

Obefazimod increases miR-124 expression to consistently modulate inflammation and fibrosis across preclinical models

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Disclosure of Conflicts of Interest

I herewith declare the following paid or unpaid consultancies, business interests, or sources of honoraria payments for the past three years, and anything else which could potentially be viewed as a conflict of interest:

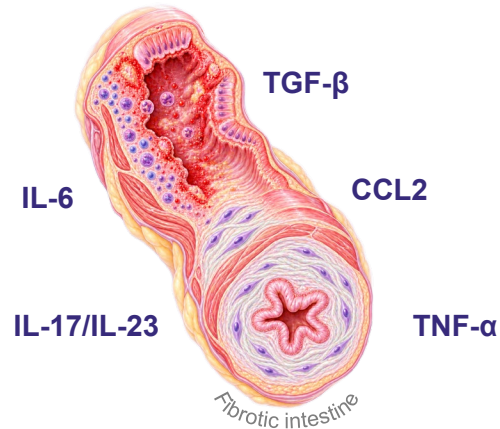
SD served as consultant or received speaker's fees from AbbVie, Abivax, Ferring, Hospira, Johnson & Johnson, Merck, MSD, Takeda, Mundipharma, Pfizer Inc, Tigenix, UCB Pharma, Vifor, Biogen, Celgene, Allergan, Celltrion, Sandoz, and Boehringer Ingelheim

Obefazimod Restores Immune Balance and Reduces Fibrotic Progression

Obefazimod's anti-fibrotic effect in Crohn's Disease Models

Medical Need

Fibrosis can be induced in Crohn's Disease driven by chronic inflammation mediated by cytokines



Clinical Evidence

- Obefazimod targets overlapping pathogenic pathways in UC and CD
- Obefazimod showed strong efficacy in moderate to severe ulcerative colitis at week 52 with a highly desirable safety profile¹

50mg dose

51.3% CLINICAL REMISSION

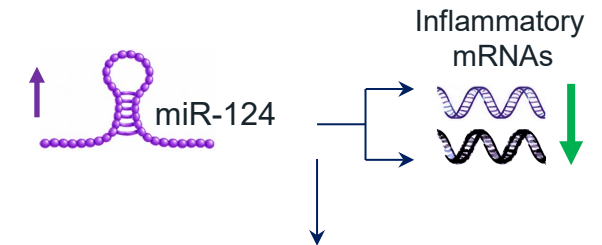
64.1% ENDOSCOPIC IMPROVEMENT



Pathogenic Axis Target Validation

Obefazimod in Fibrosis

- Obefazimod increases miR-124 expression which helps restore immune balance
- **miR-124 could also rebalance key drivers of fibrosis**

