2. SYNOPSIS

Sponsor: Shionogi Inc.	**Individual Study Table Referring to Part of the Dossier**	(*For National Authority Use only*)
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Study Title:

Phase 1, Open-label, Non-randomized, Single-dose, Parallel-group Study to Evaluate the Influence of Mild and Moderate Hepatic Impairment on the Pharmacokinetics and Safety of 0.2 mg Naldemedine Compared with Healthy Demographically-matched Subjects with Normal Hepatic Function

Investigators and Study Centers:

[redacted]

Publication (Reference): None planned.

Study Period: [redacted] March 2015 (first subject enrolled) to [redacted] July 2015 (last subject completed)

Study Phase: Phase 1

Objectives:

The primary objective of the study was:

- To evaluate the pharmacokinetics (PK) of a single oral 0.2 mg dose of naldemedine in subjects with mild or moderate hepatic impairment (HI) compared with subjects with normal hepatic function.

The secondary objective of the study was:

- To evaluate the safety and tolerability of a single oral 0.2 mg dose of naldemedine in subjects with mild or moderate HI compared with subjects with normal hepatic function.

Methodology:

This was a non-randomized, open-label, parallel cohort study. The study consisted of 3 cohorts: Cohort 1 included healthy subjects with normal hepatic function; Cohort 2 included subjects with mild HI; Cohort 3 included subjects with moderate HI. Each subject with normal hepatic function (Cohort 1) was demographically matched to a subject with moderate HI (Cohort 3) according to gender, age (± 10 years), and body

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mass index (BMI) (± 20%). The Child-Pugh classification system was used to categorize subjects into each cohort: normal hepatic function with a total point score of < 5 for the healthy matched control subjects (Cohort 1), mild HI with a total point score of 5 to 6 (Cohort 2), and moderate HI with a total point score of 7 to 9 (Cohort 3). A total of 24 subjects were enrolled in the study, with 8 subjects included in each cohort.

All subjects underwent a Screening Visit (Day -28 to Day -2) to determine study eligibility. Qualified subjects were admitted to the clinical research unit (CRU) on Day -1 and remained confined through 72 hours postdose. A single dose of naldemedine was administered orally in the morning of Day 1 after an overnight fast of at least 8 hours; subjects remained fasted for 4 hours postdose. Venous blood samples for determination of plasma naldemedine and naldemedine metabolites concentrations were collected from the predose time point until 72 hours postdose. Subjects were discharged from the CRU in the morning of Day 4 following completion of all 72-hour procedures. Subjects returned to the CRU for an End-of-Study visit on Day 15 (± 2 days).

Prohibited Therapies or Restrictions

Prohibited Therapies

- Any medications that were P-glycoprotein (P-gp) receptor and/or cytochrome P450 (CYP) 3A enzyme inhibitors from 2 weeks prior to admission to the CRU (Day −1) until study completion
- Any medications that were P-gp receptor and/or CYP3A enzyme inducers (including St John's wort) from 4 weeks prior to admission to the CRU (Day −1) until study completion
- Any medications known to affect the elimination of serum creatinine (eg, trimethoprim/sulfamethoxazole [Bactrim®] or cimetidine [Tagamet®]) and competitors of renal tubular secretion (eg, probenecid) from 4 weeks prior to admission to the CRU (Day −1) until study completion
- Healthy Subjects
  - Any prescription or non-prescription medications and non-prescription medications drugs (including herbal medicines or dietary supplements) drugs, including herbal medicine or dietary supplements, from 2 weeks prior to dose administration on Day 1 and throughout the study, unless deemed acceptable by the investigator.

