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Safety, Pharmacokinetics, and Clinical Efficacy of ADS051, a Neutrophil Modulator, in Ulcerative Colitis: Results of a Randomized Phase 1b Trial

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INTRODUCTION: **Ulcerative colitis (UC) is characterized by colonic inflammation, with neutrophils playing a key role in UC activity, prognosis, and response to therapies. Current UC therapeutics can have significant side effects and limited efficacy. ADS051 is a novel, oral, gut-restricted small molecule that modulates neutrophil migration and activation without *in vitro* suppression of T-cell activation. The primary objective of this Phase 1b multidose trial was to evaluate the safety of ADS051. Secondary objectives were clinical activity and pharmacokinetics assessment.**

Safety, Pharmacokinetics, and Clinical Efficacy of ADS051, a Neutrophil Modulator, in Ulcerative Colitis: Results of a Randomized Phase 1b Trial

- Neutrophil infiltrates in the colon are hallmark of ulcerative colitis (UC)
- ADS051 is an oral small molecule targeting neutrophil migration and activation in the colon

- This Phase 1b randomized, double-blind, placebo-controlled study evaluated safety and efficacy of ADS051 in patients with moderate-to-severe UC
- 24 patients were randomized to receive ADS051 or PBO (3:1) in ascending dose cohorts (200 mg, 800 mg, 3200 mg)

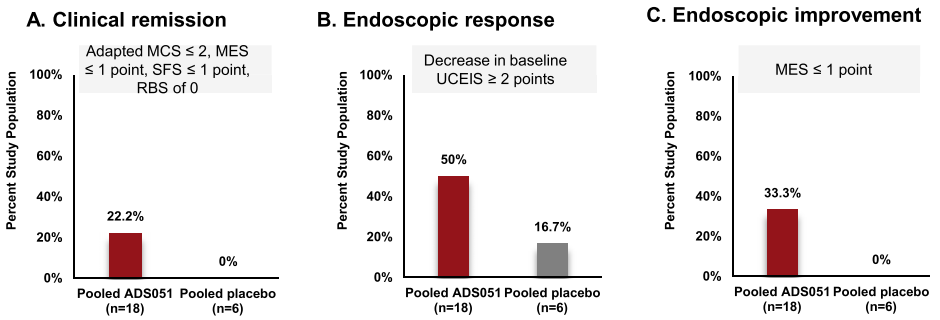
- After 28 days of treatment, ADS051:
  - ❑ was safe and well-tolerated up to 3200 mg
  - ❑ was gut restricted, with high stool concentrations and minimal systemic exposure
  - ❑ had signals of efficacy (Figures A-C)
- ADS051 has the potential to be an advance in the treatment of patients with UC

Key Results

Safety

- TEAEs were observed in 16.7% (3 of 18) in the ADS051 group and 66.7% (4 of 6) in the placebo group
- No severe AEs were observed on ADS051 vs 33% (2 of 6) on placebo

Efficacy assessments at Day 28



Clinical remission achieved in 22.2% ADS051 vs 0% placebo

Endoscopic response achieved in 50% ADS051 vs 16.7% placebo

Endoscopic improvement achieved in 33.3% ADS051 vs 0% placebo

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

Pooled ADS051 (n=18) consists of three cohorts (n=6, each), with doses 200 mg, 800 mg, or 3200 mg of ADS051 per cohort; pooled placebo (n=6) consists of three cohorts (n=2, each) of placebo

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METHODS: **This trial enrolled 24 patients with moderate-to-severe UC in 3 sequential ascending dose cohorts with 3:1 randomization to ADS051 200 mg, 800 mg, or 3,200 mg, or placebo, administered orally once daily for 28 days. Safety, tolerability, and pharmacokinetics were assessed weekly, with clinical activity end points of clinical remission, endoscopic improvement, and histologic remission evaluated at Day 28.**

RESULTS: **ADS051 was well tolerated without severe or serious adverse events. High fecal concentrations were achieved with low systemic exposure, with <1% of the daily dose of ADS051 excreted in urine. On Day 28 of the trial, clinical remission was achieved in 22.2% of the pooled ADS051 group vs 0% of the pooled placebo group. Endoscopic response was achieved in 50.0% of ADS051-dosed vs 16.7% of placebo, and endoscopic improvement was achieved in 33.3% of ADS051-dosed vs 0% of placebo.**

DISCUSSION: **Phase 1b data in patients with UC indicate a favorable safety profile for ADS051 with encouraging signals of clinical activity, supporting the advancement to a Phase 2 trial.**

KEYWORDS: ulcerative colitis; neutrophils; ADS051; gut-restricted

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D510

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INTRODUCTION

Inflammatory bowel diseases include ulcerative colitis (UC), a chronic, idiopathic, inflammatory disease that targets the colon, and Crohn's disease. Inflammation in UC is limited to the colonic mucosa, where the presentation can vary from mild erythema and friability to frank ulceration (1,2). In UC, pathophysiological mechanisms of inflammation are complex, with unclear etiology; however, genetic susceptibility, intestinal mucosal barrier function, abnormal immunoregulation, environmental factors, and microbiota are all believed to be involved (1,3). A leading hypothesis of UC pathogenesis suggests that gut inflammation results from a malfunction of the host's mucosal immunity and its interaction with enteric microflora in genetically susceptible individuals (1,3–5). The breakdown of this balance may result in the transepithelial migration of neutrophils into the colonic mucosa and the release of cytokines/chemokines and tissue-damaging agents on their activation. Interaction of activated neutrophils with other immune cells amplifies inflammation and furthers epithelial damage, ultimately leading to compromised gut barrier integrity (6,7). Consequently, the involvement of multiple factors makes it difficult to develop targeted therapies.

Biologics and novel small molecules represent modern therapies for the treatment of moderate-to-severe UC yet are also associated with safety risks and incomplete efficacy (8–18). Small molecules, including Janus kinase inhibitors such as upadacitinib, have the advantage of oral administration; however, they carry safety risks, such as serious infections, major adverse cardiovascular events, mortality, malignancy, and thrombosis, which limit their utility (9,17,18). A substantial unmet need remains for therapies that are efficacious, safe, and well tolerated. Oral agents that target the colonic mucosa with minimal systemic absorption would be advantageous, as they would be less likely to elicit general immunosuppression.

