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Small-Molecule Neutrophil Modulator ADS051 is Safe and Well-Tolerated in a Phase 1 Single Ascending Dose Study

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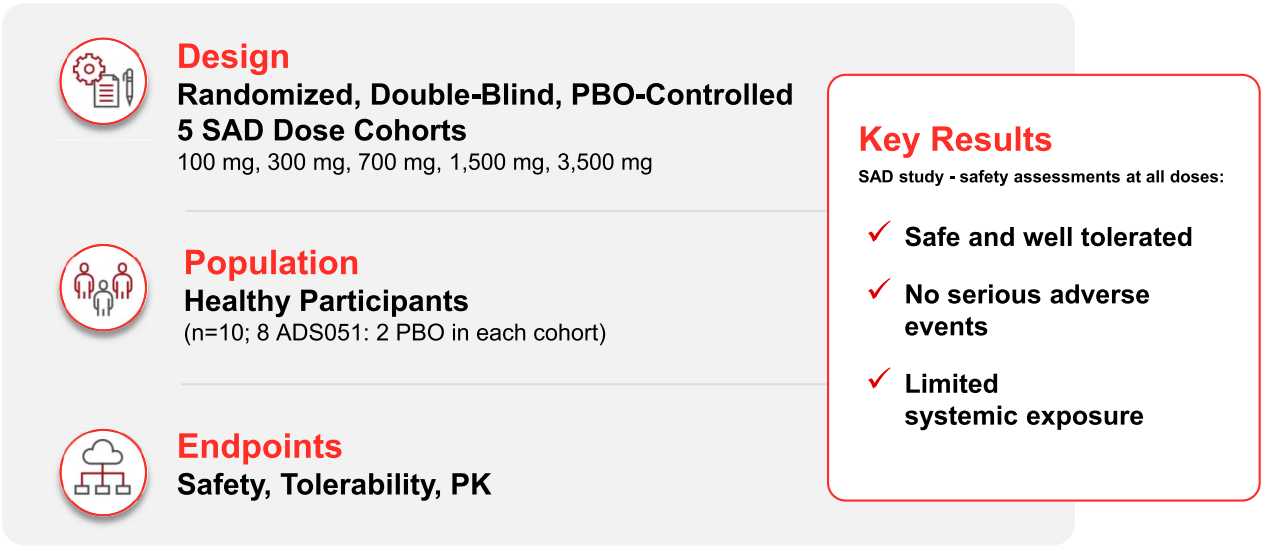
INTRODUCTION: **A need for better treatment options for moderate to severe ulcerative colitis (UC) persists because of the efficacy and safety limitations of current therapies. Neutrophil epithelial transmigration is associated with the characteristic colonic mucosal inflammation in and very likely involved with the pathogenesis and clinical symptoms of UC. ADS051 is a small-molecule inhibiting neutrophil migration and activation, which are potentially important therapeutic targets in UC. The phase 1 single ascending dose study evaluated ADS051's safety, tolerability, and pharmacokinetics in healthy volunteers.**

METHODS: **Fifty healthy adults were randomized 4:1 into 5 ascending dose cohorts to receive a single oral dose of ADS051 100 mg, 300 mg, 700 mg, 1,500 mg, 3,500 mg, or placebo. Participants were followed until 30 days after dosing. Safety and pharmacokinetics of ADS051 in stool, blood, and urine were evaluated.**

Safety of Small Molecule Neutrophil Modulator ADS051 in a Phase 1 Single Ascending Dose Study



PBO, placebo; PK, pharmacokinetics; SAD, single ascending dose. 2024. doi:10.14309/ajg.0000000000003237

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RESULTS: **ADS051 was safe and well-tolerated. Adverse events (AEs) of constipation were reported by 2 participants (5.0%) in the ADS051 1,500 mg group vs none in the placebo group. No serious AEs reported and no discontinuations due to AEs. In all dose groups, a cumulative average of 10%–24% of the ADS051 dose was recovered in stool, mostly within 48 hours after dosing. ADS051 was quantifiable in only 2 of 440 blood samples (7.64 and 69.8 ng/mL). On average, <0.035% of the ADS051 dose was excreted in urine.**

DISCUSSION: **ADS051 was safe, well-tolerated, and achieved high stool concentrations with minimal systemic exposure. ADS051 could be a safe and effective, locally acting, neutrophil-targeting agent for the treatment of UC.**

KEYWORDS: ADS051; small molecule; neutrophils; inflammatory diseases; ulcerative colitis

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D490

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INTRODUCTION

Ulcerative colitis (UC), an inflammatory bowel disease that targets the mucosal surface of the colon, is characterized by relapsing and remitting mucosal inflammation beginning in the rectum and extending to proximal colonic segments (1). UC is a complex disease with unclear pathogenesis (2–4). Multiple factors, including genetics, epigenetics, the environment, the immune system, and a dysregulated host immune response to intestinal bacteria, are important in UC pathology (1–6). The involvement of these multiple factors makes identifying targets for drug development that yield effective UC treatments challenging.

