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The baseline values of norepinephrine vary among the different groups. The epinephrine levels of the placebo group increase over time. The same pattern is observed with the norepinephrine levels in the subjects on tolvaptan.

A table listing the mean percent change from baseline (placebo corrected) in epinephrine levels is shown below:

Mean Percent Change from Baseline (Placebo Corrected) in Norepinephrine Levels

| Time after Administration, h | Mean Percent Change from Baseline in Norepinephrine Level ^a , % | | | | | |
|------------------------------|--|-----|-----|-------|-----|-----|
| | Dose Level of Tolvaptan, mg | | | | | |
| | 180 | 240 | 300 | 360 | 420 | 480 |
| 2 | 17 | 52 | -34 | -6.0 | 12 | 0.5 |
| 24 | 73 | 44 | 4.2 | -32.7 | 100 | 30 |

^a Pooled placebo corrected

At 2 h and 24 h after dosing increased as well as decreased net plasma concentrations of norepinephrine can be seen. There is no overt evidence for an effect of tolvaptan on norepinephrine, but the available data are too scarce to make a definitive determination.

Aldosterone

The below table lists the mean change from baseline (placebo corrected) in aldosterone levels measured at 2 h and 24 h after administration:

Mean Percent Change from Baseline (Placebo Corrected) in Aldosterone Levels

| Time after Administration, h | Mean Percent Change from Baseline in Aldosterone ^a Level, % | | | | | |
|------------------------------|--|-----|------|------|-----|-----|
| | Dose Level of Tolvaptan, mg | | | | | |
| | 180 | 240 | 300 | 360 | 420 | 480 |
| 2 | -28 | 16 | -9.6 | -6.5 | 11 | 11 |
| 24 | 7.5 | 33 | 26 | 1.7 | 61 | 64 |

^a Pooled placebo corrected

At 2 h post-dose, the presumed time of the peak plasma concentration of tolvaptan the effect on the aldosterone levels varies among the doses. Increased, but also decreased net aldosterone levels are observed. More consistent increases ranging between 1.7% and 64% of the net aldosterone levels are observable 24 h after administration. With the limited information available an effect of tolvaptan on aldosterone cannot be ruled out.

Pharmacodynamic-Pharmacokinetic Correlations

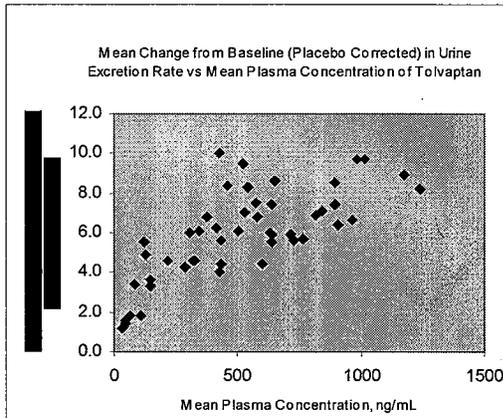
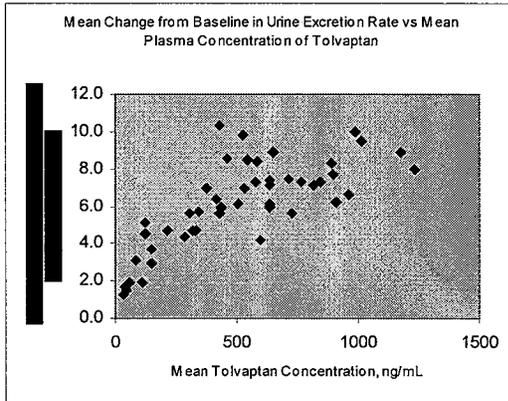
The below table lists the mean change from baseline (placebo corrected) in urine excretion rates and the corresponding mean midtime plasma concentrations of tolvaptan:

| Dose mg | Urine Collection Interval mL | Mean Change from Baseline in Excretion ^a Rate, mL/min | Midpoint Time h | Mean Mid Time Plasma ^b Concentration ng/mL |
|---------|------------------------------|--|-----------------|---|
| 180 | 0-2 | 4.4 | 1 | 432 |
| 240 | | 4.0 | | 428 |
| 300 | | 5.7 | | 768 |
| 360 | | 5.5 | | 639 |
| 420 | | 5.9 | | 715 |
| 480 | | 6.8 | | 2582 |
| 180 | 2-4 | 7.5 | 3 | 577 |
| 240 | | 4.4 | | 597 |
| 300 | | 6.4 | | 907 |
| 360 | | 8.5 | | 891 |
| 420 | | 8.2 | | 1236 |
| 480 | | 9.7 | | 1015 |
| 180 | 4-6 | 7.0 | 5 | 530 |
| 240 | | 6.1 | | 504 |
| 300 | | 5.6 | | 726 |
| 360 | | 7.4 | | 636 |
| 420 | | 8.9 | | 1173 |
| 480 | | 6.6 | | 961 |
| 180 | 6-8 | 10.0 | 7 | 429 |
| 240 | | 5.6 | | 435 |
| 300 | | 8.6 | | 651 |
| 360 | | 9.5 | | 526 |
| 420 | | 9.7 | | 986 |
| 480 | | 7.4 | | 896 |
| 180 | 8-12 | 6.8 | 10 | 374 |
| 240 | | 6.2 | | 416 |
| 300 | | 8.3 | | 545 |
| 360 | | 8.4 | | 461 |
| 420 | | 6.9 | | 820 |
| 480 | | 7.1 | | 844 |
| 180 | 12-24 | 4.6 | 18 | 216 |
| 240 | | 4.6 | | 318 |
| 300 | | 4.6 | | 328 |
| 360 | | 4.3 | | 288 |
| 420 | | 6.0 | | 634 |
| 480 | | 5.9 | | 639 |
| 180 | 24-36 | 3.8 | 30 | 84 |
| 240 | | 3.2 | | 149 |
| 300 | | 4.8 | | 126 |

| | | | | |
|-----|-------|-----|----|-----|
| 360 | | 5.4 | | 124 |
| 420 | | 6.3 | | 306 |
| 480 | | 5.7 | | 345 |
| 180 | 36-48 | 1.2 | 42 | 31 |
| 240 | | 1.8 | | 61 |
| 300 | | 1.6 | | 42 |
| 360 | | 1.4 | | 45 |
| 420 | | 1.8 | | 109 |

^a Pooled placebo corrected ^b All values except those at 1 h and 3 h after administration were obtained by logarithmic interpolation

The below figure shows a plot of the mean change from baseline (placebo corrected) in the excretion rate versus the mean plasma concentrations of tolvaptan:



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Both plots indicate that the net aquaretic effect is nonlinearly related to the plasma concentration of tolvaptan. The higher the plasma concentration, the smaller the increment in the effect. It should be noted that the lagging of the

aquaretic effect behind the plasma concentration (counter-clockwise hysteresis) contributes significantly to the variability of the data.

Conclusions

PK

The parameter estimates of OPC-41061 at dose levels ≥ 240 -480 mg can be considered reliable. The respective mean values in the 5 dose groups for the main parameters CL/F, Vz/F, and t1/2z range between 3.7 and 6.9 mL/min/kg 3.7 and 6.9 L/kg and 9.9 h and 14 h with no obvious dose dependency. Median tmax in the 6 dose groups ranges between 2.3 and 4.0 h with no trend increase with increasing dose. The kinetics of tolvaptan are dose proportional. Cmax, in contrast to AUC ∞ , increases less than dose proportional indicating that absorption of tolvaptan is slowed but bioavailability is not affected. Peak and average exposure measures show marked inter-subject variation.