Neutrophils are the first responders to injury or infection, and their migration into the colonic lumen is a characteristic and histopathologic hallmark of active UC, directly correlated with its severity (3,19,20). Guided migration of neutrophils from the submucosa across the epithelial/mucosal barrier and into the lumen is triggered by a chemotactic gradient set up by the efflux of hepoxilin A_3 (HXA_3) through the multidrug resistance protein 2 (MRP2) transporter located on the apical surface of the epithelium (21–23). The expression of MRP2 is upregulated during acute colonic inflammation (24). Another important factor in UC includes formyl peptide receptor 1 (FPR1)-mediated activation of neutrophils (6,25). This occurs when FPR1 on the surface of neutrophils is bound by N-formyl peptides released from damaged tissue mitochondria or the microbiota in the colonic lumen. Therefore, inhibiting MRP2-mediated HXA_3 secretion into the colonic lumen and blocking neutrophil FPR1 cell surface receptor-mediated activation may reduce colonic inflammation (6,24,26). A pharmacologic agent targeting these mechanisms has the potential to induce and maintain remission in patients with UC.

ADS051, a novel, oral, believed to be gut-restricted small molecule consisting of a modified cyclosporine scaffold covalently linked to 2,000-molecular weight polyethylene glycol by an amide linker, has demonstrated the ability to block both MRP2/HXA_3-mediated and FPR1-mediated neutrophil epithelial transmigration and activation in human cell-based systems (27). Unlike other molecules from the cyclosporine class, ADS051 was designed to have a low affinity for calcineurin and, thus, a greatly reduced ability to inhibit T-cell activation. In addition, PEGylation decreases the cell permeability of ADS051, resulting in limited systemic exposure, which may, in part, mitigate systemic immunosuppression (27). The current trial follows a Phase 1 single ascending dose trial that evaluated the safety and pharmacokinetics (PK) of ADS051 in healthy participants (28). Here, we present the results of a Phase 1b multiple ascending dose (MAD) clinical trial of ADS051 that evaluated the safety, efficacy, and PK of ADS051 in patients with moderately to severely active UC.

METHODS

Clinical trial design

This first-in-patient trial of ADS051 was a randomized, double-blind, placebo-controlled MAD cohort design that enrolled patients with moderately to severely active UC. Patients with prior exposure to a biologic or advanced therapies were limited to 30% of the trial population. Patients who failed 2 or more

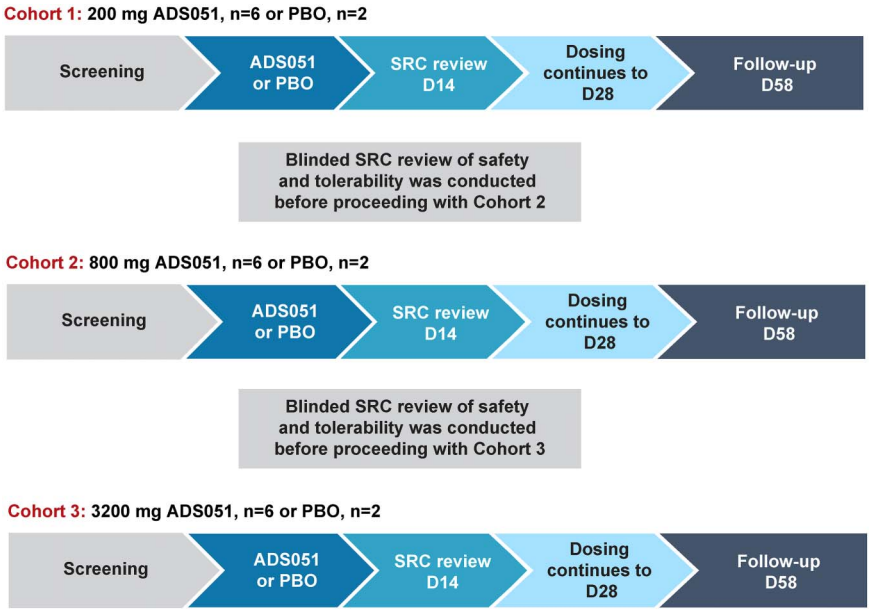

Figure 1. Phase 1b clinical trial design. A total of 8 participants per cohort were randomized to receive either ADS051 (n = 6) or placebo (n = 2) in a 3:1 randomization scheme. The sample sizes were selected empirically based on having a reasonable number of participants to assess safety and tolerability. The doses were selected based on safety, tolerability, and PK data from a single-dose trial of ADS051 (28). SRC review of safety and tolerability on Day 14 for each cohort allowed the subsequent cohorts to proceed. Patients from the lower cohort did not escalate to the next cohort. D, day; PBO, placebo; PK, pharmacokinetic; SRC, safety review committee.

advanced therapies (e.g., biologic and Janus kinase inhibitors, 2 biologics in the same class, or 2 biologics from different classes) were limited to 20% of the population. Participants were randomized 3:1 to oral, once-daily ADS051 (200 mg, 800 mg, or 3,200 mg) or placebo in sequential ascending dose cohorts (details of the randomization process are provided in the Supplementary Methods section, http://links.lww.com/AJG/D510). Participants in each cohort received ADS051 or placebo for 28 days. The follow-up period after the last dose of the study drug was 30 days. Each cohort consisted of 2 participants receiving placebo and 6 participants receiving ADS051. All participants were allowed to remain on their standard-of-care medications, including stable regimens of aminosalicylates, immunomodulators, or corticosteroids (≤20 mg prednisone or equivalent). Escalation to each higher dose was based on the safety and tolerability assessment of the previous cohort (Figure 1) conducted by a blinded safety review committee. Patients from the lower cohort did not escalate to the next cohort.

Inclusion criteria. Participants, aged 18–75 years, had a confirmed diagnosis of UC of at least 3 months of disease duration before screening (diagnosis established by endoscopy and histology) and had moderately to severely active UC, defined as a complete Mayo Clinic score (4-component composite score adapted as recommended (29) ≥6 points with a rectal bleeding subscore (RBS) ≥1 point, a stool frequency (SF) subscore ≥1 point, and a Mayo endoscopic subscore (MES) ≥2 points. In concomitant medications, the participants could have been treated with stable doses (>4 weeks) of the following UC treatments before randomization: 6-mercaptopurine, azathioprine, sulfasalazine, or 5-aminosalicylic acid. Participants could remain on oral corticosteroids only if the dose was prednisone ≤20 mg/d (budesonide ≤9 mg/d) or equivalent and if they had maintained stable doses of these oral corticosteroids for at least 2 weeks. Finally, patients with UC that involved one-third or more of the colon or whose disease had been present for ≥8 years were eligible for inclusion if they had had a colonoscopy within the past year to exclude adenomas, dysplasia, or colon cancer.

Table 1. Number of folds above efficacious threshold from simulated concentrations of ADS051 in different GI segments

	GI segment			
ADS051 dose (mg/d)	Rectum	Ascending colon	Transverse colon[a]	Descending and sigmoid colon
200	70	600	20 to 600	1,200
800	280	2,400	80 to 2,400	4,800
3,200	1,120	9,600	320 to 9,600	19,300

The reference value for efficacy is 1 μmol/L.
GI, gastrointestinal.
[a]The fluctuation within 24 hours was large, and therefore, the lowest and highest fold above efficacious threshold is presented.

