# 2. SYNOPSIS

| **Sponsor:**<br>Shionogi Inc. | **Individual Study Table Referring to Part of the Dossier** | (***For National Authority Use only***) |
|---|---|---|
| **Name of Finished Product:**<br>Not applicable | **Volume:** | |
| **Name of Active Ingredient:**<br>Naldemedine | **Page:** | |

**Study Title:** An Open-Label, One-Sequence, Two Period, Crossover, Drug-Drug Interaction Study to Evaluate the Effect of Repeated Administration of Rifampin on the Pharmacokinetics of Naldemedine in Healthy Adult Subjects

**Investigator and Study Center:**
[redacted]

**Publication (reference):** None

**Studied Period:**
[redacted] March 2014 (first subject enrolled) to
April 2014 (last subject completed)

**Study Phase:** 1

**Objectives:**

The primary objective of the study was:

To evaluate the effect of repeated administration of rifampin 600 mg on the pharmacokinetics (PK) of a single dose of naldemedine 0.2 mg compared with a single dose of naldemedine 0.2 mg administered alone, in 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 repeated administration of rifampin 600 mg, compared with a single dose of naldemedine 0.2 mg administered alone, in healthy adult subjects.

**Methodology:** An open-label, one-sequence, two-period, crossover, drug-drug interaction study to evaluate the effect of repeated administration of rifampin on the PK of naldemedine in healthy adult subjects compared with naldemedine alone.

**Number of Subjects (Planned and Analyzed):**

Number of subjects planned: 14

Number of subjects who completed the study: 14

Number of subjects analyzed for PK: 14 (14 for each treatment)

Number of subjects analyzed for safety: 14 (14 for each treatment)

**Diagnosis and Main Criteria for Inclusion:**

This study enrolled healthy subjects (male and female) aged 18 to 55 years inclusive, with a body mass index (BMI) of $\geq 18$ to $\leq 30$ ($kg/m^2$).

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|---|---|---|
| **Name of Finished Product:** Not applicable | **Volume:** | |
| **Name of Active Ingredient:** Naldemedine | **Page:** | |

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

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

**Dose and Mode of Administration:** On Days 1 and 18, 0.2 mg naldemedine (1 × 0.2 mg tablet) was administered after at least an 8-hour fast with 240 mL (8 ounces) of water. Subjects remained fasted for 4 hours postdose until lunch was provided.

**Lot Number:** [redacted]

**Duration of Treatment:**

Two non-consecutive days of single doses of naldemedine and 17 consecutive days of rifampin once daily (QD).

**Duration of study participation**: Participation was approximately 64 days (28 days screening, 22 days confinement, and 14 days follow-up).

**Reference Therapy:**

**Dose and Mode of Administration:**

**Test Product:** Rifampin capsules USP, 300 mg

**Dose and Mode of Administration:** On Days 4 to 20, 600 mg rifampin capsules (2 × 300 mg capsules) were administered after at least an 8-hour fast with 240 mL of water. On Days 4 to 17, 19, and 20, there was no food intake for 0.5 hours after dosing.

The rifampin dose on Day 18 was administered at the same time as the naldemedine dose. Subjects remained fasted for 4 hours postdose until lunch was provided.

**Lot Number:** [redacted]

**Criteria for Evaluation:**

**Pharmacokinetic Analysis:**

Serial blood samples were obtained at predose (0 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 following naldemedine dosing on Days 1 and 18 for analysis of naldemedine and its primary metabolite, nor-naldemedine, in plasma. A single blood sample was obtained at 2 hours postdose on Day 18 for analysis of rifampin concentrations in plasma.

**Bioanalytic Assessment:**

- Measurement method: Liquid chromatography/tandem mass spectrometry (LC/MS/MS); Sciex API 5000); at [redacted]
- Lower limit of quantification (LLOQ) values were 0.0100 ng/mL, 0.0400 ng/mL, and 50.0 ng/mL for naldemedine, nor-naldemedine, and rifampin, respectively

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|---|---|---|
| **Name of Finished Product:** Not applicable | **Volume:** | |
| **Name of Active Ingredient:** Naldemedine | **Page:** | |

**Pharmacokinetic Parameters:**

The estimated PK parameters ($C_{max}$, $T_{max}$, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $\lambda_z$, $t_{1/2,z}$, and $AUC_{extr}$ for naldemedine and nor-naldemedine; MRT, CL/F, and $V_z/F$ for naldemedine; and $MR_{M/U,Cmax}$ and $MR_{M/U,AUC}$ for nor-naldemedine) were summarized using descriptive statistics, including number of non-missing observations (n), arithmetic mean, standard deviation (SD), coefficient of variation (CV%), median, minimum, maximum, geometric mean, and geometric CV%. $T_{max}$ was summarized with n, arithmetic mean, SD, CV%, median, minimum, and maximum only.

