A Double-blind, Placebo-controlled, Randomized Phase 1 Study to Evaluate Safety, Tolerability, and Pharmacokinetics After Single or Repeat Twice-daily Doses of AP02, a Nebulized Formulation of Nintedanib

M. Palacios[1] , R. Boone[1] , S. Pham[1] , H. M. Lazarus[1] , C. S. Conoscenti[1], and M. Rhodes[1]
[1]Avalyn Pharma Inc., Cambridge, MA, United States.

Background

- Nintedanib is an orally dosed tyrosine kinase inhibitor that slows the progression of pulmonary fibrosis in patients with IPF and PPF, and its gastrointestinal adverse reactions, including diarrhea, can restrict its use and dosing.[1]
- AP02 is a novel solution for inhalation of nintedanib for delivery via a handheld PARI eFlow nebulizer, and is anticipated to provide increased delivery to the lung while reducing systemic exposure.
- Here we present data from the second Phase 1 study (AP02-002) that evaluated higher single and repeated AP02 doses of up to 8 mg BID for 7 days in healthy volunteers (HV).

Methods: Study Design and Demographics

- 60 healthy volunteers in total: 36 HVs in SAD; 24 HVs in MAD
- 1 single dose bronchoalveolar lavage (BAL) cohort
- Study endpoints included safety, tolerability, and plasma and epithelial lining fluid (ELF) pharmacokinetics (PK).

		SAD					MAD				Total
Cohort		Pooled	SAD 1	SAD 2	SAD 3	4 BAL	Pooled	MAD 6	MAD 7	MAD 8	TOTALS
Dose		Placebo	2mg	4mg	8mg	4mg	Placebo	2mg BID	4mg BID	8mg BID	N/A
N		6	6	6	6	12	6	6	6	6	60
Age Range		22-59	20-56	20-65	20-65	18-58	23-48	19-37	23-59	22-48	N/A
Sex	M	5	4	5	6	11	6	6	5	6	54
	F	1	2	1	0	1	0	0	1	0	6
Race	Asian	3	2	4	4	2	2	1	2	1	20
	White	2	3	2	1	7	4	4	4	4	32
	AI/AN	1	-	1	1	2	-	1	-	1	6
	Other	-	1	-	-	1	-	-	-	-	2
BMI Range		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	N/A

RESULTS: Single AP02 doses were well-tolerated in 30 HVs

Single Ascending Dose Cohorts	Placebo (n=6)	Cohort 1 (n=6)	Cohort 2 (n=6)	Cohort 3 (n=6)	Cohort 4 (n=12)
Dose	Placebo	2 mg AP02	4 mg AP02	8 mg AP02	4 mg AP02 BAL
Total Number of TEAEs	3	1	2	1	11
Number of Subjects with ≥ 1 TEAE	2 (33.3)	1 (16.7)	2 (33.3)	1 (16.7)	6 (50.0)
Dizziness	0	0	1 (16.7)	0	3 (25.0)[a]
Headache	0	1 (16.7)	0	0	1 (8.3%)
Dry Mouth	0	0	0	1 (16.7)	0
Nausea	0	0	0	0	1 (8.3)
Tooth impacted	0	0	0	0	1 (8.3)
Vomiting	0	0	0	0	1 (8.3)
Dyspnoea	0	0	0	0	1 (8.3)
Oropharyngeal discomfort	1 (16.7)	0	0	0	0
Productive cough	1 (16.7)	0	0	0	0
Throat irritation	0	0	0	0	1 (8.3)
Chills	0	0	0	0	1 (8.3)
RTI viral (viral)	1 (16.7)	0	0	0	0
Muscle spasm	0	0	0	0	1 (8.3)
Dermatitis	0	0	1 (16.7)	0	0

Drug-related adverse events (AEs) shown in purple

[a]Only 2 of 3 dizziness were considered drug related in BAL cohort

RESULTS: Repeat AP02 doses of up to 8 mg BID were well-tolerated in 18 HVs

No serious adverse events, bronchospasm or decreased oxygen saturation in any volunteer. No changes in FEV1, cough, or diarrhea.

Multiple Ascending Dose Cohorts	Placebo (n=6)	Cohort 6 (n=6)	Cohort 7 (n=6)	Cohort 8 (n=6)
Dose	Placebo	2 mg BID AP02	4 mg BID AP02	8 mg BID AP02
Total Number of TEAEs	0	3	3	2
Number of Subjects with ≥ 1 TEAE	0	1 (16.7)	3 (50.0)	2 (33.3)
Oral herpes	0	1 (16.7)	0	0
RTI (viral)	0	1 (16.7)	0	0
Viral Upper RTI	0	0	1 (16.7)	0
Chest discomfort	0	0	0	1 (16.7)
ALT increase	0	0	0	1 (16.7)
Arthralgia	0	0	1 (16.7)	0
Oropharyngeal pain	0	0	1 (16.7)	0
Dry skin	0	1 (16.7)	0	0