The plasma concentrations of the metabolite DM-4103 are much greater than those of the parent drug. Median tmax for DM-4103 ranges between 24 h and 36 h and the elimination of the compound is very protracted.

PD

The effect of all tolvaptan doses on serum Na⁺ in the 0-24 h post-dose interval is a net increase ranging between 1.2 mEq (0.87%) and 7.0 mEq (5.0 %). The onset of tolvaptan's effect on serum Na⁺ is observable with all doses at 2 h post-dose. The net peak effects on serum Na⁺ range between 5.3 and 7.0 mEq. A ceiling effect on serum Na⁺ is attained with tolvaptan doses between 180 and 480 mg. There is an apparent trend for an increase in serum K⁺ by tolvaptan. Urine excretion rates, free water clearance, plasma osmolality, at all doses of OPC-41061 are greater than after placebo. The values for baseline and placebo corrected urine excretion rate and free water clearance are similar. The onset of net aquaretic activity occurs in the first collection interval of 0-2 h and peak net effects are seen between 6 and 12 h post-dose. The duration of the aquaretic effect ranges between about 42 to 55 h for the tested doses of between 180 and 480 mg. OPC-41061 appears to decrease mean net 24 h Na⁺ excretion and increase mean net 24 h K⁺ excretion. OPC-41061 increases net AVP and PRA plasma levels.

PK-PD

The aquaretic effect is nonlinearly related to the plasma concentration of OPC-41061. The higher the plasma concentration the smaller the increment in the effect becomes. There is substantial inter-subject variation in the exposure-response relationship.

Comments

1. The sponsor should explore the exposure response profile of OPC-41061.
2. The sponsor should study the net effect of tolvaptan on the pharmacodynamic parameters by considering the impact of baseline and placebo.
3. The goal of the study, namely to determine the maximum tolerated dose is not attained.
4. The individual dose increments used in the study range between 14 % and 33 % and are too small to exert easily discernible effects.
5. Aldosterone and norepinephrine levels are measured at baseline, 2 h and 24 h post-dose. The information is too scarce to evaluate tolvaptan's potential impact on these endogenous compounds. The body position and activity levels of the subjects, known to affect aldosterone and epinephrine (and AVP and PRA) are not prescribed by the protocol.
6. Urine osmolality in mOsm per time unit, and urine Na⁺ and K⁺ excretion mEq per time unit should be plotted vs. time. The plots of the sponsor show amounts of Na⁺, K⁺ and osmolality excreted in each

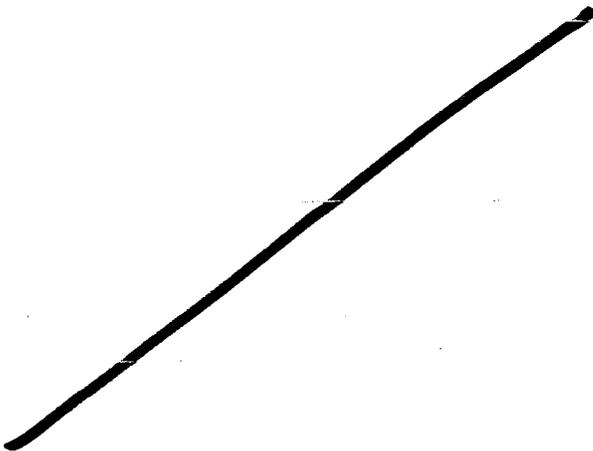
collection interval. This is misleading, because the difference in the duration of the collection intervals is not considered.

7. Pre-dose blood samples were collected to determine the plasma protein binding of OPC-41061. However, the method used and the results obtained are not reported.
8. The report should indicate the respective methods (accuracy, precision, specificity) used to measure osmolality (plasma and urine), aldosterone, epinephrine, AVP and PRA.
9. The literature reference given for the computation for free water clearance O'Connor et al. Am. Heart J. 1998;135:S249-263, is incorrect.

Study Report No. 156-96-203: "Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose Ranging, Efficacy, Safety, and Pharmacokinetic Study of OPC-41061 in Hospitalized Patients with Hyponatremia Secondary to Liver Disease"

Investigator and Study Sites

| Site No. | Investigator | Study Center |
|----------|--------------|--------------|
|----------|--------------|--------------|



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Objective

To assess the efficacy, safety and PK of daily doses of up to five (5, 10, 15, 30, and 60 mg) dose levels of OPC-41061 in patients with hyponatremia secondary to liver disease. The outcome variables include plasma sodium concentration, urine osmolality, urine volume and body weight. The safety outcome variables include adverse experiences, vital signs, neurological examinations, ECGs, laboratory tests, plasma potassium concentrations and OPC-41061 plasma concentrations.

Rationale for Dose Levels Selected

Safety assessments collected during the Phase I studies suggest that OPC-41061 is safely tolerated up to 60 mg daily for up to 28 days in healthy subjects. In addition, single doses of up to 240 mg were tolerated in healthy subjects.

Investigational Drugs and Formulations

Five (5) and 15 mg tablets and matching placebo tablets were provided by the sponsor. Lot Nos. for the formulations are not indicated in the report.

Design

The study consisted of a two-day baseline period (Study Days -1 and 0), a 13-day treatment period with study drug, a termination visit, and one follow-up evaluation 6 to 9 days after the termination visit. Five groups of nine patients were randomized on Day 1 in the following order: 5 mg, 10 mg, 15 mg, 30 mg and 60 mg. In each treatment group, 6 patients received OPC-41061 and 3 patients placebo. The daily doses of 5 mg and 10 mg of OPC-41061 were administered as one and two tablets, respectively. The daily doses of 15, 30, and 60 mg were administered as one, two, and four 15 mg tablets. The patients were hospitalized during the first four days of treatment and discharged on Day 5 after completing Study Day 5 assessments. The patients were to return to the clinic on Study Days 7, 9, 11, 13, and 14. On Study Day 13, the final dosing day, the patients could volunteer for an extra-day of hospitalization after the final dose of study drug so that additional blood samples for sodium and potassium levels in plasma could be collected. Patients were to be fasting from food from 2200 the evening before until 4 h post-dose. Study drug was to be administered together with 200 mL water. Fluid intake was to be monitored starting at 0800 on Day 0. Fluid intake over 24 h on the dosing days was to be matched as closely as possible to the fluid intake measured on Day 0.

Dose escalation was evaluated at the completion of each dose group. The inclusion and exclusion criteria used in enrolling patients for the study were the following:

3.1.1 Inclusion Criteria

Patients were required to meet the following inclusion criteria:

TABLE 3.1-1 INCLUSION CRITERIA

- | | |
|----|--|
| 1. | Age greater than or equal to 18 years. |
| 2. | Plasma sodium 120 to 135 mEq/L on study days -1 and 0. If plasma sodium was not within this range on each of these study days, the patient could not be dosed. |
| 3. | Plasma potassium 3.4 to 5.0 mEq/L on study days -1 and 0. If plasma potassium was not within this range on each of these study days, the patient could not be dosed. |
| 4. | History of liver disease for at least 30 days before screening on study day -1. |
| 5. | Child-Pugh score not to exceed 10. |
| 6. | In the judgment of the investigator, the patient had at least one of the following signs or symptoms: peripheral edema (pitting), ascites. |

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3.1.2 Exclusion Criteria

Patients were excluded if they met any of the following exclusion criteria:

