2 SYNOPSIS

Sponsor:
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Individual Study Table Referring to Part of the Dossier

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Name of Finished Product:
Not applicable

Volume:

Name of Active Ingredient:
S-297995

Page:

Study Title:

A Phase 1, Randomized, Double-Blind, Single Dose, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of S-297995 in the Reduction of Opioid-induced Nausea and Emesis in Healthy Subjects

Investigator(s) and Study Center(s): [redacted]

Publication: There has been no publication of study data prior to the approval of this clinical study report (see Appendix 16.1.11).

Studied Period:

[redacted] April 2011 (first subject enrolled) to
July 2011 (last subject completed)

Phase of Development: 1

Objectives:

The primary objective of this study was:

- To evaluate the efficacy of a single oral dose of S-297995 for the reduction of opioid-induced nausea

The secondary objectives of this study were:

- To evaluate the safety of a single oral dose of S-297995
- To evaluate the efficacy of single oral dose of S-297995 for the reduction of opioid-induced emesis
- To evaluate the pharmacokinetics (PK) of S-297995 (unchanged and metabolites [Nor-S-297995 and benzamidine]) and morphine (unchanged and metabolites [M6G and M3G])
- To evaluate S-297995 PK-pharmacodynamic relationships for nausea, emesis, and nausea with emesis

The exploratory objectives of this study were to evaluate the efficacy of oral S-297995, using a 5-point categorical verbal rating scale, in reducing the opioid-induced agonist effects of:

- Pruritus

- Warmth
- Flushing
- Sweating
- Urinary retention

Methodology:
This was a phase 1, multicenter, single dose, randomized, placebo-controlled, double-blind, parallel-group study comparing 3 dose levels of S-297995 to placebo.

At the Screening Visit, subjects were evaluated for participation in the study. At the Qualifying Visit (Visit 2), each subject received an infusion of morphine sulfate (MSO_4) at an initial loading dose of 0.10 mg/kg over a 5-minute period. Subsequent repeat doses of MSO_4, 0.05 mg/kg over 1 to 2 minutes, were administered every 10 minutes until nausea occurred or the dosage of morphine reached a total of 0.3 mg/kg. Nausea was evaluated using an 11-point Likert scale, and the number of episodes of nausea and vomiting were counted. The response at the Qualifying Visit was considered to be the baseline for each subject and a baseline response of ≥5 was required to qualify for further study participation. At Visit 3 (Treatment Period), each qualified subject was randomly assigned to one of 4 blinded study treatments on Day 1 of the Treatment Period, prior to study drug administration, and received a single dose of S-297995 or placebo one hour prior to receiving an infusion of MSO_4. During the Treatment Period, subjects received an intravenous (IV) dose of MSO_4 equal to the final dose delivered during Visit 2 (Qualification Visit) which was infused over a 20 minute period. Efficacy was evaluated by measuring the change from the baseline scores.

During the Qualifying Visit and/or the Treatment Period, if rescue medication was needed for nausea and/or emesis, IV ondansetron hydrochloride 4 mg was permitted and recorded as concomitant medication. If ineffective, promethazine hydrochloride, intramuscular injection or rectal suppository, 12.5 mg or 25 mg was permitted and recorded as concomitant medication.

If a subject required reversal of opiate-associated respiratory depression following the administration of MSO_4, naloxone hydrochloride was to be administered at a dose of 0.1 mg to 0.2 mg intravenously at 2- to 3-minute intervals until the desired response was achieved, followed by additional doses at 1- to 2-hour intervals if needed. However, this was not needed during this study.

Number of Subjects (Planned and Analyzed):

Eighty subjects were planned; 80 subjects were randomized, 80 subjects were analyzed for safety; 60 subjects were included in the analyses of PK variables.

Diagnosis and Main Criteria for Inclusion:

Eighty healthy adults between the ages of 18 and 55 years, inclusive, with a body mass index of ≥ 18.0 and ≤ 32.0 kg/m^2, and in good health based upon results of medical history, physical examinations, vital signs, 12-lead electrocardiograms (ECGs; within normal limits), and laboratory test results were enrolled.

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

Test Product, Dose, and Mode of Administration:

S-297995 tablet strengths of 0.1, 1.0, and 10.0 mg were administered orally following a fast of at least 8 hours. Lot numbers: 0.1 mg tablet [redacted]; 1.0 mg tablet [redacted]; and 10.0 mg tablet [redacted].

Reference Therapy, Dose, and Mode of Administration:

Placebo tablet matching all dose strengths of S-297995 tablets for oral administration.

