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# Obefazimod shows first evidence of dual anti-inflammatory and anti-fibrotic activity in murine *in vivo* and human *in vitro* models

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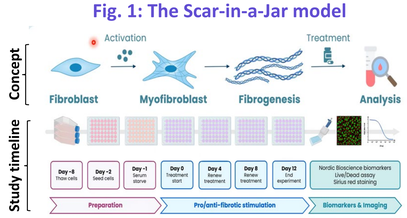
## INTRODUCTION

- Obefazimod (Obe) is an oral, once-daily (QD), small molecule that enhances expression of microRNA-124, which restores immune balance including inflammatory Th17 cells and macrophage in the mucosa. Obe has shown efficacy in patients with moderately to severely active ulcerative colitis (UC)[1-3] and is under evaluation in a phase 2b Crohn's disease (CD) trial (NCT06456593).
- miR-124 is dysregulated in fibrotic tissue, and is known to regulate fibrotic pathways such as TGF-β.[4, 5]
- Using two models, we assessed whether beyond its known anti-inflammatory effects, Obe may also have direct anti-fibrotic activity which could be useful to prevent and treat fibrosis.

## METHOD

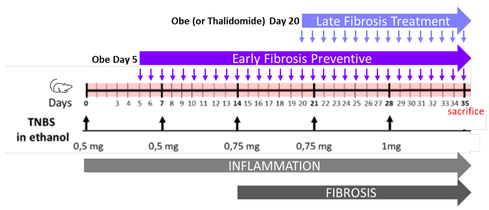
- **In vitro anti-fibrotic activity was measured in the Scar-in-a-Jar model (Figure 1)** using human small-intestinal fibroblasts stimulated by an IBD-relevant cytokine cocktail (IBD-FC). Cytotoxicity, PRO-C3, and α-SMA were quantified and normalized to viable cells; live-cell and cell-number–adjusted analyses gave comparable results. Nintedanib, omipalisib, and upadacitinib served as mechanistic comparators.

**Fig. 1: The Scar-in-a-Jar model**




- **In vivo effects were examined in a chronic TNBS-colitis mouse model (Figure 2)**, which causes long-lasting intestinal inflammation that mimics key features of CD in humans. Obe (100 mg/kg) or controls were administered orally from day 5 (anti-inflammatory plus fibrosis-preventive effect) or day 20 (early-onset anti-fibrotic effect). Disease activity, body weight, colon parameters, histology, and collagen deposition (Sirius Red) were evaluated. Statistics: One-way ANOVA with Dunnett's and Tukey's tests.

**Fig. 2: The chronic TNBS-colitis mouse model**

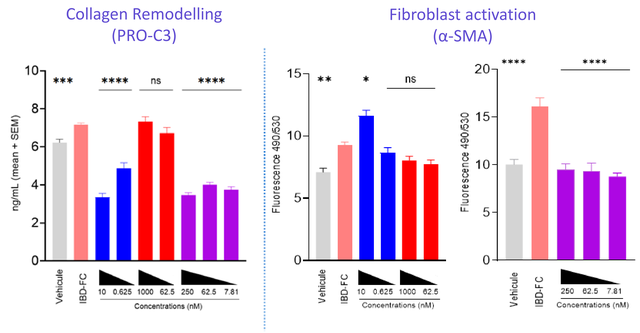



## RESULTS

### Scar-in-a-Jar model

- **Obe reduces collagen remodeling and human fibroblast activation status (Figure 3)**
  - ~50% reduction in Pro-C3 (fibrogenesis marker)
  - ~30% reduction in α-SMA (fibroblast activation marker).