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Restrictions

- Excessive eating and/or excessive drinking.
- Blood donation during the study, ≥ 400 mL of blood within 12 weeks, or ≥ 200 mL within 4 weeks prior to the Screening Visit.
- Foods and beverages containing alcohol from 72 hours prior to admission. (Day -1) until completion of the End-of-Study/Early Termination Visit.
- Foods and beverages containing caffeine from 72 hours prior to admission (Day -1) until completion of the End-of-Study/Early Termination Visit. However, soft drinks without caffeine starting 4 hours postdose were allowed.
- Red wine, Seville oranges, grapefruit or grapefruit juice, pomelo, exotic citrus fruits, or grapefruit hybrids or fruit juices containing such products from 7 days prior to admission until completion of the End-of-Study/Early Termination Visit.
- Smoking for subjects with normal hepatic function, smoking-cessation aids, consuming more than 1 pack of cigarettes per day, and all nicotine containing products other than cigarettes for subjects with mild and moderate HI.
- Vigorous exercise from 48 hours prior to the Screening Visit until completion of screening and from 48 hours prior to admission (Day -1) until completion of End-of-Study/Early Termination Visit.

Number of Subjects (Planned and Analyzed):

Number of subjects planned: 24 subjects in 3 cohorts (n=8 in each cohort) were planned.

Number of subjects enrolled: 24 subjects in 3 cohorts (n=8 in each cohort) were enrolled.

Number of subjects analyzed for PK parameter: All 24 enrolled subjects were analyzed for PK parameters.

Number of subjects analyzed for safety: All 24 enrolled subjects were analyzed for safety.

Diagnosis and Main Criteria for Inclusion:

Main Criteria for Inclusion

All Subjects

- Males and females aged 20 to 70 years at the time of signing informed consent with a body weight of > 50 kg and BMI between 18.5 and 38.0 kg/m^2

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(inclusive).

Healthy Subjects (with Normal Hepatic Function)

- Subjects with Child-Pugh classification total point score of < 5 at the Screening Visit.
- Each healthy subject was matched demographically to a subject with moderate HI with respect to gender, age (± 10 years), and BMI (± 20%).

Subjects with Hepatic Impairment

- Subjects with mild or moderate HI based on the Child-Pugh classification system at the Screening Visit.
- Subjects with stable hepatic function for at least 1 month prior to the Screening Visit and on a stable medication regimen (ie, not starting new drug[s] or changing dosage[s] within 14 days prior to study drug administration until study completion).
- Subjects with hypertension who had satisfactory control of blood pressure (eg, systolic blood pressure [SBP] < 160 mmHg and diastolic blood pressure [DBP] < 100 mmHg) were allowed to participate.

Main Criteria for Exclusion

- Subjects with a life expectancy of less than 3 months.
- Subjects with any clinically significant medical history that in the opinion of the investigator, introduced additional safety risk to the subject by participation in the study, or interfered with the study results.
- Subjects with a history of gastrointestinal surgery that would, in the opinion of the investigator, potentially interfere with absorption of the naldemedine.

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

Test Product: Naldemedine 0.2 mg tablet

Dose and Mode of Administration: Subjects with normal hepatic function, mild HI, or moderate HI (Cohorts 1, 2, and 3, respectively) received a single oral 0.2 mg dose of naldemedine on Day 1.

Lot Number: [redacted]

Duration of Treatment:

Screening Period (Day -28 to Day -2): Up to 27 days

Confinement in CRU (Day -1 to 4): Four nights, 5 days

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Drug Administration (Day 1): One day

End-of-Study Visit: Day 15 (± 2)

Total planned study duration per subject: Approximately 6 weeks

Reference Therapy:

Not applicable.

Pharmacokinetic Assessment:

Pharmacokinetic Sample Collection

Plasma Pharmacokinetics: Blood samples for determination of plasma naldemedine and the naldemedine metabolites (nor-naldemedine, naldemedine 3-*O*-β-glucuronide [naldemedine 3-G], naldemedine 6-*O*-β-glucuronide [naldemedine 6-G], and benzamidine) were collected predose (-0.25 hour) and at 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 postdose.

Urine Pharmacokinetics: Urine was collected in polypropylene vessels during the following time intervals: -12 to 0 hours predose, and at 0-12, 12-24, 24-36, 36-48, 48-60, and 60-72 hours postdose. The total volume of each urine collection was recorded. Approximately 1.0 mL aliquot of pooled (for each collection interval) urine was obtained from each urine collection for determination of urinary concentrations of naldemedine and naldemedine metabolites (nor-naldemedine, naldemedine 3-G, naldemedine 6-G, and benzamidine).