TABLE 3.1-2 EXCLUSION CRITERIA

| | |
|-----|--|
| 1. | Women who were breastfeeding and females of childbearing potential who were not using acceptable contraceptive methods (barrier or oral contraceptives). All females of child-bearing potential had to have a negative serum pregnancy test within 24 hours prior to receiving study drug. Non-childbearing potential was defined as either post-menopausal or surgically sterile. |
| 2. | History of congestive heart failure. |
| 3. | Surgery within 30 days of potential study enrollment. |
| 4. | Current spontaneous bacterial peritonitis. |
| 5. | Hepatic encephalopathy stage 2 or higher. |
| 6. | Progressive or episodic neurological disease such as multiple sclerosis or a history of multiple strokes. |
| 7. | History of hypersensitivity and/or idiosyncratic reaction to benzazepine derivatives such as benzazepin. |
| 8. | Hemoglobin <9.5 g/dL on study day -1. |
| 9. | Serum creatinine >2.2 mg/dL on study day -1. |
| 10. | Upper gastrointestinal hemorrhage within 30 days prior to potential study enrollment. |
| 11. | Hepatoma or metastatic disease of the liver. |
| 12. | Therapeutic paracentesis within one week of potential study enrollment. |
| 13. | Current transjugular intrahepatic portosystemic shunting (TIPS). |
| 14. | Use of alcohol within 7 days of potential study enrollment. |
| 15. | Poorly controlled hypothyroidism. |
| 16. | Poorly controlled hypernatremia. |
| 17. | Participation in another clinical drug trial within the past 30 days. |
| 18. | Previous participation in this or any OPC-41061 clinical trial. |
| 19. | Terminally ill or moribund condition with little chance for survival beyond 72 hours. |
| 20. | Donation of blood or plasma within 30 days prior to potential study enrollment. |
| 21. | Morbid obesity, defined as a body mass index > 28 for males and > 26 for females, calculated by dividing the patient's weight in kilograms by height in meters squared. |
| 22. | Prothrombin time of > 18.5 sec or INR > 1.7. |

Individual patient dosing was to continue on Study Days 2-13, unless one of the following events occurred, at which time an assessment by the investigator would be made regarding continuing the patient in the study:

- The patient's plasma sodium increased by more than 8 mEq/L in any four-hour period following dosing.
- The patient's plasma sodium increased by more than 15 mEq/L in the 24-hour period following dosing.
- At any time after dosing, the patient's plasma sodium equaled or exceeded 146 mEq/L.
- At any time after dosing, the patient's plasma potassium equaled or exceeded 6 mEq/L (Amendment 001).
- The patient's plasma OPC-41061 concentration reached a level considered unsafe based upon previous phase I trials.

After patients in Group 1 had completed the follow-up visit on Day 20-23, the results were to be examined by the sponsor. The following criteria had to be met on each of the possible 13 days of treatment in order for the escalation to proceed:

- The rate of correction did not exceed 8 mEq/L for any four-hour period in more than two patients.
- The overall increase in plasma sodium did not exceed 15 mEq/L within the 24-hour period following dosing in more than two patients.
- The absolute value of plasma sodium at any time after dosing did not exceed 145 mEq/L in more than two patients.
- The absolute value of plasma potassium at any time after dosing did not exceed 6 mEq/L in more than two patients (Amendment 001).
- The OPC-41061 plasma concentration did not exceed maximum levels observed in previous phase I trials.

The pharmacokineticist reviewed the plasma concentration data and advised the reduction or withholding of the dose of a particular patient when such was considered appropriate. Additionally, before moving on to the next arm of the study, the pharmacokineticist was consulted for recommendation.

The dosage of concomitant medications was to be kept constant during the study unless changes were necessary in the judgment of the investigator to protect patient safety. The schedule of administration other than diuretics was not to be modified.

The scheduled study activities are summarized in the below scheme:

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TABLE 3.3-1 SCHEDULE OF ASSESSMENTS

| Procedure | INPATIENT | | | | | | | OUT-PATIENT | | |
|---|--------------------|-------------------|----------------|----------------|----------------|----------------|----------------|---|----------------|--------------------------|
| | Baseline Day -1 | Baseline Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Days 7 ^a 9, 11, 13 ^b | Day 14 | Follow-Up Day 20 - 23 |
| Informed Consent | X | | | | | | | | | |
| History | X | | | | | | | | | |
| Physical Examination | X | | | | | | X | X ^c | X | X |
| Serum Pregnancy | X | | | | | | | | | |
| Vital Signs (Supine and Standing) | X | X | X | X | X | X | X | X | X | X |
| Temperature | X | X | X | X | X | X | X | X | X | X |
| Weight | X | X | X | X | X | X | X | X | X | X |
| Adverse Experiences ^d | | | | | | | | | | |
| Concomitant Medications ^e | | | | | | | | | | |
| Fluid Restriction | | | X | X | X | X | X | X | X | |
| Plasma Sodium and Potassium | X | X ^f | X ^g | X ^g | X ^h |
| Plasma Osmolality | | X | | | | | X | | | |
| Plasma Creatinine | | X | | | | | | | | |
| Urine Osmolality | | X | X | X | X | X | | | | |
| Urine Sodium and Potassium | | X | X | X | X | X | X | X ⁱ | X | X |
| Urine Creatinine | | X | | | | | | | | |
| Fluid Intake/Output Record ^j | | X | X | X | X | X | X | X | X | |

TABLE 3.3-1 SCHEDULE OF ASSESSMENTS (CONTINUED)

| Procedure | INPATIENT | | | | | | | OUT-PATIENT | | |
|---|--------------------|-------------------|-------|-------|-------|-------|-------|---|--------|--------------------------|
| | Baseline Day -1 | Baseline Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Days 7 ^a 9, 11, 13 ^b | Day 14 | Follow-Up Day 20 - 23 |
| Dietary / Na ⁺ Intake Record | | X | X | X | X | X | | | | |
| Safety Laboratory Tests | X | | | | | | X | X ^c | X | X |
| PT and aPTT | X | | X | | X | | | X ^c | | X |
| Neurological Examination | | X | X | X | X | X | | X | X | X |
| 12-Lead ECG | | X | X | X | X | X | X | X | X | X |
| AVF Measurement | | X | X | | | | | | | |
| OPC-41061 PK Samples | | X | X | X | X | X | X | X | X | |
| Study Drug Dosing | | X | X | X | X | X | X | X | | |
| Activity Restriction | | | X | X | X | X | | | | |

^a These measures were only done on Day 7.
^b If the patient was participating in the Study Day 13 hospitalization, additional blood samples for plasma sodium, plasma potassium and pharmacokinetic measures would be drawn.
^c Adverse experiences were recorded on an ongoing basis.
^d Concomitant medications were recorded on an ongoing basis.
^e At U08.
^f At 2, 4, 8, 12 and 23 hours postdose.
^g At 2 and 23 hours postdose.
^h At 2 hours postdose.
ⁱ Glucose patients, at pre-dose and 2 hours postdose. If the patient was participating in the Study Day 13 hospitalization, at pre-dose and 2, 3, 8, 12 and 21 hours postdose.
^j At 24 hours postdose.
^k At approximately 0800.
^l Fluid output record on Study Days -1 through 4 only.

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Safety

Hematology with differential, platelet count, serum chemistries and urinalysis were obtained on Study Days -1, 5, 7, and 14 (or termination visit) and at the follow-up visit. PT and aPTT were to be measured on Study Days-1, 1, 3, 5, 7, 9, 11, and 13 and at the follow-up visit. Scheduled 12-Lead ECGs were recorded and neurological examinations were performed throughout the study.

