2. SYNOPSIS

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Study Title: An Open-label, One-sequence, Two-period, Crossover, Drug-drug Interaction Study to Evaluate the Effect of Repeated Administration of Itraconazole or Fluconazole on the Pharmacokinetics of Naldemedine in Japanese Healthy Adult Subjects

Investigator and Clinical Research Unit:

[redacted]

Publication (Reference): None

Studied Period:

[redacted] April 2015 (first subject enrolled) to
[redacted] June 2015 (last subject completed)

Study Phase: 1

Objectives:

The primary objective of the study was:

To evaluate the effect of repeated administration of itraconazole 200 mg or fluconazole 200 mg on the pharmacokinetics (PK) of a single dose of naldemedine 0.2 mg compared to a single dose of naldemedine 0.2 mg administered alone, in Japanese healthy adult subjects.

The secondary objective of the study was:

To evaluate the safety and tolerability of a single dose of naldemedine 0.2 mg co-administered with a repeated administration of itraconazole 200 mg or fluconazole 200 mg, in Japanese healthy adult subjects.

Methodology: A single-center, open-label, one-sequence, two-period, crossover, drug-drug interaction study to evaluate the effect of repeated administration of itraconazole, a strong cytochrome P450 (CYP) 3A inhibitor (Cohort 1), or fluconazole, a moderate CYP3A inhibitor (Cohort 2) on the PK of naldemedine compared to naldemedine administered alone.

Number of Subjects (Planned and Analyzed):

Number of subjects planned: 28 (14 for each cohort)

Number of subjects who completed the study: 28 (14 for each cohort)

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Number of subjects analyzed for PK: 28 (14 for each cohort)

Number of subjects analyzed for safety: 28 (14 for each cohort)

Diagnosis and Main Criteria for Inclusion:

This study enrolled healthy subjects (male and female) aged 20 to 55 years inclusive, with a body mass index (BMI) of ≥ 18.0 to < 25.0 (kg/m^2).

Test Product, Dose and Mode of Administration, Lot Number:

Test Product: Naldemedine, 0.2-mg tablet for oral administration

Dose and Mode of Administration:

Each subject in Cohort 1 (itraconazole) and Cohort 2 (fluconazole) received a single 0.2 mg dose of naldemedine in the fasted state on Days 1 and 9 of the study.

Lot Number: [redacted]

Reference Therapy, Dose and Mode of Administration:

Test Product: Itrizole® Oral Solution 1%, Fluconazole 100-mg capsule

Dose and Mode of Administration:

Each subject in Cohort 1 received a 200 mg (20 mL) dose of Itrizole® Oral Solution 1% twice daily on Day 5 and a single 200 mg (20 mL) dose of Itrizole® Oral Solution once daily on Day 6 to 11 of the study.

Each subject in Cohort 2 received a single 400 mg (4 × 100-mg capsules) dose of fluconazole on Day 5 and a single 200 mg (2 × 100-mg capsules) dose of fluconazole once daily on Day 6 to 11 of the study.

Duration of Treatment:

Two non-consecutive days for a single dose of naldemedine and 7 consecutive days for itraconazole or fluconazole.

Duration of study participation: Participation was approximately for up to 8 weeks: up to a 28-day screening period, 12-day confinement period, and 14-day follow-up period.

Criteria for Evaluation:

Pharmacokinetic Analysis:

In each cohort, blood samples for PK analysis of plasma naldemedine and its metabolites (nor-naldemedine and naldemedine 3-*O*-*β*-D-glucuronide [naldemedine 3-G]) concentrations were collected at pre-dose (−0.25 hours), and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 60, and 72 hours post-dose on Days 1 and 9.

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Blood samples for analysis of plasma cholesterol and its metabolite (4β-hydroxycholesterol) as candidate biomarkers of potent CYP3A activity were collected at 2, 5, and 24 hours post-dose on Days 1 and 9, and Day 26 (End-of-Study Visit).

