22.9)	16 (20.3)
Chile	0	0	0	8 (25.8)	17 (35.4)	25 (31.6)
Czech Republic	6 (33.3)	13 (48.1)	19 (42.2)	6 (19.4)	8 (16.7)	14 (17.7)
Germany	1 (5.6)	2 (7.4)	3 (6.7)	2 (6.5)	0	2 (2.5)
Netherlands	1 (5.6)	0	1 (2.2)	0	0	0
Poland	3 (16.7)	1 (3.7)	4 (8.9)	3 (9.7)	4 (8.3)	7 (8.9)
United States	5 (27.8)	6 (22.2)	11 (24.4)	7 (22.6)	8 (16.7)	15 (19.0)
Region						
Number	18	27	45	31	48	79

	BID cohort			TID cohort		
	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)	All (N=45)	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)	All (N=79)
South America	0	0	0	8 (25.8)	17 (35.4)	25 (31.6)
North America	7 (38.9)	11 (40.7)	18 (40.0)	12 (38.7)	19 (39.6)	31 (39.2)
Other (Europe)	11 (61.1)	16 (59.3)	27 (60.0)	11 (35.5)	12 (25.0)	23 (29.1)
Weight (kg)						
Number	18	27	45	31	48	79
Mean (SD)	75.4 (20.2)	73.7 (14.9)	74.4 (17.1)	81.0 (20.1)	77.3 (18.8)	78.7 (19.3)
Median	71.5	72.0	72.0	77.1	75.2	75.3
Q1 ; Q3	65.5 ; 81.6	63.5 ; 85.0	63.9 ; 81.9	68.6 ; 92.0	61.5 ; 91.8	66.5 ; 92.0
Min ; Max	47 ; 132	44 ; 103	44 ; 132	47 ; 142	45 ; 125	45 ; 142
Weight group (kg) [n (%)]						
Number	18	27	45	31	48	79
<60	4 (22.2)	5 (18.5)	9 (20.0)	3 (9.7)	9 (18.8)	12 (15.2)
≥60 - <90	11 (61.1)	17 (63.0)	28 (62.2)	19 (61.3)	25 (52.1)	44 (55.7)
≥90	3 (16.7)	5 (18.5)	8 (17.8)	9 (29.0)	14 (29.2)	23 (29.1)
BMI (kg/m ²)						
Number	18	27	45	31	48	79
Mean (SD)	26.38 (6.26)	25.29 (4.61)	25.72 (5.29)	28.27 (6.27)	27.33 (5.35)	27.70 (5.71)
Median	25.35	25.10	25.23	26.47	27.76	26.70
Q1 ; Q3	22.15 ; 28.52	21.35 ; 28.03	21.98 ; 28.35	23.71 ; 34.18	24.26 ; 30.63	23.81 ; 31.55
Min ; Max	17.9 ; 46.8	16.5 ; 34.8	16.5 ; 46.8	19.8 ; 45.8	18.6 ; 41.9	18.6 ; 45.8
BMI group (kg/m ²) [n (%)]						
Number	18	27	45	31	48	79
<25	8 (44.4)	13 (48.1)	21 (46.7)	12 (38.7)	18 (37.5)	30 (38.0)
≥25 - <30	7 (38.9)	11 (40.7)	18 (40.0)	8 (25.8)	16 (33.3)	24 (30.4)
≥30	3 (16.7)	3 (11.1)	6 (13.3)	11 (35.5)	14 (29.2)	25 (31.6)

BMI: Body mass index

Table 12. Disease Characteristics at Baseline (Randomized Population)

	BID cohort			TID cohort		
	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)	All (N=45)	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)	All (N=79)
Age at onset of AD (years) ^a						
Number	18	27	45	31	48	79
Mean (SD)	9.7 (15.6)	14.7 (19.6)	12.7 (18.0)	13.4 (16.1)	12.7 (16.7)	12.9 (16.4)
Median	2.5	4.0	3.0	10.0	5.0	5.0
Q1 ; Q3	0.0 ; 10.0	2.0 ; 22.0	0.0 ; 18.0	1.0 ; 21.0	0.5 ; 19.5	1.0 ; 21.0
Min ; Max	0 ; 50	0 ; 63	0 ; 63	0 ; 65	0 ; 61	0 ; 65
Age at onset of AD (years) [n (%)]						
Number	18	27	45	31	48	79
<60	18 (100)	26 (96.3)	44 (97.8)	30 (96.8)	46 (95.8)	76 (96.2)
≥60	0	1 (3.7)	1 (2.2)	1 (3.2)	2 (4.2)	3 (3.8)
Duration of AD (years) ^b						
Number	18	27	45	31	48	79

	BID cohort			TID cohort		
	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)	All (N=45)	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)	All (N=79)
Mean (SD)	24.9 (14.2)	24.2 (16.7)	24.5 (15.6)	20.2 (11.4)	24.0 (15.6)	22.5 (14.1)
Median	23.5	24.0	24.0	22.0	21.6	22.0
Q1 ; Q3	18.0 ; 33.0	9.0 ; 40.0	16.0 ; 37.0	11.0 ; 29.0	13.0 ; 35.0	13.0 ; 32.0
Min ; Max	2 ; 53	1 ; 59	1 ; 59	2 ; 47	2 ; 61	2 ; 61
Duration group of AD (years) [n (%)]						
Number	18	27	45	31	48	79
<26	10 (55.6)	16 (59.3)	26 (57.8)	22 (71.0)	30 (62.5)	52 (65.8)
≥26	8 (44.4)	11 (40.7)	19 (42.2)	9 (29.0)	18 (37.5)	27 (34.2)
IgE levels (UI/mL) at screening visit (V1) ^e						
Number	18	27	45	31	48	79
<300	7 (38.9)	9 (33.3)	16 (35.6)	11 (35.5)	17 (35.4)	28 (35.4)
≥300	11 (61.1)	18 (66.7)	29 (64.4)	20 (64.5)	31 (64.6)	51 (64.6)
Baseline IGA score						
Number	18	27	45	31	48	79
Mean (SD)	3.4 (0.5)	3.5 (0.5)	3.5 (0.5)	3.3 (0.5)	3.4 (0.5)	3.4 (0.5)
Median	3.0	4.0	3.0	3.0	3.0	3.0
Q1 ; Q3	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0
Min ; Max	3 ; 4	3 ; 4	3 ; 4	3 ; 4	3 ; 4	3 ; 4
Baseline IGA categorical score [n (%)]						
Number	18	27	45	31	48	79
0 (clear)	0	0	0	0	0	0
1 (almost clear)	0	0	0	0	0	0
2 (mild)	0	0	0	0	0	0
3 (moderate)	10 (55.6)	13 (48.1)	23 (51.1)	21 (67.7)	30 (62.5)	51 (64.6)
4 (severe)	8 (44.4)	14 (51.9)	22 (48.9)	10 (32.3)	18 (37.5)	28 (35.4)
Baseline EASI score						
Number	18	27	45	31	48	79
Mean (SD)	23.3 (7.3)	28.0 (10.5)	26.1 (9.6)	25.4 (11.0)	29.4 (14.9)	27.8 (13.6)
Median	21.2	25.5	22.2	22.7	22.3	22.3
Q1 ; Q3	18.0 ; 25.7	20.8 ; 34.8	19.2 ; 31.8	17.0 ; 30.3	18.0 ; 41.3	17.5 ; 33.2
Min ; Max	16 ; 45	12 ; 54	12 ; 54	5 ; 56	13 ; 64	5 ; 64
Baseline EASI score by category						
Number	18	27	45	31	48	79
≤21	9 (50.0)	7 (25.9)	16 (35.6)	13 (41.9)	20 (41.7)	33 (41.8)
>21 to ≤50	9 (50.0)	18 (66.7)	27 (60.0)	17 (54.8)	22 (45.8)	39 (49.4)
>50	0	2 (7.4)	2 (4.4)	1 (3.2)	6 (12.5)	7 (8.9)
Baseline EASI score by median value						
Number	18	27	45	31	48	79
<median (22.20/22.30/22.25)	10 (55.6)	12 (44.4)	22 (48.9)	15 (48.4)	24 (50.0)	39 (49.4)
≥median (22.20/22.30/22.25)	8 (44.4)	15 (55.6)	23 (51.1)	16 (51.6)	24 (50.0)	40 (50.6)
BSA of AD ^d						

	BID cohort			TID cohort		
	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)	All (N=45)	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)	All (N=79)
Number	14	22	36	31	48	79
Mean (SD)	31.7 (11.0)	41.5 (26.7)	37.7 (22.3)	32.2 (19.0)	42.4 (24.2)	38.4 (22.8)
Median	31.5	27.3	30.8	27.0	34.5	34.0
Q1 ; Q3	20.0 ; 41.0	20.0 ; 66.0	20.0 ; 52.5	14.3 ; 50.0	26.0 ; 66.0	17.0 ; 56.0
Min ; Max	17 ; 55	10 ; 86	10 ; 86	10 ; 78	10 ; 90	10 ; 90
BSA of AD by category ^d						
[n (%)]						
Number	14	22	36	31	48	79
≥10% to <30%	5 (35.7)	11 (50.0)	16 (44.4)	16 (51.6)	20 (41.7)	36 (45.6)
≥30% to <50%	8 (57.1)	2 (9.1)	10 (27.8)	7 (22.6)	12 (25.0)	19 (24.1)
≥50%	1 (7.1)	9 (40.9)	10 (27.8)	8 (25.8)	16 (33.3)	24 (30.4)
Baseline IGA*BSA						
Number	14	22	36	31	48	79
Mean (SD)	110.3 (41.1)	143.4 (94.6)	130.5 (79.2)	109.2 (74.2)	148.1 (95.9)	132.8 (89.6)
Median	112.5	93.8	100.5	81.0	104.5	102.0
Q1 ; Q3	80.0 ; 124.5	72.0 ; 237.0	78.0 ; 157.5	44.0 ; 160.0	78.0 ; 210.0	60.0 ; 200.0
Min ; Max	51 ; 220	40 ; 328	40 ; 328	36 ; 312	30 ; 360	30 ; 360
Baseline IGA*BSA by category [n (%)]						
Number	14	22	36	31	48	79
≥0 to ≤30 (mild)	0	0	0	0	1 (2.1)	1 (1.3)
>30 to ≤130 (moderate)	11 (78.6)	13 (59.1)	24 (66.7)	22 (71.0)	26 (54.2)	48 (60.8)
>130 to ≤400 (severe)	3 (21.4)	9 (40.9)	12 (33.3)	9 (29.0)	21 (43.8)	30 (38.0)
Baseline weekly average of PP-NRS score ^e						
Number	18	27	45	31	48	79
Mean (SD)	6.87 (1.17)	7.41 (1.52)	7.20 (1.40)	7.01 (1.33)	7.61 (1.35)	7.38 (1.37)
Median	7.00	7.40	7.00	7.17	7.42	7.29
Q1 ; Q3	6.50 ; 7.57	6.20 ; 8.57	6.25 ; 8.00	6.00 ; 8.00	6.85 ; 8.25	6.83 ; 8.14
Min ; Max	4.7 ; 9.0	4.4 ; 10.0	4.4 ; 10.0	3.5 ; 9.0	4.1 ; 10.0	3.5 ; 10.0

^a Derived as (Year of first diagnosis of AD - Year of birth).

^b Derived as (Year of randomization - Year of first diagnosis of AD) + (month of randomization - month of first diagnosis of AD)/12.

^c IgE levels collected in the eCRF at screening visit.

^d In BID cohort, due to missing page in eCRF, BSA as a stand-alone questionnaire was not recorded for 9 participants while the BSA in EASI was assessed normally. This was rapidly corrected, and all these cases were reported as protocol deviation.

Itch

[00266] Notably, treatment with either dose of rilzabrutinib was associated with a favorable improvement in symptoms of itch (see **Figures 3-10** and **Tables 10** and **13-33**). In the 400 mg BID rilzabrutinib cohort, 18.5% of patients receiving rilzabrutinib achieved a ≥ 4-point change in PP-NRS from baseline at Week 16 of the study, as compared to 11.1% of patients receiving the placebo (**Figures 3-4** and **Table 18**). Meanwhile, in the 400 mg TID

rilzabrutinib cohort, 20.8% of patients treated with rilzabrutinib achieved a PP-NRS change $\geq$ 4 points, as compared to 12.9% of patients receiving the placebo (**Figures 3-4** and **Table 18**).

[00267] In general, rilzabrutinib treatment was associated with a rapid absolute and relative change in the weekly average of daily PP-NRS. Treatment with 400 mg BID rilzabrutinib yielded improvements as early as Week 2, while treatment with 400 mg TID rilzabrutinib led to improvements as early as Week 1 (**Figures 3-8** and **Tables 18-28**). Moreover, first PP-NRS reductions of $\geq$ 4 points from baseline were observed as early as Weeks 3 and 1 for patients receiving 400 mg BID rilzabrutinib and 400 mg TID rilzabrutinib, respectively (**Figures 3-4** and **9** and **Tables 18** and **29**).

[00268] Subgroup analysis further supports the positive effect of rilzabrutinib on itch (**Tables 30-33**). In general, treatment with rilzabrutinib led to a decrease in symptoms of itch, regardless of baseline demographic characteristics. However, for patients receiving either dose of rilzabrutinib, a larger percent change in PP-NRS from baseline was observed for patients in lower weight groups.

[00269] Taken together, these data suggest that rilzabrutinib improves itch in patients with AD.

Table 13. Proportion of Participants with Reduction of Weekly Average of Daily PP-NRS $\geq$ 4 Points from Baseline at Week 16 (ITT Population)

	BID cohort		TID cohort	
	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Participants with reduction of weekly average of daily PP-NRS of $\geq$ 4 points from baseline at Week 16				
Responder	2 (11.1)	5 (18.5)	4 (12.9)	10 (20.8)
Non-responder	16 (88.9)	22 (81.5)	27 (87.1)	38 (79.2)
Imputed non-responder	7 (38.9)	8 (29.6)	14 (45.2)	25 (52.1)
OR, 95% CI vs. placebo ^a		2.0 (0.32, 12.70)		1.8 (0.50, 6.11)
P-value vs. placebo ^b		0.4599		0.3725
RRD (%), 95% CI vs. placebo ^a		8.2 (-11.83, 28.32)		7.9 (-8.70, 24.56)
OR, 90% CI vs. placebo ^a		2.0 (0.43, 9.45)		1.8 (0.62, 5.00)
RRD (%), 90% CI vs. placebo ^a		8.2 (-8.60, 25.10)		7.9 (-6.03, 21.88)

^b CMH test was performed on the association between the responder status and intervention group, adjusted by randomization stratification of screening IgE levels ($<$ or $\geq$ 300 UI/mL).

Note: Participants who received any rescue medication or phototherapy before Week 16 were considered as non-responders, and missing data at Week 16 were considered as non-responders.

Table 14. Supplementary Analysis: Proportion of Participants with Reduction of Weekly Average of Daily PP-NRS $\geq$ 4 Points from Baseline at Week 16 (as-Observed Analysis; ITT Population; TID Cohort)

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Participants with reduction of weekly average of daily PP-NRS of $\geq$ 4 points from baseline at Week 16		
Responder	4 (12.9)	11 (22.9)
Non-responder	27 (87.1)	37 (77.1)
Imputed non-responder	9 (29.0)	21 (43.8)
OR, 95% CI vs. placebo ^a		2.0 (0.58, 6.89)
P-value vs. placebo ^b		0.2739
RRD (%), 95% CI vs. placebo ^a		10.0 (-6.83, 26.86)
OR, 90% CI vs. placebo ^a		2.0 (0.70, 5.64)
RRD (%), 90% CI vs. placebo ^a		10.0 (-4.12, 24.15)

CMH: Cochran-Mantel Haenszel; PP-NRS: peak pruritus numerical rating scale; CI: confidence interval.

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

^b CMH test was performed on the association between the responder status and intervention group, adjusted by randomization stratification of screening IgE levels ($<$ or $\geq$ 300 UI/mL).

Note: Data collected after study intervention discontinuation and/or after the use of any rescue medication or phototherapy were included, and missing data at Week 16 were considered as non-responders.

Table 15. Supplementary Analysis: Proportion of Participants with Reduction of Weekly Average of Daily PP-NRS $\geq$ 4 Points from Baseline at Week 16 (Hybrid Method Analysis; ITT Population; TID cohort)

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Participants with reduction of weekly average of daily PP-NRS of $\geq$ 4 points from baseline at Week 16		
Number (observed/WOCF imputed/MI imputed)	31 (17/9/5)	48 (23/13/12)
Responder	4 (14.0)	13 (27.6)
Non-responder	27 (86.0)	35 (72.4)
OR, 95% CI vs. placebo ^a		2.3 (0.68, 7.86)
P-value vs. placebo ^b		0.1792
RRD (%), 95% CI vs. placebo ^a		13.5 (-4.74, 31.78)
OR, 90% CI vs. placebo ^a		2.3 (0.82, 6.53)
RRD (%), 90% CI vs. placebo ^a		13.5 (-4.74, 31.78)

^b Each of the imputed complete data was analyzed by CMH test on the association between the responder status and intervention group, adjusted by randomization stratification of screening IgE levels ($<$ or $\geq$ 300 UI/mL).

Note: Data collected after study intervention were included. Data post the use of any rescue medication or phototherapy were set to missing and imputed by WOCF. Missing data at Week 16 after study intervention discontinuation due to lack of efficacy were imputed by WOCF; other missing data at Week 16 were imputed by MI.

Table 16. Supplementary Analysis: Proportion of Participants with Reduction of Weekly Average of Daily PP-NRS $\geq$ 4 Points from Baseline at Week 16 (High Potency TCS or Systemic Medications as Rescue Analysis; ITT Population; TID Cohort)

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Participants with reduction of weekly average of daily PP-NRS of $\geq$ 4 points from baseline at Week 16		
Responder	4 (12.9)	11 (22.9)
Non-responder	27 (87.1)	37 (77.1)
Imputed non-responder	9 (29.0)	21 (43.8)
OR, 95% CI vs. placebo ^a		2.0 (0.58, 6.89)
P-value vs. placebo ^b		0.2739
RRD (%), 95% CI vs. placebo ^a		10.0 (-6.83, 26.86)
OR, 90% CI vs. placebo ^a		2.0 (0.70, 5.64)
RRD (%), 90% CI vs. placebo ^a		10.0 (-4.12, 24.15)

^b CMH test was performed on the association between the responder status and intervention group, adjusted by randomization stratification of screening IgE levels ($<$ or $\geq$ 300 UI/mL).

Note: Participants who received high potency TCS or systemic rescue medication before Week 16 were considered as non-responders, and missing data at Week 16 were considered as non-responders.

Table 17. Supplementary Analysis: Proportion of Participants with Reduction of Weekly Average of Daily PP-NRS $\geq$ 4 Points from Baseline at Week 16 (High Potency TCS or Systemic Medications or Low to Medium TCS as Rescue Analysis; ITT Population; TID Cohort)

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Participants with reduction of weekly average of daily PP-NRS of $\geq$ 4 points from baseline at Week 16		
Responder	4 (12.9)	10 (20.8)
Non-responder	27 (87.1)	38 (79.2)
Imputed non-responder	13 (41.9)	25 (52.1)
OR, 95% CI vs. placebo ^a		1.8 (0.50, 6.11)
P-value vs. placebo ^b		0.3725
RRD (%), 95% CI vs. placebo ^a		7.9 (-8.70, 24.56)
OR, 90% CI vs. placebo ^a		1.8 (0.62, 5.00)
RRD (%), 90% CI vs. placebo ^a		7.9 (-6.03, 21.88)

^b CMH test was performed on the association between the responder status and intervention group, adjusted by randomization stratification of screening IgE levels ($<$ or $\geq$ 300 UI/mL).

Note: Participants who received high potency TCS or systemic rescue medication or consecutive use of low to medium potency TCS more than 8 days before Week 16 were considered as non-responders, and missing data at Week 16 were considered as non-responders.

Table 18. Summary of Proportion of Participants with Reduction of Weekly Average of PP-NRS ≥ 4 Points from Baseline over Time up to Week 16 (ITT Population)

	BID cohort		TID cohort	
	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Baseline				
Responder	0	0	0	0
Non-responder	18 (100)	27 (100)	31 (100)	48 (100)
Imputed non-responder	0	0	0	0
Week 1				
Responder	0	0	0	2 (4.2)
Non-responder	18 (100)	27 (100)	31 (100)	46 (95.8)
Imputed non-responder	0	0	0	0
Week 2				
Responder	0	0	0	3 (6.3)
Non-responder	18 (100)	27 (100)	31 (100)	45 (93.8)
Imputed non-responder	1 (5.6)	1 (3.7)	1 (3.2)	3 (6.3)
Week 3				
Responder	0	2 (7.4)	0	3 (6.3)
Non-responder	18 (100)	25 (92.6)	31 (100)	45 (93.8)
Imputed non-responder	2 (11.1)	3 (11.1)	3 (9.7)	5 (10.4)
Week 4				
Responder	0	2 (7.4)	0	4 (8.3)
Non-responder	18 (100)	25 (92.6)	31 (100)	44 (91.7)
Imputed non-responder	4 (22.2)	2 (7.4)	6 (19.4)	8 (16.7)
Week 5				
Responder	0	2 (7.4)	0	8 (16.7)
Non-responder	18 (100)	25 (92.6)	31 (100)	40 (83.3)
Imputed non-responder	4 (22.2)	4 (14.8)	11 (35.5)	11 (22.9)
Week 6				
Responder	0	4 (14.8)	0	6 (12.5)
Non-responder	18 (100)	23 (85.2)	31 (100)	42 (87.5)
Imputed non-responder	5 (27.8)	3 (11.1)	9 (29.0)	13 (27.1)
Week 7				
Responder	0	3 (11.1)	0	7 (14.6)
Non-responder	18 (100)	24 (88.9)	31 (100)	41 (85.4)
Imputed non-responder	4 (22.2)	3 (11.1)	9 (29.0)	14 (29.2)
Week 8				
Responder	0	3 (11.1)	0	11 (22.9)
Non-responder	18 (100)	24 (88.9)	31 (100)	37 (77.1)
Imputed non-responder	4 (22.2)	3 (11.1)	10 (32.3)	17 (35.4)
Week 9				
Responder	0	4 (14.8)	1 (3.2)	9 (18.8)
Non-responder	18 (100)	23 (85.2)	30 (96.8)	39 (81.3)
Imputed non-responder	5 (27.8)	5 (18.5)	10 (32.3)	17 (35.4)
Week 10				
Responder	0	4 (14.8)	2 (6.5)	9 (18.8)

	BID cohort		TID cohort	
	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Non-responder	18 (100)	23 (85.2)	29 (93.5)	39 (81.3)
Imputed non-responder	6 (33.3)	7 (25.9)	11 (35.5)	17 (35.4)
Week 11				
Responder	0	4 (14.8)	2 (6.5)	9 (18.8)
Non-responder	18 (100)	23 (85.2)	29 (93.5)	39 (81.3)
Imputed non-responder	6 (33.3)	6 (22.2)	11 (35.5)	18 (37.5)
Week 12				
Responder	0	3 (11.1)	2 (6.5)	9 (18.8)
Non-responder	18 (100)	24 (88.9)	29 (93.5)	39 (81.3)
Imputed non-responder	6 (33.3)	6 (22.2)	13 (41.9)	22 (45.8)
Week 13				
Responder	1 (5.6)	4 (14.8)	2 (6.5)	11 (22.9)
Non-responder	17 (94.4)	23 (85.2)	29 (93.5)	37 (77.1)
Imputed non-responder	6 (33.3)	6 (22.2)	12 (38.7)	23 (47.9)
Week 14				
Responder	2 (11.1)	4 (14.8)	3 (9.7)	9 (18.8)
Non-responder	16 (88.9)	23 (85.2)	28 (90.3)	39 (81.3)
Imputed non-responder	6 (33.3)	7 (25.9)	13 (41.9)	22 (45.8)
Week 15				
Responder	2 (11.1)	4 (14.8)	3 (9.7)	10 (20.8)
Non-responder	16 (88.9)	23 (85.2)	28 (90.3)	38 (79.2)
Imputed non-responder	6 (33.3)	7 (25.9)	13 (41.9)	23 (47.9)
Week 16				
Responder	2 (11.1)	5 (18.5)	4 (12.9)	10 (20.8)
Non-responder	16 (88.9)	22 (81.5)	27 (87.1)	38 (79.2)
Imputed non-responder	7 (38.9)	8 (29.6)	14 (45.2)	25 (52.1)

Responder: a participant with reduction of PP-NRS ≥ 4 points from baseline.