After diagnosis with moderate to severe UC, a top-down treatment approach with immunomodulator therapies is considered optimal to achieve both clinical and endoscopic remission and decrease the risk of surgeries (7–9). Recent studies in Crohn's disease have found that a top-down management approach leads to better outcomes at 1 year compared with step-up treatment (10). Furthermore, clinical response followed by clinical remission, biochemical improvement, and endoscopic improvement should be considered mandatory in treatment of inflammatory bowel disease (11). In UC, therapies include biologic agents such as anti-tumor necrosis factor-α agents (adalimumab, infliximab, and golimumab), the anti-integrin agent (vedolizumab), an anti-interleukin-12/23 agent (ustekinumab), and anti-interleukin-23 agents (risankizumab, guselkumab, and mirikizumab) all of which require parenteral administration and have risk of immunosuppression. Yet, as immunomodulators, they carry risks of infection and the potential for the development of malignancies. In addition, biologics require either intravenous or subcutaneous administration, which patients find less desirable than oral remedies. The more recent orally administered small molecules that inhibit Janus kinase 1/3 signaling messengers have been approved for treating moderate to severe UC (8,12). While some patients do achieve clinical remission (13), the increased risks of severe heart-related events, cancer, and blood clots have moved this class of agents to second-line or later-line therapies (14,15). Cyclosporine A, a calcineurin inhibitor, is a potent immunosuppressant used in severe, fulminant UC cases that likely require an urgent colectomy and continued control of UC symptoms. Yet cyclosporine A also increases the risk of infection and malignancy and, at therapeutic doses, is systemically absorbed, raising concerns for renal toxicity (16–18). Overall, many patients with UC either fail to respond (8) or lose response—over 40% of patients can lose response annually to biologics (19). Different studies have reported different rates of disease progression. Specifically, while one study reported that approximately 9% of patients progress with active disease requiring colectomy 5 years after diagnosis (20), another one reported 20% (21), supporting the continued development of new therapies (13).

Despite the many approved immunomodulators, none of them specifically target neutrophils, an abundant hallmark that characterizes the mucosal inflammation of UC. The majority of neutrophils are found in the bone marrow and, thus, are mostly absent from healthy human tissues, including the intestinal mucosa (22). Conversely, uncontrolled neutrophil presence and activity in disease states, including UC, can lead to inflammation and tissue damage (23). Neutrophil transepithelial migration is a key factor in UC pathogenesis (1,2). In fact, the degree of colonic neutrophil infiltration into the colon characterizes UC, with the more severe cases of the disease manifesting higher levels of neutrophil infiltration (24,25). For this reason, neutrophil fecal calprotectin monitoring is routinely used as a clinical biomarker for assessing UC severity to help guide therapy (23,25). As a result, neutrophils are attractive targets for therapeutic intervention (26). Localized therapeutic interventions, without systemic immunosuppression, promise to be beneficial without detrimental effects, making targeting neutrophils an exciting approach for the management of UC (25,26).

ADS051 is a small-molecule neutrophil modulator (27), which specifically modulates neutrophils through multidrug resistance protein 2 and formyl peptide receptor 1 mechanisms. When taken orally, ADS051 is gut-restricted with minimal absorption into the bloodstream (ADS051 Multiple Ascending Dose Study manuscript, unpublished data, submitted 2024) (27), limiting the potential for systemic adverse events. In addition, ADS051 is designed to not interfere with T-cell function (27), an important component of the cellular immune response needed to fight infections. Here, we report the findings of a first-in-human trial to evaluate the safety, tolerability, and pharmacokinetics (PK) of ADS051 after single-dose administration in healthy participants.

