Safety and Pharmacokinetics of Nalbuphine Following Administration of Nalbuphine ER Tablets in Subjects With Impaired Hepatic Function

Shashank Rohatagi, PhD, MBA[1], Thomas C. Marbury, MD[2], David J. Wyatt, MD[3], Thomas Sciascia, MD[1]

[1]Trevi Therapeutics, New Haven, CT, USA; [2]Orlando Clinical Research Center, Orlando, FL, USA; [3]Syneos Health Early Phase, Miami, FL, USA

Introduction

Background

- Nalbuphine is a dual-acting opioid κ-receptor agonist and opioid μ-receptor antagonist
- Imbalance of activity across the κ- and μ-opioid system has been associated with severe chronic itch conditions, and studies suggest that agonism of κ-receptors may have a therapeutic benefit in these settings[1]
- Currently, nalbuphine is available in injectable form for relief of moderate to severe pain and use in various anesthesia regimens[2]
- Evaluation of nalbuphine in a substance P-induced mouse itch model suggests that nalbuphine may be a potential therapy for pruritic conditions
- An oral, extended-release (ER) tablet formulation of nalbuphine (NAL ER) is under investigation for prurigo nodularis, a severe dermatological condition characterized by itchy skin papules and nodules with high quality-of-life impact[3]

Objective

- The primary study objectives were to evaluate the effect of hepatic impairment on the pharmacokinetics (PK) of NAL ER as a function of dose and to evaluate the safety and tolerability of NAL ER in subjects with impaired hepatic function

Methods

Study design

- This was a phase 1, open-label, non-randomized, parallel-group, ascending-dose PK study of NAL ER oral tablets in subjects with impaired hepatic function compared with healthy subjects
- Eligible subjects were men and women aged ≥18 to ≤80 years with stable hepatic impairment and body mass index (BMI) ≥18.0 to ≤40 kg/m^2
- Subjects with hepatocellular carcinoma, acute hepatic disease from infection or drug toxicity, an intrahepatic portal systemic shunt, or stage 3-4 encephalopathy were excluded
- Subjects were assigned to hepatic impairment groups according to Child-Pugh Classification (mild [A]: 5-6; moderate [B]: 7-9; severe [C]: 10-15)
- Safety and PK were assessed based on the parameters shown in **Table 1**

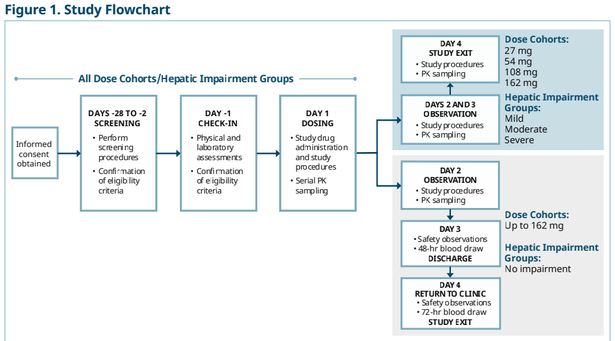
Table 1. NAL ER Dose Cohorts and Hepatic Impairment Subgroups

Ascending Dose Cohorts	Hepatic Impairment Groups
27 mg	Mild impairment (n=6–8), Moderate impairment (n=6–8), Severe impairment (n=4–6)
54 mg	Mild impairment (n=6–8), Moderate impairment (n=6–8)
108 mg	Mild impairment (n=6–8), Moderate impairment (n=6–8)
162 mg	Mild impairment (n=6–8), Moderate impairment (n=6–8)
Up to 162 mg[a]	No impairment (n=6–8)

[a]Highest dose tested in subjects with mild or moderate hepatic impairment.

- Subjects with severe impairment were enrolled upon completion of the highest dose level in subjects with mild or moderate impairment
- Subjects with no impairment were enrolled upon completion of the highest tolerated dose level in subjects with mild or moderate impairment
- Drug pharmacokinetics in the hepatic impairment population were compared with the healthy control population
- A time line of study procedures is depicted in **Figure 1**

Figure 1. Study Flowchart



PK analysis

- PK parameters (maximum observed plasma concentration [C_{max}], area under the concentration-time curve [AUC], terminal elimination half-life [$T_{½el}$], and time of maximum observed plasma concentration [T_{max}]) were calculated using noncompartmental methods
- Only observed data were used; no attempt was made to extrapolate or interpolate estimates for missing data
- All concentration values below the lower limit of quantitation and samples with no reportable value occurring prior to the first dosing were replaced by "0.00"
- For tabulation, graphical representation, and calculation purposes, all samples with no reportable value observed after administration of the first dose were set to missing

