Safety and Efficacy of Ritlecitinib and Brepocitinib in Alopecia Areata: Results from the Crossover Open-Label Extension of the ALLEGRO Phase 2a Trial

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The 24-week, double-blind period of the ALLEGRO phase 2a trial (NCT02974868) evaluated the safety and efficacy of ritlecitinib (Jak3/tyrosine kinase expressed in the hepatocellular carcinoma inhibitor) and brepocitinib (tyrosine kinase 2/Jak1 inhibitor) in patients with alopecia areata; patients could subsequently continue treatment in a 24-week single-blind extension, followed by a crossover open-label extension, described in this article. Patients who did not achieve ≥30% improvement from baseline in Severity of Alopecia Tool score at the end of the single-blind extension entered a 24-week crossover open-label extension: the ritlecitinib group switched to brepocitinib, and the brepocitinib group switched to ritlecitinib. Eighteen patients switched to brepocitinib, and five switched to ritlecitinib. Six treatment-emergent adverse events were reported by five patients; no new safety risks were observed after crossover. An exploratory efficacy evaluation showed that none of the five patients receiving ritlecitinib in the crossover open-label extension achieved ≥30% improvement from baseline in Severity of Alopecia Tool score or improvement in eyebrow/eyelash assessments. Four of 16 patients receiving brepocitinib achieved ≥30% improvement from baseline in Severity of Alopecia Tool score or better; 4 of 15 and 5 of 12 showed improvement in eyebrow and eyelash assessments, respectively. Although the small number of patients precludes firm conclusions regarding efficacy, the data suggest that some patients with alopecia areata and inadequate response to ritlecitinib after ≥24 weeks show benefit after switching to brepocitinib.

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INTRODUCTION

Alopecia areata (AA) is an autoimmune disease that has underlying immune-inflammatory pathogenesis and is characterized by nonscarring hair loss (Pratt et al., 2017). The disease course is unpredictable, and hair loss may remit for long periods, wax and wane, or be persistent (Cranwell et al., 2019; Pratt et al., 2017). The global prevalence of AA is estimated to be approximately 2% (Lee et al., 2020), and the psychosocial impact of AA on patients and their families can be substantial (Liu et al., 2018; Okhovat et al., 2019). Currently available treatments for more extensive AA have limited efficacy (Pratt et al., 2017).

The pathogenesis of AA involves cytokines such as INF-γ and IL-15, which signal through Jak (Triyangkulsri and Suchonwanit, 2018). Multiple oral Jak inhibitors are under investigation for the treatment of AA (Wang et al., 2018), including ritlecitinib, which inhibits Jak3 and the tyrosine kinase expressed in the hepatocellular carcinoma family, and brepocitinib, which inhibits tyrosine kinase 2 and Jak1.

The double-blind period of the ALLEGRO Phase 2a trial (NCT02974868) investigated the safety and efficacy of ritlecitinib and brepocitinib in 142 adults with AA and ≥50% scalp hair loss; at week 24, clinically significant hair regrowth was shown and both treatments were generally well-tolerated (King et al., 2021). After the double-blind period, the trial continued with a single-blind extension (SBE) that involved active treatment for an additional 24 weeks (Peeva et al., 2022). Inclusion in a subsequent 24-week crossover open-label extension (COE) was based on the Severity of Alopecia Tool (SALT) score at the end of the SBE. SALT is an instrument used to measure the amount of scalp hair loss, with scores ranging from 0 (no scalp hair loss) to 100 (complete scalp hair loss) (Olsen et al., 2004). Patients who did not achieve $SALT_{30}$ (≥30% improvement in the SALT score) at the end of the SBE (nonresponders) entered the 24-week COE, in which they switched from ritlecitinib to brepocitinib and vice versa.