Note: Participants who received any rescue medication or phototherapy before each timepoint were considered as non-responders up to Week 16, and missing data at each timepoint were considered as non-responders up to Week 16.

Table 19. Proportion of Participants with Reduction of Weekly Average of Daily PP-NRS ≥ 4 Points from Baseline at Week 16 - Participants with Baseline PP-NRS >7 in the ITT Population (BID Cohort)

	Placebo (N=7)	Rilzabrutinib 400mg BID (N=15)
Participants with reduction of weekly average of daily PP-NRS of ≥ 4 points from baseline at Week 16		
Responder	1 (14.3)	4 (26.7)
Non-responder	6 (85.7)	11 (73.3)
Imputed non-responder	3 (42.9)	6 (40.0)
OR, 95% CI vs. placebo ^a		1.5 (0.11, 19.64)
P-value vs. placebo ^b		0.7630
RRD (%), 95% CI vs. placebo ^a		5.5 (-27.77, 38.68)
OR, 90% CI vs. placebo ^a		1.5 (0.17, 12.99)
RRD (%), 90% CI vs. placebo ^a		5.5 (-22.43, 33.34)

^b CMH test was performed on the association between the responder status and intervention group, adjusted by randomization stratification of screening IgE levels ($<$ or ≥ 300 UI/mL).

	Placebo (N=7)	Rilzabrutinib 400mg BID (N=15)
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Note: Participants who received any rescue medication or phototherapy before Week 16 were considered as non-responders, and missing data at Week 16 were considered as non-responders.

Table 20. Proportion of Participants with Reduction of Weekly Average of Daily PP-NRS $\geq$ 4 Points from Baseline at Week 16 - Participants with Baseline PP-NRS >7 in the ITT Population (TID Cohort)

	Placebo (N=17)	Rilzabrutinib 400mg TID (N=31)
Participants with reduction of weekly average of daily PP-NRS of $\geq$ 4 points from baseline at Week 16		
Responder	2 (11.8)	6 (19.4)
Non-responder	15 (88.2)	25 (80.6)
Imputed non-responder	8 (47.1)	17 (54.8)
OR, 95% CI vs. placebo ^a		1.7 (0.31, 9.56)
P-value vs. placebo ^b		0.5376
RRD (%), 95% CI vs. placebo ^a		7.1 (-13.90, 28.03)
OR, 90% CI vs. placebo ^a		1.7 (0.41, 7.25)
RRD (%), 90% CI vs. placebo ^a		7.1 (-10.53, 24.66)

^b CMH test was performed on the association between the responder status and intervention group, adjusted by randomization stratification of screening IgE levels ($<$ or $\geq$ 300 UI/mL).

Note: Participants who received any rescue medication or phototherapy before Week 16 were considered as non-responders, and missing data at Week 16 were considered as non-responders.

Table 21. Change from Baseline in Weekly Average of PP-NRS over Time up to Week 16 (BID Cohort in ITT Population)

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for Rilzabrutinib vs. Placebo LS Mean (95% CI) ^a	P-value ^a
Week 1						
Rilzabrutinib 400mg BID (N=27)	27	7.41 (1.52)	7.08 (1.80)	-0.30 (0.23)	-0.19 (-0.90, 0.52)	0.5952
Placebo (N=18)	18	6.87 (1.17)	6.76 (1.59)	-0.12 (0.27)		
Week 2						
Rilzabrutinib 400mg BID (N=27)	27	7.41 (1.52)	6.66 (1.90)	-0.76 (0.24)	-0.59 (-1.36, 0.17)	0.1230
Placebo (N=18)	18	6.87 (1.17)	6.73 (1.61)	-0.17 (0.29)		
Week 3						
Rilzabrutinib 400mg BID (N=27)	25	7.41 (1.52)	6.07 (1.98)	-1.24 (0.25)	-0.86 (-1.63, -0.09)	0.0287
Placebo (N=18)	18	6.87 (1.17)	6.48 (1.70)	-0.38 (0.31)		
Week 4						
Rilzabrutinib 400mg BID (N=27)	26	7.41 (1.52)	5.81 (1.93)	-1.54 (0.29)	-1.04 (-1.93, -0.15)	0.0216
Placebo (N=18)	17	6.87 (1.17)	6.47 (1.90)	-0.50 (0.35)		
Week 5						

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for Rilzabrutinib vs. Placebo LS Mean (95% CI) ^a	P-value ^a
Rilzabrutinib 400mg BID (N=27)	25	7.41 (1.52)	5.73 (2.04)	-1.61 (0.32)	-0.94 (-1.90, 0.03)	0.0569
Placebo (N=18)	18	6.87 (1.17)	6.29 (1.73)	-0.67 (0.38)		
Week 6						
Rilzabrutinib 400mg BID (N=27)	26	7.41 (1.52)	5.47 (1.99)	-1.90 (0.34)	-0.96 (-2.00, 0.08)	0.0710
Placebo (N=18)	17	6.87 (1.17)	6.19 (1.90)	-0.94 (0.41)		
Week 7						
Rilzabrutinib 400mg BID (N=27)	26	7.41 (1.52)	5.61 (2.21)	-1.76 (0.36)	-1.03 (-2.13, 0.06)	0.0647
Placebo (N=18)	18	6.87 (1.17)	6.22 (1.94)	-0.73 (0.43)		
Week 8						
Rilzabrutinib 400mg BID (N=27)	26	7.41 (1.52)	5.64 (2.19)	-1.78 (0.36)	-0.73 (-1.81, 0.36)	0.1903
Placebo (N=18)	18	6.87 (1.17)	5.94 (1.95)	-1.05 (0.43)		
Week 9						
Rilzabrutinib 400mg BID (N=27)	24	7.41 (1.52)	5.48 (2.22)	-1.95 (0.35)	-0.62 (-1.67, 0.44)	0.2520
Placebo (N=18)	17	6.87 (1.17)	5.73 (2.06)	-1.33 (0.42)		
Week 10						
Rilzabrutinib 400mg BID (N=27)	23	7.41 (1.52)	5.10 (2.28)	-2.23 (0.37)	-1.02 (-2.13, 0.09)	0.0728
Placebo (N=18)	17	6.87 (1.17)	5.79 (2.04)	-1.21 (0.44)		
Week 11						
Rilzabrutinib 400mg BID (N=27)	24	7.41 (1.52)	5.28 (2.29)	-2.10 (0.37)	-0.72 (-1.85, 0.40)	0.2073
Placebo (N=18)	17	6.87 (1.17)	5.68 (1.98)	-1.38 (0.45)		
Week 12						
Rilzabrutinib 400mg BID (N=27)	24	7.41 (1.52)	5.22 (2.22)	-2.23 (0.38)	-0.71 (-1.85, 0.44)	0.2280
Placebo (N=18)	17	6.87 (1.17)	5.59 (2.03)	-1.52 (0.46)		
Week 13						
Rilzabrutinib 400mg BID (N=27)	24	7.41 (1.52)	4.77 (2.63)	-2.79 (0.49)	-1.22 (-2.70, 0.27)	0.1082
Placebo (N=18)	17	6.87 (1.17)	5.65 (2.16)	-1.57 (0.60)		
Week 14						
Rilzabrutinib 400mg BID (N=27)	24	7.41 (1.52)	4.80 (2.68)	-2.67 (0.52)	-1.25 (-2.82, 0.32)	0.1190
Placebo (N=18)	17	6.87 (1.17)	5.58 (2.26)	-1.42 (0.66)		
Week 15						
Rilzabrutinib 400mg BID (N=27)	24	7.41 (1.52)	4.76 (2.72)	-2.74 (0.54)	-1.02 (-2.63, 0.60)	0.2177
Placebo (N=18)	17	6.87 (1.17)	5.44 (2.24)	-1.72 (0.65)		
Week 16						

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for Rilzabrutinib vs. Placebo LS Mean (95% CI) ^a	P-value ^a
Rilzabrutinib 400mg BID (N=27)	23	7.41 (1.52)	4.44 (2.73)	-3.11 (0.52)	-1.51 (-3.14, - 0.13)	0.0703
Placebo (N=18)	16	6.87 (1.17)	5.79 (2.12)	-1.60 (0.66)		

^a Each of the imputed complete data were analyzed by fitting an ANCOVA model with the baseline value of PP-NRS, intervention group, randomization stratification of IgE levels (< or ≥300 UI/mL) as covariates
Note: Data collected after study intervention discontinuation were included. Data post the use of any rescue medication or phototherapy were set to missing and imputed by WOCF. Missing data after study intervention discontinuation due to lack of efficacy were imputed by WOCF, and other missing data were imputed by MI. Descriptive statistics at each Week include participants whose values were imputed using WOCF at the Week, and participants whose values were imputed by MI at the Week were excluded from the descriptive analysis.

Table 22. Change from Baseline in Weekly Average of PP-NRS over Time up to Week 16 TID Cohort in ITT population)

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for Rilzabrutinib vs. Placebo LS Mean (95% CI) ^a	P-value ^a
Week 1						
Rilzabrutinib 400mg TID (N=48)	48	7.61 (1.35)	6.70 (2.14)	-0.93 (0.20)	-0.90 (-1.53, - 0.27)	0.0054
Placebo (N=31)	31	7.01 (1.33)	7.02 (1.28)	-0.03 (0.25)		
Week 2						
Rilzabrutinib 400mg TID (N=48)	46	7.61 (1.35)	6.62 (2.31)	-1.06 (0.23)	-1.08 (-1.79, - 0.36)	0.0031
Placebo (N=31)	30	7.01 (1.33)	7.13 (1.51)	0.01 (0.29)		
Week 3						
Rilzabrutinib 400mg TID (N=48)	44	7.61 (1.35)	6.36 (2.41)	-1.22 (0.26)	-1.06 (-1.85, - 0.28)	0.0081
Placebo (N=31)	30	7.01 (1.33)	6.95 (1.54)	-0.16 (0.31)		
Week 4						
Rilzabrutinib 400mg TID (N=48)	43	7.61 (1.35)	6.36 (2.57)	-1.43 (0.28)	-1.17 (-2.02, - 0.32)	0.0068
Placebo (N=31)	30	7.01 (1.33)	6.85 (1.64)	-0.26 (0.34)		
Week 5						
Rilzabrutinib 400mg TID (N=48)	41	7.61 (1.35)	5.90 (2.68)	-1.86 (0.30)	-1.33 (-2.26, - 0.40)	0.0052
Placebo (N=31)	28	7.01 (1.33)	6.61 (1.78)	-0.53 (0.37)		
Week 6						
Rilzabrutinib 400mg TID (N=48)	40	7.61 (1.35)	6.02 (2.72)	-1.72 (0.30)	-1.30 (-2.19, - 0.41)	0.0041
Placebo (N=31)	30	7.01 (1.33)	6.73 (1.67)	-0.42 (0.35)		
Week 7						
Rilzabrutinib 400mg TID (N=48)	39	7.61 (1.35)	5.85 (2.79)	-1.75 (0.31)	-1.30 (-2.26, - 0.35)	0.0077

	n	Baseline Mean (SD)	Post-baseline Mean (SD)	Change from baseline LS Mean (SE) ^a	Change difference for Rilzabrutinib vs. Placebo LS Mean (95% CI) ^a	P-value ^a
Placebo (N=31)	30	7.01 (1.33)	6.67 (1.65)	-0.45 (0.38)		
Week 8						
Rilzabrutinib 400mg TID (N=48)	37	7.61 (1.35)	5.83 (2.93)	-2.03 (0.35)	-1.44 (-2.48, - 0.41)	0.0062
Placebo (N=31)	29	7.01 (1.33)	6.56 (1.84)	-0.58 (0.40)		
Week 9						
Rilzabrutinib 400mg TID (N=48)	37	7.61 (1.35)	5.58 (3.12)	-2.20 (0.36)	-1.57 (-2.68, - 0.47)	0.0051
Placebo (N=31)	30	7.01 (1.33)	6.58 (1.77)	-0.63 (0.44)		
Week 10						
Rilzabrutinib 400mg TID (N=48)	37	7.61 (1.35)	5.45 (2.99)	-2.00 (0.36)	-1.37 (-2.47, - 0.26)	0.0151
Placebo (N=31)	29	7.01 (1.33)	6.60 (1.88)	-0.64 (0.43)		
Week 11						
Rilzabrutinib 400mg TID (N=48)	36	7.61 (1.35)	5.61 (3.03)	-2.10 (0.36)	-1.40 (-2.51, - 0.29)	0.0133
Placebo (N=31)	29	7.01 (1.33)	6.47 (1.79)	-0.70 (0.44)		
Week 12						
Rilzabrutinib 400mg TID (N=48)	35	7.61 (1.35)	5.84 (3.17)	-2.06 (0.40)	-1.37 (-2.58, - 0.16)	0.0264
Placebo (N=31)	27	7.01 (1.33)	6.48 (2.03)	-0.69 (0.47)		
Week 13						
Rilzabrutinib 400mg TID (N=48)	36	7.61 (1.35)	5.71 (3.30)	-2.04 (0.40)	-1.34 (-2.55, - 0.14)	0.0292
Placebo (N=31)	28	7.01 (1.33)	6.45 (2.08)	-0.69 (0.47)		
Week 14						
Rilzabrutinib 400mg TID (N=48)	37	7.61 (1.35)	5.64 (3.25)	-2.25 (0.42)	-1.53 (-2.79, - 0.26)	0.0181
Placebo (N=31)	27	7.01 (1.33)	6.46 (2.38)	-0.72 (0.50)		
Week 15						
Rilzabrutinib 400mg TID (N=48)	37	7.61 (1.35)	5.64 (3.33)	-2.23 (0.42)	-1.48 (-2.76, - 0.20)	0.0230
Placebo (N=31)	27	7.01 (1.33)	6.31 (2.37)	-0.75 (0.50)		
Week 16						
Rilzabrutinib 400mg TID (N=48)	36	7.61 (1.35)	5.88 (3.30)	-2.07 (0.43)	-1.24 (-2.51, - 0.04)	0.0568
Placebo (N=31)	26	7.01 (1.33)	6.22 (2.49)	-0.83 (0.51)		

^a Each of the imputed complete data were analyzed by fitting an ANCOVA model with the baseline value of PP-NRS, intervention group, randomization stratification of IgE levels (< or ≥300 UI/mL) as covariates
Note: Data collected after study intervention discontinuation were included. Data post the use of any rescue medication or phototherapy were set to missing and imputed by WOCF. Missing data after study intervention discontinuation due to lack of efficacy were imputed by WOCF, and other missing data were imputed by MI. Descriptive statistics at each Week include participants whose values were imputed using WOCF at the Week, and participants whose values were imputed by MI at the Week were excluded from the descriptive analysis.

Table 23. Percent Change from Baseline in Weekly Average of PP-NRS over Time up to Week 16 (BID Cohort in ITT Population)

					Percent change difference for Rilzabrutinib vs. Placebo	
	n	Baseline Mean (SD)	Post- baseline Mean (SD)	Percent change from baseline LS Mean (SE) ^a	LS Mean (95% CI) ^a	P-value ^a
Week 1						
Rilzabrutinib 400mg BID (N=27)	27	7.41 (1.52)	7.08 (1.80)	-4.37 (3.17)	-3.22 (-13.15, 6.71)	0.5159
Placebo (N=18)	18	6.87 (1.17)	6.76 (1.59)	-1.15 (3.83)		
Week 2						
Rilzabrutinib 400mg BID (N=27)	27	7.41 (1.52)	6.66 (1.90)	-10.92 (3.53)	-8.68 (-19.73, 2.38)	0.1207
Placebo (N=18)	18	6.87 (1.17)	6.73 (1.61)	-2.24 (4.26)		
Week 3						
Rilzabrutinib 400mg BID (N=27)	25	7.41 (1.52)	6.07 (1.98)	-17.92 (3.60)	-12.46 (-23.35, -1.57)	0.0249
Placebo (N=18)	18	6.87 (1.17)	6.48 (1.70)	-5.46 (4.32)		
Week 4						
Rilzabrutinib 400mg BID (N=27)	26	7.41 (1.52)	5.81 (1.93)	-21.76 (4.26)	-14.82 (-27.80, -1.84)	0.0252
Placebo (N=18)	17	6.87 (1.17)	6.47 (1.90)	-6.93 (5.16)		
Week 5						
Rilzabrutinib 400mg BID (N=27)	25	7.41 (1.52)	5.73 (2.04)	-22.14 (4.49)	-13.10 (-26.65, 0.45)	0.0582
Placebo (N=18)	18	6.87 (1.17)	6.29 (1.73)	-9.04 (5.37)		
Week 6						
Rilzabrutinib 400mg BID (N=27)	26	7.41 (1.52)	5.47 (1.99)	-25.80 (4.97)	-12.38 (-27.45, 2.69)	0.1074
Placebo (N=18)	17	6.87 (1.17)	6.19 (1.90)	-13.42 (5.99)		
Week 7						
Rilzabrutinib 400mg BID (N=27)	26	7.41 (1.52)	5.61 (2.21)	-24.10 (5.21)	-13.57 (-29.35, 2.21)	0.0920
Placebo (N=18)	18	6.87 (1.17)	6.22 (1.94)	-10.53 (6.26)		
Week 8						
Rilzabrutinib 400mg BID (N=27)	26	7.41 (1.52)	5.64 (2.19)	-24.66 (5.06)	-9.40 (-24.72, 5.93)	0.2295
Placebo (N=18)	18	6.87 (1.17)	5.94 (1.95)	-15.27 (6.08)		
Week 9						
Rilzabrutinib 400mg BID (N=27)	24	7.41 (1.52)	5.48 (2.22)	-26.94 (5.01)	-7.96 (-23.14, 7.21)	0.3036
Placebo (N=18)	17	6.87 (1.17)	5.73 (2.06)	-18.98 (6.03)		
Week 10						
Rilzabrutinib 400mg BID (N=27)	23	7.41 (1.52)	5.10 (2.28)	-30.86 (5.20)	-13.85 (-29.54, 1.85)	0.0838
Placebo (N=18)	17	6.87 (1.17)	5.79 (2.04)	-17.01 (6.22)		
Week 11						

		n	Baseline Mean (SD)	Post- baseline Mean (SD)	Percent change from baseline LS Mean (SE) ^a	Percent change difference for Rilzabrutinib vs. Placebo LS Mean (95% CI) ^a	P-value ^a
Rilzabrutinib 400mg BID (N=27)	24	7.41 (1.52)	5.28 (2.29)	-28.96 (5.29)	-9.88 (-25.74, 5.98)	0.2221	
Placebo (N=18)	17	6.87 (1.17)	5.68 (1.98)	-19.08 (6.32)			
Week 12							
Rilzabrutinib 400mg BID (N=27)	24	7.41 (1.52)	5.22 (2.22)	-31.08 (5.06)	-9.61 (-24.92, 5.70)	0.2187	
Placebo (N=18)	17	6.87 (1.17)	5.59 (2.03)	-21.47 (6.10)			
Week 13							
Rilzabrutinib 400mg BID (N=27)	24	7.41 (1.52)	4.77 (2.63)	-39.04 (6.63)	-17.80 (-37.55, 1.94)	0.0771	
Placebo (N=18)	17	6.87 (1.17)	5.65 (2.16)	-21.24 (7.95)			
Week 14							
Rilzabrutinib 400mg BID (N=27)	24	7.41 (1.52)	4.80 (2.68)	-37.03 (7.06)	-17.56 (-38.58, 3.46)	0.1015	
Placebo (N=18)	17	6.87 (1.17)	5.58 (2.26)	-19.47 (8.75)			
Week 15							
Rilzabrutinib 400mg BID (N=27)	24	7.41 (1.52)	4.76 (2.72)	-38.23 (7.45)	-14.42 (-36.19, 7.35)	0.1942	
Placebo (N=18)	17	6.87 (1.17)	5.44 (2.24)	-23.81 (8.66)			
Week 16							
Rilzabrutinib 400mg BID (N=27)	23	7.41 (1.52)	4.44 (2.73)	-43.53 (6.80)	-21.98 (-43.09, -0.87)	0.0413	
Placebo (N=18)	16	6.87 (1.17)	5.79 (2.12)	-21.55 (8.37)			

^a Each of the imputed complete data were analyzed by fitting an ANCOVA model with the baseline value of PP-NRS, intervention group, randomization stratification of IgE levels (< or ≥300 UI/mL) as covariates
Note: Data collected after study intervention discontinuation were included. Data post the use of any rescue medication or phototherapy were set to missing and imputed by WOCF. Missing data after study intervention discontinuation due to lack of efficacy were imputed by WOCF, and other missing data were imputed by MI. Descriptive statistics at each Week include participants whose values were imputed using WOCF at the Week, and participants whose values were imputed by MI at the Week were excluded from the descriptive analysis.

