A phase 2a trial of brepocitinib for cicatricial alopecia

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Background: Cicatricial alopecias are chronic, progressive scarring hair-loss conditions. Molecular dysregulation is not fully understood, hindering treatment development. Th1/IFNγ signaling and Janus kinase dysregulation has shown involvement, providing rationale for this phase 2a trial with Tyrosine kinase 2/Janus kinase 1 inhibitor brepocitinib.

Methods: Randomized, placebo-controlled phase 2a trial spanning 52 weeks. Adults (≥18 years of age) with lichen planopilaris, frontal fibrosing alopecia, or central centrifugal cicatricial alopecia diagnosis were randomized 3:1 to brepocitinib 45 mg daily or placebo for 24 weeks, after which all patients received brepocitinib for another 24 weeks, with a safety follow up 4 weeks later. Lesional scalp biopsies were collected at baseline, week 24, and week 48. Coprimary endpoints were changes in lesional expression of C-C motif chemokine ligand (CCL5), changes in lesional expression of fibrosis-related markers, and safety at week 24.

Results: Patients receiving brepocitinib showed significant downregulation in CCL5 expression at week 24 (P = .004). Enrichment analysis of a subset of fibrosis markers showed trending upregulation in placebo patients ($P < .1$). Brepocitinib was well tolerated and improved clinical severity scores.

Limitations: Single-dose regimen, small placebo group.

Conclusion: Brepocitinib significantly reduces CCL5 expression and was well tolerated at week 24, meeting coprimary endpoints. Brepocitinib reduces inflammatory biomarker expression and improves clinical severity, while maintaining favorable safety profile. (J Am Acad Dermatol 2025;92:427-34.)

Key words: central centrifugal cicatricial alopecia; cicatricial alopecia; fibrosis; frontal fibrosing alopecia; IFNγ; JAK inhibitor; lichen planopilaris; phase 2a trial; scarring alopecia; systemic treatment; Th1.

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Trial registry: Dual JAK1/TYK2 Inhibitor for Cicatricial Alopecia (NCT05076006).

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INTRODUCTION

Cicatricial alopecias (CA) are chronic, progressive hair loss disorders, encompassing frontal fibrosing alopecia (FFA), lichen planopilaris (LPP), and central centrifugal cicatricial alopecia (CCCA). CA is increasing in prevalence, representing about 7% of alopecia cases seen in specialized clinics.[1] FFA and LPP, while clinically distinct, share overlapping histopathological findings.[2] FFA primarily affects postmenopausal women causing frontal hairline and eyebrow loss.[3] LPP affects all ages, causing inflammation and perifollicular hyperkeratosis, triggering scalp pruritus and dysesthesia.[4-6] CCCA occurs in Afro-American women, causing scalp vertex shedding with associated tenderness and scale.[7,8] Patients are often misdiagnosed and treated ineffectively, contributing to tremendous psychological burden.[9,10] Commonly used treatments, such as topical/intralesional steroids and hydroxychloroquine, are used off-label and not well tolerated.[11-13] Currently, there are no Food and Drug Administration-approved treatments for CA, highlighting an unmet need.[14]

Histopathologic findings in CA have demonstrated underlying lymphocytic inflammation around the hair follicle, leading to perifollicular fibrosis; however, research on molecular dysregulation has been limited.[15-17] Transcriptomic data across all 3 conditions has shown upregulation of fibrosis-related pathways.[18] The pathologic fibrotic remodeling is likely due to upregulation of inflammatory cytokines, namely T helper (Th) 1/interferon (IFN) γ, and fibrosis-related markers.[19,20] Our group has shown strong Th1 immune marker upregulation and pathway-level activation of Janus kinase (JAK) signal in FFA.[21] Fibrosis-related genes also correlated with JAK/signal transducers and activators of transcription (STAT) signaling in lesional skin.[22] JAK antagonism targets Th1/IFNγ cytokines by blocking STAT activation,[23] an effective approach in several other Th1-driven conditions, including alopecia areata.[24] Previous single patient reports and retrospective studies have shown promising outcomes for CA treatment with JAK inhibition, yet this research was limited in scale and lacked molecular evidence.[25-28] These findings provide the rationale behind this study, the first placebo-controlled clinical trial of a systemic treatment for CA.

Herein, we present the results from the first double-blind placebo-controlled single-center study evaluating the efficacy of brepocitinib, a tyrosine kinase (TYK) 2/JAK1 inhibitor, in the treatment of CA. Our mechanistic results measure changes in inflammatory and fibrosis biomarkers in lesional scalp, and our clinical results evaluate safety and clinical severity score changes.