Lot No. [redacted]

Morphine SO_4 (MSO_4) for IV administration. The maximum dose of MSO_4 to be administered during the Qualifying Visit or the Treatment Visit was 0.3 mg/kg.

Treatments Administered:

At the Qualifying Visit, each subject received an infusion of MSO_4 at an initial loading dose of MSO_4 of 0.10 mg/kg over a 5-minute period. Subsequent repeat doses of MSO_4, 0.05 mg/kg infused over 1 to 2 minutes, were administered every 10 minutes until nausea occurred or the dosage of morphine reached a total of 0.3 mg/kg or a safety cutoff criterion occurred.

During the Treatment Period, each subject was randomized into 1 of 4 treatment groups, and each was administered S-297995 as a single oral dose of 1 tablet, with 240 mL of water, 1 hour prior to the start of MSO_4 infusion on Day 1 of the Treatment Period as follows:

- Group A: 0.1 mg S-297995 tablet
- Group B: 1.0 mg S-297995 tablet
- Group C: 10.0 mg S-297995 tablet
- Group D: Placebo tablet

During the Treatment Period, subjects received an IV dose of MSO_4 equal to the final dose delivered during Visit 2 (Qualification Visit) which was infused over a 20 minute period.

Duration of Treatment:

The total study duration for each subject was approximately 62 days.

Screening assessments occurred within 33 days of the Qualifying Visit.

Subjects who had met all inclusion and no exclusion criteria at Visit 1 (Screening) returned to the clinic for the Qualifying Visit, at which time they received an intravenous (IV) administration of MSO_4. Subjects reentered the clinic for the Treatment Period at least 7 days after the end of the Qualifying Visit. After completing safety assessments, subjects were randomly assigned to one of 4 blinded study treatments on Day 1 of the Treatment Period, prior to study drug administration. The stay at the clinic was for approximately 36 hours during the Qualifying Visit and the Treatment Visit. After completion of the Treatment Period, subjects were discharged, and returned to the clinic 14 days later for Visit 4 (Follow-up/End-of-Study).

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint was the number of subjects with at least 30% reduction in nausea severity measured on an 11-point Likert scale from baseline up to 4 hours post MSO_4

administration during the study period. The highest score up to 4 hours was used to calculate the 30% reduction in nausea severity from baseline. The baseline value was established during the Qualifying Visit.

For secondary analysis purposes, the average nausea severity was defined as the average score as measured on the 11-point Likert scale within 4 hours after the final MSO_4 dose, where the starting point was the single measurement right after the start of the final dose of MSO_4 on Day 1 of the Qualifying Visit. No imputation for missing data was done.

The baseline AUC (area under the plasma concentration-time curve) in nausea severity was defined as the AUC by trapezoidal method within 4 hours after start of the MSO_4 dose, where the starting point is the single measurement right after start of the dose of MSO_4 on Day 1 of the Qualifying Visit. There was no imputation for missing data. The score at 4 hours post MSO_4 dose was estimated by linear regression between 2 adjacent time points which included 4 hours.

The secondary efficacy endpoints were as follows:

- Number of subjects with 50% reduction in nausea severity up to 4 hours after MSO_4 administration
- Cumulative distribution function (CDF) for nausea severity over time without the use of rescue medication
- Number of subjects having "0" (no nausea) at all timepoints up to 8 hours
- Highest score up to 4 hours
- Number of subjects achieving complete protection from emetic episodes over 2, 4, and 24 hours
- Number of subjects given rescue medication for the treatment of nausea and/or emesis
- Time-linked assessments of plasma levels of S-297995 and its metabolites, which was performed in the PK population consisting of those subjects receiving a dose of S-297995 and not placebo.
- Emetic episodes and time emesis occurred

The following exploratory endpoints were examined:

- 5-point Categorical Verbal Rating Scale for each of the following opioid-induced agonist effects: pruritus, flushing, warmth, sweating, and urinary retention
- Modified Observer's Assessment of Alertness / Sedation Scale
- Average nausea severity up to 4 hours
- AUC in nausea severity up to 4 hours calculated using the trapezoidal method from baseline up to 4 hours post MSO_4 administration during the Treatment Period.

Safety:

Safety was assessed by monitoring adverse events (AEs), serious adverse events (SAEs), AEs leading to study drug discontinuation, clinical laboratory evaluations, vital signs, and ECGs.