Statistical Analysis

- PK analysis was performed using validated Phoenix WinNonlin®, version 8.0 or higher
- Safety and PK data tables and listings were created using SAS®, release version 9.2 or higher

Results

Subject Disposition

- Subject disposition for each hepatic impairment group is detailed in **Table 2**

Table 2. Subject Disposition for Each Hepatic Impairment Group Within Each NAL ER Dose Cohort

Dose Cohort	27 mg			54 mg		108 mg		162 mg		162 mg
Hepatic impairment	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Mild**	**Moderate**	**Mild**	**Moderate**	**None**
Safety population	6	6	4	8	7	8	7	7	6	8
PK population	6	6	4	8	7	8	7	7	6	7
Completed study	6	6	4	8	7	8	7	7	6	8
Discontinued	0	0	0	0	0	0	0	0	0	0

NAL ER, nalbuphine extended release; PK, pharmacokinetic.

Baseline Demographics

- The study population (n=28) was 49–69 years old, 64.3% male, and 67.9% white, with a mean BMI of 30.1 kg/m^2 **(Table 3)**

Table 3. Summary of Demographic Characteristics by NAL ER Dose Cohort

Parameter	27 mg	54 mg	108 mg	162 mg	162 mg (healthy)
Age (years), n	16	15	15	13	8
Mean (SD)	60.7 (6.1)	60.3 (5.2)	59.9 (5.3)	59.1 (5.0)	55.9 (5.7)
Male Sex, n (%)	10 (62.5)	10 (66.7)	11 (73.3)	10 (76.9)	5 (62.5)
Ethnicity, n (%)					
Hispanic or Latino	1 (6.3)	2 (13.3)	2 (13.3)	2 (15.4)	8 (100)
Not Hispanic or Latino	15 (93.8)	13 (86.7)	13 (86.7)	11 (84.6)	0
Race, n (%)					
White	9 (56.3)	9 (60.0)	10 (66.7)	9 (69.2)	6 (75.0)
Black	6 (37.5)	5 (33.3)	4 (26.7)	4 (30.8)	2 (25.0)
Asian	1 (6.3)	1 (6.7)	1 (6.7)	0	0
Height (cm), n	16	15	15	13	8
Mean (SD)	169.40 (7.34)	169.61 (7.98)	171.10 (8.10)	171.76 (7.92)	163.88 (9.17)
Weight (kg), n	16	15	15	13	8
Mean (SD)	88.53 (16.41)	86.63 (17.22)	88.56 (17.63)	89.90 (17.92)	80.33 (8.40)
BMI (kg/m^2), n	16	15	15	13	8
Mean (SD)	30.750 (4.632)	30.033 (5.049)	30.153 (5.070)	30.415 (5.366)	29.963 (2.566)

BMI, body mass index; NAL ER, nalbuphine extended release; SD, standard deviation.

Plasma Nalbuphine Concentrations

- Mean ± standard deviation concentration-time profile for nalbuphine in each dose cohort showed **(Figure 2)**:
  - Dose-proportional plasma nalbuphine concentrations were observed over time in subjects with mild **(Figure 2A)** and moderate **(Figure 2B)** impairment
  - Similar pharmacokinetics of nalbuphine plasma concentration were observed over time following a single NAL ER 162 mg dose in subjects with normal hepatic function **(Figure 2D)** as seen following the same dose in subjects with moderate hepatic impairment **(Figure 2B)**
  - Nalbuphine plasma concentrations were higher in subjects with moderate impairment as compared with subjects with no impairment
  - Nalbuphine plasma concentration following NAL ER 27 mg in subjects with severe impairment **(Figure 2C)** was within the same range as that following NAL ER 162 mg in subjects with no impairment **(Figure 2D)**

Nalbuphine PK parameters

- NAL C_{max} and AUC increased in a nearly dose-proportional manner in subjects with mild or moderate hepatic impairment **(Table 4)**
- Mean NAL $T_{½el}$ and T_{max} were unchanged by level of hepatic impairment
- All metabolite exposure appeared to increase in an approximately dose-proportional manner (data not shown)
- As expected, with increased severity of hepatic impairment, metabolite exposures remained lower or similar (data not shown)

Ratios for Hepatic Impairment Subjects vs Healthy Controls

- NAL C_{max} and AUC were similar for subjects with mild hepatic impairment as compared with those with no hepatic impairment
- NAL C_{max} and AUC in subjects with moderate and severe hepatic impairment increased by ≈3- to 4-fold and ≈6- to 8-fold, respectively, versus those with no hepatic impairment

Table 4. Nalbuphine Plasma PK Parameters by NAL ER Dose and Hepatic Impairment Group

