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Nebulized nintedanib (AP02) for idiopathic pulmonary fibrosis demonstrates favorable safety and lung lining fluid exposures: results from two phase i safety, tolerability, and pharmacokinetics studies

Michelle Palacios · Rebecca Boone · Stephen Pham · Sam Francis · Jason Lickliter · Mark Surber · Deepthi Nair · Felix A. Woodhead · Howard M Lazarus · Craig S Conoscenti · Melissa Rhodes

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Abstract

Background Oral nintedanib has been associated with dose-limiting adverse events directly impacting tolerability and adherence. AP02 is a novel nintedanib solution for inhalation intended to minimize systemic exposure and thereby potentially improve tolerability. These studies assessed the safety, tolerability, and pharmacokinetics of AP02 in healthy volunteers and patients with idiopathic pulmonary fibrosis.

Methods Data were generated in 2 randomized phase I clinical studies (AP02-001 and AP02-002). AP02-001 ($n=38$) evaluated AP02 in single ascending doses up to 2.0 mg in healthy volunteers ($n=32$) and patients with idiopathic pulmonary fibrosis ($n=6$). AP02-002 evaluated AP02 in single ($n=36$) and multiple ($n=24$) ascending doses up to 8.0 mg twice daily for 7 days in healthy volunteers. Safety, tolerability, and nintedanib plasma pharmacokinetics were evaluated. AP02 and oral nintedanib bronchoalveolar lavage pharmacokinetics were assessed.

Results No serious adverse events were reported. The most common drug-related events were headache, nausea, and cough in AP02-001 and dizziness in AP02-002. Systemic exposure of the highest evaluated dose, 8.0 mg AP02 twice daily, was at a minimum 10-fold lower than the mean steady state exposure of the approved 150 mg oral nintedanib twice-daily dose. Nintedanib C_{max} and AUC_{0-12} in epithelial lining fluid following a 4.0 mg AP02 dose were predicted to exceed that of oral nintedanib by ~26-fold.

Conclusions AP02 was well tolerated in single and multiple doses up to 8.0 mg twice daily. AP02 resulted in lower systemic and higher lung exposures than oral nintedanib. These findings suggest that nebulized delivery of nintedanib may be a promising treatment for idiopathic pulmonary fibrosis.

Trial registration AP02-001 and AP02-002 were registered as ACTRN12620001141932 (November 2, 2020) and ACTRN12624000825550 (July 4, 2024), respectively, on ANZCT.

Keywords Lung diseases · Disease progression · Therapeutics · Pulmonary fibrosis · Inhaled therapies · AP02 · Nintedanib · Pharmacokinetics · Dose · Nebulizer

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Background

Idiopathic pulmonary fibrosis (IPF) is a severe, chronic, progressive, fibrosing interstitial lung disease with a poor prognosis and a median survival time from diagnosis of 3 to 5 years [1–3]. The incidence and prevalence of the disease have been increasing, with current estimates of the global prevalence of IPF in the range of 0.33 to 4.51 per 10,000 persons [4, 5].

Nintedanib is 1 of 3 oral therapeutics approved by the U.S. Food and Drug Administration and 1 of 2 approved by the European Medicines Agency for the treatment of IPF and has been shown to reduce lung function decline in patients with IPF [6–11]. Nintedanib is also approved in the U.S. and E.U. for the treatment of progressive pulmonary fibrosis (PPF) [6, 7]. The therapeutic acts by inhibiting receptor tyrosine kinases and non-receptor tyrosine kinases, blocking intracellular signaling cascades involved in the pathogenesis of interstitial lung diseases (ILD), including IPF [6]. While oral nintedanib has been demonstrated to be effective in slowing disease progression in individuals with IPF and PPF, treatment has been associated with tolerability issues. Gastrointestinal disorders such as diarrhea, nausea, and vomiting have been reported to occur when treatment is given at the approved dosages. These adverse events have led to reduced patient adherence [6, 12–14]. As a result, there is a need for more tolerable IPF therapeutics and an opportunity to improve their effectiveness, either by targeting novel pathways or by developing new treatment modalities. With direct lung delivery, pulmonary concentrations are maximized while minimizing oral adverse event–associated systemic exposure.

AP02 is a novel nintedanib solution for inhalation that is delivered by the PARI eFlow Nebulizer System (eFlow) [15]. Preclinical data and modeling suggest that, compared to oral nintedanib, lower doses have the potential to reduce systemic toxicity and improve efficacy [16].

Here, we report findings from 2 phase I studies administering AP02 via nebulization. The primary objective of the studies was to assess the safety and tolerability of AP02 when administered in single and multiple ascending doses in healthy volunteers and patients with IPF. Secondary objectives across both studies included assessing nintedanib plasma and bronchoalveolar pharmacokinetics following single or multiple doses of AP02 or a single 150 mg oral nintedanib dose.

Methods

Study design

The two phase I studies were performed to evaluate safety, tolerability, and pharmacokinetics of AP02 when administered via oral inhalation using the eFlow nebulizer. Both study 1 (AP02-001) and study 2 (AP02-002) were randomized, double-blind, placebo-controlled studies performed in Australia. Additional details on methods are provided in the supplementary material.

Study protocols complied with the International Council for Harmonisation Good Clinical Practice guideline, the recommendations of the Declaration of Helsinki, and any applicable country-specific laws, regulations, and guidelines. Protocols were approved by the local ethics committee (Alfred Hospital Ethics Committee), and all participants provided written informed consent prior to study procedures.

AP02-001

AP02-001 was a first-in-human study that had 6 cohorts in total ($n=38$). Three single ascending dose (SAD) cohorts were comprised of healthy volunteers who were randomized to receive either AP02 or placebo at a 6:2 ratio ($n=8$ per cohort). Individuals administered AP02 in these 3 sequential cohorts received either a 0.5 mg, 1.0 mg, or 2.0 mg dose. The dose level was escalated to the next cohort after the Safety Review Committee reviewed blinded safety data from all subjects in that cohort.

The bronchoalveolar lavage (BAL) cohort was comprised of healthy volunteers who received a single dose of either 2.0 mg AP02 or oral nintedanib at the approved dosage of 150 mg ($n=4$ per cohort) [6]. These cohorts underwent BAL at either 30 to 45 min or 9 h post-dose, respectively, and the concentration of nintedanib in these samples was determined. Exposure in the epithelial lining fluid (ELF), which lines the luminal surface of respiratory mucous membranes, was determined by using urea to correct for BAL dilution [17, 18]. Concentrations in this fluid are used to estimate drug concentrations in the lungs [19]. For the orally dosed cohort, the ratio of nintedanib in ELF to nintedanib in plasma was obtained based on the mean nintedanib concentration in ELF at 9 h post-dose and the mean nintedanib concentration in plasma at 8 h post-dose. This ratio was applied to human plasma data collected up to 24 h post-dose from the orally dosed cohort to predict an ELF concentration-time profile.

The last cohort in AP02-001 included 6 IPF patients who received 2.0 mg of AP02. The BAL and IPF patient cohorts were run in parallel and were not blinded as no subjects received placebo (Figs. 1 and 2). The patients with IPF did not undergo BAL.

Participants were contacted between Days 5 and 7 for a final follow-up assessment to determine if any adverse events occurred. In the case of adverse events at the final follow-up assessment, further investigation and follow up was determined by the investigator. The schedule of activities is provided in the supplementary material.

AP02-002

The AP02-002 study had 7 cohorts of healthy volunteers and did not involve patients with IPF. In the SAD cohorts, subjects were randomized to receive either single ascending doses of AP02 or placebo at a 6:2 ratio ($n=8$ per cohort). Individuals who received AP02 in these cohorts received a single dose of either 2.0 mg, 4.0 mg, or 8.0 mg. These cohorts were run sequentially, with dose escalation occurring after the review of blinded safety data by the Safety Review Committee.

