Brepocitinib for the Treatment of Dermatomyositis: Pharmacologic and Clinical Rationale

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Background

- Brepocitinib is a novel, orally available, tyrosine kinase 2 (TYK2) / Janus kinase 1 (JAK1) inhibitor in Phase 3 development for the treatment of dermatomyositis (DM), a chronic immune-mediated disease of the skin and muscles.
- DM is primarily driven by Type I interferon (IFN-I) dysregulation, with involvement of other key cytokines (e.g., IFN-γ, Interleukin (IL) -12, IL-23); IFN-I, IFN- γ, and IL-23 have been shown to play a pathogenic role in manifestations of DM across organ systems (including skin and muscle),[1-7] while IL-12 and IFN- γ are particularly implicated in DM-associated interstitial lung disease; [8] TYK2 and JAK1 are essential to the signaling of these cytokines.
- Several FDA-approved JAK inhibitors (JAKi) have been evaluated off-label in case reports and pilot studies in DM and have shown clinically meaningful efficacy and acceptable safety profiles in 145 patients (Paik et al, Clin Exp Rheumatol, 2022).
- The analyses described here support the rationale and dose selection for a Phase 3 study evaluating the safety and efficacy of brepocitinib in DM.

Methods

- Inhibition of human JAKs was assessed via recombinant enzyme inhibition assays.
- Inhibition of cytokine-induced STAT phosphorylation was assessed in human blood.
- Human PK data was used to estimate the expected in vivo suppression of cytokine signaling pathways based on daily average blood brepocitinib concentrations (Cavg).
- A cross-study dose-response analyses was based on 5 completed, placebo-controlled, dose-ranging, Phase 2 studies (psoriatic arthritis, N=218, NCT03963401; plaque psoriasis, N=212, NCT02969018; ulcerative colitis, N=167, NCT02958865; alopecia areata, N=94, NCT02974868; and hidradenitis suppurativa, N=100 NCT04092452). The response rate for each endpoint in each study was normalized to the maximum response rate for that endpoint, which was given the nominal response rate of 100%.

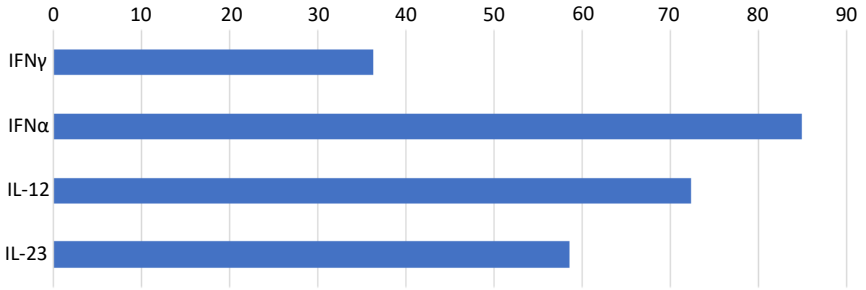
Results

In Vitro JAK and Cytokine Inhibition by Brepocitinib

Janus Kinase	IC_{50} (nM)		Cytokine	JAK pair	IC_{50} (nM)
TYK2	17		IFNα	TYK2/JAK1	30
JAK1	23		IFNγ	JAK1/JAK2	298
JAK2	77		IL-12	TYK2/JAK2	65
JAK3	6500		IL-23	TYK2/JAK2	120