Pharmacokinetic Profiling

Blood samples for the determination of plasma concentrations of OPC-41061 were collected at the following time points on:

- Day 0: at 0700 h pre-dose
- Day 1: at 1, 2, 4, 6, 8, 10, 12, 16, and 23 h post-dose
- Days 2-4: at 2 h and 23 h post-dose
- Day 5: at 2 h post-dose

Days: 7, 9, 11, and 13: at pre-dose and 3 h post-dose
Optional Day 13: at pre-dose and 2, 4, 8, 12, and 24 h post-dose
Optional Day 14: at 24 h post dose

Plasma Protein Binding

¹⁴C-OPC-41061 and an equilibrium dialysis method was used. The final concentrations of OPC-41061 were 160 ng/mL and 400 ng/mL. Depending on the availability of sample volume both or only one concentration of OPC-41061 was tested. Impact of pH, non-specific binding, stability, concentration dependency, recovery, time to equilibrium and impact of DM-4103 were investigated in preliminary experiments. The experiments were conducted at 37 °C at pH 7.4.

Bioassay

The plasma concentrations of OPC-41061 were measured by a LC/MS/MS assay using an internal standard. The method is fully validated. The method is linear (weighting $1/y^2$) in the range between 5.00 ng/mL-1000 ng/mL with a correlation coefficient of 0.998. Using QC samples precision of the method for OPC41061 is $\leq 16.9\%$ and accuracy ranges between -21.8% and 3.7% . Stability of the analyte was checked by exposing plasma for 4 h and extracts for 49 h on the autosampler at room temperature. The impact of long term freezer and freeze/thaw cycle exposures are not reported. _____, performed the measurements.

The concentrations of radio-labeled OPC-41061 in buffer and plasma of the equilibrium dialysis experiments were measured by liquid scintillation spectrometry. _____, performed the measurements.

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Pharmacokinetic Data Analysis

The following were to be determined on Days 1 and 13: C_{max}, t_{max}, AUC₀₋₂₃, t_{1/2z}, CL/F and V_z/F. Linear regression analysis was performed on log-transformed C_{max} and AUC_t versus log-transformed dose and 95% confidence intervals of the slope determined.

Pharmacodynamic Profiling

Plasma sodium and potassium were to be measured on

Day -1: at admission

Day 0: at 0700 h

Day 1: at 2, 4, 8, 12, and 23 h post-dose

Days 2-4: at 2 and 23 h post-dose

Day 5: at 2 h post-dose

Days 7, 9, 11: pre-dose and 2 h post-dose

Day 13: pre-dose, and 2, 4, 8, 12, and 24 h post-dose

Optional Day 14: 24 h post-dose

Follow-up visit: at 0800 h

The sodium levels had to be available within 45 min of blood collection.

Measurements of urine volume, osmolality, sodium, and potassium were made on cumulative urine collections during the following intervals: 0800-1200, 1200-1600, 1600-2000, and 2000-0800 on Study Days 0 through 4.

Blood samples for measurements of plasma AVP were taken pre-dose and 4 h after OPC-41061 administration on Study Day 1.

Creatinine clearance was determined from a complete 24 h urine collection from 0800 on Study Day 0 to 0800 on Study Day 1. Plasma creatinine was to be measured on Study Day 0.

Plasma osmolality was obtained on Days 0 and 5.

Baseline for plasma sodium and body weight, the two endpoints of primary interest, was defined as their observation at time point Day 0 at 0700 h. Baseline of urine osmolality and urine volume was defined as their observations performed on Day 0.

Fluid intake was to be monitored starting at 0800 on Day 1. Fluid intake over 24 h on the study drug dosing days was to be matched as closely as possible to the fluid intake measured on Day 0. The fluid intake recording intervals on Study Days 0-4 were 0800-1200, 1200-1600, 1600-2000, and 2000-0800. Administration of intravenous fluids was allowed but had to be considered for the daily intake of fluid and sodium. Fluid restriction was in effect during the outpatient period, Study Days 5 to 14. Patients were instructed to record each fluid intake on a card. Fluid intake was not allowed for 1 h prior to the 0700 h measurement of plasma sodium and prior to all 23 h post dose measurements.

On Study Days 0-4 meals were chosen by a dietician in a way to accurately estimate water and sodium intake. The dietary sodium intake was determined by the investigator, but had to be relatively constant throughout the study. A standard of 2 g/day of sodium was recommended.

Statistical Analysis

As this was an exploratory study no statistical evaluation of the data was performed. Also, no sample size determination for the study was made. Comparisons of the change from baseline were made for plasma sodium, body weight, urine osmolality and volume. The intent-to-treat population was examined.

RESULTS

The demographics of the enrolled patients are shown in the below table:

| Parameter | OPC-41061 | | | | | Pooled Placebo n = 15 |
|---------------|---------------|----------------|----------------|----------------|----------------|--------------------------|
| | 5 mg n = 6 | 10 mg n = 6 | 15 mg n = 6 | 30 mg n = 6 | 60 mg n = 6 | |
| Age (years) | | | | | | |
| Mean | 49.7 | 54.0 | 50.5 | 54.7 | 51.5 | 51.5 |
| SD | 12.7 | 13.5 | 8.5 | 4.2 | 5.3 | 10.1 |
| Range | 38-68 | 38-73 | 37-63 | 50-60 | 46-58 | 37-70 |
| Gender, n (%) | | | | | | |
| Male | 4.0 (66.6) | 4.0 (66.6) | 5.0 (83.3) | 5.0 (83.3) | 3.0 (50.0) | 11.0 (73.3) |
| Female | 2.0 (33.3) | 2.0 (33.3) | 1.0 (16.6) | 1.0 (16.6) | 3.0 (50.0) | 4.0 (26.6) |
| Race, n (%) | | | | | | |
| Caucasian | 5.0 (83.3) | 5.0 (83.3) | 3.0 (50.0) | 6.0 (100.0) | 5.0 (83.3) | 8.0 (53.3) |
| Black | 0 | 0 | 0 | 0 | 0 | 1.0 (6.6) |
| Hispanic | 1.0 (16.6) | 1.0 (16.6) | 3.0 (50.0) | 0 | 1.0 (16.6) | 5.0 (33.3) |
| Other | 0 | 0 | 0 | 0 | 0 | 1.0 (6.6) |

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Mean (SD) age, body weight (on Day-1) and Child-Pugh scores of the patients in the OPC-41061 Groups are listed in the table below:

| Dose mg | Age, years | Weight, kg | Child Pugh Score |
|---------|------------|------------|------------------|
| 5 | 50 (13) | 92 (41) | 10 (2) |
| 10 | 54 (14) | 65 (10) | 10 (2) |
| 15 | 51 (9) | 81 (13) | 10 (1) |
| 30 | 55 (4) | 74 (22) | 8 (1) |
| 60 | 52 (5) | 74 (17) | 10 (2) |

The Child-Pugh scores indicate that the patient population exhibits moderate to severe liver impairment.