Pharmacokinetic:

For each subject, the following PK parameters of S-297995, its metabolites (Nor-S-297995 and benzamidine), morphine, and its metabolites (M6G and M3G), were calculated, when possible, based on the plasma concentrations using a non-compartmental approach using WinNonlin ([redacted], Version 5.2): maximum observed concentration (C_{max}), time to maximum concentration (T_{max}), area under the concentration-time curve from Hour 0 to the last measurable concentration (AUC_{0-t}), area under the concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$), percentage of $AUC_{0-\infty}$ extrapolated to infinity ($\%AUC_{extrap}$), apparent terminal elimination rate constant (λ_z), apparent terminal phase elimination half-life ($t_{1/2,z}$), total clearance following intravenous administration (CL), volume of distribution following intravenous administration (V_z), apparent total clearance following extravascular administration (CL/F), apparent volume of distribution following extravascular administration (V_z/F), ratio of C_{max} of metabolites to C_{max} of unchanged S-297995 and MSO_4 ($MR_{M/U,Cmax}$), and ratio of AUC of metabolites to AUC of unchanged S-297995 and MSO_4 ($MR_{M/U,AUC}$).

Statistical Methods:

General:

For continuous data, summary statistics included Mean, arithmetic standard deviation (SD), coefficient of variation (CV%). Statistical analyses were conducted and are presented in accordance with the Statistical Analysis Plan (SAP). Statistical testing was performed at the 1-sided significance level of 0.05 unless stated otherwise. The Intent-to-Treat (ITT) population included all subjects that had received at least one dose of study drug. The Per Protocol (PP) population included all subjects that had completed all phases of the protocol.

For PK parameters only median, minimum (Min), maximum (Max), and number (N); for log-normal data, (eg, the PK parameters, AUCs and C_{max}), the geometric mean (GeoMean) and geometric coefficient of variation (GeoCV%) are also presented. The PK population included only those subjects who had been administered the test drug.

Data analysis was performed using SAS® Version 9.1 or WinNonlin Version 5.2.

Efficacy:

Primary Endpoint: Summary statistics included counts and proportions of subjects who had at least 30% reduction from baseline for each treatment group. The pairwise comparison between S-297995 treatment groups and placebo in proportions were performed by Pearson's Chi-square test. Confidence intervals (CIs) for the difference of proportions at the level of 90% are also provided. As a sensitivity analysis, this endpoint was also analyzed using the PP population in order to assess the possible impact of major protocol deviations on the results of this trial.

Secondary Endpoints: The analysis of the 50% reduction in nausea severity up to 4 hours was performed in a similar manner to the primary efficacy endpoint analysis, but only in the ITT population.

For nausea severity, the cumulative distribution is displayed as a continuous plot of the percent reduction from baseline by treatment group at 4 and 8 hours, respectively. For the number of subjects having "0" (no nausea) at all timepoints up to 8 hours, counts and proportions were calculated by treatment. The percent change in nausea severity from baseline to each timepoint after dosing with MSO_4 during the Treatment Period, as measured on the 11-point Likert scale, was fitted to a Mixed-Model Repeated Measurement model.

Nausea severity, its percent change, and its change from baseline to each timepoint on Day 1 and 2 during the Treatment Period were also summarized by timepoint in each treatment. The highest score up to 4 hours during the Treatment Period was summarized by treatment group. For the number of subjects achieving complete protection from emetic episodes, the number of subjects with 'No' up to 2, 4, and 24 hours, respectively, during the Treatment Period and its proportion was summarized for each treatment group.

The number of subjects given rescue medication for the treatment of nausea and/or emesis and its proportion during the Treatment Period was presented by treatment group.

In the PK population, plasma concentrations of S-297995 and its metabolite were summarized at each timepoint by treatment group and plotted over time.

For emetic episodes and the time the emesis occurred, emesis-free time was summarized using Kaplan-Meier methods. The time to first emetic episode was compared between placebo and each S-297995 treatment group by using the log-rank test.

Exploratory endpoints: Analysis was performed in the ITT population.

The frequency table for the 5-point categorical verbal rating scale for each opioid-induced agonist effect was provided at each timepoint during the Treatment Period by treatment group, and the result was analyzed by timepoint using Wilcoxon rank sum test for the pairwise comparison between S-297995 and placebo.

For the Modified Observer's Assessment of Alertness/Sedation Scale, the summary of the value and its change from baseline are provided at each timepoint during the Treatment Period by treatment group.