CAPSULE SUMMARY

- Cicatricial alopecias are chronic scarring hair-loss conditions lacking effective treatments. Th1/IFNγ and Janus kinase dysregulation, which are involved in pathogenesis, may be targeted by brepocitinib.
- Brepocitinib is well tolerated with therapeutic potential for cicatricial alopecias, supported by improvement in clinical severity and expression of inflammatory pathways, including Th1/IFNγ and Janus kinase/signal transducers and activators of transcription.

METHODS

Study design and oversight

This single-center phase 2a, prospective, randomized, double-blind, placebo-controlled study (NCT05076006) evaluated the mechanistic and clinical efficacy and safety of brepocitinib for CA. The trial encompassed a 24-week double-blind treatment period and 24-week open-label period, with a safety follow up approximately 4 weeks after treatment cessation. Adults (≥18 years old) with clinically confirmed diagnosis of CCCA, LPP, or FFA and disease duration of 6 months to 7 years were eligible.

Patients with CCCA and LPP/FFA were randomized at baseline in a 3:1 ratio to receive either oral brepocitinib monotherapy 45 mg daily or placebo for 24 weeks. Medications related to CA were washed out before baseline (see Supplementary Appendix, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1). Investigators, personnel, and patients were blinded to trial group assignments. After the week 24 visit, all patients received brepocitinib 45 mg daily.

Study protocols were conducted in accordance with ethical principles of the Declaration of Helsinki. For additional study description and eligibility criteria see Supplementary Materials, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1.

Abbreviations used:

AE:	adverse event
CA:	cicatricial alopecias
CCCA:	central centrifugal cicatricial alopecia
CCL:	C-C motif chemokine ligand
CHLG:	Change in Hair Loss Grade
DLQI:	dermatology life quality index
FFA:	frontal fibrosing alopecia
FFASI:	Frontal Fibrosing Alopecia Severity Index
IFN:	interferon
JAK:	Janus kinase
LPP:	lichen planopilaris
LPPAI:	Lichen Planopilaris Activity Index
STAT:	signal transducers and activators of transcription
Th:	T helper
TYK:	tyrosine kinase

Efficacy and safety endpoints

The coprimary endpoints included mechanistic and safety related outcomes. Mechanistic endpoints included changes from baseline in expression of C-C motif chemokine ligand (CCL) 5, a surrogate for IFNγ activity, and biomarkers of fibrosis in lesional scalp at week 24. The primary safety endpoint was measured by incidence and severity of treatment-emergent adverse events (AEs) and clinically significant changes in vital signs and laboratory parameters, which were assessed every 4 weeks through week 52.

The secondary endpoint of this study was change from baseline at weeks 24 and 48 in lesional scalp gene expression of key inflammatory and fibrosis-related markers (Supplementary Tables I-III, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1). Additional secondary clinical endpoints included changes from baseline in corresponding CA clinical assessment scores: Lichen Planopilaris Activity Index (LPPAI), Frontal Fibrosing Alopecia Severity Index (FFASI) and Change in Hair Loss Grade (CHLG).[29-31]

Biomarker and clinical evaluations

Lesional scalp biopsies (4.5 mm punch) were collected at baseline, week 24, and week 48 and analyzed by Taqman low-density array quantitative reverse transcription polymerase chain reaction (RT-PCR) to assess gene expression levels.

CA clinical assessments, eyebrow and eyelash scores, and patient reported outcomes, including dermatology life quality index (DLQI) and visual analog scale pruritus, were collected through week 48. Clinical photos of scalp and eyebrows were taken at baseline and every 8 weeks thereafter until the end of the study.

The analysis for the mechanistic coprimary endpoints was performed with the use of analysis of covariance model to assess at week 24 the significance of change versus baseline in CCL5 and fibrosis related markers (eg RT-PCR expression levels, within, and between treatment groups). We fitted a linear model including treatment (brepocitinib/placebo) and tissue (nonlesional/lesional) as fixed effects, and baseline CCL5 expression as covariate.

Gene set variation analysis was performed for a subset of key genes associated with fibrosis, previously shown to be upregulated in CA[21,22] (CTGF, SNAIL2, PAI1, COL3A, COL1A) in order to calculate a Z-score, which reflects the aggregate expression level change in a predefined set of fibrosis genes.

We performed subgroup analysis after including the CA form (CCCA, LPP, and FFA) as an additional covariate.

The safety coprimary endpoint was evaluated using descriptive statistics. AE rates, severity, and relatedness were compared between treatment groups using Fisher's exact test.

Additional details of the statistical analyses are provided in the Supplementary Materials, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1.

RESULTS

Patient characteristics

Patients were enrolled from June 9, 2021 until study completion on September 14, 2023. Fifty patients (FFA/LPP n = 26; CCCA n = 24) were randomly assigned to brepocitinib 45 mg daily or placebo. Following study enrollment closure, one FFA/LPP patient was excluded due to failure to meet inclusion criteria.