Exclusion criteria are presented in the Supplementary Information section (http://links.lww.com/AJG/D510).

Investigational medicinal product and mode of administration

The drug product for the trial consisted of ADS051 200 mg in size 0 Vcaps Plus capsules (Lonza, Basel, Switzerland) for oral dosing. The matching placebo (size, color, and odor) consisted of only an inactive excipient encapsulated in the same Vcaps Plus capsules.

Rationale for dose selection for the trial

The inhibitory concentration of ADS051 was determined to be 1 μM based on *in vitro* neutrophil transepithelial migration studies (27). When translating the *in vitro* half-maximal inhibitory concentration to select doses for studying activity in patients, other pathologic factors associated with UC were taken into consideration, such as SF, the variability of mucosal inflammation, and the presence of mucus and other eluents, that could potentially interfere with the availability of ADS051 to MRP2 at the apical surface of the colonic epithelium. The dose selection for the study (200 mg, 800 mg, and 3,200 mg per day) was based on PK, safety, and tolerability assessments, as well as evaluating biomarkers measured in the single ascending dose study (28). An exploratory Physiologically Based Pharmacokinetic (PBPK) model was developed to test the possible range of doses and concentrations in different segments of the large intestine to study MAD regimens predicted to produce local (in the large intestine), pharmacologically active concentrations. The doses of ADS051 evaluated were predicted to provide between 20-fold and 19,300-fold higher concentrations than the target efficacious ADS051 concentration of 1 μmol/L, depending on the gastrointestinal (GI) segment (Table 1). The effective threshold concentration of ADS051 was determined to be 1 μmol/L based on *ex vivo* experiments.

The models were developed and processed in an R package and MoBi. Simulations were performed using a distribution of GI transit times and GI physiological differences between individuals. This variability was reflected as the range of observations in concentrations of moieties simulated for each of the GI segments. There are other sources of variability that may not have been accounted for in this PBPK model and simulations due to lack of data, such as permeability experiments, protein binding data, and transporter data. Therefore, the range of data may be an underestimation of the range expected in patients, and a future Phase 2 dose-finding study will be performed.

End points

Primary end points. *Safety and tolerability*: Safety parameters included reported adverse events (AEs), serious adverse events, clinical laboratory test results (hematology, serum chemistry, lipid panel, coagulation, and urinalysis), vital sign measurements (heart rate, blood pressure, respiratory rate, and temperature), electrocardiogram results, and abnormal physical examination findings.

Secondary end points. *Efficacy*: Efficacy was assessed at trial Day 28 by clinical remission (defined as SF ≤1, RBS = 0, and MES ≤1), endoscopic improvement (defined as MES ≤1), change in modified Mayo Score (mMS; 3-component without the Physician Global Assessment), MES, SF, RBS, Ulcerative Colitis Endoscopic Index of Severity (UCEIS), UC-100, histologic assessments, Inflammatory Bowel Disease Questionnaire-32, and biomarkers (fecal calprotectin [FCP], C-reactive protein, and colonic tissue myeloperoxidase [MPO]). To reduce the potential for bias and/or variability in the assessment of endoscopic videos, a blinded independent central review of all endoscopic videos was performed. Similarly, a trained, blinded histopathologist central reader scored histopathology slides using the Robarts Histopathology Index, Geboes score, and Nancy Index.

Pharmacokinetics. To determine ADS051 concentration, PK collection took place at the following time points:

Stool: Days 1 (predose and 24 hours postdose), 7 and 14 (24 hours postdose), 21 and 28 (72 hours postdose), and 58 (follow-up); blood: Days 1 (predose), 7 and 14 (predose and 8 and 12 hours postdose), 21 and 28 (predose and 8 and 12 hours postdose); urine: Days 1 (predose), 14 (24 hours postdose), and 28 (72 hours postdose); colonic biopsy: Day 28. PK samples were subsequently analyzed by a central laboratory.

All AEs were coded using the Medical Dictionary for Regulatory Activities version 25.0, as described in the Supplementary Information section (http://links.lww.com/AJG/D510).

Clinical bioanalytical method

Ultrahigh-performance liquid chromatography-tandem mass spectrometry was used to assay ADS051 in whole blood, urine, stool, and colonic tissue after solid-phase extraction. The lower limit of quantification (LLOQ) of ADS051 for each assay was as follows: whole blood LLOQ = 2.5 ng/mL, urine LLOQ = 1 ng/mL, stool LLOQ = 4 ng/mL, and colonic tissue LLOQ = 4 ng/mL. All assays were validated, and PK samples were tested according to US Food and Drug Administration guidelines and Good Laboratory Practice procedures.

Statistical analyses

No formal statistical testing was performed on the safety variables. AEs were classified according to Medical Dictionary for Regulatory Activities regarding system organ class (SOC) and preferred term. The treatment-emergent AEs (TEAEs) were summarized by the ADS051 dose group, and placebo participants were pooled across cohorts. The incidence of TEAEs, the relationship to the study drug, and the severity were presented by SOC and preferred term. Descriptive statistics were used to summarize the clinical laboratory test results, vital signs, and electrocardiogram parameters.

Efficacy analyses were presented using frequency and percentage for the categorical end points and mean (SD) for the continuous end points. ADS051 concentration was measured in blood, stool, urine, and colonic tissue. Mean concentration-time profiles were plotted using nominal PK sampling times. Descriptive statistics (median, interquartile range, and N) of all blood PK parameters were calculated for each ADS051 dose level.

Ethics declarations

This trial was conducted in compliance with current International Council for Harmonisation Good Clinical Practice guidelines relating to institutional review boards or independent ethics committees and per the protocol and consensus ethical principles derived from the Declaration of Helsinki. The protocol, protocol amendments, informed consent form, investigator's brochure, and other relevant documents (e.g., advertisements) were submitted to and were reviewed and approved by an institutional review board/independent ethics committee at each trial site before initiating the trial.

