2. SYNOPSIS

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Study Title:

Phase 1, Open-label, Non-randomized Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Naldemedine in Subjects with Varying Degrees of Renal Impairment and in Matched Control Subjects with Normal Renal Function

Investigators and Study Centers:

[redacted]

Publication (Reference): None planned.

Studied Period: [redacted] February 2015 (first subject enrolled) to [redacted] July 2015 (last subject completed)

Study Phase: Phase 1

Objectives:

The primary objectives of the study were:

- To evaluate the pharmacokinetics (PK) of a single oral 0.2 mg dose of naldemedine in subjects with mild, moderate, or severe renal impairment (RI), or end-stage renal disease (ESRD) requiring hemodialysis (HD), compared with subjects with normal renal function.
- To evaluate the effect of HD on removal of naldemedine from blood.

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, moderate, or severe RI or ESRD requiring HD compared with subjects with normal renal function.

Methodology:

This was an open-label, non-randomized, and parallel cohort study. The study consisted of 5 cohorts: Cohort 1 included subjects with normal renal function; Cohort 2 included subjects with mild RI; Cohort 3 included subjects with moderate RI; Cohort 4 included subjects with severe RI; and Cohort 5 included subjects

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requiring HD. Each subject with normal renal function (Cohort 1) was demographically matched to a subject with moderate RI (Cohort 3) according to gender, age (± 10 years), and body mass index (BMI) (± 20%). Creatinine clearance (CL_{cr}), estimated by the Cockcroft-Gault (CG) equation, was used to define normal renal function (CL_{cr} ≥90 mL/min) for the healthy matched control subjects (Cohort 1). Estimated glomerular filtration rate (eGFR), according to Modification of Diet in Renal Disease (MDRD) criteria, was used to define the degree of RI for subjects with mild (eGFR ≥ 60 to < 90 mL/min/1.73 m^2; Cohort 2), moderate (eGFR ≥ 30 to < 60 mL/min/1.73 m^2; Cohort 3), and severe (eGFR <30 mL/min/1.73 m^2; Cohort 4) RI. Subjects with ESRD requiring HD (Cohort 5) had to receive HD 3 times per week for 6 months prior to the start of the study. A total of 41 subjects were enrolled in the study, 9 subjects each with normal renal function, mild RI, and moderate RI (Cohorts 1, 2, and 3, respectively), 6 subjects with severe RI (Cohort 4), and 8 subjects with ESRD requiring HD (Cohort 5).

All subjects underwent a Screening Visit (Day -28 to Day -2) to determine eligibility. Qualified subjects were admitted to the clinical research unit (CRU) on Day -1 and remained confined until after the 72-hour postdose time point.

Subjects with Normal Renal Function (Cohort 1) or Mild, Moderate, or Severe RI (Cohorts 2, 3, and 4, Respectively): Oral administration of a single 0.2 mg dose of naldemedine was given in the morning on 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 on 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).

Subjects with ESRD Requiring HD (Cohort 5): Oral administration of a single 0.2 mg dose of naldemedine was given on Day 1 (Treatment Period 1) and Day 15 (Treatment Period 2) of the study. On Day 1, naldemedine was administered 1 to 2 hours after completion of HD following a fast of least 4 hours; subjects remained fasted for 2 hours postdose. Subjects were discharged on Day 4 following completion of all 72-hour postdose procedures. Subjects were readmitted to the CRU on Day 14. On Day 15, another single 0.2 mg dose of naldemedine was administered 2 hours prior to HD, following an overnight fast of at least 8 hours; subjects remained fasted 4 hours postdose. In both treatment periods, venous blood samples were collected for determination of plasma naldemedine concentrations at predose and

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until 72-hours postdose. In addition, during Treatment Period 2, blood samples were collected from both the arterial and venous sides of the dialyzer, and aliquots of dialysate fluid were collected for PK analysis. Subjects were discharged after completion of all 72-hour procedures on Day 18. Subjects returned to the CRU for an End-of-Study Visit on Day 29 (± 2 days).