Thirty-seven patients received brepocitinib and 12 received placebo. The mean (±SD) age of patients receiving brepocitinib was 54 (±14) years and 59 (±12) years in placebo.

Across groups, 39% of patients were white, 55% were black, and 6% were other. A majority of patients were female, and a predominant proportion of CCCA patients were black, reflecting reported demographic distributions. Baseline demographic characteristics were similar across groups (Supplementary Tables IV-VII, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1).

A majority of patients [brepocitinib 45 mg daily 28/37 (76%); placebo 10/12 (83%)] completed 24 weeks

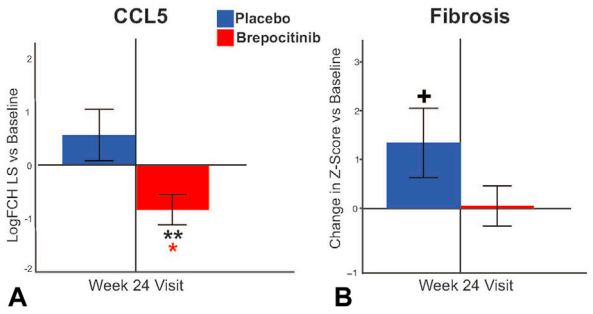

Fig 1. Primary mechanistic endpoint outcome. **A,** Change from baseline in gene expression of CCL5 in lesional scalp at week 24 based on TLDA/RT-PCR. Y-axis shows log2-fold changes in normalized RT-PCR expression and are presented as means ± SEMs. **B,** Change from baseline in gene expression of fibrosis-gene set variation analysis in lesional scalp at week 24 based on TLDA/RT-PCR. Y-axis shows differences in Z scores vs baseline in normalized RT-PCR expression and are presented as means ± SEMs. -dCt values are analyzed by mixed-effects model with time, treatment, and tissue interaction as a fixed effect and a random effect for each patient. *Black stars* indicate significance versus baseline; *red stars* indicate significance versus placebo. $^{**}P < .01$, $^{*}P < .05$, $+P < .1$. *CCL*, C-C motif chemokine ligand; *LogFCH*, log2-fold change; *LS*, lesional; *SEM*, standard error mean.

of the double-blind treatment period; 38 patients continued into the open-label phase, of which 20 FFA/LPP and 8 CCCA patients completed the trial (Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1).

Primary mechanistic endpoint outcome

CCL5 expression was significantly decreased from baseline in patients treated with brepocitinib at week 24 (P = .004). Change in CCL5 in the brepocitinib group was significantly different from placebo at week 24 (P = .01). No significant downregulation relative to baseline was observed in fibrosis-related markers in the brepocitinib group; however, enrichment analysis of a subset of fibrosis markers included in the panel showed trending upregulation at week 24 with placebo, while no worsening was observed in the brepocitinib group ($P < .10$; Fig 1).

Primary safety outcome

During the double-blind treatment period, AE were reported in 29 patients who received brepocitinib and 5 patients who received placebo (P = .03). The majority of AE were mild-to-moderate in severity, with low rates of trial discontinuation due to AE (n = 2). Among the most common AE were acne, COVID-19 infection, anemia, and elevation in serum creatinine level. Two patients receiving brepocitinib experienced serious AE (anemia and pneumonia with gastroenteritis), leading to drug discontinuation. During the open-label period, 2 patients discontinued due to anemia and one patient discontinued due to elevated creatine phosphokinase. No significant difference in AE rates was found between the placebo cross over group and the brepocitinib group (Supplementary Tables VIII and IX, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1).

Rates of mild, moderate, severe, and life-threatening AE were not significantly different between placebo and brepocitinib groups in either study phase. No cardiovascular events, thrombotic events, malignancies, or deaths in any treatment group were reported through week 52.

Key secondary endpoint outcomes

Brepocitinib significantly reduced lesional scalp expression of key inflammatory markers belonging to Th1/IFNγ (CXCL9, CXCL10), general inflammation (MMP12), T cell activation/Th1 (GZMB, IL2RA), and Th2 (CCL13, CCL18, CCL26) pathways at week 24 compared to baseline. Expression of Treg marker, FOXP3, and JAK/STAT marker, JAK3, was also significantly reduced at week 24 and remained so through week 48, compared to baseline (all $P < .05$). Th1 marker, IFNγ, and Th2 marker, IL4, were significantly downregulated at week 48 ($P < .05$; Supplementary Figs 2 and 3, Table X, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1).

Compared to placebo, expression of markers of general inflammation (MMP12), T cell activation/Th1 (GZMB, IL2RA, IL15RB), Th1/IFNγ (IFNγ, CCL5, CXCL10), Th2 (CCL13, CCL18), Treg (FOXP3), and JAK/STAT (JAK3) were significantly lower with brepocitinib at week 24 (all $P < .05$; Supplementary Figs 2 and 3, Table X, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1).

