Research letter

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

To the Editor: Key findings from a 24-week, double-blind period (DBP) of a phase 2a study (NCT02974868) indicated that the oral Janus kinase (JAK) inhibitors ritlecitinib (inhibits JAK3 and tyrosine kinase expressed in the hepatocellular carcinoma family) and brepocitinib (inhibits tyrosine kinase 2 and JAK1) were efficacious and well tolerated over 24 weeks in patients with alopecia areata and ≥50% scalp hair loss.[1]

The effects of withdrawing a JAK inhibitor following the treatment of alopecia areata have not been evaluated in a placebo-controlled trial, but uncontrolled studies of the JAK inhibitors ruxolitinib and tofacitinib have reported hair loss 8 weeks after treatment cessation.[2-5] In this phase 2a study, following the DBP and a 4-week washout period, patients continued to be part of a single-blind extension involving the same dosing regimen as that in the DBP: 200 mg of ritlecitinib once daily (for 4 weeks), followed by 50 mg once daily (for

Table I. Treatment-emergent AEs and laboratory abnormalities

	Nonresponders				Responders: Re-treatment segment	
	Ritlecitinib		Brepocitinib			
n (%)	Active n = 16	PBO n = 17	Active n = 5	PBO n = 12	Ritlecitinib n = 14	Brepocitinib n = 15
Treatment-emergent AEs and laboratory abnormalities						
AEs, n	17	22	12	32	22	17
Pts with AEs (all cause)	8 (50)	12 (71)	4 (80)	10 (83)	11 (79)	9 (60)
Pts with serious AEs*	0	0	0	0	0	1 (7)†
Pts with severe AEs‡	0	0	1 (20)	0	0	1 (7)†
DC from study because of AEs	1 (6)	0	0	0	0	1 (7)
DC from study because of laboratory values	0	0	0	0	1 (7)§	0
Pts with treatment-related AEs	5 (31)	1 (6)	0	1 (8)	2 (14)	2 (13)
Pts with serious treatment-related AEs	0	0	0	0	0	0
Pts with severe treatment-related AEs	0	0	0	0	0	0
DC from study because of treatment-related AEs	1 (6)	0	0	0	0	0
DC from study because of laboratory values	0	0	0	0	1 (7)	0
Treatment-emergent AEs in ≥3 patients in any group						
Infections or infestations	6 (38)	5 (29)	2 (40)	7 (58)	8 (57)	3 (20)
Nasopharyngitis	0	2 (12)	0	2 (17)	3 (21)	1 (7)
Skin or SC tissue	2 (13)	3 (18)	1 (20)	5 (42)	1 (7)	0
Nervous system	3 (19)	2 (12)	0	2 (17)	3 (21)	2 (13)
Investigations (SOC)‖	1 (6)	1 (6)	1 (20)	4 (33)	2 (14)	2 (13)
Gastrointestinal	1 (6)	2 (12)	1 (20)	3 (25)	1 (7)	2 (13)
Musculoskeletal or connective tissue	0	3 (18)	0	0	0	1 (7)

AE, Adverse event; *DC*, discontinued; *PBO*, placebo; *Pts*, patients; *SC*, subcutaneous; *SOC*, system organ class.

*A serious AE is based on an outcome or action associated with events that pose a threat to a patient's life or functioning and the need to fulfill an additional reporting process (reported to regulatory agencies, corporate pharmacovigilance group, or institutional review boards). The US Food and Drug Administration defines a serious AE as an event with one of the following outcomes: death, life-threatening, hospitalization, disability, which is characterized by a significant, persistent, or permanent change, impairment, damage, or disruption in the patient's body function or structure, physical activities, or quality of life; a congenital anomaly; or a condition that requires intervention to prevent permanent impairment or damage.

†Same patient with AE of lower limb fracture, considered unrelated to the study drug.

‡A severe AE is a class of AEs based on intensity (severity) and is medically significant but not immediately life-threatening, limiting self-care or activities of daily living.

§Alanine aminotransferase >2.5 × upper limit of normal, confirmed on retesting.

‖SOC investigations covered laboratory test results.

