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A Phase 1 Single and Multiple Ascending Dose (SAD/MAD) Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of AV-101, a Novel Inhaled Dry Powder Formulation of Imatinib in Healthy Adults

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BACKGROUND

- Pulmonary arterial hypertension (PAH) is a rare disease characterized by excessive pulmonary vasoconstriction and abnormal vascular remodeling[1-3]; vascular remodeling in PAH involves hyperproliferation in the pulmonary vasculature[1]
- Current therapies approved for PAH do not address the underlying pathophysiology of PAH[4]
- Imatinib, a multitargeted tyrosine kinase inhibitor initially approved for the treatment of patients with chronic myeloid leukemia,[5] has shown therapeutic promise for its antiproliferative and proapoptotic properties in preclinical PAH studies[6-9]
- When assessed in a phase 3 randomized trial (IMPRES) conducted by Novartis, oral imatinib (Gleevec®) 400 mg significantly improved 6-minute walk distance (6MWD) and hemodynamics for a subset of patients with PAH[10]
- Despite the favorable efficacy findings from the IMPRES trial, there were high rates of discontinuation and systemic adverse events (AEs),[10] and the development of oral imatinib for the treatment of PAH was discontinued
- AV-101 is a novel inhaled dry powder formulation of imatinib being developed to achieve similar activity via local exposure in respiratory tissue at a substantially lower dose, potentially circumventing the systemic AEs associated with oral imatinib

OBJECTIVE

- This phase 1 study was conducted to evaluate the safety, tolerability, and pharmacokinetics of inhaled AV-101 in healthy adult participants

METHODS

Study Design

- This was a phase 1, placebo-controlled, double-blind, randomized, 2-part study of AV-101 given as single or multiple ascending doses (SAD/MAD) in healthy adults aged 18 to 59 years
- AV-101 capsules of 2 dose strengths (1 mg or 10 mg) were inserted into a dry powder inhaler; for each dosing time point, participants inhaled 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

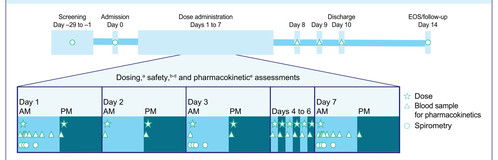
SAD Study

- The SAD study included 5 cohorts with 8 participants each (randomized to AV-101 [n = 6] or placebo [n = 2]) who were administered, in planned progression, a 1-, 3-, 10-, 30-, or 90-mg single dose of inhaled AV-101 or placebo
- An additional cohort of 8 participants received a single dose of oral imatinib 400 mg
- Blood samples were taken prior to and after dosing at 5, 20, and 40 minutes and at 1, 2, 4, 6, 9, 12, 48, and 72 hours

MAD Study

- The MAD study included 3 cohorts with up to 12 participants each (randomized to AV-101 [n = 9] or placebo [n = 3]) who were administered a 10-, 30-, or 90-mg dose of inhaled AV-101 or placebo twice daily (BID) for 7 days; only the morning dose was administered on Day 7 (**Figure 1**)
- Due to its known tolerability profile, the predicted steady-state exposure data for multiple doses of oral imatinib were obtained using a population pharmacokinetics model and data for oral imatinib 400 mg from the SAD study

Figure 1. MAD Study Design and Schedule of Assessments



EOS, end of study; MAD, multiple ascending dose; SpO_2, oxygen saturation.
*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.
†Vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) and SpO_2 were recorded at screening, on Day 0, prior to and at 1 hour after each dose, the morning of discharge on Day 10, and at the follow-up visit on Day 14.
‡Laboratory tests (hematology, biochemistry, and urinalysis) were performed at screening; on Days 0 to 3, 7, and 8; and at the follow-up visit on Day 14.
§Spirometry assessments (per American Thoracic Society guidelines) were performed at screening; on Day 0; prior to dosing and at 20 minutes, 1 hour, and 4 hours after the morning dose on Days 1, 3, and 7; and at the follow-up visit on Day 14.
¶Blood samples were taken on Days 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 to 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 (ie, Days 8, 9, and 10).