Evaluation of biomarker expression within disease subgroups (FFA/LPP and CCCA) showed that in the FFA/LPP group at week 24, brepocitinib significantly downregulated Th1/IFNγ (IFNγ, CCL5, CXCL9, CXCL10), general inflammation (MMP12), T cell activation (GZMB, IL2RA), and Th2 (IL4, CCL13, CCL18, CCL26) markers. FOXP3 and JAK3 were also significantly reduced (all $P < .05$). Expression of a majority of these biomarkers was also significantly lower with brepocitinib as compared to placebo. These markers remained significantly downregulated at week 48 in the FFA/LPP group (all $P < .05$; Supplementary Figs 4 to 6, Table XI, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1).

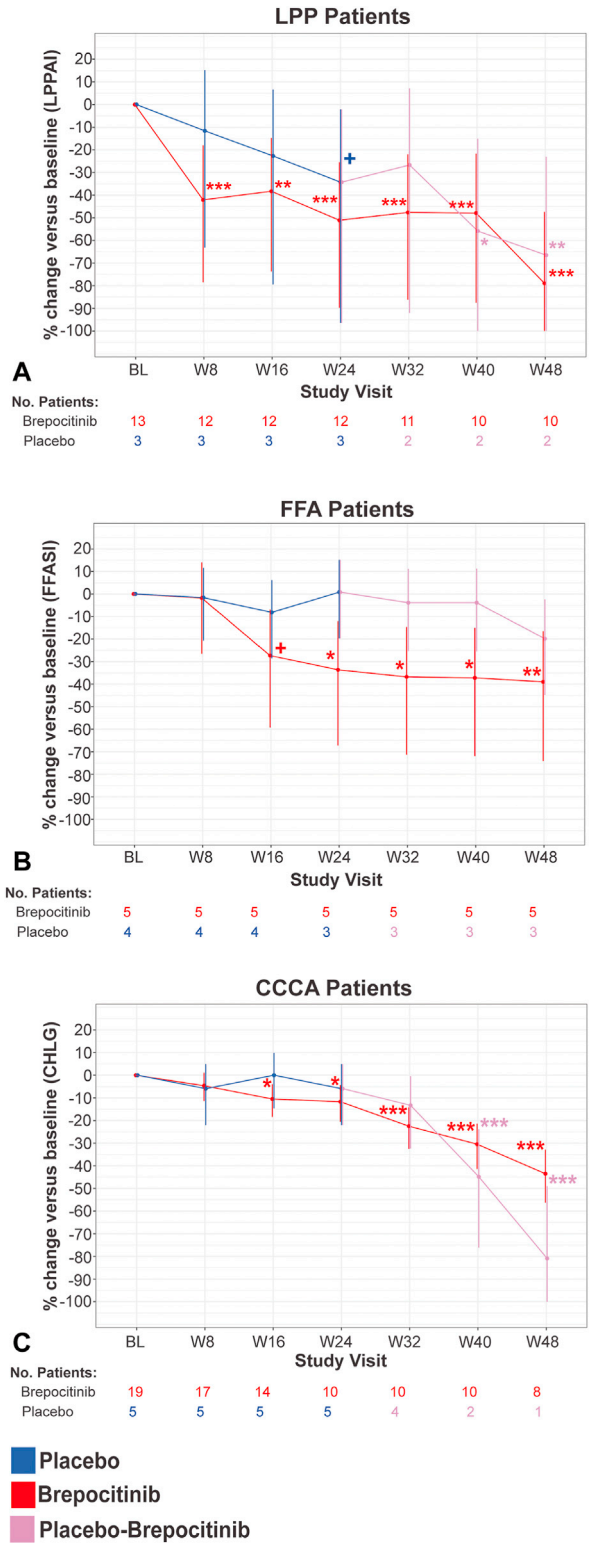

Fig 2. Secondary clinical efficacy endpoint. Mean percent change from baseline in (**A**) lichen planopilaris activity index (LPPAI) in LPP patients (**B**) frontal fibrosing alopecia severity index (FFASI) in FFA patients (**C**) central hair loss grade (CHLG) in CCCA patients. *Red*, *blue*, and *pink* represent brepocitinib, placebo, and brepocitinib after placebo (open-label), respectively. Error bars represent 90% confidence intervals. ***$P < .001$, **$P < .01$, *$P < .05$, +$P < .1$. *Red stars* represent change from baseline in the brepocitinib arm. *Blue stars* represent change from baseline in the placebo arm. *Pink stars* represent change from baseline in the open-label phase of the placebo arm. Number of patients at each time point is denoted under the respective study week visit. *CCCA*, Central centrifugal cicatricial alopecia; *FFA*, frontal fibrosing alopecia; *LPP*, lichen planopilaris.