The average nausea severity score from baseline up to 4 hours post MSO_4 administration during the Treatment Period was calculated and analyzed to calculate the 30% reduction from baseline. The average nausea severity score, percent change, and percent CDF were summarized by treatment group.

The AUC in nausea severity score was analyzed. In addition, for each AUC, the percent change and the change from baseline was summarized by treatment group.

Pharmacokinetic:

Plasma concentration data for S-297995, morphine, and their metabolites were measured in all subjects treated with S-297995 for the first 24 hours after MSO_4. The time course profiles for plasma concentrations are presented graphically in linear and semi-logarithmic scale.

For the calculation of concentration and PK parameter summary statistics, values that were below the lower limit of quantification (BLQ) were set to zero and included in descriptive statistics.

Safety:

Descriptive statistics were calculated on the safety parameters and summary statistical analyses were performed. No formal statistical tests were performed. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 14.0.

Summary of Results

Efficacy Results:

Of the 80 enrolled and randomized subjects, 78 (97.5%) completed the study. There were 20 subjects in each of the placebo and treatment groups.

The primary endpoint to achieve at least a 30% reduction in opioid induced nausea score up to 4 hours following an IV dose of MSO_4, that had been predetermined to produce nausea, was obtained with single oral doses of 1.0 mg and 10.0 mg of S-297995. There was no difference between the responses to the 1.0 mg dose when compared with the response to the 10.0 mg dose of S-297995. The dose of 0.1 mg did not result in significant reductions in nausea in this opioid naïve population. These results were corroborated by analysis of the PP population.

For times longer than 4 hours, complete protection from nausea (no nausea) up to 8 hours was significantly greater in the S-297995 1.0 mg and 10.0 mg treatment groups than in the placebo group. However, there was no difference between the 1.0 mg and 10.0 mg S-297995 treatment groups.

Summary and Statistical Analysis of the Primary Endpoint: at Least a 30% Reduction in the Highest Nausea Severity Score up to 4 Hours (Data for ITT Population)

	Placebo (N= 20)	S-297995 0.1 mg (N= 20)	S-297995 1.0 mg (N= 20)	S-297995 10.0 mg (N= 20)
At least 30% reduction from Baseline[a]	9 (45.0%)	11 (55.0%)	15 (75.0%)	15 (75.0%)
Difference of Proportions[b]		10.0%	30.0%	30.0%
90% CI of Difference		(-15.9%, 35.9%)	(5.7%, 54.3%)	(5.7%, 54.3%)
p-value[c]		0.2635	0.0264	0.0264

Source: Table 14.2.1.1.1

(xx%) = Proportion of subjects who had at least 30% reduction from baseline for each treatment group.

[a] Number of subjects with at least 30% reduction in highest nausea severity from baseline as measured on the 11-point Likert scale for up to 4 hours post MSO_4 administration during the Treatment Period.

[b] Difference of proportions between S-297995 and placebo groups.

[c] For the pairwise comparison between S-297995 and placebo in proportions, approximate one-sided p-value of Z test = ½ of p-value of Pearson's Chi-square test.

The secondary endpoint analyses supported the primary finding. However, while many of the secondary endpoints trended toward statistical significance with distinct trends away from placebo, most did not achieve significance. The analysis of subjects with at least a 50% reduction in the highest nausea score, while achieving upwards of a 25% difference from placebo, did not reach significance. The CDF also gave no more information than the conclusions reached from the primary analysis. There were a greater number of subjects without any nausea following the 1.0 and 10.0 mg doses than either the placebo or the 0.1 mg dose.

The number of subjects achieving complete protection from emesis was increased for all S-297995 treatment groups, although it was more pronounced for the 1.0 and 10.0 mg treatment groups than for the 0.1 mg treatment group. The median time to opioid-induced emesis was not estimable using the Kaplan-Meier methods for the 1.0 mg and 10.0 mg treatment groups because ≤ 50% of the subjects had an event. However, the change showed a reduction in the risk of an emetic episode with S-297995. Since no events in any group occurred after 590 minutes, the difference in median time to emesis is more likely due to a greater proportion of subjects not experiencing nausea rather than a delay in onset.

A general reduction in the opioid-induced agonist effects of pruritus, warmth, flushing, sweating, and urinary retention was observed following all doses of S-297995, reaching statistical significance at several timepoints for some endpoints compared with placebo.

Safety:

The safety of S-297995 in the presence of morphine at doses that had been demonstrated to produce AEs was difficult to separate from the AEs known to be associated with morphine. The safety of S-297995 was similar to that seen previously when it was administered alone.

