Inhalation: A Means to Improve Existing IPF Therapies

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INTRODUCTION

IPF is a fatal orphan lung disease characterized by progressive scarring, reduced exercise capacity and death from respiratory failure or co-morbidities. With a 3-5 year survival period, IPF has more deaths per year than breast cancer and only lung cancer has a worse 5 year prognosis. World-wide, only oral pirfenidone and oral nintedanib are approved to treat IPF.

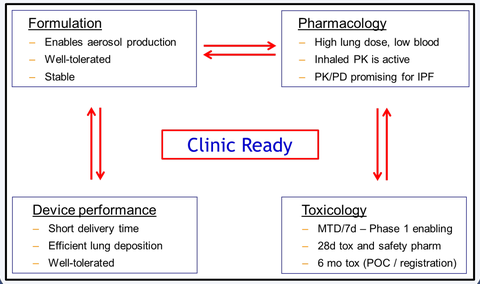
While both medicines slow IPF disease progression, each has their shortcomings. As a low potency drug, pirfenidone requires a very large oral dose to achieve efficacious lung levels. Despite the approved oral dose being large (801 mg TID), lung levels remain well-below the pirfenidone IC_{50} and associated blood levels remain unsafe and poorly tolerated (preventing dose escalation for additional efficacy). Complicating matters, dose-absorbing food, first-pass metabolism and safety-driven dose-reduction/stoppage protocols further reduce lung dose and interrupt desired maintenance therapy. Similar for nintedanib, only the highest oral dose has been shown effective and is associated with side effects challenging compliance.

To address the above shortcomings and maximize therapeutic potential, Avalyn is developing inhaled versions of pirfenidone (AP01) and nintedanib (AP02). By this approach, we have shown inhalation to be safe and well-tolerated for each, and from a recently completed 48-week study, AP01 has shown a trend to IPF disease stabilization and structural improvement in some patients.

KEY DEVELOPMENT QUESTIONS

1. Can inhalation deliver large lung dose with low blood levels?
   - Opportunity to improve efficacy and reduce side effects
2. Will inhaled pharmacokinetics support activity?
   - Each API exhibits unique pulmonary properties and challenges
3. What formulation/device best supports PK/PD relationship?
   - Use battery of cell-based and *in vivo* models to characterize
4. Is the product safe and effective in humans?
   - Tox, manufacturing and clinical studies to support registration

Inhaled Clinical Candidate Selection



AP01 (Inhaled Pirfenidone) Overview

1. AP01 Development Summary

- Low potency drug requiring a large lung dose
- Shorter inhalation time to combat rapid lung elimination
  (Reducing delivery time sways equilibrium away from elimination and towards higher lung concentration)
- Product form:
  - Aqueous solution in twist-off LDPE ampoules
  - PARI eFlow® vibrating membrane nebulizer
- Nonclinical data supported clinical advancement
- Clinical data indicates AP01 is safe and effective in treating IPF

2. AP01 Phase 1a Clinical Study (AP01-001)[1]

- SAD study in NHVs, smokers and people with IPF
- Safety, tolerability and PK study (plasma and BALF)
- Results Summary:
  - Safe and well-tolerated to max feasible dose
    - 100 mg with 8 min administration time
    - No bronchospasm or reduced O_2 saturation
  - Large lung dose with low blood levels
    - 35-fold higher ELF levels than 801 mg oral dose
    - 1/15th the systemic exposure
  - Provided dose information for AP01-002 study

3. AP01 Phase 1b Clinical Study (AP01-002; ATLAS)

- Two part, open-label safety and efficacy study in IPF
- 25 sites in 6 countries
- Part A (initial 24 wks):
  - 91 patients enrolled (targeted 100, Covid limited)
  - All patients on active drug; 50 mg QD or 100 mg BID
  - No nintedanib or oral pirfenidone allowed
  - 24-wk DSMB readout deemed all dose levels safe. For improved benefit, move all pts to 100 mg BID
  - Efficacy measures indicative of stabilizing effect
- Part B (Optional 48 wks):
  - 77 patients continued into Part B
  - 24 wks Part A (above) + 48 wks Part B = 72 wks total
  - Covid prevented immediate DSMB dose change. Majority patients remained on Part A dose for at least 48 wks (Part A + initial 24 wks of Part B)
  - Nintedanib allowed
  - Based on 48 wk data:
    - AP01 was safe and well tolerated
    - AP01 dose responsive; 100 mg BID FVC trended toward stabilization

AP01 (Inhaled Pirfenidone) Overview, cont.

Objective

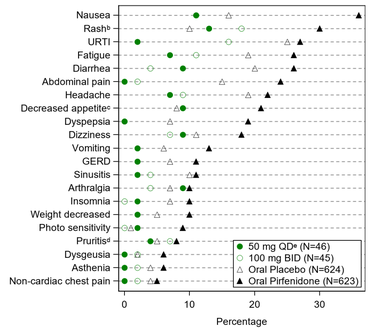
- Confirm multidose safety
- Estimate effect size and variability for dose selection
- Endpoints: safety/tolerability, FVC, cough, PRO, lung fibrosis volumes per HRCT

Eligibility

- Confident diagnosis of IPF
- Not eligible for oral pirfenidone/nintedanib per national formulary restrictions OR intolerant to or unwilling to start oral pirfenidone and nintedanib, if previously offered
- 40 ≤ FVC ≤ 90% predicted (40-50% FVC capped at 20 pts)
- Baseline similar to oral pirfenidone phase 3 studies

