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Sponsor: Pfizer Inc.

Investigational Product: PF-06651600 (ritlecitinib)

Clinical Study Report Synopsis: Protocol B7981015

Protocol Title: A Phase 2b/3 Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Investigate the Efficacy and Safety of PF-06651600 in Adult and Adolescent Alopecia Areata (AA) Subjects With 50% or Greater Scalp Hair Loss

Investigators: Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

Study Center(s): Refer to Appendix 16.1.4.1 for a list of sites involved in this study.

Publications Based on the Study: None

Study Initiation Date: 03 December 2018

Study Completion Date: 24 June 2021

Report Date: 11 March 2022

Previous Report Date(s): 22 December 2021

Phase of Development: Phase 2b/3

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Primary and Secondary Study Objectives and Endpoints:

Table S1. Study Objectives and Endpoints

Primary Objective	**Primary Endpoint**
To evaluate the efficacy of ritlecitinib compared to placebo in adult and adolescent AA participants with 50% or greater scalp hair loss on regrowth of lost hair (measured by an absolute Severity of Alopecia Tool (SALT) Score ≤20) at Week 24. Note: For the European Medicines Agency (EMA) and competent authorities in the Voluntary Harmonisation Procedure (VHP) countries,[a] the primary objective was to evaluate the efficacy of ritlecitinib compared to placebo in adult and adolescent AA participants with 50% or greater scalp hair loss on regrowth of lost hair (measured by an absolute SALT Score ≤10) at Week 24.	• Response based on an absolute SALT Score ≤20 at Week 24. Note: For the EMA and competent authorities in the VHP countries, response based on an absolute SALT Score ≤10 at Week 24 was analyzed as the primary endpoint in a separate analysis.
Key Secondary Objective	**Key Secondary Endpoint**
To evaluate the efficacy of ritlecitinib compared to placebo in adult and adolescent AA participants with 50% or greater scalp hair loss on regrowth of lost hair (as measured by an absolute SALT Score ≤10) at Week 24. Note: This key secondary objective was utilized as the primary objective for the EMA and competent authorities in the VHP countries. Additionally, this key secondary objective did not apply for the Food and Drug Administration (FDA)/ Pharmaceutical and Medical Devices Agency (PMDA).	• Response based on an absolute SALT Score ≤10 at Week 24. Note: This key secondary endpoint was utilized as the primary endpoint for the EMA and competent authorities in the VHP countries. Additionally, this key secondary endpoint did not apply for the FDA/PMDA.
To evaluate the effect of ritlecitinib on patient centered outcomes (as measured by Patient's Global Impression of Change [PGI-C] response) at Week 24. Note: This key secondary objective was only applicable for the EMA and competent authorities in the VHP countries.	• PGI-C response defined as a score of "moderately improved" or "greatly improved" at Week 24. Note: This key secondary endpoint was only applicable for the EMA and competent authorities in the VHP countries.
Secondary Objectives	**Secondary Endpoints**
To characterize the exposure response of ritlecitinib on regrowth of lost hair.	• Response based on an absolute SALT Score ≤20 at Week 24 was used to characterize the exposure response. Note: For the EMA and competent authorities in the VHP countries, response based on an absolute SALT score ≤10 at Week 24 was used to characterize the exposure response.
To assess the efficacy of ritlecitinib on regrowth of lost hair during the treatment period over time.	• Response based on an absolute SALT score ≤20 at Weeks 4, 8, 12, 18, 28, 34, 40, and 48.[b,c] • Response based on an absolute SALT score ≤10 at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.[d] • Response based on 75% improvement in SALT score from baseline (BL) ($SALT_{75}$) at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48. • Change from Baseline (CFB) in SALT scores at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48. • Response based on at least a 2-grade improvement from BL or a score of 3 in eyebrow assessment (EBA) score at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48. • Response based on at least a 2-grade improvement from BL or a score of 3 in eyelash assessment (ELA) score at

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Table S1. Study Objectives and Endpoints

	Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.
• To evaluate the effect of ritlecitinib on patient-centered outcomes and payer relevant measures to assess treatment benefit from the patient perspective and to demonstrate value.[e]	• PGI-C response defined as a PGI-C score of "moderately improved" or "greatly improved" at Weeks 4, 8, 12, 18, 24, 34, 40, and 48.[e] • CFB in alopecia areata patient priority outcomes (AAPPO) scales at Weeks 4, 8, 12, 18, 24, 34, 40, and 48.
Safety Objective	**Safety Endpoints**
• To evaluate the safety and tolerability of ritlecitinib in the treatment period over time.	• Incidence of treatment-emergent adverse events (TEAE). • Incidence of serious adverse events (SAE) and adverse events (AE) leading to discontinuation. • The incidence of clinically significant abnormalities in vital signs. • The incidence of clinically significant abnormalities in clinical laboratory values.
Pharmacokinetic (PK) Objective	**PK Endpoints**
• To characterize pharmacokinetics of ritlecitinib.	• Plasma concentrations of ritlecitinib at Weeks 4, and 8 or 12.
Exploratory Objectives	**Exploratory Endpoints**
• To collect banked biospecimens for exploratory research, unless prohibited by local regulations or ethics committee decision.	• Collection of banked biospecimens unless prohibited by local regulations or ethics committee decision. Additional information on collection and potential use is provided in in the study protocol.
• To assess the efficacy of ritlecitinib on regrowth of lost hair during the treatment period over time.	• Response based on 50% improvement in SALT score from BL ($SALT_{50}$) at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48. • Absolute SALT scores at BL, Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.
• To evaluate the effect of ritlecitinib on patient-centered outcomes and payer relevant measures to assess treatment benefit from the patient perspective and to demonstrate value.	• Improvement on PGI-C defined as "slightly improved", "moderately improved", or "greatly improved" at Weeks 4, 8, 12, 18, 24, 34, 40, and 48. • Improvement on Patient Satisfaction with Hair Growth (P-Sat) items, defined as slightly, moderately, or very satisfied, at Weeks 4, 8, 12, 18, 24, 34, 40, and 48. • CFB in EQ-5D-5L in adults or EQ-5D-Y in adolescents at Weeks 4, 12, 24, and 48. • CFB in alopecia areata resource utilization (AARU) at Weeks 12, 24, 34, and 48. • CFB in work productivity and activity impairment: alopecia areata (WPAI:AA) at Weeks 12, 24, 34, and 48. • CFB in the depression subscale score of the Hospital Anxiety and Depression scale (HADS) at Weeks 4, 8, 12, 24, and 48.[f] • CFB in the anxiety subscale score of the HADS at Weeks 4, 8, 12, 24, and 48.[f] • Improvement on HADS among participants with a BL subscale score indicative of depression who achieved a "normal' subscale score indicative of an absence of depression at Weeks 4, 8, 12, 24, and 48.[f] • Improvement on HADS among participants with a BL subscale score indicative of anxiety who achieved a "normal' subscale score indicative of an absence of anxiety at Weeks 4, 8, 12, 24, and 48.[f] • CFB in the 36 Item Short Form Health Survey version 2 (SF36v2) Acute at Weeks 4, 8, 12, 24, and 48.

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Table S1. Study Objectives and Endpoints

• To evaluate the effect of ritlecitinib on the clinician global impression of severity of scalp hair loss.	• CFB in Clinician Global Impression – Alopecia Areata (CGI-AA) at Weeks 4, 8, 12, 18, 24, 28, 34, 40, and 48.
• To evaluate efficacy of ritlecitinib in AA nail disease over time.	• CFB in fingernails affected by AA at Weeks 12, 24, 34, 40, and 48.
• To assess pharmacodynamic and disease-related biomarkers over time.	• CFB in interferon gamma-induced protein-10 (IP-10) at Weeks 4, 8, 12, and 24. • CFB in percent and absolute lymphocyte subsets (TBNK) at Weeks 4, 12, 24, and 48. • CFB in immunoglobulins (IgA, IgG, IgM) at Weeks 24 and 48.

a. The VHP countries participating in this study are Czech Republic, Germany, Hungary, Poland, and Spain.
b. For the EMA and competent authorities in the VHP countries, when SALT ≤10 is utilized for the primary endpoint, SALT ≤20 at Week 24 will be analyzed as a secondary endpoint.
c. When SALT ≤20 response at Week 24 is utilized as the primary endpoint, responses based on absolute SALT score ≤20 at Weeks 18, 12, 8 and 4 will be analyzed controlling for Type I error utilizing an appropriate testing procedure. When SALT ≤10 response at Week 24 is utilized as the primary endpoint, the response based on absolute SALT score ≤20 at Week 24 will be analyzed controlling for Type I error utilizing an appropriate testing procedure.
d. When SALT ≤20 response at Week 24 is utilized as the primary endpoint, the response based on absolute SALT score ≤10 at Week 24 will be analyzed controlling for Type I error utilizing an appropriate testing procedure. When SALT ≤10 response at Week 24 is utilized as the primary endpoint, the responses based on absolute SALT score ≤10 at Weeks 18, 12, 8 and 4 will be analyzed controlling for Type I error utilizing an appropriate testing procedure.
e. For the EMA and competent authorities in the VHP countries, the evaluation of the effect of ritlecitinib on patient centered outcomes (as measured by PGI-C response at Week 24) is a key secondary objective. The PGI-C response at Week 24 will be analyzed as a key secondary endpoint utilizing an appropriate testing procedure to control overall Type I error.
f. For the EMA and competent authorities in the VHP countries, endpoints utilizing the HADS will be analyzed as secondary endpoints.

