SAFETY AND TOLERABILITY OF INHALED NINTEDANIB DRY POWDER IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS: A RANDOMIZED PHASE 1B STUDY

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OBJECTIVE

To evaluate the safety and tolerability of Nintedanib dry powder inhalation (DPI) in patients with idiopathic pulmonary fibrosis (IPF)

CONCLUSIONS

Nintedanib DPI was safe well-tolerated in patients with IPF

- No serious adverse events
- No related gastrointestinal (GI) tolerability burden
- No treatment discontinuations
- No difference in spirometry parameters compared to placebo

This study strongly supports the ongoing phase 2 (INFLO-2) study and the ongoing development of Nintedanib DPI for fibrotic lung diseases, beginning with IPF.

INTRODUCTION

Treatments for IPF are designed to slow the progression and scar formation in the lungs. The antifibrotic agents pirfenidone, nintedanib, and nerandomilast have been shown to slow the progression of IPF, but their oral administration requires high plasma concentrations to achieve therapeutic exposure in the lungs, which is associated with negative systemic effects. Some patients are unable to tolerate oral nintedanib at the dosage needed to slow disease progression due to side effects, particularly the gastrointestinal (GI) effects (nausea, diarrhea, abdominal pain, and vomiting).

Nintedanib DPI delivers nintedanib directly to the lungs via oral inhalation through a dry powder inhaler, which may result in a lower systemic concentration of nintedanib and reduced systemic side effects while still achieving at or above the minimum therapeutic concentration in the lungs.

METHODS

INFLO-1 (NCT07344558) was a phase 1b, randomized, double-blind, placebo-controlled study of Nintedanib DPI evaluating safety and tolerability in patients with IPF. The study used a multiple ascending dose design with two nintedanib DPI dosing cohorts and four arms: 2 mg three times daily (TID), 4 mg twice daily (BID); and two placebo (empty cartridge) cohorts dosed BID or TID for 7 days.

Spirometry was performed in at least triplicate at each time point targeting a grade “A” American Thoracic Society spirometry measurement. Spirometry was measured prior to dose and 30, 90, and 180 minutes post-dose on days 1, 2, and 7 relative to start of randomized treatment. Adverse events including bronchospasm and rate of study drug reductions or discontinuations were monitored.

RESULTS

Twenty-seven participants were randomized and completed the trial, **Table 1.** All participants that received study drug remained on treatment for the planned 7-day period with no discontinuations, dose interruptions, or dose reductions.

Table 1. Baseline Characteristics

	2mg TID (N=8)	Placebo TID (N=4)	4mg BID (N=10)	Placebo BID (N=5)
Age (years) Mean (SD)	72.3(2.4)	63.0 (8.8)	77.5 (4.7)	73.4 (6.3)
Sex, n (%) Female	2 (25.0%)	2 (50.0%)	4 (40.0%)	2 (40.0%)
BMI (kg/m^2) Mean (SD)	29.5 (4.3)	30.9 (5.4)	30.2 (3.6)	31.0 (4.8)
FEV_1 (L) Mean (SD)	1.994 (0.462)	1.820 (0.365)	2.029 (0.397)	2.220 (0.328)
FEV_1 (% pred) Mean (SD)	77.6 (16.1)	69.0 (17.8)	88.0 (21.0)	87.8 (17.9)
FVC (L) Mean (SD)	2.568 (0.659)	2.308 (0.547)	2.688 (0.590)	2.752 (0.330)
FVC (% pred) Mean (SD)	76.1 (19.5)	67.8 (17.4)	87.8 (23.7)	81.8 (15.5)

BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity

Eighty-nine percent had no (61%) or mild (28%) cough. Reported cough events were generally transient post-inhalation, although some were recurrent with subsequent inhalations, and one worsened during the study with continued study drug use, **Table 2**.

There were no serious adverse events and no clinical bronchospasm events. No treatment-related gastrointestinal adverse events (diarrhea, nausea, vomiting, or abdominal discomfort) were reported.

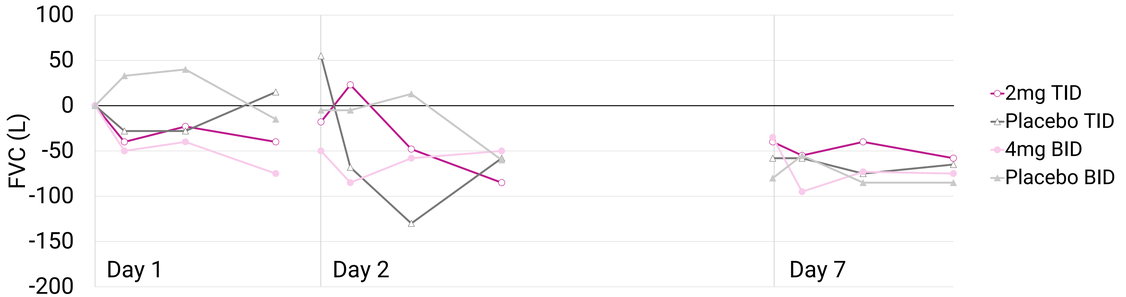
Table 2. Adverse Events

	2mg TID (N=8)	Placebo BID (N=4)	4mg BID (N=10)	Placebo BID (N=5)
Cough	4 (50%)	0	3 (30%)	0
Dysphonia*	0	0	1 (10%)	0
Incontinence*	0	0	1 (10%)	0
Diarrhea*	1 (12.5%)	0	0	0
Dry mouth	0	0	1 (10%)	0
Muscle Spasm	0	1 (25%)	0	0
Dizziness	0	0	1 (10%)	0

*Number of participants with an event (percent of participants in treatment group), *Not related to study drug per investigator*

No differences in changes in spirometry parameters, including FEV_1, FVC, and FEV_1 /FVC ratio, were observed between nintedanib DPI and placebo, **Figure 1**. INFLO-1 was the first study of Nintedanib DPI in patients with IPF. Mild cough was expected and had no clinical consequences.

Figure 1. Change in FVC from Baseline (L)



FVC (L) measured at pre-dose (first point each day) then 30-, 90-, and 180-min post-dose. All assessments are difference from average screening and day-1 pre-inhalation grade “A” measurements, shown as day 1 equal to 0.