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Sponsor: Pfizer Inc

Investigational Product: Ritlecitinib (PF-06651600)

Clinical Study Report Synopsis: Protocol B7981019

Protocol Title: A Phase 2b Randomized, Double-Blind, Placebo-Controlled, Multicenter, Dose-Ranging Study to Evaluate the Efficacy and Safety Profile of PF-06651600 With a Partially Blinded Extension Period to Evaluate the Efficacy and Safety of PF-06651600 and PF-06700841 in Subjects With Active Non-Segmental Vitiligo

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

Study Centers: This study was conducted at 80 sites (6 in Australia, 3 in Belgium, 16 in Canada, 6 in Germany, 1 in Italy, 5 in Japan, 5 in Republic of Korea, 5 in Spain, 3 in Taiwan, and 30 in the United States). 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: 26 November 2018

Study Completion Date: 05 February 2021

Report Date: 15 September 2021

Previous Report Date(s): 27 August 2021

Phase of Development: Phase 2b

Study Objectives and Endpoints: The study objectives and endpoints are provided in Table S1 for the Dose-Ranging (DR) Period and in Table S2 for the Extension (Ext) Period.

DR Period

Table S1. Study Objectives and Endpoints During Dose-Ranging Period

Type	Objectives	Endpoints
Primary		
Efficacy	To evaluate the efficacy of ritlecitinib dose/dosing regimens at Week 24 in adult participants with active non-segmental vitiligo.	• Percent change from Baseline (%CFB) in central facial-vitiligo area scoring index (F-VASI) at Week 24.

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Table S1. Study Objectives and Endpoints During Dose-Ranging Period

Type	Objectives	Endpoints
Safety	To evaluate the safety and tolerability of ritlecitinib over time in adult participants with active non-segmental vitiligo.	• Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) up to Week 24. • Incidence of specific clinical laboratory abnormalities including but not limited to anemia, neutropenia, thrombocytopenia, lymphopenia, changes in lipid profile, and liver function tests (LFTs) up to Week 24.
Secondary		
Key Secondary		
Efficacy	To evaluate the efficacy of ritlecitinib compared with placebo as measured by F-VASI at Week 24 in adult participants with active non-segmental vitiligo.	• Proportion of participants achieving central read F-VASI75 (at least 75% improvement in central read F-VASI from baseline [BL]) at Week 24.
Other Secondary		
Efficacy	To evaluate the efficacy of ritlecitinib compared with placebo as measured by other clinical assessments over time in adult participants with active non-segmental vitiligo.	• Proportion of participants achieving total-vitiligo area scoring index (T-VASI)50 at Week 24. • %CFB in T-VASI, central and local F-VASI, and self-assessment-vitiligo extent score (SA-VES), and absolute CFB in T-VASI at designated time points (except for Week 24 for central F-VASI). • Proportion of participants achieving T-VASI50/75/90/100 (at least 50%/75%/90%/100% improvement from BL in T-VASI), and central and local F-VASI50/75/90/100 at designated time points (except for Week 24 in T-VASI50 and central F-VASI75). • CFB in vitiligo specific quality of life (VitiQoL) at designated time points. • Proportion of participants achieving a static investigator global assessment (sIGA) 0 or 1, and at least a 2-point improvement at Week 24.
Key Exploratory		
Efficacy	To evaluate the efficacy of ritlecitinib compared with placebo by other efficacy markers in adult participants with active non-segmental vitiligo.	• Absolute CFB in central and local F-VASI at designated time points. • Proportion of participants achieving “very much improved” or “much improved” on patient global impression of change in vitiligo (PGIC-V). • Proportion of participants achieving a score of 4 (“a lot less noticeable”) or 5 (“no longer noticeable”) on Vitiligo Noticeability Scale (VNS). • Change of extent of depigmentation in target lesion(s).
Pharmacodynamic (PD)	To assess PD and disease-related biomarkers over time in adult	• CFB in PD and disease-related protein and/or nucleic acid biomarkers at designated time points up to Week 24 as specified in the protocol, including but

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Table S1. Study Objectives and Endpoints During Dose-Ranging Period

Type	Objectives	Endpoints
	participants with active non-segmental vitiligo.	not limited to, [redacted]. • CFB in [redacted] at designated time points up to Week 24 as specified in protocol. • CFB in [redacted] at designated time points up to Week 24 as specified in the protocol.
Pharmacokinetic (PK)	To characterize PK of ritlecitinib over 24 weeks in adult participants with active non-segmental vitiligo.	• Plasma concentrations of ritlecitinib at designated time points up to Week 24 as specified in the protocol.