Serum Protein Binding of Plasma: Blood samples for determination of serum protein unbound fraction (Fu) of naldemedine were collected on Day 1 at 0.75 and 24 hours postdose.

Bioanalytical Assessment

The concentrations of naldemedine, nor-naldemedine, naldemedine 3-G, naldemedine 6-G, and benzamidine in plasma and urine were determined using a validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) assay.

Pharmacokinetic Parameters

Plasma Pharmacokinetics: The PK parameters included: area under the plasma concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration ($AUC_{0\text{-last}}$), AUC extrapolated from time zero to infinity ($AUC_{0\text{-inf}}$), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), apparent total clearance (CL/F, naldemedine only), terminal elimination rate constant (λ_z), terminal elimination half-life ($t_{1/2,z}$), apparent volume of distribution in the terminal phase (V_z/F naldemedine only), metabolic ratio of C_{max} of metabolite to

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C_{max} of naldemedine ($MR_{M/U,Cmax}$, metabolites only), and metabolic ratio of $AUC_{0\text{-last}}$ of metabolite to $AUC_{0\text{-last}}$ of naldemedine ($MR_{M/U,AUC}$, metabolites only), and serum protein unbound fraction ($Fu = C_{unbound}/C_{total}$). The actual sampling times were used for PK parameter calculations.

Urine Pharmacokinetics: The urinary PK parameters included: cumulative amount of the drug excreted in urine from time zero to 72 hours postdose ($Aeu_{0\text{-}72}$), fraction excreted in urine from time 0 to 72 hours postdose ($Feu_{0\text{-}72}$), and renal clearance (CL_R).

Safety Assessment:

The safety and tolerability of naldemedine were assessed by monitoring of adverse events (AEs), treatment-emergent AEs (TEAEs), drug-related TEAEs, physical examinations, vital signs (SBP, DBP, pulse rate, body temperature, and respiratory rate), 12-lead electrocardiogram (ECG), and clinical laboratory assessments (hematology, serum chemistry, and urinalysis). The AEs were recorded and TEAEs, treatment-related TEAEs, significant AEs, and serious AEs (SAEs) were listed.

Statistical Methods:

Pharmacokinetics

Pharmacokinetic parameters of naldemedine and metabolites (nor-naldemedine, naldemedine 3-G, naldemedine 6-G, and benzamidine) were to be estimated based on the plasma and urinary concentrations of naldemedine, nor-naldemedine, naldemedine 3-G, naldemedine 6-G, and benzamidine by non-compartmental methods using Phoenix® WinNonlin® Version 6.4. An analysis of variance (ANOVA) model was used to perform the statistical analysis of log-transformed PK parameters C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, λ_z, $t_{1/2,z}$, CL/F, and CL_R as response variables with fixed effect terms for hepatic function (normal hepatic function, mild HI, and moderate HI).

The point estimates of the geometric mean (GM) ratio (GMR) for the log transformed PK parameters and the associated 90% confidence intervals (CIs) were constructed for the treatment differences for subjects with mild or moderate HI compared with healthy subjects with normal hepatic function. The point estimates for the GMR and 90% CIs were then back-transformed to give point estimates and the 90% CIs of the PK parameters in subjects with mild or moderate HI compared with healthy subjects with normal hepatic function.

Plasma naldemedine and metabolites concentrations were summarized for each cohort by the nominal sampling time by the following summary statistics: Number of non-missing observations (n), arithmetic mean (mean), standard deviation (SD),

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coefficient of variation (CV%), GM, and CV% for GM, median, minimum, maximum, and number of observation below lower limit of quantification (LLOQ).

Safety

The number of AEs and the number of subjects who experienced any AEs were summarized by cohort. The same summarization was performed for treatment-related AEs. Summary statistics for vital signs (blood pressure, pulse rate, respiratory rate, and body temperature), ECG parameters (heart rate, QRS, PR, QT, and Fridericia's correction for QT [QTcF] intervals), and clinical laboratory tests (hematology, serum chemistry, and urinalysis) were provided.