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Abbreviations: AA, alopecia areata; COE, crossover open-label extension; SALT, Severity of Alopecia Tool; SBE, single-blind extension; TEAE, treatment-emergent adverse event

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Table 1. Baseline Demographics

n (%)	Ritlecitinib (n = 5)	Brepocitinib (n = 18)	Total (N = 23)
Age, years			
18-44	4 (80.0)	9 (50.0)	13 (56.5)
45-64	1 (20.0)	9 (50.0)	10 (43.5)
≥65	0	0	0
Mean (SD)	31.8 (14.1)	42.7 (12.4)	40.3 (13.2)
Sex			
Female	3 (60.0)	12 (66.7)	15 (65.2)
Male	2 (40.0)	6 (33.3)	8 (34.8)
Race			
White	5 (100.0)	14 (77.8)	19 (82.6)
Black or African American	0	1 (5.6)	1 (4.3)
Asian	0	2 (11.1)	2 (8.7)
Other	0	1 (5.6)	1 (4.3)
Ethnicity			
Not Hispanic or Latino	5 (100.0)	18 (100.0)	23 (100.0)

RESULTS

The COE included five patients who switched to ritlecitinib after 24–48 weeks of treatment with brepocitinib and 18 patients who switched to brepocitinib after 24–48 weeks of treatment with ritlecitinib. The mean (SD) age was 31.8 (14.1) years in the ritlecitinib group and 42.7 (12.4) years in the brepocitinib group (Table 1). The majority of patients were female (60% in the ritlecitinib group and 67% in the brepocitinib group) and white (100% in the ritlecitinib group and 78% in the brepocitinib group). The median (range) duration of treatment in the COE was 169 (161–183) days in the ritlecitinib group and 169 (38–176) days in the brepocitinib group.

During the COE, there were six treatment-related treatment-emergent adverse events (TEAEs) in five patients (Table 2). No participants experienced TEAEs of neutropenia, a decrease in neutrophil count, an increase in blood creatinine phosphokinase, an increase in liver function test results, or an increase in transaminases. One patient in the brepocitinib group experienced a grade 3 decrease in absolute neutrophil count, and one experienced an increase in creatine kinase >3 times the upper limit of normal. No patients discontinued from the study owing to TEAEs; two patients (one each in the ritlecitinib and brepocitinib groups) had temporary discontinuations as a result of TEAEs: influenza-like illness and torticollis in the patient with ritlecitinib and bronchitis in the patient with brepocitinib. One patient in the brepocitinib group experienced a serious adverse event (gastroenteritis salmonella not considered related to the study drug). No new safety risks were observed after treatment crossover.

The COE was not powered for efficacy. Five patients in the ritlecitinib group and 17 patients in the brepocitinib group were eligible for efficacy assessments, but not all 17 patients in the brepocitinib group were evaluated for SALT score, eyebrow assessment, and eyelash assessment. Sixteen patients were evaluable for SALT assessment, 15 were evaluable for eyebrow assessment, and 12 were evaluable for eyelash assessment. No patients in the ritlecitinib group achieved $SALT_{30}$ (≥30% improvement from the SALT score) or better at the end of SBE, and none achieved a ≥1-grade improvement in eyebrow or eyelash assessments (Table 3). The brepocitinib group showed an improvement from baseline in SALT score compared with the placebo group from the double-blind period, with 4 of 16 patients achieving $SALT_{30}$ or better. Four of 15 patients in the brepocitinib group achieved a ≥1-grade improvement in eyebrow assessment, and 5 of 12 patients achieved a ≥1-grade improvement in eyelash assessment.