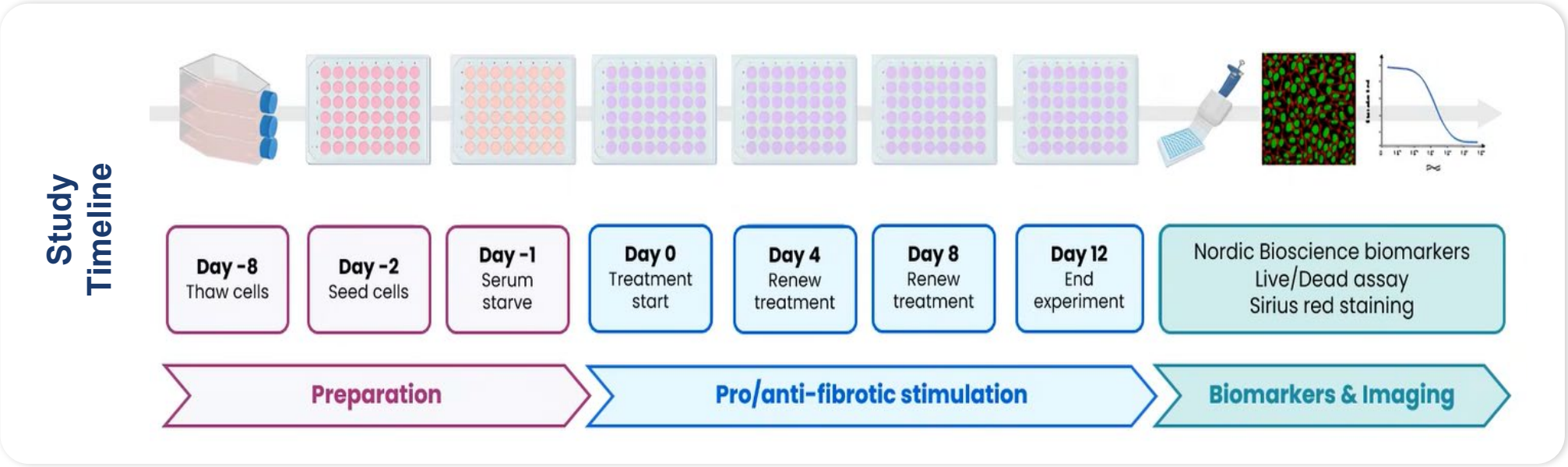
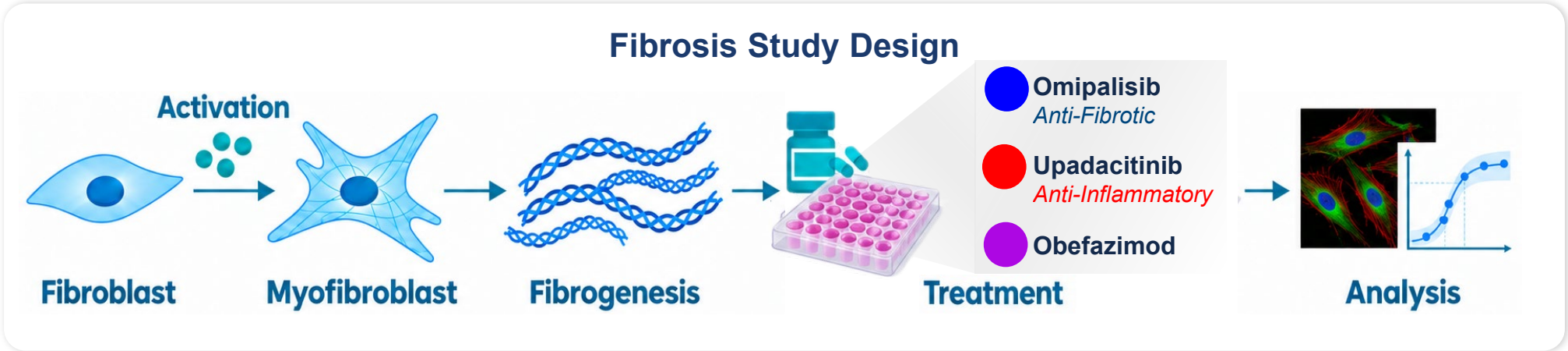