METHODS

Clinical trial design

The first-in-human trial was conducted in the United States. It was a randomized, double-blind, single ascending dose

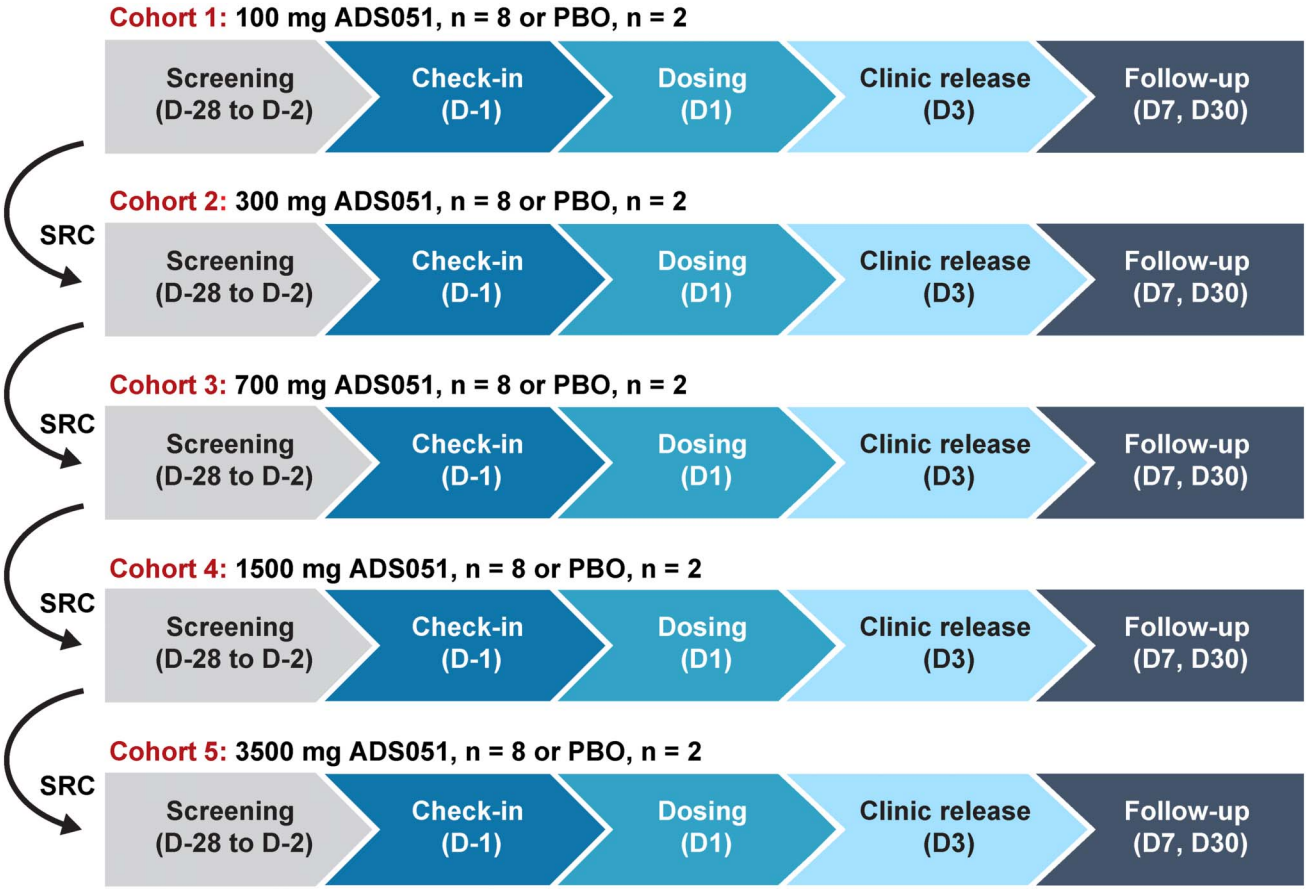

Figure 1. Single ascending dose trial phase 1 clinical trial design. A total of 10 participants per cohort were randomized to receive either ADS051 (n = 8) or placebo (n = 2) in sequential dose-escalating cohorts. Cohorts 2 through 5 were initiated after the SRC reviewed safety data through Day 3 of the current cohort and cumulative data from the prior cohort(s). D, day; PBO, placebo; SRC, safety review committee.

(SAD) trial of the safety, tolerability, and PK of oral ADS051 in 50 healthy adult male and female participants (Figure 1). Participants were randomized into 5 sequential SAD cohorts to receive single doses of ADS051 100 mg, 300 mg, 700 mg, 1,500 mg, 3,500 mg, or placebo (ADS051, n = 8 or placebo, n = 2) administered orally under fasted conditions and followed until 30 days after dosing. The primary objective of this trial was to evaluate the safety and tolerability of ADS051 after single-dose administration in healthy participants. The trial's secondary objectives were to evaluate ADS051's PK profile in blood and its fecal and urine concentrations after single-dose administration. Additional details about the SAD trial are listed under Supplementary Methods (http://links.lww.com/AJG/D490).