In Cohort 1, blood samples to measure plasma itraconazole and its metabolite (hydroxyitraconazole) concentrations were collected 2 hours after co-administration of itraconazole and naldemedine on Day 9.

In Cohort 2, blood samples to measure plasma fluconazole concentrations were collected 2 hours after co-administration of fluconazole and naldemedine on Day 9.

Pharmacokinetic Parameters:

Appropriate PK parameters were provided as follows: maximum observed plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the concentration-time curve (AUC) from time zero to the time of the last measurable concentration ($AUC_{0\text{-last}}$), AUC extrapolated from time zero to infinity ($AUC_{0\text{-inf}}$), terminal elimination rate constant (λ_z), and terminal elimination half-life ($t_{1/2,z}$) of naldemedine, nor-naldemedine, and naldemedine 3-G; apparent total clearance (CL/F) and apparent volume of distribution in the terminal phase (V_z/F) for naldemedine only; and metabolic ratio of metabolite C_{max} to naldemedine C_{max} ($MR_{M/U,Cmax}$) and metabolic ratio of metabolite $AUC_{0\text{-last}}$ to naldemedine $AUC_{0\text{-last}}$ ($MR_{M/U,AUC}$) for metabolites (nor-naldemedine and naldemedine 3-G).

Safety Assessment:

Safety was assessed by monitoring of physical examinations, vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory tests (including hematology, blood chemistry, and urinalysis), treatment-emergent adverse events (TEAEs), AEs related to naldemedine (ie, treatment related AEs), and serious adverse events (SAEs).

Exploratory Assessment:

Plasma concentrations of cholesterol and its metabolite (4β-hydroxycholesterol) were measured as candidate biomarkers of potent CYP3A activity, to investigate the correlation between CYP3A-mediated metabolism of cholesterol and the inhibition potential of the metabolism by itraconazole or fluconazole.

Statistical Methods:

Pharmacokinetics:

The PK parameters of naldemedine after co-administration of naldemedine with itraconazole (Cohort 1) or fluconazole (Cohort 2), the CYP3A inhibitor, and after

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administration of naldemedine alone were compared using an analyses of variance (ANOVA) model considering treatment condition (co-administration or naldemedine alone) as a fixed effect and subject as a random effect in each cohort for the following parameters of naldemedine: the logarithm of C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, λ_z, $t_{1/2,z}$, and CL/F. The ratios of geometric least squares means and the corresponding 90% confidence intervals (CIs) were estimated by exponentiating the mean differences in the logarithm.

If the 90% CIs for the primary parameters, C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$, are completely contained within the range of 0.8000 to 1.2500, then the conclusion is that repeated administration of CYP3A inhibitor (itraconazole or fluconazole) does not affect the PK of naldemedine.

Safety:

Safety and tolerability data were summarized descriptively. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 16.0. The overall number of subjects who experienced any TEAEs, treatment-related AEs, TEAEs that led to study discontinuation, significant TEAEs, and SAEs was counted, and the incidence and its 95% CI were summarized for each treatment period (Day 1 to prior to dosing on Day 5, dosing on Day 5 to prior to dosing on Day 9, dosing on Day 9 to 12 [discharge], after Day 12 to 26 [End-of-Study Visit]) for each cohort. The 95% CIs were calculated by using the Clopper-Pearson method. The number of subjects with TEAEs was tabulated by system organ class and preferred term. Summary statistics for vital signs (blood pressure, pulse rate, respiratory rate, and body temperature), ECG evaluations (heart rate, QRS, QT, PR, and QTc-intervals), and laboratory test evaluations (hematology, blood chemistry, and urinalysis) were calculated.