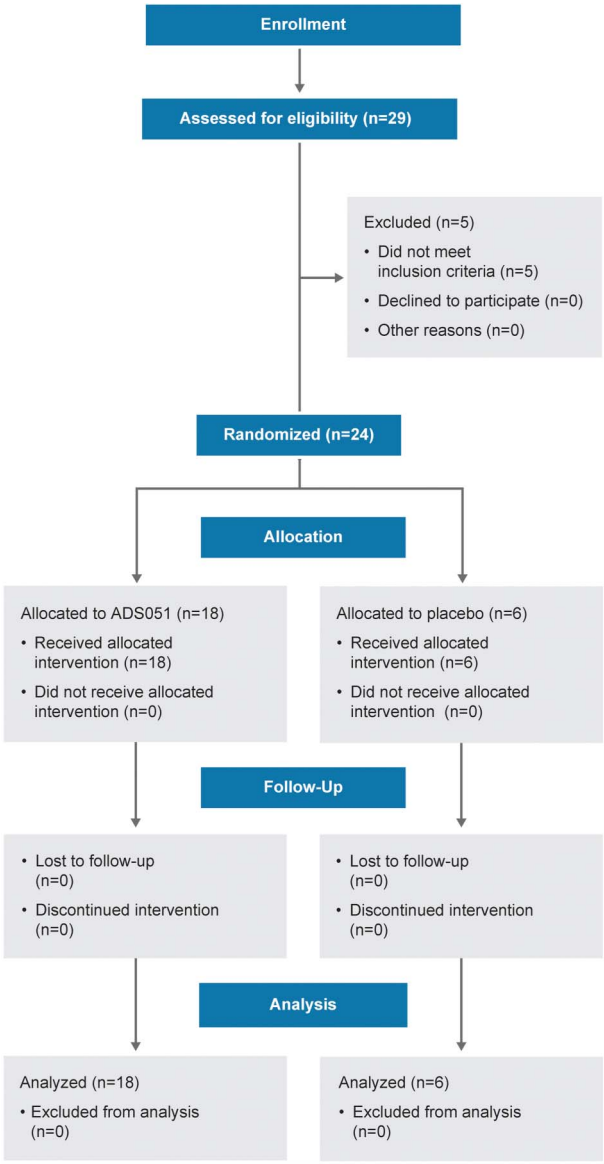

Figure 2. Consolidated Standards of Reporting Trials participant flow diagram.

Trial registration

This trial was registered on ClinicalTrials.gov as national clinical trial NCT05084261.

RESULTS

Trial participants

A total of 29 participants were screened, with 24 participants randomized at 5 trial sites across Moldova (n = 12), Georgia (n = 6), Poland (n = 5), and the United States (n = 1). All 24 enrolled participants (8 per cohort) completed the trial (Figure 2). Of the enrolled participants, most were male (54.2%), White (95.8%), and nonsmokers (91.7%), with 8.3% identified as former smokers (Table 2). Enrolled participants had a mean age of 47.2 years (range, 23–68 years), a mean weight of 76.8 kg (range, 49–116 kg), and a mean body mass index of 26.3 kg/m^2 (range, 19–33 kg/m^2; Table 2). Demographic and baseline disease characteristics were similar across treatment arms (Table 2) except for the ADS051 3,200 mg dose group, which differed from the other groups as follows: 50% of participants had pancolitis, which was not present in the ADS051 200 mg and 800 mg dose groups; disease duration was shorter (7.3 years, compared with 9.6 years and 8.5 years for the ADS051 200 mg and 800 mg dose groups, respectively); and 83.3% of participants had severe UC disease based on MES, compared with 50.0% and 33.3% in the ADS051 200 mg and 800 mg dose groups, respectively, and 16.7% in the pooled placebo group (Table 2 and Supplementary Figure 1, http://links.lww.com/AJG/D510). Other differences between groups included prior exposure to biologics. No patients in the placebo or ADS051 200 mg groups had any prior biologic exposure, while 33.3% of the participants in the 800 mg group and 16.7% of those in the 3,200 mg group had received biologic therapy in the past (Table 2). At baseline, FCP was the highest in the placebo group and the lowest in the 800 mg dose group (Table 2). Both MES and adapted Mayo Clinic score (comparable with the mMS) were lowest in the placebo group at baseline (Table 2).

Safety

Overall, ADS051 was safe and well tolerated, with no serious adverse events reported. The percentage of participants reporting at least 1 TEAE was 16.7% (3 of 18) in the ADS051 group and 66.7% (4 of 6) in the placebo group. Specifically, 1 participant (16.7%) in the ADS051 200 mg dose group, 2 participants (33.3%) in the ADS051 3,200 mg dose group, and 4 participants (66.7%) in the pooled placebo group experienced a TEAE. No participant in the ADS051 800 mg dose group experienced a TEAE (Table 3). No participant in the ADS051 groups had a grade 3 (severe) AE, compared with 33% (2 of 6) in the placebo group. In addition, 1 participant (16.7%) in the placebo group had worsening of underlying UC. The blinded safety review committee had no concerns regarding the study drug and recommended dose escalation to proceed per protocol (Table 3). ADS051 was well tolerated when dosed once daily up to 3,200 mg for 28 days, and all participants completed 28 days of treatment as specified.

The most frequently occurring TEAEs were in the SOC blood and lymphatic system disorders (n = 2; 1 participant [16.7%] in the ADS051 3,200 mg dose group experienced anemia, and 1 participant [16.7%] in the placebo group experienced 3 AEs: decreased lymphocyte count, decreased neutrophil count, and decreased white blood cell count), gastrointestinal disorders (n = 2; 1 participant [16.7%] each in the ADS051 3,200 mg dose group and the placebo group), and nervous system disorders (n = 2; 1 participant [16.7%] each in the ADS051 200 mg and the ADS051 3,200 mg dose groups; Table 3). TEAEs were reported as related to the study drug by the investigator in 3 participants overall (12.5%), with 2 (33.3%) in the ADS051 3,200 mg dose group and 1 (16.7%) in the pooled placebo group (Table 3). The related TEAEs in the ADS051 3,200 mg dose group were 1 event of grade 1 (mild) nausea on Day 2 of treatment (duration of 5 days) and 1 event of grade 1 headache on Day 1 of treatment (duration of 29 days). The related TEAE in the pooled placebo group was 1 event of grade 1 elevated liver function on Day 8 of treatment (duration of 50 days). All related events resolved, and the participants recovered. Two participants receiving placebo (33.3%) experienced a grade 3 AE, worsening of UC, and arthralgia (Table 3); these events were deemed unrelated to the study drug. No TEAEs leading to study drug discontinuation or trial withdrawal were reported.

