A Pilot Study to Assess Safety and Biomarker Responses of Ritlecitinib (JAK3/TEC Inhibitor) in Cicatricial Alopecia
PI: Emma Guttman, MD
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A Pilot Study to Assess Safety and Biomarker Responses of Ritlecitinib (JAK3/TEC Inhibitor) in Cicatricial Alopecia

Principal Investigator: Emma Guttman-Yassky, MD/PhD

Sub-Investigators: Elizabeth Andrews, MD
Joel Correa da Rosa, PhD

Study Sites: Icahn School of Medicine at Mount Sinai
Departments of Dermatology and the Immunology Institute
5 East 98 Street, 5th Floor, Box 1048
New York, NY 10029

Collaborator: Pfizer, Inc
235 E 42nd Street
New York, NY 10017
US

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LAY SUMMARY (500 words or less)

Alopecia could be subdivided into two main groups of diseases: non-scarring alopecia, such as male pattern baldness, or alopecia areata (AA), in which hair follicles are preserved, yet quiescent, and scarring alopecia, also known as cicatricial alopecia (CA), in which hair follicles are irreversibly destroyed. CA leads to scarred areas, most commonly on the scalp, that cannot re-grow hair. Despite being a long-term condition, that often has significant impact on patients' well-being, available effective treatments for these diseases are lacking. In addition, the molecular abnormalities causing CA are largely unknown. Our research involves administrating patients a new investigational drug (a JAK3/TEC inhibitor), ritlecitinib, which has shown statistically significant improvement in scalp hair loss for AA patients in a proof of concept and phase 2b/3 studies (B7981015 AA study). This is an open-label clinical trial. CA patients will be asked to provide small samples of skin and blood throughout the treatment period, to find out how they respond to the drug, and to attempt to better understand these diseases.

PUBLIC HEALTH IMPACT STATEMENT

Cicatricial Alopecia (CAs) are an increasingly common, progressive, scarring diseases, resulting in permanent hair-loss, affecting quality-of-life.[1-4] The mechanisms of CA are poorly understood,[3,5-9] and treatment options are unsatisfactory.[3,8-12]

We will assess samples of skin and blood from CA patients by molecular techniques to investigate the mechanisms of inflammation and scarring, at baseline and after treatment with the investigational product. These findings will help to identify new treatment targets and direct further investigation for the development of new therapies for these disfiguring diseases.

ABSTRACT

Cicatricial Alopecias (CAs) are progressive, disfiguring dermatoses, resulting in permanent hair loss. Patients experience anxiety, low self-esteem, and extreme distress. Despite growing incidence, with more than 5.7% of the population affected, CAs are poorly understood. As a result, current therapies are largely lacking, leading to a significant unmet need, that we wish to address. We propose to investigate the most common forms of CA, frontal fibrosing alopecia (FFA)/lichen planopilaris (LPP), and central centrifugal scarring alopecia (CCCA). Previous reports support a role for Th1/IFNγ in LPP. Favorable clinical outcomes following Janus kinase inhibitor therapy for LPP/FFA patients were reported, yet these were not coupled with molecular studies. Work recently submitted for publication by our group revealed strong Th1-skewing in FFA lesions, with concomitant upregulations of IL-23 subunits. For CCCA, the literature is even sparser, with pathogenesis relying on baseline pro-inflammatory state in afro-texture hair, with upregulated IL-1α in scalp sebum. In this study, PF-06651600 (ritlecitinib), a JAK3/TEC inhibitor which has demonstrated efficacy in improving scalp hair loss and has been shown to be overall safe and well tolerated in AA patients in a recent Phase 2b/3 study (B7981015), will be evaluated in an open label trial for all participants from another study for CCCA evaluating the effectiveness of brepocitinib, as well as de novo subjects. In addition to the much-needed, prospective trial of a new drug for these diseases, we also aim to characterize CA molecularly, and attempt to determine the relationship between inflammation and fibrosis, to ultimately identify new treatment targets, and guide future investigations of therapeutics.

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BACKGROUND

Cicatricial Alopecias (CAs) are a group of progressive, disfiguring skin disorders, resulting in permanent hair loss. The most common subtypes of CA are frontal fibrosing alopecia (FFA)/lichen planopilaris (LPP), and central centrifugal scarring alopecia (CCCA). FFA/LPP more commonly affect women, with FFA being mostly diagnosed in post-menopausal women, comprising up to 17% of new referrals to hair clinic in one study.[13] Despite some clinical differences, the distinction between FFA and LPP is not always clear, and mainly rely on distribution of skin lesions; whereas FFA chiefly involves the frontal hairline and eyebrows, LPP tends to manifest in a patchy or diffuse pattern. The histopathological findings cannot distinguish the two variants.[14] CCCA predominantly affects women of Afro-American origin, and usually manifests as hair loss starting at the vertex of the scalp and progressing circumferentially.[3] Although CCCA was reported as one of the top 5 diagnoses made in patients with skin of color, prominent barriers to care were recently reported due to poor physician-patient interactions.[15-16] CA patients could experience tremendous anxiety, low self-esteem, and extreme psychosocial stress, with reported decreased quality-of-life measures across symptomatic, functional, and global domains.[1-4] Despite being overly common, with more than 5.7% of the population being affected by CA, these diseases are poorly understood.[3,8-9] Previous research efforts mainly focus on histopathologic changes characterizing these diseases, or on the genetic susceptibilities in specific sub-populations, but the inflammatory dysregulations and their effects on hair keratins and the fibrotic process remain unclear.[5-7,17] The elusive pathogenesis of CA prevents the development of safe and efficacious treatments, as there are no studies defining the broad molecular dysregulations of these diseases.[18] As a result, the current therapeutic paradigm for CA is largely lacking,[3,8-9] and chiefly relies on retrospective studies with unsatisfactory results,[10-12] leading to a significant unmet need, that we wish to address.

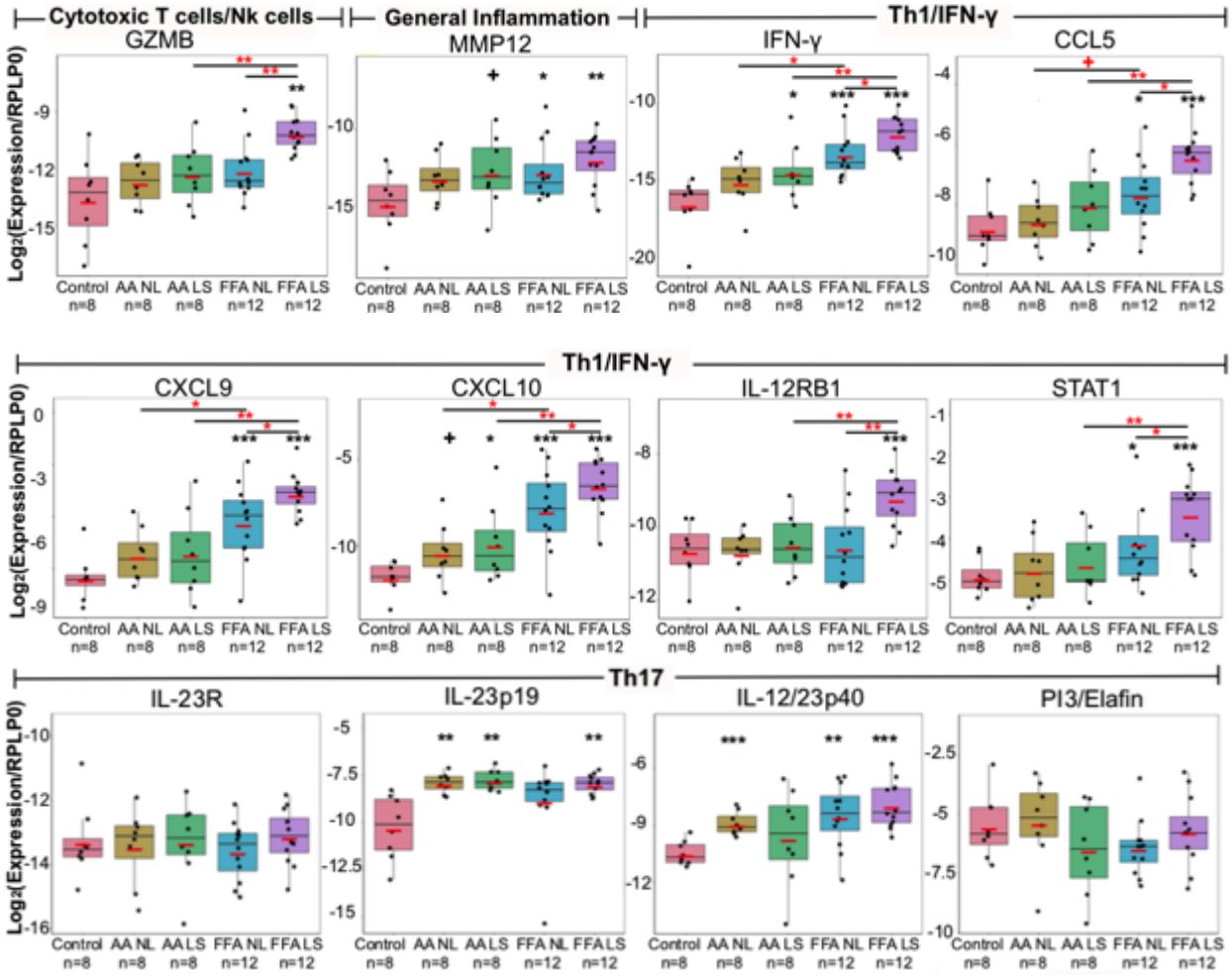
RATIONALE

Until recently, the molecular dysregulation underlying the CA has been largely unknown, hindering therapeutic development.[19] Only few studies described a limited number of markers being abnormally modulated in lesional skin from scalp of CA patients. In a study of LPP lesions, immune prevalence collapse was demonstrated in hair follicles, accompanied by a Th1-biased cytotoxic T cell response, and increased expression of interferon (IFN)-inducible chemokines (CXCL9/10/11).[20] Moreover, in skin organ culture, IFNγ was shown to induce hair follicle immune privilege collapse, raising the possibility of blocking IFN signaling and restoring immune privilege as a therapeutic approach in LPP.[20] A recent publication reported successful treatment with a broad immune antagonist, the pan-Janus kinase (JAK) inhibitor, tofacitinib, for LPP and FFA patients, with clinical response in 80% of patients, based on pre-treatment vs post-treatment lichen planopilaris activity index (LPPAI) scores ($p = .0014$).[19] Nevertheless, in this retrospective study, clinical improvements were not coupled with molecular studies.[19] For CCCA, the literature on molecular pathogenesis is even sparser, and we were unable to find data from studies investigating diseased skin with CCCA. Assumptions on CCCA pathogenesis rely on baseline pro-inflammatory state in afro-texture natural hair, where the pro-inflammatory IL-1α was found to be 18 times higher in scalp sebum collected by non-invasive application of adhesive tape, than the anti-inflammatory cytokine IL-1R.[21] A recent genetic study also found a mutation in *PADI3* in CCCA, via whole-exome sequencing that may result in improper formation of hair shaft, leading to the CCCA phenotype.[17]



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Our rationale relies primarily on a detailed study of 12 FFA patients, performed at the Laboratory of Inflammatory Skin Diseases at Mount Sinai Hospital, recently submitted for publication, in which gene and protein expression studies were performed in lesional and non-lesional skin of FFA patients. In this study, patients with relatively short duration since FFA initiated (≤7 years) were included in order to elucidate the molecular and cellular fingerprint of FFA. FFA skin samples were compared with skin samples of alopecia areata (AA) patients (a non-scarring alopecia), and controls. Analyses of biomarkers associated with fibrosis, inflammatory pathways, T cell regulation and tissue resident T cell homeostasis shed light on FFA pathogenesis. Robust, significant increases of key Th1 axis markers (IFN-γ, CCL5, CXCL9, CXCL10, IL-12RB1, STAT1) were observed in FFA scalp, not only compared to controls, but also compared to expressions seen in a highly inflammatory condition, alopecia areata (AA), which is a form of non-scarring alopecia, as shown in Figure 1. The IL-23 subunits (IL-23p19, IL-12/23p40) were significantly up-regulated in both AA and FFA compared to control scalp, suggesting pathogenic role for these markers as well. Furthermore, a similar inflammatory profile, but to a lesser extent, was also found in non-lesional scalp of FFA patients compared to scalp lesions. FFA lesions exhibited upregulation of T-regulatory cells and no suppression of hair keratins, in addition to diminished yet detectable stem cells compared with normal scalp, suggesting preservation of the potential for hair re-growth with early intervention.