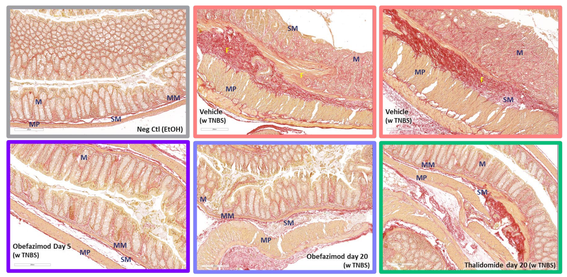
**Fig. 3: Anti-fibrotic effect on human small intestine fibroblasts**




*p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001 one-way ANOVA with Dunnett's for multiple comparison testing used. Upadacitinib marketed as Rinvoq for UC, CD, & other inflammatory disorders; Omipalisib (GSK2126458) in development for IPF & oncology indications. Pro-C3: proprietary marker of Collagen III cleavage by Nordic Biosciences; α-SMA: alpha-smooth muscle actin

- **Obe reduces collagen staining by Sirius Red and diminishes fibrosis in the chronic TNBS mouse model (Figure 5)**

**Fig. 5: Sirius Red stain for collagen deposition**

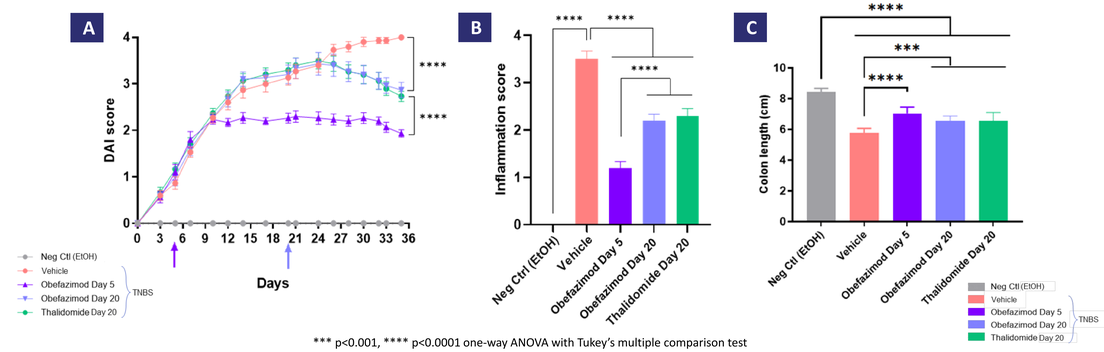



F: fibrosis, M: Mucosa; MM: Muscularis mucosae; MP: Muscularis propria; SM: Submucosa

### Chronic TNBS mouse model of fibrotic colitis

- **Obe shows anti-inflammatory effects when initiated as a fibrosis preventative or fibrosis treatment (Figure 4)**
  - ~25% & ~50% reduction in Disease Activity Index with late and early treatment, respectively
  - ~35% & ~65% reduction in histologic ulceration and Inflammation scores with late and early treatment, respectively.
  - Improved colon length with late and early treatment, similar to dual anti-inflammatory/anti-fibrotic thalidomide positive control.

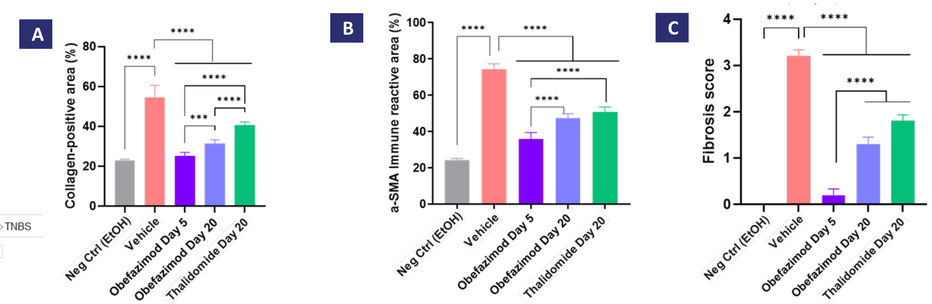
**Fig. 4: A) Disease Activity Index Score, B) Histologic Inflammation Score (day 35 ), C) Colon length (day 35 )**