**Exploratory Assessment:**

Plasma concentrations of cholesterol and its metabolites, 4β-hydroxy cholesterol and 25-hydroxy cholesterol, were measured as candidate biomarkers of potent CYP3A activity, to assess the induction potential of CYP3A activity by rifampin repeated administration.

**Safety Assessment:**

Safety was assessed by monitoring clinical laboratory test results (including hematology, blood chemistry, and urinalysis), vital signs, 12-lead electrocardiograms (ECGs), and physical examinations. Treatment-emergent adverse events (TEAEs) were collected and those related to study drug were tabulated.

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|---|---|---|
| **Name of Finished Product:** Not applicable | **Volume:** | |
| **Name of Active Ingredient:** Naldemedine | **Page:** | |

**Statistical Methods:**

**Pharmacokinetics:**

To evaluate the effect of repeated administration of rifampin on the PK of naldemedine, $C_{max}$, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $\lambda_z$, $t_{1/2,z}$, and CL/F were transformed (using natural logarithms) and analyzed using an analysis of variance (ANOVA) model. The least-squares (LS) means, ratio of geometric means between naldemedine administered with rifampin (test) compared with naldemedine administered alone (reference) and 90% confidence intervals (CIs) for the ratio of geometric means were determined for each parameter. The LS means, difference between LS means, and the upper and lower limits of the 90% CIs of difference were exponentiated to the original scale. Geometric LS means, mean ratios, and 90% CIs were presented.

Statistical comparisons of nor-naldemedine PK parameters were also performed, as described above, and presented as supportive information.

**Safety:**

Safety and tolerability data were summarized descriptively. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 16.1. Note, there were no pretreatment AEs reported in this study, only TEAEs. The number of subjects who experienced any TEAEs were summarized for each session (Naldemedine Alone, Day 1 to prior to dosing on Day 4; Rifampin Alone, from time of dosing on Day 4 to prior to dosing on Day 18; Naldemedine:Rifampin, from time of dosing on Day 18 to Day 21 [discharge]; and After Day 21, Day 21 to Day 35 [End-of-Study Visit]), and their 95% CIs were calculated using the Clopper-Pearson method, and were 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, pulse rate [PR], and QTc-intervals), and laboratory test evaluations (hematology, blood chemistry, and urinalysis) were performed.