Statistical Analysis

- Descriptive statistics and derived parameters were calculated with the Phoenix WinNonlin® (Certera) toolkit
- To assess dose proportionality, the natural log-transformed pharmacokinetic parameters for AV-101 were analyzed; parameters were considered dose proportional if the 90% confidence interval for the slope coefficient included 1
- To compare log-transformed pharmacokinetic parameters for AV-101 versus oral imatinib, an analysis of variance with a Tukey-Kramer's post hoc test for multiple comparisons was performed; 2-sided significance was set to α = 0.05

RESULTS

Participants

- A total of 82 participants (SAD, n = 48; MAD, n = 34) were included in the study; demographics are presented in **Table 1**

Table 1. Demographic Characteristics

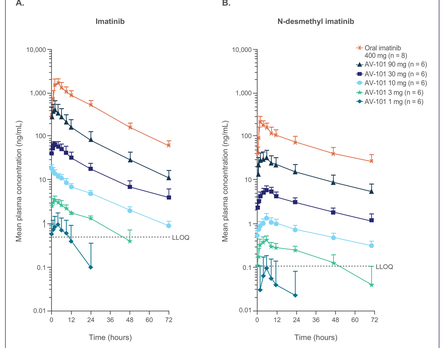
	Overall AV-101	Pooled placebo	Oral imatinib 400 mg
SAD			
Participants, n	30	10	8
Median (range) age, years	37.5 (19, 59)	34.5 (27, 49)	48.0 (36, 58)
Female, n (%)	16 (53)	6 (60)	1 (13)
Race, n (%) White Black or African American	 14 (47) 16 (53)	 3 (30) 7 (70)	 2 (25) 6 (75)
Mean (range) BMI, kg/m^2	29.4 (19, 35)	28.7 (20, 33)	28.5 (22, 34)
MAD[a]			
Participants, n	26	8	–
Median (range) age, years	40.0 (21, 58)	37.5 (22, 53)	–
Female, n (%)	9 (35)	3 (38)	–
Race, n (%) White Black or African American American Indian or Alaska Native	 18 (69) 7 (27) 1 (4)	 4 (50) 4 (50) 0	 – – –
Mean (range) BMI, kg/m^2	28.7 (19, 34)	27.2 (20, 32)	–

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.

SAD Pharmacokinetics

- Following AV-101 administration, plasma concentrations of imatinib and N-desmethyl imatinib increased in a dose-dependent but greater than dose-proportional manner (**Figure 2** and **Table 2**)
- For all AV-101 doses, lower systemic exposure was observed versus oral imatinib 400 mg (P <0.001)

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



LLOQ, lower limit of quantification; SAD, single ascending dose; SD, standard deviation.
Data are presented as mean +SD over 72 hours following administration on Day 1.

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

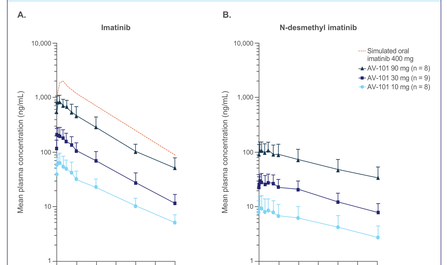
	AV-101 1 mg (n = 6)	AV-101 3 mg (n = 6)	AV-101 10 mg (n = 6)	AV-101 30 mg (n = 6)	AV-101 90 mg (n = 6)	Oral imatinib 400 mg (n = 8)
Imatinib						
C_{max}, ng/mL	1.2 (0.6)	3.8 (0.5)	20.2 (4.8)	73.8 (9.2)	423.8 (253.1)	1,712.1 (483.7)
T_{max}, h	3.0 (0.1, 4.0)	2.0 (0.1, 2.0)	0.2 (0.1, 1.1)	2.0 (0.7, 6.1)	2.1 (1.1, 2.1)	4.0 (2.0, 4.0)
$AUC_{0\text{-}t}$, 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)
$MRT_{0\text{-}t}$, 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)
$AUC_{0\text{-}t}$, 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)
$MRT_{0\text{-}t}$, 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)

$AUC_{0\text{-}t}$, 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; $t_{1/2}$, half-life; T_{max}, time of maximum observed concentration. Pharmacokinetic parameters were estimated using non-compartmental 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.

