ADS051, AN ORAL, GUT-RESTRICTED, SMALL MOLECULE NEUTROPHIL MODULATOR IN PATIENTS WITH MODERATE-TO-SEVERE ULCERATIVE COLITIS RECEIVING MULTIPLE ASCENDING DOSES

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Introduction

Ulcerative colitis (UC) results from inflammation of the colon caused by unchecked neutrophil influx and activity (1,2). Despite recent therapeutic advancements in the treatment of UC, including biologics and small molecule advanced therapies, remission rates for patients with moderate-to-severe disease rarely exceed 30%. Furthermore, 83% of patients relapse within 10 years of diagnosis. Many of today's treatments also carry significant safety concerns, including increased risk of infection and malignancy (3-6).

ADS051 is a novel, oral, gut-restricted, small molecule, modified cyclosporine scaffold covalently linked to a 2,000 molecular weight polyethylene glycol (PEG) by an amide linker. ADS051 modulates neutrophil trafficking and activity via the multidrug resistance protein 2 (MRP2)- and formyl peptide receptor 1 (*FPR1*)-mediated mechanisms in human cell-based systems. Its lack of both systemic exposure and blockage of T cell activation is intended to limit general immunosuppression (7).

The objective of this Phase 1b clinical study was to evaluate safety, efficacy, and pharmacokinetics (PK) of this novel neutrophil modulator, ADS051, in patients with moderately to severely active UC.

Methods

This Phase 1b first-in-patient study (NCT05084261) was a randomized, placebo-controlled, double-blind, multiple ascending dose (MAD) cohort design enrolling patients with moderately to severely active UC, with a complete Mayo score ≥6 and on stable, permitted standard of care (SoC) treatment with aminosalicylates, thiopurines, and/or corticosteroids (≤20 mg prednisone). Patients with prior exposure to biologics or Janus kinase inhibitors (JAKi) were limited to 30% of the total patient population; those who had failed 2 or more advanced therapies (ie, biologic and JAKi, 2 biologics in the same class, or 2 biologics from different classes) were limited to 20% of the total patient population.

Oral doses selected were based on predictive physiologically based pharmacokinetic (PB/PK) modeling incorporating data from the single ascending dose (SAD) study. The model evaluated ADS051 daily trough concentrations throughout the ascending colon and rectum, with effective target fecal concentrations of 100 µg/gram indicating potential patient benefit via inhibition of MRP2- and FPR1-associated pathways.

The 200 and 800 mg doses were considered within the predictive range in the model for ADS051's effective inhibition of the MRP2 and FPR1 targets. The 3200-mg dose was selected to assess the safety and tolerability of ADS051 at a high dose level consistent with a dose of 3500 mg used in SAD study.

Patients (n=24) were randomized to once-daily oral ADS051 (200, 800, or 3200 mg in cohorts 1, 2, and 3) or placebo (PBO) + SoC in ascending-dose groups. Each dose-escalation cohort included 8 patients randomized 3:1 (n = 6, ADS051 / n = 2, PBO) to receive active drug or PBO + SoC for 28 days, followed by 30 days off study drug (Figure 1). The study objectives are shown in Table 1.

Table 1. Phase 1b MAD Study Objectives

Phase 1b Study Objectives	
Primary	Evaluate safety and tolerability of ADS051 administered orally, once daily for 28 days
Secondary	Evaluate signals of activity measured as centrally-read endoscopy, clinical remission, clinical response, and histologic assessment
Exploratory	Changes in FCP, CRP, and MPO
PK	Blood, urine, feces, and colonic tissue concentrations

FCP, fecal calprotectin; CRP, C-reactive protein; MPO, myeloperoxidase.

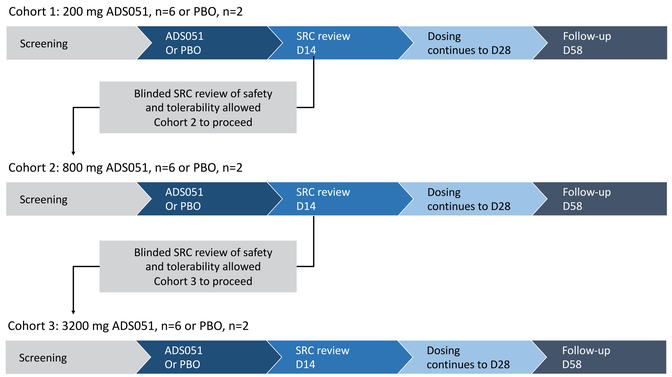


Figure 1. Phase 1b MAD Clinical Trial Design

Results

In total, 29 patients were screened at 6 study sites, with 24 enrolled at 5 study sites within Europe and the United States. All 24 patients enrolled completed the study.