TGF-β regulation & Anti-fibrotic Effect

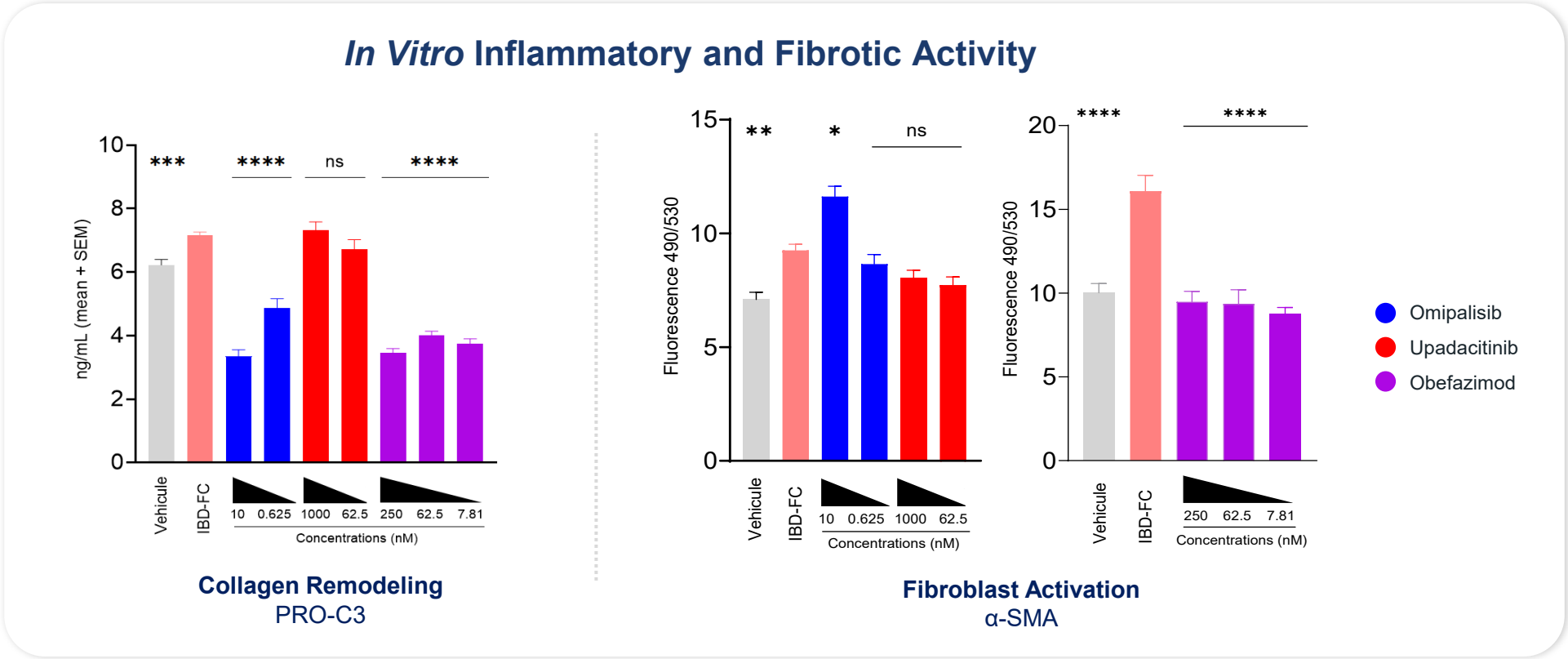
Week 52 assessment includes 8 weeks of induction + 44 weeks of maintenance treatment. | Clinical remission is defined as SFS = 0 or 1, and RBS = 0 and MES = 0 or 1 (MES of 1 modified to exclude friability) | Endoscopic improvement is defined as MES = 0 or 1 (MES of 1 modified to exclude friability); Endoscopic remission is defined as MES = 0 | CD: Crohn's disease; IL: interleukin; TNF: tumor necrosis factor; CCL2: C-C motif chemokine ligand 2; UC: ulcerative colitis; TGF: transforming growth factor

1. Sands et al., Efficacy and Safety of Obefazimod in Patients with Moderately to Severely Active Ulcerative Colitis: Results from the Phase 3, Randomized, Double-blind, Placebo-Controlled, 44-week Maintenance Trial (ABTECT-Maintenance), UEGW 2026

Obefazimod Directly Attenuates Profibrotic Activity in Human Intestinal Fibroblasts in vitro