Summary of Results

Pharmacokinetics:

<u>The Effect of Itraconazole (Strong CYP3A Inhibitor) on the PK of Naldemedine</u>

The PK parameters following administration of naldemedine alone and naldemedine plus itraconazole are shown in the table below. Repeated administration of itraconazole increased C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of naldemedine by 1.12 fold (90% CI, 0.97 to 1.30), 2.65 fold (90% CI, 2.40 to 2.93), and 2.91 fold (90% CI, 2.64 to 3.22), respectively. Repeated administration of itraconazole decreased C_{max} and $AUC_{0\text{-last}}$ of nor-naldemedine and increased $AUC_{0\text{-last}}$ of naldemedine 3-G.

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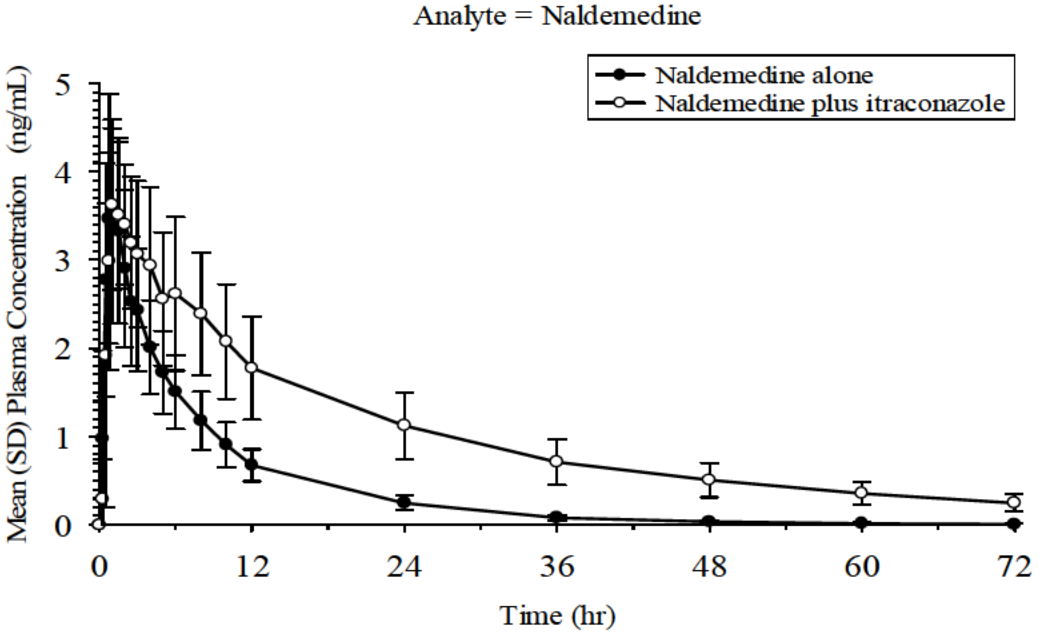
Mean (± SD) Plasma Naldemedine Concentration-Time Profiles Following Administration of Naldemedine Alone and Naldemedine plus Itraconazole (PK Parameter Population; N = 14)



Summary of Plasma Naldemedine Pharmacokinetic Parameters and Statistical Comparisons Following Administration of Naldemedine Alone and Naldemedine plus Itraconazole (PK Parameter Population)

Parameters	Plasma Naldemedine		
	Geometric Mean (CV% Geometric Mean)		Naldemedine plus Itraconazole / Naldemedine Alone Geometric Least Squares Mean Ratio[a] (90% CI: lower, upper)
	Naldemedine Alone	Naldemedine plus Itraconazole	
C_{max} (ng/mL)	3.56 (38.2)	4.00 (20.2)	1.1237 (0.9706, 1.3010)
$AUC_{0\text{-}last}$ (ng·hr/mL)	26.73 (38.2)	70.88 (34.4)	2.6517 (2.3968, 2.9338)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	26.98 (37.7)	78.64 (35.3)	2.9149 (2.6420, 3.2160)
λ_z (1/hr)	0.0665 (24.8)	0.0313 (17.8)	0.4698 (0.4291, 0.5143)
$t_{1/2,z}$ (hr)	10.4 (24.8)	22.2 (17.8)	2.1286 (1.9444, 2.3302)
CL/F (L/hr)	7.41 (37.7)	2.54 (35.3)	0.3431 (0.3109, 0.3785)

N = 14. CI, confidence interval.