Extension Period

Table S2. Study Objectives and Endpoints During Extension Period

Type	Objectives	Endpoints
Primary		
Safety	To evaluate the safety and tolerability of ritlecitinib and brepocitinib in adult participants with active non-segmental vitiligo.	• Incidence of TEAEs and SAEs during the Ext Period. • Incidence of specific clinical laboratory abnormalities including but not limited to anemia, neutropenia, thrombocytopenia, lymphopenia, changes in lipid profile, and LFTs during the Ext Period.
Key Exploratory		
Efficacy	• To evaluate the long-term efficacy of ritlecitinib, efficacy of ritlecitinib and add-on narrow band ultraviolet B (nbUVB), in adult participants with active non-segmental vitiligo. • To evaluate the efficacy of brepocitinib in a subset of adult participants with active non-segmental vitiligo.	• %CFB in T-VASI during the Ext Period. • Proportion of participants achieving T-VASI50/75/90/100, and central and local F-VASI50/75/90/100 during the Ext Period. • %CFB in T-VASI, central and local F-VASI, and SA-VES and absolute CFB in T-VASI, central and local F-VASI during the Ext Period. • CFB in VitiQoL during the Ext Period. • Proportion of participants achieving a sIGA 0 or 1, and at least a 2-point improvement during the Ext Period. • Proportion of participants achieving “very much improved” or “much improved” on PGIC-V. • Proportion of participants achieving a score of 4 (“a lot less noticeable”) or 5 (“no longer noticeable”) on VNS.
PD	To assess PD and disease-related biomarkers in adult participants with active non-segmental vitiligo.	• CFB in PD and disease-related protein and/or nucleic acid biomarkers at designated time points during the Ext Period as specified in the protocol, including but not limited to [redacted].

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Table S2. Study Objectives and Endpoints During Extension Period

Type	Objectives	Endpoints
		• CFB in [redacted] at designated time points during the Ext Period as specified in the protocol. • CFB in [redacted] at designated time points during the Ext Period as specified in the protocol.
PK	To characterize PK of ritlecitinib and brepocitinib in adult participants with active non-segmental vitiligo.	• Plasma concentrations of ritlecitinib and brepocitinib as specified in the protocol.

METHODS

Study Design: This Phase 2b study evaluated the safety, tolerability, efficacy, PK, and PD of ritlecitinib in participants with active non-segmental vitiligo. In addition, this study provided opportunities for participants to receive additional treatment in the Ext Period: ritlecitinib treatment with or without nbUVB add-on therapy, or brepocitinib.

The 24-week double-blind DR Treatment Period assessed the efficacy and safety of ritlecitinib in participants with active non-segmental vitiligo. Participants were randomized to 1 of 5 treatment groups or placebo: 2 groups with a ritlecitinib induction dose (200 mg once daily [QD] or 100 mg QD) for 4 weeks followed by maintenance dosing of 50 mg QD for 20 weeks, 3 groups with ritlecitinib dosing for 24 weeks (50 mg QD, 30 mg QD, and 10 mg QD), and matching placebo for 24 weeks (These 6 groups are hereafter referred to as 200/50 mg; 100/50 mg; 50 mg; 30 mg; 10 mg; placebo).

This study included an Ext Period to evaluate additional safety and tolerability of ritlecitinib with or without nbUVB add-on therapy. Participants in Extension Group 2 (ExtGp2) (+nbUVB) who had <10% improvement in %CFB in T-VASI at Extension Week (ExtWeek) 12 (BL=DR Period Week 24) were discontinued from treatment. The Ext Period also evaluated the safety, efficacy and tolerability of brepocitinib-only treatment (ExtGp1) in participants with vitiligo after a 4-week drug holiday with no study intervention. The drug holiday provided a wash-out period for 4 weeks between the DR Period and Ext Period only in ExtGp1.

There were 6 groups with QD dosing in the Ext Period. The groups for ritlecitinib with nbUVB add-on therapy (with ritlecitinib induction dosing of 200 mg for 4 weeks followed by maintenance dosing of 50 mg for 20 weeks [ExtGp2]) and the brepocitinib-only (induction dosing of 60 mg for 4 weeks followed by maintenance dosing of 30 mg for 16 weeks [ExtGp1]) were open-label. The other 3 ritlecitinib groups (induction dosing of 200 mg for 4 weeks followed by maintenance dosing of 50 mg for 20 weeks [ExtGp3], 50 mg for 24 weeks [ExtGp4], and 30 mg for 24 weeks [ExtGp5]) were blinded. The observation-only (no treatment) group (ExtGp6) was open-label. Participants who completed the initial