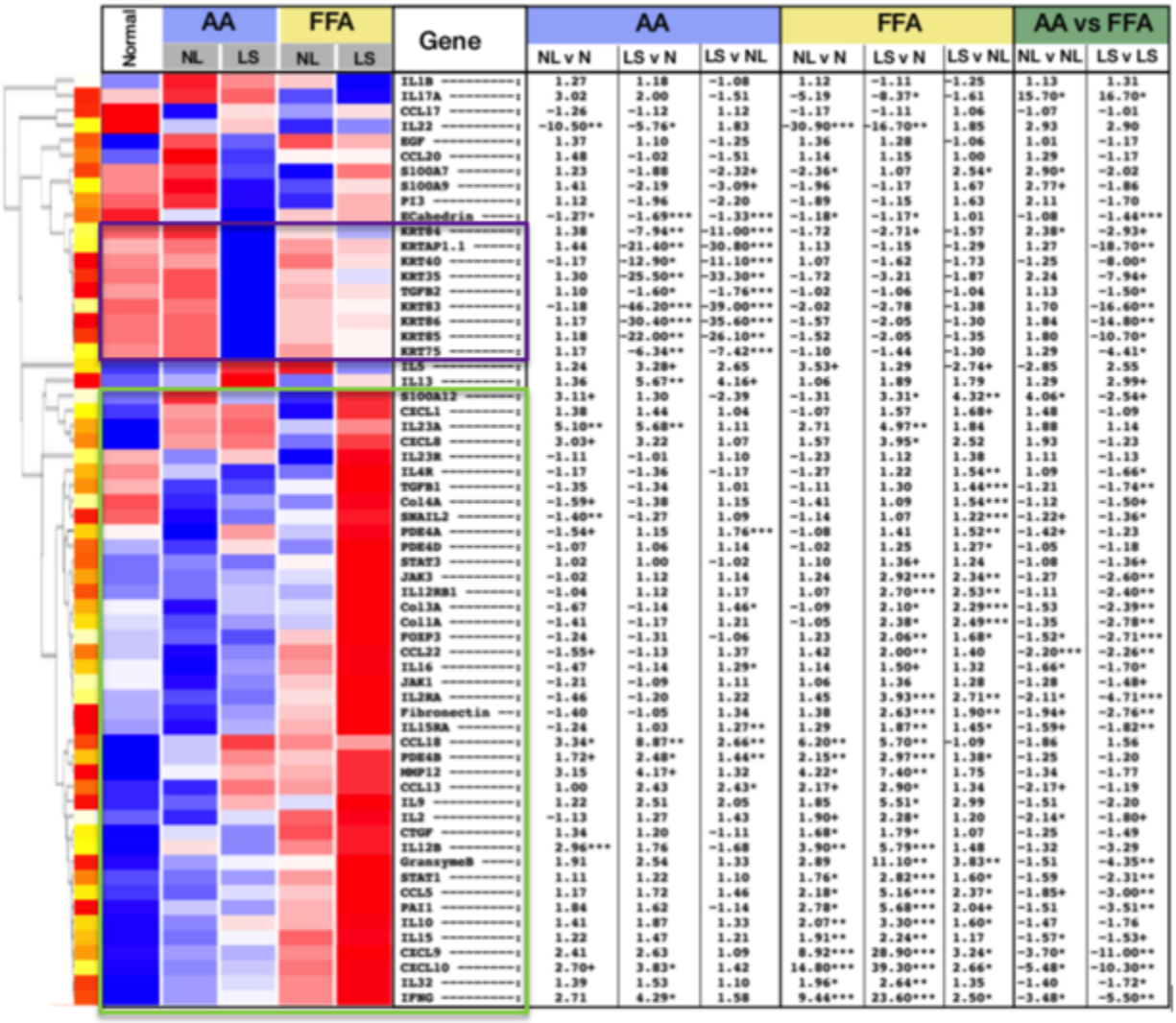


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Figure 1. Differential expression of inflammatory markers (by pathway) between AA, FFA, and control scalp by qRT-PCR. Box plots show log2 normalized mRNA expression. Black bar in the boxplot indicates median, while the red bar indicates the mean, with each black dot representing a patient. Black star indicates significance as compared to controls, whereas red stars indicate significant differences between two groups as indicated by line. NL=non-lesional, LS=lesional. +p<0.1, *p<0.05, **p<0.01, ***p<0.001.

A summary heatmap of mRNA expressions of all analyzed genes included in this cohort is presented in Figure 2 (found in "other documents"). It reveals the robust up-regulations of multiple inflammatory markers in FFA lesional skin, and, to a lesser extent, non-lesional skin, compared with the relatively moderate upregulations of these markers in AA (green box). On the other hand, as mentioned above, hair keratins were more down-regulated in AA, hinting towards a possible reversibility of the scarring process of early FFA (purple box).



Normal	AA		FFA		Gene	AA			FFA			AA vs FFA	
	NL	LS	NL	LS		NL v N	LS v N	LS v NL	NL v N	LS v N	LS v NL	NL v NL	LS v LS
					IL1B	1.27	1.18	-1.08	1.12	-1.11	-1.25	1.13	1.31
					IL17A	3.02	2.00	-1.51	-5.19	-8.37+	-1.61	15.70*	16.70*
					CCL17	-1.26	-1.12	1.12	-1.17	-1.11	1.06	-1.07	-1.01
					IL22	-10.50**	-5.76*	1.83	-30.90***	-16.70**	1.85	2.93	2.90
					EGF	1.37	1.10	-1.25	1.36	1.28	-1.06	1.01	-1.17
					CCL20	1.48	-1.02	-1.51	1.14	1.15	1.00	1.29	-1.17
					S100A7	1.23	-1.88	-2.32+	-2.36*	1.07	2.54*	2.90*	-2.02
					S100A9	1.41	-2.19	-3.09+	-1.96	-1.17	1.67	2.77+	-1.86
					PI3	1.12	-1.96	-2.20	-1.89	-1.15	1.63	2.11	-1.70
					ECahedrin	-1.27*	-1.69***	-1.33***	-1.18*	-1.17*	1.01	-1.08	-1.44***
					KRT84	1.38	-7.94**	-11.00***	-1.72	-2.71+	-1.57	2.38*	-2.93+
					KRTAP1.1	1.44	-21.40**	-30.80***	1.13	-1.15	-1.29	1.27	-18.70**
					KRT40	-1.17	-12.90*	-11.10***	1.07	-1.62	-1.73	-1.25	-8.00*
					KRT35	1.30	-25.50**	-33.30**	-1.72	-3.21	-1.87	2.24	-7.94+
					TGFB2	1.10	-1.60*	-1.76***	-1.02	-1.06	-1.04	1.13	-1.50*
					KRT83	-1.18	-46.20***	-39.00***	-2.02	-2.78	-1.38	1.70	-16.60**
					KRT86	1.17	-30.40***	-35.60***	-1.57	-2.05	-1.30	1.84	-14.80**
					KRT85	1.18	-22.00**	-26.10**	-1.52	-2.05	-1.35	1.80	-10.70*
					KRT75	1.17	-6.34**	-7.42***	-1.10	-1.44	-1.30	1.29	-4.41*
					IL5	1.24	3.28+	2.65	3.53+	1.29	-2.74+	-2.85	2.55
					IL13	1.36	5.67**	4.16+	1.06	1.89	1.79	1.29	2.99+
					S100A12	3.11+	1.30	-2.39	-1.31	3.31*	4.32**	4.06*	-2.54+
					CXCL1	1.38	1.44	1.04	-1.07	1.57	1.68+	1.48	-1.09
					IL23A	5.10**	5.68**	1.11	2.71	4.97**	1.84	1.88	1.14
					CXCL8	3.03+	3.22	1.07	1.57	3.95*	2.52	1.93	-1.23
					IL23R	-1.11	-1.01	1.10	-1.23	1.12	1.38	1.11	-1.13
					IL4R	-1.17	-1.36	-1.17	-1.27	1.22	1.54**	1.09	-1.66*
					TGFB1	-1.35	-1.34	1.01	-1.11	1.30	1.44***	-1.21	-1.74**
					Col4A	-1.59+	-1.38	1.15	-1.41	1.09	1.54***	-1.12	-1.50+
					SNAIL2	-1.40**	-1.27	1.09	-1.14	1.07	1.22***	-1.22+	-1.36*
					PDE4A	-1.54+	1.15	1.76***	-1.08	1.41	1.52**	-1.42+	-1.23
					PDE4D	-1.07	1.06	1.14	-1.02	1.25	1.27*	-1.05	-1.18
					STAT3	1.02	1.00	-1.02	1.10	1.36+	1.24	-1.08	-1.36+
					JAK3	-1.02	1.12	1.14	1.24	2.92***	2.34**	-1.27	-2.60**
					IL12RB1	-1.04	1.12	1.17	1.07	2.70***	2.53**	-1.11	-2.40**
					Col3A	-1.67	-1.14	1.46*	-1.09	2.10*	2.29***	-1.53	-2.39**
					Col1A	-1.41	-1.17	1.21	-1.05	2.38*	2.49***	-1.35	-2.78**
					FOXP3	-1.24	-1.31	-1.06	1.23	2.06**	1.68*	-1.52*	-2.71***
					CCL22	-1.55+	-1.13	1.37	1.42	2.00**	1.40	-2.20***	-2.26**
					IL16	-1.47	-1.14	1.29*	1.14	1.50+	1.32	-1.66*	-1.70*
					JAK1	-1.21	-1.09	1.11	1.06	1.36	1.28	-1.28	-1.48+
					IL2RA	-1.46	-1.20	1.22	1.45	3.93***	2.71**	-2.11*	-4.71***
					Fibronectin	-1.40	-1.05	1.34	1.38	2.63***	1.90**	-1.94+	-2.76**
					IL15RA	-1.24	1.03	1.27**	1.29	1.87**	1.45*	-1.59+	-1.82**
					CCL18	3.34*	8.87**	2.66**	6.20**	5.70**	-1.09	-1.86	1.56
					PDE4B	1.72+	2.48*	1.44**	2.15**	2.97***	1.38*	-1.25	-1.20
					MMP12	3.15	4.17+	1.32	4.22*	7.40**	1.75	-1.34	-1.77
					CCL13	1.00	2.43	2.43*	2.17+	2.90*	1.34	-2.17+	-1.19
					IL9	1.22	2.51	2.05	1.85	5.51*	2.99	-1.51	-2.20
					IL2	-1.13	1.27	1.43	1.90+	2.28*	1.20	-2.14*	-1.80+
					CTGF	1.34	1.20	-1.11	1.68*	1.79*	1.07	-1.25	-1.49
					IL12B	2.96***	1.76	-1.68	3.90**	5.79***	1.48	-1.32	-3.29
					GranzymeB	1.91	2.54	1.33	2.89	11.10**	3.83**	-1.51	-4.35**
					STAT1	1.11	1.22	1.10	1.76*	2.82***	1.60*	-1.59	-2.31**
					CCL5	1.17	1.72	1.46	2.18*	5.16***	2.37*	-1.85+	-3.00**
					PAI1	1.84	1.62	-1.14	2.78*	5.68***	2.04*	-1.51	-3.51**
					IL10	1.41	1.87	1.33	2.07**	3.30***	1.60*	-1.47	-1.76
					IL15	1.22	1.47	1.21	1.91**	2.24**	1.17	-1.57*	-1.53+
					CXCL9	2.41	2.63	1.09	8.92***	28.90***	3.24*	-3.70*	-11.00**
					CXCL10	2.70+	3.83*	1.42	14.80***	39.30***	2.66*	-5.48*	-10.30**
					IL32	1.39	1.53	1.10	1.96*	2.64**	1.35	-1.40	-1.72*
					IFNG	2.71	4.29*	1.58	9.44***	23.60***	2.50*	-3.48*	-5.50**

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Figure 2. Summary heatmap illustrating mean mRNA expressions of all analyzed genes by qRT-PCR in AA and FFA versus control scalp. Fold change differences in gene expression between tissues are shown. Red; up-regulated; blue: down-regulated genes. N=normal, NL=non-lesional, LS=lesional. Genes are ordered by unsupervised hierarchical clustering. +p<0.1, *p<0.05, **p<0.01, ***p<0.001.