Summary of Results

A total of 24 subjects were assigned to 1 of 3 cohorts at Screening, 8 subjects each with normal hepatic function, mild HI, and moderate HI. All subjects received the single 0.2 mg dose of naldemedine and completed the study according to the protocol.

The majority of the subjects were White (83.3%) and male (62.5%). The mean age, height, weight and BMI were similar across all cohorts, consistent with entry requirements.

Pharmacokinetics:

Geometric mean plasma PK parameters for naldemedine in subjects with mild or moderate HI healthy subjects with normal hepatic function were similar after administration of a single oral 0.2 mg dose of naldemedine.

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Summary of PK Parameters for Naldemedine by Cohort (PK Parameter Population)

Cohort		$AUC_{0\text{-last}}$ (ng*hr/mL)	$AUC_{0\text{-inf}}$ (ng*hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2,z}$ (hr)
Healthy Subjects	n	8	8	8	8	8
	GM	23.10	23.61	2.71	NA	13.5
	GM CV%	22.8	22.8	26.3	NA	9.3
	Mean	23.63	24.15	2.80	0.75	13.6
	SD	5.524	5.628	0.771	0.13	1.29
Mild HI	n	8	8	8	8	8
	GM	19.10	19.56	2.44	NA	14.0
	GM CV%	36.4	35.9	47.4	NA	15.1
	Mean	20.23	20.67	2.67	1.00	14.1
	SD	7.789	7.805	1.27	0.64	2.09
Moderate HI	n	8	8	8	8	8
	GM	24.18	24.82	2.93	NA	13.3
	GM CV%	21.7	21.8	16.8	NA	21.5
	Mean	24.66	25.32	2.96	0.63	13.6
	SD	5.136	5.275	0.499	0.13	2.89

Of the 4 metabolites analyzed in this study, only nor-naldemedine and naldemedine 3-G were detected in plasma. The relative exposure to nor-naldemedine and naldemedine 3-G was low, both in terms of C_{max} and $AUC_{0\text{-last}}$, and values were not substantially different between subjects with normal hepatic function and subjects with mild or moderate HI.

The GMR (90% CI) of the C_{max} of naldemedine for subjects with mild HI or moderate HI compared with subjects with normal hepatic function were 0.90 (0.69, 1.18) and 1.08 (0.82, 1.41), respectively. The GMR (90% CI) of the $AUC_{0\text{-inf}}$ of naldemedine in subjects with mild HI or moderate HI compared with subjects with normal hepatic function were 0.83 (0.66, 1.04) and 1.05 (0.83, 1.33). There were no clinically meaningful differences in PK parameters observed in subjects with mild or moderate HI compared with healthy subjects with normal hepatic function.

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Statistical Comparison of the PK Parameters of Naldemedine in Subjects with Hepatic Impairment versus Matched Healthy Subjects (PK Parameter Population)

Parameter (Unit)	Cohort	GM (GM CV%)	GM Ratio	90% CI for Ratio
$AUC_{0\text{-last}}$ (ng•hr/mL)	Healthy Subjects	23.10 (22.8)	-	-
	Mild HI	19.10 (36.4)	0.8270	0.6546, 1.0448
	Moderate HI	24.18 (21.7)	1.0470	0.8288, 1.3228
$AUC_{0\text{-inf}}$ (ng•hr/mL)	Healthy Subjects	23.61 (22.8)	-	-
	Mild HI	19.56 (35.9)	0.8284	0.6569, 1.0448
	Moderate HI	24.82 (21.8)	1.0516	0.8339, 1.3262
C_{max} (ng/mL)	Healthy Subjects	2.71 (26.3)	-	-
	Mild HI	2.44 (47.4)	0.8998	0.6864, 1.1796
	Moderate HI	2.93 (16.8)	1.0784	0.8226, 1.4137
$t_{1/2,z}$ (hr)	Healthy Subjects	13.5 (9.3)	-	-
	Mild HI	14.0 (15.1)	1.0373	0.9042, 1.1900
	Moderate HI	13.3 (21.5)	0.9852	0.8588, 1.1302

Unbound Fraction of Naldemedine

The geometric mean unbound fraction (Fu) of naldemedine was similar across cohorts with values ranging from 7.5% to 9.5%. There were no values below the LLOQ in any subject in any cohort.