Among CCCA patients receiving brepocitinib, significant downregulation of markers belonging to general inflammation (MMP12), Th1/IFNγ (CXCL10), Th2 (CCL13, CCL18, CCL26), and Th17/22 (IL23R, S100A7) was observed at week 24 as compared to baseline (all $P < .05$). No significant downregulation of fibrosis-related markers was observed in brepocitinib patients; however, trending upregulation of markers of fibrosis was observed in CCCA placebo group (Supplementary Figs 4 to 6, Table XI, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1).

Key secondary clinical efficacy outcomes

Brepocitinib significantly decreased clinical severity scores in each CA subtype through week 48. At week 24, LPP patients receiving brepocitinib showed significant mean percent change in LPPAI of −51.0% (90% CI, −79.5, to −30.2) compared to baseline ($P < .001$). Further improvement in the brepocitinib group was observed through week 48 with mean percent change of −79.2% (90% CI, −100 to −53.6) compared to baseline ($P < .001$). LPP patients receiving placebo did not achieve a statistically significant change from baseline in LPPAI at week 24; however, placebo patients who crossed over into brepocitinib in the open-label phase showed significant mean percent change of −67.5% by week 48 compared to baseline (90% CI, −100 to −30.7) ($P = .002$; Fig 2, *A*, Supplementary Table XII, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1).

FFA patients receiving brepocitinib showed significant mean percent change in FFASI score by week 24 of −33.6% (90% CI, −67.2 to −12.1) compared to baseline ($P = .02$), with further improvement at week 48 and mean percent change of −39.0% (90% CI, −74.2 to −16.5) compared to baseline ($P < .01$). At week 24, FFA patients receiving placebo showed mean numerical increase in FFASI compared to baseline [0.9% (90% CI, −19.4, 15.1)]; however, among FFA patients who crossed over into brepocitinib, numerical reduction was observed with mean

percent change of −19.6% (90% CI, −44.6 to −2.1) at week 48 from baseline (Fig 2, *B*, Supplementary Table XIII, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1).

CCCA patients receiving brepocitinib showed significant improvement in CHLG at week 16, with further improvement observed at weeks 24 and 48 with percent change in CHLG of −11.9% (90% CI, −20.8 to −4.4; $P < .05$) and −43.5% (90% CI, −56.2 to −33.0; $P < .001$) compared to baseline, respectively. CCCA patients receiving placebo showed minimal change in CHLG at week 24; however, following cross over to brepocitinib, at week 48, one patient maintained treatment and showed significant mean percent change in CHLG of −81.6% (90% CI, −100 to −50.8) compared to baseline ($P < .001$; Fig 2, *C*, Supplementary Table XIV, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1). Representative patient photos are shown in Supplementary Fig 7, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1. Eyebrow and eyelash scores remained stable in the drug group by week 48 (Supplementary Table XV, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1).

Among patients receiving brepocitinib, DLQI was significantly reduced from baseline starting at week 8 ($P = .004$), with mean percent change at week 24 of −17.6% (90% CI, −24.7, to −11.6, $P < .001$). No improvement in DLQI was observed in the placebo group at week 24 (Supplementary Fig 8, Table XVI, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1). Patients' subjective measure of itch was also significantly reduced at week 24 in the brepocitinib group with mean percent change of −31.6% (90% CI, −57.8, to −12.3; $P = .02$; Supplementary Fig 8, Table XVII, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1). When comparing the change in pruritus at weeks 24 and 48 across CA disease groups, a significantly greater reduction occurred in the LPP group compared to the CCCA and FFA groups ($P < .01$; Supplementary Table XVIII, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1).

Post hoc analysis showed that patients with shorter disease duration (less than the study cohort median of 5 years) had significantly greater clinical score percent improvement than patients with long disease duration (>5 years) at weeks 24 and 48 (all $P < .05$; Supplementary Fig 9, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1).

Correlation analysis

Spearman correlations between change from baseline in clinical severity measures and change from baseline in biomarkers in lesional scalp biopsy were conducted (Supplementary Table XIX, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1). Notably, week 24 change in FFASI positively correlated with CXCL10 ($r = 0.83$, $P = .01$). Total scalp margins, the assessment of total scalp hair loss within the FFASI scoring system, positively correlated with CCL5 ($r = 0.74$; $P = .04$). Change in pruritus, a subcategory of the LPPAI scoring system, positively correlated with changes in CCL5, CXCL9, JAK3, and CTGF ($r > 0.60$, $P < .05$ for all). Change in CHLG also positively correlated with change in IL23 subunit, IL23p19 ($r = 0.62$, $P = .02$; Supplementary Table XIX, available via Mendeley at https://data.mendeley.com/datasets/nsjbw2d8r2/1).