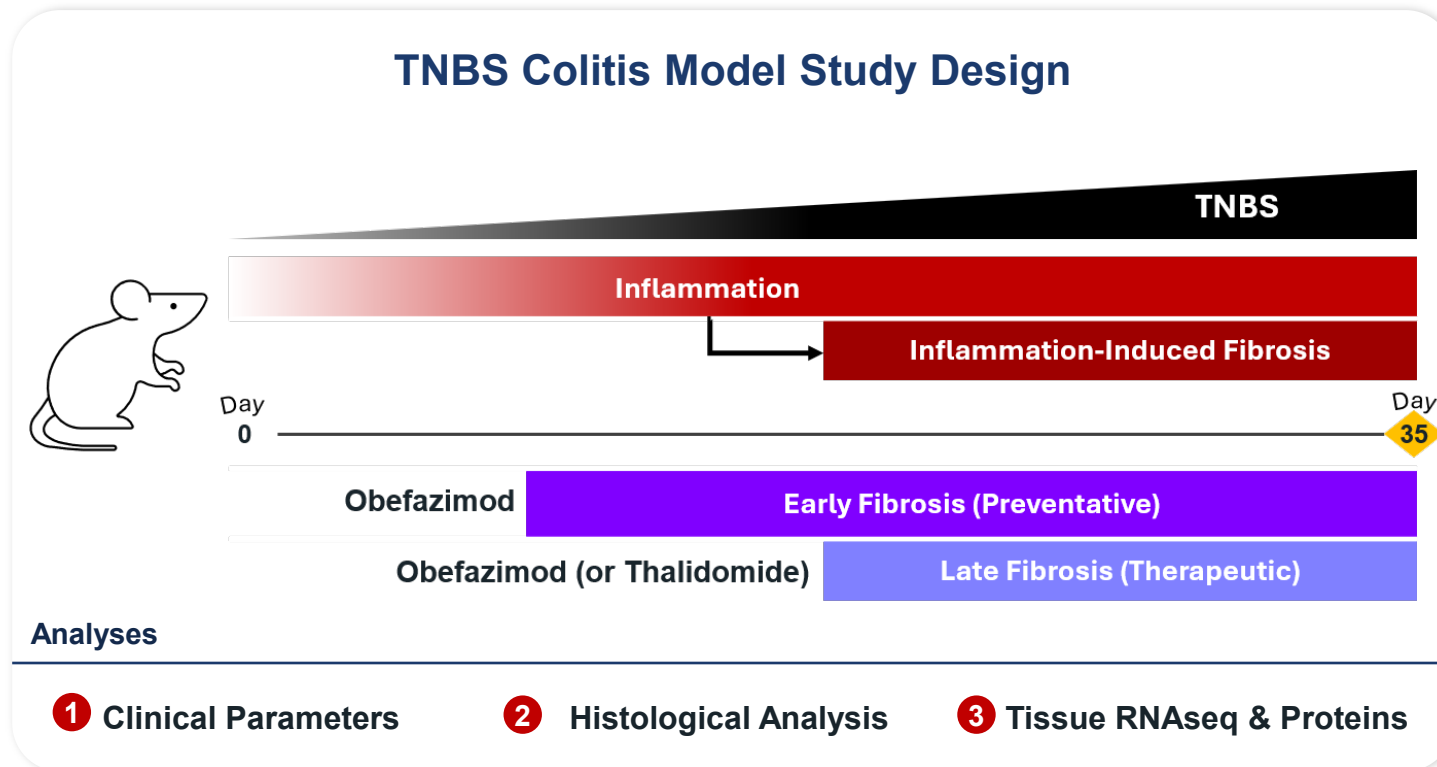
Obefazimod Directly Attenuates Profibrotic Activity in Human Intestinal Fibroblasts in vitro



Obefazimod demonstrates dual anti-inflammatory and anti-fibrotic activity, with broader effects than single-mechanism comparators:
Up to 50% reduction in PRO-C3 (fibrogenesis marker) | ~30% reduction in α-SMA (fibroblast activation marker)

Chronic TNBS Colitis Provides a Translational Model to Assess Antifibrotic Activity in Crohn's Disease (CD)

Repeated TNBS exposure induces sustained intestinal inflammation and progressive fibrotic remodeling