[a] The analyses were based on the analysis of variance model.

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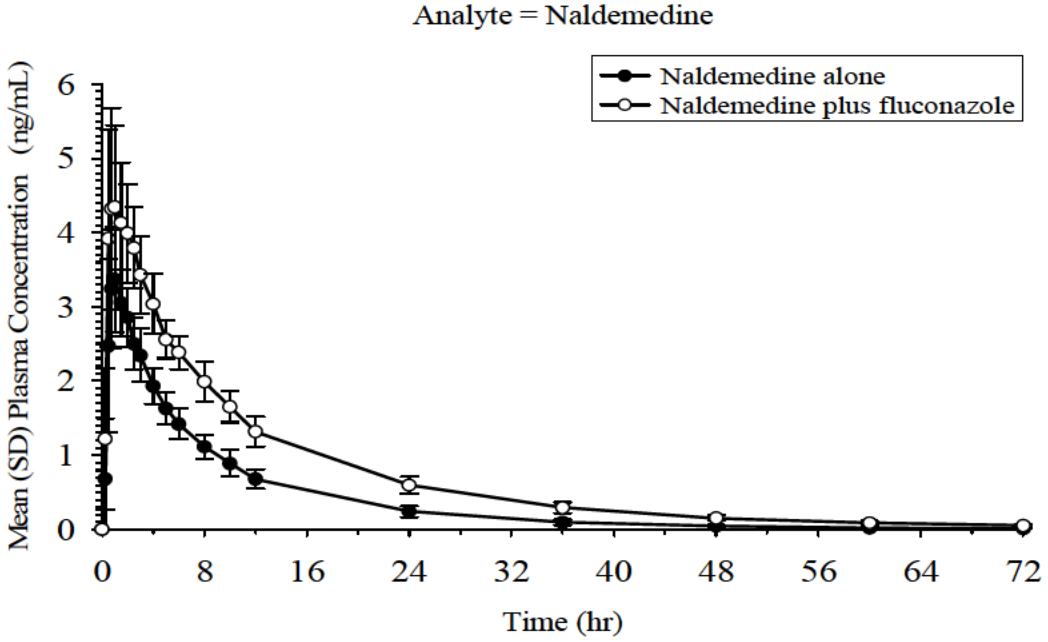
The Effect of Fluconazole (Moderate CYP3A Inhibitor) on the PK of Naldemedine

The PK parameters following administration of naldemedine alone and naldemedine plus fluconazole are shown in the table below. Repeated administration of fluconazole increased C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of naldemedine by 1.38 fold (90% CI, 1.23 to 1.55), 1.88 fold (90% CI, 1.78 to 1.98), and 1.90 fold (90% CI, 1.80 to 2.00), respectively. Repeated administration of fluconazole decreased C_{max} and $AUC_{0\text{-last}}$ of nor-naldemedine and increased those of naldemedine 3-G.

Mean (± SD) Plasma Naldemedine Concentration-Time Profiles Following Administration of Naldemedine Alone and Naldemedine plus Fluconazole (PK Parameter Population; N = 14)



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Summary of Plasma Naldemedine Pharmacokinetic Parameters and Statistical Comparisons Following Administration of Naldemedine Alone and Naldemedine plus Fluconazole (PK Parameter Population)