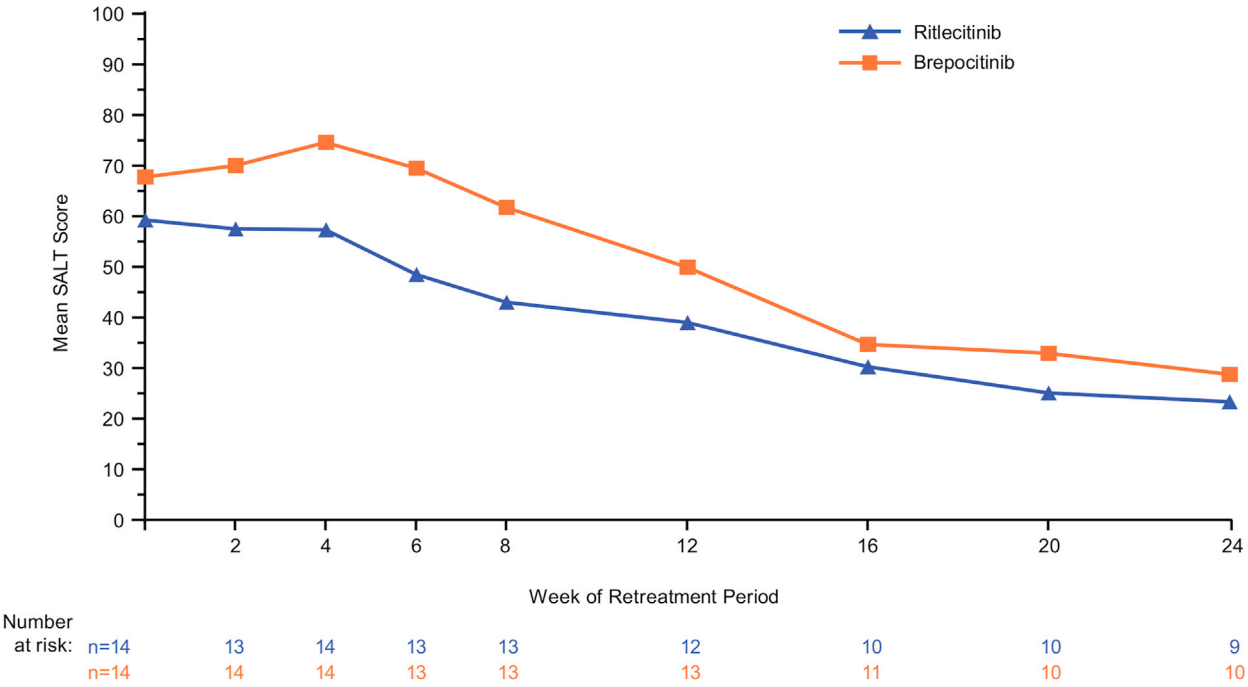

Fig 1. Mean SALT score over 24 weeks for observed cases of re-treated active responders with alopecia areata. The SALT score ranges from 0 to 100, reflecting the percentage of hair loss on the scalp (0 = no hair loss and 100 = total hair loss). A decrease in the SALT score indicates an improvement in hair regrowth. *SALT*, Severity of alopecia tool.

20 weeks); 60 mg of brepocitinib once daily (for 4 weeks), followed by 30 mg once daily (for 20 weeks); or a placebo. The investigators were aware of the treatments.

The patients in the single-blind extension were assigned to 1 of 3 groups and blinded to the treatment:

1. "Placebo nonresponders" in the DBP: received their preassigned active treatment (ritlecitinib or brepocitinib).
2. "Active nonresponders" (those who achieved <30% improvement in their severity of alopecia tool [SALT] score at week 24 compared with that at baseline in the DBP): received the same active treatment.
3. "Active responders" (those who achieved ≥30% improvement in their SALT score [$SALT_{30}$] at week 24 compared with that at baseline in the DBP): received the placebo until they met the re-treatment criterion (>30% loss of hair regrown during the DBP). Patients meeting the re-treatment criterion received 24 weeks of the same active treatment received during the DBP.

The primary endpoint was safety. The tertiary endpoints included time to meet the re-treatment criterion and $SALT_{30}$ (re-treated responders). The most common adverse events were infections and skin or nervous system disorders (Table I). All 26 treatment-related adverse events were mild or moderate. In total, 5 of 17 (29%) versus 8 of 12 DBP placebo nonresponders (67%) achieved $SALT_{30}$ with ritlecitinib and brepocitinib, respectively, after 24 weeks. For DBP active nonresponders, 2 of 16 (13%) on ritlecitinib and 0 of 5 (0%) on brepocitinib achieved $SALT_{30}$. For DBP active responders (n = 22 on ritlecitinib and n = 24 on brepocitinib), the median time from the end of DBP to re-treatment was 16.1 and 24.1 weeks, respectively. One patient did not go through withdrawal and directly received re-treatment; 4 of 22 (18%) versus 9 of 23 patients (39%) previously receiving ritlecitinib and brepocitinib, respectively, completed the withdrawal period without meeting the re-treatment criterion; and 14 of 22 (64%) and 14 of 23 patients (61%) who had received ritlecitinib and brepocitinib, respectively, met the re-treatment criterion. For both the treatments, DBP responders showed improved SALT scores during re-treatment following withdrawal (Fig 1). Following re-treatment, 8 of 14 patients (57%) receiving ritlecitinib and 8 of 15 (53%) receiving brepocitinib achieved $SALT_{30}$.

No new safety signals during withdrawal or re-treatment were observed. Efficacy appeared to decrease after re-treatment following withdrawal

compared with that with the initial response, although the study was not statistically powered to confirm this. The results suggest that to maintain hair regrowth, continuous treatment should be considered in patients with alopecia areata who tolerate and respond to ritlecitinib or brepocitinib.

