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AV-101, a Novel Inhaled Dry Powder Formulation of Imatinib, in Healthy Adult Participants: A Phase 1 Single and Multiple Ascending Dose Study

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Take Home Message:

AV-101, a dry powder inhaled formulation of imatinib, reduced systemic exposure to imatinib versus oral imatinib and was well tolerated in healthy adults. An ongoing phase 2b/3 study will evaluate AV-101 in patients with pulmonary arterial hypertension.

Abstract

Background: Oral imatinib has been shown to be effective, but poorly tolerated, in patients with advanced pulmonary arterial hypertension (PAH). To maintain efficacy while improving tolerability, AV-101, a dry powder inhaled formulation of imatinib, was developed to deliver imatinib directly to the lungs.

Methods: This phase 1, placebo-controlled, randomised single ascending dose (SAD) and multiple ascending dose (MAD) study evaluated the safety/tolerability and pharmacokinetics of AV-101 in healthy adults. The SAD study included 5 AV-101 cohorts (1, 3, 10, 30, 90 mg) and placebo, and a single-dose oral imatinib 400-mg cohort. The MAD study included 3 AV-101 cohorts (10, 30, 90 mg) and placebo; dosing occurred twice daily for 7 days.

Results: Eighty-two participants (SAD, n=48; MAD, n=34) were enrolled. For the SAD study, peak plasma concentrations of imatinib occurred within 3 hours of dosing with lower systemic exposure compared to oral imatinib (P<0.001). For the MAD study, systemic exposure of imatinib was higher after multiple doses of AV-101 compared to a single dose, but steady-state plasma concentrations were lower for the highest AV-101 cohort (90 mg) compared to simulated steady-state oral imatinib at Day 7 (P=0.0002). Across AV-101 MAD dose cohorts, the most common treatment-emergent adverse events were cough (n=7 [27%]) and headache (n=4 [15%]).

Conclusions: AV-101 was well tolerated in healthy adults, and targeted doses of AV-101 significantly reduced the systemic exposure of imatinib compared with oral imatinib. An ongoing phase 2b/phase 3 study (IMPAHCT; NCT05036135) will evaluate the safety/tolerability and clinical benefit of AV-101 for PAH.

Introduction

Pulmonary arterial hypertension (PAH) is a rare, life-limiting disease characterised by excessive pulmonary vasoconstriction and abnormal vascular remodelling [1-3], including hyperproliferation of fibroblasts, smooth muscle cells, and endothelial cells in the pulmonary vasculature [4,5]. Approved therapies for PAH management focus on the resultant vasoconstrictive pathophysiology to improve haemodynamics and exercise tolerance. These therapies do slow disease progression [6], but PAH continues to be associated with high morbidity and mortality; median survival after diagnosis is approximately 7 years in contemporary registries [7-9].

Imatinib is a small-molecule kinase inhibitor, initially approved for the treatment of chronic myeloid leukaemia [10], that inhibits tyrosine kinases involved in growth, differentiation, proliferation, survival, inflammation, metabolism, and apoptosis [10-12]. Imatinib most potently inhibits platelet-derived growth factor receptor (PDGFR), discoidin domain receptor (DDR), KIT proto-oncogene receptor tyrosine kinase (KIT), colony stimulating factor 1 receptor (CSF1R), and abelson murine leukaemia viral oncogene homolog (ABL) kinases [13]. Signalling through these kinases has been implicated (directly and indirectly) in PAH remodelling, including PDGFR-mediated proliferation and resistance to apoptosis of vascular smooth muscle cells [14,15], KIT expression in the vasculature and its influence on precursor cells [16], fibrotic signalling and recovery mediated by DDR [17] and ABL [18], and immune dysregulation via CSF1R and KIT [16,19].

Imatinib's antiproliferative and pro-apoptotic properties have been demonstrated in multiple preclinical studies; in *in vitro* and *in vivo* PAH models, imatinib reversed aspects of pulmonary vascular remodelling, attenuated right heart hypertrophy and right ventricular pressure, improved haemodynamics, and reduced vascular smooth muscle cell proliferation and neointima formation [14,15,20-22]. In a phase 2 study conducted by Novartis, patients with PAH

treated with oral imatinib demonstrated a significant reduction in pulmonary vascular resistance [23]. When assessed in a phase 3 randomised controlled trial (IMPRES), oral imatinib (400 mg) treatment resulted in significant improvements in 6-minute walk distance and haemodynamics observed in patients on ≥2 background PAH therapies with persistent symptoms [24,25]. However, patients treated with oral imatinib in the IMPRES study had high discontinuation rates and adverse events (AEs), particularly an excess of subdural haematoma in patients taking concomitant vitamin K antagonists [24]. After the IMPRES study, Novartis chose not to pursue the development of oral imatinib for PAH.

AV-101 is an inhaled dry powder formulation of imatinib developed to deliver effective concentrations of imatinib to respiratory tissue while simultaneously limiting systemic exposure and potentially circumventing systemic AEs associated with oral imatinib. The objective of the current study was to characterise the pharmacokinetics and safety/tolerability of AV-101 in healthy adult participants.

Methods

Study Design and Participants

This was a phase 1, single-centre, placebo-controlled, randomised study that evaluated the pharmacokinetics and safety/tolerability of single ascending doses (SAD) and multiple ascending doses (MAD) of AV-101. Eligible participants were healthy adults, 18-59 years of age, with no clinically significant medical conditions, a body mass index of 18.0-35.0 kg/m^2, and negative tests for COVID-19, HIV, hepatitis B, and hepatitis C. Additional details on the study design and participants are described in the Supplementary Methods. The primary safety outcomes were based on medical, physical, laboratory, and treatment-emergent AE (TEAE) evaluations.

This trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice, and the study protocol was approved by the Independent Ethics Committee/Institutional Review Board at the study centre. All participants provided written informed consent.

Selection of Doses

AV-101 dosing was based on a weight-of-evidence approach from the results of preclinical studies and pharmacokinetic modelling, with the goal of achieving substantially lower systemic exposure versus a 400-mg oral dose of imatinib. Imatinib has a demonstrated bioavailability of 98% and a peak plasma concentration (C_{max}) that is achieved within 2-4 hours post-dose [26]. A substantial dose reduction was expected using inhalation as the route of administration since 10-fold or greater dose reductions have been observed for inhaled drugs relative to their oral counterparts, even after accounting for bioavailability (e.g., albuterol, treprostinil) [27,28]. The 1-mg starting dose in the first SAD cohort was <1/100 of the dose of oral imatinib administered to patients with PAH in prior clinical trials and was therefore considered a conservative starting dose of AV-101.

