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Pharmacokinetics and Safety of Nalbuphine Extended-Release Tablets Co-Administered With Pirfenidone or Nintedanib: A Phase 1 Drug–Drug Interaction Study

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Background

- The antifibrotics pirfenidone and nintedanib are standards of care for treatment of idiopathic pulmonary fibrosis (IPF)[1]
- Many patients with IPF experience chronic cough, a burdensome clinical feature for which there are no approved therapies[2-4]
- Oral nalbuphine extended-release (NAL ER) modulates the cough reflex arc by acting as a kappa opioid receptor agonist and mu opioid receptor antagonist in both the central nervous system and the peripheral sensory nerves of the airways[5] and are under investigation for the treatment of chronic cough in patients with IPF[6-8]
- Given the possibility of concomitant use, evaluating potential drug–drug interactions between NAL ER and antifibrotic therapies is important to ensure safe co-administration

Objective

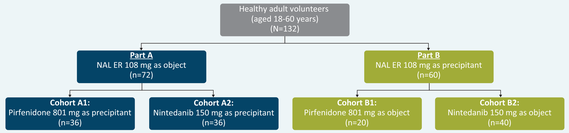
- To evaluate the pharmacokinetics (PK) and safety of co-administration of NAL ER and pirfenidone or nintedanib in healthy adults

Methods

Study Design

- This was a phase 1, open-label, two-part drug–drug interaction study conducted in healthy adults aged 18 to 60 years (**Figure 1**)
- **Part A (NAL ER as object)**
  - Cohort A1 (pirfenidone): A single dose of NAL ER 108 mg was administered on Day 1, followed by washout (Days 2-3). Pirfenidone 801 mg 3 times daily (TID) was given on Days 4-8 to steady state; NAL ER was co-administered on Day 6 with intensive PK sampling
  - Cohort A2 (nintedanib): A single dose of NAL ER 108 mg was administered on Day 1, followed by washout (Days 2-3). Nintedanib 150 mg twice daily (BID) was given on Days 4-10 to steady state; NAL ER was co-administered on Day 8 with intensive PK sampling
- **Part B (NAL ER as precipitant)**
  - Cohort B1 (pirfenidone): A single dose of pirfenidone 801 mg was administered on Day 1, followed by washout (Day 2). NAL ER 108 mg BID was given on Days 3-6 to steady state; pirfenidone was co-administered on Day 6 with intensive PK sampling
  - Cohort B2 (nintedanib): A single dose of nintedanib 150 mg was administered on Day 1, followed by washout (Days 2-3). NAL ER 108 mg BID was given on Days 4-9 to steady state; nintedanib was co-administered on Day 7 with intensive PK sampling

Figure 1. Study Design



Population

- Eligible participants were healthy adults aged 18 to 60 years who met all protocol-defined screening criteria

Endpoints

- PK endpoints
  - Primary endpoints included PK parameters (maximum observed plasma concentration [C_{max}] and area under the concentration-time curve from time zero [pre-dose] extrapolated to infinity [$AUC_{(0-inf)}$]) for each object drug at baseline and following co-administration with the interacting drug in each cohort
  - PK comparisons used geometric mean ratios (GMRs) and 90% confidence intervals (CIs) to evaluate clinical relevance of interactions
  - A sensitivity analysis of PK data parameters was repeated excluding patients who experienced emesis after dosing, as emesis is a side effect of the drugs under study
- Safety endpoints
  - Adverse events (AEs), clinical laboratory assessments, vital signs, and physical examinations

Results

Participant Disposition and Baseline Characteristics

- A total of 132 participants were enrolled
- Cohort A1 vs A2 and Cohort B1 vs B2 were generally similar in baseline characteristics (**Table 1**)

Table 1. Demographics and Baseline Characteristics

Parameter	Cohort A1 (n=36)	Cohort A2 (n=36)	Cohort B1 (n=20)	Cohort B2 (n=40)
Age, median (range), years	40.5 (19-59)	38.5 (20-59)	39.5 (19-52)	38.0 (18-60)
Female, n (%)	22 (61.1)	19 (52.8)	10 (50.0)	14 (35.0)
BMI, median (range)	27.5 (22.4-30.0)	27.5 (21.7-29.9)	25.3 (20.8-29.9)	27.0 (18.3-29.8)
Race, White, n (%)	36 (100)	36 (100)	18 (90.0)	37 (92.5)
Ethnicity, Hispanic or Latino, n (%)	36 (100)	36 (100)	20 (100)	40 (100)

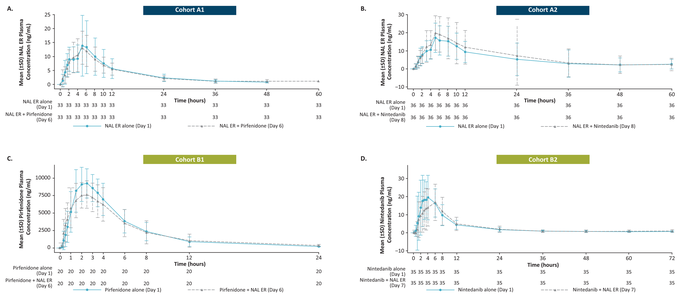
Pharmacokinetics

- **NAL ER as object (Part A)**
  - Neither pirfenidone nor nintedanib had a clinically meaningful effect on the PK of NAL ER (**Table 2**; **Figure 2A, 2B**)
- **NAL ER as precipitant (Part B)**
  - Similarly, NAL ER did not have a clinically meaningful effect on the PK of either nintedanib or pirfenidone (**Table 2**; **Figure 2C, 2D**)

