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

Brett King1, Emma Gutman-Yassky2, Elena Peeva3, Anindita Banerjee4, Linda Zhu5, Hua Zhu5, Lori Ann Cox3, Michael S. Vincent5 and Rodney Sinclair6

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.

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 SALT30 (≥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.

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 SALT30 (≥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.

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 SALT30 (≥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.
Table 1. Baseline Demographics

| Variable                  | 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 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 SALT30 (≥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 SALT30 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.

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 SALT30 or better after switching to brepocitinib.
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 SALT30 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 before first dosing (day 1). In patients receiving ritlecitinib and brepocitinib in the COE, baseline was 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 before first dosing (day 1). In patients receiving ritlecitinib and brepocitinib in the COE, baseline was defined as the last measurement before first dosing (day 1).

**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) | −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 (90% CI) | 0/5; −2 (−11 to 40), 4/16; 23 (5−45) | 0/5; −2 (−11 to 40), 2/16; 10 (−2 to 32) |
| SALT₃₀ | 0/5; −2 (−11 to 40), 2/16; 10 (−2 to 32) | 0/5; −2 (−11 to 40), 2/16; 10 (−2 to 32) |
| SALT₅₀ | 0/5; 0 (−7 to 45), 1/16; 6 (−2 to 26) | 0/5; 0 (−7 to 45), 0/16; 0 (−6 to 17) |
| SALT₇₅ | 0/5; 0 (−7 to 45), 1/16; 6 (−2 to 26) | 0/5; 0 (−7 to 45), 0/16; 0 (−6 to 17) |
| SALT₉₀ | 0/5; 0 (−7 to 45), 1/16; 6 (−2 to 26) | 0/5; 0 (−7 to 45), 0/16; 0 (−6 to 17) |
| SALT₁₀₀ | 0/5; 0 (−7 to 45), 1/16; 6 (−2 to 26) | 0/5; 0 (−7 to 45), 0/16; 0 (−6 to 17) |

Abbreviations: CI, confidence interval; SALT, Severity of Alopecia Tool. SALT₃₀, SALT₅₀, SALT₇₅, SALT₉₀, and SALT₁₀₀ indicate ≥30%, ≥50%, ≥75%, ≥90%, and 100% improvement from baseline in SALT score.

1Calculated using a linear mixed-effects model for repeated measures, with the placebo group of the double-blind period (n = 47) used as the comparator.

2Placebo data are from the double-blind period of the study.

3Calculated 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.

4In patients with an abnormal assessment at baseline.
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.

ORCID
Brett King: http://orcid.org/0000-0002-4576-4616
Emma Guttmann-Yassky: http://orcid.org/0000-0002-9363-324X
Elena Peeva: http://orcid.org/0000-0003-4869-3240
Anindita Banerjee: http://orcid.org/0000-0001-2982-2940
Linda Zhu: http://orcid.org/0000-0001-7358-8632
Hua Zhu: http://orcid.org/0000-0002-4908-0174
Lori Ann Cox: http://orcid.org/0000-0001-8420-6994
Michael S. Vincent: http://orcid.org/0000-0001-9569-4284
Rodney Sinclair: http://orcid.org/0000-0001-6751-1428

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, AnaptyBio, Arena Pharmaceuticals, Bioniz Therapeutics, Bristol Myers Squibb, Concert Pharmaceuticals, Dermavant Sciences, Horizon Therapeutics, Eli Lilly and Company, Incyte, LEO Pharma, Onsiva/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, DermaRX, DS Biopharma, Eli Lilly, Galderma, Glenmark, Innovadem 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, DermaRX, 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, MSV, RS, EP, AB, LZ, HZ, LAC, MSV, RS, EP, AB, LZ, HZ, LAC, MSV, RS, EP, AB, LZ, HZ, LAC, MSV, RS, EP, AB, LZ, HZ, LAC, MSV, RS. Factors affecting drug retention of Janus kinase inhibitors in patients with rheumatoid arthritis: the ANSWER cohort study. Sci Rep 2022;12:1134. King B, Guttmann-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. Lui 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;79:556–6. Okhovat JP, Marks DH, Manatis-Lornell A, Hagi-georges D, Locascio JJ, Senn 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 investigative assessment guidelines—part II. National Alopecia Areata Foundation. J Am Acad Dermatol 2004;51:440–7. Peeva E, Guttmann-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, GarciaValle A, et al. Efficacy and safety of switching Jak inhibitors in rheumatoid arthritis: an observational study. Clin Exp Rheumatol 2021;39:453–5. Triayangkul K, Suchonwanit P. Role of Janus kinase inhibitors in the treatment of alopecia areata. Drug Des Devel Ther 2018;12:3231–35. Wang EHC, Salleo BN, Tejeda CJ, Christiano AM. Jak inhibitors for treatment of alopecia areata. J Invest Dermatol 2018;138:1911–6.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view a copy of this license, visit http://creativecommons.org/licenses/by-nc-nd/4.0/