Investigational medicinal product and mode of administration

The drug product for this trial consisted of ADS051 powder in size 0 capsules (enteric-coated, opaque white, size 0 Vcaps Plus capsules) for oral dosing. Capsules filled with ADS051 powder, without any excipients, were coated with a polymer designed to resist a low pH gastric environment but disintegrated when exposed to ≥ pH 6.8 (post duodenum region). Matching placebo (size, color, and odor) capsules only contained inactive excipients (Avicel PH200LM) and were also enteric-coated. A combination of 100 and 200 mg dose strengths was used to achieve the various doses.

Rationale for dose selection

A nonclinical population PK model was developed using PK data from 4 animal studies assessing ADS051 levels in plasma, 2 single-dose PK studies, and two 7-day toxicokinetic studies. These studies guided dose selection for the phase 1 SAD clinical trial. A 2-compartment mammillary population PK model with first-order absorption and first-order elimination provided the best fit for the data. This model was used to scale the PK parameters allometrically to humans to predict ADS051 plasma concentrations for a 70 kg human participant following a single dose of 2.5, 5, 10, 25, 50, and 100 mg/kg corresponding to 175, 350, 700, 1,750, 3,500, and 7,000 mg doses. The plasma ADS051 AUC_{0-24} was calculated for each simulated dosing scenario and compared with the AUC_{0-24} levels following a single dose of 300 mg/kg in monkeys to establish the safety margin. The safety margin ranged from 46- to 6-fold across doses of 2.5 and 100 mg/kg, respectively.

Safety assessments

Safety assessments included monitoring adverse events (AEs), clinical laboratory testing, vital signs, physical examinations, and 12-lead electrocardiograms. All AEs were coded using the

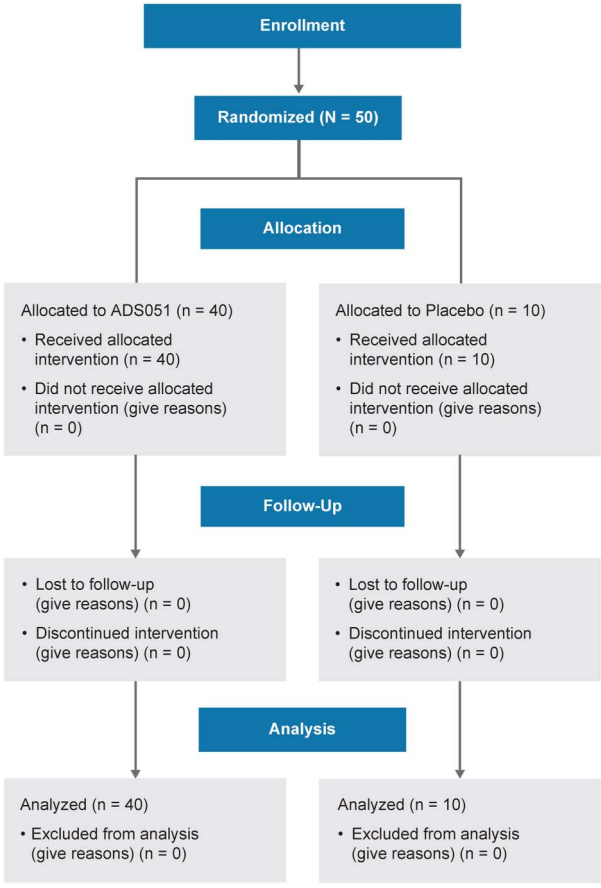

Figure 2. Single ascending dose trial Consolidated Standards of Reporting Trials participant flow diagram.

Medical Dictionary for Regulatory Activities version 23.0, and the severity of the AE was graded by the investigator according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (US Department of Health and Human Services 2017).

A blinded safety review committee (SRC), which included representatives from the sponsor and the investigator, reviewed relevant blinded data, including reported AEs, electrocardiogram (ECG) results, and laboratory test results following study drug administration through Day 3 of the most recent cohort and through Day 7 of the prior cohort. The SRC could recommend whether to progress to the next cohort, modify, or stop the trial. If the SRC found evidence of dose-limiting toxicity, no further progression to a higher dose would occur, and consideration was to be given to studying a lower dose. In addition, dose adjustments were considered required to prevent systemic exposures above the safety threshold determined in nonclinical studies. If the dose was determined not to be safe or tolerated, the study drug assignment for individual participants or the cohort could have been unblinded to the investigator and sponsor. The decision was made jointly by the sponsor and the investigator. Whole-blood PK concentrations for each cohort were measured, and blinded results were provided to the SRC as they became available. The SRC assessed the PK concentrations for consistency with predicted exposures and with concentrations shown to be safe and tolerated in nonclinical studies.