Prohibited Therapies and Restrictions

Prohibited Therapies for All Subjects:

- 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
- 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
- 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

Additional Prohibited Therapies for Healthy Subjects:

- Prescription or non-prescription drugs, including herbal medicines or dietary supplements, from 14 days prior to admission (Day -1) and throughout the study, unless deemed acceptable by the investigator

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

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- Smoking for subjects with normal renal function; smoking-cessation aids, consuming more than 1 pack of cigarettes per day, and all nicotine containing products other than cigarettes for subjects with RI and subjects with ESRD requiring HD.
- 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: Approximately 36 to 40 subjects were planned to be enrolled, 8 subjects each with normal renal function, mild or moderate RI, 4 to 8 subjects with severe RI, and 8 subjects with ESRD requiring HD.
Number of subjects enrolled: A total of 41 subjects were enrolled: 9 subjects each with normal renal function, mild RI, and moderate RI; 6 subjects with severe RI; and 8 subjects with ESRD requiring HD.

Number of subjects analyzed for PK parameters: Thirty-eight of the 41 enrolled subjects were analyzed for PK parameters.

Number of subjects analyzed for safety: All 41 enrolled subjects were analyzed for safety.

Diagnosis and Main Criteria for Inclusion:

Main Criteria for Inclusion

<u>All Subjects</u>

- Males and females aged 20 to 75 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 (inclusive).

<u>Healthy Subjects (with Normal Renal Function)</u>

- Subjects with estimated creatinine clearance (CL_{cr}): ≥ 90 mL/min, as calculated by the CG equation at the Screening Visit.
- Each healthy subject was matched demographically to a subject with moderate RI with respect to gender, age (± 10 years), and BMI (± 20%).

<u>Subjects with Renal Impairment</u>

- Subjects had mild, moderate, or severe RI based on eGFR calculated by the MDRD equation at the Screening Visit.

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- Subjects had stable renal function, defined as < 30% difference between eGFR values at Screening Visit and Day -1.
- Subjects with hypertension had satisfactory control of blood pressure (eg, systolic blood pressure [SBP] < 160 mmHg and diastolic blood pressure [DBP] < 100 mmHg.

Subjects Requiring Hemodialysis

- Subjects requiring HD at least 3 times a week for at least 6 months prior to the Screening Visit.
- Subjects were considered clinically stable with respect to underlying RI, as per investigator's discretion, and based upon a medical evaluation that included a medical history, physical examination, laboratory tests, and 12-lead electrocardiogram (ECG).
- Subjects on concomitant medications to treat underlying disease were required to be on a stable medication regimen, defined as not having started any new drug(s) or changing any dosage(s) from 14 days prior to study drug administration until study completion.
- Subjects had satisfactory control of blood pressure, in the opinion of the investigator (eg, < 160 mmHg SBP and < 100 mmHg DBP).

Main Criteria for Exclusion

- Subjects with a life expectancy of less than 3 months.
- Subjects with any clinically significant medical history which, 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 previous history of cholecystectomy were also excluded.
- 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 renal function, mild RI, moderate RI, or severe RI (Cohorts 1, 2, 3, and 4, respectively) received a single oral 0.2 mg dose of naldemedine on Day 1. Subjects with ESRD requiring HD (Cohort 5) received a single 0.2 mg dose of naldemedine on 2 separate occasions (Day 1 and Day 15).

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Lot Number: [redacted]

Duration of Treatment:

Subjects with Normal Renal Function (Cohort 1) and with Mild, Moderate, or Severe RI (Cohorts 2, 3, and 4, respectively):

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

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

Drug Administration (Day 1): One day

End-of-Study Visit: Day 15 (± 2)

Total planned study duration per subject: Approximately 3 to 6 weeks

Subjects with ESRD Requiring HD (Cohort 5):

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

Confinement in CRU (Day -1 to Day 4 and Day 14 to Day 18): Separate confinements for each Treatment Period (dosing on Day 1 and Day 15), each with a duration of 4 nights, 5 days for a total of 8 nights and 10 days

Drug Administration: 2 days, Day 1 (Treatment Period 1) and Day 15 (Treatment Period 2)

End-of-Study Visit: Day 29 (± 2 days)

Total planned study duration per subject: Approximately 5 to 8 weeks

Reference Therapy:

Not applicable.