DISCUSSION

Herein we present the first randomized placebo-controlled study of a systemic dual TYK2/JAK1 inhibitor and assessment of biomarker changes in CA tissue following treatment. Brepocitinib successfully downregulated CCL5 expression after 24 weeks of treatment, meeting a coprimary endpoint. Existing literature points to a Th1-based cytotoxic T cell response and IFNγ activation in the pathogenesis of CA, and thus the downregulation of CCL5, an IFNy-associated marker, is highly encouraging.[21,22] As a TYK2/JAK1 dual inhibitor, brepocitinib targets STAT activation of Th1/IFNγ and γc cytokines.[32] Thus, it allows for biomarker downregulation beyond the Th1 axis, including modulation of markers associated with T-cell activation, JAK/STAT signaling, Th2, and Treg.

Previous studies suggest that certain proinflammatory signals, particularly JAK/STAT, are associated with fibrotic changes.[21,22,33-36] Inflammatory changes likely precede fibrotic changes in CA. Thus, inhibition of inflammatory pathways may prevent downstream fibrosis. Expression of fibrotic markers remained stable in the brepocitinib group but worsened in the placebo group, suggesting that inhibiting inflammation may prevent fibrotic progression. Comparison of clinical improvement based on median disease duration showed greater improvement with shorter disease duration in the brepocitinib group. Earlier disease may be dominated by inflammatory dysregulation, underscoring the importance of prompt intervention, as seen in alopecia areata.[37,38]

Brepocitinib was well tolerated through week 52, with a safety profile comparable to that of previous trials, meeting another of its coprimary endpoints.[24]

Brepocitinib groups across all CA subtypes met the secondary endpoint of significant reduction in clinical severity scores by week 24, with continued improvement through week 48. Moreover,

molecular analysis correlated with clinical improvement, bridging mechanistic and clinical endpoints.

There were some limitations of the present study. The scoring schema of the CA subtypes is inherently limited by inter-rater variability and subjectivity. Future investigations are warranted to develop more reliable scoring systems. The study is also limited by a single-dose regimen, 3:1 design, and small placebo group, limiting significant comparisons between brepocitinib and placebo.

This study demonstrates that brepocitinib effectively decreases inflammatory biomarker expression and improves clinical severity measures at 24 and 48 weeks while also maintaining a favorable safety profile through 52 week follow up period. Larger scale studies utilizing brepocitinib for the treatment of CA are warranted to move towards formal approval.

Conflicts of interest

Dr Mearimanis a consultant for Abbvie. Dr Ungar is an employee of Mount Sinai and has received research funds (grants paid to the institution) from: Incyte, Rapt Therapeutics, and Pfizer. He is also a consultant for Arcutis Biotherapeutics, Bristol Myers Squib, Castle Biosciences, Fresenius Kabi, Galderma, Janssen, Lilly, Pfizer, Primus Pharmaceuticals, Sanofi, and UCB. Dr Guttman-Yassky is an employee of Mount Sinai and has received research funds (grants paid to the institution) from: Abbvie, Celgene, Eli Lilly, Janssen, Medimmune/Astra Zeneca, Novartis, Pfizer, Regeneron, Vitae, Glenmark, Galderma, Asana, Innovaderm, Dermira, UCB. They are also a consultant for Sanofi Aventis, Regeneron, Stiefel/GlaxoSmithKline, MedImmune, Celgene, Anacor, AnaptysBio, Dermira, Galderma, Glenmark, Novartis, Pfizer, Vitae, Leo Pharma, Abbvie, Eli Lilly, Kyowa, Mitsubishi Tanabe, Asana Biosciences, and Promius. Drs Oemar, Mahling, and Peeva are Pfizer employees and own stock and stock option. Authors David, Shokrian, Hawkins, Sikand, Singer, Estrada, Bose, and Pulsinelli, and Drs Duca, Dubin, Andrews, and Da Rosa have no conflicts of interest to declare.