PK assessments

Samples for PK analysis were collected from blood, stool, and urine. Whole-blood samples were collected on Day 1 predose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, and 48 hours after dosing. Stool (a single bowel movement) was collected before study drug administration (from Day −2 to Day 1), either at home or in the clinical research unit (CRU). After dosing on Day 1, all individual stools (entire stool mass) were collected throughout the 48-hour postdose period, while the participant was confined to the CRU. Participants who could not produce a stool on Day 3 (48 hours after dosing) while in the CRU were provided with a kit for stool collection at home after discharge. In addition, an individual stool (entire stool mass) was collected on Day 7 (−1 or +2 days). Urine was collected for the following intervals (pooled for each collection interval): 0 to 4, 4 to 8, 8 to 24, and 24 to 48 hours after dosing. No predose urine sample was collected.

Clinical bioanalytical method

After solid-phase extraction, an ultra-high-performance liquid chromatography-tandem mass spectrometry assay was conducted to measure ADS051 in whole blood, urine, and stool. All assays were validated, and PK samples were tested according to US Food and Drug Administration (FDA) guidelines and Good Laboratory Practice procedures.

PK analyses

As appropriate, noncompartmental PK parameters for ADS051 were calculated using Phoenix WinNonlin Version 8.3 in the PK population separately for each biological matrix. The actual sampling time was used to compute PK parameters. Individual whole-blood PK parameters were not calculated because most time points had undetectable concentrations in blood, with no more than 2 detectable concentrations above the lower limit of quantification of 5 ng/mL. Fecal and urine PK parameters were calculated, including Cum%Ae$_{f0-t2}$/Cum%Ae$_{u0-t2}$ (cumulative percentage of ADS051 dose excreted [%Ae] in stool/urine from time 0 through the end time of each collection interval).

Statistical analyses

Descriptive statistics for continuous variables included the number of participants or observations, mean, median, SD, minimum, and maximum. PK summaries additionally included the percent coefficient of variation (CV%), geometric mean, and geometric CV% unless otherwise noted. Confidence intervals were presented where appropriate. Descriptive statistics for categorical variables consisted of frequency and percentage.

Results for all placebo participants were pooled and presented together. Treatment was defined as each dose of ADS051, all doses of ADS051 combined, and the pooled placebo group. The combined ADS051 treatment did not apply to the PK summaries. In the calculation of the concentration summaries and displays in figures, if values were below the limit of quantitation, they were set to zero.

All PK analyses used actual sampling times. If actual times were missing, nominal times were used and noted in the appropriate data listing.

Table 1. Demographic and baseline characteristics

Parameter	ADS051 100 mg (n = 8)	ADS051 300 mg (n = 8)	ADS051 700 mg (n = 8)	ADS051 1,500 mg (n = 8)	ADS051 3,500 mg (n = 8)	Combined ADS051 (n = 40)	Pooled placebo (n = 10)	Overall (N = 50)
Age (yr)								
Mean (SD)	28.0 (6.61)	36.9 (7.08)	37.1 (9.98)	30.4 (9.44)	36.9 (5.67)	33.9 (8.48)	39.4 (4.65)	35.0 (8.14)
Min, max	20, 38	26, 47	24, 47	19, 49	31, 48	19, 49	30, 47	19, 49
Weight (kg)								
Mean (SD)	77.43 (11.575)	84.21 (12.307)	85.30 (14.139)	80.70 (15.403)	82.08 (17.320)	81.94 (13.835)	73.89 (11.383)	80.33 (13.665)
Min, max	56.6, 93.4	67.0, 100.8	59.8, 106.6	59.2, 103.8	44.6, 102.0	44.6, 106.6	59.2, 91.0	44.6, 106.6
Height (cm)								
Mean (SD)	171.44 (7.509)	175.69 (11.856)	175.94 (10.689)	171.44 (13.214)	174.13 (13.627)	173.73 (11.158)	169.90 (12.598)	172.96 (11.429)
Min, max	156.0, 178.0	155.0, 191.0	164.5, 192.0	156.0, 193.5	147.0, 185.0	147.0, 193.5	153.0, 191.5	147.0, 193.5
Body mass index (kg/m^2)								
Mean (SD)	26.25 (2.772)	27.36 (3.796)	27.50 (3.584)	27.35 (3.466)	26.86 (4.231)	27.07 (3.444)	25.54 (2.260)	26.76 (3.280)
Min, max	20.8, 30.2	22.3, 31.5	22.1, 31.4	21.5, 30.9	20.6, 31.8	20.6, 31.8	22.2, 29.3	20.6, 31.8
Sex, n (%)								
Female	2 (25.0)	1 (12.5)	3 (37.5)	5 (62.5)	2 (25.0)	13 (32.5)	4 (40.0)	17 (34.0)
Male	6 (75.0)	7 (87.5)	5 (62.5)	3 (37.5)	6 (75.0)	27 (67.5)	6 (60.0)	33 (66.0)
Race, n (%)								
Asian	1 (12.5)	0	0	0	0	1 (2.5)	0	1 (2.0)
Black or African American	3 (37.5)	3 (37.5)	3 (37.5)	5 (62.5)	3 (37.5)	17 (42.5)	4 (40.0)	21 (42.0)
White	4 (50.0)	5 (62.5)	5 (62.5)	3 (37.5)	5 (62.5)	22 (55.0)	6 (60.0)	28 (56.0)
Ethnicity, n (%)								
Hispanic or Latino	2 (25.0)	1 (12.5)	1 (12.5)	0	1 (12.5)	5 (12.5)	3 (30.0)	8 (16.0)
Not Hispanic or Latino	6 (75.0)	7 (87.5)	7 (87.5)	8 (100.0)	7 (87.5)	35 (87.5)	7 (70.0)	42 (84.0)