Table 24. Percent Change from Baseline in Weekly Average of PP-NRS over Time up to Week 16 (TID Cohort in ITT Population)

						Percent change difference for Rilzabrutinib vs. Placebo	
						LS Mean (95% CI) ^a	P-value ^a
	n	Baseline Mean (SD)	Post- baseline Mean (SD)	Percent change from baseline LS Mean (SE) ^a			
Week 1							
Rilzabrutinib 400mg TID (N=48)	48	7.61 (1.35)	6.70 (2.14)	-12.95 (2.87)	-13.93 (-22.96,	0.0030	
Placebo (N=31)	31	7.01 (1.33)	7.02 (1.28)	0.98 (3.57)	-4.89)		
Week 2							

	n	Baseline Mean (SD)	Post- baseline Mean (SD)	Percent change from baseline LS Mean (SE) ^a	Percent change difference for Rilzabrutinib vs. Placebo LS Mean (95% CI) ^a	P-value ^a
Rilzabrutinib 400mg TID (N=48)	46	7.61 (1.35)	6.62 (2.31)	-15.35 (3.41)	-16.85 (-27.36, -6.35)	0.0017
Placebo (N=31)	30	7.01 (1.33)	7.13 (1.51)	1.51 (4.21)		
Week 3						
Rilzabrutinib 400mg TID (N=48)	44	7.61 (1.35)	6.36 (2.41)	-17.18 (3.70)	-16.23 (-27.58, -4.88)	0.0051
Placebo (N=31)	30	7.01 (1.33)	6.95 (1.54)	-0.94 (4.52)		
Week 4						
Rilzabrutinib 400mg TID (N=48)	43	7.61 (1.35)	6.36 (2.57)	-20.87 (4.03)	-18.47 (-30.82, -6.13)	0.0034
Placebo (N=31)	30	7.01 (1.33)	6.85 (1.64)	-2.40 (4.93)		
Week 5						
Rilzabrutinib 400mg TID (N=48)	41	7.61 (1.35)	5.90 (2.68)	-26.81 (4.33)	-20.55 (-33.89, -7.21)	0.0025
Placebo (N=31)	28	7.01 (1.33)	6.61 (1.78)	-6.26 (5.35)		
Week 6						
Rilzabrutinib 400mg TID (N=48)	40	7.61 (1.35)	6.02 (2.72)	-25.10 (4.35)	-20.61 (-33.72, -7.49)	0.0021
Placebo (N=31)	30	7.01 (1.33)	6.73 (1.67)	-4.49 (5.22)		
Week 7						
Rilzabrutinib 400mg TID (N=48)	39	7.61 (1.35)	5.85 (2.79)	-25.80 (4.40)	-20.67 (-34.19, -7.15)	0.0027
Placebo (N=31)	30	7.01 (1.33)	6.67 (1.65)	-5.13 (5.39)		
Week 8						
Rilzabrutinib 400mg TID (N=48)	37	7.61 (1.35)	5.83 (2.93)	-29.54 (4.97)	-22.46 (-37.27, -7.66)	0.0029
Placebo (N=31)	29	7.01 (1.33)	6.56 (1.84)	-7.08 (5.75)		
Week 9						
Rilzabrutinib 400mg TID (N=48)	37	7.61 (1.35)	5.58 (3.12)	-31.67 (4.98)	-24.34 (-39.53, -9.14)	0.0017
Placebo (N=31)	30	7.01 (1.33)	6.58 (1.77)	-7.34 (6.02)		
Week 10						
Rilzabrutinib 400mg TID (N=48)	37	7.61 (1.35)	5.45 (2.99)	-29.09 (5.06)	-21.64 (-36.97, -6.31)	0.0057
Placebo (N=31)	29	7.01 (1.33)	6.60 (1.88)	-7.45 (6.05)		
Week 11						
Rilzabrutinib 400mg TID (N=48)	36	7.61 (1.35)	5.61 (3.03)	-30.14 (5.10)	-22.21 (-37.70, -6.72)	0.0049
Placebo (N=31)	29	7.01 (1.33)	6.47 (1.79)	-7.93 (6.12)		
Week 12						
Rilzabrutinib 400mg TID (N=48)	35	7.61 (1.35)	5.84 (3.17)	-29.60 (5.62)	-21.40 (-38.26, -4.55)	0.0128
Placebo (N=31)	27	7.01 (1.33)	6.48 (2.03)	-8.19 (6.60)		
Week 13						

	n	Baseline Mean (SD)	Post- baseline Mean (SD)	Percent change from baseline LS Mean (SE) ^a	Percent change difference for Rilzabrutinib vs. Placebo LS Mean (95% CI) ^a	P-value ^a
Rilzabrutinib 400mg TID (N=48)	36	7.61 (1.35)	5.71 (3.30)	-29.34 (5.73)	-20.96 (-38.13, -3.78)	0.0168
Placebo (N=31)	28	7.01 (1.33)	6.45 (2.08)	-8.38 (6.73)		
Week 14						
Rilzabrutinib 400mg TID (N=48)	37	7.61 (1.35)	5.64 (3.25)	-32.32 (5.97)	-23.44 (-41.65, -5.24)	0.0116
Placebo (N=31)	27	7.01 (1.33)	6.46 (2.38)	-8.88 (7.11)		
Week 15						
Rilzabrutinib 400mg TID (N=48)	37	7.61 (1.35)	5.64 (3.33)	-32.18 (5.98)	-22.84 (-41.00, -4.67)	0.0138
Placebo (N=31)	27	7.01 (1.33)	6.31 (2.37)	-9.34 (7.18)		
Week 16						
Rilzabrutinib 400mg TID (N=48)	36	7.61 (1.35)	5.88 (3.30)	-30.13 (6.08)	-19.77 (-37.82, -1.71)	0.0319
Placebo (N=31)	26	7.01 (1.33)	6.22 (2.49)	-10.36 (7.19)		

^a Each of the imputed complete data were analyzed by fitting an ANCOVA model with the baseline value of PP-NRS, intervention group, randomization stratification of IgE levels (< or ≥300 UI/mL) as covariates

Note: Data collected after study intervention discontinuation were included. Data post the use of any rescue medication or phototherapy were set to missing and imputed by WOCF. Missing data after study intervention discontinuation due to lack of efficacy were imputed by WOCF, and other missing data were imputed by MI. Descriptive statistics at each Week include participants whose values were imputed using WOCF at the Week, and participants whose values were imputed by MI at the Week were excluded from the descriptive analysis.

Table 25. Change and Percent Change in Weekly Average of Daily PP-NRS from Baseline to Week 16 (ITT Population)

	BID cohort		TID cohort	
	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Baseline				
Number	18	27	31	48
Mean (SD)	6.87 (1.17)	7.41 (1.52)	7.01 (1.33)	7.61 (1.35)
Median	7.00	7.40	7.17	7.42
Q1 ; Q3	6.50 ; 7.57	6.20 ; 8.57	6.00 ; 8.00	6.85 ; 8.25
Min ; Max	4.7 ; 9.0	4.4 ; 10.0	3.5 ; 9.0	4.1 ; 10.0
Week 16				
Number	16	23	26	36
Mean (SD)	5.79 (2.12)	4.44 (2.73)	6.22 (2.49)	5.88 (3.30)
Median	6.43	4.00	6.58	6.17
Q1 ; Q3	3.84 ; 7.62	2.43 ; 5.83	4.83 ; 8.20	3.20 ; 9.00
Min ; Max	2.0 ; 9.0	0.2 ; 10.0	0.0 ; 10.0	0.0 ; 10.0
Change from baseline				
Number (observed/imputed)	16 (11/5)	23 (19/4)	26 (17/9)	36 (23/13)
Mean (SD)	-1.22 (1.88)	-3.02 (2.49)	-0.88 (2.40)	-1.72 (2.66)
Median	-1.30	-3.00	0.07	-1.00
Q1 ; Q3	-2.12 ; 0.64	-3.90 ; -1.66	-2.45 ; 0.64	-4.05 ; 0.14
Min ; Max	-4.8 ; 1.2	-8.8 ; 0.9	-6.0 ; 2.6	-8.3 ; 2.7
LS Mean (SE) ^a	-1.60 (0.66)	-3.11 (0.52)	-0.83 (0.51)	-2.07 (0.43)

	BID cohort		TID cohort	
	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
LS Mean Diff vs. placebo (95% CI) ^a		-1.51 (-3.14, 0.13)		-1.24 (-2.51, 0.04)
P-value vs. placebo ^a		0.0703		0.0568
LS Mean Diff vs. placebo (90% CI) ^a		-1.51 (-2.88, - 0.14)		-1.24 (-2.30, - 0.17)
Percent change from baseline				
Number (observed/imputed)	16 (11/5)	23 (19/4)	26 (17/9)	36 (23/13)
Mean (SD)	-17.42 (27.59)	-41.39 (29.55)	-11.44 (35.52)	-24.96 (38.25)
Median	-15.23	-41.30	0.81	-12.41
Q1 ; Q3	-36.09 ; 8.50	-60.00 ; -22.22	-39.02 ; 9.09	-57.15 ; 1.57
Min ; Max	-70.7 ; 19.4	-97.3 ; 9.8	-100.0 ; 47.2	-100.0 ; 42.1
LS Mean (SE) ^a	-21.55 (8.37)	-43.53 (6.80)	-10.36 (7.19)	-30.13 (6.08)
LS Mean Diff vs. placebo (95% CI) ^a		-21.98 (-43.09, - 0.87)		-19.77 (-37.82, - 1.71)
P-value vs. placebo ^a		0.0413		0.0319
LS Mean Diff vs. placebo (90% CI) ^a		-21.98 (-39.69, - 4.27)		-19.77 (-34.92, - 4.62)

^a Each of the imputed complete data were analyzed by fitting an ANCOVA model with the baseline value of PP-NRS, intervention group, randomization stratification of IgE levels (< or ≥300 UI/mL) as covariates

Note: Data collected after study intervention discontinuation were included. Data post the use of any rescue medication or phototherapy were set to missing and imputed by WOCF. Missing data after study intervention discontinuation due to lack of efficacy were imputed by WOCF, and other missing data were imputed by MI. Descriptive statistics at Week 16 include participants whose values were imputed using WOCF at Week 16, and participants whose values were imputed by MI at Week 16 were excluded from the descriptive analysis.

Table 26. Supplementary Analysis: Change and Percent Change in Weekly Average of Daily PP-NRS from Baseline to Week 16 (High Potency TCS or Systemic Medications as Rescue Analysis; ITT Population)

	BID cohort		TID cohort	
	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Baseline				
Number	18	27	31	48
Mean (SD)	6.87 (1.17)	7.41 (1.52)	7.01 (1.33)	7.61 (1.35)
Median	7.00	7.40	7.17	7.42
Q1 ; Q3	6.50 ; 7.57	6.20 ; 8.57	6.00 ; 8.00	6.85 ; 8.25
Min ; Max	4.7 ; 9.0	4.4 ; 10.0	3.5 ; 9.0	4.1 ; 10.0
Week 16				
Number	16	22	24	34
Mean (SD)	5.31 (2.01)	3.96 (2.34)	5.57 (2.23)	5.27 (3.13)
Median	4.92	3.63	6.00	5.25
Q1 ; Q3	3.53 ; 7.20	2.43 ; 5.00	4.33 ; 7.07	3.14 ; 8.00
Min ; Max	2.0 ; 8.0	0.2 ; 9.6	0.0 ; 8.8	0.0 ; 10.0
Change from baseline				
Number (observed/imputed)	16 (13/3)	22 (21/1)	24 (22/2)	34 (27/7)
Mean (SD)	-1.69 (1.91)	-3.39 (2.39)	-1.43 (2.17)	-2.20 (2.64)
Median	-1.51	-3.07	-0.93	-1.54
Q1 ; Q3	-2.62 ; -0.60	-4.74 ; -1.86	-2.73 ; 0.35	-4.14 ; 0.00
Min ; Max	-4.9 ; 1.2	-8.8 ; 0.9	-6.0 ; 1.4	-8.3 ; 2.4
LS Mean (SE) ^a	-2.12 (0.57)	-3.29 (0.49)	-1.29 (0.48)	-2.56 (0.40)
LS Mean Diff vs. placebo (95% CI) ^a		-1.17 (-2.61, 0.27)		-1.27 (-2.48, - 0.05)

	BID cohort		TID cohort	
	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
P-value vs. placebo ^a		0.1103		0.0408
LS Mean Diff vs. placebo (90% CI) ^a		-1.17 (-2.38, -0.04)		-1.27 (-2.28, -0.25)
Percent change from baseline				
Number (observed/imputed)	16 (13/3)	22 (21/1)	24 (22/2)	34 (27/7)
Mean (SD)	-24.06 (26.24)	-46.05 (27.74)	-19.60 (32.12)	-31.30 (36.79)
Median	-25.12	-44.51	-13.23	-21.09
Q1 ; Q3	-40.67 ; -7.97	-61.65 ; -25.53	-40.34 ; 5.51	-63.33 ; 0.00
Min ; Max	-70.7 ; 17.9	-97.3 ; 9.8	-100.0 ; 31.3	-100.0 ; 37.0
LS Mean (SE) ^a	-28.81 (7.50)	-44.92 (6.53)	-16.76 (6.75)	-36.15 (5.61)
LS Mean Diff vs. placebo (95% CI) ^a		-16.11 (-35.22, 3.00)		-19.39 (-36.48, -2.30)
P-value vs. placebo ^a		0.0985		0.0261
LS Mean Diff vs. placebo (90% CI) ^a		-16.11 (-32.14, -0.07)		-19.39 (-33.74, -5.05)

LS: least squares; PP-NRS: peak pruritus numerical rating scale; WOCF: worst observation carried forward; MI: multiple imputation; TCS: topical corticosteroids

^a Each of the imputed complete data were analyzed by fitting an ANCOVA model with the baseline value of PP-NRS, intervention group, randomization stratification of IgE levels (< or ≥300 UI/mL) as covariates

Note: Data collected after study intervention discontinuation were included. Data post the use of high potency TCS or systemic rescue medication before Week 16 were set to missing and imputed by WOCF. Missing data after study intervention discontinuation due to lack of efficacy were imputed by WOCF, and other missing data were imputed by MI.

Descriptive statistics at Week 16 include participants whose values were imputed using WOCF at Week 16, and participants whose values were imputed by MI at Week 16 were excluded from the descriptive analysis.

Table 27. Summary of Weekly Average of Daily PP-NRS by Week up to Week 16 (ITT Population; BID Cohort)

	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)
Baseline		
Number	18	27
Mean (SD)	6.87 (1.17)	7.41 (1.52)
Median	7.00	7.40
Q1 ; Q3	6.50 ; 7.57	6.20 ; 8.57
Min ; Max	4.7 ; 9.0	4.4 ; 10.0
Week 1		
Number (observed/imputed)	18 (18/0)	27 (27/0)
Mean (SD)	6.76 (1.59)	7.08 (1.80)
Median	6.93	7.29
Q1 ; Q3	5.86 ; 8.14	6.00 ; 8.14
Min ; Max	3.3 ; 9.0	3.6 ; 10.0
Change from baseline		
Number (observed/imputed)	18 (18/0)	27 (27/0)
Mean (SD)	-0.11 (1.19)	-0.33 (1.06)
Median	-0.07	-0.17
Q1 ; Q3	-0.43 ; 0.67	-0.86 ; 0.31
Min ; Max	-3.7 ; 1.6	-2.7 ; 1.4
Percent change from baseline		
Number (observed/imputed)	18 (18/0)	27 (27/0)
Mean (SD)	-1.42 (16.98)	-4.65 (14.46)

	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)
Median	-1.00	-2.70
Q1 ; Q3	-6.38 ; 8.33	-12.50 ; 4.17
Min ; Max	-52.4 ; 25.3	-42.9 ; 19.8
Week 2		
Number (observed/imputed)	18 (17/1)	27 (26/1)
Mean (SD)	6.73 (1.61)	6.66 (1.90)
Median	7.00	6.86
Q1 ; Q3	5.57 ; 7.50	5.14 ; 8.00
Min ; Max	4.1 ; 9.0	2.6 ; 10.0
Change from baseline		
Number (observed/imputed)	18 (17/1)	27 (26/1)
Mean (SD)	-0.14 (1.07)	-0.75 (1.27)
Median	-0.18	-0.43
Q1 ; Q3	-0.83 ; 0.17	-1.33 ; 0.17
Min ; Max	-1.8 ; 2.0	-3.7 ; 1.0
Percent change from baseline		
Number (observed/imputed)	18 (17/1)	27 (26/1)
Mean (SD)	-2.39 (15.50)	-10.38 (18.43)
Median	-2.78	-4.92
Q1 ; Q3	-15.69 ; 2.44	-19.44 ; 2.17
Min ; Max	-25.6 ; 28.6	-58.9 ; 14.4
Week 3		
Number (observed/imputed)	18 (16/2)	25 (24/1)
Mean (SD)	6.48 (1.70)	6.07 (1.98)
Median	6.52	6.14
Q1 ; Q3	5.43 ; 7.57	5.00 ; 7.60
Min ; Max	3.4 ; 9.0	1.7 ; 10.0
Change from baseline		
Number (observed/imputed)	18 (16/2)	25 (24/1)
Mean (SD)	-0.39 (1.06)	-1.19 (1.33)
Median	-0.50	-1.00
Q1 ; Q3	-1.00 ; 0.29	-1.86 ; -0.40
Min ; Max	-2.1 ; 2.0	-4.5 ; 0.5
Percent change from baseline		
Number (observed/imputed)	18 (16/2)	25 (24/1)
Mean (SD)	-6.51 (16.36)	-17.25 (19.21)
Median	-7.33	-12.50
Q1 ; Q3	-15.87 ; 5.00	-24.00 ; -9.09
Min ; Max	-38.5 ; 28.6	-72.6 ; 7.1
Week 4		
Number (observed/imputed)	17 (14/3)	26 (25/1)
Mean (SD)	6.47 (1.90)	5.81 (1.93)
Median	6.57	6.14
Q1 ; Q3	5.43 ; 8.00	4.80 ; 7.00
Min ; Max	3.0 ; 9.0	1.0 ; 9.8
Change from baseline		
Number (observed/imputed)	17 (14/3)	26 (25/1)
Mean (SD)	-0.40 (1.31)	-1.55 (1.51)
Median	-0.43	-1.37
Q1 ; Q3	-1.40 ; 0.50	-2.17 ; -0.29

	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)
Min ; Max	-2.6 ; 2.0	-5.3 ; 0.4
Percent change from baseline		
Number (observed/imputed)	17 (14/3)	26 (25/1)
Mean (SD)	-6.63 (20.44)	-21.27 (21.51)
Median	-6.38	-19.41
Q1 ; Q3	-20.00 ; 7.69	-30.11 ; -3.92
Min ; Max	-46.2 ; 28.6	-84.0 ; 9.1
Week 5		
Number (observed/imputed)	18 (14/4)	25 (23/2)
Mean (SD)	6.29 (1.73)	5.73 (2.04)
Median	5.85	6.00
Q1 ; Q3	5.00 ; 7.67	4.50 ; 7.29
Min ; Max	4.0 ; 9.3	1.3 ; 10.0
Change from baseline		
Number (observed/imputed)	18 (14/4)	25 (23/2)
Mean (SD)	-0.59 (1.27)	-1.52 (1.71)
Median	-0.76	-1.57
Q1 ; Q3	-1.43 ; 0.43	-2.14 ; -0.17
Min ; Max	-2.5 ; 2.3	-6.4 ; 0.6
Percent change from baseline		
Number (observed/imputed)	18 (14/4)	25 (23/2)
Mean (SD)	-8.75 (18.68)	-21.14 (23.78)
Median	-12.17	-22.22
Q1 ; Q3	-25.00 ; 5.00	-27.42 ; -2.50
Min ; Max	-35.7 ; 32.1	-79.4 ; 13.6
Week 6		
Number (observed/imputed)	17 (13/4)	26 (24/2)
Mean (SD)	6.19 (1.90)	5.47 (1.99)
Median	6.14	5.76
Q1 ; Q3	5.00 ; 7.57	4.00 ; 7.00
Min ; Max	2.7 ; 9.6	0.8 ; 10.0
Change from baseline		
Number (observed/imputed)	17 (13/4)	26 (24/2)
Mean (SD)	-0.68 (1.41)	-1.89 (1.91)
Median	-0.95	-1.71
Q1 ; Q3	-1.50 ; 0.26	-3.14 ; -0.50
Min ; Max	-2.9 ; 2.6	-7.0 ; 1.8
Percent change from baseline		
Number (observed/imputed)	17 (13/4)	26 (24/2)
Mean (SD)	-10.37 (21.66)	-24.97 (26.07)
Median	-15.87	-20.95
Q1 ; Q3	-21.28 ; 3.46	-40.00 ; -6.38
Min ; Max	-51.3 ; 37.1	-86.7 ; 40.9
Week 7		
Number (observed/imputed)	18 (14/4)	26 (24/2)
Mean (SD)	6.22 (1.94)	5.61 (2.21)
Median	6.29	6.00
Q1 ; Q3	5.00 ; 7.57	3.86 ; 6.86
Min ; Max	2.9 ; 9.4	0.2 ; 10.0

	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)
Change from baseline		
Number (observed/imputed)	18 (14/4)	26 (24/2)
Mean (SD)	-0.65 (1.39)	-1.75 (2.01)
Median	-0.88	-1.46
Q1 ; Q3	-1.81 ; 0.43	-2.50 ; -0.29
Min ; Max	-2.7 ; 2.0	-7.0 ; 1.6
Percent change from baseline		
Number (observed/imputed)	18 (14/4)	26 (24/2)
Mean (SD)	-10.29 (21.46)	-23.46 (27.98)
Median	-12.62	-19.62
Q1 ; Q3	-26.83 ; 5.00	-41.67 ; -4.17
Min ; Max	-41.0 ; 28.6	-97.3 ; 36.4
Week 8		
Number (observed/imputed)	18 (14/4)	26 (24/2)
Mean (SD)	5.94 (1.95)	5.64 (2.19)
Median	5.90	6.00
Q1 ; Q3	4.86 ; 7.57	4.00 ; 7.00
Min ; Max	2.3 ; 9.0	0.4 ; 10.0
Change from baseline		
Number (observed/imputed)	18 (14/4)	26 (24/2)
Mean (SD)	-0.93 (1.39)	-1.71 (2.00)
Median	-1.38	-1.42
Q1 ; Q3	-1.98 ; 0.43	-3.14 ; 0.03
Min ; Max	-3.3 ; 2.0	-7.0 ; 1.0
Percent change from baseline		
Number (observed/imputed)	18 (14/4)	26 (24/2)
Mean (SD)	-14.58 (22.12)	-23.07 (26.91)
Median	-17.46	-20.04
Q1 ; Q3	-28.57 ; 5.00	-40.00 ; 0.39
Min ; Max	-50.0 ; 28.6	-93.1 ; 13.6
Week 9		
Number (observed/imputed)	17 (13/4)	24 (22/2)
Mean (SD)	5.73 (2.06)	5.48 (2.22)
Median	6.14	5.80
Q1 ; Q3	4.00 ; 6.80	3.38 ; 7.17
Min ; Max	2.3 ; 9.0	1.2 ; 10.0
Change from baseline		
Number (observed/imputed)	17 (13/4)	24 (22/2)
Mean (SD)	-1.14 (1.51)	-1.94 (1.93)
Median	-1.43	-1.77
Q1 ; Q3	-2.00 ; -0.36	-3.08 ; -0.55
Min ; Max	-3.4 ; 2.0	-7.0 ; 0.8
Percent change from baseline		
Number (observed/imputed)	17 (13/4)	24 (22/2)
Mean (SD)	-17.65 (24.09)	-26.69 (25.86)
Median	-15.87	-24.31
Q1 ; Q3	-40.00 ; -5.49	-40.00 ; -6.73
Min ; Max	-50.0 ; 28.6	-81.3 ; 12.9
Week 10		
Number (observed/imputed)	17 (12/5)	23 (20/3)