The disposition of the patients is listed in the next table:

| Patient Status | 5 mg n (%) | 10 mg n (%) | 15 mg n (%) | 30 mg n (%) | 60 mg n (%) | Pooled Placebo n (%) | Total n (%) |
|--|---------------|----------------|----------------|----------------|----------------|----------------------------|----------------|
| Randomized | 6 | 6 | 6 | 6 | 6 | 15 | 45 |
| Treated | 6 | 6 | 6 | 6 | 6 | 15 | 45 |
| Completed per protocol | 2 (33.3) | 4 (66.6) | 4 (66.6) | 4 (66.6) | 4 (66.6) | 9 (60.0) | 27 (60.0) |
| Withdrawn | | | | | | | |
| Plasma sodium exceeded protocol limit | 0 | 0 | 1 (16.6) | 0 | 0 | 0 | 1 (2.2) |
| Withdraw consent | 0 | 0 | 0 | 2 (33.3) | 0 | 1 (6.6) | 3 (6.6) |
| Adverse experience | 4 (66.6) | 0 | 1 (16.6) | 0 | 2 (33.3) | 5 (33.3) | 12 (26.6) |
| Other | 0 | 2 (33.3) | 0 | 0 | 0 | 0 | 2 (4.4) |

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Of the 45 patients enrolled, 27 completed the study per protocol. Of the 18 non-completing subjects 12 were withdrawn because of an adverse event, 3 patients withdrew consent, 1 patient was withdrawn because the plasma sodium exceeded the limit set by the protocol, and 2 patients withdrew for other reasons. The number of completing subjects was 9 in the placebo group, 2 in the 5 mg tolvaptan group and 4 in the 10, 15, 30 and 60 mg OPC-41061 groups.

Safety

Three patients died during the course of the study: a 58 year old female in the 5 mg OPC-41061 group succumbed to multi-organ failure; a 37 year old male patient in the 15 mg OPC-41061 group died of bacterial peritonitis and a 37 year old male patient in the placebo group died of hepatic failure. Ten (10) of 30 (33 %) OPC-41061 treated patients and 7 of 15 (47%) placebo treated patients reported serious treatment emergent adverse events (TEAEs). Of these only disseminated intravascular coagulation exhibited by one patient was judged to be probably drug related. The occurrence of TEAEs appeared not to be related to the dose of OPC-41061 administered. The most common of TEAEs potentially drug related included thirst (30%), ascites (10%), dizziness (10%) and orthostatic hypotension (10%). A dose dependency was not apparent.

Pharmacokinetics

The below 2 figures are linear plots of the median plasma concentration time profiles of OPC-41061 on Day 1 following a single dose of OPC-41061 and Day 13 following multiple oral doses of OPC-41061 qd:

Figure 2.4-1 Plot of median plasma concentrations of tolvaptan on Day 1 following a single oral administration of tolvaptan to patients with hyponatremia secondary to liver disease.

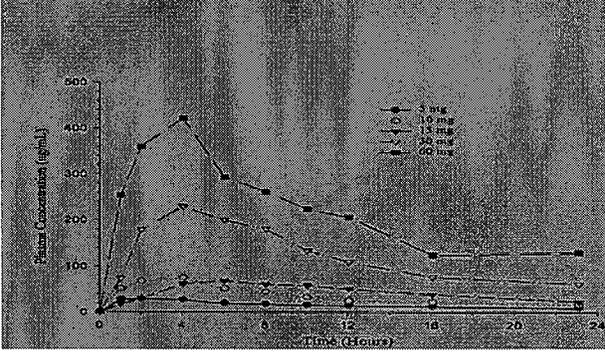


Figure 2.4-2 Plot of median plasma concentrations of tolvaptan on Day 13 following multiple oral doses (q.d.) of tolvaptan to patients with hyponatremia secondary to liver disease.



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The plasma concentrations after 10 mg, 15 mg, 30 and 60 mg OPC-41061 are measurable up to 23 h on Day 1 and 24 h on Day 13 in all subjects of the different groups. After administration of 5 mg the plasma concentrations of OPC-41061 on Day 1 are only measurable up to 16 h post-dose in all subjects, but measurable up to 24 h on Day 13 in all subjects of the group.

The 2 below tables list the sponsor's estimated median PK parameters for OPC-41061 on Day 1 following a single dose of OPC-41061 and Day 13 following multiple oral doses of OPC-41061 qd:

Median (range) pharmacokinetic parameters of tolvaptan following a single oral administration of tolvaptan on Day 1

| Dose N | C _{max} (ng/mL) | t _{max} (h) | AUC ₀₋₂₃ (ng·h/mL) | t _{1/2z} ^a (h) | CL/F (mL/min/kg) |
|--------------|-----------------------------|-------------------------|----------------------------------|---------------------------------------|---------------------|
| 5 mg N=6 | 32.94 (19.46-73.44) | 2.86 (1.92-4.00) | 334.9 (297.58-782.41) | 10.95 (7.07-14.72) | 2.37 (1.58-4.86) |
| 10 mg N=6 | 74.57 (64.11-201.30) | 3.00 (1.83-4.17) | 722.05 (666.31-1991.93) | 9.06 (6.20-33.32) | 3.18 (1.47-3.98) |
| 15 mg N=6 | 77.17 (20.25-118.67) | 5.09 (2.25-9.75) | 1055.46 (340.77-1438.5) | 13.58 (7.49-21.54) | 3.64 (2.15-7.56) |
| 30 mg N=6 | 267.23 (130.3-445.78) | 3.99 (1.17-6.00) | 3103.69 (1787.92-3579.64) | 10.97 (3.73-31.24) | 2.64 (1.84-2.92) |
| 60 mg N=6 | 420.16 (173.27-862.46) | 4.00 (3.75-8.00) | 5217.00 (2791.31-7087.13) | 31.03 (6.16-94.62) | 3.03 (1.82-3.74) |

^a For this parameter, n=4 for the 5 mg dose group and n=5 for the 30 and 60 mg dose groups.

Median (range) pharmacokinetic parameters of tolvaptan following multiple oral administration of tolvaptan (qd) on Day 13

| Dose N | C _{max} (ng/mL) | t _{max} (h) | AUC ₀₋₂₄ (ng·h/mL) | t _{1/2z} ^a (h) | CL/F (mL/min/kg) |
|--------------|-----------------------------|-------------------------|----------------------------------|---------------------------------------|---------------------|
| 5 mg N=2 | 80.33 (67.27-93.38) | 3.00 (2.00-4.00) | 946.37 (913.01-979.73) | 11.33 (7.99-14.68) | 1.45 (1.26-1.64) |
| 10 mg N=3 | 207.59 (113.58-300.95) | 3.92 (2.00-12.17) | 2690.69 (1786.47-3624.83) | 7.23 (6.17-8.32) | 1.41 (0.80-1.49) |
| 30 mg N=3 | 407.73 (233.86-917.22) | 2.00 (1.75-4.03) | 3849.49 (3349.53-5249.02) | 5.48 (4.26-23.73) | 1.63 (1.01-2.80) |
| 60 mg N=1 | 672.07 (309.7-1197.59) | 2.00 (1.00-4.00) | 7562.94 (5410.81-14701.71) | 16.22 (6.93-24.01) | 1.57 (1.10-3.85) |

^a For this parameter, n=2 for the 10 mg dose group, n=4 for the 30 mg dose group and n=3 for the 60 mg dose group.

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As discussed in the review of Study Report 156-98-202 in detail, the sponsor's estimates for λ_z , and the derived $t_{1/2z}$, AUC_{∞} and CL/F on Day 1 and λ_z and $t_{1/2z}$ on Day 13 are subject to bias. The available data can provide reliable estimates for C_{max} , t_{max} and AUC_{0-23} on Day 1, C_{max} , t_{max} , AUC_{0-24} and CL/F on Day 13. AUC_{0-23} on Day 1 and AUC_{0-24} on Day 13 are confusingly labeled AUC_t by the sponsor.

