# BREPOCITINIB PREVENTS TYPE-I INTERFERON INDUCED DAMAGE IN CULTURED MYOCYTES AND ENDOTHELIAL CELLS INDICATING A POTENTIAL ROLE IN THE TREATMENT OF DERMATOMYOSITIS

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## Background

- Dermatomyositis (DM) is a rare, debilitating, multi-system idiopathic inflammatory myopathy characterized by skin rash, perifascicular atrophy of muscle fibers and subsequent muscle weakness[1]
- DM pathogenesis involves dysregulation in signaling of Type I interferon (IFN-I), IFN-γ, IL-12, and IL-23[2]
- Janus kinases TYK2 or JAK1 are essential to the signaling of these cytokines
- Brepocitinib is a selective and potent dual inhibitor of TYK2/JAK1 and is expected to reduce signaling of these cytokines and has the potential to ameliorate symptoms of DM
- A Phase 3 clinical trial to investigate the efficacy and safety of brepocitinib (15 mg and 30 mg once daily, QD) in adults with DM is ongoing (VALOR Study, NCT05437263)

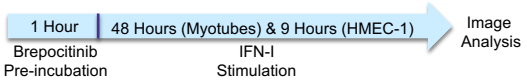
## Objective

- To evaluate the efficacy of brepocitinib in preventing IFN-I induced pathological changes characteristic of DM in human skeletal muscle and microvascular endothelial cells in vitro

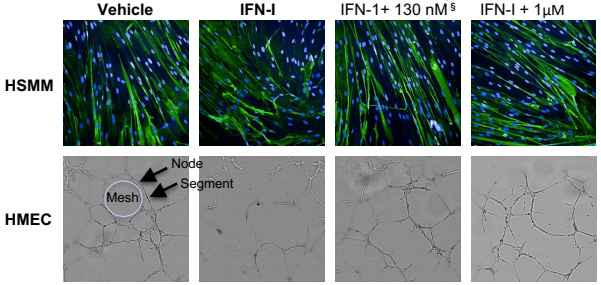
## Methods

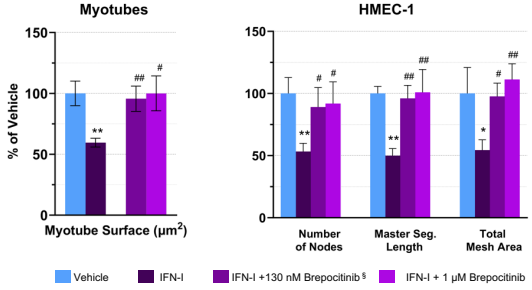
- Human skeletal muscle myoblasts (HSMM) were cultured and differentiated into myotubes and treated with DMSO (vehicle control) or IFN-I (recombinant Human IFN-α A and Human IFN-α D) to induce cellular damage
  - Immunofluorescent staining and image analysis for myosin 4 surface area were conducted 48 hours after IFN-I stimulation
- Human dermal microvascular endothelial cells (HMEC-1) were cultured and treated as above after vascular network establishment
  - Nine hours after IFN-I treatment, the number of nodes, master segment length, and total mesh area were measured under light microscopy
- Myotubes and HMEC-1 cells also were pre-incubated with brepocitinib for 1 hour prior to IFN stimulation (130 nM and 1 μM; 130 nM represents the average free [unbound] plasma concentration after 30 mg QD brepocitinib at steady state[3])
- One-way ANOVA followed by Tukey's multiple comparison post-hoc analyses were performed to determine statistical significance

## Results




**Representative Images:**




** p < 0.0001; * p < 0.001 relative to vehicle
## p < 0.0001; # p < 0.001 relative to IFN-I

§ clinically relevant free plasma concentration after 30 mg QD brepocitinib at steady state

## Results

- Myosin surface area in HSMM was reduced by ~ 40%, relative to DMSO, with IFN-I treatment
- Brepocitinib pre-incubation completely prevented IFN-I induced damage
  - Mean myosin surface areas were 96% and 100% of control values with 130 nM and 1 μM brepocitinib, respectively
- In HMEC-1, IFN-I treatment reduced the mean number of nodes, master segment length, and total mesh area, relative to DMSO treatment
  - With brepocitinib pre-incubation, this vascular damage was completely inhibited with the mean number of nodes, master segment lengths, and total mesh area ranging from 89 to 111% of vehicle control

## Conclusions

- One of the most debilitating aspects of DM is muscle weakness due to perifascicular atrophy[4]
- We report here that the brepocitinib average free plasma concentration achieved with 30 mg QD administration almost completely prevents IFN-I induced damage in human myocytes and microvasculature in culture
- Collectively, these data provide further rationale for brepocitinib in the treatment of DM
- A Phase 3 clinical trial to investigate the efficacy and safety of brepocitinib 15 mg and 30 mg in adults with dermatomyositis is ongoing (VALOR Study, NCT05437263)

[1] Marvi, et al. *Indian Journal of Dermatology* 2012;57(5):375-381.
[2] Bolko, et al. *Brain Pathology* 2021;31(3)1-13.
[3] Banfield, et al. *The Journal of Clinical Pharmacology* 2017;58(4)434-447.
[4] Regardt, et al. *The Journal of Rheumatology* 2015;42(12):2492-2495.

***Disclosure of interest*: Jiří Vencovský** Speakers bureau: Abbvie, Biogen, Boehringer, Eli Lilly, Gilead, MSD, Novartis, Pfizer, Roche, Sanofi, UCB, Werfen, Consultant of: Abbvie, Argenx, Boehringer, EliLilly, Gilead, Octapharma, Pfizer, UCB, Grant/research support from: Abbvie. **Jolie Feldman** Shareholder of: Roivant Sciences, Employee of: Priovant Therapeutics, **Lisa McConnachie** Employee of: Priovant Therapeutics, **Brendan Johnson** Shareholder of: Priovant Therapeutics, Roivant Sciences, Employee of: Priovant Therapeutics