	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)
Mean (SD)	5.79 (2.04)	5.10 (2.28)
Median	6.00	5.00
Q1 ; Q3	4.00 ; 7.57	3.00 ; 6.50
Min ; Max	3.0 ; 9.0	0.7 ; 10.0
Change from baseline		
Number (observed/imputed)	17 (12/5)	23 (20/3)
Mean (SD)	-1.08 (1.58)	-2.34 (1.91)
Median	-1.43	-1.86
Q1 ; Q3	-2.00 ; -0.05	-3.33 ; -1.33
Min ; Max	-3.8 ; 2.0	-7.0 ; 0.9
Percent change from baseline		
Number (observed/imputed)	17 (12/5)	23 (20/3)
Mean (SD)	-16.43 (24.00)	-32.40 (24.65)
Median	-16.67	-27.08
Q1 ; Q3	-33.96 ; -0.62	-50.00 ; -17.02
Min ; Max	-56.1 ; 28.6	-88.6 ; 9.8
Week 11		
Number (observed/imputed)	17 (12/5)	24 (21/3)
Mean (SD)	5.68 (1.98)	5.28 (2.29)
Median	6.00	5.25
Q1 ; Q3	4.00 ; 7.57	3.50 ; 6.75
Min ; Max	3.0 ; 9.0	0.5 ; 10.0
Change from baseline		
Number (observed/imputed)	17 (12/5)	24 (21/3)
Mean (SD)	-1.19 (1.56)	-2.14 (1.96)
Median	-1.52	-1.93
Q1 ; Q3	-2.00 ; -0.11	-3.07 ; -0.67
Min ; Max	-3.8 ; 1.3	-7.0 ; 0.9
Percent change from baseline		
Number (observed/imputed)	17 (12/5)	24 (21/3)
Mean (SD)	-17.84 (23.42)	-29.61 (25.85)
Median	-22.92	-28.18
Q1 ; Q3	-33.33 ; -1.48	-46.00 ; -9.07
Min ; Max	-56.1 ; 19.4	-92.0 ; 9.8
Week 12		
Number (observed/imputed)	17 (12/5)	24 (21/3)
Mean (SD)	5.59 (2.03)	5.22 (2.22)
Median	5.50	5.10
Q1 ; Q3	4.00 ; 7.50	3.40 ; 6.17
Min ; Max	2.3 ; 9.0	1.0 ; 10.0
Change from baseline		
Number (observed/imputed)	17 (12/5)	24 (21/3)
Mean (SD)	-1.28 (1.56)	-2.21 (1.85)
Median	-1.86	-1.81
Q1 ; Q3	-2.33 ; 0.29	-3.08 ; -1.13
Min ; Max	-3.8 ; 1.0	-7.1 ; 0.9
Percent change from baseline		
Number (observed/imputed)	17 (12/5)	24 (21/3)
Mean (SD)	-19.49 (24.08)	-30.66 (22.91)
Median	-27.66	-25.91

	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)
Q1 ; Q3	-40.00 ; 3.70	-48.33 ; -16.53
Min ; Max	-56.1 ; 19.4	-84.0 ; 9.8
Week 13		
Number (observed/imputed)	17 (12/5)	24 (21/3)
Mean (SD)	5.65 (2.16)	4.77 (2.63)
Median	5.80	4.75
Q1 ; Q3	4.29 ; 7.57	2.78 ; 6.00
Min ; Max	1.8 ; 9.0	0.4 ; 10.0
Change from baseline		
Number (observed/imputed)	17 (12/5)	24 (21/3)
Mean (SD)	-1.22 (1.77)	-2.66 (2.29)
Median	-1.43	-2.31
Q1 ; Q3	-2.20 ; 0.43	-3.25 ; -1.27
Min ; Max	-4.1 ; 1.5	-8.0 ; 0.9
Percent change from baseline		
Number (observed/imputed)	17 (12/5)	24 (21/3)
Mean (SD)	-18.45 (27.47)	-36.96 (28.09)
Median	-23.08	-34.38
Q1 ; Q3	-40.00 ; 5.00	-53.66 ; -16.92
Min ; Max	-61.4 ; 23.1	-94.2 ; 9.8
Week 14		
Number (observed/imputed)	17 (12/5)	24 (20/4)
Mean (SD)	5.58 (2.26)	4.80 (2.68)
Median	5.29	5.00
Q1 ; Q3	3.43 ; 7.57	2.75 ; 6.20
Min ; Max	2.4 ; 9.0	0.2 ; 10.0
Change from baseline		
Number (observed/imputed)	17 (12/5)	24 (20/4)
Mean (SD)	-1.29 (1.97)	-2.63 (2.42)
Median	-1.43	-2.18
Q1 ; Q3	-2.27 ; 0.43	-3.18 ; -1.13
Min ; Max	-4.6 ; 1.9	-8.0 ; 0.9
Percent change from baseline		
Number (observed/imputed)	17 (12/5)	24 (20/4)
Mean (SD)	-19.19 (29.35)	-36.22 (29.30)
Median	-21.28	-34.96
Q1 ; Q3	-40.00 ; 5.00	-50.81 ; -14.90
Min ; Max	-64.9 ; 29.7	-97.7 ; 9.8
Week 15		
Number (observed/imputed)	17 (12/5)	24 (20/4)
Mean (SD)	5.44 (2.24)	4.76 (2.72)
Median	5.50	5.00
Q1 ; Q3	3.00 ; 7.50	2.79 ; 6.00
Min ; Max	2.0 ; 9.0	0.1 ; 10.0
Change from baseline		
Number (observed/imputed)	17 (12/5)	24 (20/4)
Mean (SD)	-1.43 (1.86)	-2.67 (2.51)
Median	-2.00	-2.50
Q1 ; Q3	-2.50 ; 0.43	-3.31 ; -0.99
Min ; Max	-4.8 ; 1.0	-8.4 ; 0.9

	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)
Percent change from baseline		
Number (observed/imputed)	17 (12/5)	24 (20/4)
Mean (SD)	-21.55 (28.39)	-36.61 (30.40)
Median	-28.57	-34.74
Q1 ; Q3	-40.00 ; 5.00	-50.00 ; -13.39
Min ; Max	-70.7 ; 19.4	-98.1 ; 9.8
Week 16		
Number (observed/imputed)	16 (11/5)	23 (19/4)
Mean (SD)	5.79 (2.12)	4.44 (2.73)
Median	6.43	4.00
Q1 ; Q3	3.84 ; 7.62	2.43 ; 5.83
Min ; Max	2.0 ; 9.0	0.2 ; 10.0
Change from baseline		
Number (observed/imputed)	16 (11/5)	23 (19/4)
Mean (SD)	-1.22 (1.88)	-3.02 (2.49)
Median	-1.30	-3.00
Q1 ; Q3	-2.12 ; 0.64	-3.90 ; -1.66
Min ; Max	-4.8 ; 1.2	-8.8 ; 0.9
Percent change from baseline		
Number (observed/imputed)	16 (11/5)	23 (19/4)
Mean (SD)	-17.42 (27.59)	-41.39 (29.55)
Median	-15.23	-41.30
Q1 ; Q3	-36.09 ; 8.50	-60.00 ; -22.22
Min ; Max	-70.7 ; 19.4	-97.3 ; 9.8

WOCF: worst observation carried forward; PP-NRS: peak pruritus numerical rating scale.

Note: Data collected after study intervention discontinuation were included. Data post the use of any rescue medication or phototherapy were set to missing and imputed by WOCF. Missing data after study intervention discontinuation due to lack of efficacy were imputed by WOCF, and other missing data were imputed by MI.

Table 28. Summary of Weekly Average of Daily PP-NRS by Week up to Week 16 (ITT Population; T1D Cohort)

	Placebo (N=31)	Rilzabrutinib 400mg T1D (N=48)
Baseline		
Number	31	48
Mean (SD)	7.01 (1.33)	7.61 (1.35)
Median	7.17	7.42
Q1 ; Q3	6.00 ; 8.00	6.85 ; 8.25
Min ; Max	3.5 ; 9.0	4.1 ; 10.0
Week 1		
Number (observed/imputed)	31 (31/0)	48 (48/0)
Mean (SD)	7.02 (1.28)	6.70 (2.14)
Median	7.20	6.86
Q1 ; Q3	6.00 ; 8.00	6.00 ; 7.79
Min ; Max	4.0 ; 9.0	0.0 ; 10.0
Change from baseline		
Number (observed/imputed)	31 (31/0)	48 (48/0)
Mean (SD)	0.01 (0.87)	-0.91 (1.55)
Median	0.14	-0.30
Q1 ; Q3	-0.71 ; 0.57	-1.54 ; 0.12
Min ; Max	-1.8 ; 1.9	-6.6 ; 1.0

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Percent change from baseline		
Number (observed/imputed)	31 (31/0)	48 (48/0)
Mean (SD)	1.19 (13.23)	-12.64 (21.89)
Median	2.08	-4.22
Q1 ; Q3	-11.36 ; 8.57	-20.71 ; 1.37
Min ; Max	-23.4 ; 33.3	-100.0 ; 12.3
Week 2		
Number (observed/imputed)	30 (30/0)	46 (45/1)
Mean (SD)	7.13 (1.51)	6.62 (2.31)
Median	7.37	6.57
Q1 ; Q3	5.86 ; 8.29	5.86 ; 8.00
Min ; Max	3.9 ; 10.0	0.6 ; 10.0
Change from baseline		
Number (observed/imputed)	30 (30/0)	46 (45/1)
Mean (SD)	0.00 (1.33)	-1.02 (1.66)
Median	0.14	-0.59
Q1 ; Q3	-1.33 ; 1.00	-1.83 ; 0.00
Min ; Max	-2.3 ; 2.6	-6.5 ; 2.2
Percent change from baseline		
Number (observed/imputed)	30 (30/0)	46 (45/1)
Mean (SD)	0.95 (20.00)	-14.45 (24.15)
Median	1.85	-7.46
Q1 ; Q3	-17.39 ; 17.14	-23.53 ; 0.00
Min ; Max	-28.9 ; 47.2	-91.3 ; 31.7
Week 3		
Number (observed/imputed)	30 (28/2)	44 (43/1)
Mean (SD)	6.95 (1.54)	6.36 (2.41)
Median	7.00	6.42
Q1 ; Q3	5.67 ; 8.00	5.00 ; 7.88
Min ; Max	3.9 ; 10.0	0.0 ; 10.0
Change from baseline		
Number (observed/imputed)	30 (28/2)	44 (43/1)
Mean (SD)	-0.17 (1.34)	-1.32 (1.81)
Median	-0.07	-0.88
Q1 ; Q3	-1.00 ; 0.79	-2.50 ; 0.07
Min ; Max	-2.9 ; 2.4	-6.6 ; 1.8
Percent change from baseline		
Number (observed/imputed)	30 (28/2)	44 (43/1)
Mean (SD)	-1.52 (20.04)	-18.17 (25.77)
Median	-0.82	-9.81
Q1 ; Q3	-11.48 ; 12.18	-32.01 ; 0.85
Min ; Max	-40.2 ; 43.6	-100.0 ; 22.4
Week 4		
Number (observed/imputed)	30 (25/5)	43 (40/3)
Mean (SD)	6.85 (1.64)	6.36 (2.57)
Median	7.00	6.57
Q1 ; Q3	5.29 ; 8.20	4.29 ; 8.25
Min ; Max	4.3 ; 10.0	1.0 ; 10.0
Change from baseline		
Number (observed/imputed)	30 (25/5)	43 (40/3)

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Mean (SD)	-0.27 (1.45)	-1.34 (1.83)
Median	0.00	-0.86
Q1 ; Q3	-1.29 ; 0.64	-3.00 ; 0.14
Min ; Max	-3.0 ; 2.6	-5.7 ; 1.8
Percent change from baseline		
Number (observed/imputed)	30 (25/5)	43 (40/3)
Mean (SD)	-2.99 (21.05)	-18.99 (26.62)
Median	0.00	-10.20
Q1 ; Q3	-20.45 ; 9.09	-39.50 ; 1.64
Min ; Max	-38.3 ; 47.2	-78.1 ; 22.4
Week 5		
Number (observed/imputed)	28 (20/8)	41 (37/4)
Mean (SD)	6.61 (1.78)	5.90 (2.68)
Median	7.00	6.33
Q1 ; Q3	5.07 ; 8.07	3.71 ; 7.29
Min ; Max	3.7 ; 10.0	0.0 ; 10.0
Change from baseline		
Number (observed/imputed)	28 (20/8)	41 (37/4)
Mean (SD)	-0.47 (1.56)	-1.72 (2.08)
Median	-0.14	-1.14
Q1 ; Q3	-1.86 ; 0.46	-3.29 ; 0.00
Min ; Max	-3.3 ; 2.6	-7.0 ; 1.8
Percent change from baseline		
Number (observed/imputed)	28 (20/8)	41 (37/4)
Mean (SD)	-5.91 (23.23)	-24.01 (29.53)
Median	-1.96	-16.13
Q1 ; Q3	-20.95 ; 6.74	-43.33 ; 0.00
Min ; Max	-47.6 ; 47.2	-100.0 ; 22.4
Week 6		
Number (observed/imputed)	30 (22/8)	40 (35/5)
Mean (SD)	6.73 (1.67)	6.02 (2.72)
Median	6.67	5.93
Q1 ; Q3	5.71 ; 8.14	3.82 ; 8.00
Min ; Max	3.4 ; 10.0	0.0 ; 10.0
Change from baseline		
Number (observed/imputed)	30 (22/8)	40 (35/5)
Mean (SD)	-0.39 (1.54)	-1.59 (1.99)
Median	0.00	-1.12
Q1 ; Q3	-1.67 ; 0.64	-3.62 ; 0.11
Min ; Max	-3.3 ; 2.6	-5.7 ; 1.8
Percent change from baseline		
Number (observed/imputed)	30 (22/8)	40 (35/5)
Mean (SD)	-4.54 (22.39)	-22.68 (29.46)
Median	0.00	-14.08
Q1 ; Q3	-20.00 ; 8.57	-49.44 ; 1.16
Min ; Max	-45.5 ; 47.2	-100.0 ; 22.4
Week 7		
Number (observed/imputed)	30 (22/8)	39 (34/5)
Mean (SD)	6.67 (1.65)	5.85 (2.79)
Median	6.52	6.00

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Q1 ; Q3	5.29 ; 8.00	3.50 ; 8.00
Min ; Max	3.9 ; 10.0	0.3 ; 10.0
Change from baseline		
Number (observed/imputed)	30 (22/8)	39 (34/5)
Mean (SD)	-0.45 (1.47)	-1.71 (2.22)
Median	-0.31	-0.83
Q1 ; Q3	-1.50 ; 0.43	-3.71 ; 0.14
Min ; Max	-3.3 ; 2.6	-5.8 ; 1.8
Percent change from baseline		
Number (observed/imputed)	30 (22/8)	39 (34/5)
Mean (SD)	-5.53 (21.47)	-24.14 (31.39)
Median	-4.10	-11.11
Q1 ; Q3	-19.15 ; 6.49	-51.22 ; 1.45
Min ; Max	-41.5 ; 47.2	-95.0 ; 22.4
Week 8		
Number (observed/imputed)	29 (21/8)	37 (31/6)
Mean (SD)	6.56 (1.84)	5.83 (2.93)
Median	6.00	6.00
Q1 ; Q3	5.00 ; 8.14	3.60 ; 8.33
Min ; Max	3.7 ; 10.0	0.0 ; 10.0
Change from baseline		
Number (observed/imputed)	29 (21/8)	37 (31/6)
Mean (SD)	-0.55 (1.61)	-1.78 (2.36)
Median	0.00	-1.00
Q1 ; Q3	-1.67 ; 0.50	-4.09 ; 0.14
Min ; Max	-3.3 ; 2.6	-6.2 ; 1.8
Percent change from baseline		
Number (observed/imputed)	29 (21/8)	37 (31/6)
Mean (SD)	-7.18 (23.69)	-25.08 (33.57)
Median	0.00	-12.28
Q1 ; Q3	-30.95 ; 8.16	-55.00 ; 1.45
Min ; Max	-44.4 ; 47.2	-100.0 ; 22.4
Week 9		
Number (observed/imputed)	30 (21/9)	37 (31/6)
Mean (SD)	6.58 (1.77)	5.58 (3.12)
Median	6.68	5.60
Q1 ; Q3	5.71 ; 8.00	3.00 ; 7.86
Min ; Max	2.3 ; 10.0	0.0 ; 10.0
Change from baseline		
Number (observed/imputed)	30 (21/9)	37 (31/6)
Mean (SD)	-0.55 (1.65)	-1.93 (2.56)
Median	-0.29	-1.03
Q1 ; Q3	-1.43 ; 0.43	-3.95 ; 0.14
Min ; Max	-4.5 ; 2.6	-8.0 ; 1.8
Percent change from baseline		
Number (observed/imputed)	30 (21/9)	37 (31/6)
Mean (SD)	-6.76 (24.04)	-27.62 (35.98)
Median	-3.88	-16.00
Q1 ; Q3	-21.31 ; 7.14	-61.70 ; 1.45
Min ; Max	-65.9 ; 47.2	-100.0 ; 22.4

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Week 10		
Number (observed/imputed)	29 (20/9)	37 (31/6)
Mean (SD)	6.60 (1.88)	5.45 (2.99)
Median	6.50	5.50
Q1 ; Q3	5.71 ; 8.14	2.83 ; 7.57
Min ; Max	2.0 ; 10.0	0.0 ; 10.0
Change from baseline		
Number (observed/imputed)	29 (20/9)	37 (31/6)
Mean (SD)	-0.48 (1.68)	-2.01 (2.56)
Median	-0.14	-1.29
Q1 ; Q3	-1.17 ; 0.43	-3.90 ; 0.14
Min ; Max	-4.8 ; 2.6	-7.2 ; 1.8
Percent change from baseline		
Number (observed/imputed)	29 (20/9)	37 (31/6)
Mean (SD)	-6.13 (24.84)	-28.36 (35.37)
Median	-2.00	-16.98
Q1 ; Q3	-16.28 ; 7.14	-60.16 ; 1.69
Min ; Max	-70.7 ; 47.2	-100.0 ; 22.4
Week 11		
Number (observed/imputed)	29 (20/9)	36 (30/6)
Mean (SD)	6.47 (1.79)	5.61 (3.03)
Median	6.00	5.92
Q1 ; Q3	5.33 ; 8.00	2.50 ; 7.80
Min ; Max	1.8 ; 10.0	0.5 ; 10.0
Change from baseline		
Number (observed/imputed)	29 (20/9)	36 (30/6)
Mean (SD)	-0.65 (1.77)	-1.80 (2.47)
Median	-0.67	-1.21
Q1 ; Q3	-1.83 ; 0.43	-3.97 ; 0.15
Min ; Max	-5.0 ; 2.6	-7.0 ; 2.7
Percent change from baseline		
Number (observed/imputed)	29 (20/9)	36 (30/6)
Mean (SD)	-7.86 (25.29)	-26.12 (35.71)
Median	-9.30	-15.88
Q1 ; Q3	-23.40 ; 7.14	-65.48 ; 1.85
Min ; Max	-73.7 ; 47.2	-91.3 ; 42.1
Week 12		
Number (observed/imputed)	27 (18/9)	35 (26/9)
Mean (SD)	6.48 (2.03)	5.84 (3.17)
Median	6.75	6.00
Q1 ; Q3	5.00 ; 8.14	2.80 ; 9.00
Min ; Max	1.0 ; 10.0	0.8 ; 10.0
Change from baseline		
Number (observed/imputed)	27 (18/9)	35 (26/9)
Mean (SD)	-0.62 (1.94)	-1.79 (2.59)
Median	0.00	-1.00
Q1 ; Q3	-2.05 ; 0.43	-4.14 ; 0.14
Min ; Max	-5.8 ; 2.6	-7.2 ; 2.7
Percent change from baseline		

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Number (observed/imputed)	27 (18/9)	35 (26/9)
Mean (SD)	-7.73 (28.19)	-25.35 (36.76)
Median	0.00	-13.21
Q1 ; Q3	-25.00 ; 7.14	-60.94 ; 1.45
Min ; Max	-85.4 ; 47.2	-90.0 ; 42.1
Week 13		
Number (observed/imputed)	28 (19/9)	36 (25/11)
Mean (SD)	6.45 (2.08)	5.71 (3.30)
Median	6.25	5.89
Q1 ; Q3	5.64 ; 8.07	2.38 ; 8.50
Min ; Max	1.0 ; 10.0	0.2 ; 10.0
Change from baseline		
Number (observed/imputed)	28 (19/9)	36 (25/11)
Mean (SD)	-0.65 (1.93)	-1.86 (2.85)
Median	0.00	-1.07
Q1 ; Q3	-1.93 ; 0.46	-4.56 ; 0.15
Min ; Max	-5.8 ; 2.6	-7.2 ; 2.7
Percent change from baseline		
Number (observed/imputed)	28 (19/9)	36 (25/11)
Mean (SD)	-8.37 (28.74)	-26.11 (40.18)
Median	0.00	-14.15
Q1 ; Q3	-26.29 ; 7.14	-66.82 ; 1.85
Min ; Max	-85.4 ; 47.2	-97.1 ; 42.1
Week 14		
Number (observed/imputed)	27 (18/9)	37 (26/11)
Mean (SD)	6.46 (2.38)	5.64 (3.25)
Median	7.00	5.83
Q1 ; Q3	5.20 ; 8.14	3.33 ; 8.00
Min ; Max	0.0 ; 10.0	0.0 ; 10.0
Change from baseline		
Number (observed/imputed)	27 (18/9)	37 (26/11)
Mean (SD)	-0.60 (2.20)	-1.97 (2.74)
Median	0.14	-1.57
Q1 ; Q3	-2.14 ; 0.71	-3.95 ; 0.14
Min ; Max	-6.0 ; 2.6	-8.2 ; 2.7
Percent change from baseline		
Number (observed/imputed)	27 (18/9)	37 (26/11)
Mean (SD)	-7.98 (33.23)	-27.69 (38.49)
Median	1.61	-22.22
Q1 ; Q3	-28.85 ; 9.80	-54.25 ; 1.45
Min ; Max	-100.0 ; 47.2	-100.0 ; 42.1
Week 15		
Number (observed/imputed)	27 (18/9)	37 (25/12)
Mean (SD)	6.31 (2.37)	5.64 (3.33)
Median	6.71	5.57
Q1 ; Q3	5.00 ; 8.14	2.40 ; 8.60
Min ; Max	0.0 ; 10.0	0.2 ; 10.0
Change from baseline		
Number (observed/imputed)	27 (18/9)	37 (25/12)
Mean (SD)	-0.79 (2.25)	-1.89 (2.77)

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Median	0.00	-0.87
Q1 ; Q3	-2.29 ; 0.64	-4.12 ; 0.14
Min ; Max	-6.0 ; 2.6	-7.8 ; 2.7
Percent change from baseline		
Number (observed/imputed)	27 (18/9)	37 (25/12)
Mean (SD)	-10.27 (33.64)	-27.13 (39.34)
Median	0.00	-13.98
Q1 ; Q3	-33.62 ; 8.93	-64.84 ; 1.69
Min ; Max	-100.0 ; 47.2	-96.5 ; 42.1
Week 16		
Number (observed/imputed)	26 (17/9)	36 (23/13)
Mean (SD)	6.22 (2.49)	5.88 (3.30)
Median	6.58	6.17
Q1 ; Q3	4.83 ; 8.20	3.20 ; 9.00
Min ; Max	0.0 ; 10.0	0.0 ; 10.0
Change from baseline		
Number (observed/imputed)	26 (17/9)	36 (23/13)
Mean (SD)	-0.88 (2.40)	-1.72 (2.66)
Median	0.07	-1.00
Q1 ; Q3	-2.45 ; 0.64	-4.05 ; 0.14
Min ; Max	-6.0 ; 2.6	-8.3 ; 2.7
Percent change from baseline		
Number (observed/imputed)	26 (17/9)	36 (23/13)
Mean (SD)	-11.44 (35.52)	-24.96 (38.25)
Median	0.81	-12.41
Q1 ; Q3	-39.02 ; 9.09	-57.15 ; 1.57
Min ; Max	-100.0 ; 47.2	-100.0 ; 42.1

Note: Data collected after study intervention discontinuation were included. Data post the use of any rescue medication or phototherapy were set to missing and imputed by WOCF. Missing data after study intervention discontinuation due to lack of efficacy were imputed by WOCF, and other missing data were imputed by MI.