Due to clinical and histopathological similarities between the 3 commonest forms of scarring alopecia: LPP, FFA and CCCA, as described in many publications, these primary CAs are discussed together.[19,22-24] Furthermore, all three conditions were shown to improve with immune based treatments. LPP/FFA was shown to improve following non-specific, broad anti-inflammatory drugs, such as methotrexate,[25] or pan-JAK inhibitor (tofacitinib),[19] and common clinical practice for CCCA include topical corticosteroids, topical immunomodulators (tacrolimus and pimecrolimus), intralesional corticosteroids, and anti-inflammatory antibiotics.[3,26] We thus postulate that LPP/FFA and CCCA may be driven by similar immune polarity.[26] The findings from our FFA study, as well as previous literature, as detailed above, provide strong rationale for CA treatment that targets Th1, IL-23, and related cytokines and chemokines. We hypothesize that the inflammation driven by Th1-related cytokines and chemokines and IL-23, is causing the characteristic fibrosis of CA, leading to scarring and permanent hair loss. In this proposed trial, we will include two study arms: an arm of LPP/FFA patients, and an arm of CCCA patients.

JAK inhibitors are a group of small molecules, recently emerging as an appealing class of immune modifiers in dermatology.[27] These are antagonists of the various members of the JAK enzymes family, which consists of JAK1, JAK2, JAK3, and tyrosine kinase-2 (TYK2).[28] JAKs enable the binding and activation of the transducer and activator of transcription (STAT), by phosphorylating the cytoplasmic domain of multiple cytokine receptors. This results in translocation of the STAT into the nucleus, which greatly affects transcription. JAK antagonism therefore blocks this signaling through STAT activation,[29-31] targeting Th1/IFN-γ as well as common γ_c cytokines (shared between IL-2, IL-4, IL-9, IL-7, IL-15 and IL-21), and TYK2 also adds an IL-23 capability.[32-34] Therefore ritlecitinib,, a dual inhibitor of JAK3 and TEC, currently being investigated for a number of indications has been shown to be safe and well tolerated, with good safety profile,[35] and was chosen for this protocol.

Ritlecitinib belongs to the JAK-inhibitor family. It is a highly selective JAK3 and tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family inhibitor that potently inhibits signaling of the common γ-chain receptors for IL-15 and IL-21, which have been implicated in the pathogenic pathways of both AA[1] and LPP/FFA. Additionally, ritlecitinib inhibits the cytotoxic function of CD8+ T cells and NK cells which are highly expressed in AA and LPP/FFA. Ritlecitinib has demonstrated statistically significant improvement of scalp hair regrowth in AA patients in study B7981015. To date, approximately 48 participants with AA have been exposed to ritlecitinib in a Phase 2a study (B7931005) and approximately 708 participants with AA have been exposed to ritlecitinib in the Phase 2b/3 study B7981015. Ritlecitinib has been demonstrated to be overall well-tolerated in AA participants based on the safety data from these 2 studies. Taking into consideration the efficacy and safety data results from the recently completed Phase 2b/3 study B7981015 study in AA participants, it was

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determined that participants would likely benefit from a treatment that has already been shown to improve a type of scalp hair loss.

We will evaluate scalp and blood markers of inflammation, hair keratins and fibrosis, and our ultimate goal would be to elucidate the relations between inflammation and tissue scarring. In addition, drug safety and tolerability in this patient population will also be closely monitored.

Our research proposal is novel in that we propose to investigate the immune profile of CA patients in skin and blood, at baseline, as well as during treatment with ritlecitinib. In addition to the much-needed, prospective investigation of a new treatment modality for these diseases, we also aim to better characterize these diseases molecularly, and attempt to determine the effects of the inflammatory process on the resultant fibrosis. These findings will help to identify new treatment targets as well as direct further investigation for the development of new therapies for these disfiguring diseases.

The study will be conducted in accordance with our department's Standard Operating Procedures, which are based on US FDA Title 21 Code of Federal Regulations and ICH Good Clinical Practice guidelines

HYPOTHESIS

Ritlecitinib administration will be safe and tolerable in CA patients and will downregulate biomarkers known to be associated with inflammation and fibrosis.

OBJECTIVES

Primary Objectives:

To evaluate the safety of ritlecitinib and its effects on biomarkers of inflammation and fibrosis at week 24 and week 48, respectively, in study participants with CA.

Secondary Objectives:

To characterize the effect of ritlecitinib on scalp biomarkers, clinical endpoints, and quality of life.

OUTCOMES

PRIMARY ENDPOINTS

- Incidence and severity of Treatment- Emergent adverse events including adverse events of special interest, Serious Adverse Events, clinically significant abnormalities in vital signs and incidence of clinically significant abnormalities in clinical laboratory parameters from baseline to week 24 and 48.
- Changes in CCL5 (a surrogate for IFNγ activity) and biomarkers of fibrosis (e.g. TGFB1/2, vimentin, fibronectin, CTGF) in CA scalp from baseline to week 24 and Week 48.

SECONDARY ENDPOINTS

- Evaluate the baseline molecular dysregulations of CA by mechanistic studies on scalp and blood
- Change in scalp biomarkers from baseline to week 24 and 48.

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- Change in the applicable clinical score (Frontal Fibrosing Alopecia Severity Score – FFASI[36] for FFA; Lichen Planopilaris Activity Index Score – LPPAI[37] for LPP; Change in Central Hair Loss Grade – CHLG[38] for CCCA) from baseline to week 24 and 48.
- Change in Physician Global Assessment of Improvement (PGA-I) from baseline to weeks 24 and 48.
- Change in the Dermatology Quality of Life Index (DLQI) from baseline at week 24 and 48.
- Percent change of clinical score and PGA-I response from baseline to week 24 and 48.
- Molecular response from baseline to week 24 and 48.

STUDY DESIGN AND METHODS

This is a prospective, open-label clinical trial, in which all participants will be treated with ritlecitinib for 48 weeks. Approximately 50 participants will be enrolled. The study will take place at the Icahn School of Medicine at Mount Sinai (ISMMS).

De novo participants will have recently (less than 7 years since disease onset) been diagnosed with CA, LPP/FFA or CCCA, at the time of screening. Participants from the brepocitinib study had met this criteria at the time of enrollment into that study.

At the Baseline/Day 0 visit, subjects will initiate treatment with ritlecitinib. Participants from a previous brepocitinib will be required to undergo at least a 1-week washout period before starting on ritlecitinib in this study. All subjects will receive ritlecitinib 200 mg once-daily for 8 weeks and then 100 mg once-daily for the duration of the study.

Clinical and mechanistic evaluations will take place according to the Schedule of Activities.

The treatment period will conclude at week 48, and subjects will be asked to return for a follow up visit at week 52 (end of trial) as shown below, for continued observation of skin and hair changes.

DOSE JUSTIFICATION

Ritlecitinib will be administered as 200 mg once-daily for 8 weeks and then 100 mg once daily for the remaining 40 weeks. This dose was selected based on prior studies. Ritlecitinib has been tested at doses up to 400 mg QD or 200 mg BID for 14 days in healthy participants without a dose limiting adverse effect being demonstrated. In addition, current doses in ongoing Phase 2 clinical studies, as well as those completed to date in other indications (rheumatoid arthritis and ulcerative colitis), include dosing of ritlecitinib up to 200 mg for 8 weeks and 100 mg for 24 weeks (RA, B7921023, ongoing), and 50 mg for extended treatment up to one year or more (Phase 2b/3 Alopecia Areata, B7981015, completed). In clinical trial B7981015, patients who received 30 mg or 50 mg once-daily treatment (with or without a 4 week initial treatment of 200 mg) with ritlecitinib had 20 percent or less scalp hair loss (from baseline of 50% of more hair loss) after 24 weeks of treatment compared to placebo. Ritlecitinib has an acceptable safety profile based on all completed clinical studies to date in healthy participants and in participants with vitiligo, alopecia areata, rheumatoid arthritis, and ongoing studies in ulcerative colitis and

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Crohn's disease. The currently available nonclinical safety package supports the proposed dose of 200 mg once daily for 8 weeks. The predicted safety exposure margin for 200 mg at the NOAEL in the 8-week dog study was approximately 14-fold for AUC. The predicted safety exposure (AUC) margin for the 100 mg was approximately 3.3 relative to the predicted NOAEL exposure in the 9-month chronic dog study.

SUBJECT ELIGIBILITY

INCLUSION CRITERIA

1. Subjects of any gender, age 18 years or older, at the time of informed consent at Screening

2. Subjects who are willing and able to adhere to the study visit schedule and comply with protocol requirements.

3. Subject self-reports a history of at least 6 months of CA (LPP/FFA or CCCA). Diagnosis will be made clinically (according to the LPPAI[37], FFASI[36] and/or CHLG[38]).

4. Subject has a negative Tuberculin purified protein derivative (PPD) or QuantiFERON TB-Gold test (QFT) at screening or within the last 12 months.

5. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

   Is not a woman of childbearing potential (WOCBP)

   OR

   Is a WOCBP (all female participants, regardless of whether or not they have experienced/reported menarche, are considered WOCBP unless they are permanently sterile or confirmed infertile). A WOCBP who is sexually active must use a contraceptive method that is highly effective, with a failure rate of <1%, during the intervention period and for at least 28 days after the last dose of study intervention.

   And if a WOCBP, must have a negative highly sensitive serum pregnancy test at the screening visit and a negative urine pregnancy test at baseline performed before the first dose of study intervention.

6. Subject is judged to be in otherwise good overall health following a detailed medical and medication history, physical examination, and laboratory testing.

EXCLUSION CRITERIA

1. Subject's cause of hair loss is indeterminable and/or they have concomitant causes of alopecia, such pregnancy-related, drug-induced, telogen effluvium, or advanced androgenetic alopecia.

2. Subject has a history of CA for ≥ 7 years since their disease onset, severe fibrosing disease, or very rapid hair loss at screening (de novo patients only).

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3. Subject has a history of moderate to severe keloids on the scalp, as determined by clinical examination at screening.