Elena Peeva, MD,[a] Emma Guttman-Yassky, MD,[b] Anindita Banerjee, PhD,[a] Rodney Sinclair, MD,[c] Lori Ann Cox, DO,[d] Linda Zhu, MD, PhD,[a] Hua Zhu, PhD,[e] Michael Vincent, MD, PhD,[a] and Brett King, MD, PhD[f]

From Pfizer, Cambridge, Massachusetts[a]; Icahn School of Medicine at Mt. Sinai, New York, New York[b]; Sinclair Dermatology, Melbourne, Victoria, Australia[c]; Pfizer, Basking Ridge, New Jersey[d]; Pfizer, Shanghai, China[e]; and Yale University School of Medicine, New Haven, Connecticut.[f]

Funding sources: The study was funded by Pfizer. Pfizer designed the study in consultation with all authors, and Pfizer collected the data.

IRB approval status: NCT02974868 was a phase 2a, randomized, double-blind, multicenter study; registered November 29, 2016) with an initial 24-week primary efficacy endpoint evaluation period followed by 2 extension periods. The study was conducted in 31 centers in Australia, Canada, and the United States according to the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization, and local country regulations, where applicable. The ethics committee or institutional review board at each participating center approved the study protocol and all patients provided written informed consent.

Key words: alopecia areata; brepocitinib; drug retreatment; drug withdrawal; efficacy; extension; Janus kinase inhibitor; phase 2; ritlecitinib; safety; single-blind.

Reprints not available from the authors.

Correspondence to: Elena Peeva, MD, Pfizer Worldwide Research & Development, 300 Technology Square, Cambridge, MA 02139

E-mail: Elena.Peeva@pfizer.com

Conflicts of interest

Dr Guttman-Yassky has received institutional grants from AbbVie, Celgene, Eli Lilly, Janssen, Dermavant, DS Biopharma, Novartis, Pfizer, Regeneron, Glenmark, Galderma, Asana Biosciences, Innovaderm, Dermira, LEO Pharma, Novan, Kyowa Kirin, Concert, Union Therapeutics, and Ralexar and serves as a consultant for Sanofi, Regeneron, Celgene, Dermira, Galderma, Glenmark, Novartis, Pfizer, LEO Pharma, AbbVie, Eli Lilly, Kyowa Kirin, Mitsubishi Tanabe, Asana Biosciences, Union Therapeutics, Allergan, Amgen, Concert, DS Biopharma, EMD Serono, Escalier, and FLX Bio. Dr Sinclair provided professional services to Novartis, Merck & Co, Janssen, Samson Clinical, Pfizer, Eli Lilly and Company, Arena, Dermira, Astra Zeneca, Sanofi, AbbVie, Galderma, Principia, Reistone Pharma, Aclaris, and Sun Pharma. Dr Cox is a paid consultant to Pfizer. Dr King has served on advisory boards and/or is a consultant and/or a clinical trial investigator for AbbVie, Aclaris Therapeutics Inc, AltruBio Inc, Almirall, Arena Pharmaceuticals, Bioniz Therapeutics, Bristol-Meyers Squibb, Concert Pharmaceuticals Inc, Dermavant Sciences Inc, Eli Lilly and Company, Incyte Corp, LEO Pharma, Otsuka/Visterra Inc, Pfizer Inc, Regeneron, Sanofi Genzyme, TWi Biotechnology Inc, and Viela Bio. He is on speaker bureaus for Pfizer Inc, Regeneron, and Sanofi Genzyme. Drs Peeva, Banerjee, L. Zhu, H. Zhu, and Vincent are employees and stockholders of Pfizer.

REFERENCES

1. King B, Guttman-Yassky E, Peeva E, 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(2):379-387. https://doi.org/10.1016/j.jaad.2021.03.050
2. Crispin MK, Ko JM, Craiglow BG, et al. Safety and efficacy of the JAK inhibitor tofacitinib citrate in patients with alopecia areata. *JCI Insight*. 2016;1(15):e89776. https://doi.org/10.1172/jci.insight.89776
3. Mackay-Wiggan J, Jabbari A, Nguyen N, et al. Oral ruxolitinib induces hair regrowth in patients with moderate-to-severe alopecia areata. *JCI Insight*. 2016;1(15):e89790. https://doi.org/10.1172/jci.insight.89790
4. Jabbari A, Sansaricq F, Cerise J, et al. An open-label pilot study to evaluate the efficacy of tofacitinib in moderate to severe patch-type alopecia areata, totalis, and universalis. *J Invest Dermatol*. 2018;138(7):1539-1545. https://doi.org/10.1016/j.jid.2018.01.032
5. Park HS, Kim MW, Lee JS, et al. Oral tofacitinib monotherapy in Korean patients with refractory moderate-to-severe alopecia areata: a case series. *J Am Acad Dermatol*. 2017;77(5):978-980. https://doi.org/10.1016/j.jaad.2017.06.027

https://doi.org/10.1016/j.jaad.2021.12.008