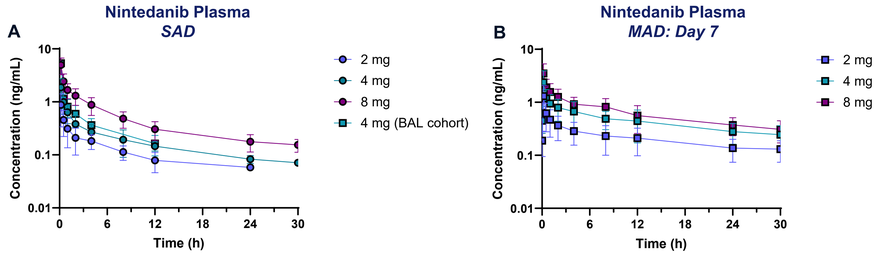
Drug-related adverse events (AEs) shown in purple

TEAE Summary

- 16 HVs reported a total of 26 non-serious TEAEs
  - **no serious events reported**
  - **none led to study withdrawal**
- 23 mild and 3 moderate severity
- **6 drug-related AEs total**
- SAD: 12 HVs reported 18 events
  - of these 6 HVs in the SAD BAL cohorts reported 11 events
- MAD: 6 HVs reported 8 events

RESULTS: Clinical Pharmacokinetics

Plasma nintedanib exposures remain below approved oral product following repeat AP02 doses of up to 8 mg



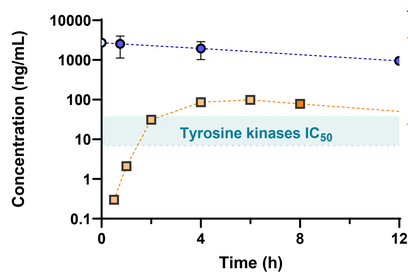
Figures 1. A) Nintedanib levels in plasma following single AP02 doses in the single ascending dose portion of the study. B) Nintedanib levels in plasma following multiple ascending doses for 7 days (13 doses). Mean ± SD shown.

PK Parameter	MAD: Day 7			Stopping Criteria	Difference from stopping criteria (oral)		
	2mg BID	4mg BID	8mg BID	150 mg	2mg BID	4mg BID	8mg BID
C_{max} (ng/mL)	1.08 (83.1%)	1.94 (84.9%)	3.11 (58.7%)	31.95	-30-fold	-17-fold	-10-fold
pAUC0-24 (hr*ng/mL)	6.54 (59.5%)	14.1 (55.5%)	22 (44.9%)	363	-56-fold	-26-fold	-17-fold

Geo Mean (%CV). Stopping criteria for this study were based on the clinical nintedanib exposures listed in the Therapeutic Goods Administration (TGA) Australian Public Assessment Report for Nintedanib esilate at the approved 150 mg BID oral dose (Ofev/Vargatef AusPAR, 2021).

RESULTS: : AP02 Reduces Systemic Exposure While Significantly Improving Lung Exposure

Inhaled delivery significantly improves lung exposure



Select nintedanib *in vitro* kinase inhibition profile

Kinase	IC_{50} (ng/mL)
VEGFR-1	18
VEGFR-2	11
VEGFR-3	7
FGFR-1	37
FGFR-2	20
PDFGR-α	32
PDFGR-β	35

Roth, 2014, et al. *Journal of Medicinal Chemistry.*

- For the 4mg AP02 cohort (dark blue circles): Single BAL samples were collected from n=4 subjects per timepoint at 45 min, 4hrs, and 12 hours post end of inhalation. ELF values were obtained by correcting for dilution using the urea dilution method. The slope between 45min and 12 hr was used to conservatively extrapolate to T_0 (light blue circle).
- For the orally dosed cohort (orange squares): A single BAL sample was collected per subject in study AP02-001 at t=9 hours (anticipated ELF T_{max}) following a single 150 mg dose (n=4 subjects). ELF value were obtained by correcting for dilution using the urea dilution method. An ELF:plasma ratio was obtained and applied to the human plasma data from this orally dosed cohort to generate an ELF concentration-time profile.

Nintedanib exposures in ELF following inhalation remain above those observed following oral dosing throughout the dosing interval

Single dose PK parameter	150 mg oral	4 mg AP02	Difference from oral
C_{max} (ng/mL)	99	2,720*	+27-fold
AUC_{0-12} (ng*h/mL)	779	20,900	+27-fold

*T_0 extrapolated
Exploratory analysis of interim data
Data represents n=4 for all timepoints except for 12 hr where n=3

CONCLUSIONS

- AP02 was well-tolerated following single doses and throughout 7 days of twice daily doses of up to the highest dose (8 mg BID).
- At the highest evaluated dose, systemic exposures following 8 mg BID dosing remained markedly below systemic exposures following oral dosing.
- Exposures in ELF exceeded IC_{50} values of target tyrosine kinases (TKs) and were ~27-fold higher than those observed following oral administration at the approved dose, suggesting establishment of clinically meaningful exposure.
- These data support AP02 as being safe and well tolerated with potential to demonstrate a treatment benefit to patients with IPF.

1. Podolanczuk A and Cottin V. Adv Ther (2023) 40:2038–2050

**AP02-002 Preliminary Study Data Captured

ATS 2025