The AV-101 capsules were of 2 dose strengths: 1 and 10 mg. For each dosing time point, participants inhaled from 1 capsule in the 1-mg and 10-mg cohorts, 3 capsules in the 3-mg and 30-mg cohorts, and 9 capsules in the 90-mg cohorts.

SAD Study

The SAD study included 5 AV-101 cohorts (1, 3, 10, 30, and 90 mg), with 8 participants randomised to AV-101 (n=6) or placebo (n=2) per cohort. Study treatment was administered in the morning after food by oral inhalation delivered via a dry powder inhaler. One additional cohort of 8 participants received a non-blinded, single dose of oral imatinib 400 mg with food

and approximately 240 mL of water. The first dose in a cohort was administered ≥5 days after dosing in the previous cohort to allow for assessment of safety/tolerability.

MAD Study

The MAD study involved 3 AV-101 cohorts (10, 30, and 90 mg), with up to 12 participants randomised to AV-101 (n=9) or placebo (n=3) per cohort, with treatment administered twice daily (BID) for 7 days, except for a single morning dose only on Day 7 (**Figure 1**). Doses of AV-101 for the MAD cohorts were determined based on results of the SAD study, with a 10-mg BID starting dose and a 90 mg BID maximum dose. Morning doses were administered approximately 30 minutes after food, and evening doses were administered approximately 12 hours later but at any time after food. The first dose in a cohort was administered ≥10 days after the first dose in the previous cohort to allow for assessment of safety/tolerability.

Pharmacokinetics

Plasma concentrations of imatinib and its major metabolite, N-desmethyl imatinib, were measured to establish their pharmacokinetic profile after AV-101 inhalation in both SAD and MAD portions, together with the plasma concentrations of imatinib following the single oral imatinib 400 mg dose administered in the SAD study. Non-compartmental pharmacokinetic analysis of the plasma concentration-versus-time profiles were performed using Phoenix® WinNonlin® (Certara) software, version 8.0 or higher.

In the SAD study, blood samples were taken prior to dosing and after dosing at 5, 20, and 40 minutes and at 1, 2, 4, 6, 9, 12, 48, and 72 hours post-dose.

For oral imatinib in the MAD study, a population pharmacokinetic model was used to simulate the steady-state pharmacokinetics of imatinib, which would be expected after approximately five

days of the 7-day dosing regimen. The population pharmacokinetic model was developed using a mixed-effects approach with a 1-compartment model and was based on the plasma concentration profiles obtained for the single oral dose of 400 mg imatinib from the SAD portion of the study. The schedule of blood samples in the MAD study are detailed in **Figure 1**. In the MAD study, the predicted imatinib steady-state exposure data obtained from the population pharmacokinetic model were compared to the observed imatinib steady-state systemic exposure for all doses of AV-101. The average concentration at steady state over 1 dosing interval (C_{av}) was used as an estimate to compare the inhaled AV-101 (10-90 mg BID) and oral imatinib (400 mg daily) dosing regimens.

Safety and Tolerability

In the SAD study, vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) and oxygen saturation (SpO_2) were evaluated pre-dose (screening and Day 0) and at multiple time points post-dose (20 minutes, 40 minutes, and 1, 2, 4, and 9 hours and prior to pharmacokinetic sampling at 24, 48 and 72 hours). Laboratory tests (haematology, biochemistry, and urinalysis) were performed pre-dose (screening and Day 0), on Days 1 and 2, and prior to discharge. Spirometry assessments (per American Thoracic Society guidelines) were performed at screening, prior to dosing, following the 20-minute and 1- and 4-hour pharmacokinetic blood samples, and at Day 4. The schedule of assessments for the MAD study are detailed in **Figure 1**.

Statistical Analyses

Descriptive statistics were used to summarize demographics and safety parameters. For each part of the study, natural log-transformed parameters for imatinib were assessed statistically for dose proportionality; parameters were considered dose proportional if the 90% confidence interval (CI) for the slope coefficient included 1. Log-transformed parameters for AV-101 (all

doses) were compared with oral imatinib using analysis of variance (ANOVA), with dose level as a fixed factor, using the Tukey-Kramer method of adjustment for multiple comparisons and a 2-sided significance level of 5%.

Results

Participant Demographics and Disposition

A total of 82 participants were included: 48 in the SAD study and 34 in the MAD study. Two participants withdrew prematurely from the study; 1 participant in the SAD 30-mg cohort withdrew consent and 1 participant in the MAD 90-mg BID cohort withdrew due to an AE of vomiting (the subject's last dose was in the evening on Day 1 and they withdrew from the study after a 24-hour observation on Day 3). Demographic characteristics from the SAD and MAD studies were generally well balanced (**Table 1**; **Supplementary Table S1**).

SAD Pharmacokinetics

Following single ascending doses of AV-101, the plasma concentrations of imatinib and N-desmethyl imatinib increased in a dose-dependent but greater than dose-proportional manner (**Figure 2**; **Table 2**). A 90-fold increase in imatinib exposure was observed across AV-101 dose levels, with statistical analysis confirming a greater than proportional increase in plasma imatinib exposure following AV-101 administration, as the 90% CI was above 1 for both C_{max} and $AUC_{0\text{-}t}$. At the 1-mg dose of AV-101, plasma concentrations of imatinib and N-desmethyl imatinib were below or near the assay's lower limit of quantification.

Plasma C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ of imatinib and N-methyl imatinib following all AV-101 doses were consistently lower than those following a single dose of oral imatinib 400 mg, indicating significantly lower systemic exposure with AV-101 (P<0.001 for all doses). The plasma C_{max} for imatinib was generally reached within 2-3 hours across AV-101 dose levels in contrast to 4

hours following a single dose of oral imatinib 400 mg. The plasma C_{max} for N-desmethyl imatinib was observed at 6 hours for inhaled AV-101 and 2 hours for oral imatinib. The plasma $t_{1/2}$ for both imatinib and N-desmethyl imatinib was consistent across AV-101 dosing cohorts from 3-90 mg. The T_{max} for imatinib ranged from 2-3 hours across AV-101 doses, with high variability except for the 10-mg dose, which resulted in a T_{max} of 0.18 (range: 0.08, 1.10) hours. The T_{max} for N-desmethyl imatinib was approximately 6 hours for all AV-101 doses.