Table 2. Demographics and baseline characteristics

	ADS051 200 mg n = 6	ADS051 800 mg n = 6	ADS051 3,200 mg n = 6	Pooled placebo n = 6	Total N = 24
Sex, %					
Female	33.3	33.3	66.7	50	45.80
Male	66.7	66.7	33.3	50	54.2
Age, yr					
Mean (SD)	55.0 (10.6)	51 (7.3)	42 (10.5)	40.7 (14.5)	47.2 (12.0)
Median (min, max)	56.5 (38, 68)	49.5 (41, 60)	46.5 (24, 52)	43 (23, 60)	48 (23, 68)
Race, %					
Not reported	0	16.7	0	0	4.2
White	100	83.3	100	100	95.8
American Indian or Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Black or African American	0	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0	0
Unknown	0	0	0	0	0
Ethnicity, %					
Hispanic/Latino	0	16.7	0	0	4.2
Not Hispanic/Latino	100	83.3	100	100	95.8
Not reported	0	0	0	0	0
Unknown	0	0	0	0	0
Smoking status, %					
Former	0	16.7	0	16.7	0.3
Never	100	83.3	100	83.3	91.7
Current	0	0	0	0	0
Weight at baseline, kg					
Mean (SD)	79.8 (11.8)	80.3 (15.4)	85 (21.7)	62.2 (15.6)	76.8 (17.8)
Median (min, max)	77.5 (65, 95)	77 (63, 108)	84.5 (49, 116)	55.0 (50, 91)	77 (49, 116)
Height at baseline, cm					
Mean (SD)	168.5 (5.4)	174.8 (5.5)	170.8 (12.8)	167.3 (8.6)	170.4 (8.6)
Median (min, max)	170 (162,175)	173 (170, 183)	169 (158, 192)	169 (152, 175)	170 (152, 192)
BMI at baseline, kg/m^2					
Mean (SD)	28.1 (3.3)	26.2 (4.4)	28.7 (4.6)	22.2 (5.0)	26.3 (4.8)
Median (min, max)	27.8 (25, 32)	24.9 (21, 23)	30.3 (20, 32)	20.7 (19, 32)	25.3 (19, 33)
Duration of UC, yr					
Mean (SD)	9.6 (8.5)	8.5 (5.9)	7.3 (5.2)	5.52 (5.35)	7.7 (6.2)
Median (min, max)	7.8 (1, 26)	5.5 (4, 18)	5.5 (4, 18)	3.74 (0.5, 12.3)	6.0 (0.5, 26)
Extent of UC disease, %					
Left-sided colitis (up to splenic flexure)	66.7	83.3	50	50	62.5
Pancolitis (entire colon)	0	0	50	16.7	16.7
Sigmoiditis	33.3	16.7	0	33.3	20.8
Isolated proctitis	0	0	0	0	0
Disease severity (MES)[a], n (%)					
Moderate disease	3 (50.0%)	4 (66.7%)	1 (16.7%)	5 (83.3%)	13 (54.2%)

Table 2. (*continued*)

	ADS051 200 mg n = 6	ADS051 800 mg n = 6	ADS051 3,200 mg n = 6	Pooled placebo n = 6	Total N = 24
Severe disease	3 (50.0%)	2 (33.3%)	5 (83.3%)	1 (16.7%)	11 (45.8%)
Baseline aMCS					
Mean (SD)	5.7 (1.6)	6.3 (1.4)	6.7 (0.8)	5.5 (0.8)	6.0 (1.2)
Baseline FCP					
Median (min, max)	1,714.0 (66, 6,001)	254.5 (42, 6,001)	1,574.5 (114, 3,949)	2,157.0 (649, 5,988)	1,242.5 (42, 6,001)
Baseline MES					
Mean (SD)	2.5 (0.5)	2.3 (0.5)	2.8 (0.4)	2.2 (0.4)	2.5 (0.5)
Prior exposure to biologic or JAKi, n (%)					
No	6 (100.0%)	4 (66.7%)	5 (83.3%)	6 (100.0%)	21 (87.5%)
Yes	0	2 (33.3%)	1 (16.7%)	0	3 (12.5%)

aMCS, adapted Mayo Clinic score (comparable with the modified Mayo Score [mMS]); BMI, body max index; FCP, fecal calprotectin; JAKi, Janus kinase inhibitors; MES, Mayo endoscopic subscore; UC, ulcerative colitis.
[a]Moderate disease was defined as an MES of 2, and severe disease was defined as an MES of 3.

Pharmacokinetic analyses

ADS051 was measurable in the stool for all doses tested (Figure 3). Blood levels of ADS051 were either undetectable or low (LLOQ = 2.5 ng/mL; Figure 3). In the 200 mg dose group, only 1 blood sample was positive for ADS051 (3.4 ng/mL). Blood levels of ADS051 were detected in participants from both the ADS051 800 mg (2.6–8.8 ng/mL) and the ADS051 3,200 mg (2.7–155.0 ng/mL) dose groups and seemed to be dose dependent. ADS051 was also detected in 24-hour urine collections, with the fraction of the dose excreted in urine being <1% of the administered dose and appearing to be dose dependent (Figure 3). This percentage is consistent with our findings in the single ascending dose trial (28). There were highly variable levels of ADS051 in colonic tissue samples, with a lower presence in the ADS051 800 mg dose group than in the ADS051 200 mg and 3,200 mg dose groups. Creatinine levels were monitored to measure the impact on renal function (Supplementary Table 1, http://links.lww.com/AJG/D510). There was no adverse effect on baseline creatinine values in the

Table 3. Treatment-emergent adverse events

	Cohort 1 ADS051 n = 6	Cohort 2 ADS051 n = 6	Cohort 3 ADS051 n = 6	Placebo n = 6	Total N = 24
Subjects with ≥1 treatment-emergent adverse event	1 (16.7%)	0%	2 (33.3%)	4 (66.7%)	7 (29.2%)
Blood and lymphatic system disorders	0%	0%	1 (16.7%)	1 (16.7%)	2 (8.3%)
Anemia	0%	0%	1 (16.7%)	0%	1 (4.2%)
B-lymphocyte abnormalities	0%	0%	0%	1 (16.7%)	1 (4.2%)
Neutrophil function disorder	0%	0%	0%	1 (16.7%)	1 (4.2%)
White blood cell disorder	0%	0%	0%	1 (16.7%)	1 (4.2%)
Gastrointestinal disorders	0%	0%	1 (16.7%)	1 (16.7%)	2 (8.3%)
Colitis ulcerative	0%	0%	0%	1 (16.7%)	1 (4.2%)
Nausea	0%	0%	1 (16.7%)	0%	1 (4.2%)
Nervous system disorders	1 (16.7%)	0%	1 (16.7%)	0%	2 (8.3%)
Headache	1 (16.7%)	0%	1 (16.7%)	0%	2 (8.3%)
Investigations	0%	0%	0%	1 (16.7%)	1 (4.2%)
Liver function test increased	0%	0%	0%	1 (16.7%)	1 (4.2%)
Musculoskeletal and connective tissue disorders	0%	0%	0%	1 (16.7%)	1 (4.2%)
Arthralgia	0%	0%	0%	1 (16.7%)	1 (4.2%)