	$AUC_{0\text{-}inf}$ (n*ng/mL)	$AUC_{0\text{-}t}$ (n*ng/mL)	C_{max} (ng/mL)	T_{max} (h)	$T_{½el}$ (h)
Mild Impairment					
27 mg, n	4	6	6	6	4
Mean	72.31	48.89	3.56	4.417	8.60
SD	26.49	30.54	1.49	2.289	2.71
54 mg, n	5	8	8	8	5
Mean	152.31	131.53	8.20	6.250	11.36
SD	65.09	59.55	3.19	3.955	2.68
108 mg, n	6	8	8	8	6
Mean	316.16	270.08	14.8	6.317	8.54
SD	102.07	105.60	5.03	4.145	2.37
162 mg, n	6	7	7	7	6
Mean	375.54	375.27	19.9	9.786	9.47
SD	128.29	118.47	6.95	7.233	1.74
Moderate Impairment					
27 mg, n	6	6	6	6	6
Mean	254.39	244.03	14.6	4.667	8.45
SD	203.03	203.18	11.3	2.658	2.54
54 mg, n	7	7	7	7	7
Mean	499.30	481.65	28.2	6.010	8.01
SD	372.97	366.18	19.9	3.337	1.50
108 mg, n	7	7	7	7	7
Mean	1011.19	999.43	49.2	7.857	8.35
SD	617.95	618.03	25.7	4.375	2.25
162 mg, n	6	6	6	6	6
Mean	1251.90	1233.95	65.4	7.167	8.70
SD	781.89	784.14	36.2	3.125	2.75
Severe Impairment					
27 mg, n	4	4	4	4	4
Mean	498.34	489.19	28.3	6.000	7.17
SD	100.74	98.54	6.19	3.464	0.85
No Impairment					
162 mg, n	7	7	7	7	7
Mean	437.81	417.78	27.0	5.567	9.87
SD	296.71	293.31	9.24	1.904	2.45

$AUC_{0\text{-}inf}$, area under the concentration-time curve from time zero to infinity; $AUC_{0\text{-}t}$, area under the concentration-time curve from time zero to last measurable concentration; C_{max}, maximum observed plasma concentration; SD, standard deviation; $T_{½el}$, terminal elimination half-life; T_{max}, time of maximum observed plasma concentration.

Safety/Tolerability

- Most treatment-emergent adverse events (TEAEs) were mild or moderate and transient
- The most frequently reported TEAEs were nervous system disorders (19 events [46.4%; 13/28]), most of which were somnolence (15 events [39.3%; 11/28) reported with all NAL ER doses except 27 mg
- No serious TEAEs occurred

Conclusions

- Based on the PK and safety results of this study
  - No dosing adjustment may be needed for patients with mild hepatic impairment when administered a daily dose of NAL ER in the 15 mg to 360 mg dose range
  - Patients with moderate hepatic impairment may be administered a lower daily dose range of ≈4 mg to ≈120 mg NAL ER
  - Subjects with severe hepatic impairment may be administered a lower daily dose of ≈2 mg to ≈45 mg NAL ER

Disclosures

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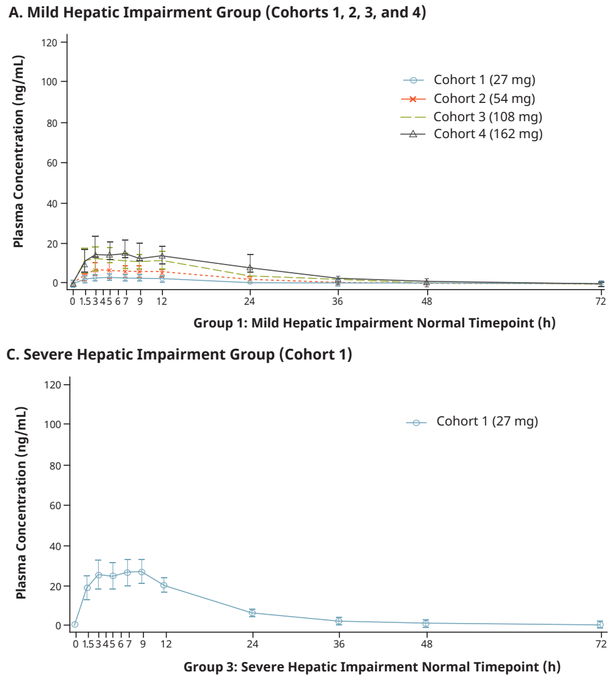
Figure 2. Mean (± SD) Nalbuphine Plasma Concentration in Each Dose Cohort for Subjects With Mild Hepatic Impairment (A), Moderate Hepatic Impairment (B), Severe Hepatic Impairment (C), No Hepatic Impairment (D)



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