

Obefazimod shows first evidence of anti-fibrotic activity in preclinical models of inflammatory bowel disease

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Conflicts of Interest

(consultant or speaker's fees): AbbVie, Abivax, Allergan, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Hospira, Johnson & Johnson, Merck, MSD, Mundipharma, Pfizer Inc, Sandoz, Takeda, Tigenix, UCB Pharma, Vifor.

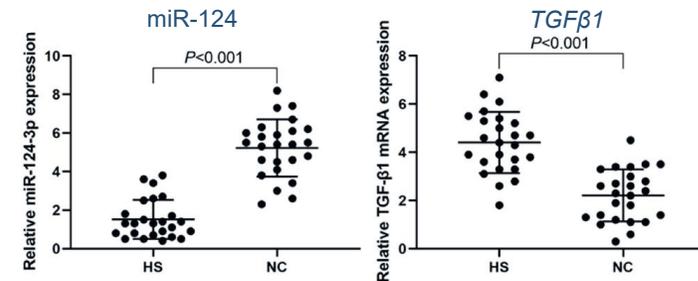
Fibrosis represents the largest unmet need in Crohn's Disease

miR-124 dysregulation may play a role in intestinal fibrosis

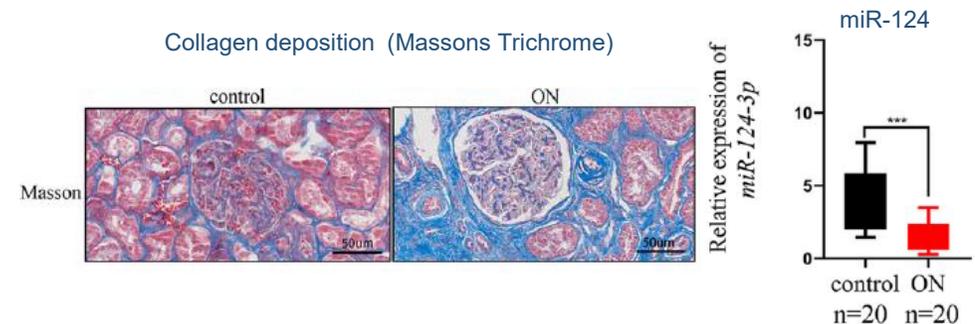
Fibrosis in CD

- Occurs in up to 50% of CD patients, with no currently approved therapies to specifically prevent or treat fibrotic complications
 - Fibrotic CD patients up to 6x more likely to require hospitalization
- Fibrosis driven by inappropriate tissue repair pathways (e.g., TGF- β) which activate fibroblasts and other cells to overproduce extracellular matrix and stiffen tissue
- Effective anti-inflammatory treatments are not anti-fibrotic
 - While fibrosis is triggered by repeated inflammatory damage to cells, once initiated it becomes inflammation-independent & established
- miR-124 is dysregulated in fibrotic tissue, and is known to regulate fibrotic pathways such as TGF- β**

Dysregulation of miR-124 in human dermal and nephrotic fibrosis samples*



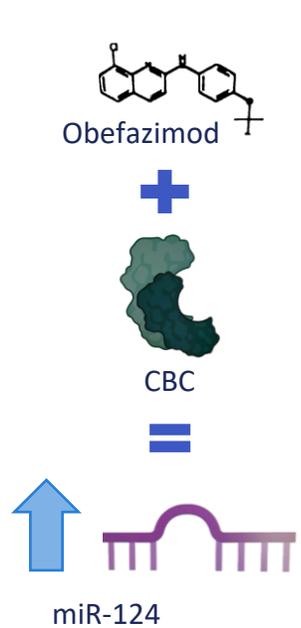
SKIN: miR-124 downregulated in human hypertrophic skin (HS) fibroblasts compared to control (NC) while TGF β is overexpressed



KIDNEY: miR-124 downregulated in human fibrotic obstructive nephropathy (ON) tissue compared to control tissue (control)

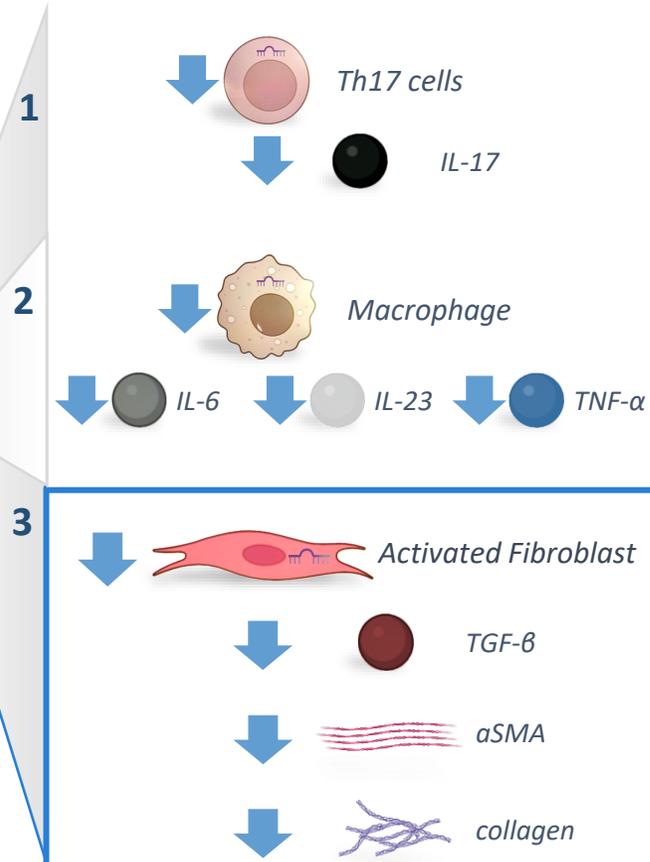
Obefazimod MoA addresses multiple hallmarks of IBD pathology including chronic inflammation and downstream fibrotic progression