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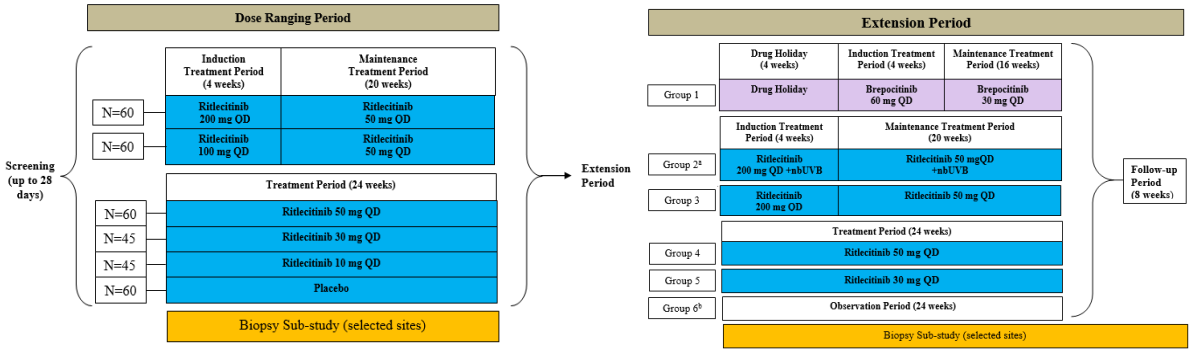
24 weeks of the protocol could enter the Ext Period. Participants who discontinued prior to Week 24 Visit were not eligible for the Ext Period.

Group mapping for the Ext Period was performed based on individual response at Week 16 of the DR Period, ie, participants were allocated to treatment in the Ext Period based on whether they were responders (who achieved ≥50% improvement in T-VASI from Baseline) or non-responders (who achieved <50% improvement in T-VASI from Baseline) at DR Period Week 16.

Schematics of the study design are shown for the DR and Ext Periods in Figure S1.

Figure S1. Study Design for Dose Ranging Period (Left) and Extension Period (Right)



a. Participants who had <10% improvement in T-VASI at ExtWeek 12 from the BL value at DR Period Week 24 were discontinued from the treatment and entered early termination and Follow Up Period.
b. Visits were conducted every 4 weeks until end of study or until ≥30% depigmentation from BL T-VASI occurred, whichever was shorter. No follow up visits were deemed to be performed for participants in ExtGp6.

Diagnosis and Main Criteria for Inclusion: Male or female adult (18-65 years of age) participants with active non-segmental vitiligo were included in this study.

Study intervention: Participants received blind-label ritlecitinib tablets 10 mg and 50 mg, matching placebo, or open-label breopcitinib tablets 5 mg and 25 mg (Table S3), according to the assigned treatment in Figure S1; all doses were oral, and dosing was QD.

Table S3. Study Intervention Description

Study Intervention Description	Vendor Lot Number	Pfizer Lot Number	Strength /Potency	Dosage Form
Placebo 6 mm Tablet	not applicable (N/A)	17-002906	0 mg	Tablet
Placebo 10 mm Tablet	N/A	17-002907	0 mg	Tablet
Placebo 10 mm Tablet	N/A	17-002908	0 mg	Tablet
Placebo 10 mm Tablet	N/A	17-002909	0 mg	Tablet
PF-06651600-15 10 mg Round White to Off-White Tablet	N/A	17-004591	10 mg	Tablet
PF-06651600-15 50 mg Round White to Off-White Tablet	N/A	18-000211	50 mg	Tablet
PF-06651600-15 50 mg Round White to Off-White Tablet	N/A	18-001308	50 mg	Tablet

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Table S3. Study Intervention Description

Study Intervention Description	Vendor Lot Number	Pfizer Lot Number	Strength /Potency	Dosage Form
Placebo 10 mm Tablet	N/A	18-001560	0 mg	Tablet
Placebo 10 mm Tablet	N/A	18-001561	0 mg	Tablet
Placebo 6 mm Tablet	N/A	18-003539	0 mg	Tablet
PF-06651600-15 50 mg Round White to Off-White Tablet	N/A	18-003615	50 mg	Tablet
Placebo 10 mm Tablet	N/A	19-000972	0 mg	Tablet
PF-06651600-15 50 mg Round White to Off-White Tablet	N/A	19-001388	50 mg	Tablet
PF-06651600-15 10 mg Round White to Off-White Tablet	N/A	18-003410	10 mg	Tablet
Placebo 10 mm Tablet	N/A	18-003540	0 mg	Tablet
Placebo 10 mm Tablet	N/A	17-001174	0 mg	Tablet
Placebo 10 mm Tablet	N/A	17-001175	0 mg	Tablet
PF-06700841-15 5 mg Round White to Off-White Tablet	N/A	18-000453	5 mg	Tablet
PF-06700841-15 25 mg Round White to Off-White Tablet	N/A	18-000455	25 mg	Tablet
PF-06700841-15 5 mg Round White to Off-White Tablet	N/A	19-000338	5 mg	Tablet
PF-06700841-15 25 mg Round White to Off-White Tablet	N/A	19-000340	25 mg	Tablet

Efficacy Evaluations: Efficacy endpoints evaluated were F-VASI – central and local, T-VASI, sIGA, target lesion(s) assessment, and patient report outcome (PRO) measures including SA-VES, VitiQoL, PGIC-V, and VNS, etc.