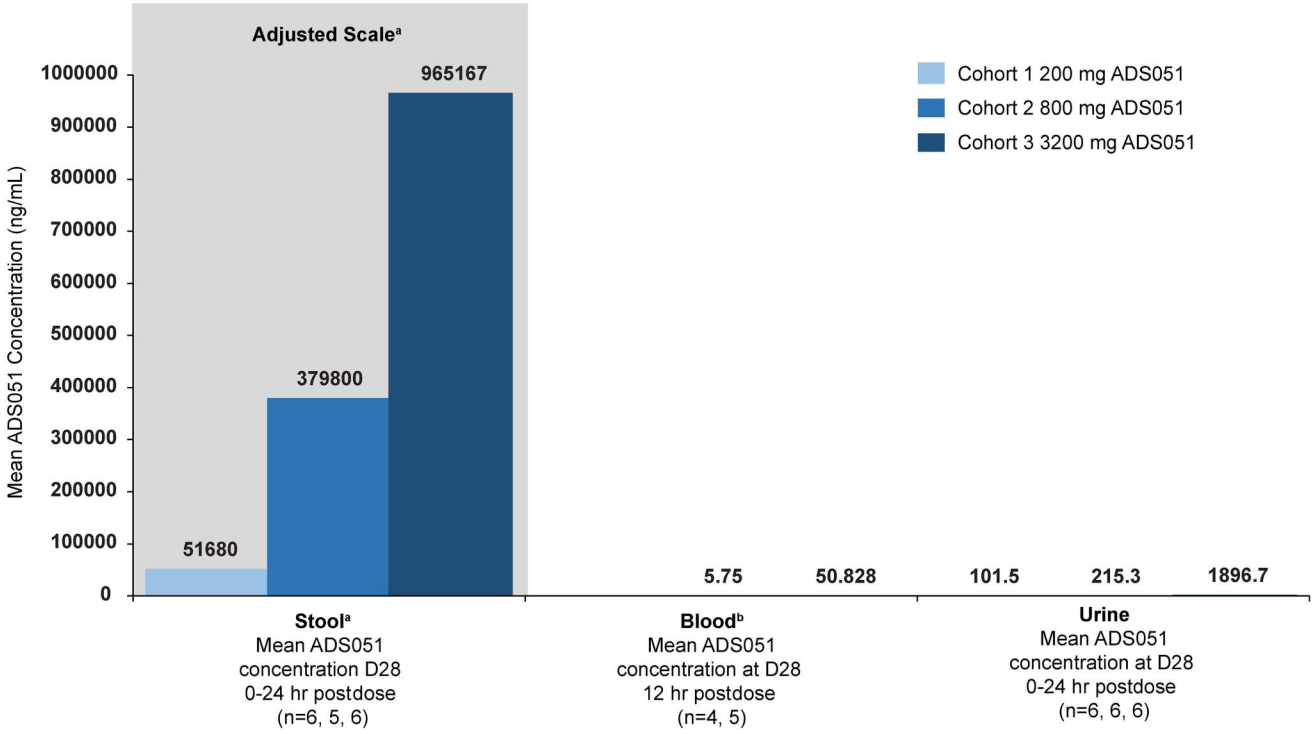

Figure 3. Pharmacokinetic analyses of stool, blood, and urine. D, day; IC50, half-maximal inhibitory concentration; LLOQ, lower limit of quantification. [a]Stool concentrations up to 8,000-fold above the target IC50 (3.3 μg/mL or 1 μM). [b]Only 1 positive sample. All other samples < LLOQ (LLOQ = 2.5 ng/mL).

ADS051 groups, as indicated by the relatively low change in creatinine measurements compared with the placebo group, which showed a greater change (increase) in creatinine at the end of treatment (Supplementary Table 1, http://links.lww.com/AJG/D510). Specifically, the mean change at the end of treatment was 7.8 for the placebo group vs −1.9, 3.2, and −1.4 for the ADS051 200 mg, 800 mg, and 3,200 mg groups, respectively (Supplementary Table 1, http://links.lww.com/AJG/D510). In addition, serum leukocyte and neutrophil levels were measured to check for signs of systemic immune suppression (Supplementary Tables 2 and 3, respectively, http://links.lww.com/AJG/D510). Similar to creatinine levels, leukocyte levels changed more, although in a reverse pattern (decrease) in the placebo group, with a mean change of −1.4 compared with −0.5, 0.8, and 0.3 for the ADS051 200 mg, 800 mg, and 3,200 mg groups, respectively (Supplementary Table 2, http://links.lww.com/AJG/D510). Similarly, neutrophil levels displayed a similar pattern to leukocyte levels in their decrease (Supplementary Table 3, http://links.lww.com/AJG/D510). Although the mean change at the end of treatment for the placebo group was −2.5, the change fluctuated at −1.3, 6.4, and 1.8 for the ADS051 200 mg, 800 mg, and 3,200 mg groups, respectively (Supplementary Table 3, http://links.lww.com/AJG/D510).

Efficacy

ADS051 clinical activity was evaluated using multiple efficacy measures on Day 28 for pooled ADS051 and pooled placebo groups. Clinical remission (SF ≤1, RBS = 0, and MES ≤1) was achieved in 22.2% (4 of 18) of ADS051 participants vs 0% for placebo (Figure 4a); endoscopic response (a decrease in UCEIS ≥2 points) was achieved in 50.0% (9 of 18) of ADS051 participants vs 16.7% (1 of 6) for placebo (Figure 4b); and endoscopic improvement (MES ≤1) was achieved in 33.3% (6 of 18) of ADS051 participants vs 0% for placebo (Figure 4c). In addition, of the 4 participants on ADS051 with clinical remission, 3 demonstrated histologic remission (Geboes score ≤2B.0 or Nancy Index = 0).

Compared with baseline, on Day 28, improvements in mMS were observed in the ADS051 200 mg and 800 mg dose groups; these groups included participants with less severe baseline MES at screening than the ADS051 3,200 mg dose group. The mean percentage decrease in mMS was 49.9% and 35.8% for the ADS051 200 mg and 800 mg dose groups, respectively, compared with 27.8% for placebo (Table 4). Compared with baseline, on Day 28, improvement in RBS compared with placebo was observed only in the ADS051 200 mg dose group, in which the mean percentage decrease in RBS was 91.7% compared with 66.7% for placebo (Supplementary Figure 2, http://links.lww.com/AJG/D510). However, a trend in reduction from baseline was observed in the 800 mg and 3,200 mg groups. Of note, the baseline RBS scores were higher in these dose groups than in the placebo and 200 mg dose groups.

At Day 28 (end of treatment), participants receiving ADS051 200 mg had the greatest reduction in FCP, with a mean change from baseline of −544.2 mg/kg (Supplementary Figure 3, http://links.lww.com/AJG/D510), while participants receiving ADS051 800 mg experienced a mean reduction of −310.0 mg/kg. In comparison, participants in the pooled placebo group had a mean increase in FCP of 1,587.2 mg/kg. For participants in the ADS051 3,200 mg dose group, there was a slight increase in the mean concentration at Day 28 compared with baseline (396.7 mg/kg); however, that increase was lower than the increase in mean concentration seen in the pooled placebo group.