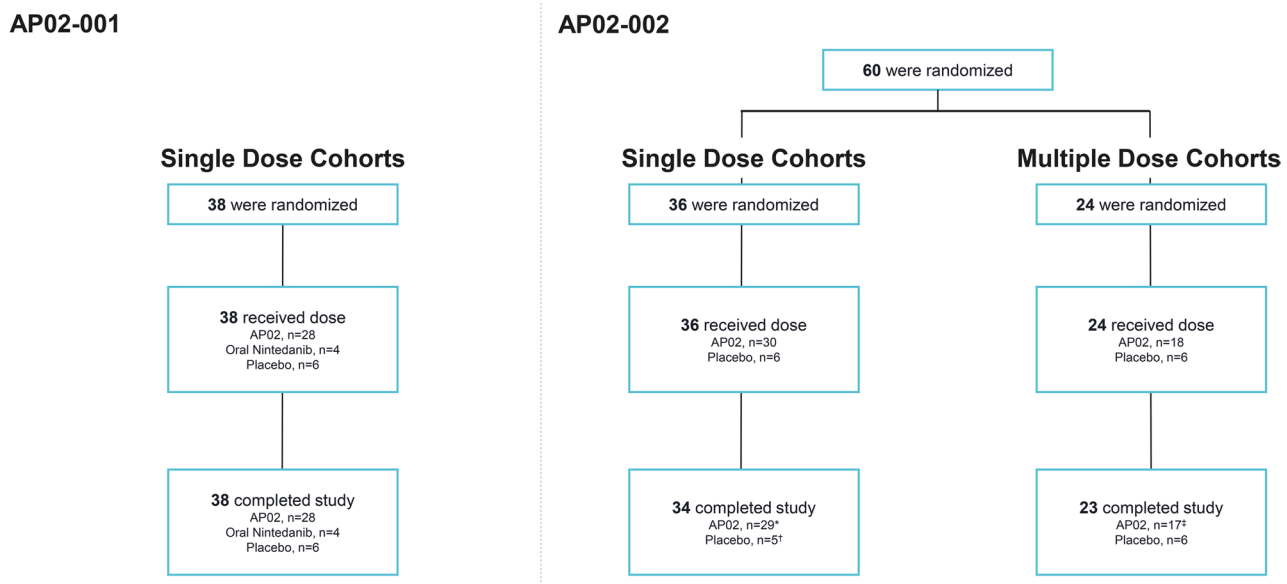


Fig. 1 Participant Disposition for AP02-001 and AP02-002. Blue arrows indicate instances where dose of AP02 was escalated between cohorts. *1 participant in the 4.0 mg AP02 BAL cohort discontinued the study (withdrawal of consent). †1 participant in the placebo group for the AP02-002 SAD cohort was lost to follow-up. This participant missed the safety assessments at the final follow-up visit. ‡1 participant in the 4.0 mg BID AP02 cohort was lost to follow-up. This participant missed the safety assessments at the final follow-up visit

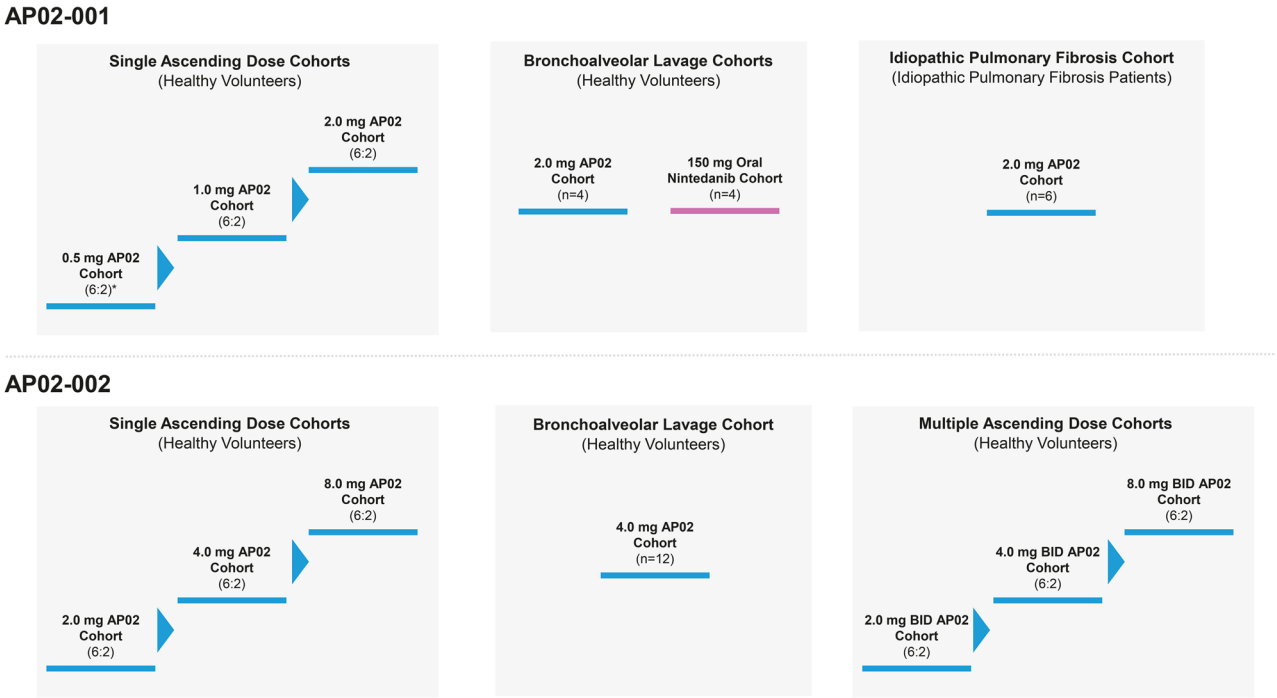


Fig. 2 Study Design for AP02-001 and AP02-002. Blue arrows indicate instances where dose of AP02 was escalated between cohorts. *Ratios represent treatment allocation (active: placebo)

In another cohort, 12 healthy volunteers received 4.0 mg AP02 and then underwent BAL with collections at 45 min,4 h, or 12 h post-treatment ($n=4$ per timepoint) to determine the ELF exposure. Sequential BALs were not performed on any of the subjects. This cohort was not blinded, as all individuals received active drug.

In the multiple ascending dose (MAD) cohorts, healthy volunteers were randomized to receive either multiple ascending doses of AP02 or placebo at a 6:2 ratio ($n=8$ per cohort). Doses were administered twice daily (BID) on Days 1 to 6 with one final dose administered on Day 7. In individuals who received AP02, doses of either 2.0 mg BID, 4.0 mg BID, or 8.0 mg BID were given to individuals in the 3 MAD cohorts, with different doses given in each cohort (Figs. 1 and 2).

For participants in the AP02-002 SAD cohorts, a final follow-up visit occurred between Days 3 and 5 to conduct clinical laboratory safety assessments and determine adverse events. For the MAD cohorts, the final follow-up visit occurred between Days 12 and 14. Any clinically significant laboratory abnormalities that were identified were followed until resolution. The schedule of activities for the SAD and MAD cohorts is provided in the supplementary material.

Participants

Key inclusion criteria for healthy volunteers in these studies included being aged 18 to 55 years for AP02-001 and aged 18 to 65 years for AP02-002. Healthy volunteers in AP02-002 also needed to have a forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio of >0.80. For patients with IPF in AP02-001, an IPF diagnosis based on 2018 professional society guidelines was required and individuals aged 18 to 80 years were included [20].

Key exclusion criteria for healthy volunteers in AP02-001 and AP02-002 included having a history of a reactive airways disease (such as asthma or chronic obstructive pulmonary disease [COPD]), cystic fibrosis, or bronchiectasis. Patients with IPF in AP02-001, however, could have a history of COPD or asthma. Full eligibility criteria are provided in the supplementary material.

Study treatment

The AP02 solution for inhalation was prepared by admixing 2 solutions (active solution and diluent) at the point of use and administered by oral inhalation following nebulization using the eFlow nebulizer. Placebo was prepared and administered in the same manner. For each study, the admixed AP02 solution consisted of the same formulation composition but with different dosing volumes. In AP02-001, the 0.5, 1.0, and 2.0 mg AP02 doses were achieved by preparing 2, 4, and 8 mL of the admixed AP02 solution. In AP02-002, the 2.0, 4.0, and 8.0 mg AP02 doses were achieved by preparing 5, 10, and 20 mL of the admixed AP02 solution. The doses investigated were based on allometric scaling from preclinical models of efficacy, projections of drug exposure in humans, and conservative margins for nonclinical assessments.

Study endpoints and analyses

The primary endpoint for both studies included measures of safety and tolerability, including assessment of adverse events, laboratory values, vital signs, and pulse oximetry, as well as physical examinations before and after study drug administration. Spirometry was conducted in the AP02-001 non-BAL cohorts and in all cohorts in AP02-002. Twelve-lead electrocardiograms were assessed in the AP02-001 BAL cohorts and in all cohorts in AP02-002. The main secondary endpoint in both studies was the analysis of nintedanib plasma pharmacokinetics. Plasma pharmacokinetics of the nintedanib metabolite BIBF1202 and bronchoalveolar pharmacokinetics of AP02 following single dosing were also secondary endpoints for the AP02-002 study. Bronchoalveolar nintedanib exposures were determined via BAL following single AP02 or oral dosing and were analyzed as an exploratory endpoint for AP02-001.Descriptive statistics were used to summarize safety and pharmacokinetic parameters.

Results

Participants and baseline characteristics

A total of 32 healthy volunteers and 6 patients with IPF were included in the AP02-001 study, and 60 healthy volunteers were included in the AP02-002 study (Figs. 1 and 2).

Description of demographic and clinical characteristics of study participants is reported in Tables 1 and 2. In AP02-001, mean (SD) age of participants was 32.8 (17.59) years and approximately half of participants were male ($n=18$ [47.4%]). Most participants were either White ($n=21$ [55.3%]) or Asian ($n=16$ [42.1%]). In the IPF cohort, 4 individuals (66.7%) were pretreated with salbutamol prior to receiving an AP02 dose, based on protocol due to smoking history and/or COPD, and the FEV_1/FVC ratio ranged from 0.702 to 0.866. The mean (SD) age of participants in the single-dose cohorts of AP02-002 was 33.4 (14.3) years and in the multiple dose cohorts of AP02-002 was 31.5 (11.4) years. The majority of participants in this study were male ($n=54$ [90%]) and White ($n=31$ [51.7%]) or Asian ($n=21$ [35.0%]).