**Summary of Results**

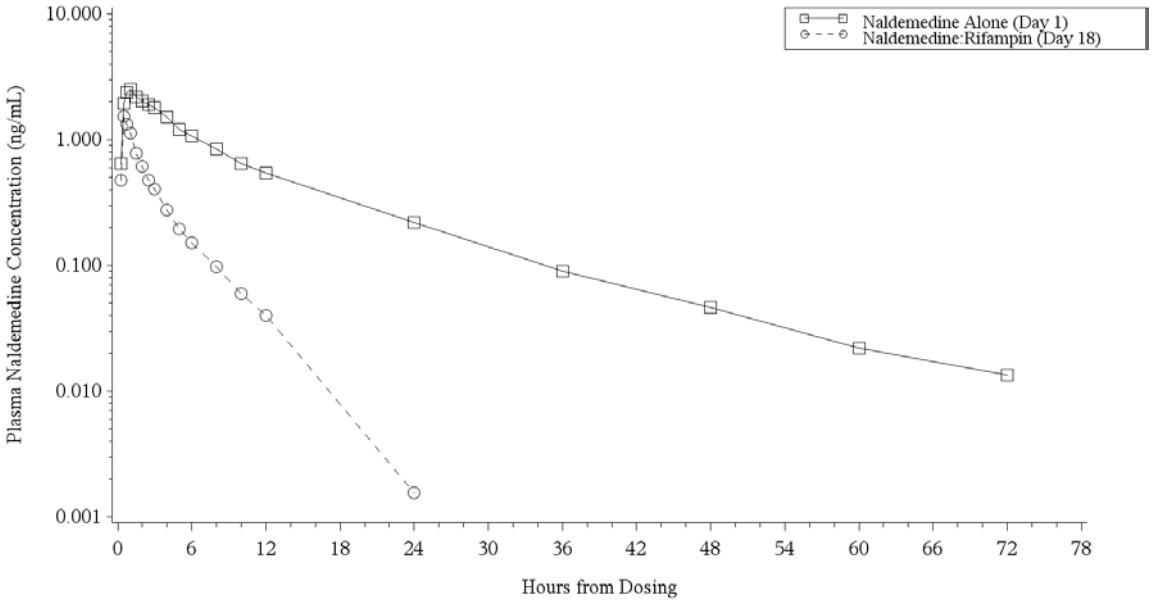
**Pharmacokinetics:**

Naldemedine

Administration of a single oral dose of 0.2 mg naldemedine on Day 18 with repeated doses of 600 mg rifampin QD on Days 4 to 20 demonstrated lower plasma naldemedine concentrations and an apparently more rapid rate of elimination compared with a single oral dose of 0.2 mg naldemedine administered alone on Day 1.

| **Sponsor:** Shionogi Inc. | **Individual Study Table Referring to Part of the Dossier** | (***For National Authority Use only***) |
|---|---|---|
| **Name of Finished Product:** Not applicable | **Volume:** | |
| **Name of Active Ingredient:** Naldemedine | **Page:** | |

**Mean Plasma Naldemedine Concentrations Versus Time Following Naldemedine Dosing on Days 1 and 18 (PK Parameter Population; N = 14) Semi-Log Scale**




**Summary of Plasma Naldemedine Pharmacokinetic Parameters (PK Parameter Population)**

| Pharmacokinetic Parameters | Geometric Mean (CV% geometric mean) | |
|---|---|---|
| | Naldemedine Alone (Day 1) (n = 14) | Naldemedine:Rifampin (Day 18) (n = 14) |
| $C_{max}$ (ng/mL) | 2.72 (25.7) | 1.68 (21.1) |
| $T_{max}$ (hr)[a] | 1.00 (0.50, 2.50) | 0.51 (0.50, 1.00) |
| $AUC_{0\text{-last}}$ (ng·hr/mL) | 21.49 (19.1) | 3.549 (16.6) |
| $AUC_{0\text{-inf}}$ (ng·hr/mL) | 21.77 (19.2) | 3.701 (16.0) |
| $\lambda_z$ (1/hr) | 0.0591 (18.5) | 0.2152 (15.5) |
| $t_{1/2,z}$ (hr) | 11.7 (18.5) | 3.22 (15.5) |
| MRT (hr) | 12.35 (18.7) | 3.61 (14.6) |
| CL/F (L/hr) | 9.19 (19.2) | 54.0 (16.0) |
| $V_z$/F (L) | 155 (18.1) | 251 (20.1) |

a $T_{max}$ is presented as median (minimum, maximum).

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|---|---|---|
| **Name of Finished Product:** Not applicable | **Volume:** | |
| **Name of Active Ingredient:** Naldemedine | **Page:** | |

The ratios of geometric LS mean naldemedine $C_{max}$, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and $t_{1/2,z}$ values following Naldemedine:Rifampin compared with Naldemedine Alone were 0.6180 (90% CI, 0.5466 to 0.6987), 0.1651 (90% CI, 0.1469 to 0.1856), 0.1700 (90% CI, 0.1512 to 0.1911), and 0.2745 (90% CI, 0.2524 to 0.2986), respectively. The geometric LS mean naldemedine $C_{max}$, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and $t_{1/2,z}$ values were approximately 38%, 83%, 83%, and 73% lower, respectively, following Naldemedine:Rifampin compared with Naldemedine Alone, and the 90% CIs for the ratios of these parameters were completely outside the 0.80 to 1.25 reference interval usually applied to establish similarity between treatments. The ratio of geometric LS mean naldemedine CL/F values following Naldemedine:Rifampin compared with Naldemedine Alone was 5.8833 (90% CI, 5.2328 to 6.6146). The geometric LS mean naldemedine CL/F value was approximately 6-fold following Naldemedine:Rifampin compared with Naldemedine Alone, and the 90% CI for the ratio of CL/F was completely outside the 0.80 to 1.25 reference interval.