min, minimum; max, maximum.

All statistical analyses were conducted using SAS Version 9.4 (SAS Institute Inc., Cary, NC) using procedures appropriate for the particular analysis.

Ethics declarations

This trial complied with the protocol, Good Clinical Practices, including International Council for Harmonisation guidelines, ethical principles originating in the Declaration of Helsinki, and applicable regulatory requirements.

Advarra Institutional Review Board (IRB; Office for Human Research Protections [OHRP]/FDA IRB Registration Number: 00000971, IRB Organization [IORG] Number: 0000635) approved the protocol, and the informed consent form before any participant was enrolled in the trial.

Trial registration

This trial was registered on ClinicalTrials.gov as national clinical trial NCT05103878.

RESULTS

Trial participants

A total of 50 healthy participants were randomized and received the study drug or placebo (5 dose groups of ADS051 with 10 participants each, 8:2), and all participants completed the trial (Figure 2). Participants had a mean age of 35.0 years (range: 19–49 years), a mean weight of 80.33 kg (range: 44.6, 106.6), and a mean body mass index of 26.76 kg/m^2 (range: 20.6, 31.8) (Table 1). A greater percentage were male participants (66.0%). The majority of participants were White (56.0%) and not Hispanic or Latino (84.0%).

Safety (primary objective)

There were no serious AEs, trial discontinuations due to AEs, deaths, or dose-limiting toxicities observed. Exposures were within the expected target; hence, no dose adjustments were necessary throughout the trial. Dose escalation progressed as planned following SRC review.

Table 2. Treatment-emergent adverse events

Preferred term	ADS051 100 mg (n = 8)	ADS051 300 mg (n = 8)	ADS051 700 mg (n = 8)	ADS051 1,500 mg (n = 8)	ADS051 3,500 mg (n = 8)	ADS051 combined (n = 40)	Pooled placebo (n = 10)
Number of subjects with at least 1 TEAE, n (%)	1 (12.5)	0	2 (25.0)	4 (50.0)	2 (25.0)	9 (22.5)	2 (20.0)
Vessel puncture site pain	0	0	1 (12.5)	2 (25.0)	2 (25.0)	5 (12.5)	0
Fatigue	0	0	0	0	0	0	1 (10.0)
Constipation	0	0	0	2 (25.0)	0	2 (5.0)	0
Abdominal pain	1 (12.5)	0	0	0	0	1 (2.5)	0
Headache	0	0	1 (12.5)	0	0	1 (2.5)	1 (10.0)
Dizziness	0	0	0	0	1 (12.5)	1 (2.5)	0
Syncope	0	0	0	0	1 (12.5)	1 (2.5)	0
Blood creatinine increased	0	0	1 (12.5)	0	0	1 (2.5)	0
Hyperhidrosis	0	0	0	0	1 (12.5)	1 (2.5)	0
Pallor	0	0	0	0	1 (12.5)	1 (2.5)	0

Adverse events were classified according to the Medical Dictionary for Regulatory Activities Version 23.0.
TEAEs, treatment-emergent adverse events.

Overall, 11 of 50 participants (22.0%) reported at least 1 treatment-emergent AE (TEAE), with 22.5% (9 of 40) and 20.0% (2 of 10) reporting TEAEs after receiving ADS051 and placebo, respectively (Table 2). The TEAEs reported by ≥2 participants who received ADS051 were vessel puncture site pain and constipation (Table 2). Vessel puncture site pain after blood sampling, the most frequently reported TEAE, was reported by 5 participants (12.5%) who received ADS051 and no participants who received placebo. Constipation was reported by 2 participants (5.0%) who received ADS051 and no participants who received placebo. All other AEs in participants who received ADS051 were reported by only 1 participant each (Table 2). All TEAEs were considered grade 1 (mild) in severity, except for 1 participant who received ADS051 3,500 mg and reported grade 2 (moderate) TEAEs of dizziness, syncope, hyperhidrosis, and pallor, which were all considered not related to study drug.