Safety evaluation

In the AP02-001 study, the maximum AP02 dose evaluated was 2.0 mg, which was deemed tolerable by the Safety Review Committee. Sixteen treatment emergent adverse events (TEAEs) were reported by 11 (28.9%) of the 38 participants. One TEAE was reported by 1 (16.7%) of the 6 participants in the placebo group and 15 TEAEs were reported by 10 (31.3%) of the 32 participants in the AP02 treatment group. No TEAEs were reported in the 0.5 mg AP02 SAD cohort or 150 mg oral nintedanib BAL cohort. The highest frequency of TEAEs overall in AP02-001 was reported in the cohort with IPF, with 83.3% of participants ($n=5$) in the cohort reporting at least 1 TEAE. Of the 16 TEAEs reported, 10 were considered possibly or probably drug-related, with the most

common drug-related events being headache ($n=2$), nausea ($n=2$), and cough ($n=2$). The drug-related events were reported by 21.1% of participants ($n=8$) (Table 3, Supplementary Table S1). These events were mild except for 1 headache in the IPF cohort that was moderate in severity (Supplementary Table S2).

In the AP02-002 study, 18 TEAEs were reported by 12 (33.3%) of the 36 participants in the SAD and BAL cohorts. A total of 33.3% ($n=2$) of the participants in the placebo group reported 3 TEAEs and 33.3% ($n=10$) of participants in the AP02 treatment group reported 15 TEAEs. The 4.0 mg AP02 BAL cohort had the highest frequency of participants that reported TEAEs, with 50% of participants ($n=6$) reporting 11 of the 18 TEAEs. Four of the 18 TEAEs reported in the SAD and BAL cohorts were considered drug-related, with the most common event being dizziness (Table 4, Supplementary Table S3). TEAEs reported in the single-dose studies were either mild ($n=16$) or moderate ($n=2$) in severity (Supplementary Table S4). Eight TEAEs were reported by 6 (25%) of 24 participants in the MAD cohorts, with all 6 of these participants being part of the AP02 treatment group (33.3%). Two of these TEAEs were considered drug-related (Table 4, Supplementary Table S3). TEAEs reported in the multiple dose cohorts were all mild ($n=7$) or moderate ($n=1$) in severity (Supplementary Table S4). No TEAEs of diarrhea were reported.

None of the TEAEs reported led to withdrawal from the studies and no serious adverse events or deaths were reported in either study. Furthermore, no bronchospasm, oxygen desaturation, or TEAEs related to vital signs, electrocardiograms, physical examinations, or spirometry were reported during either study.

Plasma pharmacokinetic evaluation

Single-dose cohorts

In participants administered a single dose of AP02 in the AP02-001 study (3 SAD cohorts, 2.0 mg AP02 BAL cohort, and IPF patient cohort) and the AP02-002 study (3 SAD cohorts and 4.0 mg AP02 BAL cohort), median time to maximum nintedanib plasma concentration (T_{max}) was observed early, with all AP02 dosed cohorts reporting a median T_{max} within 0.40 h after end of inhalation (Figs. 3 and 4; Table 5). Conversely, in participants administered oral nintedanib in the AP02-001 study, plasma nintedanib levels reached a median T_{max} at 6 h (Fig. 3). Mean plasma BIBF1202 concentration over time displayed a similar trend to nintedanib, with participants administered AP02 having a median BIBF1202 T_{max} within 0.40 h after end of inhalation, and participants who received oral nintedanib having a later BIBF1202 T_{max} of 6.00 h (Supplementary Tables S5 and S6).

Nintedanib systemic exposure generally increased with increasing AP02 dose. In AP02-001, geometric mean values for the area under the concentration-time curve from time 0 to 24 h (AUC_{0-24}) and maximum observed concentration (C_{max}) were 0.47 h*ng/mL and 0.33 ng/mL, respectively, for the 0.5 mg AP02 cohort; 1.81 h*ng/mL and 1.02 ng/mL, respectively, for the 1.0 mg AP02 cohort; and 2.17 h*ng/mL and 1.05 ng/mL, respectively, for the 2.0 mg AP02 cohort. In AP02-002, geometric mean values for area under the concentration-time curve from time 0 to the last measurable concentration (AUC_{0-last}) and C_{max} were 1.61 h*ng/mL and 0.93 ng/mL, respectively, for the 2.0 mg AP02 cohort; 4.4 h*ng/mL and 1.69 ng/mL, respectively, for the 4.0 mg AP02 cohort; and 13.4 h*ng/mL and 4.75 ng/mL, respectively, for 8.0 mg AP02 cohort. In the AP02-001 study, the elimination half-life ($T_{½\ el}$) of nintedanib was fastest following the administration of the 0.5 mg dose and was comparable for the 1.0 and 2.0 mg doses with median half-lives of 0.90, 5.09, and 4.66 h, respectively. A similar trend was observed in the AP02-002 study, with a median $T_{½el}$ of 8.76, 14.6, and 13.2 h following a single 2.0 mg, 4.0 mg, and 8.0 mg dose of AP02, respectively (Table 5). BIBF1202 pharmacokinetic parameters can be found in Supplementary Tables S5 and S6.

Plasma nintedanib AUC_{0-24} and C_{max} following a single 2.0 mg AP02 dose was approximately 68-fold and 15-fold lower, respectively compared to systemic exposure following a single 150 mg oral nintedanib dose in this study (Table 5).

In AP02-001, patients with IPF administered 2.0 mg AP02 (Cohort 6) had a median T_{max} (0.40 h) comparable to T_{max} in healthy volunteers administered the same dose of AP02 in the SAD cohort (0.37 h). Plasma exposure

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Table 1 Demographic characteristics of study participants in AP02-001

Category	SAD Cohorts				BAL Cohorts		IPF Cohort	
Statistics	Placebo (*N*=6)	0.5 mg AP02 (*N*=6)	1.0 mg AP02 (*N*=6)	2.0 mg AP02 (*N*=6)	2.0 mg AP02 (*N*=4)	150 mg Oral Nintedanib (*N*=4)	2.0 mg AP02 (*N*=6)	Overall (*N*=38)
Age (Years)								
n	6	6	6	6	4	4	6	38
Mean (SD)	24.5 (5.43)	23.3 (5.05)	28.2 (8.82)	30.5 (5.99)	23.5 (4.04)	23.3 (3.59)	69.8 (9.60)	32.8 (17.59)
Median	24.5	22.5	27.0	31.0	22.5	22.5	73.0	27.5
Min, Max	19, 31	18, 30	19, 40	23, 39	20, 29	20, 28	51, 78	18, 78
Sex, *n* (%)								
M	1 (16.7)	4 (66.7)	2 (33.3)	4 (66.7)	1 (25.0)	3 (75.0)	3 (50.0)	18 (47.4)
F	5 (83.3)	2 (33.3)	4 (66.7)	2 (33.3)	3 (75.0)	1 (25.0)	3 (50.0)	20 (52.6)
Race*, *n* (%)								
Asian	3 (50.0)	2 (33.3)	4 (66.7)	4 (66.7)	1 (25.0)	2 (50.0)	0	16 (42.1)
Black or African American	0	0	0	0	0	0	0	0
White	2 (33.3)	4 (66.7)	2 (33.3)	2 (33.3)	3 (75.0)	2 (50.0)	6 (100.0)	21 (55.3)
American Indian or Alaskan Native	0	0	0	0	0	0	0	0
Other	1 (16.7)	0	0	0	0	0	0	1 (2.6)
BMI (kg/m^2)								
n	6	6	6	6	4	4	6	38
Min, Max	20.0, 27.6	19.6, 25.9	18.3, 27.6	20.5, 30.8	18.8, 28.4	21.0, 30.7	22.6, 32.8	18.3, 32.8
FVC								
n	6	6	6	6	4	4	6	38
Mean (SD)	3.7 (0.72)	4.3 (1.21)	4.0 (1.12)	4.4 (1.14)	4.0 (1.34)	4.7 (0.91)	3.0 (0.92)	4.0 (1.10)
Median	3.8	4.4	3.9	4.5	3.9	5.1	2.7	4.0
Min, Max	3.0, 5.0	2.8, 6.3	2.6, 5.4	2.9, 5.8	2.6, 5.8	3.4, 5.3	2.0, 4.1	2.0, 6.3
FEV_1								
n	6	6	6	6	4	4	6	38
Mean (SD)	3.3 (0.80)	3.8 (1.00)	3.3 (0.80)	3.6 (0.72)	3.5 (1.09)	4.0 (0.60)	2.4 (0.76)	3.4 (0.91)
Median	3.1	3.9	3.4	3.6	3.4	3.9	2.1	3.3
Min, Max	2.5, 4.7	2.4, 5.3	2.1, 4.1	2.8, 4.6	2.3, 5.0	3.3, 4.8	1.7, 3.5	1.7, 5.3
Smoking History, *n* (%)								
Never	5 (83.3)	5 (83.3)	6 (100)	5 (83.3)	2 (50.0)	4 (100)	2 (33.3)	29 (76.3)

Table 1 (continued)

Category Statistics	SAD Cohorts				BAL Cohorts		IPF Cohort	
	Placebo (*N*=6)	0.5 mg AP02 (*N*=6)	1.0 mg AP02 (*N*=6)	2.0 mg AP02 (*N*=6)	2.0 mg AP02 (*N*=4)	150 mg Oral Nintedanib (*N*=4)	2.0 mg AP02 (*N*=6)	Overall (*N*=38)
Former	0	0	0	1 (16.7)	0	0	4 (66.7)	5 (13.2)
Current	1 (16.7)	1 (16.7)	0	0	2 (50.0)	0	0	4 (10.5)