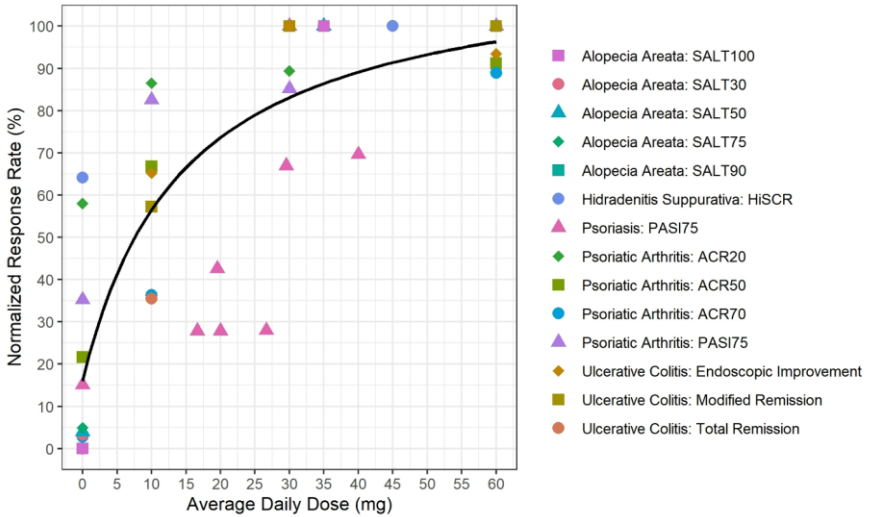
In vitro, brepocitinib potently and selectively inhibits TYK2 and JAK1, with half-maximal inhibitory concentration (IC_{50}) values at least 3-fold lower than those for JAK2 and JAK3. The most potent inhibition is evident with IFN-I signaling, consistent with the potent dual inhibition of TYK2 and JAK1 by brepocitinib.

Estimated Inhibition of Cytokine Signaling (%) at Average Brepocitinib Blood Concentration



Brepocitinib inhibited cytokine signaling pathways implicated in DM that engage TYK2 and/or JAK1, including IFNα, IFNγ, IL-12, and IL-23. Estimated inhibition of these cytokine signaling pathways at the Cavg of brepocitinib 30 mg QD is shown above. This in vitro cytokine inhibition profile translates to dose-responsive (below) and robust clinical efficacy (right).

Normalized Efficacy Response Rate Versus Average Daily Dose of Brepocitinib by Study



SALT = Severity of Alopecia Tool; HiSCR = Hidradenitis Suppurativa Clinical Response; PASI = Psoriasis Area and Severity Index; ACR = American College of Rheumatology

Across Phase 2 study responder endpoints, brepocitinib demonstrated dose-dependent efficacy with minimal increases in efficacy at doses greater than 30 mg.

Primary Efficacy Endpoint Results of Phase 2 Studies with Brepocitinib

Study Population	Pathogenic Cytokine Overlap with DM	Brepocitinib Dose (QD)	Primary Endpoint Result (placebo adjusted) (N)	Statistical Significance
Psoriatic Arthritis	INF-I (α, β), IFN-II (γ), IL-12, IL-23	30 mg	23.4% ACR20 RR at week 16 (N=218)	P = 0.0197
Plaque Psoriasis	INF-I (α, β), IFN-II (γ), IL-12, IL-23	30 mg	-10.1 CFB in PASI Score at week 12 (N=212)	P < 0.0001
Ulcerative Colitis	IFN-II (γ), IL-12, IL-23	30 mg	-2.28 CFB in Mayo Score at week 8 (N=167)	P = 0.0005
Alopecia Areata	IFN-II (γ), IL-23	30 mg	49.18 CFB in SALT Score at week 24 (N=94)	P < 0.0001
Hidradenitis Suppurativa	IFN-II (γ), IL-12, IL-23	45 mg	18.7% HiSCR Rate at week 16 (N=100)	P = 0.0298

CFB = change from baseline; RR = response rate

Brepocitinib has been investigated in 5 completed Phase 2 placebo-controlled studies in psoriatic arthritis, plaque psoriasis, ulcerative colitis, alopecia areata, and hidradenitis suppurativa. In each, clinically meaningful and statistically significant results were achieved across a diverse array of organ systems (e.g., skin, joints, gastrointestinal). These clinical data, along with the overlapping pathogenic cytokine profile, support the rationale for evaluating brepocitinib in DM.

Conclusions

- There is strong clinical evidence supporting JAKi for the treatment of DM.
- Brepocitinib is unique amongst the JAKi class for its potent dual inhibition of TYK2 and JAK1 and is therefore well suited to address the cytokine signaling dysregulations implicated in the pathogenesis of DM (particularly IFN-I), with relevant inhibition expected to occur in a clinically relevant dose range.
- Collectively, these analyses support the evaluation of brepocitinib 15 and 30 mg QD for the treatment of DM in a robust, well-controlled, Phase 3 study (NCT05437263).

Disclosures

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R Aggarwal: consulting fees from Priovant Therapeutics.

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