Table 29. Time to First PP-NRS Reduction ≥ 4 points from Baseline during the 16-Week Intervention Period (ITT Population)

	BID cohort		TID cohort	
	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Number of participants with weekly average of daily PP-NRS reduction ≥ 4 from baseline	2 (11.1)	7 (25.9)	4 (12.9)	13 (27.1)
Kaplan-Meier estimate for probability of a participant with event (95% CI) up to				
Week 1	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	0.042 (0.008, 0.126)
Week 2	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	0.084 (0.027, 0.184)
Week 3	0.000 (0.000, 0.000)	0.077 (0.013, 0.217)	0.000 (0.000, 0.000)	0.106 (0.039, 0.212)
Week 4	0.000 (0.000, 0.000)	0.077 (0.013, 0.217)	0.000 (0.000, 0.000)	0.106 (0.039, 0.212)
Week 5	0.000 (0.000, 0.000)	0.077 (0.013, 0.217)	0.000 (0.000, 0.000)	0.200 (0.099, 0.327)

	BID cohort		TID cohort	
	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Week 6	0.000 (0.000, 0.000)	0.154 (0.048, 0.315)	0.000 (0.000, 0.000)	0.224 (0.116, 0.355)
Week 7	0.000 (0.000, 0.000)	0.154 (0.048, 0.315)	0.000 (0.000, 0.000)	0.224 (0.116, 0.355)
Week 8	0.000 (0.000, 0.000)	0.154 (0.048, 0.315)	0.000 (0.000, 0.000)	0.299 (0.171, 0.439)
Week 9	0.000 (0.000, 0.000)	0.196 (0.071, 0.366)	0.033 (0.002, 0.145)	0.299 (0.171, 0.439)
Week 10	0.000 (0.000, 0.000)	0.196 (0.071, 0.366)	0.067 (0.012, 0.192)	0.299 (0.171, 0.439)
Week 11	0.000 (0.000, 0.000)	0.196 (0.071, 0.366)	0.067 (0.012, 0.192)	0.299 (0.171, 0.439)
Week 12	0.000 (0.000, 0.000)	0.196 (0.071, 0.366)	0.067 (0.012, 0.192)	0.299 (0.171, 0.439)
Week 13	0.059 (0.004, 0.235)	0.238 (0.097, 0.415)	0.067 (0.012, 0.192)	0.299 (0.171, 0.439)
Week 14	0.118 (0.020, 0.312)	0.238 (0.097, 0.415)	0.101 (0.026, 0.239)	0.299 (0.171, 0.439)
Week 15	0.118 (0.020, 0.312)	0.238 (0.097, 0.415)	0.101 (0.026, 0.239)	0.299 (0.171, 0.439)
Week 16	0.118 (0.020, 0.312)	0.283 (0.125, 0.466)	0.137 (0.043, 0.285)	0.299 (0.171, 0.439)
HR, 95% CI vs. placebo ^a		2.837 (0.589, 13.676)		2.762 (0.898, 8.501)
P-value vs. placebo ^a		0.1937		0.0765

^a HR: hazard ratio; derived from Cox proportional hazards model, including intervention, randomization stratification of IgE levels (< or ≥300 UI/mL) as covariates.

Note: for participants who received any rescue medication or phototherapy, data before the medications/procedures were used but after the medications/procedures start, the data were not used and were censored at Week 16 (Day 113). Participants without events were censored at Day 113 or their last PP-NRS assessment date if discontinued from the study, whichever was earlier.

Table 30. Subgroup Analysis: Proportion of Participants with Reduction of Weekly Average of Daily PP-NRS ≥ 4 Points from Baseline at Week 16 by Subgroup (ITT Population; BID Cohort)

	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)
Age Group 1 (years)		
≥18 - <40	12	15
Responder	1 (8.3)	2 (13.3)
Non-responder	11 (91.7)	13 (86.7)
Imputed non-responder	5 (41.7)	6 (40.0)
OR, 95% CI vs. placebo ^a		1.7 (0.13, 21.27)
P-value vs. placebo ^b		0.6869
RRD (%), 95% CI vs. placebo ^a		5.0 (-18.25, 28.25)
OR, 90% CI vs. placebo ^a		1.7 (0.20, 14.16)
RRD (%), 90% CI vs. placebo ^a		5.0 (-14.51, 24.51)
≥40 - <65	6	10
Responder	1 (16.7)	2 (20.0)
Non-responder	5 (83.3)	8 (80.0)
Imputed non-responder	2 (33.3)	2 (20.0)
OR, 95% CI vs. placebo ^a		1.3 (0.09, 17.65)
P-value vs. placebo ^b		0.8728

	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)
RRD (%), 95% CI vs. placebo ^a		3.3 (-35.45, 42.11)
OR, 90% CI vs. placebo ^a		1.3 (0.14, 11.53)
RRD (%), 90% CI vs. placebo ^a		3.3 (-29.21, 35.88)
≥65	0	2
Responder	0	1 (50.0)
Non-responder	0	1 (50.0)
Imputed non-responder	0	0
OR, 95% CI vs. placebo ^a		NE (NE, NE)
P-value vs. placebo ^b		NE
RRD (%), 95% CI vs. placebo ^a		NE (NE, NE)
OR, 90% CI vs. placebo ^a		NE (NE, NE)
RRD (%), 90% CI vs. placebo ^a		NE (NE, NE)
Overall p-value for interaction ^c		0.8713
Age Group 2 (years)		
<40	12	15
Responder	1 (8.3)	2 (13.3)
Non-responder	11 (91.7)	13 (86.7)
Imputed non-responder	5 (41.7)	6 (40.0)
OR, 95% CI vs. placebo ^a		1.7 (0.13, 21.27)
P-value vs. placebo ^b		0.6869
RRD (%), 95% CI vs. placebo ^a		5.0 (-18.25, 28.25)
OR, 90% CI vs. placebo ^a		1.7 (0.20, 14.16)
RRD (%), 90% CI vs. placebo ^a		5.0 (-14.51, 24.51)
≥40	6	12
Responder	1 (16.7)	3 (25.0)
Non-responder	5 (83.3)	9 (75.0)
Imputed non-responder	2 (33.3)	2 (16.7)
OR, 95% CI vs. placebo ^a		1.7 (0.13, 20.58)
P-value vs. placebo ^b		0.6968
RRD (%), 95% CI vs. placebo ^a		8.3 (-30.26, 46.93)
OR, 90% CI vs. placebo ^a		1.7 (0.20, 13.74)
RRD (%), 90% CI vs. placebo ^a		8.3 (-24.06, 40.72)
Overall p-value for interaction ^c		0.9761
Gender		
Male	8	12
Responder	0	2 (16.7)
Non-responder	8 (100)	10 (83.3)
Imputed non-responder	3 (37.5)	4 (33.3)
OR, 95% CI vs. placebo ^a		NE (NE, NE)
P-value vs. placebo ^b		0.2355
RRD (%), 95% CI vs. placebo ^a		16.7 (-4.42, 37.75)
OR, 90% CI vs. placebo ^a		NE (NE, NE)
RRD (%), 90% CI vs. placebo ^a		16.7 (-1.03, 34.36)
Female	10	15
Responder	2 (20.0)	3 (20.0)
Non-responder	8 (80.0)	12 (80.0)
Imputed non-responder	4 (40.0)	4 (26.7)
OR, 95% CI vs. placebo ^a		1.0 (0.14, 7.39)
P-value vs. placebo ^b		1.0000
RRD (%), 95% CI vs. placebo ^a		0.0 (-32.01, 32.01)
OR, 90% CI vs. placebo ^a		1.0 (0.19, 5.36)

	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)
RRD (%), 90% CI vs. placebo ^a		0.0 (-26.86, 26.86)
Overall p-value for interaction ^c		0.4624
Ethnicity		
Hispanic or Latino	4	5
Responder	1 (25.0)	2 (40.0)
Non-responder	3 (75.0)	3 (60.0)
Imputed non-responder	2 (50.0)	0
OR, 95% CI vs. placebo ^a		2.0 (0.11, 35.81)
P-value vs. placebo ^b		0.6547
RRD (%), 95% CI vs. placebo ^a		15.0 (-45.37, 75.37)
OR, 90% CI vs. placebo ^a		2.0 (0.18, 22.52)
RRD (%), 90% CI vs. placebo ^a		15.0 (-35.66, 65.66)
Not Hispanic or Latino or other	14	22
Responder	1 (7.1)	3 (13.6)
Non-responder	13 (92.9)	19 (86.4)
Imputed non-responder	5 (35.7)	8 (36.4)
OR, 95% CI vs. placebo ^a		2.1 (0.19, 21.97)
P-value vs. placebo ^b		0.5512
RRD (%), 95% CI vs. placebo ^a		6.5 (-13.19, 26.18)
OR, 90% CI vs. placebo ^a		2.1 (0.28, 15.01)
RRD (%), 90% CI vs. placebo ^a		6.5 (-10.03, 23.02)
Overall p-value for interaction ^c		0.9860
Duration of AD (years)		
<26	10	16
Responder	2 (20.0)	2 (12.5)
Non-responder	8 (80.0)	14 (87.5)
Imputed non-responder	3 (30.0)	4 (25.0)
OR, 95% CI vs. placebo ^a		0.6 (0.07, 4.88)
P-value vs. placebo ^b		0.6131
RRD (%), 95% CI vs. placebo ^a		-7.5 (-37.12, 22.12)
OR, 90% CI vs. placebo ^a		0.6 (0.09, 3.45)
RRD (%), 90% CI vs. placebo ^a		-7.5 (-32.36, 17.36)
≥26	8	11
Responder	0	3 (27.3)
Non-responder	8 (100)	8 (72.7)
Imputed non-responder	4 (50.0)	4 (36.4)
OR, 95% CI vs. placebo ^a		NE (NE, NE)
P-value vs. placebo ^b		0.1172
RRD (%), 95% CI vs. placebo ^a		27.3 (0.95, 53.59)
OR, 90% CI vs. placebo ^a		NE (NE, NE)
RRD (%), 90% CI vs. placebo ^a		27.3 (5.19, 49.36)
Overall p-value for interaction ^c		0.2086
Baseline weight (kg)		
<60	4	5
Responder	0	1 (20.0)
Non-responder	4 (100)	4 (80.0)
Imputed non-responder	2 (50.0)	0
OR, 95% CI vs. placebo ^a		NE (NE, NE)
P-value vs. placebo ^b		0.3711
RRD (%), 95% CI vs. placebo ^a		20.0 (-15.06, 55.06)

	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)
OR, 90% CI vs. placebo ^a		NE (NE, NE)
RRD (%), 90% CI vs. placebo ^a		20.0 (-9.42, 49.42)
≥60 - <90	11	17
Responder	1 (9.1)	3 (17.6)
Non-responder	10 (90.9)	14 (82.4)
Imputed non-responder	5 (45.5)	6 (35.3)
OR, 95% CI vs. placebo ^a		2.1 (0.19, 23.72)
P-value vs. placebo ^b		0.5349
RRD (%), 95% CI vs. placebo ^a		8.6 (-16.28, 33.40)
OR, 90% CI vs. placebo ^a		2.1 (0.28, 16.12)
RRD (%), 90% CI vs. placebo ^a		8.6 (-12.29, 29.40)
≥90	3	5
Responder	1 (33.3)	1 (20.0)
Non-responder	2 (66.7)	4 (80.0)
Imputed non-responder	0	2 (40.0)
OR, 95% CI vs. placebo ^a		0.5 (0.02, 12.90)
P-value vs. placebo ^b		0.6933
RRD (%), 95% CI vs. placebo ^a		-13.3 (-77.17, 50.50)
OR, 90% CI vs. placebo ^a		0.5 (0.03, 7.65)
RRD (%), 90% CI vs. placebo ^a		-13.3 (-66.90, 40.24)
Overall p-value for interaction ^c		0.7698
Baseline weight (kg)		
<90	15	22
Responder	1 (6.7)	4 (18.2)
Non-responder	14 (93.3)	18 (81.8)
Imputed non-responder	7 (46.7)	6 (27.3)
OR, 95% CI vs. placebo ^a		3.1 (0.31, 31.03)
P-value vs. placebo ^b		0.3211
RRD (%), 95% CI vs. placebo ^a		11.5 (-8.96, 31.99)
OR, 90% CI vs. placebo ^a		3.1 (0.45, 21.44)
RRD (%), 90% CI vs. placebo ^a		11.5 (-5.67, 28.70)
≥90	3	5
Responder	1 (33.3)	1 (20.0)
Non-responder	2 (66.7)	4 (80.0)
Imputed non-responder	0	2 (40.0)
OR, 95% CI vs. placebo ^a		0.5 (0.02, 12.90)
P-value vs. placebo ^b		0.6933
RRD (%), 95% CI vs. placebo ^a		-13.3 (-77.17, 50.50)
OR, 90% CI vs. placebo ^a		0.5 (0.03, 7.65)
RRD (%), 90% CI vs. placebo ^a		-13.3 (-66.90, 40.24)
Overall p-value for interaction ^c		0.4447
Baseline BMI (kg/m ²)		
<25	8	13
Responder	0	3 (23.1)
Non-responder	8 (100)	10 (76.9)
Imputed non-responder	4 (50.0)	3 (23.1)
OR, 95% CI vs. placebo ^a		NE (NE, NE)
P-value vs. placebo ^b		0.1521
RRD (%), 95% CI vs. placebo ^a		23.1 (0.17, 45.98)
OR, 90% CI vs. placebo ^a		NE (NE, NE)
RRD (%), 90% CI vs. placebo ^a		23.1 (3.86, 42.30)

	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)
≥25 - <30	7	11
Responder	1 (14.3)	2 (18.2)
Non-responder	6 (85.7)	9 (81.8)
Imputed non-responder	3 (42.9)	3 (27.3)
OR, 95% CI vs. placebo ^a		1.3 (0.10, 18.19)
P-value vs. placebo ^b		0.8336
RRD (%), 95% CI vs. placebo ^a		3.9 (-30.62, 38.41)
OR, 90% CI vs. placebo ^a		1.3 (0.15, 11.95)
RRD (%), 90% CI vs. placebo ^a		3.9 (-25.07, 32.86)
≥30	3	3
Responder	1 (33.3)	0
Non-responder	2 (66.7)	3 (100)
Imputed non-responder	0	2 (66.7)
OR, 95% CI vs. placebo ^a		0.0 (NE, NE)
P-value vs. placebo ^b		0.3173
RRD (%), 95% CI vs. placebo ^a		-33.3 (-86.68, 20.01)
OR, 90% CI vs. placebo ^a		0.0 (NE, NE)
RRD (%), 90% CI vs. placebo ^a		-33.3 (-78.10, 11.43)
Overall p-value for interaction ^c		0.4894
Baseline IGA		
3 (moderate)	10	13
Responder	1 (10.0)	2 (15.4)
Non-responder	9 (90.0)	11 (84.6)
Imputed non-responder	4 (40.0)	3 (23.1)
OR, 95% CI vs. placebo ^a		1.6 (0.13, 21.10)
P-value vs. placebo ^b		0.7101
RRD (%), 95% CI vs. placebo ^a		5.4 (-21.64, 32.41)
OR, 90% CI vs. placebo ^a		1.6 (0.19, 13.99)
RRD (%), 90% CI vs. placebo ^a		5.4 (-17.30, 28.07)
4 (severe)	8	14
Responder	1 (12.5)	3 (21.4)
Non-responder	7 (87.5)	11 (78.6)
Imputed non-responder	3 (37.5)	5 (35.7)
OR, 95% CI vs. placebo ^a		1.9 (0.16, 22.20)
P-value vs. placebo ^b		0.6098
RRD (%), 95% CI vs. placebo ^a		8.9 (-22.49, 40.35)
OR, 90% CI vs. placebo ^a		1.9 (0.24, 14.97)
RRD (%), 90% CI vs. placebo ^a		8.9 (-17.44, 35.30)
Overall p-value for interaction ^c		0.9510
Baseline BSA category		
<median (30.75)	6	12
Responder	1 (16.7)	3 (25.0)
Non-responder	5 (83.3)	9 (75.0)
Imputed non-responder	2 (33.3)	3 (25.0)
OR, 95% CI vs. placebo ^a		1.7 (0.13, 20.58)
P-value vs. placebo ^b		0.6968
RRD (%), 95% CI vs. placebo ^a		8.3 (-30.26, 46.93)
OR, 90% CI vs. placebo ^a		1.7 (0.20, 13.74)
RRD (%), 90% CI vs. placebo ^a		8.3 (-24.06, 40.72)
≥median (30.75)	8	10

	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)
Responder	1 (12.5)	2 (20.0)
Non-responder	7 (87.5)	8 (80.0)
Imputed non-responder	4 (50.0)	3 (30.0)
OR, 95% CI vs. placebo ^a		1.8 (0.13, 23.70)
P-value vs. placebo ^b		0.6801
RRD (%), 95% CI vs. placebo ^a		7.5 (-26.26, 41.26)
OR, 90% CI vs. placebo ^a		1.8 (0.20, 15.59)
RRD (%), 90% CI vs. placebo ^a		7.5 (-20.83, 35.83)
Overall p-value for interaction ^c		0.9601
Baseline EASI category		
<median (22.20)	10	12
Responder	2 (20.0)	3 (25.0)
Non-responder	8 (80.0)	9 (75.0)
Imputed non-responder	5 (50.0)	3 (25.0)
OR, 95% CI vs. placebo ^a		1.3 (0.18, 10.12)
P-value vs. placebo ^b		0.7854
RRD (%), 95% CI vs. placebo ^a		5.0 (-29.85, 39.85)
OR, 90% CI vs. placebo ^a		1.3 (0.24, 7.31)
RRD (%), 90% CI vs. placebo ^a		5.0 (-24.25, 34.25)
≥median (22.20)	8	15
Responder	0	2 (13.3)
Non-responder	8 (100)	13 (86.7)
Imputed non-responder	2 (25.0)	5 (33.3)
OR, 95% CI vs. placebo ^a		NE (NE, NE)
P-value vs. placebo ^b		0.2905
RRD (%), 95% CI vs. placebo ^a		13.3 (-3.87, 30.54)
OR, 90% CI vs. placebo ^a		NE (NE, NE)
RRD (%), 90% CI vs. placebo ^a		13.3 (-1.10, 27.77)
Overall p-value for interaction ^c		0.6400
Screening IgE levels (UI/mL)		
<300	7	9
Responder	2 (28.6)	2 (22.2)
Non-responder	5 (71.4)	7 (77.8)
Imputed non-responder	2 (28.6)	1 (11.1)
OR, 95% CI vs. placebo ^a		0.7 (0.07, 6.92)
P-value vs. placebo ^b		0.7782
RRD (%), 95% CI vs. placebo ^a		-6.3 (-49.45, 36.75)
OR, 90% CI vs. placebo ^a		0.7 (0.11, 4.80)
RRD (%), 90% CI vs. placebo ^a		-6.3 (-42.52, 29.82)
≥300	11	18
Responder	0	3 (16.7)
Non-responder	11 (100)	15 (83.3)
Imputed non-responder	5 (45.5)	7 (38.9)
OR, 95% CI vs. placebo ^a		NE (NE, NE)
P-value vs. placebo ^b		0.1600
RRD (%), 95% CI vs. placebo ^a		16.7 (-0.55, 33.88)
OR, 90% CI vs. placebo ^a		NE (NE, NE)
RRD (%), 90% CI vs. placebo ^a		16.7 (2.22, 31.12)
Overall p-value for interaction ^c		0.3218
Region ^d		

	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)
North America	7	11
Responder	1 (14.3)	3 (27.3)
Non-responder	6 (85.7)	8 (72.7)
Imputed non-responder	4 (57.1)	3 (27.3)
OR, 95% CI vs. placebo ^a		2.3 (0.18, 27.37)
P-value vs. placebo ^b		0.5301
RRD (%), 95% CI vs. placebo ^a		13.0 (-23.95, 49.93)
OR, 90% CI vs. placebo ^a		2.3 (0.28, 18.31)
RRD (%), 90% CI vs. placebo ^a		13.0 (-18.01, 43.99)
Other (Europe)	11	16
Responder	1 (9.1)	2 (12.5)
Non-responder	10 (90.9)	14 (87.5)
Imputed non-responder	3 (27.3)	5 (31.3)
OR, 95% CI vs. placebo ^a		1.4 (0.11, 18.00)
P-value vs. placebo ^b		0.7858
RRD (%), 95% CI vs. placebo ^a		3.4 (-20.07, 26.89)
OR, 90% CI vs. placebo ^a		1.4 (0.17, 11.98)
RRD (%), 90% CI vs. placebo ^a		3.4 (-16.29, 23.11)
Overall p-value for interaction ^c		0.8122

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

^c Logistic regression model was for the interaction test including intervention group, plus the subgroup variable and the subgroup-by-intervention in the model.

^d North America: USA, Canada; South America: Chile; Other (Europe): Czech Republic, Germany, Netherlands, Poland.

Note: Participants who received any rescue medication or phototherapy before Week 16 were considered as non-responders, and missing data at Week 16 were considered as non-responders.