The safety profile for S-297995 was similar across the dose range studied here. It was also similar to that reported in the Investigator's Brochure for other single dose studies.

The treatment-emergent adverse events (TEAEs) related to S-297995 were mostly mild in severity; there were some moderate TEAEs (headaches in each treatment group, upper abdominal pain in the 10.0 mg group); there were no severe TEAEs.

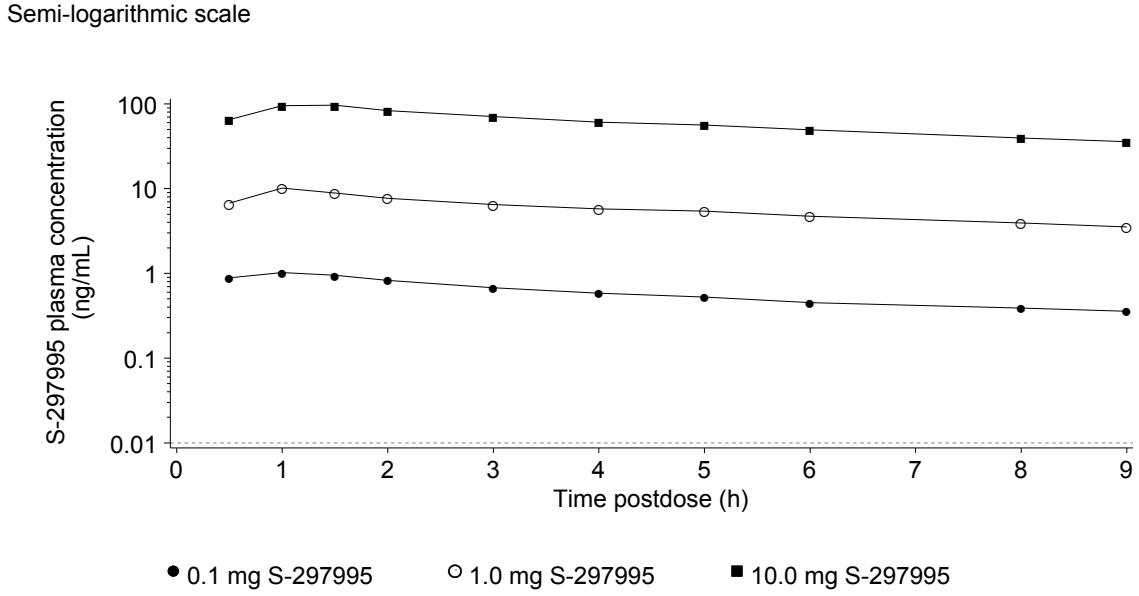
The TEAEs related to MSO_4 were mostly mild in severity; there were some moderate TEAEs that were reported in all treatment groups, including vomiting (57.5% of subjects), pruritus (27.5% of subjects), feeling hot (18.8% of subjects), hyperhidrosis (7.5% of subjects), flushing (6.3% of subjects), and headache (5.0% of subjects); there were no severe TEAEs.

No subjects required the use of naloxone HCl rescue medication for respiratory depression throughout this study, which indicates that use of IV morphine dosing as an inducer of emesis was safe when administered in the manner used in this study, and it indicates that S-297995 did not increase the propensity of AEs from the morphine dose; in fact it appears to have helped reduced the AEs. No deaths or SAEs occurred during this study. No AE led to study discontinuation. All AEs were resolved.

Pharmacokinetics:

S-297995 was characterized by a rapid absorption phase, with median T_{max} values ranging from 0.97 to 1.5 hours postdose across the 0.1 to 10.0 mg dose range. After reaching C_{max}, plasma concentrations of S-297995 declined in a monophasic manner, with dose independent mean $t_{1/2, z}$ of 6 to 7 hours. Systemic exposure (based on AUC_{0-t} and C_{max}) increased in a dose-proportional manner consistent with previous clinical pharmacology studies.

Geometric Mean Plasma Concentrations of S-297995 Following Single Oral Doses With Coadministration of Morphine



The main plasma metabolite, Nor-S-297995, was formed relatively slowly, with the median T_{max} occurring between 6 and 8.7 hours postdose. Concentrations of Nor -S-297995 were considerably lower than parent compound as C_{max} was approximately 7% to 13% and AUC was approximately 13% to 18% of that for the parent drug. Similar to S-297995, Nor-S-297995 disposition kinetics appeared to be monophasic, with $t_{1/2, z}$ values ranging from 8 to 11 hours. Dose proportionality could only be accurately calculated over the 1.0 and 10.0 mg dose levels; however, AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} generally appeared to increase in a dose proportional manner.