METHODS

Study Design

This study evaluated the efficacy and safety of multiple doses/regimens of ritlecitinib (PF-06651600) compared with placebo in adult and adolescent participants with alopecia areata (AA) having 50% or greater scalp hair loss over 24 weeks of treatment (Placebo-Controlled Period). This was followed by a 24-week Extension Period, during which all participants received ritlecitinib, including participants who had received placebo during the initial 24 weeks (Figure S1).

In this report, treatment groups during the Placebo-Controlled Period are referred to as 200/50 mg, 200/30 mg, 50 mg, 30 mg, 10 mg, and placebo. Treatment groups during the Extension Period are referred to in the same way, except for participants from placebo who transitioned to active treatment, referred to as pbo-200/50 mg, and pbo-50 mg (Figure S1).

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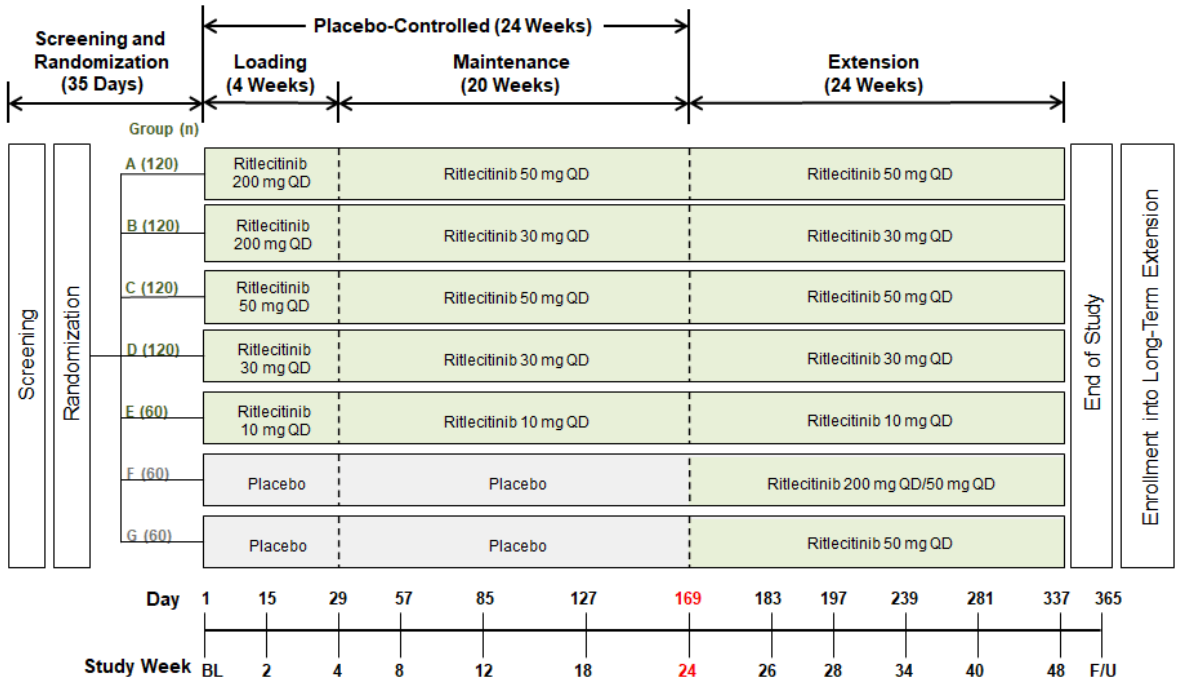
Figure S1. Study Design



Diagnosis and Main Criteria for Inclusion

Inclusion Criteria

Key inclusion criteria were:

- Male or female participants ≥12 years of age at time of informed consent/assent.
- Adolescent participants below the age of 18 years were only enrolled in this study if permitted by the sponsor, local competent authority, and Institutional Review Board (IRB)/Ethics Committee (EC).
- Otherwise, only participants ≥18 years of age (or age specified by applicable reviewer) were enrolled in those countries, regions, or sites. Within VHP countries in the European Union (EU), participants had to be between 18 and 74 years of age (inclusive) at the time of informed consent.
- Had to meet the following AA criteria:
    a. A clinical diagnosis of AA with no other etiology of hair loss (eg, telogen effluvium, androgenic alopecia, etc.).
    b. ≥50% hair loss on the scalp (measured by SALT), including alopecia totalis (AT) (complete [100%] scalp hair loss) and alopecia universalis (AU) (complete

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[100%] scalp, facial, and body hair loss), without evidence of terminal hair regrowth within 6 months at both Screening and BL visits.

- Photographs taken at Screening were submitted to the Sponsor or designee for verification of SALT score ≥50 and hair loss due to AA. Participants were not randomized until verification was confirmed.

c. Current episode of hair loss ≤10 years.

Exclusion Criteria

Key exclusion criteria were:

- Other types of alopecia (including, but not limited to, traction and scarring alopecia, telogen effluvium). Participants with known androgenic alopecia were excluded.
- Other scalp disease that could impact AA assessment (eg, scalp psoriasis, dermatitis, etc.).
- Active systemic diseases that could cause hair loss (eg, lupus erythematosus, thyroiditis, systemic sclerosis, lichen planus, etc.).
- Any of the psychiatric conditions as described in the protocol.
- Hearing loss with progression over the previous 5 years, sudden hearing loss, middle or inner ear disease, or other auditory condition considered acute, fluctuating, or progressive.
- Previous use of any JAK inhibitor for use in any disease indication or any non-B-cell selective lymphocyte-depleting agent.
- Current or recent history of clinically significant severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine (particularly thyroid disease which can be associated with hair loss), pulmonary, cardiovascular, psychiatric, immunologic/rheumatologic or neurologic disease; or have any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that could increase the risk associated with study participation or study intervention administration, or interfere with the interpretation of study results; or in the opinion of the investigator or Pfizer (or designee), the participant was inappropriate for entry into this study.
- Any present malignancies or history of malignancies, except for adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.
- History of any lymphoproliferative disorder, history of lymphoma, history of leukemia, or signs and symptoms suggestive of current lymphatic or lymphoid disease.

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- History (single episode) of disseminated herpes zoster or disseminated herpes simplex, or a recurrent (more than one episode of) localized, dermatomal herpes zoster.

- Adolescent participants 12 to <18 years old without a documented history of varicella zoster virus (VZV) vaccination or presence of VZV immunoglobulin (IgG) antibodies (Ab).

- History of systemic infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator within 6 months prior to Day 1.

- Active acute or chronic infection requiring treatment with oral antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks prior to Day 1 or superficial skin infection within 1 week prior to Day 1. NOTE: participants could be rescreened after the infection resolved.

- Known immunodeficiency disorder, including positive serology for human immunodeficiency virus (HIV) at Screening or a first-degree relative with a hereditary immunodeficiency.

- Infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) according to the Protocol-specified testing algorithm.

- Evidence of untreated or inadequately treated active or latent Mycobacterium tuberculosis (TB) infection as evidenced by the any of the criteria listed in the Protocol.

Study Treatment

Table S2. Investigational Product Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/ Potency	Dosage Form
Placebo 10 mm tablet	n/a	18-001558 18-001559 18-001560 18-001556 18-001557 19-000043 17-001175	0 mg	Tablet
Placebo 6 mm tablet	n/a	18-001563 18-001564 18-003539 16-005309 17-002906	0 mg	Tablet
PF-06651600-15 10 mg Round white to off-white tablet	n/a	18-003614 18-001307 19-000951 17-004591	10 mg	Tablet
PF-06651600-15 50 mg Round white to off-white tablet	n/a	18-003616 18-000399	50 mg	Tablet

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Table S2. Investigational Product Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/ Potency	Dosage Form
		19-001387 17-004590 18-001308		

Efficacy Evaluations

Efficacy evaluations were done at study visits as described in Table S1.

SALT is a quantitative assessment of AA severity based on scalp terminal hair loss. SALT ≤20 indicates less than or equal to 20% scalp hair loss; SALT ≤10 indicates less than or equal to 10% scalp hair loss.