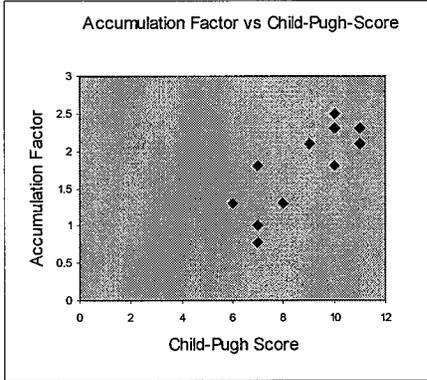
The median peak concentrations are attained between 2.9 and 5.1 h after single dose administration and between 2.0 h and 3.9 h after multiple dose administration. On Day 1 the mean percent coefficient of variation about C_{max} , CV, ranges between 44 % and 57 %. The percent coefficient of variation about mean C_{max} on Days 1 and 13 ranges between 45 % and 59 %. The percent coefficient of variation about mean AUC_{0-23} on Day 1 or AUC_{0-24} on Day 13 ranges between 20 % and 54 %, respectively, indicating marked inter-subject variation. The mean CL/F ranges between 1.45 and 1.63 mL/min/kg and is smaller than in healthy subjects as determined in other studies.

The accumulation factor, RAUC, determined from $AUC_{0-24}(\text{Day 13})/AUC_{0-23}(\text{Day 1})$ is available in the following patients:

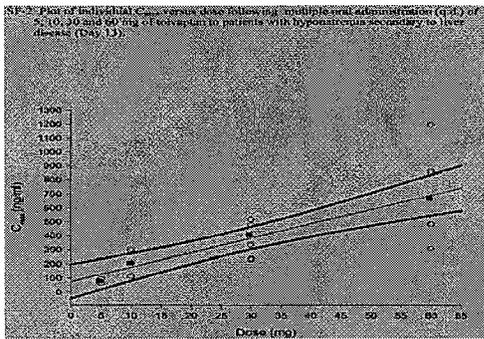
| Subject | Child-Pugh Score | Dose, mg | RAUC |
|---------|------------------|----------|------|
| 1 | 10 | 5 | 1.8 |
| 6 | 8 | | 1.3 |
| 11 | 11 | 10 | 2.1 |
| 15 | 7 | | 1.8 |
| 18 | 10 | | 2.5 |
| 31 | 10 | 30 | 2.5 |
| 32 | 6 | | 1.3 |
| 34 | 7 | | 1.0 |
| 36 | 9 | | 2.1 |
| 39 | 11 | 60 | 2.0 |
| 41 | 10 | | 2.3 |
| 42 | 11 | | 2.3 |

| | | |
|----|---|------|
| 45 | 7 | 0.77 |
|----|---|------|

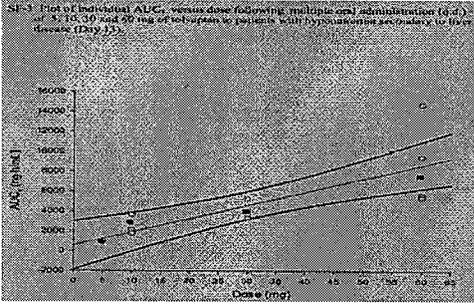
The median accumulation factor, RAUC, in the patients with hyponatremia secondary to liver disease is 2.0 and greater than in healthy subjects as determined in other studies. The RAUC in the individual patients increases with an increase in the Child-Pugh (CP) score as shown in the below figure:



C_{max} and AUC₀₋₂₄ on Day 13 appear to increase in a dose proportionate manner as shown in the below 2 figures:



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The PK of OPC-41061 in patients with hyponatremia secondary to liver disease is dose proportionate.

Plasma Protein Binding

The median percentage of OPC-41061 unbound to plasma protein at concentrations of 160 ng/mL and 400 ng/mL ranges from 1.28% to 2.37% and 1.59% to 1.85%, respectively, across the 5 dose groups.

Pharmacodynamics

Plasma Na⁺

The below table lists the mean change from baseline in plasma Na⁺ concentrations during Days 1-4, 5, 7, 9, 11 and 13 after initiation of the OPC-41061 and placebo treatments:

TABLE 6.4-1. MEAN(SD) CHANGES FROM BASELINE IN PLASMA SODIUM CONCENTRATION (mEq/L): OBSERVED-CASE ANALYSIS

| Study Day Time Post-Dose | OPC-41061 | | | | | Pooled Placebo n = 15 |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|----------------------|-----------------------------|
| | 5 mg n = 6 | 10 mg n = 6 | 15 mg n = 6 | 30 mg n = 6 | 60 mg n = 6 | |
| Baseline | 128.5 ± 3.0 (n=6) | 129.2 ± 3.7 (n=6) | 128.5 ± 3.5 (n=6) | 127.0 ± 4.0 (n=6) | 128.6 ± 2.2 (n=6) | 128.7 ± 4.1 (n=15) |
| Day 1 | | | | | | |
| 2 h | 0.0 ± 2.2 (n=6) | -0.5 ± 2.0 (n=6) | -2.5 ± 2.4 (n=6) | 0.5 ± 1.6 (n=6) | -1.2 ± 2.6 (n=6) | -0.7 ± 2.2 (n=6) |
| 4 h | 1.3 ± 1.8 (n=6) | 1.8 ± 1.2 (n=6) | 4.2 ± 1.3 (n=6) | 1.3 ± 1.8 (n=6) | 0.4 ± 3.6 (n=6) | 0.9 ± 2.9 (n=15) |
| 8 h | 0.0 ± 4.7 (n=6) | 3.3 ± 3.1 (n=6) | 1.8 ± 3.8 (n=6) | 3.2 ± 1.4 (n=6) | 2.0 ± 3.4 (n=6) | -1.4 ± 3.4 (n=15) |
| 12 h | 3.8 ± 2.6 (n=6) | 3.5 ± 3.5 (n=6) | 3.0 ± 3.6 (n=6) | 3.0 ± 2.4 (n=6) | 3.0 ± 3.6 (n=6) | -0.9 ± 2.4 (n=15) |
| 23 h | 1.3 ± 3.4 (n=6) | 3.0 ± 2.4 (n=6) | 2.2 ± 3.9 (n=6) | 2.8 ± 2.7 (n=6) | 0.0 ± 4.3 (n=6) | -0.3 ± 2.4 (n=15) |
| Day 2 | | | | | | |
| 2 h | 1.0 (n=1) | — | 3.0 (n=1) | 2.0 ± 2.0 (n=1) | 0.4 ± 6.7 (n=1) | 1.0 ± 1.0 (n=1) |
| 23 h | 0.9 ± 2.9 (n=6) | 3.2 ± 1.6 (n=5) | 3.8 ± 2.3 (n=6) | 3.3 ± 3.5 (n=6) | 3.3 ± 2.6 (n=6) | 1.5 ± 1.4 (n=15) |
| Day 3 | | | | | | |
| 2 h | 1.0 (n=1) | — | 4.0 (n=1) | 1.7 ± 2.1 (n=1) | 3.6 ± 3.7 (n=1) | -1.1 ± 2.3 (n=1) |
| 23 h | 0.8 ± 3.4 (n=6) | 4.2 ± 1.6 (n=5) | 2.2 ± 4.1 (n=6) | 3.7 ± 4.2 (n=6) | 6.8 ± 2.8 (n=6) | 0.5 ± 2.7 (n=1) |
| Day 4 | | | | | | |
| 2 h | — | — | 4.0 (n=1) | 2.0 (n=1) | 2.0 (n=1) | 2.0 ± 4.2 (n=1) |
| 23 h | 1.2 ± 4.0 (n=4) | 3.2 ± 2.8 (n=5) | 1.8 ± 3.2 (n=6) | 1.7 ± 3.2 (n=6) | 3.0 ± 1.8 (n=5) | 0.2 ± 2.9 (n=13) |

