Brepocitinib Inhibits Key Pathogenic Cytokine Signaling in Dermatomyositis Patients

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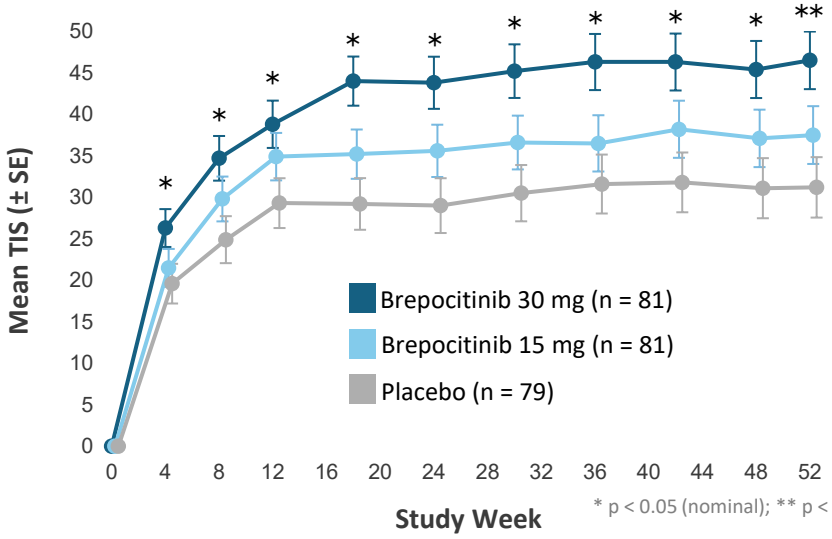
Background/Objectives

- Brepocitinib is an oral, selective TYK2/JAK1 inhibitor that demonstrated statistically significant and clinically meaningful efficacy in N=241 adults with active dermatomyositis (DM) in the Phase 3 VALOR trial (NCT05437263)[1]
- Brepocitinib is hypothesized to exert clinical benefit through inhibition of cytokines implicated in DM pathogenesis such as Type I interferons (IFNα/β), Type II interferon (IFNγ), IL-12/23, and IL-6
- This study aimed to measure the degree of inhibition of selected TYK2/JAK1-mediated cytokines (IFNα, IFNβ, and IL-6) with brepocitinib over 24 hours using *ex vivo* peripheral blood mononuclear cells (PBMCs) from DM patients

In a 52-Week placebo-controlled Phase 3 trial in active DM, brepocitinib 30 mg QD demonstrated statistically significant results on Total Improvement Score (TIS) and all key secondary endpoints despite greater reduction in corticosteroid dose than placebo[1]



* p < 0.05 (nominal); ** p < 0.001

Primary Endpoint
30 mg vs. Placebo at Week 52
TIS Δ = 15.3 points (p = 0.0006)

Corticosteroid Reduction Among Subjects on Background Oral Steroids

Week 48-52 Dose	Brepo 30mg	Placebo
≤2.5 mg/day	62%	34%
Off steroids	42%	23%

Doses reported as prednisone-equivalent

The observed brepocitinib 30 mg safety profile in VALOR was consistent with previous brepocitinib clinical trials. Adverse events of special interest (which included cardiovascular events, thromboembolic events, malignancies, viral reactivations, and LFT elevations) did not occur with greater frequency in the brepocitinib 30 mg group than the placebo group. All participants received standard of care medications.[1]

References

1. Data on file

Disclosures

Christina Charles-Schoeman: Consultant or received research funding from Abbvie, Alexion, BMS, Boehringer Ingelheim, CSL Behring, Galapagos, Immunovant, Janssen, Octapharma, Pfizer, Priovant Therapeutics, Recludix, Sana Biotechnology. **Brendan M Johnson:** Employee of Priovant Therapeutics. This work was sponsored by Priovant Therapeutics.

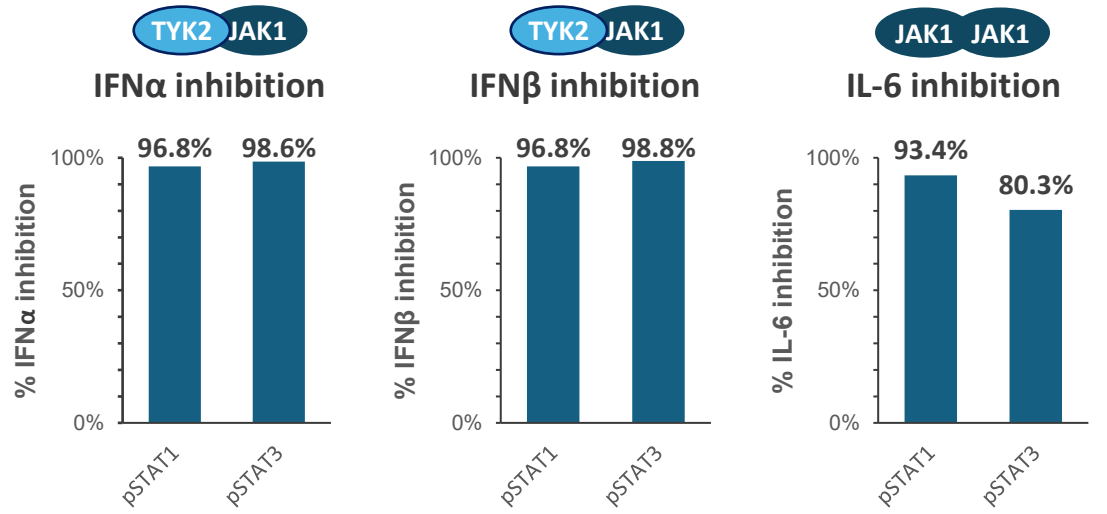
Methods

- PBMCs from a unique cohort of 5 DM patients on standard therapies (oral steroids, n=3; oral nonsteroid DMARDs, n=2) were pooled, pretreated with brepocitinib [0.0192 to 1500 nM], and stimulated with IFNα, IFNβ, or IL-6
- IC_{50} curves were generated for inhibition of downstream STAT1 and STAT3 phosphorylation (pSTAT1, pSTAT3) from each cytokine using flow cytometry
- Percent inhibition of cytokine signaling was calculated based on daily average concentration using:

$$(\text{free } C_{avg} \times 100) / (\text{free } C_{avg} + IC_{50}).$$

Results

Brepocitinib 30 mg QD provides 96-99% inhibition of IFNα and IFNβ signaling and 80-93% inhibition of IL-6 signaling over 24 hours



Conclusions

- **Brepocitinib 30 mg QD results in profound inhibition of IFNα, IFNβ, and IL-6 signaling over 24 hours based on *ex vivo* PBMC stimulation**
- **Sustained daily inhibition of TYK2- and JAK1-dependent inflammatory pathways central to DM pathogenesis may explain the observed clinical benefits in DM patients**
- **Clinical and mechanistic data collected to date suggest brepocitinib 30 mg QD has the potential to be the first targeted, disease-modifying therapy for patients with active DM**