4. Other scalp disease that may impact assessment (e.g., scalp psoriasis, dermatitis, etc.).

5. Subject is pregnant or breastfeeding.

6. Participation in other studies involving investigational drug(s) within 4 weeks or within 5 half-lives (if known), whichever is longer, prior to study entry and/or during study participation (de novo patients only).

7. Active systemic diseases that may cause hair loss (e.g., systemic lupus erythematosus, thyroiditis, systemic sclerosis, etc.).

8. Any Psychiatric condition in the opinion of the investigator precludes participation in the study.

9. Subjects with a Columbia Suicide Severity Rating Scale (C-SSRS) score of "yes" on questions 4 and/or 5 at Visit 2 (Baseline).

10. Current or recent history of clinically significant severe, progressive, or uncontrolled renal (including but not limited to active renal disease or recent kidney stones), hepatic, hematological, gastrointestinal, metabolic, endocrine (particularly thyroid disease which can be associated with hair loss), pulmonary, cardiovascular, psychiatric, immunologic/rheumatologic or neurologic disease; or have any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration, or interfere with the interpretation of study results; or in the opinion of the investigator, the subject is inappropriate for entry into this study, or unwilling/unable to comply with STUDY PROCEDURES.

11. History of thromboembolic events including DVT and PE or history of inherited coagulopathies.

12. Any present malignancies or history of malignancies with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.

13. History of any lymphoproliferative disorder such as Epstein Barr Virus (EBV) related lymphoproliferative disorder, history of lymphoma, history of leukemia, or signs and symptoms suggestive of current lymphatic or lymphoid disease.

14. History (single episode) of disseminated herpes zoster or disseminated herpes simplex, or a recurrent (more than one episode of) localized, dermatomal herpes zoster.

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15. History of systemic infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator within 6 months prior to Day 0.

16. Active acute or chronic infection requiring treatment with oral antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks prior to Day 0 or superficial skin infection within 1 week prior to Day 0.

17. Significant trauma or major surgery within 1 month of signing informed consent.

18. Considered in imminent need for surgery or with elective surgery scheduled to occur during the study.

19. Active hepatitis B, hepatitis C, human immunodeficiency virus (HIV), or positive HIV serology at the time of screening for subjects determined by the investigators to be at high-risk for this disease.

20. **ANY** of the following abnormalities in the clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat, if deemed necessary:
    1. Absolute neutrophil count of $<1.2 \times 10^9/L$ ($<1200/mm^3$);
    2. Hemoglobin <11.0 g/dL or hematocrit <33%;
       - Platelet count of $<150 \times 10^9/L$ ($<150,000/mm^3$);
    3. Absolute lymphocyte count of $<0.80 \times 10^9/L$ ($<800/mm^3$);
    4. Estimated Glomerular Filtration Rate (eGFR) less than 60 mL/ml/min/1.73m^2 based on CKD-Epi 2021 (creatine equation);
    5. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values >2 times the ULN;
    6. Total bilirubin ≥ 1.5 times the ULN; participants with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is ≤ ULN.

21. Have an active history of alcohol or substance abuse within 1 year prior to Day 0.

22. Donation of blood in excess of 500 mL within 8 weeks prior to Day 0.

23. Subject has received a live attenuated vaccine ≤ 6 weeks prior to study screening.

24. Subject has any uncertain or clinically significant laboratory abnormalities that may affect interpretation of study data or endpoints, at determined by the PI.

25. History of adverse systemic or allergic reactions to components of study drug.

26. Use of systemic immunosuppressive medications, including, but not limited to, cyclosporine, systemic corticosteroids, mycophenolate mofetil, azathioprine, methotrexate, within 8 weeks prior to baseline visit.

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27. Use of other non-biologic systemic agent for CA, including, 5α-reductase inhibitors, hydroxychloroquine, or retinoids, within 4 weeks prior to baseline visit.

28. Use of an intralesional corticosteroids or oral JAK inhibitor (tofacitinib, ruxolitinib, or any JAK1/TYK2 product) within 4 weeks prior to the baseline visit (de novo patients only).

29. Subject has used topical corticosteroids, and/or tacrolimus, and/or pimecrolimus or cyclosporine within 1 week before the baseline visit.

30. Subject has been previously treated with biological drugs in the last 12 weeks for other indications.

31. Subjects previously tested with a positive or indeterminable PPD or QFT result, including subjects that completed standard tuberculosis therapy.

32. Screening 12-lead ECG that demonstrates clinically significant abnormalities requiring treatment, e.g. acute myocardial infarction, serious tachy or brady arrhythmias or that are indicative of serious underlying heart disease (e.g. cardiomyopathy, major congenital heart disease, low voltage in all leads, Wolff-Parkinson-White syndrome and other clinically relevant abnormalities which may affect participant safety or interpretation of study results. A history of additional risk factors for Torsades de Pointes (TdP) (e.g. heart failure, hypokalemia, family history of long QT syndrome).

    - If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated 2 more times and the average of 3 QTc or QRS values should be used to determine the participants' eligibility. Participants with average screening value QTcF > 450 ms should be excluded.

33. The use of prohibited and permitted CYP3A substrates are provided in Appendix 2.1 and 2.2, respectively and medications that prolong the QT/QTcF interval in Appendix 3.

34. Have hearing loss with progression over the previous 5 years, or sudden hearing loss, or middle or inner ear disease such as otitis media, cholesteatoma, Meniere's disease, labyrinthitis, or other auditory condition that is considered acute, fluctuating, or progressive.

PROCEDURES

CLINICAL PROCEDURES

After providing informed consent, subjects will be assessed for study eligibility during the screening/washout period (up to 4 weeks prior to baseline), which includes a review of past and current medical conditions, detailed review of past and current medications, a brief physical examination, and clinical assessments (FFAI/LLPAI/CHLG, whichever applies). The following laboratory tests will be performed on all participants: complete blood count (CBC) with differential,

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complete metabolic panel (CMP), high sensitivity C-reactive protein (CRP), urinalysis, and serum pregnancy (where applicable). If subject did not participate in the previous brepocitinib study, additional testing will include HIV, hepatitis B surface antigen (HbsAg), hepatitis C virus antibodies,

Subjects who meet inclusion and exclusion criteria will return for baseline assessments and clinical photographs at Day 0. Blood samples and skin biopsies will be collected for gene expression and proteomic studies. Two 4.5 mm scalp biopsies will be performed at baseline, one from lesional skin (from frontal scalp in FFA patients, and from the edge of lesions in LPP and CCCA patients) and one from non-lesional skin (taken from clinically non-involved scalp areas, ≥5cm from any lesional areas). Thereafter, only lesional biopsies. Blood sampling for mechanistic studies will be collected at weeks 12, 24, 36 and 48. For any subject previously enrolled in the brepocitinib study, these biopsies will not be required as the data will be obtained from the last visit in that study.

The following procedures/assessments will take place at each visit:

Visit 1 – Screening (within 4 weeks of baseline)*****

- Sign and date an IRB-approved informed consent and HIPPA agreement
- Review Inclusion and Exclusion Criteria
- Record gender, race, ethnicity, and medical history (including personal and family history of CA or other dermatological diseases, and autoimmune diseases)
- Brief physical exam, including: height (cm), weight (kg), blood pressure, and heart rate
- 12 –lead ECG (in triplicate); if QTcF exceeds 450 ms, the ECG should be repeated 2 more times and the average of the three QTcF used to determine eligibility.
- Record all prior systemic and topical therapies/treatments used for CA
- PPD test or Quantiferon blood test as outlined in Inclusion/Exclusion criteria if applicable
- HIV, HBV, and HCV screening, if applicable.
- Serum HCG for all female subjects of child-bearing potential to confirm subject is not pregnant
- Safety labs, including: Complete blood count (CBC), Comprehensive metabolic panel (CMP), and C-reactive protein (CRP), urinalysis
- Clinical assessment (for FFA - Frontal Fibrosing Alopecia Severity Score – FFASI,[36] for LPP – Lichen Planopilaris Activity Index Score – LPPAI,[37] for CCCA - Change in Central Hair Loss Grade – CHLG[38]; eyebrow/eyelash score).
- Record all other concomitant medications and adverse events
- Audiological evaluation
- Contraception check

*** Can occur at last visit of brepocitinib study. Items that are performed at last visit of brepocitinib study do not need to be repeated.**

Visit 2 – Baseline (Day 0)

- Confirm all Inclusion and Exclusion criteria have been met
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Confirm proper contraception is being used
- Urine pregnancy test for all female subjects of child-bearing potential to confirm subject is not pregnant

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- Obtain vital signs (BP and heart rate)
- Clinical assessment (FFASI/LPPAI/CHLG; eyebrow/eyelash score)
- Questionnaires (DLQI and VAS)
- Clinical photos of scalp and eyebrows
- Collect blood and urine for safety labs (including cystatin-C and CPK)
- Fasting Lipid Panel
- Collect blood sample for mechanistic endpoints
- Collect blood for genetic assay
- Collect blood for PK
- Perform biopsies of lesional and non-lesional skin of the scalp*****
- Record concomitant medications and adverse events
- Dispense and administer study drug

*** Data for this procedures will be collected from Week 48 visit of the brepocitinib study for those who participated in that study.**

Visit 3, 4, 5, 6, 7 – Weeks 4, 8, 12, 16, 20

- Confirm proper contraception is being used
- Urine pregnancy test for all female subjects of child-bearing potential to confirm subject is not pregnant
- Obtain vital signs (BP and heart rate)
- Clinical assessment (FFASI/LPPAI/CHLG; eyebrow/eyelash score)
- Questionnaires (DLQI and VAS) (Weeks 8 and 16)
- Collect blood and urine for safety labs (including cystatin-C and CPK)
- Collect blood sample for mechanistic endpoints (week 8 only)
- Collect blood for PK (Week 4 and 20)
- Perform biopsy of lesional skin of the scalp (Week 8 only)
- Clinical photos of scalp and eyebrows (Weeks 8 and 16)
- 12 –lead ECG (Weeks 8 and 16)
- Columbia Suicide Severity Rating Scale (C-SSRS) (Weeks 8 and 16)
- Dispense/collect study drug
- Record concomitant medications and adverse events

Visit 8 – Week 24

- Confirm proper contraception is being used
- Urine pregnancy test for all female subjects of child-bearing potential to confirm subject is not pregnant
- Obtain vital signs (BP and heart rate)
- 12 –lead ECG
- Audiological evaluation
- Clinical assessment (FFASI/LPPAI/CHLG; eyebrow/eyelash score)
- Questionnaires (DLQI and VAS)
- Collect blood and urine for safety labs (including cystatin-C and CPK)
- Fasting Lipid Panel
- Collect blood sample for mechanistic endpoints
- Clinical photos of scalp and eyebrows
- Perform biopsy of lesional skin of the scalp

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- Columbia Suicide Severity Rating Scale (C-SSRS)
- Record concomitant medications and adverse events

Visit 9, 10, 11, 12, 13 and 14 – Weeks 28, 32, 36, 40, 44 and 48

- Confirm proper contraception is being used
- Urine pregnancy test for all female subjects of child-bearing potential to confirm subject is not pregnant
- Obtain vital signs (BP and heart rate)
- Clinical assessment (FFASI/LPPAI/CHLG; eyebrow/eyelash score)
- Questionnaires (DLQI and VAS) (Weeks 32, 40 and 48)
- Collect blood and urine for safety labs (including cystatin-C and CPK)
- Fasting lipids panel (Weeks 48)
- Blood for mechanistic endpoint (Week 48)
- Perform biopsy of lesional skin of the scalp (optional)
- Clinical photos of scalp and eyebrows (Weeks 32, 40 and 48)
- 12 –lead ECG (Weeks 32, 40, 48)
- Audiological Evaluation (Week 48 only)
- Columbia Suicide Severity Rating Scale (C-SSRS) (Weeks 32 and 40)
- Dispense/Collect study drug (no drug is dispensed at Week 48)
- Record concomitant medications and adverse events
- Perform biopsy of lesional skin of the scalp (Week 48 only)

Visit 15 – Week 52 Follow-up

- Clinical assessment (FFASI/LPPAI/CHLG; eyebrow/eyelash score)
- Questionnaires (DLQI and VAS)
- Medical photos of scalp and eyebrows
- Record concomitant medications and adverse events

Early Termination Visit

In the event a study subject wants to withdraw early from the study or the subject is being discontinued from the study for any reason, the following procedures should be followed:

- Confirm proper contraception is being used
- Urine pregnancy test for all female subjects of child-bearing potential to confirm subject is not pregnant
- Obtain vital signs (BP and heart rate)
- 12-lead ECG
- Audiological Evaluation
- Clinical assessment (FFASI/LPPAI/CHLG; eyebrow/eyelash score)
- Questionnaires (DLQI and VAS)
- Collect blood and urine for safety labs (including cystatin-C and CPK)
- Collect blood sample for mechanistic endpoints
- Perform biopsy of lesional skin of the scalp
- Clinical photos of scalp and eyebrows
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Collect unused study drug
- Record concomitant medications and adverse events

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Monitoring of AEs and SAEs will begin once the participant has provided informed consent for the study. All study procedures will be completed at designated intervals during the study (see Table 1).