MAD Pharmacokinetics

Systemic exposure of imatinib and N-desmethyl imatinib was higher following multiple versus single AV-101 doses, suggesting modest accumulation. Plasma concentrations of imatinib and N-desmethyl imatinib increased in a dose-proportional manner following multiple AV-101 doses (**Figure 3**; **Table 3**). While C_{max} and AUC_{tau} increased by 12.9-fold and 13.5-fold for imatinib, the corresponding increase was 11.7-fold and 12.0-fold for N-desmethyl imatinib, respectively, which was equivalent to a 9-fold increase from 10 mg to 90 mg AV-101. Statistical analysis confirmed the dose-proportional increase in plasma imatinib exposure, as the 90% CI contained or was close to 1 for both C_{max} and AUC_{tau}. Imatinib C_{trough} following AV-101 administration reached a plateau by Day 4. Overall, all AV-101 doses showed a lower steady-state systemic exposure (C_{max} and AUC_{tau}) compared with that modelled for oral imatinib at Day 7 (P=0.0002); despite BID dosing, steady-state plasma concentrations for AV-101 90 mg remained below the simulated steady-state concentrations for oral imatinib 400 mg (**Figure 4**).

Safety and Tolerability

In the SAD study, 10 TEAEs were experienced by 9 (19%) participants, including 8 who received AV-101 and 1 who received placebo; no participant who received oral imatinib 400 mg reported a TEAE. All TEAEs were grade 1 (mild); events following AV-101 included headache

(n=3), dizziness (n=2), cough, diarrhoea, dyspnoea, and nausea (n=1 each). No participant discontinued due to a TEAE.

In the MAD study, 32 TEAEs were experienced by 10 (29%) participants, including 9 who received AV-101 and 1 who received placebo (**Table 4**). All TEAEs were grade 1 or 2; all grade 2 TEAEs occurred in the 90-mg cohort and resolved by the end of the study. The most common TEAEs were cough and headache, occurring primarily in the 90-mg cohort. In this cohort, participants were required to complete 9 inhalations at each dosing time point to achieve the 90-mg dose of AV-101; coughing typically began after 3-4 inhalations and resolved within a few minutes after the inhalations were complete. Only 1 participant experienced grade 2 coughing. One participant in the 90-mg cohort discontinued dosing on Day 1 due to vomiting and withdrew from the study on Day 3.

There were no clinically significant changes in spirometry, suggesting coughing during AV-101 inhalations did not negatively impact lung function at 20 minutes or up to 4 hours after dosing. There were also no clinically significant changes in physical examination, vital signs, electrocardiogram, or haematology, clinical chemistry, and urinalysis values. Transient alterations in mean neutrophil counts within the normal range were observed in some dosing cohorts but returned to baseline levels after 3-4 days.

Discussion

This study showed that systemic exposure to imatinib and its metabolite N-desmethyl imatinib was greatly reduced when imatinib was delivered as an inhaled dry powder (AV-101) using locally targeted doses of 1-90 mg versus oral administration of 400 mg in healthy adult participants, and that AV-101 was generally well tolerated. Following a single dose of AV-101, plasma concentrations of imatinib and N-desmethyl imatinib increased in a dose-dependent but

greater than dose-proportional manner; following multiple doses of AV-101, plasma concentrations increased in a dose-proportional manner. Moderate plasma accumulation of imatinib and N-desmethyl imatinib was observed with repeated AV-101 doses; however, systemic exposure following AV-101 remained significantly lower than the observed single-dose and simulated multiple-dose, steady-state exposure of oral imatinib 400 mg.

As expected from the lower systemic exposure of imatinib, AV-101 was generally well tolerated with both single and repeated doses from 1-90 mg. In phase 2 and 3 studies with oral imatinib 400 mg, key systemic AEs included gastrointestinal toxicities and oedema [24,25]. In the present study, 2 participants (AV-101 90-mg BID cohort) experienced grade 1 nausea; no participant experienced oedema. While myelosuppression was observed in prior oral imatinib studies [24,25], only transient increases and decreases in mean neutrophil counts (within normal range) were observed following AV-101. Six-month inhaled toxicology data in non-human primates also suggested no safety concerns following AV-101 (data on file). The more favourable safety/tolerability profile following AV-101 versus oral imatinib is not unexpected given the reduction in systemic imatinib exposure [29].

The most common TEAEs with AV-101 (MAD study) included cough and headache, primarily at the 90-mg BID dose; this may reflect the 9 inhalations/dose required for this cohort. Inhalation of drugs can cause sensitisation or direct irritant effects, including cough [30]. However, coughing events were typically mild and did not affect lung function, as spirometry assessments performed 20 minutes 4 hours after dosing were normal. Multiple inhalations may also have led to the AEs of vomiting and, consequently, the discontinuation of treatment by 1 participant in the AV-101 90-mg MAD cohort. To establish a practical dosing regimen and to mitigate potential coughing and headaches, future AV-101 studies (IMPAHCT; NCT05036135) will decrease the

amount of inhaled dry powder relative to the 90-mg dose by ≥60% and use only 2 versus 9 inhalations/dose.

The determination of an appropriate dose that can be administered in a convenient and practical manner, while maintaining efficacious lung concentrations throughout a dosing period, is challenging. At the reference dose for oral imatinib (400 mg), efficacy and plasma levels are well established, but there are no corresponding lung concentration estimates over time. Furthermore, animal models do not translate well in terms of dose or disease pathology in humans although aerosolized imatinib has exhibited positive responses in such models [31,32]. Consequently, we relied on animal studies to generate lung and plasma time-course data and employed pharmacokinetic modelling to guide dosing estimates. In this regard, intratracheal instillation studies of imatinib in Sprague-Dawley rats demonstrated high lung to plasma exposure ratios relative to orally-administered imatinib (manuscript in preparation). Additional pharmacokinetic parameters from rat and non-human primate data, as well as data from this SAD/MAD study, enabled construction of a semi-physiologic, compartmental model based on work by Hendrickx, et al [33] to simulate lung exposure via inhalation as well as oral administration. These exercises provided further guidance on lung doses for the ongoing phase 2b/phase 3 study, and we expect that a 35-mg BID inhaled dose of AV-101 will achieve similar lung exposure to that of oral imatinib 400 mg. These estimates also account for extrapolation of lung-deposited doses to nominal capsule doses for use with the dry powder inhalers based on well-established *in vitro* techniques such as inertial cascade impaction.