Table 2. TEAEs in the 24-Week, Crossover, Open-Label Extension of the ALLEGRO Phase 2a Trial

Variable, n (%)	Ritlecitinib (n = 5)	Brepocitinib (n = 18)[1]	Total (N = 23)
All-cause TEAEs			
Total number of TEAEs	9	17	26
Patients with TEAEs	4 (80)	9 (50)	13 (57)
Patients with serious TEAEs	0	1 (6)[2]	1 (4)
Patients with severe TEAEs	0	1 (6)[2]	1 (4)
Patients discontinued from the study owing to TEAEs	0	0	0
Patients discontinued from study drug owing to TEAEs but continued study	0	0	0
Patients with dose reduction or temporary discontinuation due to TEAEs	1 (20)[3]	1 (6)[4]	2 (9)
Treatment-related TEAEs			
Total number of TEAEs	2[5]	4[6]	6
Patients with TEAEs	2 (40)	3 (17)	5 (22)
Patients with serious TEAEs	0	0	0
Patients with severe TEAEs	0	0	0
Patients discontinued from the study owing to TEAEs	0	0	0
Patients discontinued from study drug owing to TEAEs but continued study	0	0	0
Patients with dose reduction or temporary discontinuation due to TEAEs	0	1 (6)[4]	1 (4)

Abbreviation: TEAE, treatment-emergent adverse event.
[1]One patient classified as a responder to ritlecitinib at the end of the single-blind extension was included in the brepocitinib group during the crossover extension. This patient was included in the analyses of safety but not of efficacy.
[2]*Salmonella* gastroenteritis that did not lead to discontinuation.
[3]Moderate-severity influenza-like illness and torticollis that led to temporary discontinuation of study drug.
[4]Moderate-severity bronchitis that led to temporary discontinuation of study drug.
[5]One each of nausea and upper respiratory tract infection.
[6]One each of acne, bronchitis, rhinitis, and upper respiratory tract infection.

DISCUSSION

In the COE of the ALLEGRO phase 2a trial, both ritlecitinib and brepocitinib had an acceptable safety and tolerability profile, with no new safety risks observed after treatment crossover. Safety findings in the COE were consistent with those of the double-blind period and SBE (King et al., 2021; Peeva et al., 2022). Although this study was not powered to evaluate efficacy, approximately one quarter of patients who were unresponsive to treatment with ritlecitinib for ≥24 weeks achieved $SALT_{30}$ or better after switching to brepocitinib.

Table 3. Exploratory Efficacy Endpoints at Week 24 of the Crossover Open-Label Extension of the ALLEGRO Phase 2a Trial

Endpoint	Ritlecitinib (n = 5)	Brepocitinib (n = 17)
Reduction from baseline in SALT score, least-squares mean difference versus placebo (90% CI)[1]	−6 (−115 to 102), n = 2	17 (12 to 22), n = 12
Patients with predefined improvement in scalp hair loss; n/N % difference from placebo[2] (90% CI)[3]		
$SALT_{30}$	0/5; −2 (−11 to 40)	4/16; 23 (5−45)
$SALT_{50}$	0/5; −2 (−11 to 40)	2/16; 10 (−2 to 32)
$SALT_{75}$	0/5; −2 (−11 to 40)	2/16; 10 (−2 to 32)
$SALT_{90}$	0/5; 0 (−7 to 45)	1/16; 6 (−2 to 26)
$SALT_{100}$	0/5; 0 (−7 to 45)	0/16; 0 (−6 to 17)
Patients with a ≥1-grade improvement in eyebrow assessment; n/N % difference from placebo (90% CI)[3,4]	0/5; −15 (−29 to 29)	4/15; 12 (−8 to 36)
Patients with a ≥1-grade improvement in eyelash assessment; n/N % difference from placebo (90% CI) [3,4]	0/4; −14 (−29 to 35)	5/12; 27 (2−54)

Abbreviations: CI, confidence interval; SALT, Severity of Alopecia Tool.
$SALT_{30}$, $SALT_{50}$, $SALT_{75}$, $SALT_{90}$, and $SALT_{100}$ indicate ≥30%, ≥50%, ≥75%, ≥90%, and 100% improvement from baseline in SALT score.
[1]Calculated using a linear mixed-effects model for repeated measures, with the placebo group of the double-blind period (n = 47) used as the comparator.
[2]Placebo data are from the double-blind period of the study.
[3]Calculated using Chan and Zhang's exact method, with the placebo group of the double-blind period (n = 47) used as the comparator and missing data imputed as nonresponders.
[4]In patients with an abnormal assessment at baseline.