Immunohistochemistry of colonic tissue biopsies was performed to evaluate the quantitative change of MPO from baseline to Day 28,

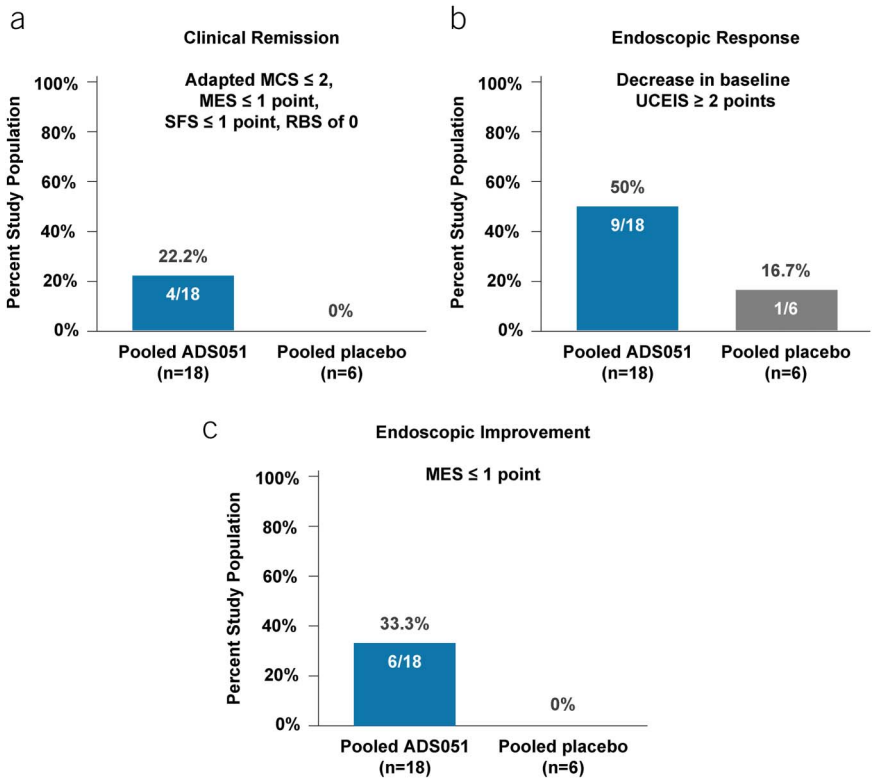

Figure 4. Efficacy assessments. (**a**) Clinical remission. (**b**) Endoscopic response. (**c**) Endoscopic improvement. As part of efficacy assessments for the MAD trial, clinical remission, endoscopic response, and endoscopic improvement were measured for pooled ADS051 and pooled placebo per the criteria shown. MAD, multiple ascending dose; MCS, Mayo Clinic score; MES, Mayo endoscopic subscore; RBS, Mayo rectal bleeding subscore; SFS, Mayo stool frequency subscore; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

based on the MPO-positive cells within the epithelium and lamina propria (Supplementary Figure 4, http://links.lww.com/AJG/D510). Analysis of the data revealed a high degree of variability in the expression of MPO at baseline; nevertheless, despite this variability, participants treated with ADS051 200 mg consistently exhibited a trend in the reduction in the density of MPO-positive cells in the epithelium when compared with the placebo group. This is evident from lower median values of the change from baseline for the density of MPO-positive cells in the epithelium (Supplementary Figure 4a, http://links.lww.com/AJG/D510), but not in the lamina propria (Supplementary Figure 4b, http://links.lww.com/AJG/D510). Specifically, percentage change values from baseline in the density of MPO-positive cells in the epithelium were −79.49 for ADS051 200 mg vs −37.27 for placebo, while percentage change values from baseline in the density of MPO-positive cells in the lamina propria were −60.11 for ADS051 200 mg vs −66.42 for placebo. By contrast, percentage change values from baseline in the density of MPO-positive cells in both the epithelium and the lamina propria were increased for both the ADS051 800 mg and the 3,200 mg dose groups compared with placebo (Supplementary Figure 4, http://links.lww.com/AJG/D510).

Dose-guiding PBPK model

Simulations showed that there were differences in the concentration of ADS051 in various segments of the large intestine, which was expected due to diverse transit times and volumes (Table 1). Generally, steady-state concentrations were reached on Day 3 after the start of administration. The ascending colon seemed to have the largest fluctuation in concentration during the 24-hour dosing interval.

Table 4. Change from baseline in mMS

	ADS051 200 mg n = 6	ADS051 800 mg n = 6	ADS051 3,200 mg n = 6	Pooled placebo n = 6
mMS (mean) at baseline	5.7	6.3	6.7	5.5
mMS (mean) at Day 28	3.0	4.2	5.2	4.0
Percentage change (mean) in mMS	−49.9	−35.8	−17.7	−27.8

mMS, modified Mayo Score.

DISCUSSION

In this first-in-patient Phase 1b MAD trial, ADS051 was safe and generally well tolerated in patients with moderate-to-severe UC when administered at doses ranging from 200 mg to 3,200 mg/d for 28 days. In addition, high levels of ADS051 were measured in the stool, <1% of the drug was recovered in the urine, and, depending on the dose, serum levels were low to nondetectable. These findings show that ADS051 is predominantly gut restricted when dosed orally in patients with UC. Colonic tissue levels were variable and did not appear to be associated with dose cohort or severity, albeit the study size was small. As an example, the lowest and highest concentrations of ADS051 in colonic tissue were observed in the highest cohort (with the greatest severity). We intend to further examine colonic tissue, stool, and blood concentrations and the potential association with the safety and activity of ADS051 in the Phase 2 study. The clinical activity data indicated that participants with moderate-to-severe UC receiving ADS051 for 28 days had a favorable outcome compared with the pooled placebo group across key efficacy end points, including clinical remission, endoscopic response, and endoscopic improvement. ADS051 also demonstrated a reduction in FCP, although no statistical analyses were performed. Of note, efficacy outcomes showed signals of clinical activity in favor of the ADS051 200 mg and 800 mg doses compared with placebo. The 3,200 mg dose seemed to show a favorable trend regarding change in FCP compared with placebo, but did not result in clinical remission or endoscopic improvement after 28 days of treatment. One limitation of this study was the lack of disease severity randomization in this small number of participants; hence, there were more patients with a greater severity of UC in the third cohort or highest dose group (3,200 mg), while in the first and second cohort disease severity was evenly distributed.

Participants in the 200 mg and 800 mg dose groups experienced clinical remission and/or endoscopic improvement at 28 days of treatment, whereas those in the 3,200 mg dose group demonstrated only improvement in clinical response as determined by UCEIS criteria. One possibility is that the patient population was more severe in the 3,200 mg dose group compared with the other groups, where 83.3% of patients had severe disease in the 3,200 mg dose group. (Table 2 and Supplementary Figure 1, http://links.lww.com/AJG/D510). Therefore, baseline severity of disease differences in patient populations represents a potential limitation of this study.