**Summary of the Statistical Comparisons of Plasma Naldemedine Pharmacokinetic Parameters: Naldemedine:Rifampin Versus Naldemedine Alone (PK Parameter Population)**

| Pharmacokinetic Parameter | Geometric LS Means | | Mean Ratio | 90% Confidence Interval |
|---|---|---|---|---|
| | Naldemedine:Rifampin (Test) (n = 14) | Naldemedine Alone (Reference) (n = 14) | | |
| $C_{max}$ | 1.68 | 2.72 | 0.6180 | 0.5466 – 0.6987 |
| $AUC_{0\text{-last}}$ | 3.549 | 21.49 | 0.1651 | 0.1469 – 0.1856 |
| $AUC_{0\text{-inf}}$ | 3.701 | 21.77 | 0.1700 | 0.1512 – 0.1911 |
| $\lambda_z$ | 0.2152 | 0.0591 | 3.6424 | 3.3489 – 3.9616 |
| $t_{1/2,z}$ | 3.22 | 11.7 | 0.2745 | 0.2524 – 0.2986 |
| CL/F | 54.0 | 9.19 | 5.8833 | 5.2328 – 6.6146 |

Parameters were ln-transformed prior to analysis.
Geometric least-squares (LS) means are calculated by exponentiating the LS means from the ANOVA.
Mean Ratio = (Test/Reference).

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|---|---|---|
| **Name of Finished Product:** Not applicable | **Volume:** | |
| **Name of Active Ingredient:** Naldemedine | **Page:** | |

Nor-naldemedine

Administration of a single oral dose of 0.2 mg naldemedine on Day 18 with repeated doses of 600 mg rifampin QD on Days 4 to 20 demonstrated higher plasma nor-naldemedine concentrations with more rapid time to peak mean nor-naldemedine concentration compared with a single oral dose of 0.2 mg naldemedine administered alone on Day 1. The geometric mean $MR_{M/U,Cmax}$ and $MR_{M/U,AUC}$ values were higher following Naldemedine:Rifampin compared with Naldemedine Alone. Most notably, geometric mean $MR_{M/U,AUC}$ was 0.085 following Naldemedine Alone and 1.265 following Naldemedine:Rifampin.

**Summary of Plasma Nor-naldemedine Pharmacokinetic Parameters (PK Parameter Population)**

| Pharmacokinetic Parameters | Geometric Mean (CV% geometric mean) | |
|---|---|---|
| | Naldemedine Alone (Day 1) (n = 14)[a] | Naldemedine:Rifampin (Day 18) (n = 14) |
| $C_{max}$ (ng/mL) | 0.113 (33.9) | 0.358 (13.5) |
| $T_{max}$ (hr)[b] | 4.00 (2.50, 5.00) | 1.50 (1.01, 2.00) |
| $AUC_{0\text{-last}}$ (ng·hr/mL) | 1.656 (58.4) | 4.063 (17.8) |
| $AUC_{0\text{-inf}}$ (ng·hr/mL) | NC[c] | 4.696 (17.5) |
| $\lambda_z$ (1/hr) | 0.0370 (21.4) | 0.0781 (23.1) |
| $t_{1/2,z}$ (hr) | 18.7 (21.4) | 8.88 (23.1) |
| $MR_{M/U,Cmax}$ | 0.046 (28.8) | 0.235 (25.0) |
| $MR_{M/U,AUC}$ | 0.085 (66.6) | 1.265 (26.5) |

a n=13 for $\lambda_z$ and $t_{1/2,z}$
b $T_{max}$ is presented as median (minimum, maximum)
c $AUC_{0\text{-inf}}$ was not summarized, because all individual $AUC_{extr}$ values were >20%
$MR_{M/U,Cmax}$ = (nor-naldemedine $C_{max}$)/(naldemedine $C_{max}$) × (naldemedine MW)/(nor-naldemedine MW)
$MR_{M/U,AUC}$ = (nor-naldemedine $AUC_{0\text{-last}}$)/(naldemedine $AUC_{0\text{-last}}$) × (naldemedine MW)/(nor-naldemedine MW)
where the molecular weight (MW) of naldemedine is 570.64 g/mol and the MW of nor-naldemedine is 516.55 g/mol

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|---|---|---|
| **Name of Finished Product:** Not applicable | **Volume:** | |
| **Name of Active Ingredient:** Naldemedine | **Page:** | |

The ratios of geometric LS mean nor-naldemedine $C_{max}$ and $AUC_{0\text{-last}}$ values following Naldemedine:Rifampin compared with Naldemedine Alone were 3.1745 (90% CI, 2.7094 to 3.7195) and 2.4530 (90% CI, 1.9112 to 3.1483), respectively. The geometric LS mean nor-naldemedine $C_{max}$ and $AUC_{0\text{-last}}$ values were approximately 3.2- and 2.5-fold higher following Naldemedine:Rifampin compared with Naldemedine Alone, and the 90% CIs for the ratios of these parameters were completely outside the 0.80 to 1.25 reference interval. The ratio of geometric LS mean nor-naldemedine $t_{1/2,z}$ values following Naldemedine:Rifampin compared with Naldemedine Alone was 0.4758 (90% CI, 0.4241 to 0.5339). The geometric LS mean nor-naldemedine $t_{1/2,z}$ value was approximately 52% lower following Naldemedine:Rifampin compared with Naldemedine Alone, and the 90% CI for the ratio of $t_{1/2,z}$ was outside the 0.80 to 1.25 reference interval.