Data on switching between oral Jak inhibitors in the treatment of AA are limited. However, in rheumatoid arthritis, efficacy has been shown in patients who switch to a different Jak inhibitor after an inadequate response to a previous Jak inhibitor (Ebina et al., 2022; Retuerto et al., 2021). This analysis was limited by the small number of patients, single-dosage regimen of each study drug, and open-label study design.

In conclusion, ritlecitinib and brepocitinib had an acceptable safety and tolerability profile during COE, with no new safety signals observed after treatment crossover. Although the small number of patients precludes any firm conclusions regarding efficacy, the COE data suggest that some patients with AA unresponsive to treatment with ritlecitinib for ≥24 weeks show benefit after switching to brepocitinib. Further studies are needed to assess the risk and benefit of switching patients who are unresponsive to ritlecitinib to brepocitinib.

MATERIALS AND METHODS

Study design

The study design, including inclusion and exclusion criteria, of the ALLEGRO Phase 2a randomized, double-blind, multicenter trial and results from the double-blind period and SBE were published previously (King et al., 2021; Peeva et al., 2022). In the 24-week, double-blind period, patients aged ≥18 years with AA and ≥50% scalp hair loss were randomly assigned 2:1:2:1 to receive ritlecitinib (200 mg once daily for 4 weeks followed by 50 mg once daily for 20 weeks) or placebo or brepocitinib (60 mg once daily for 4 weeks followed by 30 mg once daily for 20 weeks) or placebo (Figure 1).

After a 4-week washout period after week 24, patients continued in the SBE in one of three groups: (i) placebo nonresponders received active treatment with ritlecitinib (200 mg once daily for 4 weeks followed by 50 mg once daily for 20 weeks) or brepocitinib (60 mg once daily for 4 weeks followed by 30 mg once daily for 20 weeks, (ii) active nonresponders (patients who had <30% improvement from baseline in SALT score at week 24) received the same active treatment (loading dose for 4 weeks followed by maintenance dose for 20 weeks), and (iii) active responders (patients who achieved $SALT_{30}$) switched to placebo (for up to 24 weeks) until they met the retreatment criterion (>30% loss of hair regrown) and then received 24 weeks of the same active treatment they received during the double-blind period. In the SBE, investigators were aware of treatment assignment, but patients were blinded to treatment. Patients who entered the SBE as nonresponders (placebo or active nonresponders) and remained as nonresponders at the end of the SBE were eligible to enter the COE.

After a 4-week washout period, patients who had received ritlecitinib during the SBE were assigned to brepocitinib during the COE and vice versa. In the COE, patients received ritlecitinib (200 mg once daily for 4 weeks followed by 50 mg once daily for 20 weeks) or brepocitinib (60 mg once daily for 4 weeks followed by 30 mg once daily for 20 weeks). The primary safety endpoint of the COE was the incidence of TEAEs and laboratory abnormalities. Exploratory efficacy results for patients in the COE were compared with those of the placebo patients in the double-blind period, with baseline defined as the last measurement before first dosing (day 1). In patients receiving ritlecitinib and brepocitinib in the COE, baseline was defined as the last measurement at week 24 of SBE. Exploratory efficacy endpoints included the mean change from baseline in SALT score; percentage of patients achieving $SALT_{30}$, $SALT_{50}$ (≥50% improvement in the SALT score), $SALT_{75}$ (≥70% improvement in the SALT score), $SALT_{90}$ (≥90% improvement in the SALT score), and $SALT_{100}$ (100% improvement in the SALT score); and percentage of patients achieving a ≥1-grade improvement in eyebrow and eyelash assessments (4-point scales: 0 [none], 1 [minimal eyebrows/eyelashes], 2 [moderate eyebrows/eyelashes], 3 [normal]).