The observed plasma concentrations of inhaled AV-101 indicated rapid emergence of imatinib into the circulation, with appreciable plasma levels apparent 5 minutes post-dose. In contrast with 400 mg oral imatinib, plasma levels were not predicted to be observed for at least 20 minutes. These data provide confirmation that the source of imatinib is primarily via the lungs.

Additionally, plasma levels appeared sustained for 4-6 hours, though these levels may reflect an oral contribution (albeit small compared to a 400-mg oral dose) from inhaled drug that is deposited in the oropharynx and subsequently swallowed and absorbed. Nevertheless, the plasma concentration-time profiles of imatinib over the first 15-30 minutes are indicative of dissolution rate-limited absorption, otherwise a rapid initial decline in plasma levels would be expected since imatinib is considered a high permeability drug [34]. These data are supported by intratracheal instillation studies in rats with suspension versus solution formulations of imatinib (data on file).

Numerous preclinical studies have shown kinase inhibitors to be effective in targeting pathways implicated in the pathogenesis of PAH (e.g., PDGF, FGF2, VEGF, EGF, c-KIT, and Src) [4,16,21], including imatinib, nilotinib, nintedanib, dasatinib, and sorafenib [14,15,20,21,35,36]. Despite promising preclinical results, the effectiveness of these other kinase inhibitors has largely not translated to the clinical PAH setting [37-41]. While oral imatinib demonstrated significant clinical benefit for PAH as add on therapy in the IMPRES trial, it was associated with poor systemic tolerability that prohibited its further development. These data suggested altering the delivery route of imatinib instead of the drug itself could lead to a more favourable benefit/risk profile.

In conclusion, this study showed that lower doses of imatinib via AV-101 dry powder inhalation resulted in significantly lower systemic exposure of imatinib in healthy adult participants compared to oral imatinib. Moreover, AV-101 was generally well tolerated with repeated dosing, supporting further development for treatment of PAH.

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Conflicts of Interests:

Hunter Gillies, Ralph Niven, and Benjamin Dake are employees of Aerovate Therapeutics, Inc. Murali M. Chakinala received research grants/funding from Acceleron Pharma, Actelion, Eiger Biopharmaceuticals, Gossamer Bio, Medtronic, and United Therapeutics Corporation; served as a consultant for Actelion, Altavant Sciences, Inc., Express Scripts Holding Company, Liquidia Technologies, Inc., PhaseBio Pharmaceuticals, United Therapeutics Corporation, and WebMD LLC (Medscape). Jeremy P. Feldman received honoraria from Acceleron Pharma, Altavant Sciences, Bayer, Gilead Sciences, and United Therapeutics Corporation. Marc Humbert received research grants/funding from Acceleron Pharma, Aerovate Therapeutics, Altavant Sciences, Inc., Bayer, Janssen Pharmaceuticals, Merck, Morphogen-IX Limited, and United Therapeutics Corporation; and received honoraria from Acceleron Pharma, Actelion, Bayer, GlaxoSmithKline, Merck, and United Therapeutics Corporation. Martin Kankam is an employee of Altasciences Kansas, Inc.; and received research grants/funding from Actelion, Acurx, Biogen, BioXcel, DynPort Vaccine Company, Grifols, Jazz Pharmaceuticals, Novo Nordisk, Novus, Pfizer, Urovant Sciences, ViroDefense, and the US Food and Drug Administration/National Institutes of Health. Nicholas S. Hill, Marius M. Hoeper, and Vallerie V. McLaughlin have no disclosures to declare.

Table 1. Demographic Characteristics

	Overall AV-101	Pooled placebo	Oral imatinib 400 mg
SAD			
Participants, n	**30**	**10**	**8**
Median (range) age, years	37.5 (19, 59)	34.5 (27, 49)	48.0 (36, 58)
Female, n (%)	16 (53)	6 (60)	1 (13)
Race, n (%)			
White	14 (47)	3 (30)	2 (25)
Black or African American	16 (53)	7 (70)	6 (75)
Mean (range) BMI, kg/m^2	29.4 (18.7, 34.9)	28.7 (19.8, 33.3)	28.5 (22.0, 33.9)
MAD[a]			
Participants, n	**26**	**8**	
Median age, years (range)	40.0 (21, 58)	37.5 (22, 53)	—
Female, n (%)	9 (35)	3 (38)	—
Race, n (%)			
White	18 (69)	4 (50)	—
Black or African American	7 (27)	4 (50)	
American Indian or Alaska Native	1 (4)	0	
Mean (range) BMI, kg/m^2	28.7 (18.9, 34.4)	27.2 (19.7, 32.4)	—

BID, twice daily; BMI, body mass index; MAD, multiple ascending dose; SAD, single ascending dose.
[a]Dose given BID for 7 days, with only the morning dose administered on Day 7.

Table 2. Pharmacokinetic Parameters Following SAD of Inhaled AV-101 or Oral Imatinib 400 mg