All cohorts were comprised of healthy volunteers with the exception of the IPF cohort that was comprised of patients with IPF

BAL Bronchoalveolar lavage, *BMI* Body mass index, *F* Females, *FVC* Forced vital capacity, FEV_1 Forced expiratory volume in 1 s, *IPF* Idiopathic pulmonary fibrosis, *M* Males, *N* Number of subjects dosed, *n* (%) Number and percent of subjects, *SAD* Single ascending dose, *SD* Standard deviation

*All enrolled participants identified as either White, Asian, or White/Asian

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Table 2 Demographic characteristics of study participants in AP02-002

Category Statistics	SAD Cohorts				BAL Cohort	MAD Cohorts				
	Placebo – SAD Cohorts (*N*=6)	2.0 mg AP02 (*N*=6)	4.0 mg AP02 (*N*=6)	8.0 mg AP02 (*N*=6)	4.0 mg AP02 (*N*=12)	Placebo – MAD Cohorts (*N*=6)	2.0 mg BID AP02 (*N*=6)	4.0 mg BID AP02 (*N*=6)	8.0 mg BID AP02 (*N*=6)	Overall (*N*=60)
Age (Years)										
n	6	6	6	6	12	6	6	6	6	60
Mean (SD)	31.2 (14.1)	35.3 (15.3)	38.3 (20.0)	33.0 (16.9)	31.4 (11.1)	31.5 (9.3)	26.7 (7.2)	39.0 (16.9)	28.8 (8.4)	N/A
Median	25.5	29.5	31.0	27.5	28.0	30.0	25.0	36.0	26.0	N/A
Min, Max	22, 59	20, 56	20, 65	20, 65	18, 58	23, 48	19, 37	23, 59	22, 45	N/A
Sex, *n* (%)										
M	5 (83.3)	4 (66.7)	5 (83.3)	6 (100.0)	11 (91.7)	6 (100.0)	6 (100.0)	5 (83.3)	6 (100.0)	54 (90)
F	1 (16.7)	2 (33.3)	1 (16.7)	0 (0)	1 (8.3)	0 (0)	0 (0)	1 (16.7)	0 (0)	6 (10)
Race*, *n* (%)										
Asian	3 (50.0)	2 (33.3)	4 (66.7)	4 (66.7)	2 (16.7)	2 (33.3)	1 (16.7)	2 (33.3)	1 (16.7)	20 (33.3)
Black or African American	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
White	2 (33.3)	3 (50.0)	2 (33.3)	1 (16.7)	7 (58.3)	4 (66.7)	4 (66.7)	4 (66.7)	4 (66.7)	32 (53.3)
American Indian or Alaskan Native	1 (16.7)	0 (0)	0 (0)	1 (16.7)	2 (16.7)	0 (0)	1 (16.7)	0 (0)	1 (16.7)	6 (10.0)
Other	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (3.33)
Multiple	0 (0)	0 (0)	0 (0)	0 (0)	1 (8.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BMI (kg/m^2)										
n	6	6	6	6	12	6	6	6	6	60
Min, Max	19.8, 29.5	21.3, 30.5	23.1, 29.9	19.6, 27.9	18.6, 29.5	24.7, 30.4	21.5, 28.2	24.3, 31.7	22.5, 31.1	18.6, 31.7

All cohorts were comprised of healthy volunteers

BID Twice daily, *BMI* Body mass index, *F* Females, *M* Males, *MAD* Multiple ascending doses, *N/A* Not applicable, *N* Number of subjects dosed, *n* (%) Number and percent of subjects, *SAD* Single ascending dose, *SD* Standard deviation

*All enrolled participants identified as either White, Asian, American Indian or Alaska Native, or Middle Eastern

Table 3 Frequency of subjects experiencing treatment-emergent adverse events in AP02-001

MedDRA® System Organ Class MedDRA® Preferred Term	All Placebo (*N*=6) *n* (%)	SAD Cohorts			BAL Cohorts		IPF Cohort	Overall (*N*=38) *n* (%)
		0.5 mg AP02 (*N*=6) *n* (%)	1.0 mg AP02 (*N*=6) *n* (%)	2.0 mg AP02 (*N*=6) *n* (%)	2.0 mg AP02 (*N*=4) *n* (%)	150 mg Oral Nintedanib (*N*=4) *n* (%)	2.0 mg AP02 (*N*=6) *n* (%)	
Total number of TEAEs	1	0	1	1	7	0	6	16
Number of subjects with at least 1 TEAE	1 (16.7)	0	1 (16.7)	1 (16.7)	3 (75.0)	0	5 (83.3)	11 (28.9)
Number of subjects with at least 1 study drug–related TEAE	1 (16.7)	0	0	1 (16.7)	3 (75.0)	0	3 (50.0)	8 (21.1)
Nervous system disorders	0	0	0	0	2 (50.0)	0	3 (50.0)	5 (13.2)
Headache	0	0	0	0	1 (25.0)*	0	2 (33.3)*†	3 (7.9)*‡
Dizziness	0	0	0	0	0	0	1 (16.7)*	1 (2.6)*
Presyncope	0	0	0	0	1 (25.0)*	0	0	1 (2.6)*
Gastrointestinal disorders	0	0	0	0	2 (50.0)	0	1 (16.7)	3 (7.9)
Nausea	0	0	0	0	1 (25.0)*	0	1 (16.7)*	2 (5.3)*
Abdominal pain	0	0	0	0	1 (25.0)	0	0	1 (2.6)
Respiratory, thoracic, and mediastinal disorders	1 (16.7)	0	0	0	1 (25.0)	0	1 (16.7)	3 (7.9)
Cough	1 (16.7)*	0	0	0	1 (25.0)	0	1 (16.7)*	3 (7.9)*§
Vascular disorders	0	0	0	0	1 (25.0)	0	0	1 (2.6)
Flushing	0	0	0	0	1 (25.0)*	0	0	1 (2.6)*
Hypotension	0	0	0	0	1 (25.0)	0	0	1 (2.6)
General disorders and administration site conditions	0	0	0	1 (16.7)	0	0	0	1 (2.6)
Chest pain	0	0	0	1 (16.7)*	0	0	0	1 (2.6)*
Metabolism and nutrition disorders	0	0	1 (16.7)	0	0	0	0	1 (2.6)
Iron deficiency	0	0	1 (16.7)	0	0	0	0	1 (2.6)
Musculoskeletal and connective tissue disorders	0	0	0	0	0	0	1 (16.7)	1 (2.6)
Back pain	0	0	0	0	0	0	1 (16.7)	1 (2.6)

The safety population consisted of all 38 enrolled participants. "All Placebo" reflects placebo subjects pooled from SAD cohorts; "Overall" included results from all treatment groups (including placebo)

AE Adverse event, *BAL* Bronchoalveolar lavage, *IPF* Idiopathic pulmonary fibrosis, *MedDRA®* Medical Dictionary for Regulatory Activities, Version 23.1., *N* Number of subjects dosed, *n* (%) Number and percent of subjects with treatment-emergent adverse events, *SAD* Single ascending dose, *TEAE* Treatment-emergent adverse event

*Possibly or probably drug-related adverse events

†1 of 2 headache events was considered to be drug-related in the IPF cohort

‡2 of 3 headache events were considered to be drug-related in the overall study population

§ 2 of 3 cough events were considered to be drug-related in the overall study population

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Table 4 Frequency of subjects experiencing treatment-emergent adverse events in AP02-002

MedDRA® System Organ Class MedDRA® Preferred Term	SAD Cohorts				BAL Cohort	MAD Cohorts			
	Placebo-SAD Cohort (*N*=6) *n* (%)	2.0 mg AP02 (*N*=6) *n* (%)	4.0 mg AP02 (*N*=6) *n* (%)	8.0 mg AP02 (*N*=6) *n* (%)	4.0 mg AP02 (*N*=12) *n* (%)	Placebo-MAD Cohort (*N*=6) *n* (%)	2.0 mg BID AP02 (*N*=6) *n* (%)	4.0 mg BID AP02 (*N*=6) *n* (%)	8.0 mg BID AP02 (*N*=6) *n* (%)
Total Number of TEAEs	3	1	2	1	11	0	3	3	2
Number of subjects with at least 1 TEAE	2 (33.3)	1 (16.7)	2 (33.3)	1 (16.7)	6 (50.0)	0	1 (16.7)	3 (50.0)	2 (33.3)
Number of subjects with at least 1 study drug–related TEAE									
Nervous system disorders									
Headache	0	1 (16.7)	0	0	1 (8.3)	0	0	0	0
Dizziness	0	0	1 (16.7)*	0	3 (25.0)*†	0	0	0	0
Presyncope	0	0	0	0	0	0	0	0	0
Gastrointestinal disorders									
Nausea	0	0	0	0	1 (8.3)	0	0	0	0
Abdominal pain	0	0	0	0	0	0	0	0	0
Dry mouth	0	0	0	1 (16.7)	0	0	0	0	0
Tooth impacted	0	0	0	0	1 (8.3)	0	0	0	0
Vomiting	0	0	0	0	1 (8.3)	0	0	0	0
Respiratory, thoracic, and mediastinal disorders									
Productive cough	1 (16.7)	0	0	0	0	0	0	0	0
Dyspnoea	0	0	0	0	1 (8.3)	0	0	0	0
Throat irritation	0	0	0	0	1 (8.3)*	0	0	0	0
Oropharyngeal pain	0	0	0	0	0	0	0	1 (16.7)	0
Oropharyngeal discomfort	1 (16.7)	0	0	0	0	0	0	0	0
Infections and infestations									
RTI viral	1 (16.7)	0	0	0	0	0	1 (16.7)	0	0
Oral herpes	0	0	0	0	0	0	1 (16.7)	0	0
Viral upper RTI	0	0	0	0	0	0	0	1 (16.7)	0
Vascular disorders									
Flushing	0	0	0	0	0	0	0	0	0
Hypotension	0	0	0	0	0	0	0	0	0
General disorders and administration site conditions									
Chest pain	0	0	0	0	0	0	0	0	0
Chest discomfort	0	0	0	0	0	0	0	0	1 (16.7)*
Chills	0	0	0	0	1 (8.3)	0	0	0	0
Metabolism and nutrition disorders									
Iron deficiency	0	0	0	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders									
Back pain	0	0	0	0	0	0	0	0	0
Muscle spasms	0	0	0	0	1 (8.3)				