Obe ↑ miR-124



Obefazimod Restoring Balance

Restoring Balance without Immunosuppression



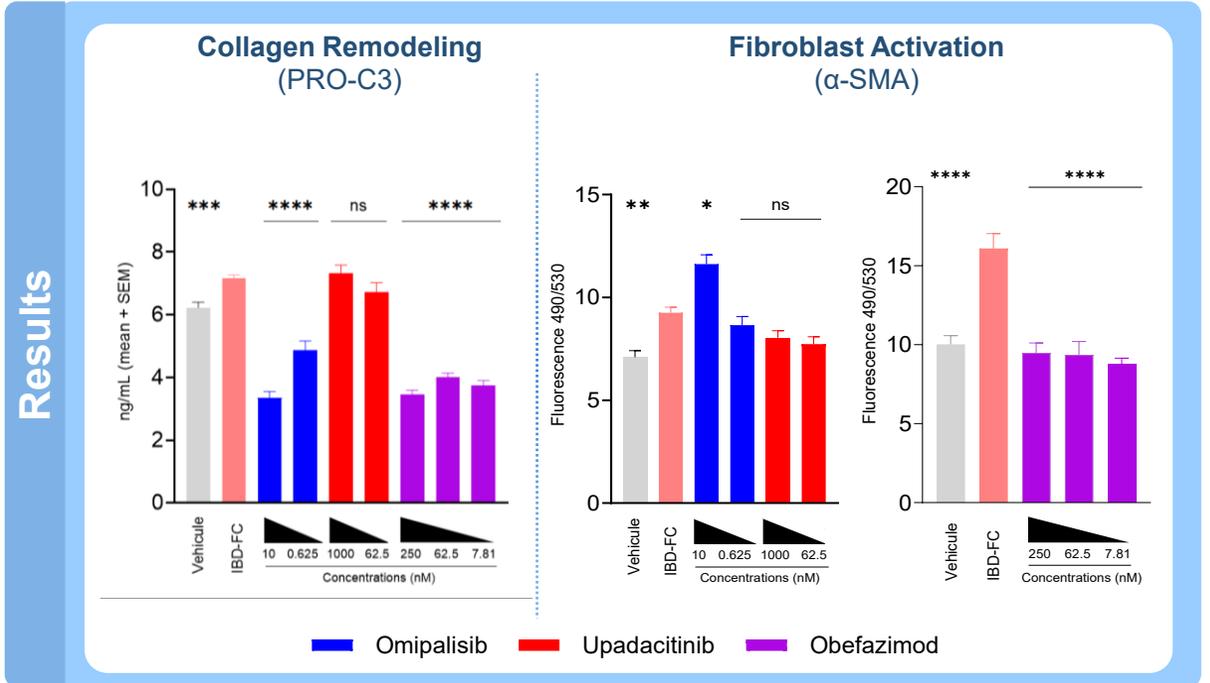
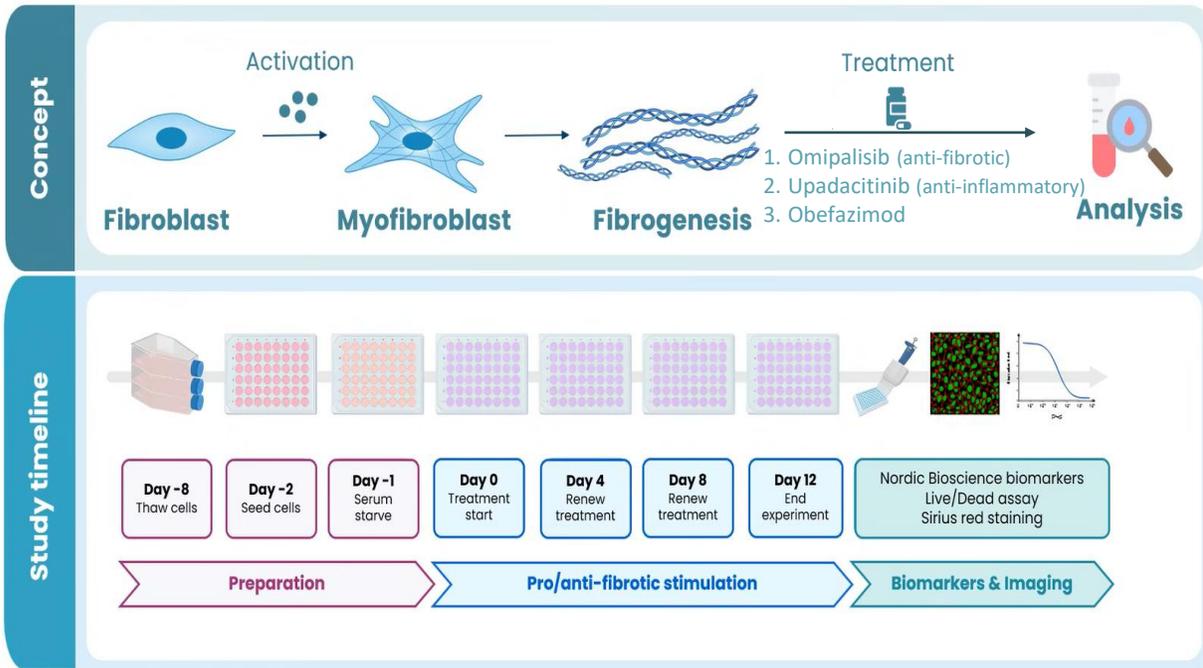
Obefazimod (Obe) enhances expression of microRNA-124 which