Imatinib						
	AV-101 1 mg (n=6)	**AV-101 3 mg (n=6)**	**AV-101 10 mg (n=6)**	**AV-101 30 mg (n=6)**	**AV-101 90 mg (n=6)**	**Oral imatinib 400 mg (n=8)**
C_{max}, ng/mL	1.2 (0.6)	3.8 (0.5)	20.2 (4.8)	73.8 (9.2)	423.8 (253.1)	1,712.1 (483.7)
T_{max}, h	3.0 (0.1, 4.0)	2.0 (0.1, 2.0)	0.2 (0.1, 1.1)	2.0 (0.7, 6.1)	2.1 (1.1, 2.1)	4.0 (2.0, 4.0)
AUC_{0-t}, ng*h/mL	9.9 (10.9)	65.4 (13.7)	319.0 (54.0)	1,279.3 (306.0)	6,673.9 (3,251.8)	32,665.8 (7,641.0)
MRT_{0-t}, h	4.8 (3.1)	15.0 (4.2)	21.0 (0.7)	18.4 (2.1)	17.2 (2.3)	19.5 (1.2)
$t_{1/2}$, h	9.0 (2.2)[a]	19.6 (4.0)	20.0 (1.1)	19.3 (2.9)	16.1 (2.5)	15.4 (1.4)
N-desmethyl imatinib						
	AV-101 1 mg (n=4)	**AV-101 3 mg (n=6)**	**AV-101 10 mg (n=6)**	**AV-101 30 mg (n=6)**	**AV-101 90 mg (n=6)**	**Oral imatinib 400 mg (n=8)**
C_{max}, ng/mL	0.1 (0.1)	0.4 (0.1)	1.4 (0.3)	6.2 (1.3)	33.2 (14.7)	228.9 (61.3)
T_{max}, h	6.0 (4.0, 6.2)	6.0 (6.0, 6.0)	6.0 (6.0, 6.0)	6.1 (1.0, 9.0)	6.1 (2.1, 9.1)	2.0 (2.0, 4.0)
AUC_{0-t}, ng*h/mL	2.6 (NR)[b]	11.8 (4.1)	45.8 (8.6)	182.6 (45.7)	986.5 (433.6)	4,783.9 (1,457.3)
MRT_{0-t}, h	9.0 (NR)[b]	22.0 (7.0)	28.4 (1.0)	25.3 (2.8)	26.4 (1.5)	24.9 (1.2)
$t_{1/2}$, h	NR (NC)[c]	34.8 (9.2)	40.5 (8.4)	32.2 (3.5)	31.9 (5.6)	32.5 (4.5)

AUC_{0-t}, area under the concentration-time curve from dose administration at time 0 to $T_{last,}$ where T_{last} is the time of last measurable observed concentration; C_{max}, maximum observed concentration; MRT, mean residence time; NC, not calculated; NR, not reportable; SAD, single ascending dose; SD, standard deviation; $t_{½}$, half-life; T_{max}, time of maximum observed concentration.
Pharmacokinetic parameters were estimated using non-compartment analyses.
Data are presented as mean (±SD) except T_{max}, which is presented as median (range).
[a]n=3.
[b]n=2.
[c]n=1.

Table 3. Pharmacokinetic Parameters Following MAD (Day 7) of Inhaled AV-101 or Simulated Oral Imatinib 400 mg at Steady State

Imatinib				
	AV-101 10 mg (n=8)	**AV-101 30 mg (n=9)**	**AV-101 90 mg (n=8)**	**Simulated steady-state oral imatinib 400 mg**
$C_{max,ss}$, ng/mL	69.2 (31.1)	214.8 (88.2)	890.4 (236.8)	2,155
C_{av}, ng/mL	49.1 (24.0)	159.6 (64.5)	663.8 (208.5)	1,251
T_{max}, h	0.7 (0.1, 2.0)	0.1 (0.1, 2.0)	1.6 (0.17, 2.1)	3.3
$C_{min,ss}$, ng/mL	31.7 (14.3)	118.2 (47.4)	533.6 (183.4)	—
AUC_{tau}, ng*h/mL	589.6 (288.2)	1,915.6 (773.8)	7,965.2 (2,501.7)	—
AUC_{0-24}, ng*h/mL	—	—	—	30,033
N-desmethyl imatinib				
	AV-101 10 mg (n=8)	**AV-101 30 mg (n=9)**	**AV-101 90 mg (n=8)**	
$C_{max,ss}$, ng/mL	9.9 (6.5)	30.0 (12.5)	116.6 (48.3)	
T_{max}, h	1.0 (0.7, 6.0)	1.1 (0.7, 9.0)	2.1 (1.1, 9.1)	
$C_{min,ss}$, ng/mL	6.6 (3.9)	22.6 (9.0)	83.5 (38.8)	
AUC_{tau}, ng*h/mL	100.2 (64.3)	322.2 (134.7)	1,198.5 (532.6)	

AUC_{0-24}, area under the curve from 0 to 24 hours; AUC_{tau}, area under the curve for the 0-to-12-hour–dosing interval at steady state; C_{av}, average concentration during a dosing interval at steady state; $C_{max,ss}$, maximum observed concentration during a dosing interval at steady state; $C_{min,ss}$, minimum observed concentration during a dosing interval at steady state; MAD, multiple ascending doses; NA, not available; SD, standard deviation; T_{max}, time of the maximum observed concentration.
Pharmacokinetic parameters were estimated using non-compartmental analyses.
Data are presented as mean (±SD) except T_{max} is presented as median (range).

Table 4. MAD Study Summary of TEAEs

	AV-101 10 mg (n=8)	AV-101 30 mg (n=9)	AV-101 90 mg (n=9)	Overall AV-101 (n=26)	Pooled placebo (n=8)
Number of TEAEs reported	2	2	27	31	1
Participants with ≥1 TEAE, n (%)	2 (25)	1 (11)	6 (67)	9 (35)	1 (13)
TEAE severity, n (%)					
Grade 1	2 (100)	2 (100)	19 (70.4)	23 (74.2)	1 (100)
Grade 2	0	0	8 (29.6)	8 (25.8))	0
Grade ≥3	0	0	0	0	0
TEAEs in ≥2 participants, n (%)					
Cough	1 (13)	1 (11)	5 (56)	7 (27)	0
Headache	0	0	4 (44)	4 (15)	0
Throat irritation	0	1 (11)	1 (11)	2 (8)	0
Musculoskeletal pain	0	0	2 (22)	2 (8)	0
Nausea	0	0	2 (22)	2 (8)	0
Chest discomfort	0	0	2 (22)	2 (8)	0
Participants with ≥1 drug-related TEAE, n (%)	0	1 (11)	6 (67)	7 (27)	0
Serious TEAE, n	0	0	0	0	0

MAD, single ascending doses; TEAE, treatment-emergent adverse event.
TEAEs were reported throughout the study and classified according to the *Medical Dictionary for Regulatory Activities* (MedDRA) version 23; severity of TEAEs was categorized using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.

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Figure Legends

Figure 1. MAD Study Design and Schedule of Assessments.

EOS, end of study; EOT, end of treatment; MAD, multiple ascending doses; SpO_2, oxygen saturation.

[a]The morning dose of AV-101 or placebo was administered within 30 minutes of food, and the evening dose of AV-101 was administered approximately 12 hours later.