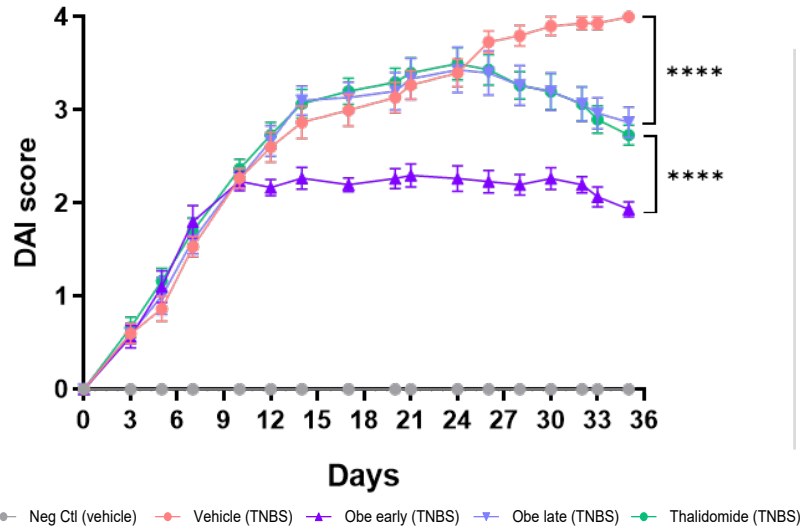


TNBS Murine Model

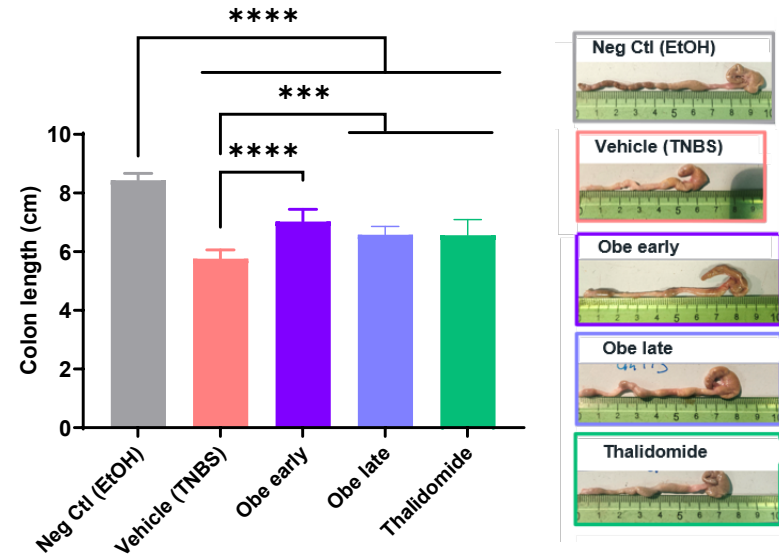
- Sustained, deep transmural inflammation mimics key features of human CD and drives intestinal fibrosis
- Submucosal fibrillar collagen deposition marks the onset of fibrosis
- **Early Obe treatment – preventive:** tests Obe's potential to control inflammation and prevent fibrosis
- **Late Obe treatment – treatment:** tests Obe's potential to halt ongoing inflammation and fibrosis

Obefazimod Rebalances Intestinal Immunity, Reducing Clinical Disease Activity and Histologic Inflammation