Pharmacokinetic Assessment:

Pharmacokinetic Samples

Plasma Pharmacokinetics; Blood samples for determination of plasma concentration of naldemedine and the naldemedine metabolites, nor-naldemedine and benzamidine, were collected predose (-0.25 hr) 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 composite urine was obtained from each urine collection for determination of urinary naldemedine and naldemedine metabolites, nor-naldemedine and benzamidine concentrations.

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Serum Protein Binding: Blood samples for determination of serum protein unbound fraction (Fu) of naldemedine were collected on Day 1 at 0.75 and 24 hours postdose. In addition, for subjects with ESRD requiring HD (Cohort 5) only, serum protein binding was determined at 0.75 and 24 hours postdose on Day 15 (Treatment Period 2).

Hemodialysis Sampling: During HD for subjects with ESRD (Cohort 5), arterial and venous blood samples and aliquots from the dialysate solution were collected at 3, 4, 5, and 6 hours postdose or at the end of HD.

Bioanalytical Assessment

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

Pharmacokinetic Parameters

Plasma PK; The PK parameters included: area under the plasma concentration-time curve (AUC) from time zero to the time of the last quantifiable postdose concentration ($AUC_{0\text{-last}}$), AUC extrapolated from time zero to infinity ($AUC_{0\text{-inf}}$), maximum observed 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 C_{max} of naldemedine ($MR_{M/U,Cmax}$), and metabolic ratio of $AUC_{0\text{-last}}$ of metabolite to $AUC_{0\text{-last}}$ of naldemedine ($MR_{M/U,AUC}$), fraction of the total body pool of drug removed by HD (Fr), hemodialysis clearance (CL_{hd}), and serum protein unbound fraction ($Fu = C_{unbound}/C_{total}$). For subjects with ESRD requiring HD, the amount of naldemedine recovered in dialysate (AR) and the fraction of naldemedine recovered in dialysate (AR/Dose) were also calculated. The actual sampling times were used for PK parameter calculations.

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

Safety Assessments:

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), ECGs, and clinical laboratory data (hematology, serum chemistry, and

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urinalysis). The AEs were recorded and TEAEs, drug-related TEAEs, significant AEs, and serious adverse events (SAEs) were listed.

Statistical Methods:

Pharmacokinetics

Pharmacokinetic parameters for naldemedine and its metabolites (nor-naldemedine and benzamidine) were to be estimated based on the plasma and urinary concentrations of naldemedine, nor-naldemedine, 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 variable and with fixed effect terms for renal function (normal renal function mild, moderate, or severe RI, and ESRD requiring HD [Treatment Period 1]).

The point estimates of the geometric mean (GM) ratio (GMR) and their associated 90% confidence intervals (CIs) were constructed for the treatment differences: mild, moderate or severe RI versus healthy subjects with normal renal function and ESRD requiring HD (Treatment Period 1) versus healthy subjects with normal renal function. The point estimates and 90% CIs were then back-transformed to give point estimates and 90% CIs for the GMR of the PK parameters in subjects with mild, moderate, or severe RI and subjects with ESRD requiring HD (Treatment Period 1) compared with healthy subjects with normal renal 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), 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, respiration rate, and body temperature), ECG parameters (heart rate, QRS, QT, PR, and QT interval corrected for heart rate [QTc], and Fridericia's correction for QT [QTcF] intervals), and clinical laboratory tests (hematology, serum chemistry, and urinalysis) are provided.