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Table 4 (continued)

MedDRA® System Organ Class MedDRA® Preferred Term	SAD Cohorts				BAL Cohort	MAD Cohorts			
	Placebo-SAD Cohort (*N*=6) *n* (%)	2.0 mg AP02 (*N*=6) *n* (%)	4.0 mg AP02 (*N*=6) *n* (%)	8.0 mg AP02 (*N*=6) *n* (%)	4.0 mg AP02 (*N*=12) *n* (%)	Placebo-MAD Cohort (*N*=6) *n* (%)	2.0 mg BID AP02 (*N*=6) *n* (%)	4.0 mg BID AP02 (*N*=6) *n* (%)	8.0 mg BID AP02 (*N*=6) *n* (%)
Arthralgia	0	0	0	0	0	0	0	1 (16.7)	0
Skin and subcutaneous tissue disorders									
Dermatitis	0	0	1 (16.7)	0	0	0	0	0	0
Dry skin	0	0	0	0	0	0	1 (16.7)	0	0
Hepatobiliary disorders									
ALT increase	0	0	0	0	0	0	0	0	1 (16.7)*

ALT Alanine aminotransferase, *BAL* Bronchoalveolar lavage, *BID* Twice daily, *IPF* Idiopathic pulmonary fibrosis, *MAD* Multiple ascending doses, *MedDRA*®Medical Dictionary for Regulatory Activities, Version 23.1., *N* Number of subjects dosed, *n* (%) Number and percent of subjects with treatment-emergent adverse events, *RTI* Respiratory tract infection, *SAD* Single ascending dose, *TEAE* Treatment-emergent adverse event

*Possibly or probably drug-related adverse events

†2 of 3 dizziness events were considered to be drug-related in the BAL cohort

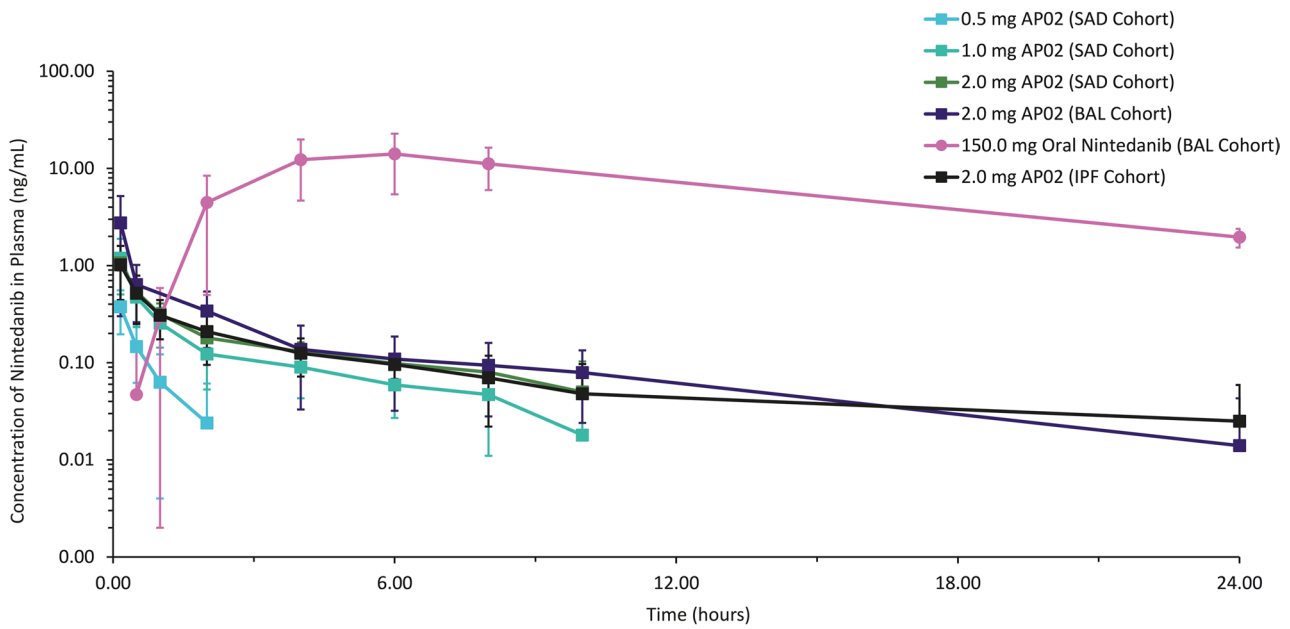


Fig. 3 Nintedanib plasma concentrations by treatment in single-dose cohorts in AP02-001. Nintedanib plasma levels following AP02 doses in the single ascending dose portion of the AP02-001 study, a 2.0 mg dose of AP02 and a 150 mg oral dose of nintedanib in the BAL cohorts, and a 2.0 mg dose of AP02 in patients with IPF. 6 participants were included in the 0.5 mg and 1.0 mg AP02 cohorts for this analysis. 5 participants were included in the 2.0 mg AP02 healthy volunteer and IPF cohorts for this analysis. 4 participants were included in the BAL cohorts for this analysis. Mean ± SD values for each cohort were plotted at nominal times. Data are shown on a semi-log scale

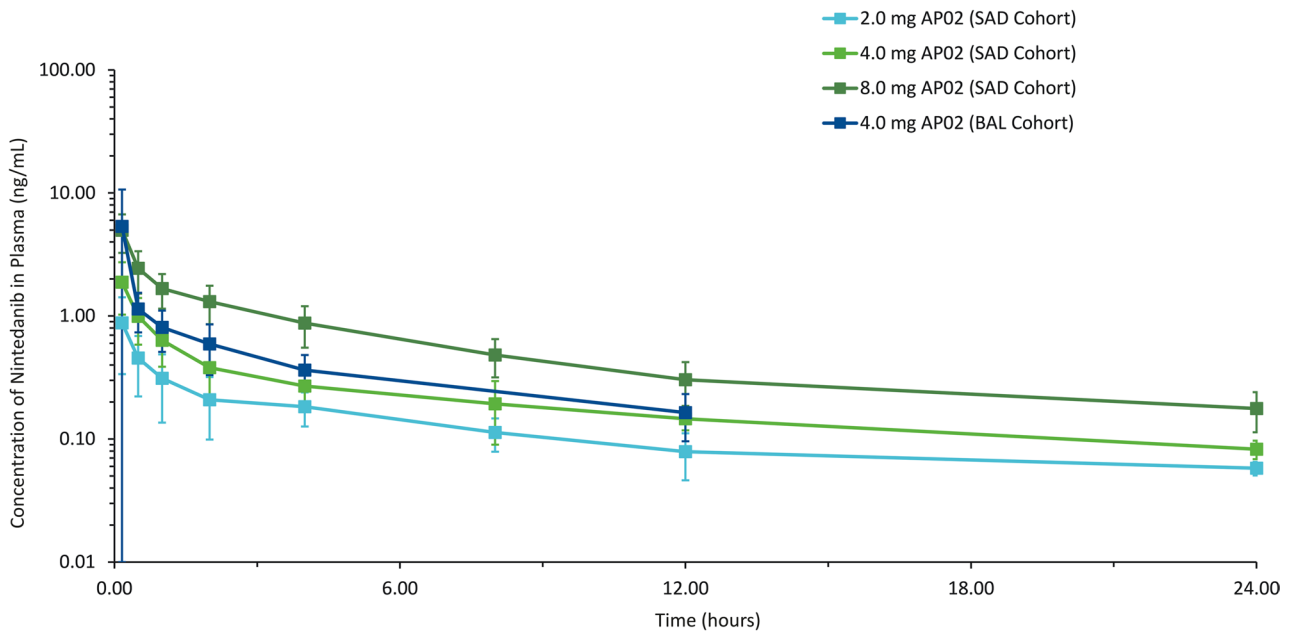


Fig. 4 Nintedanib plasma concentrations by treatment in single-dose cohorts in AP02-002. Nintedanib plasma levels following AP02 doses in the single ascending dose portion of the AP02-002 study and a 4.0 mg dose of AP02 in the BAL cohort. 6 participants were included in each SAD cohort and 12 participants were included in the BAL cohort for this analysis. Mean ± SD values for each cohort were plotted at nominal times. Data are shown on a semi-log scale