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| Day | Time | 5 mg (n) | 10 mg (n) | 15 mg (n) | 30 mg (n) | 60 mg (n) | Placebo (n) |
|----------------|----------|------------------|-----------------|-------------------|-----------------|-----------------|-------------------|
| Day 5 | 2 h | 0.2 ± 5.4 (n=5) | 2.0 ± 2.6 (n=5) | 1.7 ± 3.7 (n=6) | 3.3 ± 5.4 (n=6) | 4.2 ± 3.5 (n=3) | -0.3 ± 6.5 (n=12) |
| Day 7 | Pre-dose | 3.5 ± 6.5 (n=4) | 3.8 ± 1.6 (n=5) | 4.2 ± 2.9 (n=5) | 2.3 ± 3.7 (n=6) | 5.6 ± 3.8 (n=5) | 1.8 ± 4.2 (n=13) |
| | 2 h | ... | ... | ... | 5.5 ± 0.7 (n=2) | ... | ... |
| Day 9 | Pre-dose | 0.3 ± 4.2 (n=3) | 3.9 ± 2.3 (n=5) | 2.4 ± 6.8 (n=5) | 3.2 ± 2.7 (n=5) | 4.4 ± 4.7 (n=5) | 2.0 ± 5.6 (n=10) |
| | 2 h | ... | ... | ... | 2.0 (n=1) | ... | ... |
| Day 10 | Pre-dose | 3.5 ± 0.7 (n=2) | 3.4 ± 2.1 (n=5) | 4.4 ± 5.5 (n=5) | 3.4 ± 2.7 (n=5) | 7.8 ± 6.8 (n=5) | 3.0 ± 4.4 (n=9) |
| | 2 h | ... | ... | 3.0 (n=1) | 4.4 ± 2.1 (n=5) | 1.0 (n=1) | ... |
| Day 13 | Pre-dose | 4.0 ± 4.7 (n=4) | 0.5 ± 3.4 (n=5) | 4.8 ± 9.3 (n=5) | 2.2 ± 2.7 (n=5) | 3.8 ± 2.8 (n=5) | 3.3 ± 4.9 (n=9) |
| | 2 h | 1.5 ± 7.5 (n=7) | 3.4 ± 2.9 (n=5) | 0.5 ± 3.8 (n=4) | 0.2 ± 3.0 (n=5) | 8.3 ± 4.2 (n=4) | 1.4 ± 2.9 (n=9) |
| | 4 h | 0.3 ± 4.9 (n=2) | 1.7 ± 2.3 (n=3) | 1.7 ± 9.2 (n=2) | 0.6 ± 3.3 (n=5) | 3.0 ± 4.6 (n=4) | 3.1 ± 3.0 (n=7) |
| | 8 h | 0.5 ± 3.9 (n=2) | 2.0 ± 4.6 (n=3) | 4.0 (n=1) | 4.0 ± 4.4 (n=5) | 4.2 ± 3.0 (n=4) | 2.0 ± 4.4 (n=7) |
| | 12 h | 3.8 ± 3.5 (n=2) | 2.3 ± 6.7 (n=2) | 4.0 (n=1) | 4.0 ± 2.9 (n=5) | 4.0 ± 7.0 (n=5) | 0.5 ± 3.0 (n=9) |
| | 23 h | 1.8 ± 2.1 (n=2) | 0.3 ± 3.5 (n=2) | 14.0 ± 11.3 (n=2) | 8.2 ± 5.3 (n=5) | 6.8 ± 3.2 (n=4) | 2.2 ± 3.3 (n=6) |
| Day 14 | 24 h | 3.3 ± 8.1 (n=4) | 3.0 ± 1.8 (n=4) | 6.2 ± 9.5 (n=5) | 2.7 ± 1.2 (n=5) | 6.4 ± 3.2 (n=4) | 3.0 ± 3.8 (n=9) |
| Follow-Up Days | | 0.8 ± 10.3 (n=2) | 0.0 ± 2.0 (n=2) | 1.8 ± 3.4 (n=2) | 2.5 ± 4.4 (n=3) | 1.6 ± 4.0 (n=3) | 2.9 ± 2.8 (n=11) |

Measurement at 0700 following morning of day 0.

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The below table summarizes the mean change from baseline (corrected for placebo) in plasma Na⁺ observed over 5 days after initiation of the multiple dose regimens of OPC-41061

Mean Change from Baseline (Placebo Corrected) in Plasma Na⁺ Over a Period of 4 Days

| Day, Time Post-Dose | Mean Change from Baseline (Placebo Corrected) in Plasma Na ⁺ (mEq) ^{a,b} | | | | |
|---------------------|--|------------------|-----------|-----------|------------------|
| | Dose Level of OPC-41061 | | | | |
| | 5 mg n=6 | 10 mg n=6 | 15 mg n=6 | 30 mg n=6 | 60 mg n=6 |
| Day 1 | | | | | |
| 2 h | 0.7 | 0.2 | -1.8 | 1.2 | -0.5 |
| 4 h | 2.4 | 2.7 | -0.3 | 2.1 | 1.4 |
| 8 h | 1.1 | 4.4 | 2.9 | 4.3 | 3.2 |
| 12 h | 2.1 | 1.4 | 3.9 | 3.9 | 3.9 |
| 23 h | 2.0 | 3.5 | 2.7 | 3.3 | 6.5 |
| Day 2 | | | | | |
| 23 h | 0.2 | 2.7 ^c | 3.3 | 2.8 | 5.7 |
| Day 3 | | | | | |
| 23h | 0 | 3.7 ^c | 1.7 | 3.2 | 5.5 ^c |
| Day 4 | | | | | |
| 23 h | 1.0 ^c | 3.0 ^c | 1.3 | 4.5 | 4.8 ^c |
| Day 5 | | | | | |
| 2 h | 0.5 ^c | 2.9 ^c | 2.0 | 4.1 | 4.5 ^c |

^a Pooled placebo corrected ^b only data with n ≥ 5 considered ^c n=5

Results on n ≥ 5 subjects are only available on Days 1-5. Both data sets suggest a net increase in plasma Na⁺ on Days 1 through 5 in the patients on OPC-41061. However, considering the significant standard deviation about the mean values it appears that a relevant net effect on plasma Na⁺ in the first 4 treatment days may be achieved only at the 60 mg dose level. The onset of the effect on Na⁺ appears to occur at about 8 h post-dose on Day 1 and the time duration of the effect appears to last through the 24 dose interval on Days 1 through 4.