PK Evaluations: PK samples were collected and analyzed using a validated analytical method.

In the DR Period, blood samples for PK were collected pre-dose on Day 1 and at Weeks 4, 8, 12, and 24; at 0.5 hours post-dose at Weeks 8 and 12; and 0.5, 1, 2, and 4 hours post-dose at Weeks 4 and 24.

In ExtGp2, ExtGp3, ExtGp4, and ExtGp5, blood samples for PK were collected pre-dose at ExtWeeks 4, 8, 12 and 24; at 0.5 hours post-dose at ExtWeeks 8 and 12; and 0.5, 1, 2, and 4 hours post-dose at ExtWeeks 4 and 24.

In ExtGp1, blood samples for PK were collected pre-dose at ExtWeeks 4, 8, 12, 16, and 24; at 0.5 hours post-dose at ExtWeeks 12 and 16; and 0.5, 1, 2, and 4 hours post-dose at ExtWeeks 8 and 24.

PD Evaluations: Blood samples for the analyses of [redacted] were collected and analyzed.

Safety Evaluations: Safety evaluations included adverse events (AEs), SAEs, clinical laboratory tests, vital signs, electrocardiograms (ECGs), audiometry, and special safety assessment of dermatological events, etc.

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Statistical Methods: The defined analysis sets are provided in Table S4.

Table S4. Analysis Sets - DR and Ext Periods

Analysis Set	Definition	Baseline
Full Analysis Set (FAS) - DR Period	All participants who received at least 1 dose of randomized study intervention and had a BL and at least 1 post-BL measurement (after taking randomized study intervention)	Day 1 of the DR Period
Safety Analysis Set (SAS)	All participants who received at least 1 dose of study intervention.	Day 1 of the DR Period
Extension Analysis Set (EAS)	All participants who received at least 1 dose of planned study intervention in the Ext Period.	Week 24 of the DR Period (or previous non-missing visit)
Extension Analysis Set Group 1 (EASG1)	All participants assigned to Group 1 in the EAS	Week 24 of the DR Period (or previous non-missing visit)
Extension Analysis Set Groups 2&3 (EASG23)	All participants assigned to Groups 2 and 3 in the EAS	Week 24 of the DR Period (or previous non-missing visit)
Extension Analysis Set Group 3 (EASG3)	All participants assigned to Group 3 in the EAS	Day 1 of the DR Period
PK Concentration Population	All participants who received at least 1 dose of ritlecitinib and in whom at least 1 concentration value was reported	

Efficacy Analysis

DR Period

- **Primary Endpoint:** The primary endpoint was analyzed using an analysis of covariance (ANCOVA) model which included treatment, baseline efficacy score, and Fitzpatrick skin type as covariates. Observed case (OC) analysis was used to manage missing data for analyses involving ANCOVA models.

  Multiple comparisons were conducted applying a Hochberg procedure using observed p-values. Three pairwise comparisons were adjusted for multiplicity for the primary endpoint only in this order: ritlecitinib 200 mg/50 mg vs placebo, ritlecitinib 100 mg/50 mg vs placebo and then ritlecitinib 50 mg vs placebo.

  Also, a 4-parameter Bayesian maximum effect (E_{max}) model was used to characterize the dose response in participants treated with ritlecitinib up to Week 24.

- **Key Secondary Endpoint:** The key secondary endpoint was analyzed by first treating the missing data (non-coronavirus infectious disease 2019 [COVID-19] related) as non-responders and then applying Chan and Zhang exact confidence interval (CI) method at Week 24 (and other intermediate time points). Missing data due to COVID-19 for central F-VASI75 were removed from analysis.

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- **Other Secondary Endpoints:** The secondary endpoints were analyzed by first treating the missing data as non-responders and then applying Chan and Zhang exact CI method at Week 24 (and other intermediate time points). Missing data due to COVID-19 for the binary endpoints were removed from analysis.

  %CFB and CFB in T-VASI at Week 24 were analyzed using the same statistical model as the primary endpoint.

Ext Period: Descriptive statistics were provided for the exploratory efficacy analysis. The continuous variables were summarized with n, mean, median, standard deviation (SD), etc.

PK Analysis: PK concentrations were summarized and presented with summary statistics and non-compartmental PK parameter estimates were provided when appropriate.

Safety Analysis: AEs were summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. Safety data other than AEs were listed and summarized by treatment.

RESULTS

Participant Disposition and Demography: A total of 578 participants were screened, and there were 212 screen failures.