Similar results for Fu were observed at the 0.75 and 24 hr time points within each cohort, suggesting that protein binding was independent of naldemedine concentration over the range of concentrations evaluated in this study. The Fu values at each time point were also similar across cohorts, suggesting that potential alterations in serum protein levels as a result of HI did not affect the degree of naldemedine protein binding.

Urinary Pharmacokinetics

Concentrations of naldemedine, naldemedine 3-G, and benzamidine were quantifiable in the urine. Concentrations of nor-naldemedine and naldemedine 6-G were below the LLOQ in the urine for all subjects.

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The Feu_{0-72} was consistent across cohorts, with naldemedine excreted in urine predominantly unchanged. Naldemedine 3-G was the primary metabolite excreted in urine, followed by benzamidine; although, benzamidine concentrations were quantifiable in only one subject. There was a trend toward increased urinary elimination of naldemedine 3-G with an increasing degree of HI; however, the relative fraction of naldemedine 3-G excreted in urine represented < 1% of the administered dose of naldemedine in subjects in all cohorts.

Safety:

Administration of a single oral 0.2 mg dose of naldemedine was well-tolerated in healthy subjects with normal hepatic function, as well as subjects with mild or moderate HI.

Reported AEs were consistent with the known safety profile of naldemedine. A higher proportion of subjects in the HI cohorts reported TEAEs compared with the normal hepatic function cohort. Overall, the most frequently reported events were diarrhea, abdominal pain, flatulence, and somnolence. All TEAEs were considered by the investigator to be related to study treatment.

No deaths, fatal AEs, or SAEs were reported in the study. There were no TEAEs that resulted in a subject withdrawing from the study and no severe TEAEs reported in any subject.

There were no clinically meaningful findings or changes in laboratory results, ECG parameters, or vital sign measurements during the study.

CONCLUSIONS

Pharmacokinetics:

The following conclusions were obtained based on the results of pharmacokinetic analyses:

- The GMR (90% CI) of the C_{max} of naldemedine for subjects with mild HI or moderate HI compared with subjects with normal hepatic function were 0.90 (0.69, 1.18) and 1.08 (0.82, 1.41), respectively. The GMR (90% CI) of the AUC_{0-inf} of naldemedine in subjects with mild HI or moderate HI compared with subjects with normal hepatic function were 0.83 (0.66, 1.04) and 1.05 (0.83, 1.33), respectively.
- There were no clinically meaningful differences in PK parameters observed in subjects with mild or moderate HI compared with healthy subjects with normal hepatic function.

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- The geometric mean unbound fraction (Fu) of naldemedine was similar across cohorts (7.5% to 9.5%), suggesting that HI did not affect the degree of naldemedine protein binding. Similar results were observed at the 0.75 and 24 hr time points within each cohort, suggesting that protein binding was independent of naldemedine concentration over the range of concentrations evaluated in this study.

Safety:

The following conclusions were obtained based on the results of safety analyses:

- Administration of a single oral 0.2 mg dose of naldemedine was well-tolerated in healthy subjects with normal hepatic function, as well as subjects with mild or moderate HI.
- Reported AEs were consistent with the known safety profile of naldemedine. A higher proportion of subjects in the HI cohorts reported TEAEs compared with the normal hepatic function cohort. Overall, the most frequently reported events were diarrhea, abdominal pain, flatulence, and somnolence. All reported TEAEs were mild in intensity, with the exception of 1 subject with mild HI who had moderate abdominal pain. All TEAEs were considered by the investigator to be related to study treatment.
- No deaths, fatal AEs, or SAEs were reported in the study. There were no TEAEs that resulted in a subject withdrawing from the study and no severe TEAEs reported in any subject.
- There were no clinically meaningful findings or changes in laboratory results, ECG parameters, or vital sign measurements during the study.

Final Report Date: 08 January 2016