Table 31. Subgroup Analysis: Proportion of Participants with Reduction of Weekly Average of Daily PP-NRS $\geq$ 4 Points from Baseline at Week 16 by Subgroup (ITT Population; T1D Cohort)

	Placebo (N=31)	Rilzabrutinib 400mg T1D (N=48)
Age Group 1 (years)		
≥ 18 - <40	23	31
Responder	2 (8.7)	7 (22.6)
Non-responder	21 (91.3)	24 (77.4)
Imputed non-responder	11 (47.8)	19 (61.3)
OR, 95% CI vs. placebo ^a		3.1 (0.57, 16.38)
P-value vs. placebo ^b		0.1798
RRD (%), 95% CI vs. placebo ^a		13.9 (-4.80, 32.57)
OR, 90% CI vs. placebo ^a		3.1 (0.75, 12.51)
RRD (%), 90% CI vs. placebo ^a		13.9 (-1.80, 29.57)
≥ 40 - <65	6	16
Responder	1 (16.7)	3 (18.8)
Non-responder	5 (83.3)	13 (81.3)
Imputed non-responder	3 (50.0)	5 (31.3)
OR, 95% CI vs. placebo ^a		1.2 (0.10, 13.88)
P-value vs. placebo ^b		0.9122
RRD (%), 95% CI vs. placebo ^a		2.1 (-33.34, 37.51)
OR, 90% CI vs. placebo ^a		1.2 (0.14, 9.30)
RRD (%), 90% CI vs. placebo ^a		2.1 (-27.65, 31.81)
≥ 65	2	1

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Responder	1 (50.0)	0
Non-responder	1 (50.0)	1 (100)
Imputed non-responder	0	1 (100)
OR, 95% CI vs. placebo ^a		0.0 (NE, NE)
P-value vs. placebo ^b		0.4795
RRD (%), 95% CI vs. placebo ^a		-50.0 (-100.00, 19.30)
OR, 90% CI vs. placebo ^a		0.0 (NE, NE)
RRD (%), 90% CI vs. placebo ^a		-50.0 (-100.00, 8.15)
Overall p-value for interaction ^c		0.6398
Age Group 2 (years)		
<40	23	31
Responder	2 (8.7)	7 (22.6)
Non-responder	21 (91.3)	24 (77.4)
Imputed non-responder	11 (47.8)	19 (61.3)
OR, 95% CI vs. placebo ^a		3.1 (0.57, 16.38)
P-value vs. placebo ^b		0.1798
RRD (%), 95% CI vs. placebo ^a		13.9 (-4.80, 32.57)
OR, 90% CI vs. placebo ^a		3.1 (0.75, 12.51)
RRD (%), 90% CI vs. placebo ^a		13.9 (-1.80, 29.57)
≥40	8	17
Responder	2 (25.0)	3 (17.6)
Non-responder	6 (75.0)	14 (82.4)
Imputed non-responder	3 (37.5)	6 (35.3)
OR, 95% CI vs. placebo ^a		0.6 (0.08, 4.89)
P-value vs. placebo ^b		0.6744
RRD (%), 95% CI vs. placebo ^a		-7.4 (-42.41, 27.70)
OR, 90% CI vs. placebo ^a		0.6 (0.12, 3.53)
RRD (%), 90% CI vs. placebo ^a		-7.4 (-36.77, 22.06)
Overall p-value for interaction ^c		0.2636
Gender		
Male	16	17
Responder	1 (6.3)	3 (17.6)
Non-responder	15 (93.8)	14 (82.4)
Imputed non-responder	6 (37.5)	12 (70.6)
OR, 95% CI vs. placebo ^a		3.2 (0.30, 34.64)
P-value vs. placebo ^b		0.3235
RRD (%), 95% CI vs. placebo ^a		11.4 (-10.26, 33.06)
OR, 90% CI vs. placebo ^a		3.2 (0.44, 23.64)
RRD (%), 90% CI vs. placebo ^a		11.4 (-6.78, 29.57)
Female	15	31
Responder	3 (20.0)	7 (22.6)
Non-responder	12 (80.0)	24 (77.4)
Imputed non-responder	8 (53.3)	13 (41.9)
OR, 95% CI vs. placebo ^a		1.2 (0.26, 5.33)
P-value vs. placebo ^b		0.8440
RRD (%), 95% CI vs. placebo ^a		2.6 (-22.45, 27.61)
OR, 90% CI vs. placebo ^a		1.2 (0.33, 4.18)
RRD (%), 90% CI vs. placebo ^a		2.6 (-18.42, 23.58)
Overall p-value for interaction ^c		0.5296
Ethnicity		

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Hispanic or Latino	10	21
Responder	1 (10.0)	6 (28.6)
Non-responder	9 (90.0)	15 (71.4)
Imputed non-responder	4 (40.0)	10 (47.6)
OR, 95% CI vs. placebo ^a		3.6 (0.37, 34.94)
P-value vs. placebo ^b		0.2554
RRD (%), 95% CI vs. placebo ^a		18.6 (-8.24, 45.39)
OR, 90% CI vs. placebo ^a		3.6 (0.53, 24.24)
RRD (%), 90% CI vs. placebo ^a		18.6 (-3.93, 41.08)
Not Hispanic or Latino or other	21	27
Responder	3 (14.3)	4 (14.8)
Non-responder	18 (85.7)	23 (85.2)
Imputed non-responder	10 (47.6)	15 (55.6)
OR, 95% CI vs. placebo ^a		1.0 (0.21, 5.27)
P-value vs. placebo ^b		0.9593
RRD (%), 95% CI vs. placebo ^a		0.5 (-19.56, 20.62)
OR, 90% CI vs. placebo ^a		1.0 (0.27, 4.06)
RRD (%), 90% CI vs. placebo ^a		0.5 (-16.33, 17.39)
Overall p-value for interaction ^c		0.4605
Duration of AD (years)		
<26	22	30
Responder	4 (18.2)	7 (23.3)
Non-responder	18 (81.8)	23 (76.7)
Imputed non-responder	11 (50.0)	18 (60.0)
OR, 95% CI vs. placebo ^a		1.4 (0.35, 5.41)
P-value vs. placebo ^b		0.6563
RRD (%), 95% CI vs. placebo ^a		5.2 (-16.96, 27.26)
OR, 90% CI vs. placebo ^a		1.4 (0.43, 4.34)
RRD (%), 90% CI vs. placebo ^a		5.2 (-13.40, 23.71)
≥26	9	18
Responder	0	3 (16.7)
Non-responder	9 (100)	15 (83.3)
Imputed non-responder	3 (33.3)	7 (38.9)
OR, 95% CI vs. placebo ^a		NE (NE, NE)
P-value vs. placebo ^b		0.2024
RRD (%), 95% CI vs. placebo ^a		16.7 (-0.55, 33.88)
OR, 90% CI vs. placebo ^a		NE (NE, NE)
RRD (%), 90% CI vs. placebo ^a		16.7 (2.22, 31.12)
Overall p-value for interaction ^c		0.5065
Baseline weight (kg)		
<60	3	9
Responder	0	3 (33.3)
Non-responder	3 (100)	6 (66.7)
Imputed non-responder	2 (66.7)	4 (44.4)
OR, 95% CI vs. placebo ^a		NE (NE, NE)
P-value vs. placebo ^b		0.2689
RRD (%), 95% CI vs. placebo ^a		33.3 (2.54, 64.13)
OR, 90% CI vs. placebo ^a		NE (NE, NE)
RRD (%), 90% CI vs. placebo ^a		33.3 (7.49, 59.18)
≥60 - <90	19	25
Responder	4 (21.1)	4 (16.0)

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Non-responder	15 (78.9)	21 (84.0)
Imputed non-responder	9 (47.4)	13 (52.0)
OR, 95% CI vs. placebo ^a		0.7 (0.15, 3.32)
P-value vs. placebo ^b		0.6705
RRD (%), 95% CI vs. placebo ^a		-5.1 (-28.35, 18.24)
OR, 90% CI vs. placebo ^a		0.7 (0.20, 2.59)
RRD (%), 90% CI vs. placebo ^a		-5.1 (-24.60, 14.50)
≥90	9	14
Responder	0	3 (21.4)
Non-responder	9 (100)	11 (78.6)
Imputed non-responder	3 (33.3)	8 (57.1)
OR, 95% CI vs. placebo ^a		NE (NE, NE)
P-value vs. placebo ^b		0.1453
RRD (%), 95% CI vs. placebo ^a		21.4 (-0.07, 42.92)
OR, 90% CI vs. placebo ^a		NE (NE, NE)
RRD (%), 90% CI vs. placebo ^a		21.4 (3.39, 39.47)
Overall p-value for interaction ^c		0.4232
Baseline weight (kg)		
<90	22	34
Responder	4 (18.2)	7 (20.6)
Non-responder	18 (81.8)	27 (79.4)
Imputed non-responder	11 (50.0)	17 (50.0)
OR, 95% CI vs. placebo ^a		1.2 (0.30, 4.57)
P-value vs. placebo ^b		0.8264
RRD (%), 95% CI vs. placebo ^a		2.4 (-18.68, 23.49)
OR, 90% CI vs. placebo ^a		1.2 (0.37, 3.67)
RRD (%), 90% CI vs. placebo ^a		2.4 (-15.29, 20.10)
≥90	9	14
Responder	0	3 (21.4)
Non-responder	9 (100)	11 (78.6)
Imputed non-responder	3 (33.3)	8 (57.1)
OR, 95% CI vs. placebo ^a		NE (NE, NE)
P-value vs. placebo ^b		0.1453
RRD (%), 95% CI vs. placebo ^a		21.4 (-0.07, 42.92)
OR, 90% CI vs. placebo ^a		NE (NE, NE)
RRD (%), 90% CI vs. placebo ^a		21.4 (3.39, 39.47)
Overall p-value for interaction ^c		0.3593
Baseline BMI (kg/m ²)		
<25	12	18
Responder	1 (8.3)	5 (27.8)
Non-responder	11 (91.7)	13 (72.2)
Imputed non-responder	6 (50.0)	9 (50.0)
OR, 95% CI vs. placebo ^a		4.2 (0.43, 41.87)
P-value vs. placebo ^b		0.1997
RRD (%), 95% CI vs. placebo ^a		19.4 (-6.49, 45.38)
OR, 90% CI vs. placebo ^a		4.2 (0.62, 28.97)
RRD (%), 90% CI vs. placebo ^a		19.4 (-2.32, 41.21)
≥25 - <30	8	16
Responder	1 (12.5)	4 (25.0)
Non-responder	7 (87.5)	12 (75.0)
Imputed non-responder	4 (50.0)	7 (43.8)

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
OR, 95% CI vs. placebo ^a		2.3 (0.22, 25.24)
P-value vs. placebo ^b		0.4865
RRD (%), 95% CI vs. placebo ^a		12.5 (-18.73, 43.73)
OR, 90% CI vs. placebo ^a		2.3 (0.32, 17.21)
RRD (%), 90% CI vs. placebo ^a		12.5 (-13.71, 38.71)
≥30	11	14
Responder	2 (18.2)	1 (7.1)
Non-responder	9 (81.8)	13 (92.9)
Imputed non-responder	4 (36.4)	9 (64.3)
OR, 95% CI vs. placebo ^a		0.3 (0.03, 4.42)
P-value vs. placebo ^b		0.4088
RRD (%), 95% CI vs. placebo ^a		-11.0 (-37.52, 15.45)
OR, 90% CI vs. placebo ^a		0.3 (0.04, 2.93)
RRD (%), 90% CI vs. placebo ^a		-11.0 (-33.27, 11.19)
Overall p-value for interaction ^c		0.4249
Baseline IGA		
3 (moderate)	21	30
Responder	3 (14.3)	7 (23.3)
Non-responder	18 (85.7)	23 (76.7)
Imputed non-responder	9 (42.9)	16 (53.3)
OR, 95% CI vs. placebo ^a		1.8 (0.41, 8.07)
P-value vs. placebo ^b		0.4278
RRD (%), 95% CI vs. placebo ^a		9.0 (-12.24, 30.33)
OR, 90% CI vs. placebo ^a		1.8 (0.52, 6.36)
RRD (%), 90% CI vs. placebo ^a		9.0 (-8.82, 26.91)
4 (severe)	10	18
Responder	1 (10.0)	3 (16.7)
Non-responder	9 (90.0)	15 (83.3)
Imputed non-responder	5 (50.0)	9 (50.0)
OR, 95% CI vs. placebo ^a		1.8 (0.16, 20.03)
P-value vs. placebo ^b		0.6353
RRD (%), 95% CI vs. placebo ^a		6.7 (-18.67, 32.01)
OR, 90% CI vs. placebo ^a		1.8 (0.24, 13.60)
RRD (%), 90% CI vs. placebo ^a		6.7 (-14.60, 27.93)
Overall p-value for interaction ^c		0.9007
Baseline BSA category		
<median (34.00)	17	22
Responder	4 (23.5)	4 (18.2)
Non-responder	13 (76.5)	18 (81.8)
Imputed non-responder	6 (35.3)	11 (50.0)
OR, 95% CI vs. placebo ^a		0.7 (0.15, 3.43)
P-value vs. placebo ^b		0.6856
RRD (%), 95% CI vs. placebo ^a		-5.3 (-31.16, 20.47)
OR, 90% CI vs. placebo ^a		0.7 (0.20, 2.67)
RRD (%), 90% CI vs. placebo ^a		-5.3 (-27.01, 16.32)
≥median (34.00)	14	26
Responder	0	6 (23.1)
Non-responder	14 (100)	20 (76.9)
Imputed non-responder	8 (57.1)	14 (53.8)
OR, 95% CI vs. placebo ^a		NE (NE, NE)
P-value vs. placebo ^b		0.0542

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
RRD (%), 95% CI vs. placebo ^a		23.1 (6.88, 39.27)
OR, 90% CI vs. placebo ^a		NE (NE, NE)
RRD (%), 90% CI vs. placebo ^a		23.1 (9.49, 36.67)
Overall p-value for interaction ^c		0.1455
Baseline EASI category		
<16	3	3
Responder	1 (33.3)	2 (66.7)
Non-responder	2 (66.7)	1 (33.3)
Imputed non-responder	1 (33.3)	1 (33.3)
OR, 95% CI vs. placebo ^a		4.0 (0.13, 119.23)
P-value vs. placebo ^b		0.4561
RRD (%), 95% CI vs. placebo ^a		33.3 (-42.11, 100.00)
OR, 90% CI vs. placebo ^a		4.0 (0.23, 69.08)
RRD (%), 90% CI vs. placebo ^a		33.3 (-29.98, 96.64)
≥16	28	45
Responder	3 (10.7)	8 (17.8)
Non-responder	25 (89.3)	37 (82.2)
Imputed non-responder	13 (46.4)	24 (53.3)
OR, 95% CI vs. placebo ^a		1.8 (0.44, 7.46)
P-value vs. placebo ^b		0.4153
RRD (%), 95% CI vs. placebo ^a		7.1 (-8.94, 23.06)
OR, 90% CI vs. placebo ^a		1.8 (0.55, 5.94)
RRD (%), 90% CI vs. placebo ^a		7.1 (-6.36, 20.49)
Overall p-value for interaction ^c		0.7757
Baseline EASI category		
<median (22.30)	15	24
Responder	3 (20.0)	5 (20.8)
Non-responder	12 (80.0)	19 (79.2)
Imputed non-responder	6 (40.0)	13 (54.2)
OR, 95% CI vs. placebo ^a		1.1 (0.21, 5.23)
P-value vs. placebo ^b		0.9506
RRD (%), 95% CI vs. placebo ^a		0.8 (-25.12, 26.79)
OR, 90% CI vs. placebo ^a		1.1 (0.27, 4.04)
RRD (%), 90% CI vs. placebo ^a		0.8 (-20.95, 22.62)
≥median (22.30)	16	24
Responder	1 (6.3)	5 (20.8)
Non-responder	15 (93.8)	19 (79.2)
Imputed non-responder	8 (50.0)	12 (50.0)
OR, 95% CI vs. placebo ^a		3.9 (0.42, 37.50)
P-value vs. placebo ^b		0.2115
RRD (%), 95% CI vs. placebo ^a		14.6 (-5.53, 34.70)
OR, 90% CI vs. placebo ^a		3.9 (0.60, 26.11)
RRD (%), 90% CI vs. placebo ^a		14.6 (-2.30, 31.47)
Overall p-value for interaction ^c		0.4085
Screening IgE levels (UI/mL)		
<300	11	17
Responder	2 (18.2)	2 (11.8)
Non-responder	9 (81.8)	15 (88.2)
Imputed non-responder	4 (36.4)	9 (52.9)
OR, 95% CI vs. placebo ^a		0.6 (0.07, 5.03)

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
P-value vs. placebo ^b		0.6417
RRD (%), 95% CI vs. placebo ^a		-6.4 (-33.88, 21.04)
OR, 90% CI vs. placebo ^a		0.6 (0.10, 3.58)
RRD (%), 90% CI vs. placebo ^a		-6.4 (-29.46, 16.63)
≥300	20	31
Responder	2 (10.0)	8 (25.8)
Non-responder	18 (90.0)	23 (74.2)
Imputed non-responder	10 (50.0)	16 (51.6)
OR, 95% CI vs. placebo ^a		3.1 (0.59, 16.59)
P-value vs. placebo ^b		0.1693
RRD (%), 95% CI vs. placebo ^a		15.8 (-4.45, 36.06)
OR, 90% CI vs. placebo ^a		3.1 (0.77, 12.69)
RRD (%), 90% CI vs. placebo ^a		15.8 (-1.19, 32.80)
Overall p-value for interaction ^c		0.2561
Region ^d		
South America	8	17
Responder	0	4 (23.5)
Non-responder	8 (100)	13 (76.5)
Imputed non-responder	4 (50.0)	9 (52.9)
OR, 95% CI vs. placebo ^a		NE (NE, NE)
P-value vs. placebo ^b		0.1425
RRD (%), 95% CI vs. placebo ^a		23.5 (3.37, 43.69)
OR, 90% CI vs. placebo ^a		NE (NE, NE)
RRD (%), 90% CI vs. placebo ^a		23.5 (6.61, 40.45)
North America	12	19
Responder	3 (25.0)	5 (26.3)
Non-responder	9 (75.0)	14 (73.7)
Imputed non-responder	6 (50.0)	11 (57.9)
OR, 95% CI vs. placebo ^a		1.1 (0.20, 5.63)
P-value vs. placebo ^b		0.9361
RRD (%), 95% CI vs. placebo ^a		1.3 (-30.18, 32.82)
OR, 90% CI vs. placebo ^a		1.1 (0.27, 4.31)
RRD (%), 90% CI vs. placebo ^a		1.3 (-25.12, 27.75)
Other (Europe)	11	12
Responder	1 (9.1)	1 (8.3)
Non-responder	10 (90.9)	11 (91.7)
Imputed non-responder	4 (36.4)	5 (41.7)
OR, 95% CI vs. placebo ^a		0.9 (0.05, 16.54)
P-value vs. placebo ^b		0.9498
RRD (%), 95% CI vs. placebo ^a		-0.8 (-23.85, 22.33)
OR, 90% CI vs. placebo ^a		0.9 (0.08, 10.37)
RRD (%), 90% CI vs. placebo ^a		-0.8 (-20.14, 18.62)
Overall p-value for interaction ^c		0.6192

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

^c Logistic regression model was for the interaction test including intervention group, plus the subgroup variable and the subgroup-by-intervention in the model.

^d North America: USA, Canada; South America: Chile; Other (Europe): Czech Republic, Germany, Netherlands, Poland.

Note: Participants who received any rescue medication or phototherapy before Week 16 were considered as non-responders, and missing data at Week 16 were considered as non-responders.

Table 32. Subgroup Analysis: Percent Change in Weekly Average of PP-NRS from Baseline to Week 16 by Subgroup (BID Cohort in ITT Population)

	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)
Age Group 1 (years)		
≥18 - <40		
Baseline mean (SD)	7.07 (0.96)	7.29 (1.53)
Number (observed/imputed)	10 (7/3)	13 (9/4)
Mean % change (SD)	-9.82 (24.37)	-29.72 (30.09)
LS Mean % change (SE) ^a	-13.06 (9.55)	-28.91 (9.20)
LS Mean Diff vs. placebo (95% CI) ^a		-15.84 (-41.48, 9.79)
LS Mean Diff vs. placebo (90% CI) ^a		-15.84 (-37.35, 5.66)
≥40 - <65		
Baseline mean (SD)	6.47 (1.54)	7.85 (1.55)
Number (observed/imputed)	6 (4/2)	8 (8/0)
Mean % change (SD)	-30.08 (30.12)	-53.32 (21.59)
LS Mean % change (SE) ^a	-35.69 (11.00)	-50.39 (9.15)
LS Mean Diff vs. placebo (95% CI) ^a		-14.70 (-43.32, 13.92)
LS Mean Diff vs. placebo (90% CI) ^a		-14.70 (-38.72, 9.31)
≥65		
Baseline mean (SD)	NE (NE)	6.13 (0.18)
Number (observed/imputed)	0	2 (2/0)
Mean % change (SD)	NE (NE)	-69.52 (24.24)
LS Mean % change (SE) ^a	NE (NE)	NE (NE)
LS Mean Diff vs. placebo (95% CI) ^a		NE (NE, NE)
LS Mean Diff vs. placebo (90% CI) ^a		NE (NE, NE)
Overall p-value for interaction ^b		0.6606
Age Group 2 (years)		
<40		
Baseline mean (SD)	7.07 (0.96)	7.29 (1.53)
Number (observed/imputed)	10 (7/3)	13 (9/4)
Mean % change (SD)	-9.82 (24.37)	-29.72 (30.09)
LS Mean % change (SE) ^a	-13.06 (9.55)	-28.91 (9.20)
LS Mean Diff vs. placebo (95% CI) ^a		-15.84 (-41.48, 9.79)
LS Mean Diff vs. placebo (90% CI) ^a		-15.84 (-37.35, 5.66)
≥40		
Baseline mean (SD)	6.47 (1.54)	7.56 (1.56)
Number (observed/imputed)	6 (4/2)	10 (10/0)
Mean % change (SD)	-30.08 (30.12)	-56.56 (21.78)
LS Mean % change (SE) ^a	-33.44 (10.95)	-54.71 (8.23)
LS Mean Diff vs. placebo (95% CI) ^a		-21.27 (-48.28, 5.73)
LS Mean Diff vs. placebo (90% CI) ^a		-21.27 (-43.93, 1.39)
Overall p-value for interaction ^b		0.5387
Gender		
Male		
Baseline mean (SD)	7.00 (1.23)	7.21 (1.41)
Number (observed/imputed)	8 (5/3)	10 (8/2)
Mean % change (SD)	-13.84 (22.85)	-41.46 (26.87)
LS Mean % change (SE) ^a	-13.55 (9.32)	-43.30 (8.33)
LS Mean Diff vs. placebo (95% CI) ^a		-29.75 (-54.17, -5.33)
LS Mean Diff vs. placebo (90% CI) ^a		-29.75 (-50.24, -9.25)

	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)
Female		
Baseline mean (SD)	6.77 (1.18)	7.58 (1.63)
Number (observed/imputed)	8 (6/2)	13 (11/2)
Mean % change (SD)	-21.00 (32.86)	-41.34 (32.54)
LS Mean % change (SE) ^a	-23.99 (12.35)	-38.63 (10.64)
LS Mean Diff vs. placebo (95% CI) ^a		-14.64 (-47.41, 18.13)
LS Mean Diff vs. placebo (90% CI) ^a		-14.64 (-42.14, 12.86)
Overall p-value for interaction ^b		0.5169
Ethnicity		
Hispanic or Latino		
Baseline mean (SD)	6.27 (1.81)	7.41 (1.64)
Number (observed/imputed)	3 (2/1)	5 (5/0)
Mean % change (SD)	-32.58 (37.87)	-64.20 (23.51)
LS Mean % change (SE) ^a	-33.72 (15.79)	-64.20 (13.69)
LS Mean Diff vs. placebo (95% CI) ^a		-30.48 (-72.51, 11.54)
LS Mean Diff vs. placebo (90% CI) ^a		-30.48 (-65.75, 4.78)
Not Hispanic or Latino or other		
Baseline mean (SD)	7.05 (0.95)	7.41 (1.53)
Number (observed/imputed)	13 (9/4)	18 (14/4)
Mean % change (SD)	-13.92 (25.34)	-35.06 (28.36)
LS Mean % change (SE) ^a	-15.04 (8.85)	-35.50 (7.69)
LS Mean Diff vs. placebo (95% CI) ^a		-20.46 (-42.78, 1.86)
LS Mean Diff vs. placebo (90% CI) ^a		-20.46 (-39.19, -1.73)
Overall p-value for interaction ^b		0.6736
Duration of AD (years)		
<26		
Baseline mean (SD)	6.84 (1.21)	7.04 (1.51)
Number (observed/imputed)	8 (7/1)	14 (12/2)
Mean % change (SD)	-26.87 (29.12)	-40.42 (26.78)
LS Mean % change (SE) ^a	-28.05 (10.87)	-37.88 (8.92)
LS Mean Diff vs. placebo (95% CI) ^a		-9.83 (-36.91, 17.25)
LS Mean Diff vs. placebo (90% CI) ^a		-9.83 (-32.56, 12.89)
≥26		
Baseline mean (SD)	6.92 (1.21)	7.96 (1.41)
Number (observed/imputed)	8 (4/4)	9 (7/2)
Mean % change (SD)	-7.97 (24.07)	-42.91 (35.09)
LS Mean % change (SE) ^a	-7.13 (11.73)	-45.81 (10.50)
LS Mean Diff vs. placebo (95% CI) ^a		-38.68 (-70.27, -7.09)
LS Mean Diff vs. placebo (90% CI) ^a		-38.68 (-65.19, -12.17)
Overall p-value for interaction ^b		0.1680
Baseline weight (kg)		
<60		
Baseline mean (SD)	7.45 (0.90)	7.85 (1.42)
Number (observed/imputed)	3 (2/1)	5 (5/0)
Mean % change (SD)	3.70 (14.94)	-40.48 (30.52)
LS Mean % change (SE) ^a	-7.63 (17.87)	-37.97 (12.31)
LS Mean Diff vs. placebo (95% CI) ^a		-30.33 (-72.85, 12.18)
LS Mean Diff vs. placebo (90% CI) ^a		-30.33 (-65.99, 5.33)
≥60 - <90		