MECHANISTIC PROCEDURES

Blood Analyses

- OLINK MSD and Singulex platforms will be used to assess for biomarkers in blood. These platforms are able to evaluate more than 200 analytes, including all the inflammatory markers that are analyzed in skin, as well as cardiovascular markers, and neuro-immunological markers, including cytokines and chemokines related to Th1, Th2, Th17, Treg, PDE-related markers, and more.
- PAX DNA for genetic analyses. DNA samples will be collected from all participants on Day 0 and archived for future analysis. Based on recent publications, we will seek known genetic variations strongly associated with FFA or CCCA.[7,17] for FFA, genome-wide significant association were found at four genomic loci: 2p22.2, 6p21.1, 8q24.22 and 15q2.1.[7] For CCCA, a whole-exome sequencing study found a mutation in *PADI3*, which encodes peptidyl arginine deiminase, type III, an enzyme that post-translationally modifies other proteins that are essential to hair-shaft formation. *PADI3* mutation may result in improper formation of hair shaft, leading to the CCCA phenotype.[17] Of note, the CCCA-related variant was identified in a group of 16 CCCA patients,[17] underscoring the great potential of such data collection. These susceptibility loci, as well as future possible variants to be published, will be explored, and we also aim to correlate genetic variants with molecular and clinical findings/responses.

Skin Analyses

We will perform gene expression studies using RT-PCR and RNAseq, single-cell RNAseq, as well as protein expression studies using immunohistochemistry. We will also perform OLINK proteomic studies on scalp biopsies.

Immunohistochemistry (IHC) will be performed as described on frozen sections,[39-40] using purified mouse anti-human monoclonal antibodies. Cell counts will be quantified using Image J V1.42 software (National Institutes of Health, Bethesda, MD).

RNA will be extracted for Quantitative real-time PCR (qRT-PCR) with the miRNAeasy Mini Kit (Qiagen, Hilden, Germany). Reverse transcription to cDNA from RNA will be performed using the High Capacity cDNA Reverse Transcription Kit, and cDNA will be amplified with TaqMan Gene Expression Master Mix (Applied Biosystems, Foster City, CA). TaqMan Low Density Array/TLDA cards will be used for qRT-PCR. Eukaryotic 18S rRNA will be used as an endogenous control. Expression values (threshold cycle [Ct]) will be normalized to Rplp0.

We will also perform single cell analyses on 8 patients with CCCA and 8 with FFA/LPP (a total of 16 patients), with the same number of biopsies per patient (16x4-3 lesional and

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one non lesional=64 total biopsies), at similar weeks as other biopsies. Biopsies will be divided as follows: ¼ for single cell, ¼ for gene expression and half for OCT.

Audiological Evaluation

All participants will have an audiological evaluation at times specified in the Schedule of Activities. A full audiological evaluation must be completed and results reviewed to assess the participant's eligibility prior to the participant taking the first dose of ritlecitinib. This evaluation includes: audiological history, otoscopic examination, pure tone audiometry, air and bone conduction, speech audiometry, and immittance audiometry. At subsequent visits, updated audiological history, otoscopic examination, and pure tone audiometry will be performed; based upon results, additional audiometry assessments may be required. For participants who terminate early from the study, efforts must be made to complete the audiological evaluation. If there is a clinically meaningful, treatment-emergent decline in hearing from baseline, the subject must be promptly evaluated by a medically qualified specialist to assess for possible causes and to determine if the participant should be discontinued from the study.

Discontinued participants must be followed up off-treatment with appropriate testing at regular intervals, until; hearing returns to baseline or is determined to be clinically stable. The current version of the Audiometry study guide provides details on assessments required for auditory evaluation which are to be performed as per the Audiometry study guide.

CLINICAL OVERVIEW OF POTENTIAL RISKS

Ritlecitinib

The potential risks for ritlecitinib include: (1) viral reactivation; (2) serious infections and opportunistic infections (3) malignancy and lymphoproliferative disorders; (4) Thromboembolism; Dermatological effects (e.g. rash, folliculitis, urticaria) (5) decreased lymphocyte counts; (6) change in neutrophil counts; (7) decreased platelet count; (8) alterations in the lipid profile.

In preclinical studies, in dogs only, ritlecitinib administration for 9 months resulted in a reversible increase in incidence and/or severity of axonal dystrophy. The morphologic features and characteristics of axonal dystrophy as assessed by light and electron microscopy are not indicative of a degenerative process. Axonal dystrophy in CNS/PNS observed in chronic dog toxicity studies was reversible, monitorable and when accompanied by functional Brainstem Auditory Evoked Potential (BAEP) threshold and waveform changes, adverse at 13 x multiples of exposure relative to 100 mg (unbound AUC). Axonal dystrophy was not considered an adverse finding in the absence of accompanying functional changes (clinical signs or BAEP) at 2.9 x exposure relative to 100 mg (unbound AUC).

Based upon the preclinical findings in dogs, participants in clinical studies with ritlecitinib will undergo audiological evaluation prior to, and at protocol-specified intervals during the study treatment period. Treatment-emergent adverse events associated with hearing loss have been reported in the completed AA study (B7981015) and in the completed B7981005 UC study.

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These events have occurred across all treatment groups, including placebo, and are undergoing adjudication by a neurosafety committee external to Pfizer. Peripheral neurological events are also safety events of interest for ritlecitinib, based upon preclinical findings in dogs. There were no TEAE of peripheral neuropathy reported in the completed B7981015 AA study. Participants experiencing TEAE neurological events of interest in ongoing studies with ritlecitinib should be referred to a neurologist for further evaluation.

In the recently completed B7981015 AA study (48 weeks), the most common treatment-emergent AEs reported in ≥5 % of participants were nasopharyngitis, headache, and upper respiratory tract infection. The most commonly reported (≥5% in any treatment group) dermatologic events were acne, folliculitis, and urticaria. There were no major adverse cardiac events (MACE), deaths or opportunistic infections in the trial. Eight participants who were treated with ritlecitinib developed mild to moderate herpes zoster. There was one serious adverse event of pulmonary embolism in the ritlecitinib 50mg group. There were two malignancies (both breast cancers) reported in the ritlecitinib 50mg group. No participants met protocol discontinuation criteria for laboratory test values and there were no SAEs associated with laboratory values.

In pregnant animals, ritlecitinib was associated with fetal skeletal variations, fetal skeletal and visceral malformations, and lower fetal body weights. It is not known whether ritlecitinib is secreted into human milk. Due to its investigational nature, ritlecitinib should not be administered to pregnant female participants, breastfeeding female participants, or fertile female participants of childbearing potential who are unwilling or unable to use contraception as defined in each protocol. Pregnancy testing is required throughout the study treatment period, as defined in the study protocol. Male participants are not required to use contraception to minimize partner exposure to ritlecitinib.

For further safety information on ritlecitinib, refer to the Investigator's Brochure.

PRIOR TREATMENT

All relevant treatment received by the subject within 30 days before screening will be recorded. Over-the-counter drugs (e.g. vitamins, acetaminophen) taken by the subject within 14 days before screening will also be recorded.

CONCOMITANT TREATMENT

Concomitant medications are permitted for the treatment of stable, chronic illness. Use of such concomitant medication or other medications that may be required throughout the study will be recorded (including the reason for treatment and name, dose, unit, route, and the date of treatment as appropriate) until week 52 or Early Termination.

PROHIBITED TREATMENT

All treatments prohibited during the screening period are also prohibited throughout the course of the study. No live attenuated vaccinations are permitted through the study.

MEASURES TO MINIMIZE/AVOID BIAS

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Subject Identification

Approximately 50 subjects will be enrolled in the study. Subjects are numbered sequentially. Each subject will be assigned a unique number and will keep this number for the duration of the study. Subject numbers will not be reassigned or reused for any reason. Subjects who discontinue or withdraw from the study before receiving a treatment assignment code, who re-enroll at a later time must be assigned a new subject number. Subjects should be identified only by their assigned identified code number. The investigator must maintain a subject master log linking the subject number to the subject's name. The investigator must follow all applicable privacy laws in order to protect a subject's privacy and confidentiality.

PHARMACOKINETICS

Blood samples will be collected into appropriately labeled tubes containing K_2EDTA at times specified in the Schedule of Events (Table 1) section of the protocol for measurement of ritlecitinib. Blood will be collected at the time points identified in the Schedule of Events section of the protocol. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. The date and exact time of the sample collection is to be noted on the source document and data collection tool (e.g., CRF). Samples obtained outside the windows specified in the Schedule of Events may be considered a protocol deviation.

- Further details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the lab manual.
- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.
- As part of understanding the PK of the IP, samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report. The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (e.g. sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented and reported to Pfizer. On a case-by-case basis, Pfizer may make a determination as to whether sample integrity has been compromised.

SAFETY REPORTING

Definition of an Adverse Event

An Adverse Event (AE) is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition include:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements, changes

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or worsening in physical examination findings), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
- Is associated with accompanying clinical symptoms.
- Requires additional diagnostic testing or medical/surgical intervention.
- Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.

NOTE: Merely repeating an abnormal laboratory test in the absence of any of the above conditions does not constitute an AE. Any abnormal test that is determined to be an error does not require recording as an AE.

- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. Note that anticipated day-to day fluctuations of pre-existing disease or conditions present at the start of the study that **do not worsen** do not meet AE criteria.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses must be reported regardless of sequelae.

Definition of a Serious Adverse Event

An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death;
- Is life- threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization. In general hospitalization signifies that the participant has been detained (usually an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Hospitalization for elective treatment of a preexisting treatment that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in a congenital anomaly/birth defect.

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include

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intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of drug dependency or drug abuse.

Method of Detecting AEs and SAEs
Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences. Examples of non-directive questions include: "How have you felt since your last clinical visit?" and "have you had any new or changed health problems since you were last here?"

Time period and frequency for collecting AE and SAE information
The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (i.e., before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days after the last administration of the study intervention or until study completion or withdrawal, whichever is longer.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.
If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the Case Report Form (CRF) and the SAE reported using the Pfizer CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

Reporting SAEs to Pfizer Safety
All SAEs occurring in a participant during the active collection period are to be reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to Pfizer within 24 hours of it being available. It is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to Pfizer Safety.