Table 5 Nintedanib plasma pharmacokinetic parameters by treatment in single-dose cohorts (AP02-001 and AP02-002)

	AP02-001						*AP02-002*			
	SAD Cohorts			BAL Cohorts		IPF Cohort	SAD Cohorts			BAL Cohort
Parameter (Units) Statistics	0.5 mg AP02 (*N*=6)	1.0 mg AP02 (*N*=6)	2.0 mg AP02 (*N*=5)	2.0 mg AP02 (*N*=4)	150 mg Oral Nintedanib (*N*=4)	2.0 mg AP02 (*N*=5)	2.0 mg AP02 (*N*=6)	4.0 mg AP02 (*N*=6)	8.0 mg AP02 (*N*=6)	4.0 mg AP02 BAL (*N*=12)
AUC_{0-24} (h*ng/mL)										
n	2	5	5	3	4	5	-	-	-	-
Geometric mean (%CV)	0.473 (21.5)	1.810 (24.9)	2.169 (18.2)	4.19 (33.0)	146.704 (37.4)	2.099 (55.7)	-	-	-	-
Min, Max	0.41, 0.55	1.38, 2.45	1.75, 2.66	3.01, 5.71	100.01, 238.38	1.19, 4.45	-	-	-	-
AUC_{0-last} (h*ng/mL)										
n	-	-	-	-	-	-	5	6	6	12
Geometric mean (%CV)	-	-	-	-	-	-	1.61 (171.5)	4.4 (87.5)	13.4 (40.1)	4.92 (39.1)
Min, Max	-	-	-	-	-	-	0.226, 4.33	1.02, 7.35	7.03, 19.8	2.46, 9.67
C_{max} (ng/mL)										
n	6	6	5	4	4	5	5	6	6	12
Geometric mean (%CV)	0.332 (52.4)	1.020 (71.8)	1.052 (17.6)	1.684 (219.3)	15.285 (51.5)	0.910 (54.5)	0.934 (63.5)	1.69 (57.6)	4.75 (34.6)	3.74
Min, Max	0.161, 0.669	0.362, 2.100	0.801, 1.250	0.282, 5.850	8.270, 25.900	0.539, 1.980	0.337, 1.38	0.704, 3.04	2.89, 7.95	1.13, 19.1
T_{max} (h)										
n	6	6	5	4	4	5	6	6	6	12
Median	0.2170	0.2670	0.3670	0.2915	6.0000	0.4000	0.17	0.18	0.17	0.17
Min, Max	0.217, 0.233	0.250, 0.283	0.333, 0.383	0.250, 0.400	4.000, 8.000	0.383, 0.417	0.17, 0.17	0.17, 0.35	0.17, 0.20	0.02, 0.20
$T_{½el}$ (h)										
n	2	5	3	2	1	3	4	6	6	10
Median	0.9025	5.0938	4.6560	8.9730	-	10.7420	8.76	14.6	13.2	5.55
Min, Max	0.902, 0.903	2.834, 6.295	4.080, 7.087	6.123, 11.823	6.384, 6.384	3.029, 17.896	5.47, 17.6	5.1, 19.9	8.93, 27.1	3.24, 9.57

In the AP02-001 study, 6 participants were included in the 0.5 mg and 1.0 mg AP02 cohorts, 5 participants were included in the 2.0 mg AP02 healthy volunteer and IPF cohorts, and 4 participants were included in the BAL cohorts for this analysis. In the AP02-002 study, 6 participants were included in each SAD cohort and 12 participants were included in the BAL cohort for this analysis

AUC_{0-24}Area under the concentration-time curve, from time 0 to 24 h, AUC_{0-last}Area under the concentration-time curve from 0 to the last measurable concentration, *BAL* Bronchoalveolar lavage, C_{max}Maximum observed concentration, *IPF* Idiopathic pulmonary fibrosis, *N* Number of subjects dosed, *n* Number of observations, *SAD* Single ascending dose, $T_{½el}$Elimination half-life, T_{max}Time of observed, C_{max} *%CV* Percent coefficient of variation, '-' Not calculated

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of nintedanib was also similar between these 2 cohorts, with geometric mean values AUC_{0-24} and C_{max} in the IPF cohort being 2.10 h*ng/mL and 0.91 ng/mL, respectively. Median $T_{½el}$ of nintedanib in the IPF cohort was 10.74 h, which was slightly higher than what was observed in the 2.0 mg AP02 SAD cohort (Table 5).

Multiple-dose cohorts

Participants administered BID doses of AP02 for up to 7 days in the AP02-002 study also had rapid median T_{max} plasma nintedanib ranging from 0.17 to 0.18 h on both days 1 and 7 (Figs. 5 and 6; Table 6). BIBF1202 concentration levels in these cohorts followed a similar trend (Supplementary Table S6).

Plasma exposures of nintedanib on Day 1 were generally similar in participants administered 2.0 mg and 4.0 mg AP02 BID, with geometric mean values of AUC_{0-last} of 2.19 and 2.65 h*ng/mL, respectively, and C_{max} of 1.59 and 1.31 ng/mL, respectively. Exposures were higher following administration of 8.0 mg AP02 BID, with an AUC_{0-last} of 7.13 h*ng/mL and C_{max} of 3.18 ng/mL. On Day 7, exposures increased with an increase in dosage, with the highest being observed in the 8.0 mg AP02 BID cohort (AUC_{0-last}=17.9 h*ng/mL and C_{max}=3.11 ng/mL). $T_{½el}$ was comparable across cohorts, with shorter elimination half-lives on Day 1 (4.68, 6.63, and 5.79 h for the 2.0 mg, 4.0 mg, and 8.0 mg AP02 BID cohorts, respectively) compared to Day 7 (16.9, 19.4, and 17.1 h for the 2.0 mg, 4.0 mg, and 8.0 mg AP02 BID cohorts, respectively) (Table 6).

The mean steady state exposures of the approved oral 150 mg BID dose are an AUC_{0-24} of 363 h*ng/mL and C_{max} of 31.97 ng/mL [21]. Predicted AUC_{0-24} values were calculated by multiplying AUC_{0-tau} values by 2. Of note, predicted AUC_{0-24} and C_{max} geometric mean values across all AP02 multiple dose cohorts on Day 7 were 10- to 56-fold lower than these oral exposure levels.

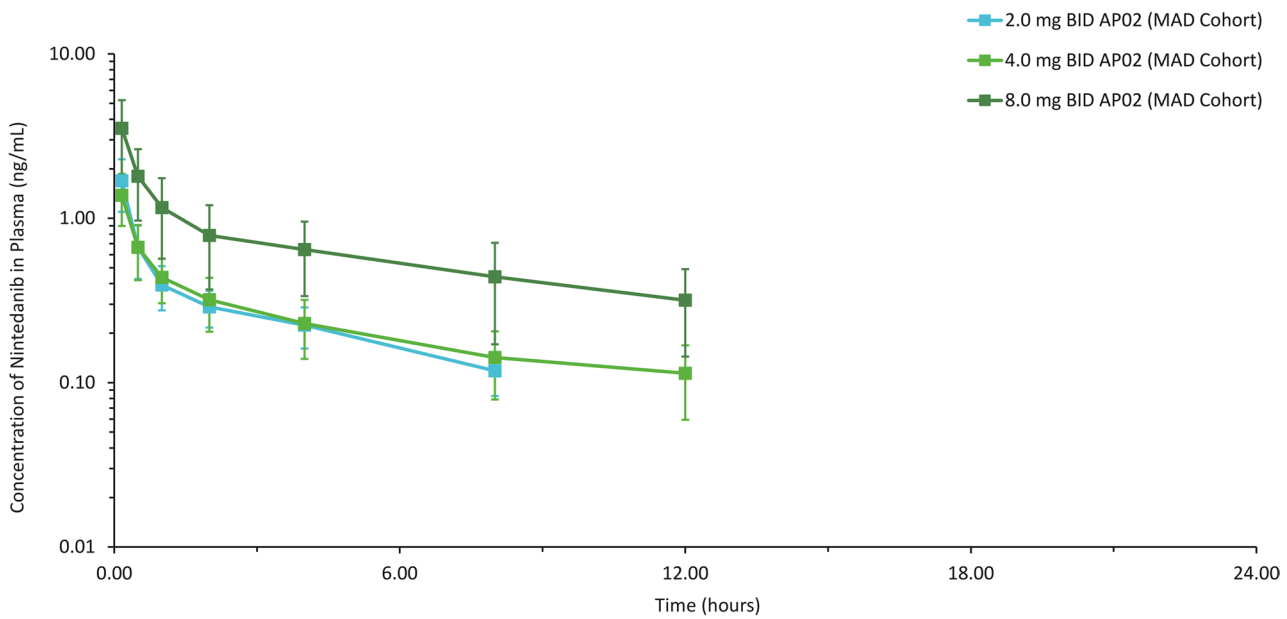


Fig. 5 Nintedanib plasma concentrations by treatment in multiple-dose cohorts in AP02-002 on day 1. Nintedanib plasma levels on day 1 of treatment in the multiple ascending dose cohorts. The 12 h post-dose sample was collected after the 12-hour dose was administered for all participants in the AP02 2.0 mg BID group and therefore was excluded from the pharmacokinetic analysis. 6 participants were included in each MAD cohort for this analysis. Mean ± SD values for each cohort were plotted at nominal times. Data are shown on a semi-log scale