REFERENCES

1. Whiting DA. Cicatricial alopecia: clinico-pathological findings and treatment. *Clin Dermatol*. 2001;19(2):211-225. (In eng). https://doi.org/10.1016/s0738-081x(00)00132-2
2. Gálvez-Canseco A, Sperling L. Lichen planopilaris and frontal fibrosing alopecia cannot be differentiated by histopathology. *J Cutan Pathol*. 2018;45(5):313-317. (In eng). https://doi.org/10.1111/cup.13112
3. MacDonald A, Clark C, Holmes S. Frontal fibrosing alopecia: a review of 60 cases. *J Am Acad Dermatol*. 2012;67(5):955-961. (In eng). https://doi.org/10.1016/j.jaad.2011.12.038
4. Tan E, Martinka M, Ball N, Shapiro J. Primary cicatricial alopecias: clinicopathology of 112 cases. *J Am Acad Dermatol*. 2004;50(1):25-32.
5. Matta M, Kibbi A-G, Khattar J, Salman SM, Zaynoun ST. Lichen planopilaris: a clinicopathologic study. *J Am Acad Dermatol*. 1990;22(4):594-598.
6. Mehregan DA, Van Hale HM, Muller SA. Lichen planopilaris: clinical and pathologic study of forty-five patients. *J Am Acad Dermatol*. 1992;27(6):935-942.
7. Meinhard J, Stroux A, Lünnemann L, Vogt A, Blume-Peytavi U. Lichen planopilaris: epidemiology and prevalence of subtypes — a retrospective analysis in 104 patients. *J Dtsch Dermatol Ges*. 2014;12(3):229-235. https://doi.org/10.1111/ddg.12264
8. Callender VD, Wright DR, Davis EC, Sperling LC. Hair breakage as a presenting sign of early or occult central centrifugal cicatricial alopecia: clinicopathologic findings in 9 patients. *Arch Dermatol*. 2012;148(9):1047-1052. (In eng). https://doi.org/10.1001/archdermatol.2011.3428
9. Singh R, Wilborn D, Lintzeri D-A, Blume-Peytavi U. Health-related quality of life (hrQoL) among patients with primary cicatricial alopecia (PCA): a systematic review. *J Eur Acad Dermatol Venereol*. 2023;37(12):2462-2473. https://doi.org/10.1111/jdv.19381
10. Akintilo L, Hahn EA, Yu JMA, Patterson SSL. Health care barriers and quality of life in central centrifugal cicatricial alopecia patients. *Cutis*. 2018;102(6):427-432. (In eng).
11. Harries M, Sinclair R, Macdonald-Hull S, Whiting D, Griffiths C, Paus R. Management of primary cicatricial alopecias: options for treatment. *Br J Dermatol*. 2008;159(1):1-22.
12. Rakowska A, Gradzińska A, Olszewska M, Rudnicka L. Efficacy of isotretinoin and acitretin in treatment of frontal fibrosing alopecia: retrospective analysis of 54 cases. *J Drugs Dermatol*. 2017;16(10):988-992.
13. Rácz E, Gho C, Moorman P, Noordhoek Hegt V, Neumann H. Treatment of frontal fibrosing alopecia and lichen planopilaris: a systematic review. *J Eur Acad Dermatol Venereol*. 2013;27(12):1461-1470.
14. Larrondo J, McMichael AJ. Scarring alopecia. *Dermatol Clin*. 2023;41(3):519-537. (In eng). https://doi.org/10.1016/j.det.2023.02.007
15. Starace M, Orlando G, Alessandrini A, Baraldi C, Bruni F, Piraccini BM. Diffuse variants of scalp lichen planopilaris: clinical, trichoscopic, and histopathologic features of 40 patients. *J Am Acad Dermatol*. 2020;83(6):1659-1667.
16. Mobini N, Tam S, Kamino H. Possible role of the bulge region in the pathogenesis of inflammatory scarring alopecia: lichen planopilaris as the prototype. *J Cutan Pathol*. 2005;32(10):675-679.
17. Miteva M, Tosti A. Pathologic diagnosis of central centrifugal cicatricial alopecia on horizontal sections. *Am J Dermatopathol*. 2014;36(11):859-864; quiz 865-867. (In eng). https://doi.org/10.1097/dad.0000000000000174
18. Wang EHC, Monga I, Sallee BN, et al. Primary cicatricial alopecias are characterized by dysregulation of shared gene expression pathways. *PNAS Nexus*. 2022;1(3):pgac111. https://doi.org/10.1093/pnasnexus/pgac111
19. Meyer KC, Tiede S, Harries MJ, Kloepper JE, Paus R. IFN-gamma induces bulge immunoprivilege collapse and may cause epithelial stem cell exhaust. *J Invest Dermatol*. 2010;130:S42.
20. Moretti S, Amato L, Massi D, Bianchi B, Gallerani I, Fabbri P. Evaluation of inflammatory infiltrate and fibrogenic cytokines in pseudopelade of Brocq suggests the involvement of T-helper 2 and 3 cytokines. *Br J Dermatol*. 2004;151(1):84-90.
21. Del Duca E, Ruano Ruiz J, Pavel A, et al. Frontal fibrosing alopecia shows robust T helper 1 and Janus kinase 3 skewing. *Br J Dermatol*. 2020;183(6):1083-1093.
22. Dubin C, Glickman JW, Del Duca E, et al. Scalp and serum profiling of frontal fibrosing alopecia reveals scalp immune