The PGI-C asks the subject to evaluate the improvement or worsening of their AA as compared with the start of the study using a single-item, "Since the start of the study, my alopecia areata has: …". The participant selected one of seven responses ranging from "greatly improved" to "greatly worsened." PGI-C response was defined as a score of "moderately improved" or "greatly improved".

ELA is a numeric rating scale (NRS) developed to characterize eyelash hair loss. The numeric rating scale ranges from 0 (no eyelash hair) to 3 (normal eyelash hair).

EBA is an NRS developed to characterize eyebrow hair loss. The numeric rating scale ranges from 0 (no eyebrow hair) to 3 (normal eyebrow hair).

AAPPO is a self-administered questionnaire that measures hair loss, emotional symptoms, and activity limitations over the past week.

CGI-AA is a single clinician-reported item developed to assess the clinical impression of severity of scalp hair loss.

The number of fingernails affected by AA were counted at BL and all subsequent visits.

Patient-centered outcomes and payer-relevant measures included P-Sat, EQ-5D-5L (EQ-5D-Y), AARU, WPAI:AA, HADS, and SF36v2 up to Week 48.

Pharmacokinetic and Pharmacodynamic Evaluations:

To characterize the PK of ritlecitinib, plasma concentrations of ritlecitinib were measured pre-dose on Day 1 and pre-dose, 30 min, and 1, 2 or 3 hours post-dose at Weeks 4, 8, and 12.

Pharmacodynamic evaluations were as described in Table S1.

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Safety Evaluations

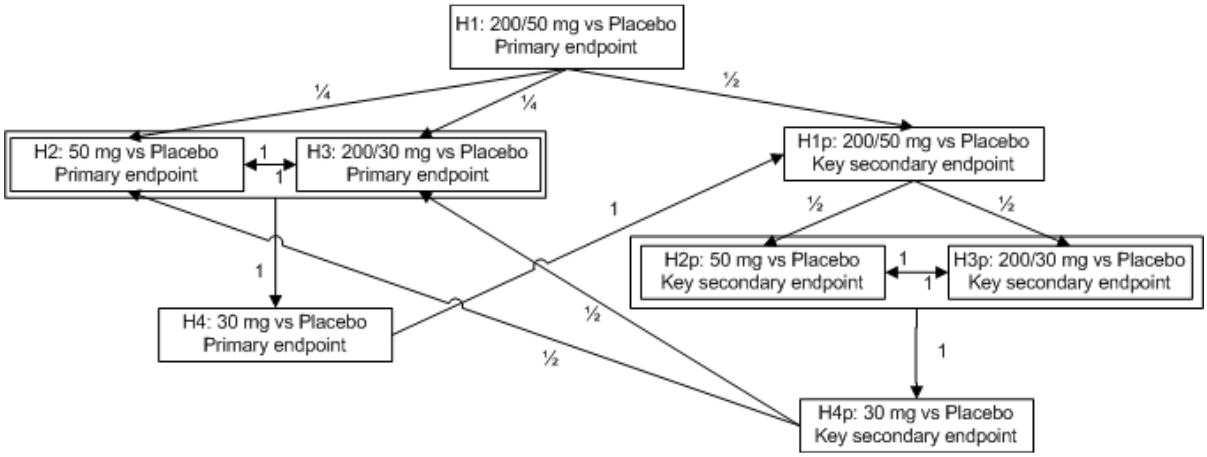
Safety evaluations included the incidence of TEAEs, SAEs, and AEs leading to discontinuation. Also included were the incidence of clinically meaningful abnormalities in vital signs, electrocardiogram (ECG), audiological evaluation, physical examination, and clinical laboratory values.

Statistical Methods

This study will support submission in several regions with different requirements. Different testing procedures for multiple comparisons were specified for the overall study, for the FDA/PMDA, and for the EMA and competent authorities in the VHP countries.

For the overall study, the SALT ≤20 response at Week 24 was the primary endpoint and the SALT ≤10 response at Week 24 was analyzed as a key secondary endpoint. The hypotheses, tested at an overall significance level (α) of 0.05, were that each ritlecitinib group was superior to placebo. A total of 8 hypotheses were tested (H1-H4, H1p-H4p). The family-wise Type I error was strongly controlled using a gatekeeping approach as shown in Figure S2.

Figure S2. Schematic and Graphical Presentation for Multiple Testing Procedure Incorporating a Key Secondary Endpoint



The numbers on each edge indicate the transition rule for the weights on alpha allocation once a hypothesis was rejected.

For the FDA/PMDA, the SALT ≤20 response at Week 24 was the primary endpoint and no endpoint was analyzed as key secondary. The hypotheses, tested at an overall significance level (α) of 0.00125, were that each ritlecitinib group was superior to placebo. A total of 4 hypotheses were tested (H1-H4). The family-wise Type I error was strongly controlled using a gate-keeping approach as shown in Figure S3.

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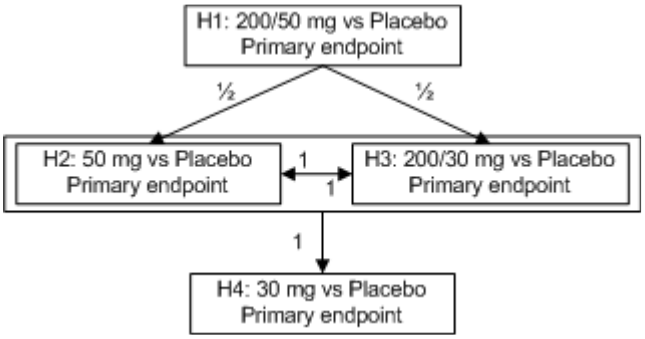
Figure S3. Schematic and Graphical Presentation for Multiple Testing Procedure Without a Key Secondary Endpoint



The numbers on each edge indicate the transition rule for the weights on alpha allocation once a hypothesis was rejected.

For the EMA and competent authorities in the VHP countries, the SALT ≤10 response at Week 24 was the primary endpoint and PGI-C response at Week 24 was analyzed as a key secondary endpoint. The hypotheses, tested at an overall significance level (α) of 0.01, were that each ritlecitinib group was superior to placebo. A total of 8 hypotheses were tested (H1-H4, H1p-H4p). The family-wise Type I error was strongly controlled using a gate-keeping approach as shown in Figure S2.

RESULTS

Participant Disposition

A total of 1097 participants were screened and 718 participants were randomized to treatment. Of these, 715 (99.6%) received treatment (3 participants were not treated) and 101 (14.1%) discontinued treatment. The number of participants discontinuing during the Placebo-Controlled Period was similar across treatment groups, except for 30 mg, which had a higher (11.4%) discontinuation rate. During the Extension Period (Week 25-48), discontinuation rates ranged from 3.8% (50 mg) to 8.5 % (200/30 mg). Overall, 614 (85.5%) of participants completed treatment (Table S3).

- During the Placebo-Controlled Period (up to Week 24), the most common reasons for discontinuation were ‘withdrawal by participant’, ‘AE’, and ‘physician decision’ (which included discontinuation due to COVID-19-related reasons).

- In the Extension Period (Weeks 25-48), the primary reasons for discontinuation were ‘lack of efficacy’, ‘withdrawal by participant’, ‘AE’, and ‘other’. Overall, the most common reasons for discontinuation were ‘withdrawal by participant’, ‘AE’, ‘Lost to Follow-up’, ‘lack of efficacy’, and ‘physician decision’(which included discontinuation due to COVID-19-related reasons).

Overall, few (24 [3.3%]) participants discontinued due to COVID-19-related reasons, and discontinuation was similar across treatment groups. The most common reasons for discontinuation due to COVID-19-related reasons were ‘withdrawal by participant’ and

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'physician decision'. The majority of these discontinuations occurred in the Placebo-Controlled period (up to Week 24) (20 [2.8%] participants).