	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)
Baseline mean (SD)	6.68 (1.30)	7.33 (1.56)
Number (observed/imputed)	10 (6/4)	14 (11/3)
Mean % change (SD)	-14.81 (27.17)	-39.68 (32.23)
LS Mean % change (SE) ^a	-15.08 (10.20)	-40.34 (9.54)
LS Mean Diff vs. placebo (95% CI) ^a		-25.26 (-53.62, 3.11)
LS Mean Diff vs. placebo (90% CI) ^a		-25.26 (-49.06, -1.46)
≥90		
Baseline mean (SD)	6.81 (1.08)	7.25 (1.70)
Number (observed/imputed)	3 (3/0)	4 (3/1)
Mean % change (SD)	-47.24 (11.39)	-48.54 (24.00)
LS Mean % change (SE) ^a	-49.26 (9.85)	-45.51 (8.11)
LS Mean Diff vs. placebo (95% CI) ^a		3.75 (-21.47, 28.97)
LS Mean Diff vs. placebo (90% CI) ^a		3.75 (-17.41, 24.92)
Overall p-value for interaction ^b		0.5550
Baseline weight (kg)		
<90		
Baseline mean (SD)	6.89 (1.23)	7.45 (1.51)
Number (observed/imputed)	13 (8/5)	19 (16/3)
Mean % change (SD)	-10.54 (25.62)	-39.89 (30.94)
LS Mean % change (SE) ^a	-12.94 (8.97)	-39.91 (7.99)
LS Mean Diff vs. placebo (95% CI) ^a		-26.98 (-50.27, -3.68)
LS Mean Diff vs. placebo (90% CI) ^a		-26.98 (-46.52, -7.43)
≥90		
Baseline mean (SD)	6.81 (1.08)	7.25 (1.70)
Number (observed/imputed)	3 (3/0)	4 (3/1)
Mean % change (SD)	-47.24 (11.39)	-48.54 (24.00)
LS Mean % change (SE) ^a	-49.26 (9.85)	-45.51 (8.11)
LS Mean Diff vs. placebo (95% CI) ^a		3.75 (-21.47, 28.97)
LS Mean Diff vs. placebo (90% CI) ^a		3.75 (-17.41, 24.92)
Overall p-value for interaction ^b		0.2891
Baseline BMI (kg/m²)		
<25		
Baseline mean (SD)	6.99 (0.98)	7.65 (1.52)
Number (observed/imputed)	7 (4/3)	12 (10/2)
Mean % change (SD)	1.74 (17.71)	-41.43 (35.52)
LS Mean % change (SE) ^a	-1.46 (13.55)	-43.52 (9.73)
LS Mean Diff vs. placebo (95% CI) ^a		-42.06 (-73.97, -10.16)
LS Mean Diff vs. placebo (90% CI) ^a		-42.06 (-68.84, -15.29)
≥25 - <30		
Baseline mean (SD)	6.77 (1.54)	7.03 (1.51)
Number (observed/imputed)	6 (4/2)	8 (8/0)
Mean % change (SD)	-24.87 (27.24)	-48.05 (18.54)
LS Mean % change (SE) ^a	-27.29 (10.70)	-42.43 (10.33)
LS Mean Diff vs. placebo (95% CI) ^a		-15.14 (-45.20, 14.92)
LS Mean Diff vs. placebo (90% CI) ^a		-15.14 (-40.36, 10.08)
≥30		
Baseline mean (SD)	6.81 (1.08)	7.77 (1.80)
Number (observed/imputed)	3 (3/0)	3 (1/2)
Mean % change (SD)	-47.24 (11.39)	-23.48 (28.29)
LS Mean % change (SE) ^a	-42.57 (11.09)	-28.16 (11.09)

	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)
LS Mean Diff vs. placebo (95% CI) ^a		14.41 (-37.29, 66.11)
LS Mean Diff vs. placebo (90% CI) ^a		14.41 (-23.82, 52.64)
Overall p-value for interaction ^b		0.0788
Baseline IGA		
3 (moderate)		
Baseline mean (SD)	6.79 (0.80)	6.89 (1.61)
Number (observed/imputed)	8 (6/2)	11 (10/1)
Mean % change (SD)	-14.75 (29.00)	-38.13 (26.90)
LS Mean % change (SE) ^a	-18.57 (11.03)	-35.18 (10.22)
LS Mean Diff vs. placebo (95% CI) ^a		-16.61 (-45.40, 12.18)
LS Mean Diff vs. placebo (90% CI) ^a		-16.61 (-40.77, 7.54)
4 (severe)		
Baseline mean (SD)	6.98 (1.58)	7.90 (1.29)
Number (observed/imputed)	8 (5/3)	12 (9/3)
Mean % change (SD)	-20.10 (27.82)	-44.39 (32.67)
LS Mean % change (SE) ^a	-16.97 (11.34)	-47.76 (8.93)
LS Mean Diff vs. placebo (95% CI) ^a		-30.79 (-59.49, -2.08)
LS Mean Diff vs. placebo (90% CI) ^a		-30.79 (-54.88, -6.69)
Overall p-value for interaction ^b		0.6198
Baseline BSA category		
<median (30.75)		
Baseline mean (SD)	6.06 (1.27)	6.80 (1.49)
Number (observed/imputed)	5 (4/1)	9 (9/0)
Mean % change (SD)	-16.17 (36.89)	-58.96 (24.95)
LS Mean % change (SE) ^a	-23.58 (14.26)	-50.83 (12.39)
LS Mean Diff vs. placebo (95% CI) ^a		-27.25 (-66.29, 11.80)
LS Mean Diff vs. placebo (90% CI) ^a		-27.25 (-60.00, 5.51)
≥median (30.75)		
Baseline mean (SD)	7.26 (1.11)	7.91 (1.66)
Number (observed/imputed)	7 (4/3)	10 (7/3)
Mean % change (SD)	-15.64 (29.08)	-37.31 (27.94)
LS Mean % change (SE) ^a	-15.95 (12.27)	-38.41 (9.65)
LS Mean Diff vs. placebo (95% CI) ^a		-22.46 (-53.35, 8.43)
LS Mean Diff vs. placebo (90% CI) ^a		-22.46 (-48.38, 3.46)
Overall p-value for interaction ^b		0.6133
Baseline EASI category		
<median (22.20)		
Baseline mean (SD)	6.86 (1.24)	6.80 (1.49)
Number (observed/imputed)	9 (5/4)	9 (9/0)
Mean % change (SD)	-11.03 (33.56)	-58.96 (24.95)
LS Mean % change (SE) ^a	-13.40 (10.42)	-52.98 (11.73)
LS Mean Diff vs. placebo (95% CI) ^a		-39.58 (-70.69, -8.47)
LS Mean Diff vs. placebo (90% CI) ^a		-39.58 (-65.68, -13.48)
≥median (22.20)		
Baseline mean (SD)	6.89 (1.17)	7.90 (1.40)
Number (observed/imputed)	7 (6/1)	14 (10/4)
Mean % change (SD)	-25.65 (16.17)	-30.10 (27.26)
LS Mean % change (SE) ^a	-22.80 (11.16)	-33.01 (6.92)
LS Mean Diff vs. placebo (95% CI) ^a		-10.21 (-36.80, 16.39)

	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)
LS Mean Diff vs. placebo (90% CI) ^a		-10.21 (-32.52, 12.10)
Overall p-value for interaction ^b		0.1117
Screening IgE levels (UI/mL)		
<300		
Baseline mean (SD)	6.19 (1.11)	7.58 (1.49)
Number (observed/imputed)	6 (5/1)	9 (8/1)
Mean % change (SD)	-39.23 (23.89)	-42.30 (31.82)
LS Mean % change (SE) ^a	-39.13 (12.10)	-42.15 (10.42)
LS Mean Diff vs. placebo (95% CI) ^a		-3.02 (-36.10, 30.07)
LS Mean Diff vs. placebo (90% CI) ^a		-3.02 (-30.78, 24.75)
≥300		
Baseline mean (SD)	7.31 (1.04)	7.33 (1.56)
Number (observed/imputed)	10 (6/4)	14 (11/3)
Mean % change (SD)	-4.34 (21.09)	-40.81 (29.21)
LS Mean % change (SE) ^a	-6.62 (10.19)	-40.08 (8.58)
LS Mean Diff vs. placebo (95% CI) ^a		-33.46 (-58.15, -8.77)
LS Mean Diff vs. placebo (90% CI) ^a		-33.46 (-54.18, -12.74)
Overall p-value for interaction ^b		0.1112
Region ^c		
North America		
Baseline mean (SD)	6.42 (1.50)	7.43 (1.65)
Number (observed/imputed)	5 (3/2)	10 (8/2)
Mean % change (SD)	-18.03 (35.16)	-51.70 (30.61)
LS Mean % change (SE) ^a	-20.26 (15.04)	-54.08 (10.63)
LS Mean Diff vs. placebo (95% CI) ^a		-33.82 (-69.37, 1.74)
LS Mean Diff vs. placebo (90% CI) ^a		-33.82 (-63.65, -3.98)
Other (Europe)		
Baseline mean (SD)	7.16 (0.87)	7.40 (1.48)
Number (observed/imputed)	11 (8/3)	13 (11/2)
Mean % change (SD)	-17.15 (25.44)	-33.47 (27.23)
LS Mean % change (SE) ^a	-17.54 (8.69)	-32.36 (8.41)
LS Mean Diff vs. placebo (95% CI) ^a		-14.82 (-39.02, 9.38)
LS Mean Diff vs. placebo (90% CI) ^a		-14.82 (-35.13, 5.49)
Overall p-value for interaction ^b		0.4579

^a Each of the imputed complete data was analyzed by fitting an ANCOVA model with baseline PP-NRS value, study intervention group as covariate. Analysis was based on the same imputed dataset using WOCF/MI from primary analysis of the primary endpoint.

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

^c North America: USA, Canada; Other (Europe): Czech Republic, Germany, Netherlands, Poland.

Note: Data collected after study intervention discontinuation were included. Data post the use of any rescue medication or phototherapy were set to missing and imputed by WOCF. Missing data after study intervention discontinuation due to lack of efficacy were imputed by WOCF, and other missing data were imputed by MI. Descriptive statistics at Week 16 include participants whose values were imputed using WOCF at Week 16, and participants whose values were imputed by MI at Week 16 were excluded from the descriptive analysis.

Table 33. Subgroup Analysis: Percent Change in Weekly Average of PP-NRS from Baseline to Week 16 by Subgroup (TID Cohort in ITT Population)

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Age Group 1 (years)		
≥18 - <40		
Baseline mean (SD)	6.67 (1.19)	7.80 (1.14)
Number (observed/imputed)	19 (12/7)	22 (12/10)
Mean % change (SD)	-7.44 (38.57)	-24.58 (40.36)
LS Mean % change (SE) ^a	-2.78 (8.66)	-30.86 (7.99)
LS Mean Diff vs. placebo (95% CI) ^a		-28.07 (-52.34, -3.80)
LS Mean Diff vs. placebo (90% CI) ^a		-28.07 (-48.44, -7.71)
≥40 - <65		
Baseline mean (SD)	8.42 (0.46)	7.12 (1.57)
Number (observed/imputed)	5 (3/2)	13 (11/2)
Mean % change (SD)	-20.81 (23.72)	-27.65 (36.76)
LS Mean % change (SE) ^a	-24.33 (15.47)	-31.51 (9.14)
LS Mean Diff vs. placebo (95% CI) ^a		-7.17 (-43.36, 29.01)
LS Mean Diff vs. placebo (90% CI) ^a		-7.17 (-37.54, 23.19)
≥65		
Baseline mean (SD)	6.67 (2.36)	9.86 (NC)
Number (observed/imputed)	2 (2/0)	1 (0/1)
Mean % change (SD)	-26.00 (36.77)	1.45 (NC)
LS Mean % change (SE) ^a	-42.59 (NE)	34.63 (NE)
LS Mean Diff vs. placebo (95% CI) ^a		77.22 (NE, NE)
LS Mean Diff vs. placebo (90% CI) ^a		77.22 (NE, NE)
Overall p-value for interaction ^b		0.5713
Age Group 2 (years)		
<40		
Baseline mean (SD)	6.67 (1.19)	7.80 (1.14)
Number (observed/imputed)	19 (12/7)	22 (12/10)
Mean % change (SD)	-7.44 (38.57)	-24.58 (40.36)
LS Mean % change (SE) ^a	-2.78 (8.66)	-30.86 (7.99)
LS Mean Diff vs. placebo (95% CI) ^a		-28.07 (-52.34, -3.80)
LS Mean Diff vs. placebo (90% CI) ^a		-28.07 (-48.44, -7.71)
≥40		
Baseline mean (SD)	7.99 (1.27)	7.28 (1.66)
Number (observed/imputed)	7 (5/2)	14 (11/3)
Mean % change (SD)	-22.29 (24.63)	-25.57 (36.17)
LS Mean % change (SE) ^a	-22.67 (12.47)	-30.55 (8.59)
LS Mean Diff vs. placebo (95% CI) ^a		-7.88 (-37.71, 21.95)
LS Mean Diff vs. placebo (90% CI) ^a		-7.88 (-32.91, 17.15)
Overall p-value for interaction ^b		0.3298
Gender		
Male		
Baseline mean (SD)	7.17 (1.10)	7.74 (1.40)
Number (observed/imputed)	14 (10/4)	15 (5/10)
Mean % change (SD)	-2.68 (27.39)	-10.49 (38.23)
LS Mean % change (SE) ^a	-2.10 (9.54)	-19.02 (9.58)
LS Mean Diff vs. placebo (95% CI) ^a		-16.92 (-43.98, 10.15)
LS Mean Diff vs. placebo (90% CI) ^a		-16.92 (-39.63, 5.80)
Female		
Baseline mean (SD)	6.84 (1.55)	7.55 (1.34)
Number (observed/imputed)	12 (7/5)	21 (18/3)

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Mean % change (SD)	-21.66 (42.07)	-35.30 (35.61)
LS Mean % change (SE) ^a	-17.53 (9.99)	-35.53 (7.19)
LS Mean Diff vs. placebo (95% CI) ^a		-18.00 (-42.22, 6.21)
LS Mean Diff vs. placebo (90% CI) ^a		-18.00 (-38.32, 2.32)
Overall p-value for interaction ^b		0.9663
Ethnicity		
Hispanic or Latino		
Baseline mean (SD)	6.97 (1.11)	7.44 (1.04)
Number (observed/imputed)	9 (6/3)	16 (11/5)
Mean % change (SD)	-12.64 (37.96)	-36.18 (40.27)
LS Mean % change (SE) ^a	-8.50 (13.05)	-43.11 (9.48)
LS Mean Diff vs. placebo (95% CI) ^a		-34.61 (-66.65, -2.58)
LS Mean Diff vs. placebo (90% CI) ^a		-34.61 (-61.49, -7.73)
Not Hispanic or Latino or other		
Baseline mean (SD)	7.03 (1.44)	7.75 (1.56)
Number (observed/imputed)	17 (11/6)	20 (12/8)
Mean % change (SD)	-10.80 (35.35)	-15.99 (34.99)
LS Mean % change (SE) ^a	-9.99 (7.70)	-19.30 (7.21)
LS Mean Diff vs. placebo (95% CI) ^a		-9.31 (-30.08, 11.46)
LS Mean Diff vs. placebo (90% CI) ^a		-9.31 (-26.74, 8.12)
Overall p-value for interaction ^b		0.2079
Duration of AD (years)		
<26		
Baseline mean (SD)	7.00 (1.33)	7.84 (1.50)
Number (observed/imputed)	19 (11/8)	21 (12/9)
Mean % change (SD)	-14.68 (39.60)	-28.92 (40.32)
LS Mean % change (SE) ^a	-12.54 (8.47)	-30.76 (7.72)
LS Mean Diff vs. placebo (95% CI) ^a		-18.22 (-41.03, 4.59)
LS Mean Diff vs. placebo (90% CI) ^a		-18.22 (-37.37, 0.92)
≥26		
Baseline mean (SD)	7.01 (1.39)	7.24 (0.99)
Number (observed/imputed)	7 (6/1)	15 (11/4)
Mean % change (SD)	-2.63 (20.74)	-19.43 (35.77)
LS Mean % change (SE) ^a	-1.60 (12.16)	-28.23 (8.96)
LS Mean Diff vs. placebo (95% CI) ^a		-26.63 (-56.43, 3.16)
LS Mean Diff vs. placebo (90% CI) ^a		-26.63 (-51.64, -1.63)
Overall p-value for interaction ^b		0.7017
Baseline weight (kg)		
<60		
Baseline mean (SD)	6.43 (2.10)	7.48 (1.47)
Number (observed/imputed)	3 (1/2)	6 (5/1)
Mean % change (SD)	-4.61 (41.45)	-49.10 (33.09)
LS Mean % change (SE) ^a	2.80 (21.52)	-45.44 (13.63)
LS Mean Diff vs. placebo (95% CI) ^a		-48.24 (-98.87, 2.39)
LS Mean Diff vs. placebo (90% CI) ^a		-48.24 (-90.73, -5.76)
≥60 - <90		
Baseline mean (SD)	7.21 (1.18)	7.71 (1.15)
Number (observed/imputed)	17 (10/7)	19 (12/7)
Mean % change (SD)	-13.15 (39.65)	-20.86 (37.37)

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
LS Mean % change (SE) ^a	-11.00 (9.40)	-28.65 (8.45)
LS Mean Diff vs. placebo (95% CI) ^a		-17.65 (-42.72, 7.42)
LS Mean Diff vs. placebo (90% CI) ^a		-17.65 (-38.69, 3.39)
≥90		
Baseline mean (SD)	6.78 (1.44)	7.52 (1.68)
Number (observed/imputed)	6 (6/0)	11 (6/5)
Mean % change (SD)	-10.01 (23.47)	-18.89 (40.48)
LS Mean % change (SE) ^a	-9.61 (11.93)	-22.07 (9.73)
LS Mean Diff vs. placebo (95% CI) ^a		-12.46 (-42.73, 17.81)
LS Mean Diff vs. placebo (90% CI) ^a		-12.46 (-37.86, 12.94)
Overall p-value for interaction ^b		0.5777
Baseline weight (kg)		
<90		
Baseline mean (SD)	7.10 (1.30)	7.65 (1.22)
Number (observed/imputed)	20 (11/9)	25 (17/8)
Mean % change (SD)	-11.87 (38.92)	-27.64 (37.77)
LS Mean % change (SE) ^a	-9.25 (8.46)	-33.01 (7.19)
LS Mean Diff vs. placebo (95% CI) ^a		-23.77 (-45.74, -1.79)
LS Mean Diff vs. placebo (90% CI) ^a		-23.77 (-42.21, -5.32)
≥90		
Baseline mean (SD)	6.78 (1.44)	7.52 (1.68)
Number (observed/imputed)	6 (6/0)	11 (6/5)
Mean % change (SD)	-10.01 (23.47)	-18.89 (40.48)
LS Mean % change (SE) ^a	-9.61 (11.93)	-22.07 (9.73)
LS Mean Diff vs. placebo (95% CI) ^a		-12.46 (-42.73, 17.81)
LS Mean Diff vs. placebo (90% CI) ^a		-12.46 (-37.86, 12.94)
Overall p-value for interaction ^b		0.5935
Baseline BMI (kg/m ²)		
<25		
Baseline mean (SD)	6.96 (1.46)	7.71 (1.45)
Number (observed/imputed)	11 (6/5)	13 (9/4)
Mean % change (SD)	-4.16 (31.66)	-37.37 (32.50)
LS Mean % change (SE) ^a	-1.98 (9.51)	-35.82 (8.45)
LS Mean Diff vs. placebo (95% CI) ^a		-33.84 (-59.11, -8.58)
LS Mean Diff vs. placebo (90% CI) ^a		-33.84 (-55.04, -12.64)
≥25 - <30		
Baseline mean (SD)	7.13 (1.08)	7.59 (1.17)
Number (observed/imputed)	7 (4/3)	13 (9/4)
Mean % change (SD)	-9.10 (42.92)	-29.41 (39.81)
LS Mean % change (SE) ^a	-5.00 (14.96)	-35.34 (10.95)
LS Mean Diff vs. placebo (95% CI) ^a		-30.34 (-67.08, 6.40)
LS Mean Diff vs. placebo (90% CI) ^a		-30.34 (-61.18, 0.49)
≥30		
Baseline mean (SD)	6.97 (1.45)	7.52 (1.50)
Number (observed/imputed)	8 (7/1)	10 (5/5)
Mean % change (SD)	-23.49 (35.23)	-3.06 (37.21)
LS Mean % change (SE) ^a	-20.39 (12.36)	-15.92 (11.31)
LS Mean Diff vs. placebo (95% CI) ^a		4.47 (-28.71, 37.66)
LS Mean Diff vs. placebo (90% CI) ^a		4.47 (-23.38, 32.32)

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Overall p-value for interaction ^b		0.1921
Baseline IGA		
3 (moderate)		
Baseline mean (SD)	6.92 (1.48)	7.46 (1.18)
Number (observed/imputed)	17 (12/5)	18 (14/4)
Mean % change (SD)	-11.88 (36.25)	-31.91 (36.01)
LS Mean % change (SE) ^a	-11.91 (8.43)	-35.08 (7.67)
LS Mean Diff vs. placebo (95% CI) ^a		-23.17 (-45.69, -0.65)
LS Mean Diff vs. placebo (90% CI) ^a		-23.17 (-42.07, -4.27)
4 (severe)		
Baseline mean (SD)	7.20 (0.96)	7.87 (1.61)
Number (observed/imputed)	9 (5/4)	18 (9/9)
Mean % change (SD)	-10.61 (36.26)	-18.02 (40.17)
LS Mean % change (SE) ^a	-4.86 (11.59)	-20.57 (8.55)
LS Mean Diff vs. placebo (95% CI) ^a		-15.71 (-44.29, 12.88)
LS Mean Diff vs. placebo (90% CI) ^a		-15.71 (-39.69, 8.28)
Overall p-value for interaction ^b		0.4841
Baseline BSA category		
<median (34.00)		
Baseline mean (SD)	6.60 (1.53)	7.53 (1.50)
Number (observed/imputed)	15 (11/4)	12 (11/1)
Mean % change (SD)	-24.65 (40.93)	-38.21 (31.66)
LS Mean % change (SE) ^a	-22.49 (10.05)	-40.13 (9.71)
LS Mean Diff vs. placebo (95% CI) ^a		-17.64 (-45.47, 10.19)
LS Mean Diff vs. placebo (90% CI) ^a		-17.64 (-40.99, 5.72)
≥median (34.00)		
Baseline mean (SD)	7.50 (0.83)	7.68 (1.24)
Number (observed/imputed)	11 (6/5)	24 (12/12)
Mean % change (SD)	6.57 (13.83)	-18.34 (40.12)
LS Mean % change (SE) ^a	4.52 (8.95)	-19.97 (6.48)
LS Mean Diff vs. placebo (95% CI) ^a		-24.50 (-46.34, -2.66)
LS Mean Diff vs. placebo (90% CI) ^a		-24.50 (-42.82, -6.17)
Overall p-value for interaction ^b		0.7632
Baseline EASI category		
<16		
Baseline mean (SD)	5.26 (1.53)	7.39 (0.54)
Number (observed/imputed)	2 (2/0)	2 (2/0)
Mean % change (SD)	-69.51 (43.12)	-62.61 (13.41)
LS Mean % change (SE) ^a	-66.85 (25.35)	-55.42 (32.00)
LS Mean Diff vs. placebo (95% CI) ^a		11.43 (-82.25, 105.11)
LS Mean Diff vs. placebo (90% CI) ^a		11.43 (-67.16, 90.02)
≥16		
Baseline mean (SD)	7.19 (1.18)	7.63 (1.39)
Number (observed/imputed)	24 (15/9)	34 (21/13)
Mean % change (SD)	-6.60 (31.20)	-22.75 (38.15)
LS Mean % change (SE) ^a	-5.19 (6.93)	-26.87 (5.72)
LS Mean Diff vs. placebo (95% CI) ^a		-21.68 (-39.45, -3.90)
LS Mean Diff vs. placebo (90% CI) ^a		-21.68 (-36.59, -6.76)
Overall p-value for interaction ^b		0.7604