and fibrosis dysregulation with no systemic involvement. *J Am Acad Dermatol*. 2022;86(3):551-562.
23. Williams NK, Bamert RS, Patel O, et al. Dissecting specificity in the Janus kinases: the structures of JAK-specific inhibitors complexed to the JAK1 and JAK2 protein tyrosine kinase domains. *J Mol Biol*. 2009;387(1):219-232. (In eng). https://doi.org/10.1016/j.jmb.2009.01.041
24. King B, Guttman-Yassky E, Peeva E, et al. Safety and efficacy of ritlecitinib and brepocitinib in alopecia areata: results from the crossover open-label extension of the ALLEGRO phase 2a trial. *JID Innov*. 2022;2(6):100156. (In eng). https://doi.org/10.1016/j.xjidi.2022.100156
25. Workman K, Kindred C. Hair regrowth in a patient with central centrifugal cicatricial alopecia after a 2-month trial of baricitinib. *JAAD Case Rep*. 2023;39:109-111.
26. Yang CC, Khanna T, Sallee B, Christiano AM, Bordone LA. Tofacitinib for the treatment of lichen planopilaris: a case series. *Dermatol Ther*. 2018;31(6):e12656. https://doi.org/10.1111/dth.12656
27. Plante J, Eason C, Snyder A, Elston D. Tofacitinib in the treatment of lichen planopilaris: a retrospective review. *J Am Acad Dermatol*. 2020;83(5):1487-1489.
28. Moussa A, Bhoyrul B, Asfour L, Kazmi A, Eisman S, Sinclair RD. Treatment of lichen planopilaris with baricitinib: a retrospective study. *J Am Acad Dermatol*. 2022;87(3):663-666.
29. Chiang C, Sah D, Cho BK, Ochoa BE, Price VH. Hydroxychloroquine and lichen planopilaris: efficacy and introduction of Lichen Planopilaris Activity Index scoring system. *J Am Acad Dermatol*. 2010;62(3):387-392. (In eng). https://doi.org/10.1016/j.jaad.2009.08.054
30. Holmes S, Ryan T, Young D, Harries M. Frontal Fibrosing Alopecia Severity Index (FFASI): a validated scoring system for assessing frontal fibrosing alopecia. *Br J Dermatol*. 2016;175(1):203-207. (In eng). https://doi.org/10.1111/bjd.14445
31. Olsen EA, Callender V, Sperling L, et al. Central scalp alopecia photographic scale in African American women. *Dermatol Ther*. 2008;21(4):264-267. (In eng). https://doi.org/10.1111/j.1529-8019.2008.00208.x
32. Fensome A, Ambler CM, Arnold E, et al. Dual inhibition of TYK2 and JAK1 for the treatment of autoimmune diseases: discovery of ((S)-2, 2-difluorocyclopropyl)((1 R, 5 S)-3-(2-((1-methyl-1 H-pyrazol-4-yl) amino) pyrimidin-4-yl)-3, 8-diazabicyclo [3.2. 1] octan-8-yl) methanone (PF-06700841). *J Med Chem*. 2018;61(19):8597-8612.
33. Nguyen JK, Austin E, Huang A, Mamalis A, Jagdeo J. The IL-4/IL-13 axis in skin fibrosis and scarring: mechanistic concepts and therapeutic targets. *Arch Dermatol Res*. 2020;312:81-92.
34. Kuzumi A, Yoshizaki A, Matsuda KM, et al. Interleukin-31 promotes fibrosis and T helper 2 polarization in systemic sclerosis. *Nat Commun*. 2021;12(1):5947. (In eng). https://doi.org/10.1038/s41467-021-26099-w
35. Dees C, Tomcik M, Palumbo-Zerr K, et al. JAK-2 as a novel mediator of the profibrotic effects of transforming growth factor β in systemic sclerosis. *Arthritis Rheum*. 2012;64(9):3006-3015.
36. Chakraborty D, Šumová B, Mallano T, et al. Activation of STAT3 integrates common profibrotic pathways to promote fibroblast activation and tissue fibrosis. *Nat Commun*. 2017;8(1):1130.
37. Guttman-Yassky E, Pavel AB, Diaz A, et al. Ritlecitinib and brepocitinib demonstrate significant improvement in scalp alopecia areata biomarkers. *J Allergy Clin Immunol*. 2022;149(4):1318-1328.
38. King B, Bergfeld W, Brzewski P, et al. Impact of disease history on the efficacy of ritlecitinib (PF-06651600) in patients with alopecia areata: post hoc analysis of the ALLEGRO phase 2b/3 study. *SKIN J Cutan Med*. 2022;6(6):s101.