Table S3. Disposition Events Summary up to Week 48 (FAS) (Protocol B7981015)

Number (%) of Participants	Ritlecitinib 200/50 mg QD (N=132) n (%)	Ritlecitinib 200/30 mg QD (N=130) n (%)	Ritlecitinib 50 mg QD (N=130) n (%)	Ritlecitinib 30 mg QD (N=132) n (%)	Ritlecitinib 10 mg QD (N=63) n (%)	Placebo->Ritlecitinib 200/50 mg QD (N=65) n (%)	Placebo->Ritlecitinib 50 mg QD (N=66) n (%)	Total (N=718) n (%)
Disposition Phase: Up to Week 24								
Discontinued	10 (7.6)	6 (4.6)	9 (6.9)	15 (11.4)	5 (7.9)	2 (3.1)	5 (7.6)	52 (7.2)
Adverse Event	3 (2.3)	0	2 (1.5)	4 (3.0)	2 (3.2)	0	1 (1.5)	12 (1.7)
Lack of Efficacy	0	0	0	0	0	1 (1.5)	0	1 (0.1)
Lost to Follow-Up	1 (0.8)	0	1 (0.8)	2 (1.5)	1 (1.6)	0	0	5 (0.7)
Non-Compliance With Study Drug	0	0	0	0	0	0	0	0
Physician Decision	0	1 (0.8)	2 (1.5)	5 (3.8)	0	0	1 (1.5)	9 (1.3)
Pregnancy	1 (0.8)	0	0	0	1 (1.6)	0	1 (1.5)	3 (0.4)
Protocol Deviation	1 (0.8)	1 (0.8)	0	0	0	0	0	2 (0.3)
Withdrawal By Participant	4 (3.0)	4 (3.1)	4 (3.1)	4 (3.0)	1 (1.6)	1 (1.5)	2 (3.0)	20 (2.8)
Other	0	0	0	0	0	0	0	0
Disposition Phase: EXTENSION (Week 25-48)								
Discontinued	6 (4.5)	11 (8.5)	5 (3.8)	9 (6.8)	5 (7.9)	3 (4.6)	4 (6.1)	43 (6.0)
Adverse Event	0	2 (1.5)	2 (1.5)	1 (0.8)	0	0	2 (3.0)	7 (1.0)
Lack of Efficacy	2 (1.5)	1 (0.8)	0	3 (2.3)	3 (4.8)	0	1 (1.5)	10 (1.4)
Lost to Follow-Up	0	0	2 (1.5)	1 (0.8)	1 (1.6)	2 (3.1)	0	6 (0.8)

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Table S3. Disposition Events Summary up to Week 48 (FAS) (Protocol B7981015)

Number (%) of Participants	Ritlecitinib 200/50 mg QD (N=132) n (%)	Ritlecitinib 200/30 mg QD (N=130) n (%)	Ritlecitinib 50 mg QD (N=130) n (%)	Ritlecitinib 30 mg QD (N=132) n (%)	Ritlecitinib 10 mg QD (N=63) n (%)	Placebo->Ritlecitinib 200/50 mg QD (N=65) n (%)	Placebo->Ritlecitinib 50 mg QD (N=66) n (%)	Total (N=718) n (%)
Non-Compliance With Study Drug	0	1 (0.8)	0	0	0	0	0	1 (0.1)
Physician Decision	0	1 (0.8)	0	1 (0.8)	1 (1.6)	0	0	3 (0.4)
Pregnancy	0	0	0	0	0	0	0	0
Protocol Deviation	0	0	0	0	0	0	0	0
Withdrawal By Participant	3 (2.3)	2 (1.5)	1 (0.8)	1 (0.8)	0	1 (1.5)	1 (1.5)	9 (1.3)
Other	1 (0.8)	4 (3.1)	0	2 (1.5)	0	0	0	7 (1.0)
Disposition Phase: Overall								
Discontinued	16 (12.1)	18 (13.8)	17 (13.1)	29 (22.0)	10 (15.9)	5 (7.7)	9 (13.6)	104 (14.5)
Adverse Event	3 (2.3)	2 (1.5)	4 (3.1)	5 (3.8)	2 (3.2)	0	3 (4.5)	19 (2.6)
Lack of Efficacy	2 (1.5)	1 (0.8)	0	4 (3.0)	3 (4.8)	1 (1.5)	1 (1.5)	12 (1.7)
Lost to Follow-Up	1 (0.8)	1 (0.8)	3 (2.3)	4 (3.0)	2 (3.2)	2 (3.1)	0	13 (1.8)
Non-Compliance With Study Drug	0	1 (0.8)	0	0	0	0	0	1 (0.1)
Physician Decision	0	2 (1.5)	2 (1.5)	6 (4.5)	1 (1.6)	0	1 (1.5)	12 (1.7)
Pregnancy	1 (0.8)	0	0	1 (0.8)	1 (1.6)	0	1 (1.5)	4 (0.6)
Protocol Deviation	1 (0.8)	1 (0.8)	0	0	0	0	0	2 (0.3)
Withdrawal By Participant	7 (5.3)	6 (4.6)	6 (4.6)	6 (4.5)	1 (1.6)	2 (3.1)	3 (4.5)	31 (4.3)
Other	1 (0.8)	4 (3.1)	2 (1.5)	3 (2.3)	0	0	0	10 (1.4)
Completed	116 (87.9)	112 (86.2)	113 (86.9)	103 (78.0)	53 (84.1)	60 (92.3)	57 (86.4)	614 (85.5)

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Table S3. Disposition Events Summary up to Week 48 (FAS) (Protocol B7981015)

	Ritlecitinib 200/50 mg QD (N=132)	Ritlecitinib 200/30 mg QD (N=130)	Ritlecitinib 50 mg QD (N=130)	Ritlecitinib 30 mg QD (N=132)	Ritlecitinib 10 mg QD (N=63)	Placebo->Ritlecitinib 200/50 mg QD (N=65)	Placebo->Ritlecitinib 50 mg QD (N=66)	Total (N=718)
Number (%) of Participants	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**

Information in 'Adverse Event' row was from Disposition CRF page.
Included data up to Week 48 and follow-up period (if applicable).
PFIZER CONFIDENTIAL SDTM Creation: 13JUL2021 (13:20) Source Data: adds Table Generation: 09AUG2021 (22:47)
(Database snapshot date : 12JUL2021) Output File: ./nda1 cdisc/B7981015/adds s001
Table 14.1.1.2.2 Ritlecitinib is for Pfizer internal use.

Participant Demography and Other Baseline Characteristics

Overall, demographic characteristics were balanced across treatment groups.

- The majority of participants (613 [85.4%]) were adults ≥18 years of age. The mean age of all participants was 33.7 years.

- The study randomized 105 adolescents (12 to 17 years of age), at sites in Australia, Chile, China, Japan, Mexico, Russian Federation, Republic of Korea and the US. Since randomization was stratified, the distribution of adolescent participants across treatment groups was similar.

- There were more female (62.1%) than male (37.9%) participants. Most participants were White (68.0%), 25.9% were Asian, and 3.8% were Black or African American; 12.1% were Hispanic/Latino

- The median duration since AA diagnosis (6.9 years) was similar across treatment groups. The median duration of the current AA episode was 2.5 years.

The distribution of participants by AA severity was balanced across treatment groups. This was consistent with the stratified randomization planned to achieve a target enrollment of approximately 40% AT/AU and 15% adolescent participants

- AA history was similar across treatment groups. A total of 330 (46.0%) participants were classified as AT/AU, based on a BL SALT score of 100%. Randomization was stratified by AT/AU and the distribution of participants classified as AT/AU versus non-AT/non-AU was similar across treatment groups.

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- The mean (SD) BL SALT score was similar across treatment groups, ranging from 88.3 (16.87) to 93.0 (11.50).

Efficacy Results

Treatment with ritlecitinib 200/50 mg, 200/30 mg, 50 mg and 30 mg resulted in greater scalp hair regrowth at Week 24 compared with placebo, as measured by significantly greater proportion of response based on SALT ≤20 (or SALT ≤10, as appropriate).

Primary and Key Secondary Endpoints

The study was tested at an overall significance level (α) of 0.05. While this significance level was deemed sufficient for a declaration of effect, more stringent levels have been advised by regulatory agencies for submission of this study to support marketing authorization, namely α=0.01 for the EMA and competent authorities in the VHP countries and α=0.00125 for the FDA.

The key efficacy results are therefore summarized separately for the overall study, for the FDA/PMDA and for the EMA and competent authorities in the VHP countries, based on the respective planned analyses. Key efficacy results of the primary and key secondary endpoints were:

- For the overall study, ritlecitinib 200/50 mg, 200/30 mg, 50 mg and 30 mg met the primary endpoint (response based on SALT ≤20 at Week 24) and the key secondary endpoint (response based on SALT ≤10 at Week 24) at an overall significance level (α) of 0.05.
- For the FDA/PMDA, ritlecitinib 200/50 mg, 200/30 mg, 50 mg and 30 mg met the primary endpoint (response based on SALT ≤20 at Week 24) at an overall significance level (α) of 0.00125.
- For the EMA and competent authorities in the VHP countries, ritlecitinib 200/50 mg, 200/30 mg, 50 mg and 30 mg met the primary endpoint (response based on SALT ≤10 at Week 24) and the key secondary endpoint (PGI-C response at Week 24) at an overall significance level (α) of 0.01.

Ritlecitinib 10 mg was included in the study to support the estimation of the exposure response, therefore comparison of 10 mg with placebo was not included in the overall assessment of efficacy. Comparative statistics between 10 mg and placebo groups are shown in efficacy tables for completeness only but were not part of the overall testing plan.