Follow up of AEs and SAEs
After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate

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information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Exposure During Pregnancy or Breastfeeding, and Occupational Exposure
Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness, irrespective of whether they are accompanied by an AE/SAE. Occupational exposure occurs when a person comes in direct, unplanned contact with the investigational product, during the performance of job duties.

Adverse Events of Special Interest
Adverse Events of Special Interest for ritlecitinib include:
(1) viral reactivation
(2) serious infections and opportunistic infections
(3) malignancy and lymphoproliferative disorders
(4) hematological abnormalities and other alterations in laboratory parameters: change in lymphocyte counts, decreased platelet counts
(5) Thromboembolic/cardiovascular events
(6) Dermatologic events (e.g rash, folliculitis, urticaria)
(7) Neurological events (including audiological events)

INFORMED CONSENT

Prior to the initiation of any study related procedures, the potential subjects will be given a copy of the most recent IRB stamped and approved informed consent to read. Additionally, the PI or study staff member who has been designated to consent will discuss the specifics of the study including but not limited to the purpose of the research, procedures, time commitment, required tasks, test article or device, alternative treatments, benefits, risks, confidentiality etc. in a comprehensible (non-scientific) manner, using language readily understandable by the subject. Subjects will be told that participation is voluntary and that, if they do not consent, they will not be penalized. The person consenting will assure the voluntariness of the subject.

DISCONTINUATION OF TREATMENT AND WITHDRAWAL OF SUBJECTS

The reasons why a subject may discontinue or be withdrawn from the study include, but are not limited to the following: subject request, protocol violation, loss to follow up, subject non-compliance, study termination by investigators, and a confirmed grade 3 or higher adverse event, which is suspected to be related to test article administration. Subjects that elect to withdraw from the trial due to lack of efficacy and/or exacerbation of disease will undergo the procedures required at an early termination visit.

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Stopping Rules

Patients will be permanently discontinued from study treatment in the event of:

- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin
- Female participants confirmed as pregnant during the study
- Any infection that is opportunistic, such as active TB and other infections whose nature or course may suggest an immuno-compromised status
- Treatment with any prohibited concomitant medication or procedure
- Other reasons that may lead to the permanent discontinuation of study drug include certain AEs deemed related to the study drug.
- Columbia Suicide Severity Rating Scale (C-SSRS): a "YES" answer to questions 4 and/or 5.
- If an individual participant demonstrates an eGFR decline of at least 30% compared to the subject's baseline eGFR then the participant should not be further dosed and adequate, immediate, supportive measures including immediate evaluation by a nephrologist (preferably within 24 hours) with appropriate management and treatment as clinically indicated. Results should be repeated as indicated by the nephrologist or weekly at a minimum until the eGFR returns to baseline ±15%, or the renal parameters are deemed to be stable by the nephrologist and/or PI. If the subject cannot be seen by a nephrologist within 24 hours (as described above), then the subject should be sent to a local emergency room for evaluation and treatment as clinically indicated.
- If the following lab results are abnormal, participants will be retested in a window of 7-10 days and reassessed. If the test results remain abnormal, participants will be discontinued from the study:

  Hematology

  Absolute Neutrophil Count: $<1000/mm^3$; $<1.0 \times 10^9/L$

  Hemoglobin: <8.0 g/dL; <4.96 mmol/L; <80 g/L
- Hemoglobin drop ≥ 2 g/dL from baseline on two consecutive blood draws with associated symptoms; **or** hemoglobin drop ≥ 3 g/dL from baseline on two consecutive blood draws without associated symptoms.

  Platelet count: $<75,000/mm^3$; $<75.0 \times 10^9/L$

  Lymphocytes: $<500/mm^3$; $<0.5 \times 10^9/L$

  Chemistry

  AST or ALT >3.0x ULN) that meet ANY of the following:

  >3 times the upper limit of normal with at least one total bilirubin value >2 times the upper limit of normal;

  >3 times the upper limit of normal accompanied by signs or symptoms consistent with hepatic injury (eg, new onset elevated PT/INR);

  Two sequential AST or ALT elevations >5 times the upper limit of normal, regardless of total bilirubin or accompanying signs or symptoms.

  Total bilirubin >1.5x ULN

  CPK >10x ULN

  Total bilirubin ≥1.5 x ULN; subjects with a history of Gilbert's syndrome may have a

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direct bilirubin measured and would be eligible for this study provided the direct bilirubin is ≤ ULN

- Other intercurrent illnesses or major surgery
- An infection that requires systemic treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agents or requires oral treatment with such agents for longer than 2 weeks.
- An infection that requires hospitalization with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agents or requires oral treatment with such agents for longer than 1 week.
- Treatment with systemic corticosteroids or non-steroidal immunosuppressive/ immunomodulating medications (e.g., cyclosporine, methotrexate, azathioprine, mycophenalate-mofetil, Janus kinase inhibitors, biologic agents, etc.).

Duration of study drug suspension should be reviewed on a case by case basis and can be discussed among the PIs.

STATISTICAL CONSIDERATIONS

SAMPLE SIZE CALCULATION

A sample size of 50 completers allows 90% power at 2.5[1]% significance to detect at week 24 a minimum log2-fold-change (FCH) of **-0.64** from baseline in CCL5 RT-PCR expression with a one-sided[2] paired t-test. Based on a recent study [41] that compared 12 FFA subjects with 8 controls, our calculations assume a standard deviation (SD) of 1.4 in RT-PCR normalized CCL5 log2-expressions. The same formulation and an SD =1.5 taken from the same study, applied to CXCR3, a marker of fibrosis, provide 90% power to detect a minimum log2-FCH = -0.67. Among completers, we expect to enroll 20 *de novo* participants. This sample size allows x % power at 2.5% significance to detect minimum log2-fold changes of - 1.04 and -1.102 in CCL5 and CXCR3, respectively in a sub-group analysis. Calculations are performed in G*Power 3.1.

DATA ANALYSES

A Repeated Measures ANOVA will be used to analyze the changes over time, induced by Ritlecitinib, in CCL5 (a surrogate for IFNγ activity) expression level at weeks 24 and 48. The least-square means for estimated effects at each time point and their differences will be provided, together with their 90% confidence intervals (CI). A mixed-effects model will include CA subtypes (LPP/FFA and CCCA), time point (baseline, weeks 24 and 48), and tissue (lesional/non-lesional) as fixed factors. The CCL5 expression level will be log2 transformed before the analysis, and means estimates will be back-transformed into corresponding estimates for the ratio to baseline. Changes in CXCR3, a biomarker of fibrosis, and other biomarkers measured by qRT-PCR will be analyzed similarly. P-values will be adjusted by the Benjamini-Hochberg procedure. Change from baseline in clinical and quality of life scores at weeks 24 and 48 will be analyzed with non-parametric tests (Wilcoxon and Friedman), also performed within CA subtypes. We will use the

[1] Bonferroni correction for two primary outcomes.
[2] Our research hypothesis states down-regulation of gene expression mediated by ritlecitinib, therefore we use one-sided t-tests.

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Spearman correlation coefficient to correlate changes in clinical and quality of life scores with dysregulated biomarkers. Within the subgroup of participants in the brepocitinib study, we will compare 95% confidence intervals for biomarkers changes from baseline between brepocitinib and ritlecitinib. We will also compare changes from baseline for biomarkers between *de novo* participants and the ones who took part in the brepocitinib study with two-sided unpaired t-tests.

All research data will be identified using a unique identifier assigned to each study participant upon study enrollment; study participants' names will not be associated with any research data. The personal computers used to store and analyze the research data will be used by the PI and his designees and will be encrypted and password protected. The data will be periodically backed up using a backup system. These safety checks will ensure that the risks to subjects' confidentiality are minimal.

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Table 1. Schedule of Events (+/- 3 day window is allowed for visits 3 through 15)

Visit Week	(-4 to 0)	0	4	8	12	16	20	24	28	32	36	40	44	48	52	
Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Early Termin-ation
Visit Type	Screening	BL												End of Treat-ment	F/U	
Informed Consent	X															
Inc/Exc Criteria	X	X														
Demographics and Medical Hx	X[1]															
TB Screening[2]	X															
HIV[3], HBV[3], HCV[3]	X[1]															
Safety Labs (Blood and Urine)	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Fasting Lipid Panel		X						X						X		
Cystatin C (and eGFR)) and CPK		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Pregnancy Test[4]	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Brief Physical Exam[5]	X[1]															
Vitals[6]	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
CA Clinical Assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECGs [7]	X[1]			X		X		X		X		X		X		X
Audiological Evaluation [8]	X							X						X		X
Blood for Gene Analyses		X														
Blood for Mechanistic Studies		X		X				X						X		X
Blood for PK [9]		X	X				X									
C-SSRS[10]		X		X		X		X		X		X		X		X
Questionnaires (DLQI and VAS)		X		X		X		X		X		X		X	X	X

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Medical Photos of Scalp and Eyebrows		X		X		X		X		X		X		X	X	X
Non-Lesional Scalp Biopsy		X[1]														
Lesional Scalp Biopsy		X[1]		X				X						X[12]		X
Dispense Study Drug [11]		X	X	X	X	X	X	X	X	X	X	X	X			
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Not applicable for subjects that participated in and completed the brepocitinib study if procedure/assessment was performed and collected at the Week 48 visit (for non-lesional biopsy – do not collect if collected at baseline of brepocitinib study).

[2] PPD or QuantiFERON TB-Gold test (if previous test performed more than 12 months ago)

[3] HIV testing, either in blood or POCT, HBS-ag and HCV-ab

[4] Where applicable, serum BHCG at screening, urine tests at all other visits to be performed prior to dosing female participants of childbearing potential with Investigational Product (IP). Two negative pregnancy tests are required before receiving IP (1 negative Serum Pregnancy Test at Screening and 1 negative Urine pregnancy test at the baseline visit before IP administration).

[5] Brief physical will include General Appearance, Skin, HEENT, Heart, Chest & Lung, Abdomen and neurologic.

[6] Includes height and weight (only at screening), blood pressure, and pulse;

[7] ECG collected in triplicate at screening 2-4 minutes apart. The mean of the triplicates will be the baseline for the participant. Single ECGs will be collected at all other time points.

[8] Audiological assessment includes audiological history, otoscopic examination, pure tone audiometry, air and bone conduction, speech audiometry, and immittance audiometry. At subsequent visits, updated audiological history, otoscopic examination, and pure tone audiometry will be performed; based upon results, additional audiometry assessments may be required. For details, refer to the Audiometry Study Guide. All procedures must be performed as per the Audiometry Study Guide. For participants who terminate early from the study, efforts must be made to complete the audiological evaluation.

[9] Blood for PK will be collected as follows: Week 0 prior to dosing; and at Week 4 and Week 20 at pre-dose and at 0.5 hours, 1 hour and 2 hours post dose.

[10] C-SSRS Screening/Baseline survey to be completed at baseline prior to randomization; C-SSRS Since Last Visit survey to be used at all other visits.

[11] Ritlecitinib administered as 200 mg QD for the first 8 weeks then 100 mg QD for remainder of study.

[12] Week 48 lesional biopsy is Optional

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REFERENCES

1 Katoulis, A. C. et al. Quality of life and psychosocial impact of scarring and non-scarring alopecia in women. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG 13, 137-142, doi:10.1111/ddg.12548 (2015).

2 Marks, D. H. et al. The Medical and Psychosocial Associations of Alopecia: Recognizing Hair Loss as More Than a Cosmetic Concern. American journal of clinical dermatology 20, 195-200, doi:10.1007/s40257-018-0405-2 (2019).