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Baseline EASI category		
<median (22.30)		
Baseline mean (SD)	6.47 (1.47)	7.47 (1.36)
Number (observed/imputed)	12 (9/3)	12 (11/1)
Mean % change (SD)	-26.94 (39.53)	-44.68 (35.21)
LS Mean % change (SE) ^a	-22.59 (10.53)	-43.30 (9.11)
LS Mean Diff vs. placebo (95% CI) ^a		-20.72 (-48.60, 7.17)
LS Mean Diff vs. placebo (90% CI) ^a		-20.72 (-44.11, 2.68)
≥median (22.30)		
Baseline mean (SD)	7.51 (0.96)	7.76 (1.36)
Number (observed/imputed)	14 (8/6)	24 (12/12)
Mean % change (SD)	1.85 (26.32)	-15.10 (36.46)
LS Mean % change (SE) ^a	1.70 (8.27)	-15.43 (6.67)
LS Mean Diff vs. placebo (95% CI) ^a		-17.13 (-38.02, 3.75)
LS Mean Diff vs. placebo (90% CI) ^a		-17.13 (-34.66, 0.39)
Overall p-value for interaction ^b		0.8516
Screening IgE levels (UI/mL)		
<300		
Baseline mean (SD)	6.87 (1.08)	7.60 (1.35)
Number (observed/imputed)	9 (7/2)	11 (8/3)
Mean % change (SD)	-18.93 (37.79)	-35.24 (35.84)
LS Mean % change (SE) ^a	-14.10 (11.51)	-35.80 (9.61)
LS Mean Diff vs. placebo (95% CI) ^a		-21.70 (-51.68, 8.28)
LS Mean Diff vs. placebo (90% CI) ^a		-21.70 (-46.85, 3.46)
≥300		
Baseline mean (SD)	7.08 (1.46)	7.62 (1.38)
Number (observed/imputed)	17 (10/7)	25 (15/10)
Mean % change (SD)	-7.47 (34.78)	-20.44 (39.10)
LS Mean % change (SE) ^a	-6.98 (8.71)	-26.38 (7.35)
LS Mean Diff vs. placebo (95% CI) ^a		-19.40 (-41.94, 3.13)
LS Mean Diff vs. placebo (90% CI) ^a		-19.40 (-38.31, -0.49)
Overall p-value for interaction ^b		0.8618
Region ^c		
South America		
Baseline mean (SD)	6.98 (1.26)	7.57 (0.87)
Number (observed/imputed)	7 (4/3)	13 (8/5)
Mean % change (SD)	-4.47 (30.37)	-24.46 (34.91)
LS Mean % change (SE) ^a	-0.43 (13.89)	-37.24 (10.13)
LS Mean Diff vs. placebo (95% CI) ^a		-36.82 (-71.46, -2.17)
LS Mean Diff vs. placebo (90% CI) ^a		-36.82 (-65.89, -7.75)
North America		
Baseline mean (SD)	6.96 (1.64)	7.86 (1.90)
Number (observed/imputed)	10 (6/4)	14 (8/6)
Mean % change (SD)	-16.05 (38.78)	-32.29 (46.59)
LS Mean % change (SE) ^a	-14.09 (12.18)	-29.74 (9.92)
LS Mean Diff vs. placebo (95% CI) ^a		-15.65 (-46.53, 15.24)
LS Mean Diff vs. placebo (90% CI) ^a		-15.65 (-41.57, 10.27)
Other (Europe)		
Baseline mean (SD)	7.07 (1.10)	7.28 (0.76)

	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Number (observed/imputed)	9 (7/2)	9 (7/2)
Mean % change (SD)	-11.74 (38.61)	-14.28 (28.71)
LS Mean % change (SE) ^a	-10.38 (10.46)	-19.70 (10.53)
LS Mean Diff vs. placebo (95% CI) ^a		-9.32 (-38.77, 20.13)
LS Mean Diff vs. placebo (90% CI) ^a		-9.32 (-34.04, 15.39)
Overall p-value for interaction ^b		0.5146

^a Each of the imputed complete data was analyzed by fitting an ANCOVA model with baseline PP-NRS value, study intervention group as covariate. Analysis was based on the same imputed dataset using WOCF/MI from primary analysis of the primary endpoint.

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

^c North America: USA, Canada; South America: Chile; Other (Europe): Czech Republic, Germany, Netherlands, Poland.

Note: Data collected after study intervention discontinuation were included. Data post the use of any rescue medication or phototherapy were set to missing and imputed by WOCF. Missing data after study intervention discontinuation due to lack of efficacy were imputed by WOCF, and other missing data were imputed by MI. Descriptive statistics at Week 16 include participants whose values were imputed using WOCF at Week 16, and participants whose values were imputed by MI at Week 16 were excluded from the descriptive analysis.

Safety

[00270] In general, rilzabrutinib was well tolerated with an acceptable safety profile in AD patients. In the 400 mg BID rilzabrutinib cohort, 55.6% of patients receiving either the placebo or rilzabrutinib experienced a TEAE (see **Table 34**). Meanwhile, in the 400 mg TID cohort, 61.3% of patients who received the placebo and 79.2% of patients who received rilzabrutinib experienced a TEAE. The most frequent TEAEs were infections, which occurred at a higher rate in patients receiving the placebo, and gastrointestinal effects (*e.g.*, nausea and diarrhea). No ALT increase above 3X ULN was observed in patients receiving rilzabrutinib. Furthermore, while two patients experienced SAEs, no deaths occurred.

[00271] **Table 34. Overview of Adverse Event Profile: Treatment-Emergent Adverse Events (Safety Population)**

n (%)	BID cohort		TID cohort	
	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Participants with any TEAE	10 (55.6)	15 (55.6)	19 (61.3)	38 (79.2)
Participants with any severe TEAE	0	1 (3.7)	1 (3.2)	3 (6.3)
Participants with any treatment emergent SAE	0	0	1 (3.2)	1 (2.1)
Participants with any TEAE leading to death	0	0	0	0

n (%)	BID cohort		TID cohort	
	Placebo (N=18)	Rilzabrutinib 400mg BID (N=27)	Placebo (N=31)	Rilzabrutinib 400mg TID (N=48)
Participants with any TEAE leading to permanent study intervention discontinuation	0	2 (7.4)	2 (6.5)	9 (18.8)
Participants with any treatment emergent AESI	3 (16.7)	0	2 (6.5)	0
Participants with any TEAE related to IMP	1 (5.6)	11 (40.7)	4 (12.9)	23 (47.9)

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

Note: One participant (ID: 017207-528-0001-00001) in rilzabrutinib 400mg BID group had pre-treatment AE leading to permanent study discontinuation, and this participant was not counted in this table.

Example 3: Rilzabrutinib Reduces Expression of Itch-Associated Biomarkers

[00272] Serum samples were collected from the study described in Example 2, and the effect of rilzabrutinib treatment on the expression of itch-associated biomarkers was evaluated. Over the course of this 16 week, double-blind, placebo controlled study, N=124 patients with atopic dermatitis (AD) were administered a placebo, 800 mg/day (400 mg BID) rilzabrutinib, or 1200 mg/day (400 mg TID) rilzabrutinib.

[00273] For all cohorts, serum samples were collected at baseline, Week 2, Week 8, and Week 16. Serum levels of the Th2-related cytokine thymus and activation-regulated chemokine (TARC) were measured using an ELISA assay. Notably, rilzabrutinib treatment led to a reduction in serum TARC levels (**Figure 11**). Patients receiving 800 mg/day and 1200 mg/day rilzabrutinib exhibited an 11.4% and 34.5% reduction in median total serum levels of TARC, respectively, relative to patients receiving the placebo.

[00274] At baseline and Week 16, lesional and non-lesional skin samples were collected, using a tape-stripping procedure, from 24 patients in the 800 mg/day cohort and 27 patients in the 1200 mg/day cohort. RNA sequencing (RNA-seq) was performed on the skin tape strips, and gene set enrichment analysis was used to identify pathways of genes altered following rilzabrutinib treatment (*see* Subramanian A et al., 2005).

[00275] At Week 16, lesional skin samples exhibited a downregulation of various itch-related pathways (NGF-TrkA, TPH1, IL-31, NMBR, Alox5AP, and TPS1; **Figure 12**).

[00276] More pronounced effects were observed for NGF (a neurotrophic factor that binds to TrkA receptor and mediates nerve development and neuronal sensitivity to stimuli), TPH1 (serotonin biosynthesis), IL-31 (a pro-inflammatory pruritogenic cytokine that induces itch upon receptor binding), and NMBR (binding of the neuropeptide, neuromedin B, to NMBR induces transmission of itch signals pathways). Consistent with this, a slight reduction in median serum IL-31 levels was also observed with rilzabrutinib 1200 mg/day at Week 16 (0.44% decrease vs placebo; data not shown).

[00277] Thus, RNA-seq and supervised gene set enrichment analysis data show that inhibition of BTK with rilzabrutinib dampens itch signaling not only through inhibition of pruritogen secretion but also by reducing neurosensory signaling.

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Embodiments:

Non-limiting embodiments of the disclosure include:

1. A method of treating itch associated with atopic dermatitis (AD) 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).
2. A method of treating itch associated with prurigo nodularis (PN) 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).

3. A method of treating itch associated with atopic dermatitis (AD) 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, wherein the human patient in need thereof has at least one of:
 - (a) an inadequate response to topical corticosteroids (TCS); and
 - (b) an intolerance to TCS.
4. A method of treating itch associated with prurigo nodularis (PN) 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, wherein the human patient in need thereof has at least one of:
 - (a) an inadequate response to topical corticosteroids (TCS); and
 - (b) an intolerance to TCS.
5. The method of any one of Embodiments 1-4, wherein the human patient has moderate-to-severe AD.
6. The method of any one of Embodiments 1-5, wherein the human patient has moderate AD.
7. The method of any one of Embodiments 1-5, wherein the human patient has severe AD.
8. The method of any one of Embodiments 1-7, wherein the human patient has an inadequate response to topical corticosteroids (TCS).

9. The method of any one of Embodiments 1-8, wherein the human patient has an intolerance to TCS.
10. The method of any one of Embodiments 1-9, wherein the human patient has at least two, for example, at least three, at least four, at least five, at least six, or all of the following characteristics:
 - (a) a history of atopic dermatitis (AD) for at least 12 months;
 - (b) an Eczema Area and Severity Index (EASI) score ≥ 12 ;
 - (c) an Investigator's Global Assessment (IGA) score ≥ 3 on the 0 to 4 IGA scale;
 - (d) a body surface area (BSA) of AD involvement score ≥ 10 ;
 - (e) an inadequate response or intolerance to topical corticosteroids (TCS) within 6 months prior to treatment;
 - (f) an inadequate response to one or more of cyclosporine, methotrexate, azathioprine, and mycophenolate; and
 - (g) a baseline Peak Pruritis Numerical Rating Scale (PP-NRS) score for maximum itch intensity of ≥ 4 .
11. The method of any one of Embodiments 1-10, wherein the human patient achieves a Peak Pruritis Numerical Rating Scale (PP-NRS) score that is lower than baseline PP-NRS.
12. The method of any one of Embodiments 1-11, wherein the human patient achieves a PP-NRS score that is at least four points lower than baseline PP-NRS.
13. The method of any one of Embodiments 1-12, wherein the human patient achieves a PP-NRS score that is lower than baseline PP-NRS within three weeks of treatment.
14. The method of any one of Embodiments 1-13, wherein the human patient achieves a PP-NRS score that is at least four points lower than baseline PP-NRS within three weeks of treatment.
15. The method of any one of Embodiments 1-14, wherein the human patient achieves a PP-NRS score that is lower than baseline PP-NRS within two weeks of treatment.

16. The method of any one of Embodiments 1-15, wherein the human patient achieves a PP-NRS score that is lower than baseline PP-NRS within one week of treatment.
17. The method of any one of Embodiments 1-16, wherein the human patient achieves a PP-NRS score that is at least four points lower than baseline PP-NRS within one week of treatment.
18. The method of any one of Embodiments 1-17, wherein the human patient has baseline IgE levels of <300 UI/mL.
19. The method of any one of Embodiments 1-18, wherein the human patient has baseline IgE levels ≥ 300 UI/mL.
20. The method of any one of Embodiments 1-19, wherein the human patient receives at least one concomitant treatment chosen from: low-to-medium potency TCS, topical crisaborole, and topical calcineurin inhibitors.
21. The method of any one of Embodiments 1-20, wherein the treatment period is at least 16 weeks.
22. The method of any one of Embodiments 1-21, comprising administering to the human patient 400 mg of at least one compound chosen from rilzabrutinib and pharmaceutically acceptable salts thereof.
23. The method of any one of Embodiments 1-22, wherein the at least one compound consists of at least one compound chosen from the (E) isomer of rilzabrutinib and pharmaceutically acceptable salts thereof.
24. The method of any one of Embodiments 1-22, wherein the at least one compound consists of at least one compound chosen from the (Z) isomer of rilzabrutinib and pharmaceutically acceptable salts thereof.
25. The method of any one of Embodiments 1-22, 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.

26. The method of any one of the preceding Embodiments, comprising administering to the human patient rilzabrutinib twice or thrice a day.
27. The method of any one of the preceding Embodiments, comprising administering to the human patient 400 mg of rilzabrutinib twice or thrice a day.
28. The method of any one of Embodiments 1-27, comprising administering to the human patient 400 mg of rilzabrutinib twice a day.
29. The method of any one of Embodiments 1-27, comprising administering to the human patient 400 mg of rilzabrutinib thrice a day.
30. The method of any one of Embodiments 1-23 or 26-29, wherein the at least one compound is the (E) isomer of rilzabrutinib.
31. The method of any one of Embodiments 1-22, 24, or 26-29, wherein the at least one compound is the (Z) isomer of rilzabrutinib.
32. The method of any one of Embodiments 1-22 or 25-29, wherein the at least one compound consists of a mixture of (E) and (Z) isomers of rilzabrutinib.
33. The method of any one of the preceding Embodiments, wherein the at least one compound is orally administered to the human patient.
34. 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.
35. The method of any one of the preceding Embodiments, wherein the at least one compound is administered with water.
36. The method of any one of Embodiments 1-25 and 33-35, wherein the at least one compound is rilzabrutinib.

37. The method of any one of Embodiments 1, 2, and 5-36, wherein the method further comprises administering at least one topical corticosteroid (TCS).
38. The method of Embodiment 37, wherein the patient is administered the TCS prior to administration of the 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.
39. The method of Embodiment 37, wherein the patient is administered the TCS after administration of the 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.
40. The method of Embodiment 37, wherein the patient is administered both the TCS and the 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 on the same day or days.
41. The method of any one of Embodiments 1-36, wherein the only therapeutic agent administered is the 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.
42. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction in serum levels of TARC or IL-31.
43. The method of any one of the preceding Embodiments, wherein the human patient achieves at least a 10% reduction in serum levels of TARC.
44. The method of any one of the preceding Embodiments, wherein the human patient achieves at least a 20% reduction in serum levels of TARC.

45. The method of any one of the preceding Embodiments, wherein the human patient achieves at least a 30% reduction in serum levels of TARC.
46. The method of any one of the preceding Embodiments, wherein the human patient achieves a reduction in the expression of one or more of NGF-TrkA, TPH1, IL-31, NMBR, Alox5AP, and TPS1 in lesional skin.
47. 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof.
48. 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof.
49. 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof.
50. 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof.

51. 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof, wherein the patient has at least one of an inadequate response to topical corticosteroids (TCS); and an intolerance to TCS.
52. 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof, wherein the patient has at least one of an inadequate response to topical corticosteroids (TCS); and an intolerance to TCS.
53. 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof, wherein the patient has at least one of an inadequate response to topical corticosteroids (TCS); and an intolerance to TCS.
54. 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof, wherein the patient has at least one of an inadequate response to topical corticosteroids (TCS); and an intolerance to TCS.

[00278] 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.

[00279] 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.

[00280] 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 itch associated with atopic dermatitis (AD) 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. A method of treating itch associated with prurigo nodularis (PN) 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).
3. A method of treating itch associated with atopic dermatitis (AD) 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, wherein the human patient in need thereof has at least one of:
 - (a) an inadequate response to topical corticosteroids (TCS); and
 - (b) an intolerance to TCS.
4. A method of treating itch associated with prurigo nodularis (PN) 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, wherein the human patient in need thereof has at least one of:
 - (a) an inadequate response to topical corticosteroids (TCS); and
 - (b) an intolerance to TCS.

5. The method of any one of claims 1-4, wherein the human patient has moderate-to-severe AD.
6. The method of any one of the preceding claims, wherein the human patient has moderate AD.
7. The method of any one of claims 1-5, wherein the human patient has severe AD.
8. The method of any one of the preceding claims, wherein the human patient has an inadequate response to topical corticosteroids (TCS).
9. The method of any one of the preceding claims, wherein the human patient has an intolerance to TCS.
10. The method of any one of the preceding claims, wherein the human patient has at least two, for example, at least three, at least four, at least five, at least six, or all of the following characteristics:
 - (a) a history of atopic dermatitis (AD) for at least 12 months;
 - (b) an Eczema Area and Severity Index (EASI) score ≥ 12 ;
 - (c) an Investigator's Global Assessment (IGA) score ≥ 3 on the 0 to 4 IGA scale;
 - (d) a body surface area (BSA) of AD involvement score ≥ 10 ;
 - (e) an inadequate response or intolerance to topical corticosteroids (TCS) within 6 months prior to treatment;
 - (f) an inadequate response to one or more of cyclosporine, methotrexate, azathioprine, and mycophenolate; and
 - (g) a baseline Peak Pruritis Numerical Rating Scale (PP-NRS) score for maximum itch intensity of ≥ 4 .
11. The method of any one of the preceding claims, wherein the human patient achieves a Peak Pruritis Numerical Rating Scale (PP-NRS) score that is lower than baseline PP-NRS.

12. The method of any one of the preceding claims, wherein the human patient achieves a PP-NRS score that is at least four points lower than baseline PP-NRS.
13. The method of any one of the preceding claims, wherein the human patient achieves a PP-NRS score that is lower than baseline PP-NRS within three weeks of treatment.
14. The method of any one of the preceding claims, wherein the human patient achieves a PP-NRS score that is at least four points lower than baseline PP-NRS within three weeks of treatment.
15. The method of any one of the preceding claims, wherein the human patient achieves a PP-NRS score that is lower than baseline PP-NRS within two weeks of treatment.
16. The method of any one of the preceding claims, wherein the human patient achieves a PP-NRS score that is lower than baseline PP-NRS within one week of treatment.
17. The method of any one of the preceding claims, wherein the human patient achieves a PP-NRS score that is at least four points lower than baseline PP-NRS within one week of treatment.
18. The method of any one of claims 1-17, wherein the human patient has baseline IgE levels of <300 UI/mL.
19. The method of any one of claims 1-17, wherein the human patient has baseline IgE levels ≥ 300 UI/mL.
20. The method of any one of the preceding claims, wherein the human patient receives at least one concomitant treatment chosen from: low-to-medium potency TCS, topical crisaborole, and topical calcineurin inhibitors.
21. The method of any one of the preceding claims, wherein the treatment period is at least 16 weeks.

22. The method of any one of the preceding claims, comprising administering to the human patient 400 mg of at least one compound chosen from rilzabrutinib and pharmaceutically acceptable salts thereof.
23. The method of any one of claims 1-22, wherein the at least one compound consists of at least one compound chosen from the (E) isomer of rilzabrutinib and pharmaceutically acceptable salts thereof.
24. The method of any one of claims 1-22, wherein the at least one compound consists of at least one compound chosen from the (Z) isomer of rilzabrutinib and pharmaceutically acceptable salts thereof.
25. The method of any one of claims 1-22, 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.
26. The method of any one of the preceding claims, comprising administering to the human patient rilzabrutinib twice or thrice a day.
27. The method of any one of the preceding claims, comprising administering to the human patient 400 mg of rilzabrutinib twice or thrice a day.
28. The method of any one of claims 1-27, comprising administering to the human patient 400 mg of rilzabrutinib twice a day.
29. The method of any one of claims 1-27, comprising administering to the human patient 400 mg of rilzabrutinib thrice a day.
30. The method of any one of claims 1-23 or 26-29, wherein the at least one compound is the (E) isomer of rilzabrutinib.
31. The method of any one of claims 1-22, 24, or 26-29, wherein the at least one compound is the (Z) isomer of rilzabrutinib.

32. The method of any one of claims 1-22 or 25-29, wherein the at least one compound consists of a mixture of (E) and (Z) isomers of rilzabrutinib.
33. The method of any one of the preceding claims, wherein the at least one compound is orally administered to the human patient.
34. 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.
35. The method of any one of the preceding claims, wherein the at least one compound is administered with water.
36. The method of claims 1-25 and 33-35, wherein the at least one compound is rilzabrutinib.
37. The method of any one of claims 1, 2, and 5-36, wherein the method further comprises administering at least one topical corticosteroid (TCS).
38. The method of claim 37, wherein the patient is administered the TCS prior to administration of the 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.
39. The method of claim 37, wherein the patient is administered the TCS after administration of the 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.
40. The method of claim 37, wherein the patient is administered both the TCS and the 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 on the same day or days.

41. The method of any one of claims 1-36, wherein the only therapeutic agent administered is the 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.
42. The method of any one of the preceding claims, wherein the human patient achieves a reduction in serum levels of TARC or IL-31.
43. The method of any one of the preceding claims, wherein the human patient achieves at least a 10% reduction in serum levels of TARC.
44. The method of any one of the preceding claims, wherein the human patient achieves at least a 20% reduction in serum levels of TARC.
45. The method of any one of the preceding claims, wherein the human patient achieves at least a 30% reduction in serum levels of TARC.
46. The method of any one of the preceding claims, wherein the human patient achieves a reduction in the expression of one or more of NGF-TrkA, TPH1, IL-31, NMBR, Alox5AP, and TPS1 in lesional skin.
47. 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof.
48. 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof.

49. 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof.
50. 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof.
51. 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof, wherein the patient has at least one of an inadequate response to topical corticosteroids (TCS); and an intolerance to TCS.
52. 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof, wherein the patient has at least one of an inadequate response to topical corticosteroids (TCS); and an intolerance to TCS.
53. 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof, wherein the patient has at

least one of an inadequate response to topical corticosteroids (TCS); and an intolerance to TCS.

54. 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 itch associated with prurigo nodularis (PN) in a human patient in need thereof, wherein the patient has at least one of an inadequate response to topical corticosteroids (TCS); and an intolerance to TCS.