SALT ≤20 Response at Week 24

Analyzed as a primary endpoint for the study and for the FDA/PMDA, the proportion of participants with response based on a SALT score ≤20 at Week 24 in ritlecitinib 200/50 mg (30.65%), 200/30 mg (22.31%), 50 mg (23.39%), and 30 mg (14.29%) was significantly different from placebo (1.54%) Figure S4.

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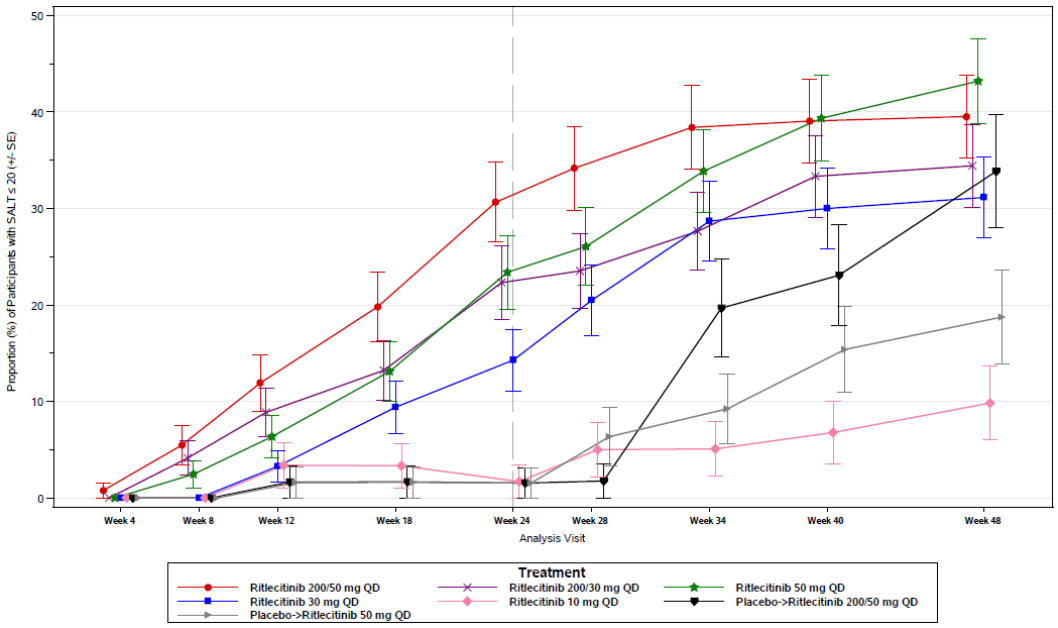
Figure S4. Response Based on Salt Score ≤20 up to Week 48 (FAS)



Cases with missing data at that timepoint due to COVID-related reasons are excluded.
Cases with missing data at that timepoint due to reasons unrelated to COVID-19 are considered as non-response.
PFIZER CONFIDENTIAL SDTM Creation: 13JUL2021 (13:56) Source Data: adas Table Generation: 28JUL2021 (22:42)
(Database snapshot date : 12JUL2021) Output File: ./nda1_cdisc/B7981015/adas_f502c

SALT ≤10 Response at Week 24

Analyzed as the primary endpoint for the EMA and competent authorities in the VHP countries, the proportions of participants with response based on a SALT score ≤10 at Week 24 in ritlecitinib 200/50 mg (21.29%), 200/30 mg (12.87%), 50 mg (13.42%), and 30 mg (10.62%) were significantly different from placebo (1.54%) (Figure S5). Similar results were obtained when this endpoint was analyzed as a key secondary endpoint for the overall study.

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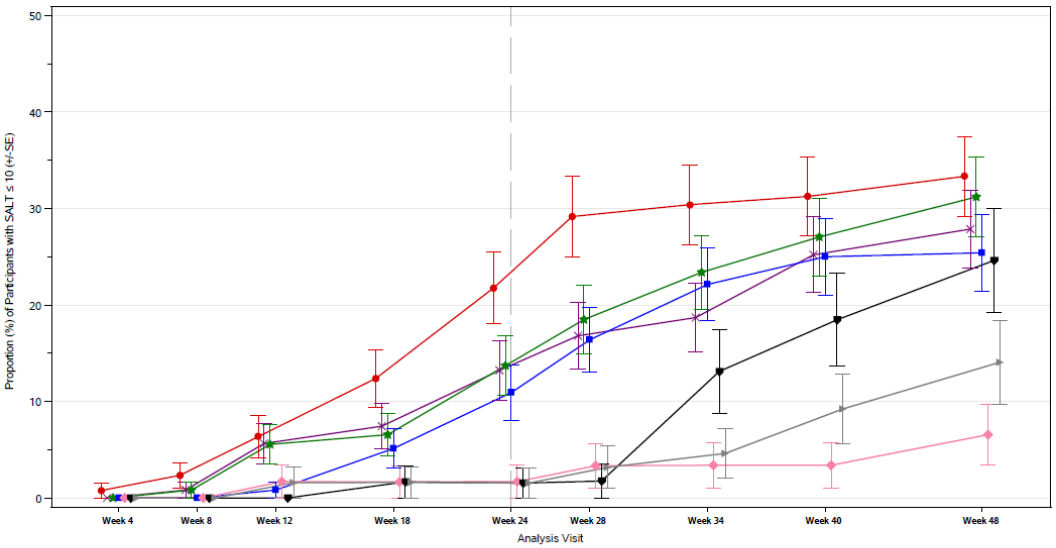
Figure S5. Response Based on SALT Score ≤10 up to Week 48 (FAS)



Cases with missing data at that timepoint due to COVID-related reasons are excluded.
Cases with missing data at that timepoint due to reasons unrelated to COVID-19 are considered as non-response.
PFIZER CONFIDENTIAL SDTM Creation: 13JUL2021 (13:56) Source Data: adas Table Generation: 28JUL2021 (22:42)
(Database snapshot date : 12JUL2021) Output File: ./nda1_cdisc/B7981015/adas_10_f502c

PGI-C Response at Week 24

A significantly larger PGI-C response rate was seen in ritlecitinib 200/50 mg (52.19%), 200/30 mg (45.40%), 50 mg (49.17%), and 30 mg (41.95%) at Week 24 compared with placebo (9.23%). This was a key secondary endpoint for the EMA and competent authorities in the VHP countries (Figure S6).

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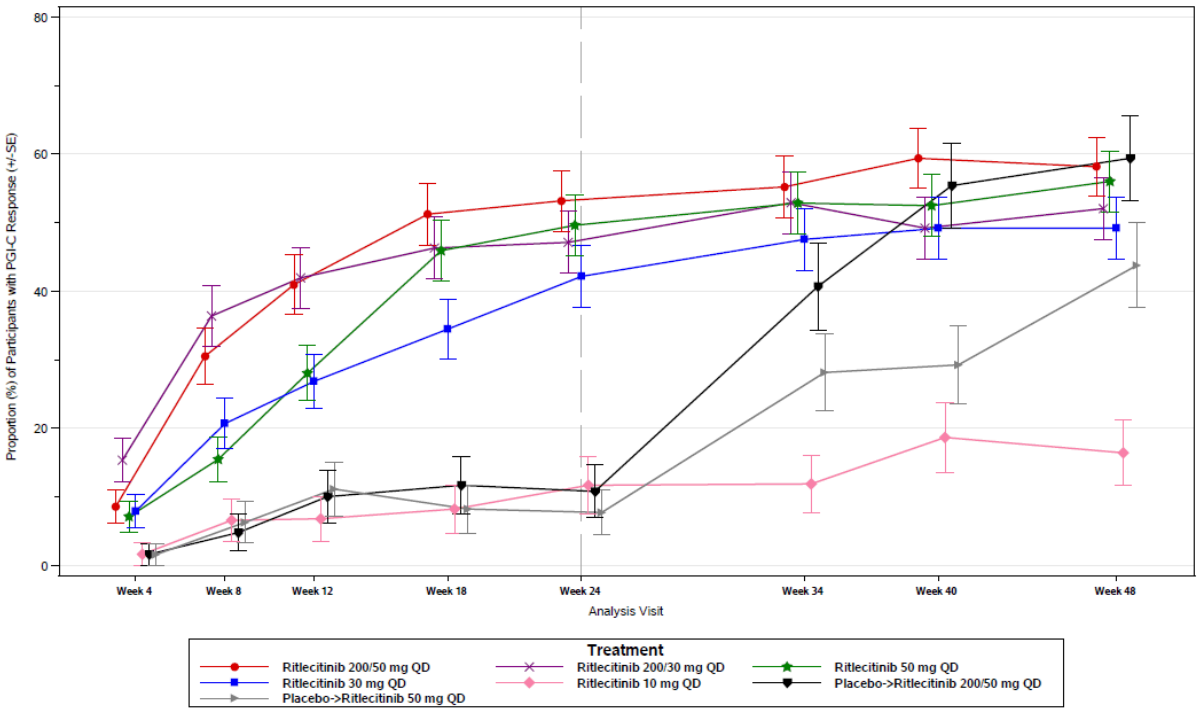
Figure S6. PGI-C Response up to Week 48 (FAS)



PGI-C response is defined as "moderately improved" or "greatly improved".
Cases with missing data at that timepoint due to COVID-related reasons are excluded.
Cases with missing data at that timepoint due to reasons unrelated to COVID-19 are considered as non-response.
PFIZER CONFIDENTIAL SDTM Creation: 13JUL2021 (12:49) Source Data: adpi Table Generation: 06DEC2021 (08:57)
(Database snapshot date : 12JUL2021) Output File: ./nda1_cdisc/B7981015/adpi_res_f102c

Examination of Subgroups for Primary and Key Secondary Endpoints

The difference between each ritlecitinib group and placebo in the proportion of response based on SALT ≤20/SALT ≤10/PGI-C response at Week 24 was generally consistent across most subgroups for all doses.