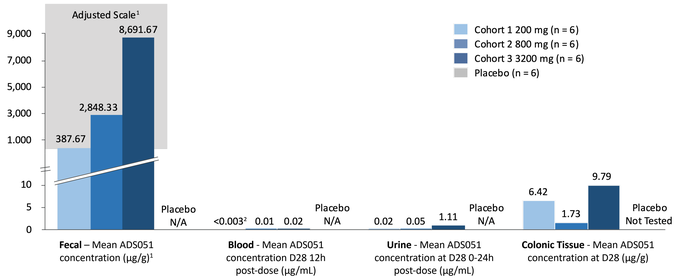
Safety

In terms of safety, 16.7% of all patients who received ADS051 reported at least one treatment-emergent adverse event vs 66.7% in the placebo group, as depicted in Table 2. No serious adverse events were reported. This study demonstrated favorable safety and tolerability of three dose levels (200, 800, and 3200 mg) of ADS051 administered orally, once daily for 28 days.

Table 2. Phase 1b MAD Treatment-Emergent Adverse Events by Preferred Term

	Cohort 1 200 mg	Placebo	Cohort 2 800 mg	Placebo	Cohort 3 3200 mg	Placebo	Total
	n = 6	n = 2	n = 6	n = 2	n = 6	n = 2	n = 24
Subjects with ≥1 TEAE	1 (16.7%)	1 (50.0%)	0%	1 (50.0%)	2 (33.5%)	2 (100%)	7 (29.2%)
Anaemia	0%	0%	0%	0%	1 (16.7%)	0%	1 (4.2%)
B lymphocyte abnormalities	0%	1 (50.0%)	0%	0%	0%	0%	1 (4.2%)
Neutrophil function disorder	0%	1 (50.0%)	0%	0%	0%	0%	1 (4.2%)
White blood cell disorder	0%	1 (50.0%)	0%	0%	0%	0%	1 (4.2%)
Colitis ulcerative	0%	0%	0%	0%	0%	1 (50%)	1 (4.2%)
Nausea	0%	0%	0%	0%	1 (16.7%)	0%	1 (4.2%)
Headache	1 (16.7%)	0%	0%	0%	1 (16.7%)	0%	2 (8.3%)
Liver function test increased	0%	0%	0%	0%	0%	1 (50%)	1 (4.2%)
Arthralgia	0%	0%	0%	0%	0%	1 (50%)	1 (4.2%)

High stool concentrations of ADS051 were attained at all dose levels, while systemic exposure was low, with <1% of daily dose of ADS051 excreted in urine (Figure 2), consistent with gut restriction after oral dosing.

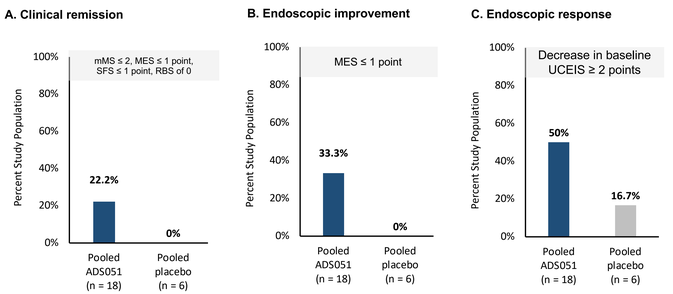


¹Stool concentrations up to 8000-fold above the target IC50 (3.3 µg/mL or 1 µM)
²Only 1 positive sample. All other samples <LLOQ (LLOQ = 0.0025 µg /mL)

Figure 2. ADS051 Concentration Excreted in Feces, Blood, Urine, and Colonic Tissue

Efficacy

On Day 28, for pooled ADS051 vs pooled PBO, clinical remission was achieved in 22.2% vs 0%, endoscopic improvement (centrally-read) in 33.3% vs 0%, and endoscopic response (centrally-read) (UCEIS) was achieved in 50% vs 17% (Figure 3A-C).



mMS, modified Mayo score; MES, Mayo endoscopic subscore; SFS, Mayo stool frequency subscore; RBS, Mayo rectal bleeding subscore; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

Figure 3. Efficacy Assessments for Phase 1b MAD Study

Summary and Conclusions

- This Phase 1b MAD study demonstrates favorable safety and tolerability of 3 doses (200, 800, and 3200 mg) of ADS051 administered orally, once daily, for 28 days in patients with moderate-to-severe UC (Table 2).
- PK data demonstrate that ADS051 is gut-restricted, as designed, with minimal systemic drug exposure (Figure 2).
- ADS051 efficacy measures indicate encouraging signals of pharmacologic activity and clinical benefit in the 200- and 800-mg ADS051 groups vs the PBO group after 28 days of treatment (Figure 3).
- Safety and tolerability of the 3200-mg dose group were equivalent to the lower dose cohorts with substantially higher fecal concentrations of ADS051.
- The Phase 1b MAD data indicate that ADS051 may be an important therapeutic advancement as a safe and effective, once-daily oral therapy for patients with UC.
- These findings warrant additional investigation of ADS051 in larger clinical studies.

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COI Declarations:
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