The study was conducted according to the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference on Harmonization, and local country regulations, where applicable. Either a centralized ethics committee or institutional review board (Bellberry Human Research Ethics Committee, Adelaide, South Australia; Copernicus Group Independent Review Board, Cary, NC; Western Institutional Review Board, Puyallup,

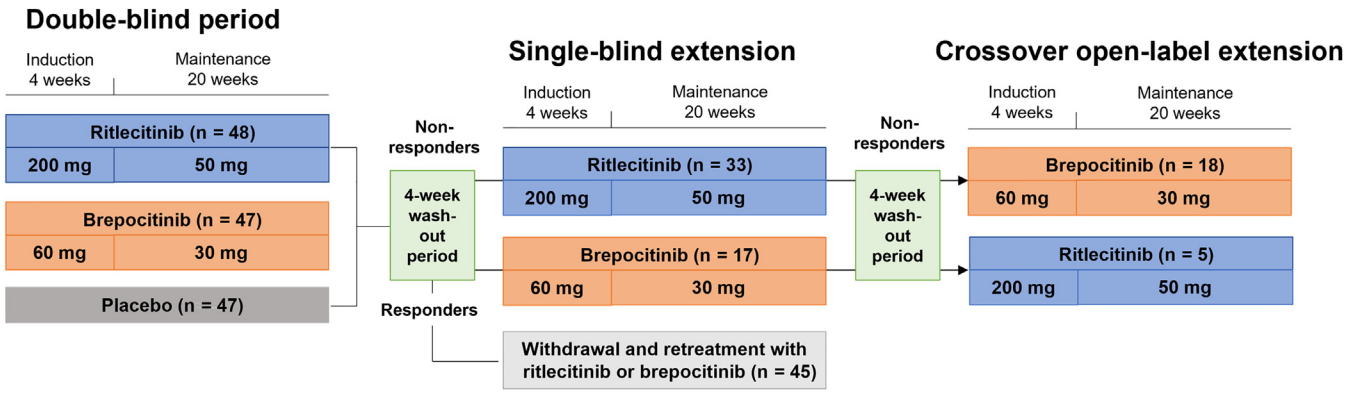

Figure 1. Study design.

Washington) or the ethics committee or institutional review board at the participating center (Rockefeller University Institutional Review Board, the University of Manitoba Bannatyne Campus Biomedical Research Ethics Board, University of Utah Institutional Review Board) approved the study protocol, and all patients provided written informed consent.

Data availability statement

On request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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CONFLICT OF INTEREST

BK has served on advisory boards and/or is a consultant and/or a clinical trial investigator for AbbVie, Aclaris Therapeutics, AltruBio, Almirall, AnaptysBio, Arena Pharmaceuticals, Bioniz Therapeutics, Bristol Myers Squibb, Concert Pharmaceuticals, Dermavant Sciences, Horizon Therapeutics, Eli Lilly and Company, Incyte, LEO Pharma, Otsuka/Visterra, Pfizer, Regeneron, Sanofi Genzyme, TWi Biotechnology, and Viela Bio. He is on speaker bureaus for AbbVie, Incyte, Pfizer, Regeneron, and Sanofi Genzyme. EGY declares receiving institutional grants from AbbVie, Asana BioSciences, Celgene, Dermavant, Dermira, DS Biopharma, Eli Lilly, Galderma, Glenmark, Innovaderm Research, Janssen, LEO Pharma, Novan, Novartis, Pfizer, Ralexar Therapeutics, Regeneron, and Union Therapeutics and reports receiving honoraria and/or consultation fees from AbbVie, Allergan, Amgen, Asana Biosciences, Celgene, Concert, Dermira, DS Biopharma, Eli Lilly, EMD Serono, Escalier Biosciences, FLX Bio, Galderma, Glenmark, Kyowa, LEO Pharma, Mitsubishi Tanabe, Novartis, Pfizer, Regeneron, Sanofi Aventis, and Union Therapeutics. EP, AB, LZ, HZ, LAC, and MSV are employees of Pfizer and hold stock and/or stock options with Pfizer. RS declares providing professional services to AbbVie, Aerotech, Akesobio, Arena, Amgen, Arcutis, Ascend, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Celgene, Coherus Biosciences, Connect, Cutanea, Demira, Eli Lilly, Galderma, GlaxoSmithKline, Janssen, LEO Pharma, MedImmune, Merck & Co, MSD, Novartis, Oncobiologics, Pfizer, Regeneron, Reistone, Roche, Samson Clinical, Sanofi, and Sun Pharma.