- Considering subgroups by age, the differences in the proportions of response based on SALT ≤20/SALT ≤10/PGI-C response at Week 24 between ritlecitinib and placebo were similar in adolescents and adults.

- Considering subgroups by severity of AA at BL:

  - The proportion of SALT ≤20 response at Week 24 for ritlecitinib versus placebo was lower in participants with AT/AU than in those with non-AT/AU. For ritlecitinib 200/50 mg, 200/30 mg, 50 mg, and 30 mg, the 95% CI for the difference in proportion of responders based on SALT ≤20 at Week 24 between ritlecitinib and placebo excluded zero in both subgroups, indicating a treatment effect in both participants with AT/AU and non-AT/AU at a nominal significance level (α) of 0.05.

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- The difference in SALT ≤10 response at Week 24 for ritlecitinib versus placebo was lower in participants with AT/AU than in those without AT/AU. In participants with non-AT/AU, the 95% CI for the difference in the proportion of responders based on SALT ≤10 at Week 24 between ritlecitinib and placebo excluded zero for ritlecitinib 200/50 mg, 200/30 mg, 50 mg and 30 mg. In participants with AT/AU, the 95% CI for the difference in proportion of responders based on SALT ≤10 at Week 24 between ritlecitinib and placebo excluded zero for ritlecitinib 200/50 mg and 200/30 mg.

- The difference in the proportions of participants with PGI-C response at Week 24 between ritlecitinib and placebo was similar in participants with AT/AU and non-AT/AU.

Secondary Endpoints

Exposure-Response of Ritlecitinib on the Regrowth of Scalp Hair

The results of this analysis demonstrated a positive relationship between dose and response based on SALT ≤20 at Week 24, and a significant effect of loading dose. The treatment effects of ritlecitinib estimated from this analysis were similar to those from the primary analysis of SALT ≤20 at Week 24.

The results of this analysis also demonstrated a positive relationship between dose and response based on SALT ≤10 at Week 24. The treatment effects of ritlecitinib estimated from this analysis were similar to those from the primary analysis of SALT ≤10 at Week 24.

SALT ≤20/SALT ≤10/SALT$_{75}$/EBA/ELA/PGI-C Responses up to Week 48

- The proportion of participants with SALT ≤20/SALT ≤10/ SALT$_{75}$/EBA[a]/ELA/PGI-C response increased from Week 4 to Week 24 in ritlecitinib 200/50 mg, 200/30 mg, 50 mg, and 30 mg; the increase was greater than in 10 mg and placebo. The proportion of participants with a response continued to increase after Week 24.

- At Week 24, the proportion of participants with SALT ≤20/SALT ≤10/ SALT$_{75}$/EBA response was larger in participants who had received a 200 mg loading dose for 4 weeks than in participants treated for 24 weeks at a single dose level.

    - By Week 48, the proportion of participants with SALT ≤20/SALT ≤10/ EBA/ELA/ PGI-C was similar between the participants who had received a 200 mg loading dose for 4 weeks and those who were treated for 48 weeks without a loading dose

[a] EBA and ELA responses were evaluated in participants without normal EBA/ELA at BL.

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AAPPO Scales up to Week 48

Up to Week 24, the proportion of participants reporting an improvement (achieving a score of 0 [no hair loss] or 1 [little hair loss]) on AAPPO hair loss items 1-4 (scalp, eyebrow, eyelash, body hair) increased in ritlecitinib 200/50 mg, 200/30 mg, 50 mg, and 30 mg; the increase was greater than in 10 mg and placebo. In participants who had received placebo, after transitioning to active treatment (pbo–200/50 mg and pbo–50 mg) the proportion of participants with improvement on AAPPO items 1-4 increased from Week 24 to Week 48.

Mean BL scores of AAPPO Emotional Symptoms and Activity Limitations scores corresponded to Emotional Symptoms that occurred 'never', ‘rarely’, or ‘sometimes’ and Activity Limitations that were ‘not at all’ or ‘a little’. Up to Week 24, the LSM CFB indicated mean Emotional Symptoms scores improved modestly in all groups, including placebo. There was no apparent difference between any active treatment group and placebo. In ritlecitinib 200/50 mg, 200/30 mg, 50 mg, and 30 mg, the improvement in LSM CFB in Emotional Symptoms score continued through Week 48.

Exploratory Endpoints

Response Based on $SALT_{50}$/Absolute SALT Score/Improvement on PGI-C up to Week 48

- The proportion of responders (participants showing $SALT_{50}$) consistently increased from Week 4 to Week 24 in ritlecitinib 200/50 mg, 200/30 mg, 50 mg, and 30 mg, and was greater than in 10 mg or placebo.
- The proportion of participants reporting any improvement on PGI-C consistently increased from Week 4 to Week 24 in ritlecitinib 200/50 mg, 200/30 mg, 50 mg, and 30 mg, and was greater than in 10 mg or placebo.
- Absolute SALT scores decreased (improved) consistently from Week 4 to Week 24 in ritlecitinib 200/50 mg, 200/30 mg, 50 mg, and 30 mg compared with 10 mg and placebo.
- These exploratory endpoints continued to show improvement in ritlecitinib 200/50 mg, 200/30 mg, 50 mg, and 30 mg after Week 24.

Number of Fingernails Affected by AA - Change from Baseline

At Week 24, the mean number of fingernails affected by AA decreased in all treatment groups, including placebo, with no dose-dependence. This decrease continued through Week 48.

CGI-AA

The CGI-AA is a single clinician-reported item developed to assess the clinical impression of severity of scalp hair loss. The rater is asked to rate the subject’s current hair loss on a scale ranging from ‘None (no hair loss)’ to ‘Very severe or complete hair loss’, with higher scores indicating more severe hair loss. The proportion of participants with improvement in CGI-AA (with a score ≥2 at BL) increased over time in active treatment groups;

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improvement was greater in ritlecitinib 200/50 mg, 200/30 mg, 50 mg, and 30 mg than in 10 mg or placebo. The proportion of participants with improvement in CGI-AA improved in all groups up to Week 48.

Patient-Reported Outcomes

- **P-Sat**: Up to Week 24, the proportion of participants showing improvement in all 3 aspects of P-Sat (amount of hair grown, overall hair grown back, and quality of new hair) was greater in all active treatment groups than in placebo. From Week 24 to Week 48, the improvement was maintained, however, there were only small additional changes in the initial active groups. In the active treatment groups, improvement was seen as early as Week 4; the largest increase in each aspect of P-Sat occurred between Week 4 and Week 8.

- **EQ-5D-5L/EQ-VAS/EQ-5D-5Y**: From Weeks 4 to 24, mean CFB indicated that mean EQ-VAS (visual analogue scale) in both adults and adolescents, and EQ-5D-5L in adults index scores did not change.

- **AARU**: The proportion of participants with any HCP visits was similar across groups at BL and through Week 48.

- **WPAI:AA**: The mean percent work time missed, impairment while working, overall work impairment, and activity impairment WPAI:AA scores at BL were similar across treatment groups.

- **HADS**:

    - Mean depression and anxiety scores were consistent with normal depression/anxiety scores (ie, no depression/no anxiety) at BL and at Week 24 for all groups. Overall, LSM of CFB was similar between all ritlecitinib groups and placebo up to Week 24 and the LS mean CFB was similar among ritlecitinib groups up to Week 48.

    - The proportion of participants with a BL subscale score indicative of depression/ anxiety that indicated an improvement in depression/anxiety from BL was similar between active ritlecitinib groups through Week 48; only a small subset of participants reported scores indicative of depression/anxiety at BL.