An additional limitation of the study is its short duration. Numerous studies have demonstrated that a longer course of therapy benefits patient response, specifically a patient's ability to achieve an endoscopic improvement or clinical remission; variations in time to clinical response are characteristic of many UC treatments (14). For example, current Selecting Therapeutic Targets in Inflammatory Bowel Disease guidelines estimate a mean treatment duration of ≥8 weeks is required to achieve clinical remission in moderate-to-severe UC with nonsteroidal therapy (30).

Although 2 participants in the placebo group reported clinical worsening of the disease, no participants in the ADS051 group experienced clinical worsening of UC.

In conclusion, this study shows that treatment with ADS051 is not only safe and well tolerated by patients with moderate-to-severe UC but also ADS051 is associated with improved outcome in as short as 28 days of treatment. Larger ADS051 clinical trials with prolonged and typical duration of treatment with balanced patient baseline characteristics are warranted to confirm these results.

In this trial, designed to evaluate safety and tolerability of ADS051 over a 28-day treatment period, that length of exposure to the drug in patients with disease may not have been sufficient to fully evaluate clinical remission and endoscopic improvement in participants with UC. This factor, along with the fact that 25% of patients in the second and third cohort dose groups had prior biologic exposure, could have contributed to the modest, yet promising clinical response.

The development of ADS051, a novel, oral, gut-restricted small molecule modulator of neutrophil trafficking and activation without *in vitro* suppression of T-cell activation, is based on structural modifications to the cyclosporine scaffold. ADS051 is designed to retain the ability to inhibit both neutrophil pathways of interest, MRP2 and FPR1. Modifications of linker attachment to this small molecule drug treatment were also undertaken to eliminate the T-cell suppressive activity of cyclosporine (27). In addition, the molecule was covalently attached through the linker to a 2,000-molecular weight polyethylene glycol to achieve the desired property of remaining in the colonic lumen to enable targeted local activity at the site of inflammation on the gut mucosa where the MRP2 receptor is overly expressed (27). Gut-restricted ADS051 was predicted to lack systemic immunosuppressive activity (27). This Phase 1b trial in patients with moderate-to-severe UC provides evidence for the gut-restricted property of ADS051 with a good safety and tolerability profile when administered using a once-daily dose range of 200 mg–3,200 mg for up to 28 days. There was no clinical evidence of adverse immunosuppressive activity, as indicated by a lack of systemic or gastrointestinal infections during the 28-day dosing period of ADS051 or during the 30-day period after the last dose of the study drug. Nevertheless, future studies are needed to confirm the gut-restricted property of ADS051 by several means, including measuring regional tissue concentrations of the drug and monitoring for increased risk of infection. The mechanism of action of ADS051 is to inhibit neutrophil transmigration into the colonic epithelial barrier via inhibition of epithelial MRP2. In addition, *in vitro* neutrophil activation has been shown to be influenced by ADS051 through an inhibitory interaction for the FPR1 pathway, where N-formyl peptides are blocked by ADS051 exposure (27). Because neutrophil epithelial transmigration in response to colonic inflammation is a critical factor in the pathogenesis and relapsing/remitting clinical course of UC (3), continued clinical development of ADS051 in patients with UC will be beneficial and is supported by both preclinical studies and the clinical studies reported herein and in the related report (27,28).

In conclusion, ADS051 is an investigational, novel, oral, gut-restricted small molecule targeting neutrophil trafficking and activation through the MRP2 and FPR1 pathways. Phase 1b data from patients with moderate-to-severe UC indicate favorable safety and tolerability profiles, with encouraging signals of clinical activity that support the continued clinical development of ADS051 into Phase 2.

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CONFLICTS OF INTEREST

Guarantor of the article: Jessica R. Allegretti, MD, MPH, FACG.

Specific author contributions: Planning and/or conducting the trial: Adiso coauthors, trial investigators, P.G. Collecting and/or interpreting the data: P.G., Adiso coauthors. Drafting the manuscript: All authors. Approval of final draft: All authors have approved the final version of this manuscript.

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Potential competing interests: J.R.A. is a consultant for Janssen, Pfizer, AbbVie, Finch Therapeutics, Seres Therapeutics, Ferring, Merck, Bristol Myers Squibb, and Adiso Therapeutics, Inc; is a speaker for Bristol Myers Squibb, AbbVie, and Janssen; and receives research support from Pfizer, Janssen, and Merck. A.S.C. is a consultant for Janssen, AbbVie, Aegirbio, Spherix, Artizan, Food Is Good, Clario, Pfizer, Fresenius Kabi, Fzata, Bristol Myers Squibb, Procise, Prometheus, Samsung, Adiso Therapeutics, Inc, and Lilly. P.S.D. is a consultant for AbbVie, Abivax, Bristol Myers Squibb, GSK, Janssen, Lilly, Pfizer, Takeda, Roivant, and Adiso Therapeutics, Inc; has received grant support from Bristol Myers Squibb, Janssen, Pfizer, and Takeda; and has licensing royalties from Precidiag. ACS is a consultant for ClearB Therapeutics, Surrozen, Adiso Therapeutics, Inc, and Astria Therapeutics. R.F. has ownership of shares in Adiso Therapeutics, Inc, was a paid employee of Bacainn Therapeutics, was a board member of Bacainn Therapeutics, and has co-inventorship of Adiso's patent applications. C.K.M. was an employee of Adiso Therapeutics, Inc, and is an inventor of patents owned by Adiso Therapeutics, Inc. P.G. is a consultant to Adiso Therapeutics, Inc. R.G. was consultant chief medical officer for Adiso Therapeutics, Inc, during this trial. J.C.R., L.C., B.D., B.W.M., and M.Q. are/were employees of Adiso Therapeutics, Inc, at the time of this trial. R.T., T.T., and B.W.S. were principal investigators for this trial.

Study Highlights

WHAT IS KNOWN

- ✓ Ulcerative colitis (UC) is an inflammatory bowel disease that significantly affects patients' quality of life.
- ✓ Unchecked neutrophil influx in UC causes inflammation of the mucosal layer of the colon.
- ✓ Neutrophil migration is triggered by multidrug resistance protein 2-mediated efflux of hepoxilin A_3 into the colonic lumen.
- ✓ Unmet need persists for safer and oral therapeutics with potential for enhanced and durable remission in UC.

WHAT IS NEW HERE

- ✓ ADS051, an oral neutrophil modulator, demonstrated safety and tolerability in patients with moderate-to-severe UC.
- ✓ ADS051 is designed to be gut restricted, with high fecal concentration and minimal systemic exposure after oral dosing.
- ✓ ADS051 demonstrated signals of efficacy with safety and tolerability in patients with UC after 28 days of treatment.

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