Plasma concentrations of the metabolite benzamidine were BLQ at all timepoints for all subjects who received S-297995.

Following a single IV infusion of morphine, maximum plasma concentrations of morphine and the 2 metabolites analyzed (M6G and M3G) were observed close to the end of infusion across all dose groups. Morphine appeared to decline in a monophasic manner, with GeoMean $t_{1/2, z}$ values ranging from 1.7 to 1.8 hours, consistent with known morphine PK. Mean systemic exposure of all 3 analytes (based on $AUC_{0\,t}$, and C_{max}) was similar across all dose groups, demonstrating that increasing doses of S-297995 had no effect on the PK of morphine.

CONCLUSIONS

Efficacy Conclusions:

- The efficacy of a single oral dose of S-297995 for the reduction of opioid-induced nausea of at least 30% was statistically significantly demonstrated up to 4 hours post dose for the 1.0 and the 10.0 mg dose of S-297995. A similar finding was also true for emesis for as long as 24 hours. There were no differences between the 1.0 and the 10.0 mg dose up to 8 hours; however, 10.0 mg did extend the efficacy to 24 hours.

Pharmacokinetic Conclusions:

- S-297995 was rapidly absorbed, with median T_{max} values ranging from 0.97 to 1.5 hours postdose across the 0.1 to 10.0 mg dose range. Plasma concentrations declined in a monophasic manner, with a GeoMean $t_{1/2, z}$ of 6 to 7 hours. Systemic exposure increased in a dose proportional manner over the dose range 0.1 to 10.0 mg.

- Metabolite Nor-S-297995 was slowly formed, with the median T_{max} occurring between 6 and 8.7 hours postdose. Systemic exposure of Nor-S-297995 was 7% to 18% of the C_{max} and AUC, respectively, of the parent compound. Similar to S-297995, Nor-S-297995 disposition kinetics appeared to be monophasic, with $t_{1/2, z}$ values ranging from 8 to 11 hours. Benzamidine was not measurable at any timepoint at which plasma samples were taken.

- Maximum morphine plasma concentrations were observed in samples close to the end of infusion across all treatment groups. Mean systemic exposure of morphine (as based upon C_{max} and AUC) and terminal elimination half-lives were similar across dose groups, with mean $t_{1/2, z}$ values ranging from 1.7 to 1.8 hours.

- Morphine metabolites M6G and M3G were formed rapidly, with a median T_{max} of 0.5 hours post start of morphine infusion observed in all groups. Mean systemic exposure of both metabolites (as based upon C_{max} and AUC) was similar across dose groups with C_{max} being between approximately 76% and 92% of that for morphine for M3G and between 11% and 14% for M6G.

- An increase in S-297995 dose appeared to have no impact on the PK of morphine or its metabolites M6G and M3G.

- The PK of S-297995 does not appear to be influenced by the presence of morphine at any of the doses used in this study (0.1 to 10.0 mg S-297995).

Safety Conclusions:

- No deaths or SAEs occurred during this study. No AE led to study discontinuation. All AEs were resolved.

- Overall, 427 TEAEs were reported by the 80 subjects (100% of the enrolled and randomized study population), with 116, 96, 100, and 115 TEAEs reported in the placebo, 0.1 mg S-297995, 1.0 mg S-297995, and 10.0 mg S-297995 treatment groups, respectively. The severity of the 427 reported TEAEs was: 271 mild, 156 moderate, and no severe TEAEs.

- Overall, 100% of subjects from the placebo and all 3 treatment groups had TEAEs, with a similar number of TEAEs occurring in all treatment groups and the placebo group. The SOCs with the greatest frequency of TEAEs was gastrointestinal (GI) disorders and skin and subcutaneous tissue disorders. Frequently reported TEAEs were vomiting, hyperhidrosis, pruritus, feeling hot, and flushing. All of these TEAEs are indicative of opioid-induced AEs.

- The severity of TEAEs related to S-297995 was mostly mild; there were some moderate TEAEs and no severe TEAEs. The most frequently reported TEAEs related to S-297995 treatment were reported in the SOCs of nervous system disorders (most common was headache), GI disorders, and renal and urinary disorders.

- The TEAEs related to MSO_4 were mostly mild in severity, consistent with the well-known opioid profile.

- No clinically significant mean changes in any laboratory parameter, vital signs, physical examination, or ECG were observed.

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