- **DR Period:** 366 participants were randomized to the DR Period, 364 (99.5%) of whom received treatment and were included in the SAS, including 66 (18.1%) participants who discontinued study intervention. Participants in the DR Period had a mean age of 44.98 years and 53.0% were female. Most participants were White (67.6%), and Not Hispanic or Latino (83.2%).

- **Ext Period:** 295 participants entered the Ext Period, 293 of whom were mapped to treatment (ExtGp3, n=187; ExtGp2, n=43; ExtGp1, n=55; ExtGp4 = 6; ExtGp5 = 2; ExtGp6 = 0) based on whether they were responders or non-responders, and were included in the EAS, including 56 (19.1%) participants who discontinued study intervention. There was a lower percentage of female participants (38.2%) in ExtGp1 compared with ExtGp2 (55.8%), and ExtGp3 (57.2%).

Efficacy Results

DR Period

- **Primary Endpoint:** Adjusted for multiple comparisons, the %CFB in central F-VASI at Week 24 was significantly greater for ritlecitinib doses 200/50 mg, 100/50 mg and 50 mg compared with placebo (least squares [LS] mean difference: -23.2, -23.2, and -20.6, respectively (Hochberg $p < 0.05$).

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The dose-response for central F-VASI by 4-parameter Bayesian E_{max} modeling showed the estimated effect on %CFB in central F-VASI for a 75 mg dose was -23.70; the additive effect of induction dosing was estimated to be -5.83.

- **Key Secondary Endpoint:** The proportion of participants that achieved central F-VASI75 was higher in the ritlecitinib 200/50 mg, 100/50 mg, and 50 mg groups than placebo (difference from placebo: 12.1%, 8.5%, and 7.7%, respectively; one-sided $p < 0.05$) at Week 24.

- **Other Secondary Endpoints**

  - No ritlecitinib group differentiated from placebo for the proportion of participants that achieved T-VASI50 at Week 24.

  - The only groups that differentiated from placebo in LS mean %CFB in T-VASI were the ritlecitinib 30 mg group at Week 4 (one-sided $p = 0.0490$) and the 100/50 mg group at Week 24 (one-sided $p = 0.0357$).

  - Regarding LS mean %CFB in central F-VASI, ritlecitinib 200/50 mg and 100/50 mg groups (with induction dose) produced an earlier separation from placebo than ritlecitinib 50 mg and 30 mg groups (no induction dose), both in all participants and in participants with BL central F-BSA ≥0.5.

  - Regarding LS mean %CFB in local F-VASI, there was mostly no difference between any ritlecitinib group and placebo at any visit considering all participants, while in participants with BL central F-BSA ≥0.5 separation from placebo was seen with ritlecitinib 200/50 mg, 100/50 mg, and 50 mg at multiple time points.

  - There was significant (unadjusted one-sided $p < 0.05$) difference between placebo and all ritlecitinib groups in LS mean %CFB in SA-VES from Week 4 to Week 24.

  - The only groups that showed a larger LS mean absolute CFB in T-VASI than placebo were the 30 mg group at Week 4 ($p = 0.0231$) and the 100/50 mg group at Week 24 ($p = 0.0274$).

  - The proportion of participants meeting T-VASI50 was similar between all ritlecitinib groups and placebo at all time points, and no participant in any ritlecitinib group met T-VASI75/90/100 during DR Period.

  - Participants in the ritlecitinib 200/50 mg and 100/50 mg groups, who received an induction dose for 4 weeks, showed separation from placebo in central F-VASI50 as early as Week 16, continuing through Week 24. Ritlecitinib 50 mg and 30 mg showed separation from placebo in central F-VASI50 at Week 24. No

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ritlecitinib dose separated from placebo in the proportion of participants achieving central F-VASI90 and no participant in any group met central F-VASI100.

- Ritlecitinib did not increase the proportion of participants that achieved local F-VASI50/75/90/100 at any time up to Week 24, compared with placebo.
- There were no differences between ritlecitinib and placebo in LS mean CFB in the VitiQoL total score, or in any of the 3 individual domain scores at any time.
- No participant treated with ritlecitinib achieved sIGA 0 ('clear') or 1 ('almost clear') and at least a 2-point improvement.

- **Exploratory Endpoints**
  - Targeted lesions: Ritlecitinib 200/50 mg, 100/50 mg, 50 mg, and 30 mg promoted repigmentation in stable lesions. In active lesions, depigmentation was reduced with ritlecitinib 200/50 mg, 100/50 mg, and 30 mg. The magnitude of the reduction was small in active lesions, compared with stable lesions.
  - PGIC-V: Only ritlecitinib 100/50 mg differentiated from placebo in the proportion of participants that achieved "very much improved" or "much improved" on PGIC-V at Week 24.
  - VNS: There was no separation between any ritlecitinib dose and placebo in the proportion of participants achieving a score of 4 or 5 on the VNS.