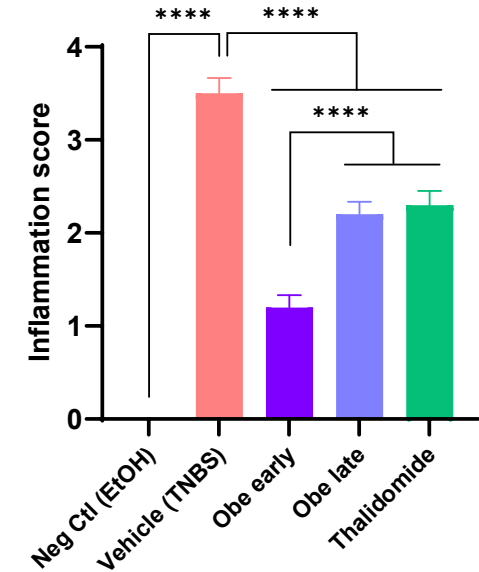
Obefazimod Anti-Inflammatory Activity



Disease Activity Index Score

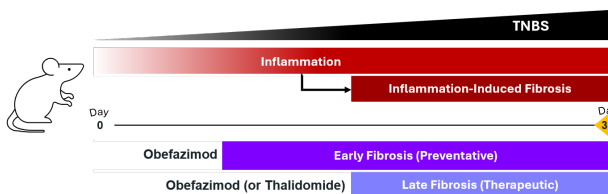


Colon Length (Day 35)



Inflammation Score (Day 35)

TNBS Colitis Model



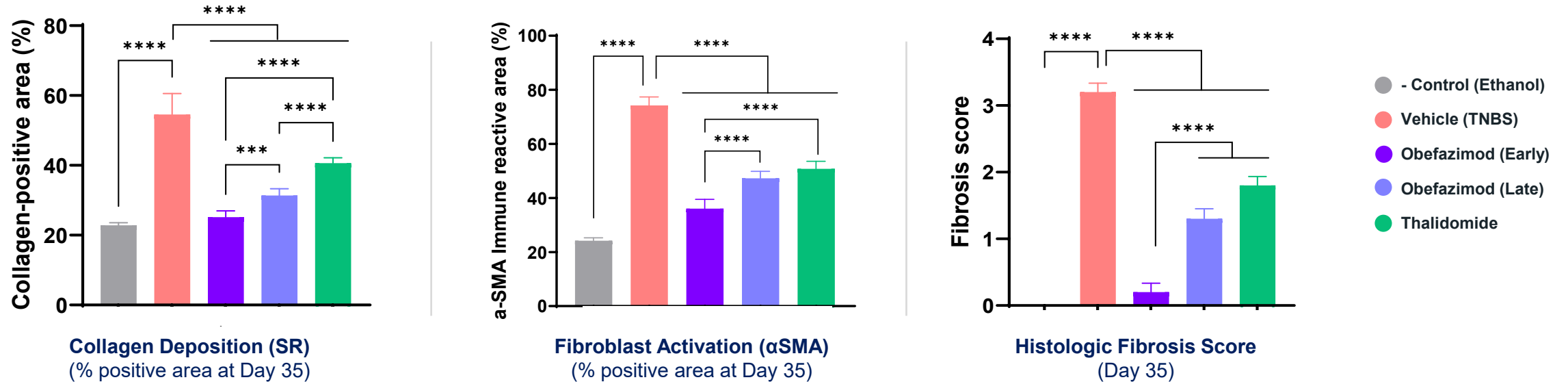
Obefazimod maintains anti-inflammatory activity across early and established stages of fibrotic disease:

- Reduction in Disease Activity Index (including weight loss protection)
- Improved colon length with both early and late treatment
- Reduction in histologic ulceration and inflammation scores

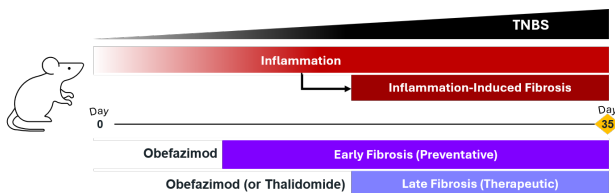
Obefazimod Demonstrates Broad Antifibrotic Activity With Both Preventive and Therapeutic Treatment

Concordant reductions in collagen deposition and remodeling, fibroblast activation, and histologic fibrosis