- restores immune balance including inflammatory Th17 cells and macrophage in the mucosa
- AND
- has shown efficacy in patients with moderately to severely active ulcerative colitis (UC)

Hypothesis that beyond its known anti-inflammatory effects, obefazimod may also have direct anti-fibrotic activity which could be useful to prevent and treat fibrosis

Apolit et al. Clin Transl Gastroenterol, 2023 | Vermeire et al., J Crohns Colitis, 2023 | Abivax Data on File | Images made with BioRender; *Additional mRNAs and cell types may be targeted by miR-124 & obefazimod, and can also play roles in IBD and fibrosis

Obefazimod shows an anti-fibrotic effect on human small intestine fibroblasts the scar-in-a-jar model



Conclusions

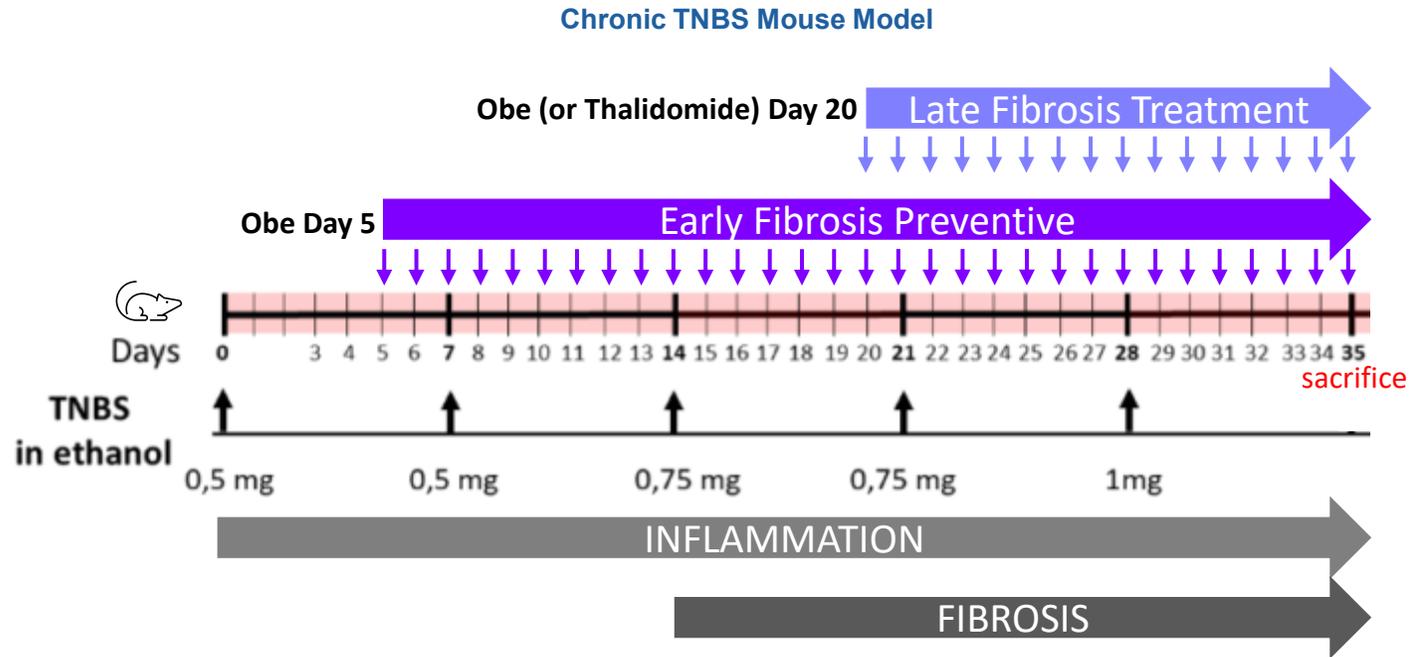
Obefazimod reduces human fibroblast populations and activation status

- ~50% reduction in Pro-C3 (fibrogenesis marker)
- ~30% reduction in αSMA (fibroblast activation marker)