*** p<0.001, **** p<0.0001 one-way ANOVA with Tukey's multiple comparison test

- **Obefazimod shows anti-fibrotic effects when initiated as a fibrosis preventative or fibrosis treatment (Figure 6)**
  - ~45% & ~55% reduction in Collagen Deposition (fibrogenesis marker) with late and early treatment, respectively
  - ~40% & ~50% reduction in α-SMA (fibroblast activation marker) with late and early treatment, respectively
  - ~60% & ~90% reduction in histologic Fibrosis Score with late and early treatment, respectively

**Fig. 6: A) Collagen deposition (% positive area at day 35, Sirius Red), B) α-SMA (% positive area at day 35), C) Histologic Fibrosis Score (day 35)**




## REFERENCES

1. Vermeire S, et al. *J Crohns Colitis*. 2023;17:1689-97; 2. Vermeire S, et al. *Gastroenterology*. 2021;160:2595-98.e3; 3. Vermeire S, et al. *Lancet Gastroenterol Hepatol*. 2022;7:1024-35; 4. Zhang S et al. Adv Clin Exp Med, 2021; 5. Xia et al. Sci Rep, 2023.

## DISCLOSURES

SD (consultant or speaker's fees) AbbVie, Ferring, Hospira, Johnson & Johnson, Merck, MSD, Takeda, Mundipharma, Pfizer Inc, Tigenix, UCB Pharma, Vifor, Biogen, Celgene, Allergan, Celltrion, Sandoz, Boehringer Ingelheim; FM (consultant or speaker's fees) AbbVie, Amgen, Biogen, Celgene, Celltrion, Dr Falk Pharma, Ferring Pharmaceuticals, Hospira, Janssen, Laboratórios Vitória, MSD, Pfizer, Sandoz, Takeda, UCB, Vifor (Grant) GEDII and National Science Foundation; BS (consultant or speaker's fees) AbbVie, AltruBio, Abivax, Boehringer Ingelheim, BMS, Dr. Falk Pharma, Eli Lilly, Endpoint Health, Falk, Galapagos, Gilead, Janssen, Landos, Materia Prima, Predictimmune, Pfizer, and Takeda; AlfaSigma, CED Service GmbH, MSD, Ferring, Tr1x bio (Grant) Pfizer; RA (consultant or speaker's fees) AbbVie, Abivax, AstraZeneca, BMS, Celltrion Healthcare, Galapagos, J&J, Lilly, MSD, Pfizer, and Takeda Pharma; BV (consultant or speaker's fees) Abbvie, Agomab, Alfasigma, Biogen, BMS, Celltrion, Eli Lily, Falk, Ferring, Galapagos, Materia Prima, J&J, Pfizer, Sandoz, Takeda, Tillots Pharma, Truvion and Viatris, Alimentiv, Anaptys Bio, Applied Strategic, Astrazeneca, Atheneum, BenevolentAI, Biora Therapeutics, Boxer Capital, BMS, Domain Therapeutics, Guidepont, Landos, Merck, Mirador Therapeutics, Mylan, Nxera, Inotrem, Ipsos, Sanofi, Santa Ana Bio, Sapphire Therapeutics, Sosei Heptares, Viatris (Grant) AbbVie, Biora Therapeutics, Celltrion, Landos, Pfizer, Sanofi, Sosei Heptares/Nxera, Takeda [Stock options) Vagustim, Thethis Pharma

## CONCLUSIONS

- **In these first studies, two independent assay systems demonstrated that Obe reduces collagen deposition and fibroblast activation while confirming its established anti-inflammatory activity.**
- **These data indicate that Obe may uniquely and directly modulate both inflammatory and fibrotic pathways in key cell types in IBD.**
- **The anti-fibrotic potential of Obe will be further evaluated in the ongoing Phase 2b CD trial.**



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