MAD Pharmacokinetics

- Following multiple inhaled administrations of AV-101 (BID over 7 days), plasma concentrations of imatinib and N-desmethyl imatinib increased in a dose-proportional manner (**Figure 3** and **Table 3**)
- For all AV-101 doses, lower steady-state systemic exposure was observed compared to the simulated steady-state exposure of oral imatinib 400 mg 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**)

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



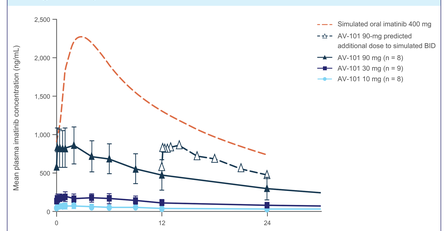
MAD, multiple ascending dose; SD, standard deviation.
Data are presented as mean +SD over 72 hours following administration on Day 7.

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

	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
Imatinib				
$C_{max,ss}$, 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)	–
$AUC_{0\text{-}24}$, 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)	Simulated steady-state oral imatinib 400 mg
$C_{max,ss}$, 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)	–

$AUC_{0\text{-}24}$, 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 dose; 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}, which is presented as median (range).

Figure 4. Concentration-time Profiles for Imatinib Following MAD (Day 7) Over 24 Hours of Inhaled AV-101 With Simulated BID Dosing and Simulated Oral Imatinib 400 mg at Steady State



BID, twice daily; SD, standard deviation.
Data are presented as mean ± SD over 72 hours following administration on Day 7.

Safety and Tolerability

- In the SAD part of the study, the most common treatment-emergent AEs (TEAEs) were dizziness (AV-101, n = 2; placebo, n = 1) and headache (AV-101, n = 3)
- In the MAD part of the study, the most common TEAEs were short periods of cough (AV-101, n = 7 [27%]) and headache (AV-101, n = 4 [15%]; **Table 4**), primarily in the 90-mg cohort
  - All TEAEs were grade 1 or 2 in severity; all grade 2 TEAEs occurred in the MAD 90-mg cohort and resolved by the end of the study
  - Although coughing was the most common TEAE, only 1 participant experienced grade 2 coughing, and spirometry testing indicated that AV-101 inhalations did not negatively impact lung function at 20 minutes after dosing
  - Only 1 participant discontinued due to an AE (vomiting), which occurred on Day 1
- There were no clinically important changes in vital signs or hematology, clinical chemistry, and urinalysis values

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)
TEAEs in ≥2 participants, n (%) Cough Headache Throat irritation Musculoskeletal pain Nausea Chest discomfort	 1 (13) 0 0 0 0 0	 1 (11) 0 1 (11) 0 0 0	 5 (56) 4 (44) 1 (11) 2 (22) 2 (22) 2 (22)	 7 (27) 4 (15) 2 (8) 2 (8) 2 (8) 2 (8)	 0 0 0 0 0 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, multiple ascending dose; 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.

Conclusions

- AV-101 was generally well tolerated in healthy adult participants
- Lower doses of AV-101, delivered by dry powder inhalation, significantly reduced systemic exposure to imatinib compared with oral imatinib in healthy adult participants
- Coughing and headache were the most frequent TEAEs in the MAD portion of the study, which mainly occurred at the highest dose of AV-101

Future Studies

- To mitigate coughing, future studies of AV-101 will decrease the amount of dry powder inhaled with the 90-mg dose by ≥60% (ie, 2 capsules per dose vs 9 capsules per dose)
- An ongoing phase 2b/phase 3 will evaluate whether AV-101 delivers clinical benefit with an acceptable safety and tolerability profile in patients with PAH (NCT05036135)

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DISCLOSURES

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