[b]PK blood samples were taken on Day 1 and 7 prior to and after the morning dose at 5, 20, and 40 minutes and at 1, 2, 4, 6, 9, and 12 hours. On Days 2-6, blood samples for pharmacokinetic evaluation were taken prior to dosing only. Additional samples were taken at 24, 48, and 72 hours after the final dose (i.e., on Days 8, 9, and 10).

[c]Spirometry assessments (per American Thoracic Society guidelines) were performed at screening; on Day 0; prior to dosing and at 20 minutes, 60 minutes, and 4 hours after the morning dose on Days 1, 3, and 7; and at the follow-up visit on Day 14.

[d]Vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) and SpO_2 were recorded at screening, on Day 0, prior to each dose, at 1 hour after each dose, the morning of discharge on Day 10, and the follow-up visit on Day 14.

[e]Laboratory tests (haematology, biochemistry, and urinalysis) were performed at screening; on Days 0-3, 7, and 8; and at the follow-up visit on Day 14.

Figure 2. Concentration-time Profiles for (A) Imatinib and (B) N-desmethyl Imatinib Following SAD of Inhaled AV-101 or Oral Imatinib 400 mg.

Data are presented as mean +SD over 72-hours following administration on Day 1.

LLOQ, lower limit of quantification; SAD, single ascending dose; SD, standard deviation.

Figure 3. Concentration-time Profiles for (A) Imatinib and (B) N-desmethyl Imatinib Following MAD (Day 7) of Inhaled AV-101 or Simulated Oral Imatinib 400 mg at Steady State.

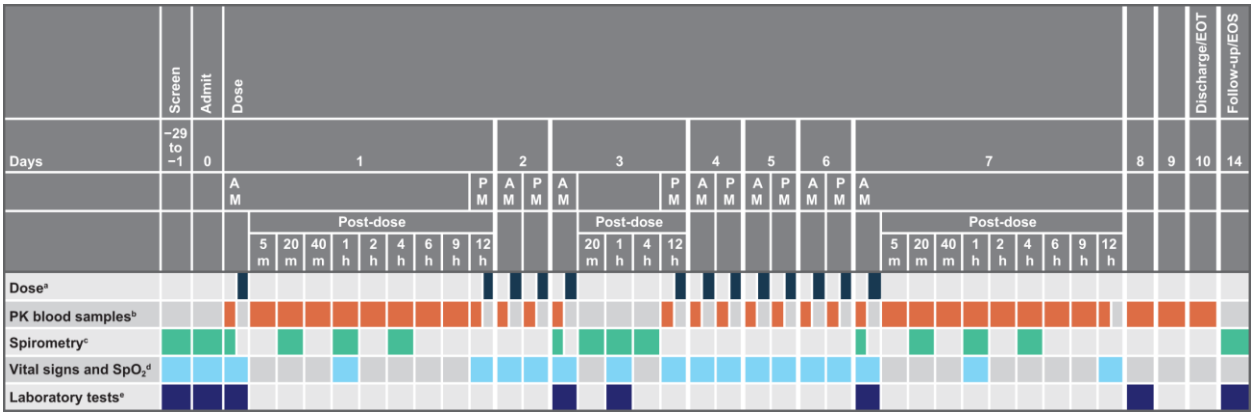
Data are presented as mean +SD over 72-hours following administration on Day 7.

MAD, multiple ascending doses; SD, standard deviation.

Figure 4. Plasma Concentrations of AV-101 (BID) and Simulated Oral Imatinib 400 mg at Steady State (Day 7).

Data are presented as mean ±SD over 72-hours following administration on Day 7.

BID, twice daily; SD, standard deviation.