Ext Period

ExtGp3 - Long Term Effect of Ritlecitinib Treatment

- Central and Local F-VASI
  - All treatment sequences in ExtGp3 showed greater improvement in %CFB and absolute CFB in central F-VASI and local F-VASI from Week 24 to Week 48 than between Day 1 and Week 24. There was no plateau in improvement at Week 48.
  - Long-term ritlecitinib treatment (from Week 24 to Week 48) increased the proportion of participants who achieved central F-VASI50/75/90 and local F-VASI50/75/90, with the greatest improvement occurring post-Week 32.
- T-VASI

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- All treatment sequences in ExtGp3 showed greater improvement in %CFB in T-VASI and absolute CFB in T-VASI from Week 24 to Week 48 than between Day 1 and Week 24.

- Long-term ritlecitinib treatment (from Week 24 to Week 48) increased the proportion of participants that achieved T-VASI25/50/75 at Week 48 compared with Week 24.

- SA-VES: From Week 24 to Week 48, most treatment sequences in ExtGp3 showed an increase in LS mean %CFB in SA-VES.

- VitiQoL: Continued improvement in the mean CFB VitiQoL total score was mostly observed in all treatment sequences in ExtGp3.

- PGIC-V and VNS: The proportion of responders on the PGIC-V and VNS increased from Week 24 to Week 48 in all treatment sequences in ExtGp3.

ExtGp2 vs ExtGp3 - Additive Effect of nbUVB Treatment

The OC analysis showed an apparent additive effect of nbUVB; however, the LOCF analysis, which included 9 discontinued participants in ExtGp2 who met the discontinuation criterion of <10% improvement in %CFB in T-VASI at ExtWeek 12, showed that the additive effect of nbUVB was less pronounced and even no additive effect. The results from OC analysis are summarized below.

- Central F-VASI

  - The LS mean %CFB in central F-VASI was larger in ExtGp2 compared with ExtGp3 at ExtWeek 16 ($p = 0.0078$) and ExtWeek 24 ($p = 0.0090$).

  - The addition of nbUVB treatment to ritlecitinib 200/50 mg did not increase the proportion of participants who achieved central F-VASI50/75/90/100 over 24 weeks.

- Local F-VASI: The addition of nbUVB treatment to ritlecitinib 200/50 mg increased the %CFB in local F-VASI, and the proportion of participants achieving local F-VASI50/75/90.

- T-VASI: The addition of nbUVB treatment to ritlecitinib 200/50 mg increased the %CFB in T-VASI, and the proportion of participants achieving T-VASI50 at Week 24; there was no additive effect on T-VASI75/90/100.

- VitiQoL: The LS mean CFB in vitiQoL total score from DR Week 24 to ExtWeek 24 was larger in ExtGp2 than ExtGp3.

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- SA-VES: The addition of nbUVB treatment to ritlecitinib 200/50 mg increased the LS mean %CFB in SA-VES during the 24-week Ext Period.

- PGIC-V and VNS: The proportion of responders on the PGIC-V and VNS was higher in ExtGp2 than ExtGp3.

ExtGp1 - Effect of brepocitinib: the LS mean %CFB in central F-VASI consistently increased from ExtWeek 4 to ExtWeek 24.

PK Results

- The median plasma ritlecitinib concentrations were similar between Week 4 and Week 24 in participants who received the same dose throughout the DR Period (ie, 50 mg, 30 mg, 10 mg), while the median plasma concentrations were higher at Week 4 than Week 24 in participants who received a 200 mg or 100 mg induction dose.

- Independent of which treatment was received in the DR Period, participants who received ritlecitinib 200/50 mg, with or without nbUVB in the Ext Period, had median ritlecitinib concentrations comparable to those for the 200/50 mg group during the DR Period.

- Median maximum brepocitinib plasma concentrations (C_{max}) were observed at 1 hour post-dose at Weeks 8 and 24 following 60 mg and 30 mg doses.

PD Results

- [redacted]: During the DR Period at Week 24, the median %CFB values of [redacted] in the 200/50 mg (-23.7) and 100/50 mg (-14.5) groups, which received 50 mg for 20 weeks, were similar in magnitude to the 50 mg (-18.5) group, which received 50 mg for 24 weeks. During the Ext Period, the 200 mg/50 mg was the only ritlecitinib group to retain ≥95% of observations at ExtWeek 24, and small reductions in median %CFB of [redacted] were observed at ExtWeeks 4 and 24.

- [redacted]: There were no significant changes in [redacted] from BL during either the DR or Ext Period except for the following:

  - [redacted]: Reductions in [redacted] were observed at Week 4, but the values returned to BL at Week 24.

  - [redacted]: Reductions in [redacted] were observed at Week 4 in a dose dependent manner; these reductions in [redacted] was still present in the 200/50 mg, 100/50 mg and 50 mg groups at Week 24.