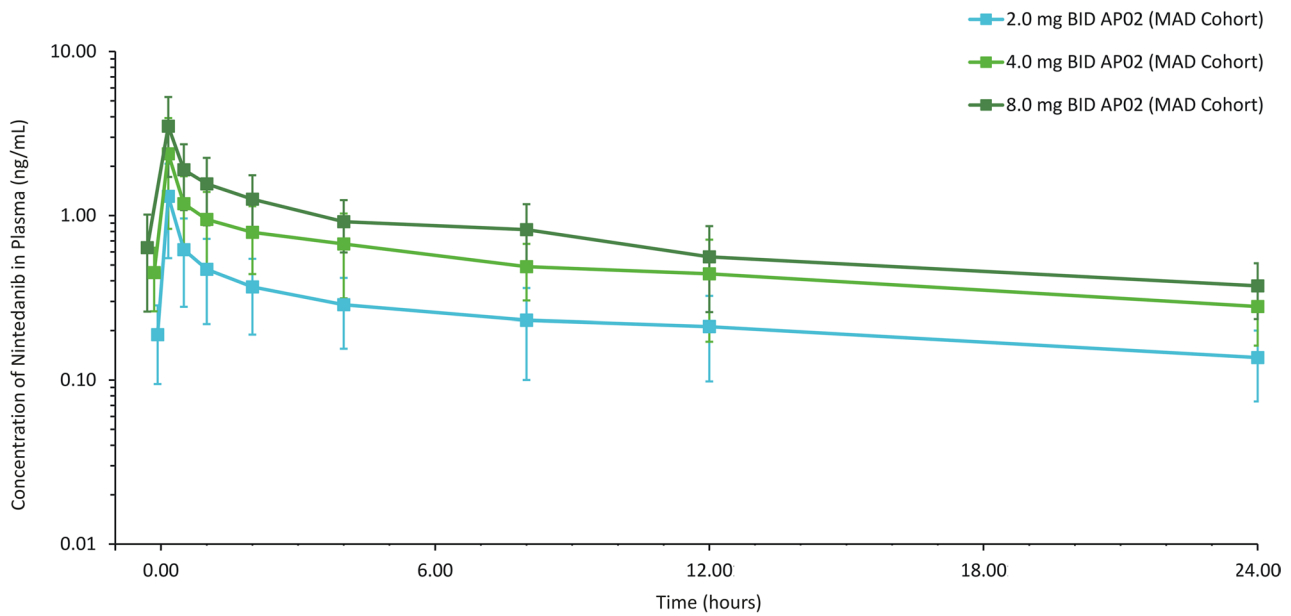


Fig. 6 Nintedanib plasma concentrations by treatment in multiple-dose cohorts in AP02-002 on day 7. Nintedanib plasma levels following multiple ascending doses for 7 days (13 doses). 6 participants were included in each MAD cohort for this analysis. Mean ± SD values for each cohort were plotted at nominal times. Data are shown on a semi-log scale

Table 6 Nintedanib plasma pharmacokinetic parameters by treatment in multiple-dose cohorts (AP02-002)

Parameter (units) Statistics	Day 1			Day 7		
	2.0 mg BID AP02 (*N*=6)	4.0 mg BID AP02 (*N*=6)	8.0 mg BID AP02 (*N*=6)	2.0 mg BID AP02 (*N*=6)	4.0 mg BID AP02 (*N*=6)	8.0 mg BID AP02 (*N*=6)
AUC_{0-tau} (h*ng/mL)						
n	6	6	6	6	6	6
Geometric mean (%CV)	2.53 (33.8)	2.74 (33.7)	7.27 (51.1)	3.27 (59.5)	7.06 (55.5)	11 (44.9)
Min, Max	1.41, 3.55	1.79, 4.37	4.42, 13.6	1.67, 6.13	3.28, 12.4	7.11, 16.6
C_{max} (ng/mL)						
n	6	6	6	6	6	6
Geometric mean (%CV)	1.59 (41.6)	1.31 (38.4)	3.18 (54.6)	1.08 (83.1)	1.94 (84.9)	3.11 (58.7)
Min, Max	0.815, 2.5	0.732, 2.13	1.66, 5.84	0.376, 2.43	0.799, 4.68	1.56, 5.98
T_{max} (h)						
n	6	6	6	6	6	6
Median	0.17	0.18	0.17	0.167	0.184	0.167
Min, Max	0.17, 0.17	0.17, 0.23	0.17, 0.20	0.167, 0.167	0.167, 0.233	0.167, 0.317
$T_{½el}$ (h)						
n	6	6	6	6	6	5
Median	4.68	6.63	5.79	16.9	19.4	17.1
Min, Max	3.73, 5.4	3.93, 10.2	4.39, 7.08	9.56, 25.9	13.1, 37.4	16.4, 26.3

AUC_{0-tau} Area under the concentration-time curve from 0 to the end of the dosing interval, *BID* Twice daily, *C_{max}* Maximum observed concentration, *N* Number of subjects dosed, *n* Number of observations, *$T_{½el}$* Elimination half-life, *T_{max}* Time of observed C_{max}, *%CV* Percent coefficient of variation, '-' Not calculated

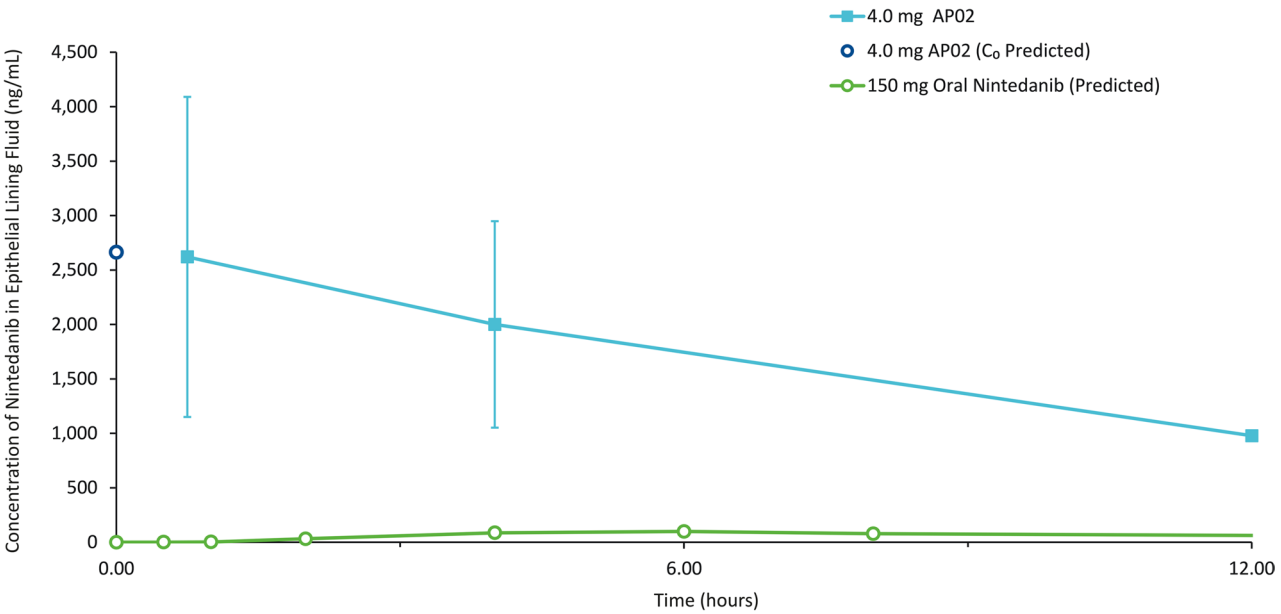


Fig. 7 Nintedanib Epithelial Lining Fluid Exposure in AP02-002. Predicted epithelial lining fluid exposures over a 12-hour dosing interval. For the 4 mg AP02 BAL cohort, single BAL samples were collected from n = 4 subjects per timepoint at the nominal times of 45 min, 4 h, and 12 h post–end of inhalation. The slope between 45 min and 12 h was used to conservatively extrapolate C_0 (dark blue open circle). For the orally dosed cohort, a single BAL sample was collected per subject in study AP02-001 at t = 9 h following a single 150 mg dose (n = 4 subjects). ELF values were obtained by using urea to correct for BAL dilution across studies. An ELF: plasma ratio was obtained (at 8–9 h) and applied to the human plasma data (collected to 24 h post-dose) from the orally dosed cohort to predict an ELF concentration-time profile (green open circles). C_0, drug concentration at time 0

Bronchoalveolar pharmacokinetic evaluation

In AP02-001, concentrations of nintedanib observed in the BAL samples were approximately 9-fold higher following a single dose 2.0 mg AP02 administration when compared to a single 150 mg oral nintedanib dose, with geometric mean values of 3.70 and 0.43 ng/mL, respectively.