- **SF36v2**: BL normalized mean SF-36v2 scores for all 8 domains and physical (PCS) and mental (MCS) component scores were balanced across treatment groups and approximated US population norms (mean=50, SD=10). From Weeks 4 to 24, normalized mean scores were similar across groups; similar trends were observed for all groups from Week 24 to 48.

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Pharmacokinetic and Pharmacodynamic Results

The mean plasma concentrations of ritlecitinib were similar between Weeks 4, 8, and 12 in participants who received the same dose throughout the Placebo-Controlled Period (ie, 50 mg, 30 mg, 10 mg). The difference in plasma concentration between groups was proportional to the difference in dose. The mean plasma concentrations were higher at Week 4 in participants who received a 200 mg loading dose for 4 weeks. At Weeks 8 and 12, mean plasma concentrations were similar between all participants who received 50 mg (200/50 mg versus 50 mg) or 30 mg (200/30 mg versus 30 mg), independent of whether they had received a loading dose during the first 4 weeks.

Safety Results

Adverse Events

The proportion of participants who experienced all-causality TEAEs was similar across treatment groups up to Week 24 (Placebo-Controlled Period) and up to Week 48 (overall).

- Up to Week 24: in active treatment groups, range 69.4% (10 mg) to 75.4% (50 mg) compared with placebo (71.0%).
- Up to Week 48: across treatment groups range 75.8% (10 mg) to 86.4% (pbo–50 mg) (Table S4).

Up to Week 48, the incidence of TEAEs, SAEs, severe TEAEs, permanent discontinuations and temporary drug discontinuations was not dose dependent across treatment groups.

- No dose-dependent increase was observed in the number of participants with TEAEs in active treatment groups.
- 14 participants experienced treatment-emergent SAEs, which were generally balanced across treatment groups.
- 27 participants experienced severe TEAEs which were generally balanced across treatment groups. (This excludes 1 TEAE of headache [severe, related] that was reported erroneously.)
- 22 participants permanently discontinued from the study or study drug due to an TEAE.
    - The TEAEs most frequently resulting in permanent discontinuation from the study or study drug were urticaria, pregnancy, or headache
- There were no deaths.

There were an additional 6 TEAEs experienced by 4 participants not reported in summary tables, all mild in severity, (1 TEAE each in 200/50 mg, 50 mg, and 10 mg; 3 TEAEs in 30

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mg). None of these TEAEs were serious, related to study intervention, or resulted in a change in study intervention or discontinuation from the study.

Table S4. Overall Summary of Treatment-Emergent Adverse Events (All Causalities) up to Week 48 (SAS) (Protocol B7981015)

Number (%) of Participants	Ritlecitinib 200/50 mg QD n (%)	Ritlecitinib 200/30 mg QD n (%)	Ritlecitinib 50 mg QD n (%)	Ritlecitinib 30 mg QD n (%)	Ritlecitinib 10 mg QD n (%)	Placebo->Ritlecitinib 200/50 mg QD n (%)	Placebo->Ritlecitinib 50 mg QD n (%)
Participants evaluable for adverse events	131	129	130	132	62	65	66
Number of adverse events	410	345	363	409	161	180	192
Participants with adverse events	108 (82.4)	105 (81.4)	110 (84.6)	106 (80.3)	47 (75.8)	54 (83.1)	57 (86.4)
Participants with serious adverse events	4 (3.1)	2 (1.6)	2 (1.5)	1 (0.8)	2 (3.2)	0	3 (4.5)
Participants with severe adverse events	5 (3.8)	8 (6.2)	2 (1.5)	7 (5.3)	2 (3.2)	2 (3.1)	2 (3.0)
Participants permanently discontinued from study due to adverse events[a]	4 (3.1)	2 (1.6)	4 (3.1)	6 (4.5)	2 (3.2)	0	4 (6.1)
Participants with temporary drug discontinuation due to adverse events	17 (13.0)	16 (12.4)	20 (15.4)	16 (12.1)	5 (8.1)	13 (20.0)	8 (12.1)

Included data up to Week 48 and follow-up period (if applicable).
Except for the Number of Adverse Events, participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that the participant was discontinued from the study or study drug.
MedDRA v24.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 13JUL2021 (13:21) Source Data: adae Table Generation: 09AUG2021 (17:54)
(Database snapshot date : 12JUL2021) Output File: ./nda1_cdisc/B7981015/adae_s010c
Table 14.3.1.2.3.1 Ritlecitinib is for Pfizer internal use.

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Incidence of Adverse Events

- The most frequently reported TEAEs (by preferred term [PT]) in any group during both the Placebo-Controlled and Extension Periods included nasopharyngitis, headache, and upper respiratory tract infection.

- The incidence of nasopharyngitis, dizziness, and urinary tract infection was higher in participants treated with ritlecitinib. For the 200/50 mg and 200/30 mg groups, incidence was also higher for folliculitis, upper respiratory tract infection, and urticaria.

- Most TEAEs were mild to moderate in severity.

- Up to Week 24, 20 severe TEAEs were reported across all ritlecitinib treatment groups (excluding 1 TEAE of headache [severe, related] in ritlecitinib 30 mg that was reported erroneously). The incidence of severe TEAEs was low in all treatment groups (range: 50 mg, 2 [1.5%] to 200/30 mg, 5 [3.9%]).

    - Up to Week 48, an additional 7 severe TEAEs were reported. Overall, the incidence of severe TEAEs ranged from 2 (1.5%) in 50 mg to 8 (6.2%) in 200/30 mg.

- The most frequently reported severe TEAEs (n ≥1.6% of participants) were pruritus (2 [1.6%]), alopecia areata 2 [1.6%]), and blood creatine phosphokinase increased (2 [1.6%]) in 200/30 mg and vertigo positional (1 [1.6%]) and myalgia (2 [1.6%]) in 10 mg.

Serious Adverse Events

Treatment-emergent SAEs reported during the study were generally balanced across treatment groups.

- 14 participants experienced 16 SAEs up to Week 48, 11 of which occurred in 10 participants during the Placebo-Controlled Period (up to Week 24).

- No SAE was reported during the initial 4 weeks of treatment in participants receiving 200 mg loading dose.

All SAEs were considered by the investigator as unrelated to study drug, except in 3 participants (sepsis and empyema; breast cancer; and eczema). All SAEs were resolved except for conversion disorder (resolved with sequelae), breast cancer (resolving) and invasive lobular breast carcinoma (not resolved).

Other Safety Events of Interest

Overall, 4 (0.6%) participants experienced 5 TEAEs of **serious infection**. Of these, 4 TEAEs in 3 participants occurred in the Placebo-Controlled Period (200/50 mg: sepsis and empyema [both severe], and appendicitis [moderate]; 30 mg: diverticulitis [moderate]), and 1 TEAE in 1 participant occurred in the Extension Period (200/30 mg: appendicitis [severe]). These

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SAEs were in the Infections and Infestations SOC; all TEAEs were recovered and 2 TEAEs (sepsis and empyema in 1 participant) were considered by the investigator as related to study treatment.

There were no TEAEs adjudicated as **opportunistic infections** and no TEAEs of **tuberculosis** up to Week 48.

Up to Week 48, 8 (1.1%) participants experienced **herpes zoster** (7 coded to the PT herpes zoster, 1 to varicella zoster virus infection); 4 of the TEAEs occurred up to Week 24. All occurred in in ritlecitinib-treated participants (200/50 mg: 1 participant; 200/30 mg: 2 participants; 50 mg: 5 participants). Participants with TEAEs of herpes zoster ranged in age from 28 to 65 years and most were female (6 participants). None of the TEAEs were disseminated or multidermatomal, all were mild to moderate in severity, all participants recovered, and no participant discontinued from the study due to these TEAEs. None of these TEAEs were considered serious.

Up to Week 48, 21 (2.9%) participants experienced **herpes simplex** (18 coded to the preferred term of herpes simplex, 1 to herpes simplex reactivation, 1 to herpes virus infection, and 2 to oral herpes); 14 of the TEAEs occurred up to Week 24. Up to Week 48, herpes simplex was reported across all treatment groups (range: 0.8% [200/50 mg] to 4.5% [30 mg and pbo−50 mg]) with no dose-dependence; 3 of the TEAEs occurred in placebo.

Up to Week 48, there were no **major adverse cardiovascular events**.

- There was 1 TEAE adjudicated by an external Cardiovascular Adjudication Committee to meet criteria for a cardiovascular and thromboembolic event of pulmonary embolism. The study drug was withdrawn and the participant (50 mg) was discontinued from the study as a result of the TEAE. The outcome of the TEAE was recovered/resolved.

Up to Week 48, there were 36 participants with TEAEs that were adjudicated to meet criteria as **neurosafety events of interest** (EOI) by an external Neurosafety Event Adjudication Committee; in 30 participants these TEAEs were adjudicated to meet criteria for neurological EOI terms and in 6 participants these TEAEs were adjudicated to meet criteria for the audiological EOI term sensorineural hearing loss.