Parameters	Plasma Naldemedine		
	Geometric Mean (CV% Geometric Mean)		Naldemedine plus Fluconazole / Naldemedine Alone
	Naldemedine Alone	Naldemedine plus Fluconazole	Geometric Least Squares Mean Ratio[a] (90% CI: lower, upper)
C_{max} (ng/mL)	3.48 (23.7)	4.81 (16.1)	1.3831 (1.2316, 1.5532)
$AUC_{0\text{-last}}$ (ng·hr/mL)	26.93 (16.5)	50.58 (13.3)	1.8782 (1.7827, 1.9789)
$AUC_{0\text{-inf}}$ (ng·hr/mL)	27.18 (16.5)	51.60 (13.5)	1.8987 (1.8049, 1.9973)
λ_z (1/hr)	0.0683 (24.2)	0.0497 (13.1)	0.7267 (0.6670, 0.7917)
$t_{1/2,z}$ (hr)	10.1 (24.2)	14.0 (13.1)	1.3761 (1.2630, 1.4992)
CL/F (L/hr)	7.36 (16.5)	3.88 (13.5)	0.5267 (0.5007, 0.5541)

N = 14. CI, confidence interval.

[a] The analyses were based on the analysis of variance model.

Exploratory Analysis:

The 4β-hydroxycholesterol/cholesterol ratios were decreased approximately 18% to 23% after administration of itraconazole once daily for 7 days relative to prior to administration of itraconazole, at the same time points. In addition, the 4β-hydroxycholesterol/cholesterol ratio was comparable 15 days after the last administration of itraconazole relative to prior to administration of itraconazole. The concentrations of 4β-hydroxycholesterol after administration of itraconazole were approximately 32% to 38% lower than those prior to administration of itraconazole at the same sampling time point.

The 4β-hydroxycholesterol/cholesterol ratios prior to and after administration of fluconazole once daily for 7 days were comparable throughout the study period.

These results indicate that the plasma concentrations of 4β-hydroxycholesterol and the 4β-hydroxycholesterol/cholesterol ratio can be used as biomarkers to detect a strong inhibition of CYP3A enzyme activity in humans.

Safety:

In Cohort 1 (co-administration with itraconazole), 5 of 14 subjects (35.7%) experienced at least 1 TEAE. TEAEs were reported in 1 subject (7.1%) after administration of naldemedine alone, 2 subjects (14.3%) after administration of

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itraconazole alone, 1 subject (7.1%) after co-administration of naldemedine and itraconazole, and 5 subjects (35.7%) during the follow-up period (after Day 12).

In Cohort 2 (co-administration with fluconazole), 2 of 14 subjects (14.3%) experienced at least 1 TEAE. TEAEs were reported in 1 subject (7.1%) after administration of naldemedine alone, none after administration of fluconazole alone or co-administration of naldemedine and fluconazole, and 1 subject (7.1%) during the follow-up period (after Day 12).

All TEAEs except diarrhea in Cohort 1 were considered not related to naldemedine or the interacting drug by the Investigator or sub-Investigator. The diarrhea was reported in 1 subject after co-administration of naldemedine and itraconazole and it was considered related to naldemedine by the Investigator or sub-Investigator. All TEAEs were mild in severity and resolved without any intervention. No deaths, SAEs, or AEs leading to withdrawal from the study were reported. No abnormal findings for ECGs, clinical laboratory test results, or vital sign measurements were reported.

CONCLUSIONS

Pharmacokinetics:

- Repeated administration of itraconazole increased C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of naldemedine by 1.12 fold, 2.65 fold, and 2.91 fold, respectively. Repeated administration of itraconazole decreased C_{max} and $AUC_{0\text{-last}}$ of nor-naldemedine and increased $AUC_{0\text{-last}}$ of naldemedine 3-G.
- Repeated administration of fluconazole increased C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of naldemedine by 1.38 fold, 1.88 fold, and 1.90 fold, respectively. Repeated administration of fluconazole decreased C_{max} and $AUC_{0\text{-last}}$ of nor-naldemedine and increased those of naldemedine 3-G.

Safety:

- A single 0.2 mg dose of naldemedine was generally safe and well-tolerated when administered alone or co-administered with itraconazole or fluconazole to Japanese healthy adult subjects.

Draft Report Date: 19 October 2015