3 Dlova, N. C., Salkey, K. S., Callender, V. D. & McMichael, A. J. Central Centrifugal Cicatricial Alopecia: New Insights and a Call for Action. J Investig Dermatol Symp Proc 18, S54-S56, doi:10.1016/j.jisp.2017.01.004 (2017).

4 Chiang, Y. Z., Bundy, C., Griffiths, C. E., Paus, R. & Harries, M. J. The role of beliefs: lessons from a pilot study on illness perception, psychological distress and quality of life in patients with primary cicatricial alopecia. The British journal of dermatology 172, 130-137, doi:10.1111/bjd.13259 (2015).

5 Ma, S. A., Imadojemu, S., Beer, K. & Seykora, J. T. Inflammatory features of frontal fibrosing alopecia. J Cutan Pathol 44, 672-676, doi:10.1111/cup.12955 (2017).

6 Tziotzios, C., Stefanato, C. M., Fenton, D. A., Simpson, M. A. & McGrath, J. A. Frontal fibrosing alopecia: reflections and hypotheses on aetiology and pathogenesis. Exp Dermatol 25, 847-852, doi:10.1111/exd.13071 (2016).

7 Tziotzios, C. et al. Genome-wide association study in frontal fibrosing alopecia identifies four susceptibility loci including HLA-B*07:02. Nat Commun 10, 1150, doi:10.1038/s41467-019-09117-w (2019).

8 Vano-Galvan, S. et al. Frontal fibrosing alopecia: a multicenter review of 355 patients. J Am Acad Dermatol 70, 670-678, doi:10.1016/j.jaad.2013.12.003 (2014).

9 Kanti, V. et al. Frontal fibrosing alopecia: demographic and clinical characteristics of 490 cases. J Eur Acad Dermatol Venereol, doi:10.1111/jdv.15735 (2019).

10 Ho, A. & Shapiro, J. Medical therapy for frontal fibrosing alopecia: A review and clinical approach. Journal of the American Academy of Dermatology, doi:10.1016/j.jaad.2019.03.079 (2019).

11 Rakowska, A., Gradzinska, A., Olszewska, M. & Rudnicka, L. Efficacy of Isotretinoin and Acitretin in Treatment of Frontal Fibrosing Alopecia: Retrospective Analysis of 54 Cases. J Drugs Dermatol 16, 988-992 (2017).

12 Racz, E., Gho, C., Moorman, P. W., Noordhoek Hegt, V. & Neumann, H. A. Treatment of frontal fibrosing alopecia and lichen planopilaris: a systematic review. J Eur Acad Dermatol Venereol 27, 1461-1470, doi:10.1111/jdv.12139 (2013).

13 MacDonald, A., Clark, C. & Holmes, S. Frontal fibrosing alopecia: a review of 60 cases. Journal of the American Academy of Dermatology 67, 955-961, doi:10.1016/j.jaad.2011.12.038 (2012).

14 Galvez-Canseco, A. & Sperling, L. Lichen planopilaris and frontal fibrosing alopecia cannot be differentiated by histopathology. J Cutan Pathol 45, 313-317, doi:10.1111/cup.13112 (2018).

15 Alexis, A. F., Sergay, A. B. & Taylor, S. C. Common dermatologic disorders in skin of color: a comparative practice survey. Cutis 80, 387-394 (2007).

16 Akintilo, L., Hahn, E. A., Yu, J. M. A. & Patterson, S. S. L. Health care barriers and quality of life in central centrifugal cicatricial alopecia patients. Cutis 102, 427-432 (2018).

17 Malki, L. et al. Variant PADI3 in Central Centrifugal Cicatricial Alopecia. The New England journal of medicine 380, 833-841, doi:10.1056/NEJMoa1816614 (2019).

18 Harries, M. J. et al. Lichen Planopilaris and Frontal Fibrosing Alopecia as Model Epithelial Stem Cell Diseases. Trends Mol Med 24, 435-448, doi:10.1016/j.molmed.2018.03.007 (2018).



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19 Yang, C. C., Khanna, T., Sallee, B., Christiano, A. M. & Bordone, L. A. Tofacitinib for the treatment of lichen planopilaris: A case series. Dermatologic therapy 31, e12656, doi:10.1111/dth.12656 (2018).
20 Harries, M. J. et al. Lichen planopilaris is characterized by immune privilege collapse of the hair follicle's epithelial stem cell niche. J Pathol 231, 236-247, doi:10.1002/path.4233 (2013).
21 Beach, R. A., Wilkinson, K. A., Gumedze, F. & Khumalo, N. P. Baseline sebum IL-1alpha is higher than expected in afro-textured hair: a risk factor for hair loss? J Cosmet Dermatol 11, 9-16, doi:10.1111/j.1473-2165.2011.00603.x (2012).
22 Harries, M. J. & Paus, R. The pathogenesis of primary cicatricial alopecias. Am J Pathol 177, 2152-2162, doi:10.2353/ajpath.2010.100454 (2010).
23 Anzai, A., Wang, E. H. C., Lee, E. Y., Aoki, V. & Christiano, A. M. Pathomechanisms of immune-mediated alopecia. Int Immunol 31, 439-447, doi:10.1093/intimm/dxz039 (2019).
24 Bolduc, C., Sperling, L. C. & Shapiro, J. Primary cicatricial alopecia: Lymphocytic primary cicatricial alopecias, including chronic cutaneous lupus erythematosus, lichen planopilaris, frontal fibrosing alopecia, and Graham-Little syndrome. Journal of the American Academy of Dermatology 75, 1081-1099, doi:10.1016/j.jaad.2014.09.058 (2016).
25 Naeini, F. F., Saber, M., Asilian, A. & Hosseini, S. M. Clinical Efficacy and Safety of Methotrexate versus Hydroxychloroquine in Preventing Lichen Planopilaris Progress: A Randomized Clinical Trial. Int J Prev Med 8, 37, doi:10.4103/ijpvm.IJPVM_156_17 (2017).
26 Sundberg, J. P. et al. Cicatricial Alopecia Research Foundation meeting, May 2016: Progress towards the diagnosis, treatment and cure of primary cicatricial alopecias. Experimental dermatology 27, 302-310, doi:10.1111/exd.13495 (2018).
27 Ciechanowicz, P., Rakowska, A., Sikora, M. & Rudnicka, L. JAK-inhibitors in dermatology: current evidence and future applications. J Dermatolog Treat 30, 648-658, doi:10.1080/09546634.2018.1546043 (2019).
28 Williams, N. K. 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 387, 219-232, doi:10.1016/j.jmb.2009.01.041 (2009).
29 Ghoreschi, K. & Gadina, M. Jakpot! New small molecules in autoimmune and inflammatory diseases. Experimental dermatology 23, 7-11, doi:10.1111/exd.12265 (2014).
30 Flanagan, M. E. et al. Discovery of CP-690,550: a potent and selective Janus kinase (JAK) inhibitor for the treatment of autoimmune diseases and organ transplant rejection. J Med Chem 53, 8468-8484, doi:10.1021/jm1004286 (2010).
31 Papp, K. et al. A Randomized Phase 2b Trial of Baricitinib, an Oral JAK1/JAK2 Inhibitor, in Patients with Moderate-to-Severe Psoriasis. The British journal of dermatology, doi:10.1111/bjd.14403 (2016).
32 Waldmann, T. A. The biology of IL-15: implications for cancer therapy and the treatment of autoimmune disorders. J Investig Dermatol Symp Proc 16, S28-30, doi:10.1038/jidsymp.2013.8 (2013).
33 Xing, L. et al. Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. Nat Med 20, 1043-1049, doi:10.1038/nm.3645 (2014).
34 Ishizaki, M. et al. Involvement of tyrosine kinase-2 in both the IL-12/Th1 and IL-23/Th17 axes in vivo. Journal of immunology 187, 181-189, doi:10.4049/jimmunol.1003244 (2011).
35 Banfield, C. et al. The Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of a TYK2/JAK1 Inhibitor (PF-06700841) in Healthy Subjects and Patients With Plaque Psoriasis. J Clin Pharmacol 58, 434-447, doi:10.1002/jcph.1046 (2018).

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Effective Date: 8/22/2023
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36 Holmes, S. et al. Frontal Fibrosing Alopecia Severity Index (FFASI): a validated scoring system for assessing frontal fibrosing alopecia. The British journal of dermatology 175, 203-207, doi:10.1111/bjd.14445 (2016).
37 Chiang, C., Sah, D., Cho, B. K., Ochoa, B. E. & Price, V. H. Hydroxychloroquine and lichen planopilaris: efficacy and introduction of Lichen Planopilaris Activity Index scoring system. Journal of the American Academy of Dermatology 62, 387-392, doi:10.1016/j.jaad.2009.08.054 (2010).
38 Olsen, E. A. et al. Central scalp alopecia photographic scale in African American women. Dermatologic therapy 21, 264-267, doi:10.1111/j.1529-8019.2008.00208.x (2008).
39 Esaki, H. et al. Identification of novel immune and barrier genes in atopic dermatitis by means of laser capture microdissection. J Allergy Clin Immunol 135, 153-163, doi:10.1016/j.jaci.2014.10.037 (2015).
40 Zhou, L. et al. Age-specific changes in the molecular phenotype of patients with moderate-to-severe atopic dermatitis. The Journal of allergy and clinical immunology 144, 144-156, doi:10.1016/j.jaci.2019.01.015 (2019).
41 Del Duca, E., et al. "Frontal Fibrosing Alopecia Shows Robust T Helper 1 and Janus Kinase 3 Skewing." *British Journal of Dermatology*, vol. 183, no. 6, 2020, pp. 1083–93, https://doi.org/10.1111/bjd.19040.

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APPENDIX 1. CLINICAL ASSESSMENTS/SCORING

LPPAI[37]

Date of visit				
LPPAI (see below)				
SCALE: 0-3 A Pruritus				
B Pain				
C Burning				
D Erythema				
E Perifollic erythema				
F Perifollicular scale				
Crusting				
Pustules				
Pull test: Anagen/Total **(0=-, 1=+)**				
Spreading? **no (0) ? (1) yes (2)**				
Dimensions / Extent				
Loss follicular mark				
Tufting				
Telangiectasia				
Atrophy				
Pigment change				
Other skin, nail, mucous membrane				
Labs CBC				
AST/ALT/Alk Phos				
G6PD				
Eye exam				
BUN/CR				
Blood Pressure				
Culture & Sensitivities				
Treatment/ Comments				
Biopsy				
Photographs				
F/u visit:				

LPPAI (0-10) = (A+B+C+D+E+F)/3 + 2.5(pull test) + 1.5(spread/2)

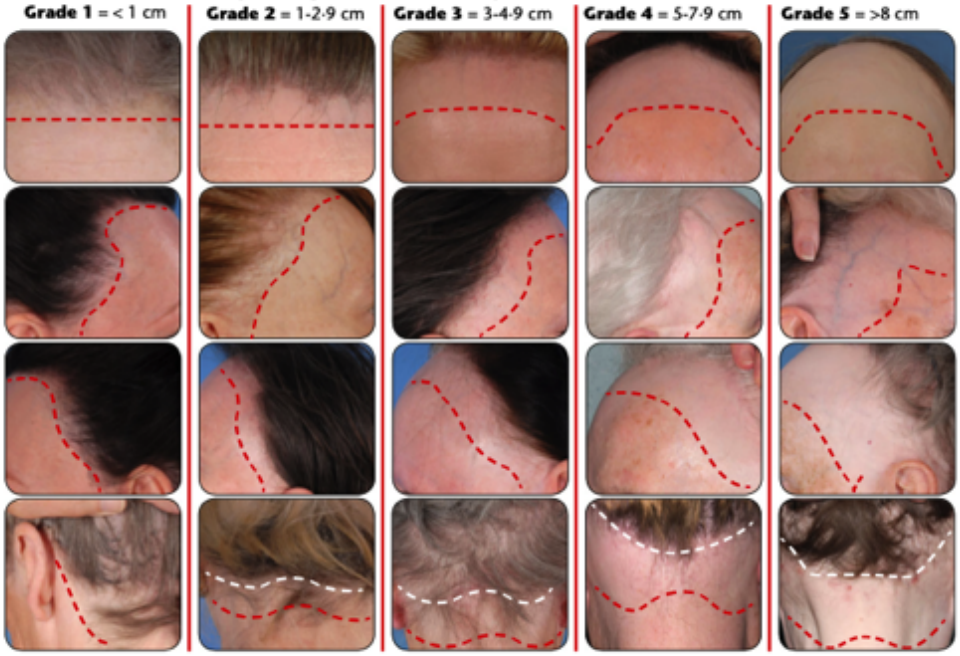
Scale: **0** = negative **1**= +/- **2** = + **3** = ++,+++