- The adjudicated **neurological EOI** were well distributed across treatment groups. A total of 25 of these participants experienced TEAEs up to Week 24.

- The TEAEs that were adjudicated to meet criteria for the **audiological EOI** term sensorineural hearing loss were balanced across active treatment groups (2 each in 200/50 mg and 30 mg; 1 each in 200/30 mg and 50 mg), except for 10 mg and the groups randomized to receive placebo during the first 24 weeks. All TEAEs adjudicated by the external NSEAC to meet criteria for the audiological EOI term sensorineural hearing loss reflect only the outcome of the protocol-specified audiologic testing, as none of those

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TEAEs were spontaneously reported by study participants. None of the adjudicated TEAEs met criteria for the EOI term central hearing disorder.

Up to Week 48, 2 participants each experienced 1 TEAE of **malignancy**. During the Placebo-Controlled Period: (200/50 mg) SAE of invasive lobular breast carcinoma unrelated to study treatment. During the Extension Period: (50 mg) SAE of breast cancer, related to study treatment. Both of these malignancy TEAEs were severe and met adjudication criteria as events of breast cancer.

- Up to Week 48, no TEAEs of **squamous cell carcinoma** or **basal cell carcinoma** were reported and there were no reports of adjudicated **non-melanoma skin cancer**.

Dermatological events were generally balanced across ritlecitinib and placebo treatment groups.

Up to Week 48, 229 (32.0%) participants experienced dermatological TEAEs (range: 27.4% [10 mg] to 37.2% [200/30 mg]).

- The most common dermatological TEAEs (≥5%) across treatment groups were acne (7.8%), folliculitis (6.6%), and urticaria (5.5%).
- Rash was experienced more frequently in 50 mg (5.4% of participants) compared with other groups (0.0% to 3.8%).
- Folliculitis, urticaria, and pruritus were reported more frequently in 200/50 mg (folliculitis, 8.4%; urticaria, 6.9%; pruritus, 3.1%) and 200/30 mg groups (folliculitis, 8.5%; urticaria, 7.0%; pruritus, 5.4%) compared with other groups, including placebo.
- The proportion of participants that experienced TEAEs in the MedDRA HLT (high-level term) of Acne (including PTs of acne, acne cystic, dermatitis acneiform) ranged across treatment groups from 6.1% (200/50 mg) to 13.6% (pbo–50 mg).
- There was 1 SAE among the dermatological TEAEs: 1 participant in the 10 mg group experienced an SAE of eczema on Study Day 147. The participant had a co-morbidity of atopic dermatitis on arms and legs. The TEAE of eczema was assessed by the investigator as related to study treatment. Study drug was withdrawn and the participant discontinued from the study. The outcome was recovered/resolved.
- Up to Week 48, mild-to-moderate urticarias were reported in 41 participants (including 3 in the placebo arm).
    - 25 participants received treatment.
    - 3 participants (1 in 200/30 mg, and 2 in 50 mg) were permanently discontinued from study or study drug due to TEAEs of urticaria.

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Exposure during pregnancy was reported for 4 participants up to Week 48. All TEAEs were considered not related to study treatment; 3 participants (200/50 mg, 30 mg, and placebo) had study drug withdrawn and were discontinued from the study. 1 participant had completed study treatment by the time the site was made aware of the pregnancy. [redacted]

COVID-19-related TEAEs were reported in 26 participants, including 13 participants with TEAEs of COVID-19 or suspected COVID-19 up to Week 48. The number of participants with of COVID-19 TEAEs ranged from 1 in 200/30 mg (0.8%) and pbo–50 mg (1.5%) to 7 (5.4%) in 50 mg. All of these TEAEs were mild or moderate in severity, not considered related to study drug, and all participants recovered. None of the TEAEs were SAEs and no participant was discontinued from the study due to the COVID-19-related TEAE.

Deaths

No deaths were reported

Laboratory Parameters

No SAEs related to laboratory abnormalities were reported.

Hematology: Treatment with ritlecitinib was associated with changes in hematological parameters, some of which were dose dependent.

- There were slight, transient decreases in hemoglobin after initiation of treatment with ritlecitinib . Hemoglobin levels were stable from Week 4 up to Week 48.

- Small, early decreases in platelets were observed with ritlecitinib treatment; however, there was no dose dependence. Platelet levels remained stable at the lower level up to Week 48.

- There were small, variable changes in leukocytes from BL in the first weeks of the study, which was more apparent in 200/30 mg. Leukocyte levels remained stable up to Week 48.

- There were small, variable changes in neutrophils early after initiation of treatment with ritlecitinib. Neutrophil levels were stable from Week 4 up to Week 48.

- Dose-dependent early decreases in absolute lymphocyte levels, CD3 (T lymphocytes) and T lymphocyte subsets (CD4 and CD8) were observed. After the initial decrease, the levels partially recovered and remained stable up to Week 48.

- There was no change in CD19 (B lymphocyte) cells in any treatment group.

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- There was a dose-dependent early decrease in CD16/56 (NK cells), which was the most apparent in groups who had received a 200 mg loading dose (200/50 mg and 200/30 mg) of ritlecitinib for 4 weeks.

Chemistry

Lipids: After initiation of treatment with ritlecitinib, there were small, transient increases in total cholesterol, HDL cholesterol, and LDL cholesterol (relative to placebo), which were dose-dependent. There were no long-term changes across the groups in LDL cholesterol lipid profile up to Week 24 or up to Week 48.

Liver Function: Overall, there were no clinically concerning effects of ritlecitinib on ALT, AST, bilirubin, or alkaline phosphatase. Up to Week 48, the incidence of elevations in hepatic enzymes was low and not dose dependent, and there were no potential Hy's law cases.

Creatine Kinase: Up to Week 48, there were no clinically meaningful changes in CK across treatment groups, and no cases of rhabdomyolysis were reported.

Vital Signs, ECG, and Physical Findings

Vital Signs: There were no clinically meaningful mean changes across treatment groups in systolic blood pressure, diastolic blood pressure, or pulse rate up to Week 48.

ECG: There were no clinically meaningful changes in QTcF across treatment groups during the study up to Week 48, and no participant met the protocol-specified discontinuation criteria of confirmed QTcF >500 milliseconds.

Physical Findings: There were no clinically meaningful mean changes across treatment groups in height or body weight up to Week 48 in adults. There were changes in height and body weight up to Week 48 in adolescents; however, these changes were not considered clinically meaningful given the age of these participants. The changes were consistent across treatment groups.

CONCLUSIONS

Efficacy

- Ritlecitinib 200/50 mg, 200/30 mg, 50 mg, and 30 mg were significantly superior to placebo on clinician-assessed and patient-reported endpoints, including SALT ≤20, SALT ≤10, and PGI-C responses.
    - Overall efficacy was lower in participants with AT/AU compared with participants with non-AT/AU.
    - Overall efficacy was similar in adult and adolescent participants.

CLINICAL STUDY REPORT SYNOPSIS

- Exposure response modelling based on SALT ≤20 and SALT ≤10 response at Week 24 showed a positive relationship between dose and response. The effect of loading dose was significant for the SALT ≤20 response; however, for the SALT ≤10 response, the p-value did not reach statistical significance.

- Ritlecitinib 200/50 mg, 200/30 mg, 50 mg, and 30 mg produced significantly higher response rates of scalp hair regrowth and were nominally superior to placebo at Week 24 in producing improvement in eyebrows and eyelashes.

- Continued improvement in efficacy endpoints was seen between Week 24 and Week 48, although this Extension Period was not placebo-controlled.

- Although the Week 24 efficacy of dose regimens with a loading dose was higher than corresponding dose regimens without a loading dose, the Week 48 efficacy of dose regimens with or without a loading dose was comparable.

Safety

- Ritlecitinib was safe and well-tolerated in participants treated with ritlecitinib for up to 48 weeks.

- No deaths were reported.

- There were no dose-dependent trends in SAEs, severe TEAEs, or TEAEs leading to discontinuation.

- There were few serious infections and no opportunistic infections. All TEAEs of herpes zoster were mild to moderate and occurred in participants treated with ritlecitinib.

- Dose regimens with a 200 mg loading dose had a higher incidence of some TEAEs (eg, folliculitis, urticaria, dizziness, influenza, upper respiratory tract infection, pruritus, and urinary tract infection) compared to their respective maintenance dose (50 mg or 30 mg) and larger decreases in some hematological parameters (such as lymphocytes and lymphocyte subsets).

- There were mild and mostly transient changes in hematological parameters and lipids, some of which were dose dependent. There were no clinically meaningful trends for hepatic laboratory parameters or CK.