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Safety Results

DR Period - TEAEs and SAEs

In general, no dose dependency was observed among the 6 different groups in terms of TEAEs.

- In total, there were 277 (76.1%) participants with 756 all-causality TEAEs, and 126 (34.6%) participants with 195 treatment-related AEs.
- There were 4 (1.1%) participants with SAEs; none were treatment-related.
- The majority of all TEAEs (both all-causality and treatment-related) across treatment groups were mild or moderate in severity. Severe AEs were reported in 11 (3.0%) participants, and in 3 participants severe AEs were treatment-related.
- There were no deaths (DR or Ext Period).
- There were 19 (5.2%) and 12 (3.3%) participants who were discontinued from the study due to all-causality and treatment-related AEs, respectively. 27 (7.4%) and 8 (2.2%) participants had dose reduced or temporary discontinuation due to all-causality and treatment-related AEs, respectively.
- Eleven (3.0%) participants discontinued study intervention due to COVID-19 related reasons.
- The 3 most frequently reported preferred term TEAEs were: nasopharyngitis, upper respiratory tract infection (URTI), and headache (all-causality); nasopharyngitis, diarrhea, and headache (treatment-related).

Ext Period – TEAEs and SAEs

Overall, no trend was observed among the 3 different groups (brepocitinib, ritlecitinib with or without nbUVB) in terms of TEAEs.

- In total, there were 194 (66.2%) participants with 454 all-causality TEAEs, and 68 (23.2%) participants with 99 treatment-related TEAEs.
- There were 2 (0.7%) participants with SAEs, and in 1 participant the SAE (from brepocitinib group) was treatment-related.
- The majority of all TEAEs (both all-causality and treatment-related) across treatment groups were mild or moderate in severity. There were 8 (2.7%) participants with severe AEs (2 from brepocitinib group and 6 from ExtGp3), and in 1 participant (from brepocitinib group) the severe AE was treatment-related.

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- There were 10 (3.4%) and 8 (2.7%) participants who were discontinued from the study due to all-causality and treatment-related AEs, respectively. 18 (61%) and 7 (2.4%) participants had dose reduced or temporary discontinuation due to all-causality and treatment-related AEs, respectively.

- Nine (3.1%) participants discontinued study intervention due to COVID-19 related reasons.

- The 3 most frequently reported all-causality preferred term TEAEs were urinary tract infection, URTI, and headache. The 2 treatment-related TEAEs that occurred in >1.0% of participants across treatment groups were decreased neutrophil count and headache.

ExtGp3 (DR and Ext) – TEAEs and SAEs

- Overall, there were 162 (86.6%) participants with 647 all-causality TEAEs, and 82 (43.9%) participants with 152 treatment-related TEAEs.

- There were 4 (2.1%) participants with SAEs; none were treatment-related.

- The majority of all TEAEs (both all-causality and treatment-related) during the entire study were mild or moderate in severity. There were 12 (6.4%) participants with severe AEs; none were treatment-related. The frequency of severe AEs was similar in the DR (3.7%) and Ext (3.2%) Periods.

- Six (3.2%) participants in ExtGp3 were discontinued from the study due to TEAEs (all treatment-related; 5 were discontinued due to AEs reported during the Ext Period). 20 (10.7%) and 3 (1.6%) participants had dose reduced or temporary discontinuation due to all-causality and treatment-related AEs, respectively.

- The 3 most frequently reported preferred TEAEs (both all-causality and treatment-related) were nasopharyngitis, URTI, and headache.

Laboratory Evaluations: Without regard to BL abnormality, 233 (64.0%) participants in the DR Period and 208 (71.5%) participants in the Ext Period experienced laboratory abnormalities. The proportion was similar across treatment groups in both the DR and Ext Periods.

- **Chemistry**

    - There were no clinically meaningful changes in lipid profile across treatment groups in the DR or Ext Period.

    - No trends in creatine kinase (CK) were noted with ritlecitinib in the DR or Ext Period. A total of 27 participants in the DR Period and 15 participants in the Ext

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Period had CK >3 × upper limit of normal (ULN); 7 participants in the study had CK >10 × ULN. No clinically significant events of myoglobinuria, acute renal failure or heart failure were noted.

- A total of 15 ritlecitinib treated participants experienced isolated and transient decline from BL in serum creatinine-based estimated glomerular filtration rate (eGFR) ≥30%. None of the declines were associated with similar changes in cystatin-C based eGFR or resulted in adverse renal events or discontinuation from the study.

- In terms of alanine aminotransferase, aspartate aminotransferase, or total bilirubin, no trends were noted, and there was no participant with cases that met Hy's law criteria.