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Summary of Results

A total of 41 subjects were assigned to 1 of 5 cohorts based on whether subjects had normal renal function or varying degrees of renal impairment at Screening, 9 subjects each with normal renal function, mild RI and moderate RI, 6 subjects with severe RI, and 8 subjects with ESRD requiring HD. All subjects received the required oral 0.2 mg dose(s) of naldemedine and completed the study according to the protocol.

Most enrolled subjects were White (68.3%) and 58.5% of subjects were male. The mean age of subjects with normal renal function (62.8 years) was similar to that of subjects with mild RI or severe RI (61.2 years in both cohorts). Subjects with moderate RI were slightly older (mean age: 66.6 years) and subjects with ESRD requiring HD were younger (mean age: 51.8 years) compared with subjects in the other cohorts. All subjects were of normal height and weight with a mean BMI of 28.8 kg/m^2, which was consistent across cohorts.

Pharmacokinetics:

Thirty-eight of 41 subjects were included in PK parameter population. The geometric mean plasma PK parameters for naldemedine were similar in subjects with mild, moderate, or severe RI compared with healthy subjects with normal renal function following a single oral 0.2 mg dose of naldemedine.

Geometric mean plasma PK parameters for naldemedine were also similar in subjects with ESRD requiring HD (Treatment Period 1) compared with subjects in the other cohorts. Geometric mean plasma PK parameters were likewise similar in subjects with ESRD when a single 0.2 mg dose of naldemedine was administered before or after HD.

For the dose of naldemedine administered prior to HD in subjects with ESRD, hemodialysis clearance (CL_{hd}) (GM [GM CV%]) was 1.66 L/hr (14.4%). The fraction of naldemedine recovered in dialysate (AR/Dose) (GM [GM CV%]) was 0.0266 (32.8%) and the Fr (GM [GM CV%]) was 0.082 (84.7%) where calculable (4 of 8 subjects).

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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 Subject	n	8	8	8	8	8
	GM	22.94	23.55	3.39	NA	13.8
	GM CV%	18.3	18.9	20.7	NA	17.7
	Mean	23.27	23.90	3.46	0.66	13.9
	SD	4.165	4.362	0.741	0.13	2.49
Mild RI	n	8	8	8	8	8
	GM	24.62	25.35	3.01	NA	14.2
	GM CV%	23.5	24.6	23.7	NA	25.4
	Mean	25.21	26.01	3.08	0.50	14.6
	SD	5.837	6.263	0.700	0.19	3.21
Moderate RI	n	8	8	8	8	8
	GM	23.81	24.97	2.56	NA	17.2
	GM CV%	22.4	23.6	25.5	NA	23.1
	Mean	24.34	25.58	2.63	0.78	17.5
	SD	5.607	6.205	0.630	0.36	3.48
Severe RI	n	6	6	6	6	6
	GM	30.41	32.44	2.76	NA	18.7
	GM CV%	16.1	18.1	13.4	NA	15.7
	Mean	30.74	32.88	2.78	0.67	18.9
	SD	4.894	6.057	0.384	0.13	2.94
ESRD (Treatment Period 1)	n	8	8	8	8	8
	GM	18.88	19.49	2.81	NA	15.2
	GM CV%	17.3	17.9	24.8	NA	28.1
	Mean	19.12	19.75	2.89	0.76	15.7
	SD	3.146	3.358	0.675	0.23	4.42
ESRD (Treatment Period 2)	n	8	8	8	8	8
	GM	18.13	18.63	2.23	NA	15.0
	GM CV%	25.9	26.1	26.5	NA	24.1
	Mean	18.70	19.22	2.30	1.06	15.4
	SD	5.450	5.628	0.684	0.56	3.65

Note: For subjects with ESRD requiring HD, 0.2 mg naldemedine was administered after HD in Treatment Period 1 and before HD in Treatment Period 2.