**Summary of the Statistical Comparisons of Plasma Nor-naldemedine Pharmacokinetic Parameters: Naldemedine:Rifampin Versus Naldemedine Alone (PK Parameter Population)**

| Pharmacokinetic Parameter | Geometric LS Means | | Mean Ratio | 90% Confidence Interval |
|---|---|---|---|---|
| | Naldemedine:Rifampin (Test) (n = 14) | Naldemedine Alone (Reference) (n = 14)[a] | | |
| $C_{max}$ | 0.358 | 0.113 | 3.1745 | 2.7094 – 3.7195 |
| $AUC_{0\text{-last}}$ | 4.063 | 1.656 | 2.4530 | 1.9112 – 3.1483 |
| $\lambda_z$ | 0.0781 | 0.0371 | 2.1017 | 1.8732 – 2.3581 |
| $t_{1/2,z}$ | 8.88 | 18.7 | 0.4758 | 0.4241 – 0.5339 |

Parameters were ln-transformed prior to analysis.
Geometric least-squares (LS) means are calculated by exponentiating the LS means from the ANOVA.
Mean Ratio = (Test/Reference).
a Subject 1013 data are missing for $\lambda_z$ and $t_{1/2,z}$ on Day 1.

## Exploratory Analysis:

The ratio of 4β-hydroxy cholesterol/cholesterol was increased approximately 5-fold after rifampin treatment; however, the ratio of 25-hydroxy cholesterol/cholesterol remained fairly consistent, irrespective of rifampin treatment. These results indicate that plasma 4β-hydroxy cholesterol/cholesterol ratio can be used as a biomarker to evaluate increases in CYP3A activity in humans.

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|---|---|---|
| **Name of Finished Product:** Not applicable | **Volume:** | |
| **Name of Active Ingredient:** Naldemedine | **Page:** | |

**Safety:**

There were no TEAEs reported by any of the 14 subjects (0.0%) following Naldemedine Alone. TEAEs were reported by 14 of the 14 subjects (100.0%) following Rifampin Alone, and in 1 of the 14 subjects (7.1%) following Naldemedine:Rifampin. The most frequent TEAE in the study was mild chromaturia, considered to be definitely related to rifampin, reported by 14 of the 14 subjects following Rifampin Alone. The TEAE of chromaturia was expected and the subjects had been informed that rifampin may produce a reddish coloration of urine, sweat, sputum, and tears. There were no TEAEs related to Naldemedine Alone or Naldemedine:Rifampin reported. No deaths, SAEs, or TEAEs leading to withdrawal were reported. No abnormal findings in ECGs, clinical laboratory results, or vital signs were found.

**CONCLUSIONS**

**Pharmacokinetics:**

- Administration of a single 0.2 mg dose of naldemedine following repeated doses of 600 mg rifampin resulted in decreased naldemedine maximum concentration and overall exposure, with naldemedine geometric means for $C_{max}$, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and $t_{1/2,z}$ approximately 38%, 83%, 83%, and 73% lower, respectively, than those following administration of a single 0.2 mg dose of naldemedine alone.
- Administration of a single dose of naldemedine following repeated doses of rifampin resulted in higher nor-naldemedine maximum concentrations and overall exposures and reduced nor-naldemedine time to peak, with nor-naldemedine geometric means for $C_{max}$ and $AUC_{0\text{-last}}$ approximately 3.2- and 2.5-fold higher, respectively, and geometric mean apparent $t_{1/2,z}$ values approximately 52% lower than those following administration of naldemedine alone.

**Safety:**

- The results of this study demonstrated that a single dose of naldemedine 0.2 mg co-administered with repeated administration of rifampin 600 mg, compared with a single dose of naldemedine 0.2 mg administered alone, is safe and well-tolerated in healthy adult subjects.

**Report Date:** 18 December 2014

**Prepared in:** Microsoft Word 2010