Screen
Admit
Dose
Discharge/EOT
Follow-up/EOS
Days
−29 to −1
0
1
2
3
4
5
6
7
8
9
10
14
AM
PM
Post-dose
5 m
20 m
40 m
1 h
2 h
4 h
6 h
9 h
12 h
Dose[a]
PK blood samples[b]
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Vital signs and SpO2[d]
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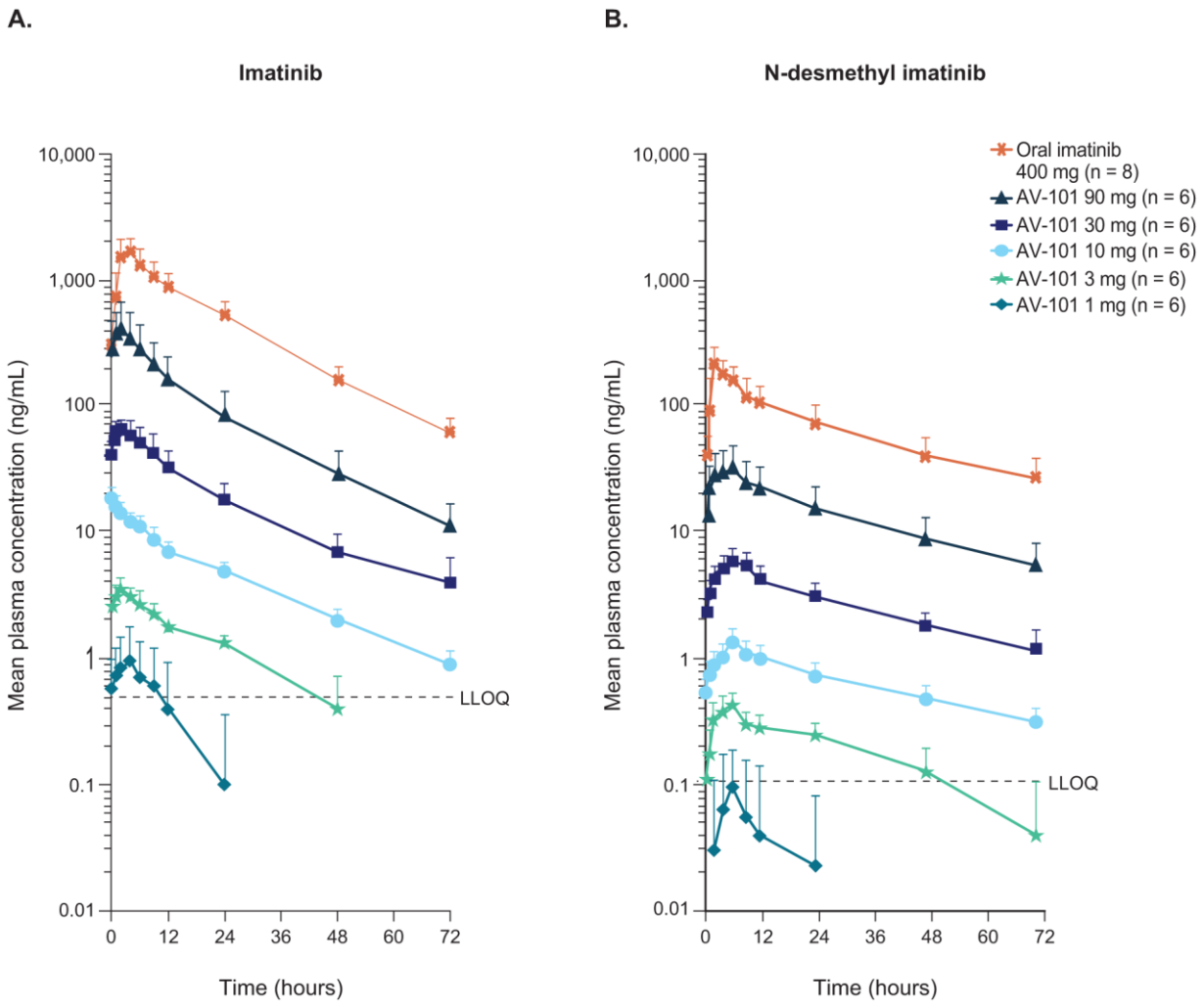
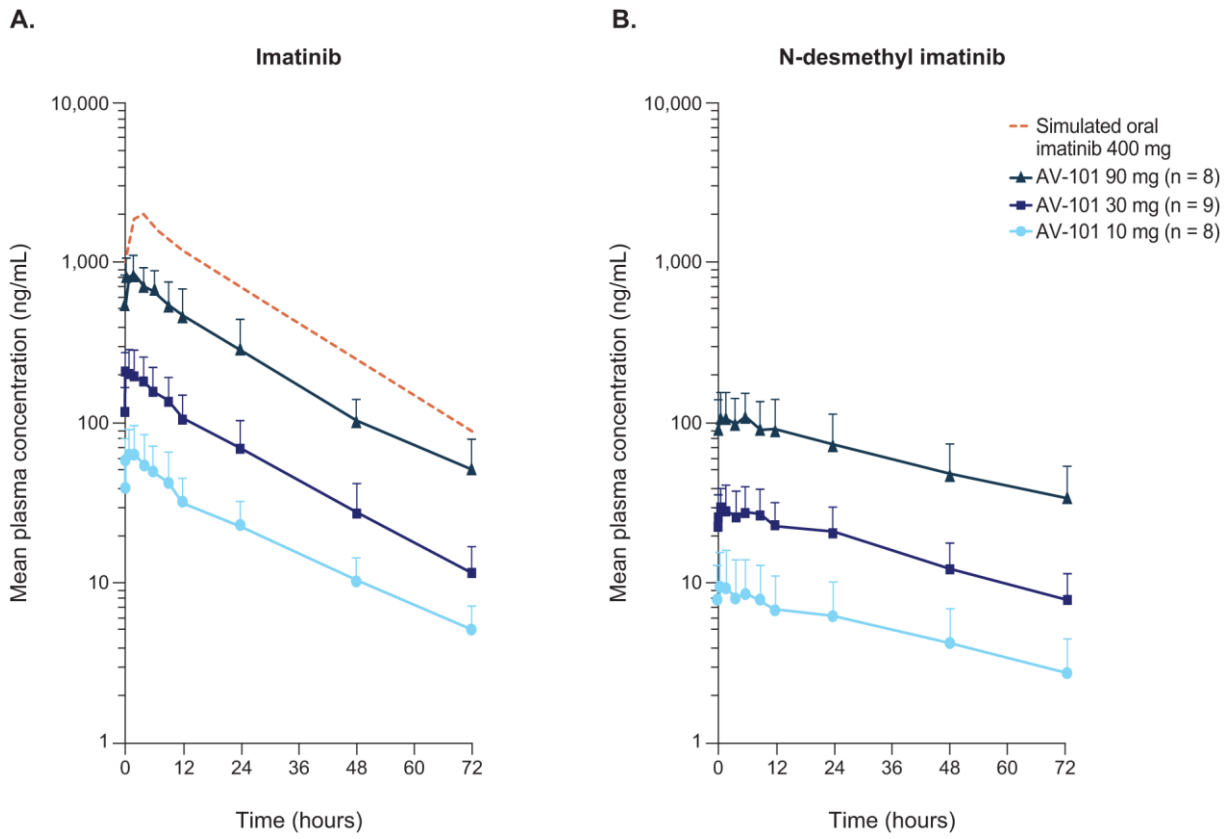
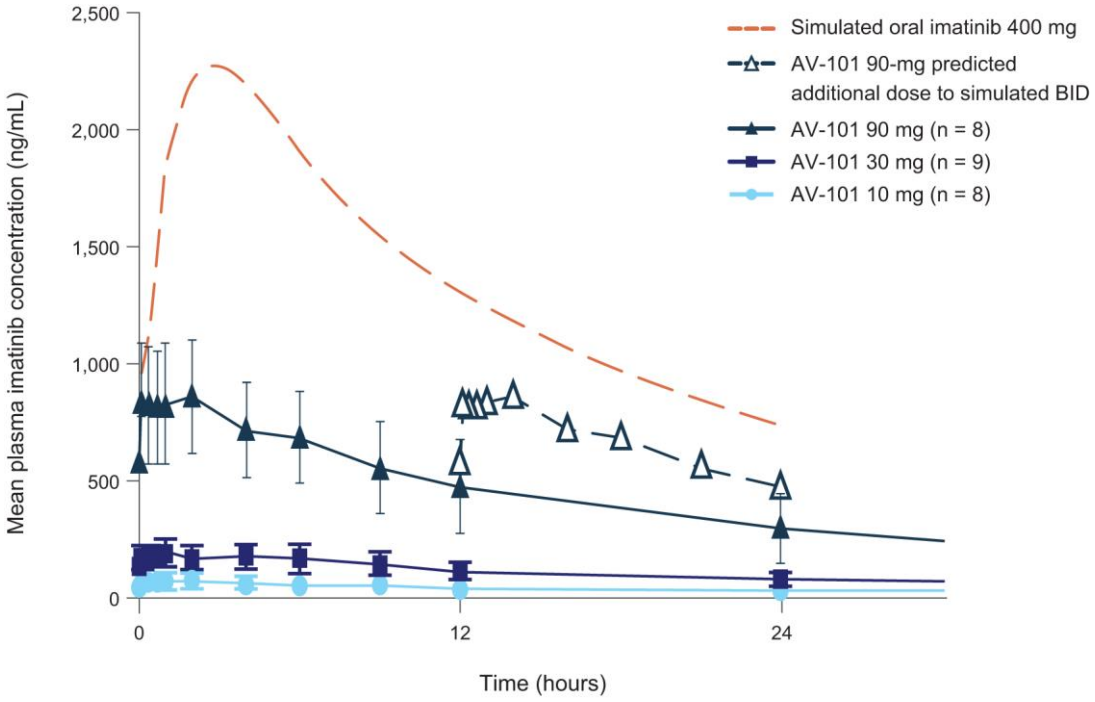