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The relative exposure of nor-naldemedine to naldemedine was low, both in terms of C_{max} and $AUC_{0\text{-last}}$, in subjects with normal renal function and subjects with mild, moderate, or severe RI. $MR_{MU,AUC}$ was 0.082, 0.075, 0.061, and 0.105 in subjects with normal renal function or mild, moderate, or severe RI, respectively.

The relative exposure of nor-naldemedine to naldemedine was low, both in terms of C_{max} and $AUC_{0\text{-last}}$, in subjects with ESRD requiring HD. Following administration of a single 0.2 mg dose of naldemedine after HD in Treatment Period 1, $MR_{MU,AUC}$ in subjects with ESRD was 0.281, which was higher compared with values observed in subjects with normal renal function (0.082) or mild, moderate, or severe RI (0.075, 0.061, and 0.105, respectively).

Plasma concentrations of the metabolite benzamidine were below the LLOQ in all subjects at all time points.

Unbound Fraction of Naldemedine

The geometric mean Fu of naldemedine was similar across cohorts with values ranging from 6% to 9%. There was no apparent effect of RI on naldemedine serum protein binding.

Similar values were also observed in subjects in each cohort at the 0.75- and 24-hour time points, suggesting that protein binding was independent of naldemedine concentration over the concentration range observed in this study.

Urinary Pharmacokinetics

Concentrations of naldemedine and benzamidine were quantifiable in the urine. Concentrations of nor-naldemedine were below the LLOQ of the assay in urine samples for all subjects.

Results for urinary PK parameters demonstrated decreased urinary excretion of naldemedine with decreasing renal function. The appearance of benzamidine concentrations in urine was sparse and too limited to make any correlations with renal function status.

Safety:

Administration of a single oral 0.2 mg dose of naldemedine was well-tolerated in healthy subjects with normal renal function, as well as subjects with varying degrees of RI, including subjects with ESRD requiring HD.

Reported AEs were consistent with the known safety profile of naldemedine. There were no notable differences across the cohorts in the proportions of subjects who

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reported events or the types of TEAEs reported. The most frequently reported TEAEs were headache, nausea, and diarrhea.

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

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

CONCLUSIONS

Pharmacokinetics:

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

- Geometric mean ratios (90% CI) for the C_{max} of naldemedine in subjects with mild, moderate, or severe RI or with ESRD requiring HD compared with healthy subjects with normal renal function were 0.89 (0.74, 1.07), 0.75 (0.63, 0.91), 0.81 (0.66, 1.00), and 0.83 (0.69, 1.00), respectively. Geometric mean ratios (90% CI) for the $AUC_{0\text{-}inf}$ of naldemedine in subjects with mild, moderate or severe RI and with ESRD requiring HD compared with healthy subjects with normal renal function were 1.08 (0.90, 1.28), 1.06 (0.89, 1.26), 1.38 (1.14, 1.67), and 0.83 (0.69, 0.99), respectively.
- There were no clinically meaningful differences in PK parameters observed in subjects with mild, moderate, or severe RI, or in subjects with ESRD requiring HD, compared with subjects with normal renal function.
- The geometric mean Fu of naldemedine was similar across cohorts (6.0% to 9.2%), suggesting that RI did not affect the degree of naldemedine protein binding. Similar results were observed at the 0.75- and 24-hour time points within each cohort, suggesting that protein binding was independent of naldemedine concentration over the range of concentrations evaluated in this study.
- A very small amount of naldemedine was removed from plasma by HD. The fraction of naldemedine recovered in dialysate (GM [GM CV%]) was 2.7% (32.8%) during 3- to 4- hour HD period.

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 renal function, as well as subjects

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with varying degrees of RI, including subjects with ESRD requiring HD.

- Reported AEs were consistent with the known safety profile of naldemedine. There were no notable differences across the cohorts in the proportions of subjects who reported events or the types of TEAEs reported. The most frequently reported TEAEs were headache, nausea, and diarrhea. All TEAEs were mild in intensity.
- No deaths, fatal AEs, or other 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