Obefazimod Antifibrotic Activity



TNBS Colitis Model



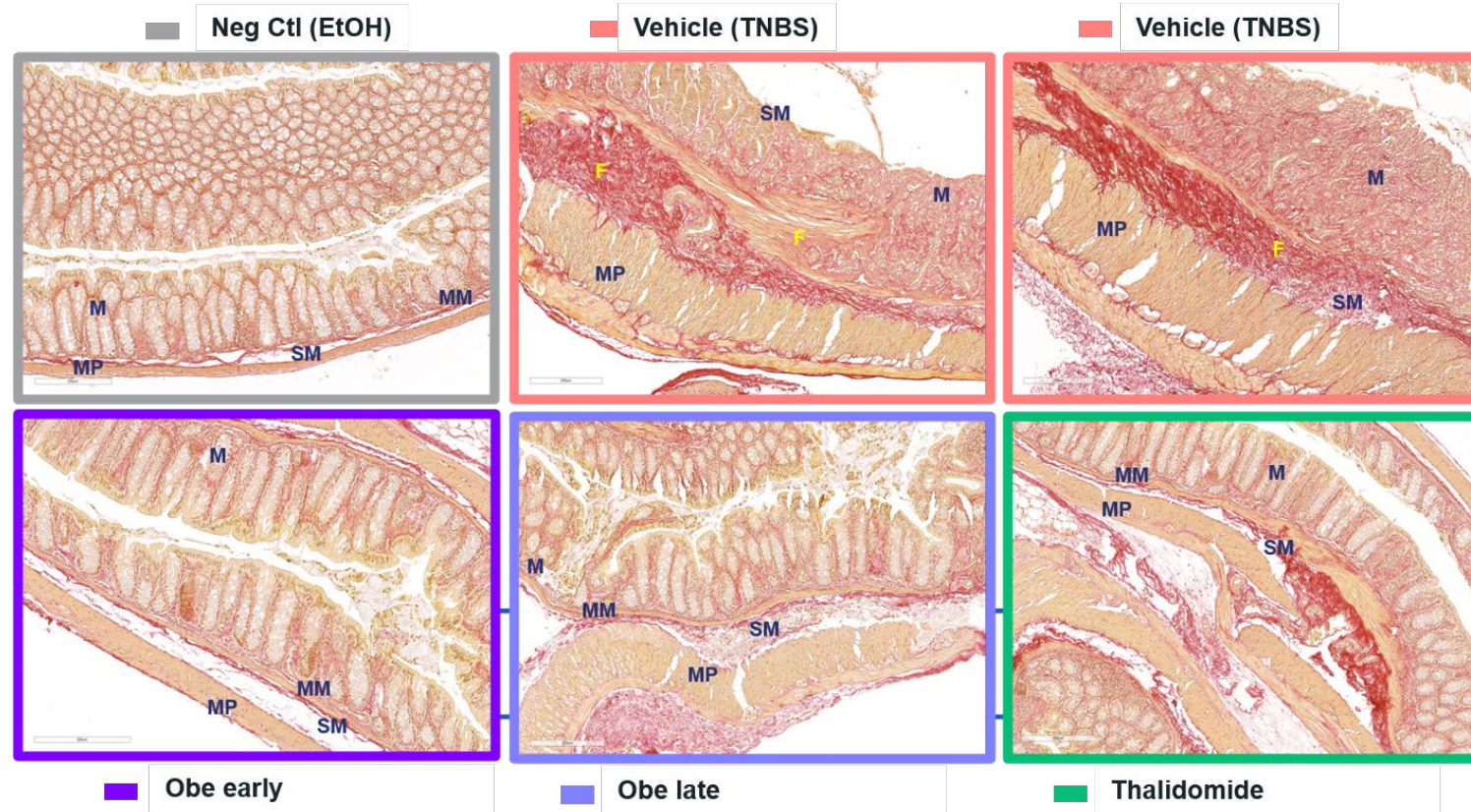
Obefazimod demonstrates substantial antifibrotic activity in both fibrosis prevention & treatment settings:

- Obefazimod reduced collagen deposition and fibroblast activation by ~50%, demonstrating a substantial antifibrotic effect
- ~60% & ~90% reduction in histologic Fibrosis Score with late and early treatment, respectively