Of all the laboratory tests collected during the trial, only 2 participants had results that were considered clinically significant. One participant who received ADS051 (100 mg) had abnormal urine bacteria, leukocyte esterase, nitrite, erythrocyte, and leukocyte results on Day 2, all considered clinically significant. Urinalysis was repeated on the same day, and follow-up results were considered not clinically significant. No AE corresponding to these findings was reported. Another participant who received ADS051 (700 mg) presented with slightly increased serum creatinine compared with the normal range (1.37 mg/dL; normal range, 0.70–1.34 mg/dL) on Day 1, which was considered not clinically significant. On Days 2 and 3, the participant's creatinine results were within the reference range. On Day 7, the participant presented a high creatinine result (2.59 mg/dL) that was considered clinically significant and therefore reported as a grade 1 (mild) TEAE, which was considered unrelated to the study drug by the investigator. On Day 17, repeat serum chemistry testing was completed, the creatinine result was within the normal range, and the AE of increased blood creatinine was considered recovered/resolved. BUN was normal throughout the trial. The cause of this increase in this patient is unknown.

There were no clinically meaningful abnormal measurements in individual vital signs, and no abnormal individual vital sign measurements were reported as AEs. Similarly, no abnormal individual safety 12-lead ECG results were reported as clinically significant, and no AEs related to ECGs were reported.

PK (secondary objective)

Fecal PK parameters are summarized in Table 3. In all dose groups, a cumulative average of approximately 10%–24% of the ADS051 dose was recovered in stool as ADS051. Most ADS051 was excreted within 48 hours after dosing, and <1% was excreted in the single Day 7 stool sample collected. The maximum percentage of the dose recovered as ADS051 from a single participant was 55.6% (ADS051 700 mg group). The average peak fecal concentrations of ADS051 per dose group increased proportionally to the dose. PK data suggest that BT051 has very limited systemic exposure and is primarily excreted in the feces, demonstrating limited gut absorption. However, since no stool was collected between Days 3 and 7, the cumulative excretion through Day 7 was underestimated and should be interpreted with caution.

Urine PK parameters are summarized in Table 3. In all dose groups, urinary concentrations of ADS051 were quantifiable in all but 2 participants. On average, <0.035% of the ADS051 dose was excreted as ADS051 in the first 48 hours after dosing. There was no apparent relationship between the percentage of ADS051 dose excreted in urine and the ADS051 dose.

Concentrations of ADS051 were quantifiable (lower limit of quantification 5 ng/mL) in only 2 whole-blood samples of the 440 samples analyzed post ADS051 dose. The 2 quantifiable ADS051

Table 3. Summary of mean (CV%) [min, max] cumulative percentage of ADS051 dose excreted in stool and urine

Parameter	ADS051 100 mg (n = 8)	ADS051 300 mg (n = 8)	ADS051 700 mg (n = 8)	ADS051 1,500 mg (n = 8)	ADS051 3,500 mg (n = 8)
Stool					
Cum%$Aef_{0\text{-}12}$ (%)	0 (NA) [0, 0]	1.974 (180.0) [0, 8.86]	2.698 (282.8) [0, 21.6]	4.423 (244.4) [0, 31.0]	0.9356 (185.2) [0, 3.86]
Cum%$Aef_{0\text{-}24}$ (%)	0 (NA) [0, 0]	3.137 (130.4) [0, 8.86]	3.370 (225.4) [0, 21.6]	4.425 (244.3) [0, 31.0]	0.9364 (185.0) [0, 3.86]
Cum%$Aef_{0\text{-}48}$ (%)[a]	12.34 (65.5) [0, 20.5]	18.03 (107.4) [0.000405, 46.7]	21.14 (86.9) [0.000297, 55.5]	11.07 (92.9) [0, 31.0]	9.979 (96.9) [0.0967, 28.9]
Cum%$Aef_{0\text{-}72}$ (%)[a,b]	13.29 (54.1) [0, 20.5]	20.70 (92.5) [0.000405, 49.1]	23.58 (82.2) [0.000297, 55.6]	15.00 (72.1) [1.36, 31.3]	10.13 (96.7) [0.0967, 28.9]
Cum%$Aef_{0\text{-day 7}}$ (%)[a,c]	13.39 (52.9) [0, 20.5]	21.31 (86.5) [2.45, 49.1]	23.69 (81.8) [0.0284, 55.6]	15.18 (70.5) [1.59, 31.3]	10.19 (95.8) [0.0993, 28.9]
Urine					
Cum%$Aeu_{0\text{-}4}$ (%)	0.0008284 (112.0)	0.003623 (89.3)	0.0009847 (177.7)	0.0006669 (137.4)	0.0004534 (80.6)
Cum%$Aeu_{0\text{-}8}$ (%)	0.007378 (61.6)	0.008319 (29.1)	0.004800 (85.0)	0.002763 (46.2)	0.002405 (53.6)
Cum%$Aeu_{0\text{-}24}$ (%)	0.01644 (27.2)	0.01523 (26.6)	0.01103 (47.3)	0.007940 (99.5)	0.005434 (47.7)
Cum%$Aeu_{0\text{-}48}$ (%)	0.01948 (15.2)	0.01803 (35.3)	0.03316 (150.7)	0.01255 (59.9)	0.009561 (53.2)