Table 2. Pharmacokinetic Interaction Summary

Cohort	Object	Precipitant	GMR, % (95% CI) C_{max}	GMR, % (95% CI) $AUC_{(0-inf)}$
A1 (n=33)	NAL ER	Pirfenidone	88.4 (73.9-105.8)	96.6 (81.3-114.7)
A2 (n=36)	NAL ER	Nintedanib	114.3 (103.9-125.7)	119.4 (111.9-127.4)
B1 (n=20)	Pirfenidone	NAL ER	83.1 (75.2-91.7)	89.4 (80.7-99.1)
B2 (n=35)	Nintedanib	NAL ER	79.9 (72.9-87.7)	93.8 (87.2-100.9)

Figure 2. Mean Plasma Nalbuphine Concentrations Over Time (A and B) and Mean (±SD) Plasma Pirfenidone and Nintedanib Concentrations Over Time (C and D)



- In a sensitivity analysis of participants without emesis (vomiting; **Table 4**), PK results were consistent with the primary analysis across cohorts, with no clinically meaningful interactions observed (**Table 3**)

Table 3. Sensitivity Analysis of PK Parameters

Cohort	Object	Precipitant	GMR, % (95% CI) C_{max}	GMR, % (95% CI) $AUC_{(0-inf)}$
A1 (n=33)	NAL ER	Pirfenidone	82.5 (63.6-107.0)	93.8 (86.5-101.7)
A2 (n=36)	NAL ER	Nintedanib	116.4 (105.4-128.9)	117.14 (110.7-123.9)
B1 (n=20)	Pirfenidone	NAL ER	82.56 (74.4-91.6)	88.5 (79.4-98.7)
B2 (n=35)	Nintedanib	NAL ER	80.6 (73.1-88.9)	94.5 (87.3-102.4)

Sensitivity analysis excludes participants with emesis.

Safety and tolerability

- A summary of treatment-emergent AEs (TEAEs) is shown in **Table 4**
  - Most TEAEs were mild (Grade ≤2) and no deaths or serious AEs (SAEs) were reported
  - One participant in Cohort B2 discontinued due to hypersensitivity considered related to nintedanib
  - Common TEAEs were vomiting, dizziness, headache, and nausea
- There were no clinically significant trends in laboratory parameters, vital signs, or physical examination findings in either Part A or Part B

Table 4. Overall Summary of Adverse Events

Parameter, n (%)	Cohort A1 (n=36)	Cohort A2 (n=36)	Cohort B1 (n=20)	Cohort B2 (n=40)
TEAE	18 (50.0)	12 (33.3)	9 (45.0)	22 (55.0)
TEAE by maximum CTCAE grade				
Grade 1	7 (19.4)	10 (27.8)	7 (35.0)	13 (32.5)
Grade 2	11 (30.6)	2 (5.6)	2 (10.0)	9 (22.5)
Grades 3-5	0	0	0	0
NAL ER–related TEAE	18 (50.0)	10 (27.8)	7 (35.0)	20 (50.0)
NAL ER–related TEAE when NAL ER taken alone	9 (25.0)	5 (13.9)	NA	NA
Pirfenidone-related TEAE	18 (50.0)	NA	1 (5.0)	NA
Pirfenidone-related TEAE when pirfenidone taken alone	0	NA	1 (5.0)	NA
Nintedanib-related TEAE	NA	8 (22.2)	NA	10 (25.0)
Nintedanib-related TEAE when nintedanib taken alone	NA	0	NA	1 (2.5)
SAE	0	0	0	0
TEAE leading to study discontinuation	0	0	0	1 (2.5)
TEAE occurring in ≥10% of participants				
Vomiting	16 (44.4)	7 (19.4)	4 (20.0)	10 (25.0)
Dizziness	7 (19.4)	2 (5.6)	1 (5.0)	9 (22.5)
Headache	6 (16.7)	0	3 (15.0)	4 (10.0)
Nausea	5 (13.9)	0	1 (5.0)	3 (7.5)

Conclusions

- No clinically meaningful PK interactions were observed between NAL ER and either pirfenidone or nintedanib, including in the sensitivity analyses excluding participants with emesis
- NAL ER administered alone or in combination with pirfenidone or nintedanib was generally safe and well tolerated, and most AEs were mild to moderate in severity
- The results of this study demonstrate that NAL ER is unlikely to cause, or be affected by, a clinically meaningful drug interaction with pirfenidone or nintedanib

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Abbreviations

AE, adverse event; $AUC_{(0-inf)}$, area under the concentration-time curve from time zero (pre-dose) extrapolated to infinity; BID, twice daily; BMI, body mass index; CI, confidence interval; C_{max}, maximum observed plasma concentration; CTCAE, Common Terminology Criteria for Adverse Events; GMR, geometric mean ratio; IPF, idiopathic pulmonary fibrosis; NA, not applicable; NAL ER, nalbuphine extended release; PK, pharmacokinetics; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event; TID, 3 times daily.

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Disclosures

JC is employed by Trevi Therapeutics Inc. as Chief Development Officer and a Corporate Officer of the company.

CH and **RSF** are an employees and shareholders of Trevi Therapeutics Inc.

WK is a paid consultant to Trevi Therapeutics, Inc.

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