A.
Imatinib
B.
N-desmethyl imatinib
Oral imatinib
400 mg (n = 8)
AV-101 90 mg (n = 6)
AV-101 30 mg (n = 6)
AV-101 10 mg (n = 6)
AV-101 3 mg (n = 6)
AV-101 1 mg (n = 6)
Mean plasma concentration (ng/mL)
10,000
1,000
100
10
1
0.1
0.01
LLOQ
0
12
24
36
48
60
72
Time (hours)


A.
Imatinib
Mean plasma concentration (ng/mL)
10,000
1,000
100
10
1
0
12
24
36
48
60
72
Time (hours)
B.
N-desmethyl imatinib
Simulated oral imatinib 400 mg
AV-101 90 mg (n = 8)
AV-101 30 mg (n = 9)
AV-101 10 mg (n = 8)
Mean plasma concentration (ng/mL)
Time (hours)


Simulated oral imatinib 400 mg
AV-101 90-mg predicted additional dose to simulated BID
AV-101 90 mg (n = 8)
AV-101 30 mg (n = 9)
AV-101 10 mg (n = 8)
Mean plasma imatinib concentration (ng/mL)
2,500
2,000
1,500
1,000
500
0
0
12
24
Time (hours)

Supplemental Appendix for "AV-101, a Novel Inhaled Dry Powder Formulation of Imatinib, in Healthy Adult Participants: A Phase 1 Single and Multiple Ascending Dose Study"

Supplemental Methods

Inclusion and Exclusion Criteria

Adequate respiratory function was determined as forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) ≥80% of predicted at the screening visit and baseline, together with a normal chest X-ray. Participants could not have been a chronic smoker of any kind within the preceding 5 years or consumed any nicotine-containing products for ≥180 days prior to the study, although participants with occasional (non-daily) use of electronic cigarettes or marijuana were not specifically excluded. Participants were excluded if they had a history of clinically significant medical or psychiatric conditions, in particular respiratory conditions (e.g., asthma or chronic cough) or cardiac conditions (e.g., heart failure, hypokalaemia, long QT syndrome). Other exclusion criteria included a recent history (within the preceding 2 years) of alcoholism or drug abuse, consumption of 600 mg caffeine/day or within 12 hours before dosing and 2 hours after dosing on pharmacokinetic sampling days, and difficulty or inability to use the inhaler device effectively during the study.

Patient Allocation and Dose Escalation

Randomization to AV-101 or placebo within each inhaled SAD and MAD dose cohort was conducted by a sponsor representative not involved in data management or safety review, with randomisation codes supplied to the study site pharmacist. For both the SAD and MAD parts of the study, a safety review team (SRT; principal investigator and sponsor medical monitor) reviewed the safety data at the end of each dose period and decided whether to proceed with dose escalation to the subsequent cohort; ≥6 participants in the SAD cohorts and ≥9

participants in the MAD cohorts (including participants receiving AV-101 or placebo) who had completed dosing were required by the SRT to make the dose escalation decision.

As specified in the protocol, if at any time a participant demonstrated a ≥15% decline in predicted FEV_1 together with symptoms suggestive of bronchospasm, they were withdrawn from the study. If more than 2 participants experienced a symptomatic treatment related ≥15% decline in predicted FEV_1 from baseline, dosing ceased for those participants and the SRT met to discuss whether to proceed with dosing for the remainder of that cohort. If 1 participant in a dose cohort experienced a grade 4 adverse event (AE) or if ≥3 participants experienced a grade 3 AE, dosing was paused for that cohort and the SRT assessed whether to continue dosing in that cohort, with IRB approval. If ≥2 participants in a dose cohort experienced a grade 4 AE, dosing was stopped for that cohort and no further dose escalation was undertaken if the AEs were considered drug-related.

Supplemental Table S1. Demographic Characteristics for Individual AV-101 Dosing Cohorts

	AV-101 1 mg	AV-101 3 mg	AV-101 10 mg	AV-101 30 mg	AV-101 90 mg
SAD					
Participants, n	**6**	**6**	**6**	**6**	**6**
Median (range) age, years	35.5 (28, 58)	39.5 (25, 48)	38.5 (33, 59)	45.5 (33, 57)	33.5 (19, 56)
Female, n (%)	3 (50)	3 (50)	2 (33)	3 (50)	5 (83)
Race, n (%)					
White	4 (67)	3 (50)	2 (33)	3 (50)	2 (33)
Black or African American	2 (33)	3 (50)	4 (67)	3 (50)	4 (67)
Mean (range) BMI, kg/m^2	27.4 (23.0, 31.3)	29.1 (25.0, 32.0)	31.0 (27.7, 33.9)	28.2 (18.7, 32.8)	31.2 (27.3, 34.9)
MAD[a]					
Participants, n			**8**	**9**	**9**
Median age, years (range)	—	—	44.5 (29, 55)	37.0 (21, 58)	47.0 (29, 58)
Female, n (%)	—	—	2 (25)	1 (11)	6 (67)
Race, n (%)					
White	—	—	4 (50)	8 (89)	6 (67)
Black or African American			4 (50)	1 (11)	2 (22)
American Indian or Alaska Native			0	0	1 (11)
Mean (range) BMI, kg/m^2	—	—	28.3 (18.9, 34.4)	28.2 (24.1, 31.8)	29.6 (25.0, 33.0)

BID, twice daily; BMI, body mass index; MAD, multiple ascending dose; SAD, single ascending dose.
[a]Dose given BID for 7 days, with only the morning dose administered on Day 7.