CV%, percentage of coefficient of variation; Cum%$Aef_{0\text{-}t}$, cumulative percentage of dose excreted in stool from time 0 through end time of each collection interval; Cum%$Aeu_{0\text{-}t}$, cumulative percentage of dose excreted in urine from time 0 through end time of each collection interval; min, minimum; max, maximum; NA, not applicable.
[a]Fecal excretion is underestimated for the 100 mg cohort: no weight was recorded for stool provided by 1 participant during the 24- to 48-hr interval despite quantifiable analyte concentrations.
[b]The actual upper limit of the 0- to 72-hr time interval was 55.10 hr.
[c]Because no stool was collected on Days 3 through 7, this cumulative value is underestimated.

samples consisted of 1 sample (7.64 ng/mL) collected at 12 hours after dosing from a participant who received ADS051 1,500 mg and 1 sample (69.8 ng/mL) at 24 hours after dosing from a participant who received ADS051 700 mg. Therefore, PK parameters were not calculated.

DISCUSSION

This first-in-human, phase 1 SAD trial demonstrated that single oral doses of ADS051 up to 3,500 mg were safe and well-tolerated in healthy volunteers. There were no dose-limiting toxicities, serious AEs, or trial discontinuation due to AEs. Pharmacokinetic data demonstrated minimal systemic absorption of ADS051, with the majority excreted in the stool within 24 to 48 hours after dosing, consistent with animal studies (Table 3) (27). All 5 doses administered were associated with ADS051 stool concentrations higher than the IC50 for human neutrophil epithelial transmigration and activation inhibition *in vitro* (27). This suggests that ADS051 luminal concentrations can realistically be safely achieved such that inhibition of multidrug resistance protein 2-associated migration of neutrophils across the mucosa may be possible.

The safety, tolerability, and PK data of this SAD trial in healthy volunteers support continued clinical development of ADS051 as a novel oral neutrophil-targeted nonsystemic therapy for the treatment of UC.

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CONFLICTS OF INTEREST

Guarantor of the article: Adam S. Cheifetz, MD.

Specific author contributions: Planning and/or conducting the trial: Adiso Coauthors, P.G. Collecting and/or interpreting the data: P.G., Adiso Coauthors. Drafting the manuscript: all authors. All authors have approved the submitted final draft.

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Potential competing interests: A.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. J.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. R.F. has ownership of shares in Adiso Therapeutics, Inc., was a paid employee of Bacainn Therapeutics, was a board member of Bacainn, 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. E.H. and P.G. were/are consultants to Adiso Therapeutics, Inc. A.C.S. is a consultant for ClearB Therapeutics, Surrozen, Adiso Therapeutics, Inc., eGenesis and Astria Therapeutics. M.Q., B.D., and B.W.M. are/were employees of Adiso Therapeutics, Inc., at the time of this trial.

Study Highlights

WHAT IS KNOWN

- ✓ Unmet medical need persists for ulcerative colitis (UC) therapies.
- ✓ Current treatments are limited by side effects and efficacy thresholds.
- ✓ Influx of activated neutrophils into the colonic mucosa is a hallmark of UC.
- ✓ Despite being a hallmark of UC, the neutrophil is still an overlooked therapeutic target.
- ✓ ADS051 is a novel small molecule that inhibits neutrophil migration and activation.

WHAT IS NEW HERE

- ✓ Conducted phase 1, randomized, double-blind, placebo-controlled, single ascending dose trial of ADS051 in healthy participants.
- ✓ ADS051 was safe and well-tolerated as a single oral dose up to 3,500 mg.
- ✓ ADS051 had no serious adverse events or trial discontinuations due to adverse events.
- ✓ ADS051 achieved high fecal concentrations with minimal systemic exposure.

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