To determine whether nintedanib was still detectable in lung ELF during a 12-hour dosing interval, BAL samples were collected longitudinally at 45 min, 4 h, and 12 h post-dose in study AP02-002 following a single 4.0 mg dose. Nintedanib concentrations were detectable in ELF up to 12 h post-dose and exceeded ELF concentrations following a single 150 mg oral dose in study AP02-001 (Fig. 7).

Nintedanib works by inhibiting multiple receptor tyrosine kinases that have been shown to contribute to ILD pathogenesis, including VEGFR1, VEGFR2, VEGFR3, FGFR1, FGFR2, PDFGR-α, and PDFGR -β. The half maximal inhibitory concentration (IC_{50}) values for these kinases range from 7 to 37 ng/mL [6, 22]. Notably, exposures in ELF following a 4.0 mg dose of AP02 also exceeded IC_{50} values of these target tyrosine kinases. An additional exploratory analysis was performed to compare nintedanib ELF exposure following a 4.0 mg AP02 dosing versus oral dosing. Nintedanib C_{max} (C_0; extrapolated to the end of inhalation) and $AUC_{0–12}$ in ELF following the AP02 dose was estimated to exceed ELF exposure following oral dosing by 27-fold and 26-fold, respectively. Taken together, these data support attainment of nintedanib ELF exposures associated with efficacy.

Discussion

The goal of these studies was to assess the safety, tolerability, and pharmacokinetics of single and multiple doses of AP02 in healthy volunteers and patients with IPF. AP02 was well tolerated in single and multiple doses up to 8.0 mg in healthy volunteers and at a single dose of 2.0 mg in patients with IPF, the highest doses evaluated in these populations. TEAEs were mostly mild in severity; none led to study withdrawal, and no serious adverse events or deaths were reported.

Systemic exposure was generally increased with increasing doses of AP02 and was similar between healthy volunteers and patients with IPF who received the same AP02 dose. A single 2.0 mg dose of AP02 resulted in approximately 68-fold lower plasma AUC_{0-24} and 15-fold lower C_{max} compared to exposure observed following oral nintedanib dosing in healthy volunteers in AP02-001. Additionally, in all MAD cohorts, in which 8.0 mg BID was the highest evaluated dose, systemic exposure following AP02 administration remained 10- to 56-fold lower than the mean steady state exposures of the approved oral 150 mg BID dose [21]. Lung exposure, conversely, was higher in individuals who received AP02 compared to oral nintedanib, with nintedanib exposure being ~26-fold higher in ELF following a 4.0 mg AP02 dose compared to oral nintedanib. Together, these findings suggest that direct lung delivery of AP02 by oral inhalation can improve lung exposure of nintedanib while reducing systemic exposure.

While this study used human ELF nintedanib concentrations as a surrogate for lung tissue exposure due to the feasibility of collection, sustained lung exposure over a 12-hour interval was demonstrated. Nintedanib is ~98% bound to human plasma proteins [6]. ELF contains protein at ~36.8 g/L similar to the level of albumin in plasma [23]. Therefore, binding to proteins likely retains nintedanib in ELF. Nintedanib is considered a high-permeability compound, with low gastrointestinal absorption and bioavailability as a consequence of P-glycoprotein transporter influence [24]. P-glycoprotein expression in the lung is lower relative to the gastrointestinal tract, likely modulating absorption but not to the extent occurring in the gastrointestinal tract [25]. Consequently, non-metabolic loss of nintedanib from lung ELF is likely influenced by protein binding and a modest rate of permeability to lung tissue and the vasculature.

Results from the studies reported here contribute significantly to the growing therapeutic space for IPF by demonstrating a favorable safety profile as well as evidence that suggests a delivery of higher lung nintedanib levels using the eFlow nebulizer compared to the oral formulation. Dosing with AP02 in the AP02-002 study also resulted in ELF exposure levels that exceeded the published IC50 values of select target tyrosine kinases, suggesting that AP02 may be effective in reducing IPF-associated disease activity. Further investigations are required to determine whether the increased nintedanib levels found in the lungs of healthy volunteers and decreased systemic levels translate to increased efficacy in patients with IPF.

Small sample sizes across cohorts are a limitation of these studies, as it reduces the possibility of detecting rare adverse events. However, as the safety profile of oral nintedanib is well characterized and the systemic exposure of nintedanib following AP02 administration was markedly lower than that of the oral formulation, the likelihood of novel systemic adverse events in studies with larger cohort sizes may be low. An additional limitation is that ELF concentrations were used as a surrogate for lung tissue exposure; however, it is unclear the extent to which the ELF concentrations represented relevant lung tissue exposure given that IPF pathophysiology involves the alveolar wall and interstitium [26, 27]. In addition, the ELF concentration-time profile following oral dosing was estimated based on BAL collection at a single timepoint. Specifically, an ELF: plasma ratio was obtained (at 8 to 9 h) and applied to the human plasma data (collected to 24 h after the end of inhalation) from the orally dosed cohort to predict an ELF concentration-time profile. Nintedanib T_{max} is ~4 h, thus the BAL collection time followed the period of maximum absorption and allowed for equilibrium of distribution between ELF and plasma. An additional limitation of this study is that the average age of most participants in these SAD and MAD cohorts is younger than the mean age of patients with IPF, which is 65 to 70 years [5]. Nonetheless, the age of the IPF cohort assessed in this study (mean=69.8 years) reflects what is observed in the real world.

It is notable that no participants in the oral nintedanib cohort reported TEAEs normally associated with oral therapy. The small sample size of this cohort may have contributed to this outcome. The short duration of treatment may have also played a role; it has been reported that the onset of diarrhea occurs around 60 days post–treatment initiation [12, 28]. Additionally, only a single dose of oral nintedanib was given to participants, which differs from the approved dosage of oral nintedanib, which is BID.

The use of inhaled therapeutics to minimize systemic exposure and associated toxicity has been employed in other diseases. In management of both asthma and COPD, for example, inhaled bronchodilators and corticosteroids have a crucial role in treatment [29]. Several other forms of inhaled therapeutics are also being investigated for use in IPF. A nintedanib dry powder inhalation was shown to be safe and well tolerated in a recent phase I study, and inhalable poly(lactic-co-glycolic acid) nintedanib nanoparticles have also been recently formulated and demonstrated promising results in vitro [30–32].

Conclusions

These studies demonstrated that AP02 was well tolerated in a single 2.0 mg dose in patients with IPF and in single and multiple doses up to 8.0 mg in healthy volunteers, which were the highest doses evaluated in these populations. AP02 also resulted in a lower systemic exposure and a higher ELF exposure relative to oral nintedanib at the approved dosage. Subsequent clinical development will include more dedicated safety and tolerability studies in a larger number of patients with IPF. These findings support the further clinical advancement of AP02 and suggest that an inhaled delivery of a proven efficacious agent may be a promising new treatment option for IPF.

Abbreviations

$AUC_{0–24}$	Area under the concentration-time curve from time 0 to 24 h
$AUC_{0–last}$	Area under the concentration-time curve from time 0 to the last measurable concentration
$AUC_{0–12}$	Area under the concentration-time curve from time 0 to 12 h
BAL	Bronchoalveolar lavage
BID	Twice daily
C_0	Drug concentration at time 0
COPD	Chronic obstructive pulmonary disease
C_{max}	Maximum plasma drug concentration
ELF	Epithelial lining fluid
FEV_1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
IC_{50}	Half maximal inhibitory concentration
IPF	Idiopathic pulmonary fibrosis
ILD	Interstitial lung disease
MAD	Multiple ascending dose
SAD	Single ascending dose
SD	Standard deviation
$T_{½ el}$	Elimination half-life
T_{max}	Time to maximum plasma drug concentration
TEAE	Treatment-emergent adverse event

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Authors' contributions All authors wrote and reviewed the manuscript. MP, RB, SP, MS, HML, CSC, and MR designed the research. SF and JL performed the research. MP, RB, SP, SF, JL, MS, DN, FW, HML, CSC, and MR analyzed the data. All authors are accountable for all aspects of the work.

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Data availability All requests for data will be reviewed by the corresponding author to verify whether the request is subject to confidentiality obligations.

Declarations

Ethics approval and consent to participate Protocols were approved by a local ethics committee (Alfred Hospital Ethics Committee), and all participants provided written informed consent prior to study procedures.

Consent for publication Not applicable.

Competing interests MP, SP, DN, FW, HML, CSC, and MR are employees of Avalyn Pharma Inc and hold stock options in Avalyn Pharma Inc. RB was an employee of Avalyn Pharma Inc at the time of the study. SF declares that they have no competing interests. JL reports payments from Avalyn Pharma Inc made to his institution for the present manuscript. MS is a former employee of Avalyn Pharma Inc.

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Authors and Affiliations

Michelle Palacios[1] · Rebecca Boone[2] · Stephen Pham[1] · Sam Francis[3] · Jason Lickliter[3] · Mark Surber[2] · Deepthi Nair[1] · Felix A. Woodhead[1] · Howard M Lazarus[1] · Craig S Conoscenti[1] · Melissa Rhodes[1]

✉ Michelle Palacios
mpalacios@avalynpharma.com

[1] Avalyn Pharma Inc., 105 West First St., Boston, MA 02127, USA

[2] Avalyn Pharma Inc., Seattle, WA, USA

[3] Nucleus Network Ltd., Melbourne, VIC, Australia