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AUTHOR CONTRIBUTIONS

Conceptualization: BK, EP, AB; Data Curation: EP, AB, LZ, HZ, LAC, MSV; Writing – Original Draft Preparation: BK, EP; Writing – Review and Editing: BK, EGY, EP, AB, LZ, HZ, LAC, MSV, RS

REFERENCES

Cranwell WC, Lai VW, Photiou L, Meah N, Wall D, Rathnayake D, et al. Treatment of alopecia areata: an Australian expert consensus statement. Australas J Dermatol 2019;60:163–70.

Ebina K, Hirano T, Maeda Y, Yamamoto W, Hashimoto M, Murata K, et al. Factors affecting drug retention of Janus kinase inhibitors in patients with rheumatoid arthritis: the ANSWER cohort study. Sci Rep 2022;12:134.

King B, Guttman-Yassky E, Peeva E, Banerjee A, Sinclair R, Pavel AB, et al. A phase 2a randomized, placebo-controlled study to evaluate the efficacy and safety of the oral Janus kinase inhibitors ritlecitinib and brepocitinib in alopecia areata: 24-week results. J Am Acad Dermatol 2021;85:379–87.

Lee HH, Gwillim E, Patel KR, Hua T, Rastogi S, Ibler E, et al. Epidemiology of alopecia areata, ophiasis, totalis, and universalis: a systematic review and meta-analysis. J Am Acad Dermatol 2020;82:675–82.

Liu LY, King BA, Craiglow BG. Alopecia areata is associated with impaired health-related quality of life: a survey of affected adults and children and their families. J Am Acad Dermatol 2018;79:556–8.e1.

Okhovat JP, Marks DH, Manatis-Lornell A, Hagigeorges D, Locascio JJ, Senna MM. Association between alopecia areata, anxiety, and depression: a systematic review and meta-analysis [e-pub ahead of print] J Am Acad Dermatol 2019. https://doi.org/10.1016/j.jaad.2019.05.086. Accessed July 1, 2022.

Olsen EA, Hordinsky MK, Price VH, Roberts JL, Shapiro J, Canfield D, et al. Alopecia areata investigational assessment guidelines–part II. National Alopecia Areata Foundation. J Am Acad Dermatol 2004;51:440–7.

Peeva E, Guttman-Yassky E, Banerjee A, Sinclair R, Cox LA, Zhu L, et al. Maintenance, withdrawal and re-treatment with ritlecitinib and brepocitinib in patients with alopecia areata in a single-blind extension of a phase 2a randomized clinical trial. J Am Acad Dermatol 2022;87:390–3.

Pratt CH, King LE Jr, Messenger AG, Christiano AM, Sundberg JP. Alopecia areata. Nat Rev Dis Primers 2017;3:17011.

Retuerto M, Trujillo E, Valero C, Fernandez-Espartero C, Soleto CY, Garcia-Valle A, et al. Efficacy and safety of switching Jak inhibitors in rheumatoid arthritis: an observational study. Clin Exp Rheumatol 2021;39:453–5.

Triyangkulsri K, Suchonwanit P. Role of Janus kinase inhibitors in the treatment of alopecia areata. Drug Des Devel Ther 2018;12:2323–35.

Wang EHC, Sallee BN, Tejeda CI, Christiano AM. JAK inhibitors for treatment of alopecia areata. J Invest Dermatol 2018;138:1911–6.