Profound effect of obefazimod suggests dual anti-inflammatory and anti-fibrotic effects which are greater than singular anti-fibrotics (omipalisib) or anti-inflammatories (upadacitinib)

*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 one-way ANOVA with Dunnet'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

Methods: chronic TNBS mouse model of fibrotic colitis

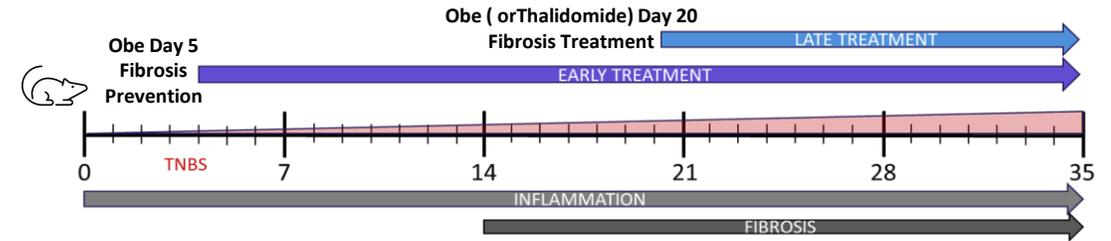


- Standard CD mouse model which causes long-lasting intestinal inflammation that mimics key features of CD in humans
 - strong inflammatory response similar to the human condition, with inflammation extending through the entire intestinal wall (transmural inflammation)
 - Appearance of fibrillar collagen in the submucosa, considered the onset of fibrosis
- **Obe treatment initiated on either day 5 (anti-inflammatory + fibrosis-preventive effect) or from day 20 (early-onset anti-fibrotic effect)**



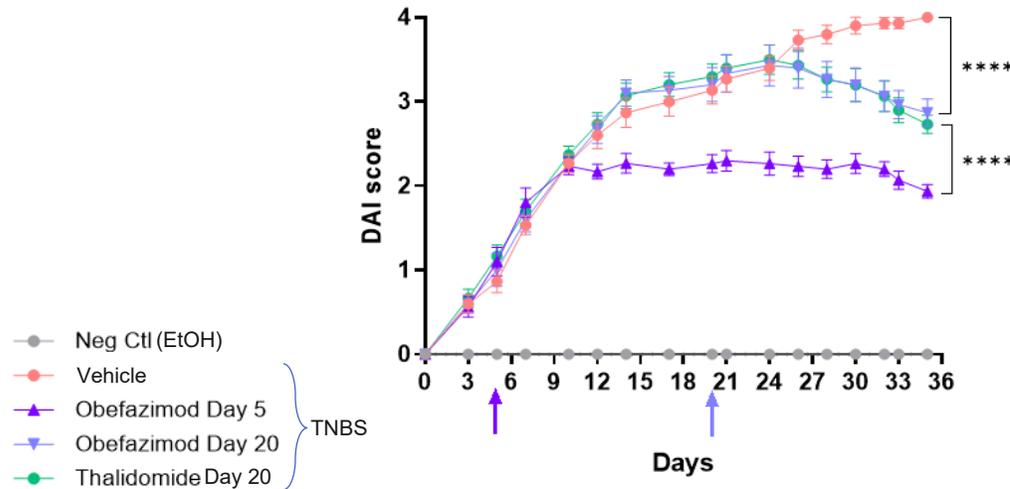
Obefazimod improves clinical and histologic inflammation in the chronic TNBS mouse model of fibrotic colitis

Chronic TNBS Mouse Model

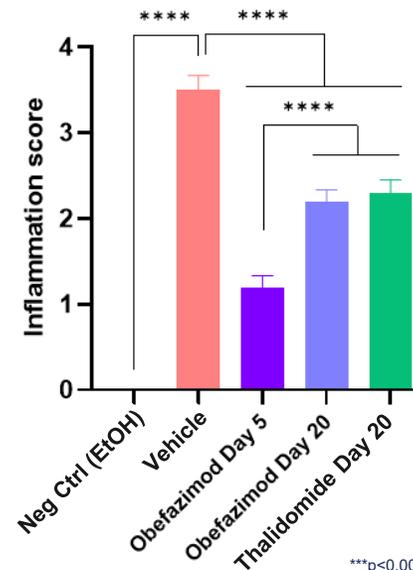


Results

Disease Activity Index Score



Histologic Inflammation Score (at day 35)



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

Conclusions

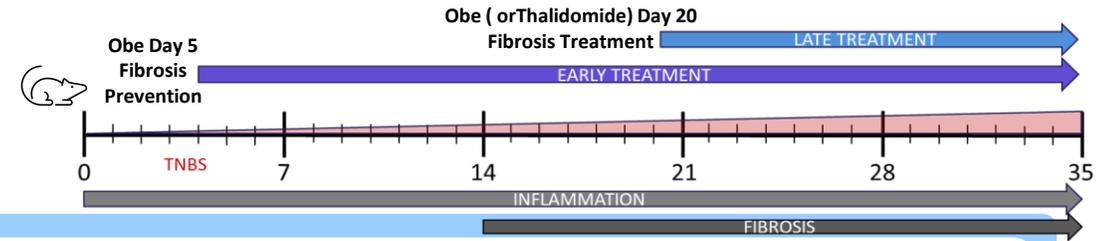
Obefazimod shows anti-inflammatory effects when initiated as a **fibrosis preventative** or **fibrosis treatment**:

- ~25% & ~50% reduction in Disease Activity Index (including weight loss protection) with late and early treatment, respectively
- ~35% & ~65% reduction in histologic ulceration and Inflammation scores with late and early treatment, respectively

Obefazimod effects are similar to dual anti-inflammatory/anti-fibrotic thalidomide positive control

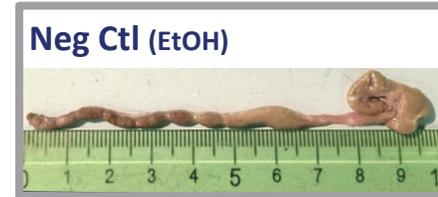
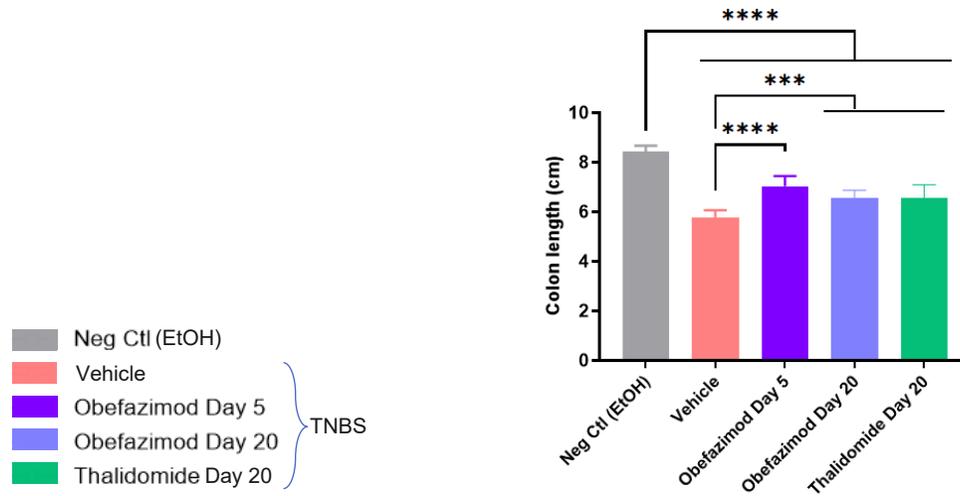
Obefazimod leads to improved colon length in the chronic TNBS mouse model

Chronic TNBS Mouse Model



Results: Day 35

Colon Length
(at day 35)



***p<0.001 vs Ng Ctl, ##p<0.001 vs vehicle, ###p<0.001 vs vehicle by one-way ANOVA with Tukey's multiple comparisons test

Conclusions

Obefazimod shows anti-inflammatory effects when initiated as a **fibrosis preventative** or **fibrosis treatment**:

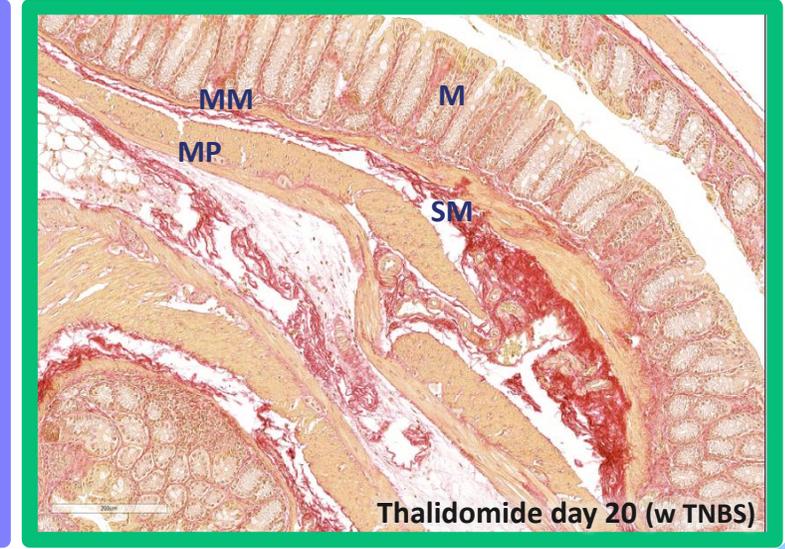
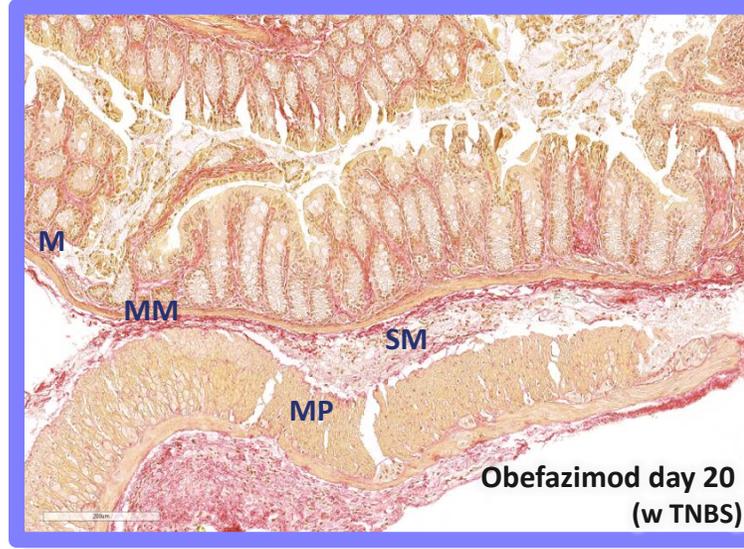
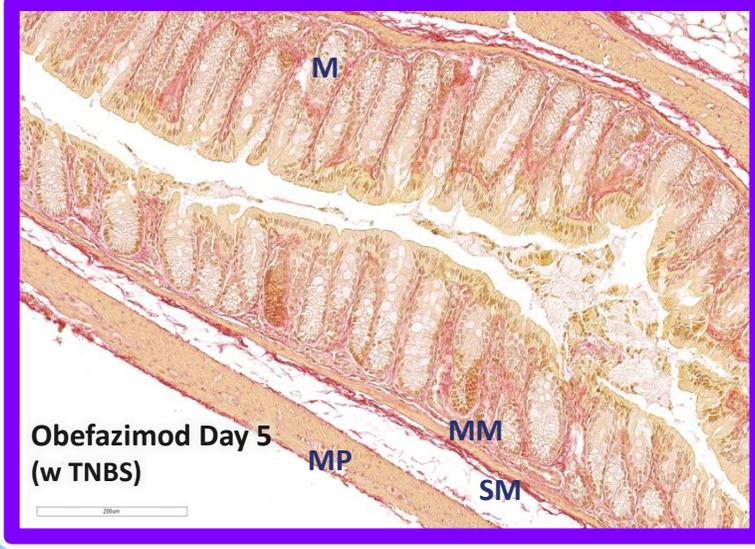
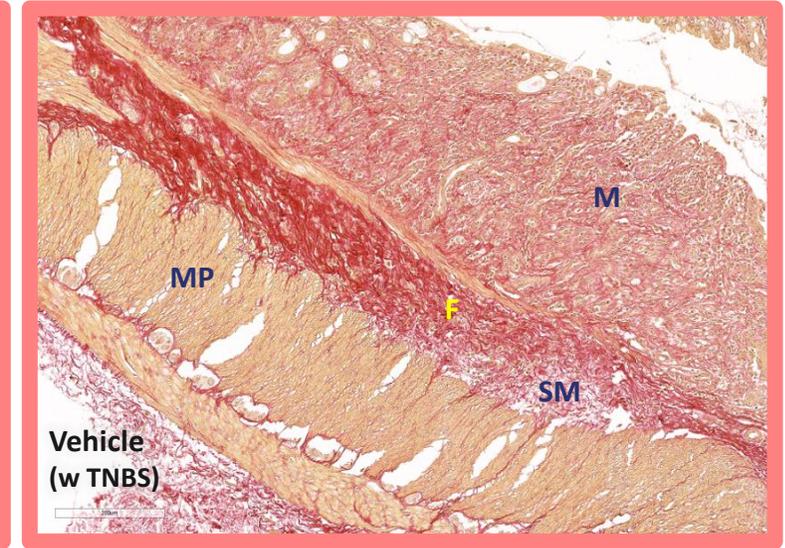
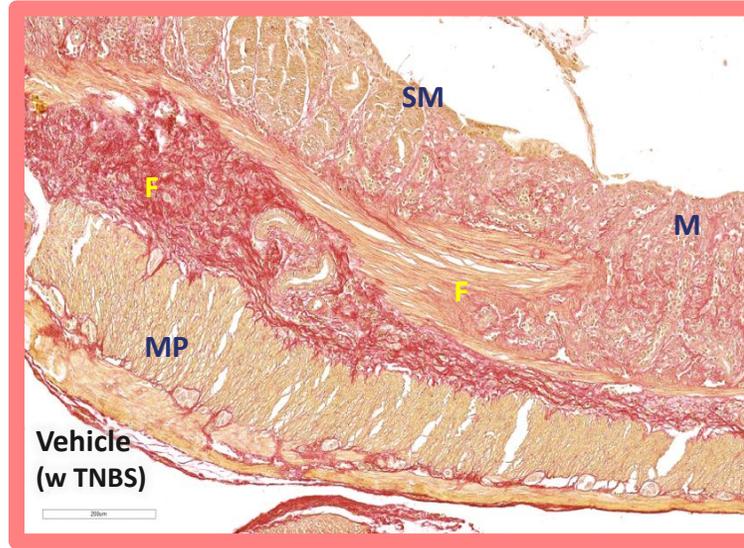
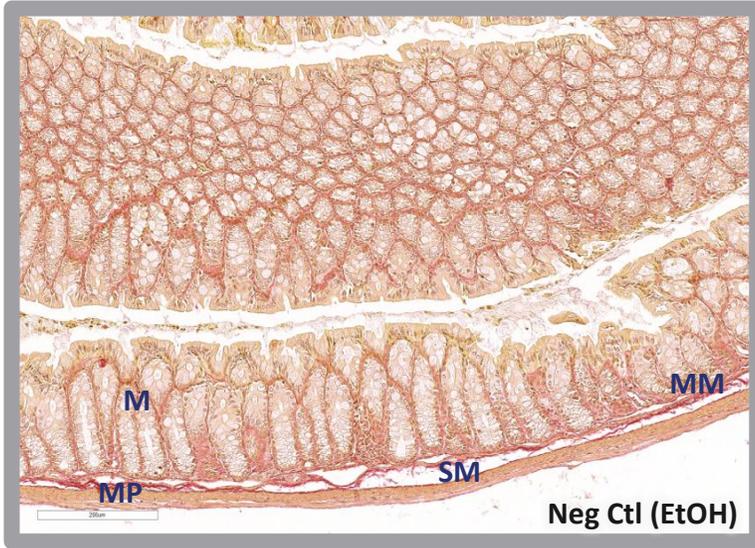
- Improved colon length with both early and late treatment