Adverse Events

Percent AEs observed with inhaled AP01 (50 mg QD and 100 mg BID; ATLAS) and oral pirfenidone (CAPACITY and ASCEND)

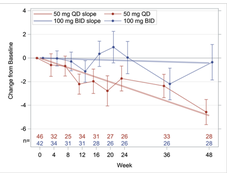


a. Occurring in ≥ 5% of Esbriet® patients and more commonly than placebo in CAPACITY and ASCEND
b. For ATLAS, rash includes rash, rash macular, rash papular, rash erythematous, and rash pruritic
c. Per MedDRA updates anorexia now codes to decreased appetite
d. For ATLAS, pruritis includes pruritis and pruritis generalized
e. 50 mg QD patients transitioned to 100 mg BID: After transition nausea, diarrhea, and rash from patient; weight increased from 1 patient are reported in 50 mg QD

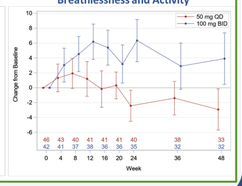
Efficacy

Change from Baseline in Lung Function and Quality of Life

Change from Baseline in FVC % Predicted



Change from Baseline in KBILD Breathlessness and Activity

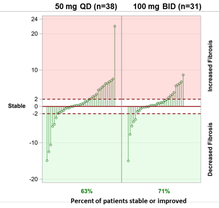


AP01 (Inhaled Pirfenidone) Overview, cont.

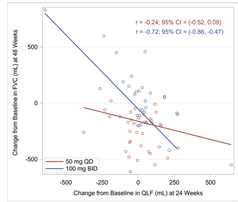
Efficacy - cont.

24 Week Change from Baseline in Whole Lung Quantitative Lung Fibrosis using HRCT Scans

Change from Baseline in Percent of Lung with Fibrosis



QLF and FVC Change Correlated Well



Take-Aways

- AP01 adverse events were fewer than observed in oral pirfenidone phase 3 studies; similar to placebo
- Change in FVC percent predicted was dose responsive (p=0.022) with high dose nearing stabilization
- Quantitative HRCT well-correlated with FVC changes
- Quantitative HRCT showed reduced fibrosis in both AP01 dose levels; high dose more effective
- PRO outcomes paralleled above observations

Future Plans

- Test hypothesis that AP01 is superior in both efficacy and safety to oral pirfenidone
- Phase 3, 52-wk, head-to-head, double dummy, 100 mg BID inhaled AP01 vs 801 mg TID oral pirfenidone
- 90% power; 60 mL FVC 52-wk difference
  - Oral Ascend 52-wk FVC decline 164 mL
  - Inhaled ATLAS 48-wk FVC decline 34 mL

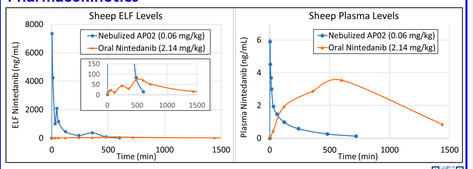
AP02 (Inhaled Nintedanib) Overview

1. AP02 Development Summary

- Higher potency drug requiring a smaller lung dose
- Shorter inhalation time to combat rapid lung elimination
  (Reducing delivery time sways equilibrium away from elimination and towards higher lung concentration)
- Initial product form (AP02):
  - Aqueous solution in twist-off LDPE ampoules
  - PARI eFlow® vibrating membrane nebulizer
- Dry powder formulation developed for potential bridge
- Nonclinical data supported clinical advancement
- Initial clinical data indicates AP02 is safe, well tolerated and delivers high lung levels with low systemic exposure

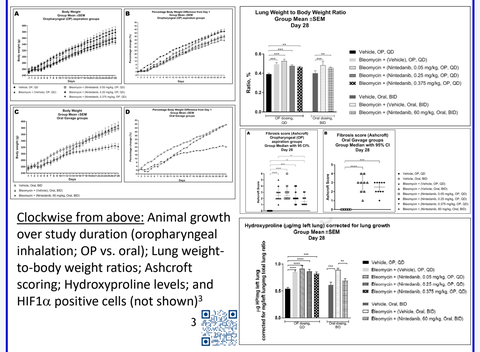
AP02 (Inhaled Nintedanib) Overview, cont.

Pharmacokinetics



Bleomycin Model[2]

Oropharyngeal aspiration (OP; inhalation) induced bleomycin injury on days 1, 2, 3 and 6. Oral (BID) and OP (QD) nintedanib treatment days 8 thru 27



Clockwise from above: Animal growth over study duration (oropharyngeal inhalation; OP vs. oral); Lung weight-to-body weight ratios; Ashcroft scoring; Hydroxyproline levels; and HIF1α positive cells (not shown)[3]

Additional nonclinical studies included:

- Detailed pharmacokinetic analysis in all species
- Inhalation PK inhibited IPF-conditioned cellular matrix profibrotic activity[4]
- Inhalation inhibited αSMA and IL-1b induction and fibrosis in the silica pulmonary fibrosis model[4]

Other Updates

- Dry powder formulation developed for potential bridge
- Fixed combination pirfenidone and nintedanib product developed (AP03). Phase 1a-enabling tox complete

Next Steps

- Complete Phase 1a (final cohort underway; IPF patients)
- Based upon projected dose, select nebulized AP02 or pivot to DPI formulation for Phase 2 POC

REFERENCES

Available within embedded QR codes