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FFASI3[6]

Frontal Fibrosing Alopecia Severity Index (FFASI)



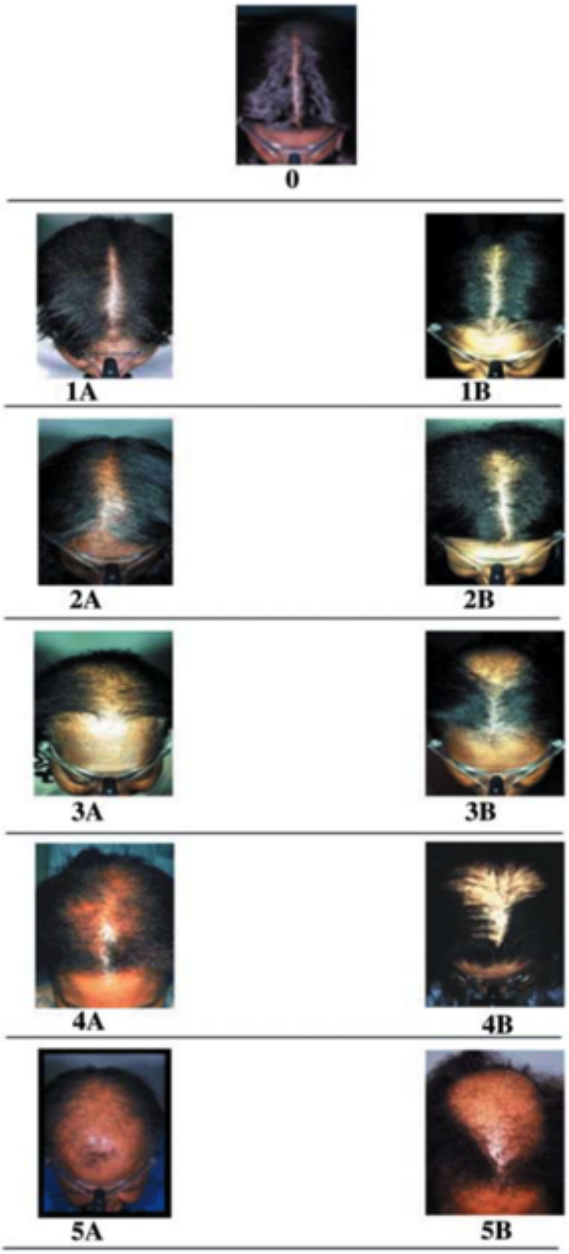
Date														
Scalp margin	**Grade: 1 - 5** No loss = Score 0 Grade 1 = Score 4 Grade 2 = Score 8 Grade 3 = Score 12 Grade 4 = Score 16 Grade 5 = Score 20													
	Frontal Band: Score 0 if not inflamed, normal density; Score 2 if inflamed or reduced density; Score 4 if inflamed and reduced density													
Frontal														
R lateral														
L lateral														
Posterior														
Frontal Band														
Total	/84	/84	/84	/84	/84	/84	/84	/84	/84	/84	/84	/84	/84	/84
Other Hair loss	**No loss Score 0** **Partial loss Score 1** **Complete loss Score 2**													
eyebrow loss														
eyelash loss														
flexural loss (axillary, pubic)														
upper limb hair loss														
lower limb hair loss														
Additional features	**Absent Score 0** **Present Score 1**													
typical scalp LPP														
facial papules														
cutaneous LP / LP variants														
oral mucosal LP														
genital mucosal LP														
nail LP														
Total	/16	/16	/16	/16	/16	/16	/16	/16	/16	/16	/16	/16	/16	/16
Combined Total	/100	/100	/100	/100	/100	/100	/100	/100	/100	/100	/100	/100	/100	/100

Fig 1. Frontal Fibrosing Alopecia Severity Index (FFASI).

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CHLG[38]



Eyelash/Eyebrow Assessment Score

0= None
1= Minimal eyelashes/eyebrows
2= Moderate eyelashes/eyebrows
3= Prominent eyelashes/eyebrows
4= Very prominent eyelashes/eyebrows

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DLQI

The aim of this questionnaire is to measure how much your skin problem has affected your life over the last week. Please check one box for each question.			
1.	Over the last week, how itchy, sore, painful, or stinging has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐
2.	Over the last week, how embarrassed or self-conscious have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐
3.	Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?	Very much A lot A little Not at all	☐ ☐ ☐ ☐
4.	Over the last week, how much has your skin influenced the clothes you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐
5.	Over the last week, how much has your skin affected any social or leisure activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐
6.	Over the last week, how much has your skin made it difficult for you to do any sport?	Very much A lot A little Not at all	☐ ☐ ☐ ☐
7.	Over the last week, has your skin prevented you from working or studying?	Very much A lot A little Not at all	☐ ☐ ☐ ☐
8.	Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?	Very much A lot A little Not at all	☐ ☐ ☐ ☐
9.	Over the last week, how much has your skin caused any sexual difficulties?	Very much A lot A little Not at all	☐ ☐ ☐ ☐
10.	Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐

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VAS

Init: _____ ID#:_____

Date: _____

Subject VAS:

Draw a vertical line across the present line to represent the average for the last 3 days or nights regarding how much itching, burning, and pain you have experienced:

Itching:



Burning:



Pain:



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APPENDIX 2: PROHIBITED AND PERMITTED CYP3A INDUCERS AND SUBSTRATES

This is not an all-inclusive list. Study personnel should stay current and consult with their pharmacy to exclude all concomitant medications that are moderate to potent CYP3A inducers or sensitive or moderate sensitive CYP3A substrates. If a medication is a sensitive or moderate sensitive CYP3A substrate and is not listed below as prohibited or permitted, consultation with the Sponsor is required.

The list of drugs prohibited for potential DDI concerns with the IMP may be revised during the course of the study with written notification from Pfizer, to include or exclude specific drugs or drug categories for various reasons (e.g., emerging DDI results for the IMP, availability of new information in literature on the DDI potential of other drugs).
Investigators should consult the product label for any other medication used during the study for information regarding medication that is prohibited for concomitant use.

Appendix 2.1 Prohibited Concomitant CYP3A Inducers and Substrates

Sensitive CYP3A Substrates##	Moderate Sensitive CYP3A Substrates§	Moderate to Potent CYP3A Inducers**
Dasatinib	Aprepitant	Avasimibe#
Dronedarone	Eliglustat	Bosentan
Ebastine	Pimozide	Barbiturates
Lomitapide	Rilpivirine	Carbamazepine#
Nisoldipine		Efavirenz
Sirolimus		Etravirine
Tacrolimus		Mitotane#
Tolvaptan		Modafinil
		Nafcillin
		Phenobarbital#
		Phenytoin#
		Rifabutin#
		Rifampin #
		St. John's Wort#
		Talviraline

** All prohibited drugs that are CYP3A inducers require at least a 28 day or 5 half-lives (whichever is longer) washout prior to the first dose of study intervention.
In a situation where appropriate medical care of a participant requires the use of a prohibited CYP3A inducer: Moderate to potent inducers of CYP3A are not permitted in the study EXCEPT in emergency situations. *Note: Mitotane is not permitted for any duration due to its long half-life; however, if necessary mitotane may be used in an emergency, however the participant will then be discontinued from the study.* Topical (including skin or mucous membranes) application of antimicrobial and antifungal medications is permitted.
Notated as potent inducers.
Sensitive CYP3A substrates are drugs that demonstrate an increase in concentration-time curve (AUC) of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical drug-drug interaction (DDI) studies.
§ Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold.

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Appendix 2.2 Permitted Concomitant CYP3A Substrates

Sensitive CYP3A Substrates[a]	**Moderate Sensitive CYP3A Substrates**[b]
Alfentanil	Alprazolam
Avanafil	Atorvastatin
Buspirone	Colchicine
Darifenacin	Rivaroxaban
Eletriptan	Tadalafil
Eplerenone	
Felodipine	
Lovastatin	
Lurasidone	
Midazolam	
Naloxegol	
Quetiapine	
Sildenafil	
Simvastatin	
Ticagrelor	
Triazolam	
Vardenafil	

a. Sensitive CYP3A substrates are drugs that demonstrate an increase in concentration-time curve (AUC) of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical drug-drug interaction (DDI) studies. Topical (including skin or mucous membranes) application of antimicrobial and antifungal medications is permitted.

b. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold.

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APPENDIX 3: MEDICATIONS PROLONGING QT INTERVAL

Examples provided do not represent an all-inclusive list of medications. If there is a question about whether a particular medication is prohibited, the medication should be discussed with the sponsor.

- Medications that prolong QT interval.
    - Medications listed as "known risk of TdP" are prohibited (eg, azithromycin, citalopram, haloperidol).
    - Medications listed as "possible risk of TdP" may be prohibited according to the following guidance:
        - Psychiatric drugs (including antidepressants, antipsychotics, etc.) and anticonvulsants: prohibited unless approved by the Sponsor.
        - Antihypertensives: prohibited unless if approved by the Sponsor.
        - All other drugs are prohibited.
- Drugs in the category of "conditional risk of TdP" are not considered prohibited provided that there are no known drug-drug interaction issues or coexisting predisposing conditions that would preclude their use.

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APPENDIX 4: COMPONENTS OF SAFETY LAB TESTING

CBC w/Diff

- White blood cell
- Red blood cell
- Hemoglobin
- Hematocrit
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Red cell distribution width (RDW)
- Platelet
- Mean Platelet Volume
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

Complete Metabolic Panel

- Glucose
- Sodium
- Potassium
- Chloride
- CO2 Total
- Anion Gap
- Urea Nitrogen
- Creatinine
- GFR Estimate
- Calcium
- Albumin
- Alk Phosphatase
- ALT(SGPT)
- AST(SGOT)
- Bilirubin Total
- Total Protein

Lipid Panel

- Cholesterol
- Triglycerides
- HDL Cholesterol
- LDL Cholesterol
- Chol/HDL Chol Ratio

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APPENDIX 5 - AMENDMENTS

Amendment 1 Dated October 6, 2022

Page 1 Cover Page – Added Amendment 1 Date October 6, 2022

Page 15 Visit 9, 10, 11, 12, 13 and 14 – Weeks 28, 32, 36, 40, 44 and 48 – added "no drug is dispensed at Week 48"

Page 16 Skin Analysis – removed immunofluorescence from the section and added "single-cell RNAseq"

Page 26 Table 1. Schedule of Events – Dispense Drug row – "X" was removed from Week 48 column.

Page 39 Added "APPENDIX 4: COMPONENTS OF SAFETY LAB TESTING"

Page 40 Added "APPENDIX 5 – AMENDMENTS"

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