Obefazimod effects are similar to dual anti-inflammatory/anti-fibrotic thalidomide positive control

Obefazimod reduces collagen staining by Sirius Red and profoundly diminishes fibrosis in the chronic TNBS mouse model

- Neg Ctl (EtOH)
 - Vehicle
 - Obefazimod Day 5
 - Obefazimod Day 20
 - Thalidomide Day 20
- } TNBS

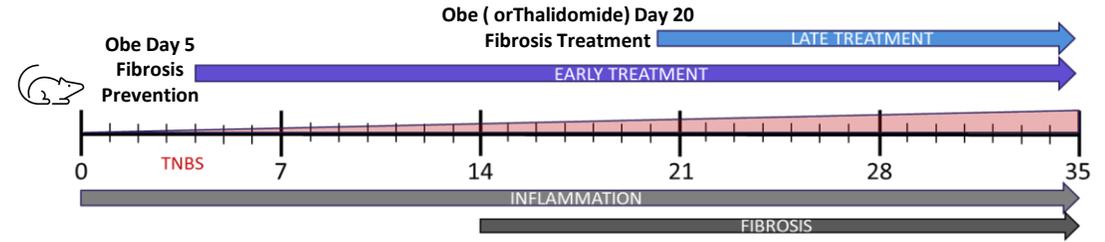
Results: Day 35



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

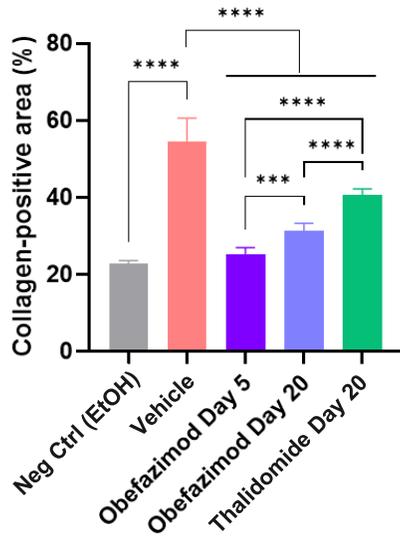
Obefazimod leads to reduced fibrosis in the chronic TNBS mouse model

Chronic TNBS Mouse Model

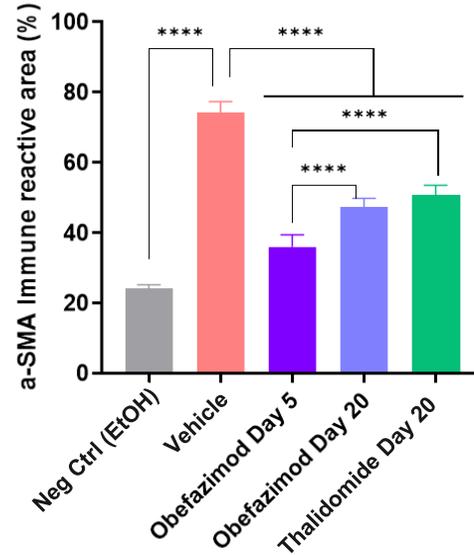


Results: Day 35

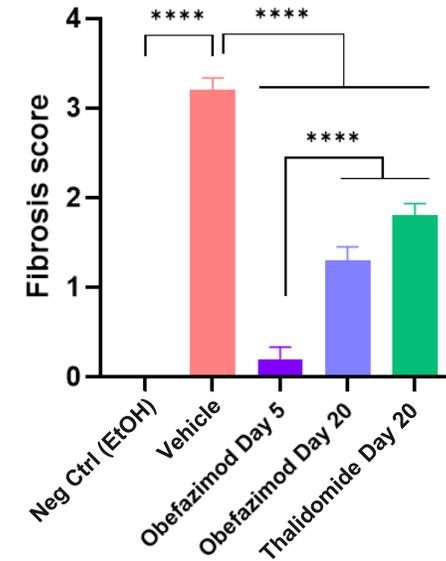
Collagen Deposition
(% positive area at day 35 – Sirius Red)



α -SMA
(% positive area at day 35)



Histologic Fibrosis Score
(at day 35)



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

Conclusions

Obefazimod shows anti-fibrotic effects when initiated as a **fibrosis preventative** or **fibrosis treatment**:

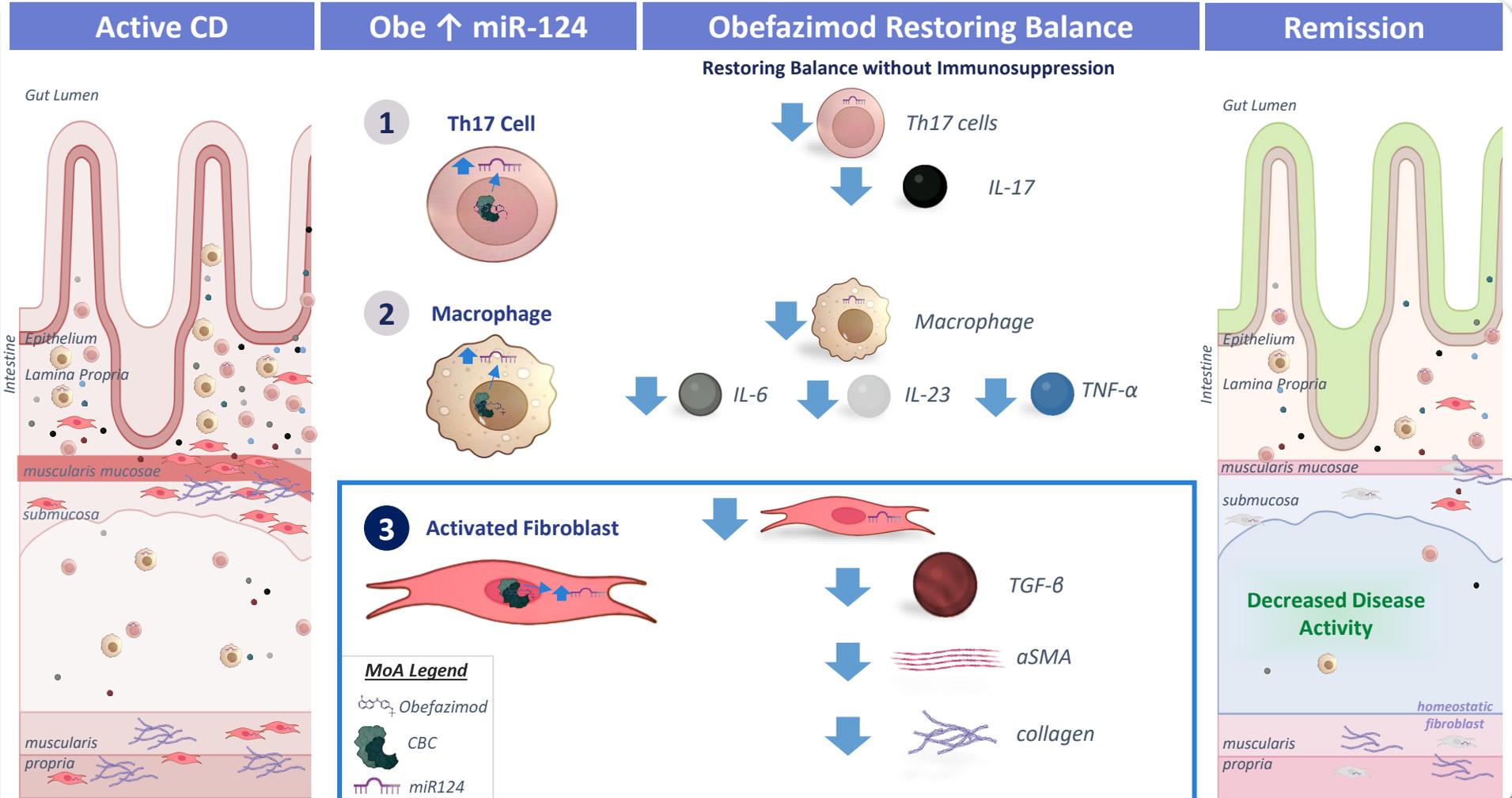
- ~45% & ~55% reduction in **Collagen Deposition** (fibrogenesis marker) with late and early treatment, respectively
- ~40% & ~50% reduction in **α SMA** (fibroblast activation marker) with late and early treatment, respectively
- ~60% & ~90% reduction in histologic **Fibrosis Score** with late and early treatment, respectively

Obefazimod effects are more profound than dual anti-inflammatory/anti-fibrotic thalidomide positive control

Obefazimod restores immune balance and reduces fibrotic progression

Anti-fibrotic potential will be further investigated in the ongoing phase 2b ENHANCE-CD trial

- In human fibroblasts, obe shows a profound effect on markers of fibrotic activity & fibroblast activation
- In animal models, obe is effective at both preventing and halting fibrosis
- In the ENHANCE-CD trial, obe will be further investigated for anti-fibrotic activity in addition to anti-inflammatory effects in patients with Crohn's disease



Apoliti et al. Clin Transl Gastroenterol, 2023 | Vermeire et al., J Crohns Colitis, 2023 | Abivax Data on File | Images made with BioRender; ENHANCE-CD Phase 2b trial (NCT#06456593)
 *Additional mRNAs & cell types may be targeted by miR-124 & obefazimod, and can also play roles in IBD & fibrosis