*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 one-way ANOVA with Tukey's multiple comparisons testing used | SR: Sirius Red; α-SMA: alpha-smooth muscle actin

Obefazimod Substantially Attenuates Intestinal Fibrosis, Demonstrated by Reduced Sirius Red-Positive Collagen Deposition

Histological Analysis (Day 35)



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

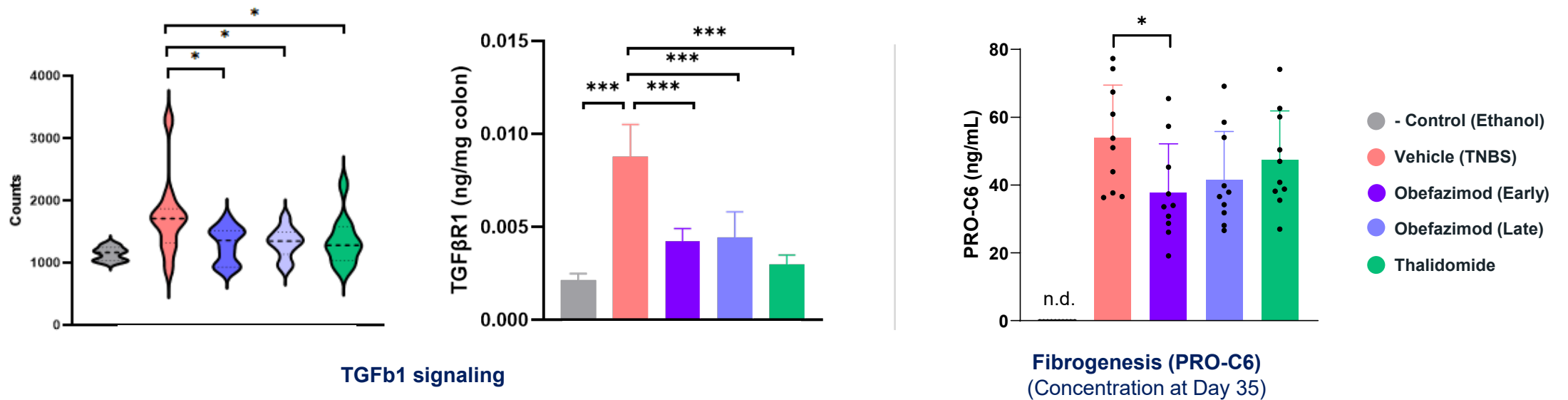
Histologically, TNBS produced substantial submucosal collagen deposition, demonstrated by Sirius Red staining.

Obefazimod markedly reduced this collagen accumulation with both early and late treatment.

Importantly, the effect with late treatment indicates that the observation is not limited to prevention during the initial inflammatory phase.

Obefazimod Rebalances the TGF- β Pathway to Control Matrix Remodeling

Obefazimod Antifibrotic Activity



Obefazimod rebalances TGF- β signaling to control matrix remodeling in in vivo models:

- Reduction of TGFb1R transcript and ~50% reduction in TGFbR1 protein with both late and early treatment
- Reduction of expression of additional collagen processing and matrix remodeling pathways
- Reduction of PRO-C6 (COL6a3/endotrophin), a biomarker of ongoing remodeling of the extracellular matrix

Conclusions

- Obefazimod enhances miR-124, an endogenous regulatory node that rebalances immune responses and links immunoregulation with tissue remodeling
 - Reduced intestinal inflammation & disease activity
 - Broad antifibrotic activity across collagen deposition, fibroblast activation, & histologic fibrosis
 - Consistent effects with early & late treatment, consistent coordinated miR-124-mediated rebalancing of immune and TGF- β -related pathways
- **NEXT STEP:** Translational analyses in ENHANCE-CD will further characterize obefazimod's anti-fibrotic and anti-inflammatory effects in patients with Crohn's disease