- **Hematology**: The mean absolute values of hematology parameters (platelets, lymphocytes, neutrophils, hemoglobin, hematocrit, erythrocytes, and reticulocytes/erythrocytes) for all participants stayed within the normal ranges in the DR and Ext Periods.

  - No participant met common terminology criteria for adverse events (CTCAE, v5.0 hereafter) ≥Grade 2 thrombocytopenia. Isolated Grade 1 AEs of thrombocytopenia (1) and platelet decrease (1) were reported without any other accompanying clinical symptoms.

  - No participant met CTCAE ≥Grade 4 criteria for lymphocytes. There were 6 participants with lymphocyte events that were AEs, none were severe.

  - No participant met CTCAE ≥Grade 4 criteria for neutrophils in ritlecitinib groups. There were 12 participants with neutrophil events that were AEs, none were severe.

  - No participant met CTCAE Grade 3/4 criteria for hemoglobin. A total of 2 participants met CTCAE Grade 2.

Other Safety Evaluations

- There were 6 participants with clinically significant improvement from BL and 4 participants with clinically significant worsening from BL in hearing. All the 4 worsening cases were unilateral and mild in severity, and assessed as not related to the study intervention by an external consultant.

- There were 2 participants with non-melanoma skin cancers, both unrelated to study intervention.

- Seven participants had confirmed cases of herpes simplex.

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- Five participants had confirmed cases of herpes zoster.
- Twelve participants had rash.
- Cases from 26 participants were adjudicated, including malignancy (2), opportunistic infections of special interest infection (3), histopathology event (1), neuro-audiology (3), and neurology (18).
- There were 4 confirmed cases of COVID-19.
- No clinically significant vital sign abnormalities were observed.
- There were 2 participants with clinically meaningful changes in ECG, both unrelated to study intervention.

Conclusions

Efficacy

- Ritlecitinib 200/50 mg, 100/50 mg, and 50 mg met the primary endpoint of %CFB in central F-VASI at Week 24 and the key secondary endpoint of the proportion of participants with central F-VASI75 at Week 24.
    - In participants with BL central F-BSA ≥0.5, the %CFB in central and local F-VASI at Week 24 was significantly different from placebo in the ritlecitinib 200/50 mg, 100/50 mg, and 50 mg groups.
    - Long-term (up to 48 weeks) ritlecitinib treatment produced greater improvement in %CFB in central F-VASI, with the greatest improvement occurring post Week 32; there was no plateau in improvement at Week 48.
    - Results were similar at Week 48 for the %CFB in central and local F-VASI when including only participants with BL central F-BSA ≥0.5.
    - The benefit of nbUVB treatment added to ritlecitinib treatment was limited and the comparison rendered inaccurate due to the protocol-required forced discontinuation in the nbUVB arm.
- Induction dosing (4 weeks of ritlecitinib 200 mg or 100 mg, followed by 50 mg for 20 weeks) produced an earlier separation from placebo in %CFB in central F-VASI than continuous dosing of 50 mg for 24 weeks; however, results were similar at Week 24 for ritlecitinib treatments with and without induction dosing.
- Ritlecitinib treatment promoted repigmentation in stable lesions and stabilized (ie, prevented or reduced further depigmentation) in active lesions over 24 weeks.

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- Consistent improvement was seen in the PROs SA-VES, VitiQoL, PGIC-V, and VNS with long-term (48 week) ritlecitinib treatment.

Safety

- Ritlecitinib was generally safe and well-tolerated during the 24-week DR Period, with no unexpected safety findings in participants treated continuously with ritlecitinib for up to 48 weeks.
    - There were no dose-dependent trends in SAEs, severe AEs, AEs leading to discontinuation, other significant AEs (infections, dermatological events, including herpes zoster AEs, and hearing test abnormalities), or in the most frequently reported AEs across treatment groups in the DR and Ext Periods. There were no SAEs reported that were assessed as related to ritlecitinib. There were no deaths.
    - The incidence of AEs was similar during induction and maintenance dosing; participants who received 200 mg induction dosing in both the DR and Ext Periods (200/50 mg→200/50 mg sequence) did not have an increased number of TEAEs.
    - The overall incidence and number of AEs was lower during the Ext Period (Weeks 24 to 48) compared with the DR Period (Day 1 to Week 24).
- No clinically meaningful trends for hematology, liver function, kidney function, lipids, or chemistry lab parameters were observed in participants treated with ritlecitinib during the 24-week DR Period, and no new clinically meaningful trends in the lab parameters were detected in participants treated continuously with ritlecitinib for up to 48 weeks.
- For the 55 participants that received brepocitinib during the Ext Period, the incidence of AEs (including SAEs, severe AEs, AEs leading to discontinuation, other significant AEs) was similar to the other treatment groups in the Ext Period, and no new clinically meaningful trends for hematology, liver, renal, lipids or chemistry lab parameters were observed.