Plasma K⁺

The below table summarizes the change from baseline in the plasma K⁺ concentrations over 14 days after initiation of the treatments:

TABLE 6.4.5 MEAN±SD CHANGES FROM BASELINE IN PLASMA POTASSIUM CONCENTRATION (MEQ/L): OBSERVED-CASE ANALYSIS

| Study Day Time Post-Dose | OPC-41061 | | | | | Placebo |
|-----------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|----------------------|
| | 5 mg | 10 mg | 15 mg | 30 mg | 60 mg | |
| Baseline ^a | 4.3 ± 0.4 (n=6) | 4.1 ± 0.3 (n=6) | 4.1 ± 0.2 (n=6) | 4.4 ± 0.3 (n=6) | 4.4 ± 0.5 (n=6) | 4.3 ± 0.4 (n=15) |
| Day 1 | | | | | | |
| 2 h | 0.1 ± 0.2 (n=6) | 0.3 ± 0.6 (n=6) | -0.1 ± 0.3 (n=6) | -0.0 ± 0.2 (n=6) | 0.3 ± 0.8 (n=6) | -1.1 ± 0.5 (n=15) |
| 4 h | -0.0 ± 0.2 (n=6) | 0.1 ± 0.3 (n=6) | 0.2 ± 0.3 (n=6) | -0.0 ± 0.2 (n=6) | -0.1 ± 0.3 (n=6) | 0.0 ± 0.7 (n=15) |
| 8 h | -0.2 ± 0.1 (n=6) | -0.0 ± 0.4 (n=6) | 0.1 ± 0.4 (n=6) | 0.2 ± 0.2 (n=6) | 0.0 ± 0.2 (n=6) | -0.1 ± 0.4 (n=15) |
| 12 h | -0.3 ± 0.3 (n=6) | 0.0 ± 0.4 (n=6) | 0.3 ± 0.3 (n=6) | 0.2 ± 0.3 (n=6) | 0.1 ± 0.5 (n=6) | -0.1 ± 0.5 (n=15) |
| 23 h | -0.1 ± 0.4 (n=6) | -0.1 ± 0.4 (n=6) | -0.0 ± 0.3 (n=6) | 0.2 ± 0.2 (n=6) | 0.1 ± 0.2 (n=6) | -0.0 ± 0.4 (n=15) |
| Day 2 | | | | | | |
| 2 h | 0.1 (n=1) | --- | 0.0 (n=1) | -0.1 ± 0.2 (n=2) | 0.1 ± 0.6 (n=2) | -0.3 ± 0.2 (n=3) |
| 23 h | 0.2 ± 0.4 (n=6) | -0.1 ± 0.4 (n=5) | -0.1 ± 0.3 (n=6) | 0.4 ± 0.4 (n=6) | 0.0 ± 0.4 (n=6) | -0.1 ± 0.4 (n=15) |
| Day 3 | | | | | | |
| 2 h | 0 (n=1) | --- | 0.2 (n=1) | -0.2 ± 0.3 (n=3) | 0.2 ± 0.2 (n=2) | -0.1 ± 0.6 (n=3) |
| 23 h | -0.1 ± 0.6 (n=6) | -0.1 ± 0.3 (n=5) | -0.0 ± 0.7 (n=6) | 0.0 ± 0.4 (n=6) | -0.1 ± 0.7 (n=6) | 0.0 ± 0.7 (n=13) |
| Day 4 | | | | | | |
| 2 h | --- | --- | -0.2 (n=1) | -0.1 ± 0.4 (n=2) | 1.5 (n=2) | 0.5 ± 1.3 (n=2) |
| 23 h | -0.3 ± 0.6 (n=5) | -0.2 ± 0.3 (n=5) | 0.3 ± 1.0 (n=6) | 0.4 ± 0.5 (n=6) | -0.2 ± 0.6 (n=5) | 0.0 ± 0.5 (n=13) |

The treatments appear not to impact the plasma K⁺ levels.

The below table summarizes the mean change from baseline (placebo corrected) in plasma K⁺ observed over 5 days after initiation of the multiple dose regimens of OPC-41061:

Mean Change from Baseline (Placebo Corrected) in Plasma K⁺ over a Period of 4 Days

| Day, Time Post-Dose | Mean Change from Baseline (Placebo Corrected) in Plasma K ⁺ ^{a,b} | | | | |
|---------------------|---|-------------------|--------------|--------------|-------------------|
| | Dose Level of OPC-41061 | | | | |
| | 5 mg n=6 | 10 mg n=6 | 15 mg n=6 | 30 mg n=6 | 60 mg n=6 |
| Day 1 | | | | | |
| 2 h | 0 | 0.4 | 0.1 | 0.1 | 0.4 |
| 4 h | 0 | 0.1 | 0.2 | 0 | -0.1 |
| 8 h | -0.1 | 0.1 | 0.2 | 0.3 | 0.1 |
| 12 h | -0.2 | 0.1 | 0.4 | 0.3 | 0.2 |
| 23 h | -0.1 | -0.1 | 0 | 0.2 | 0.1 |
| Day 2 | | | | | |
| 23 h | 0.3 | 0 ^c | 0 | 0.5 | 0.1 |
| Day 3 | | | | | |
| 23h | -0.1 | -0.1 ^c | 0 | 0 | -0.1 ^c |
| Day 4 | | | | | |
| 23 h | -0.5 ^c | -0.2 ^c | 0.3 | 0.4 | -0.2 ^c |
| Day 5 | | | | | |
| 2 h | -0.3 ^c | -0.1 ^c | -0.1 | 0.2 | -0.3 ^c |

^a Pooled placebo corrected ^b only data with n ≥ 5 considered ^c n=5

There is no consistent pattern in the mean change from baseline in plasma K⁺ concentrations suggesting that OPC-41061 regimens of 5-60 mg qd have no discernible impact on plasma K⁺ during the observation period of 5 days.

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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Urine Volume

The below table lists the mean change from baseline in the 24 h urine volumes on Days 1 through 4 after initiation of the regimens:

The mean change from baseline in the 24 h urine volume is shown below:

TABLE 6.4-4 MEAN±SD CHANGES FROM BASELINE IN 24-HOUR URINE VOLUME (mL): OBSERVED-CASE ANALYSIS

| Study Day | OPC-41061 | | | | | Placebo n=15 |
|---------------|---------------------------|---------------------------|---------------|---------------|----------------------------|-----------------------------|
| | 5 mg n=6 | 10 mg n=6 | 15 mg n=6 | 30 mg n=6 | 60 mg n=6 | |
| 24-h Baseline | 3385.2±1604.2 | 1899.5±1634.6 | 2288.3±1464.4 | 1836.8±1045.0 | 2922.2±1994.0 | 4127.5±5593.3 |
| Day 1 | 508.0±1046.7 | 1717.2±1734.6 | 862.8±741.9 | 1754.2±1121.1 | 2505.3±2567.0 | -1556.4±4351.5 |
| Day 2 | 66.5±1237.6 | 423.8±1849.6 | 689.0±1249.6 | 1575.0±1516.5 | 1233.2±2018.9 | -1682.6±4298.8 |
| Day 3 | 442.3±1710.5 | 274.2±1833.0 ^a | 376.7±845.1 | 909.7±1289.8 | 6430.1±8722.6 | -1794.5±4570.8 |
| Day 4 | 235.6±1808.9 ^b | 847.6±1377.0 ^b | 353.0±1349.8 | 476.5±917.0 | 2823.8±5041.3 ^a | -1792.0±4565.4 ^a |
| a: | n=5 | | | | | |
| b: | n=13 | | | | | |

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All OPC-41061 doses increase the mean 24 h urine volumes on Days 1-4 beyond the baseline levels. In contrast, the mean 24 h volumes of the pooled placebo group on Days 1-4 are smaller than the baseline value reflecting fluid restriction.

The below tables list the mean change from baseline (with/out correction for placebo) in the 24 h urine excretion rate:

Mean Change from Baseline in 24 h Urine Excretion Rate over 4 Days

| Study Day | Mean Change from Baseline in 24 Urine Excretion Rate mL/min ^a | | | | |
|-----------|---|-------------------|--------------|--------------|------------------|
| | Dose Level of OPC-41061 | | | | |
| | 5 mg n=6 | 10 mg n=6 | 15 mg n=6 | 30 mg n=6 | 60 mg n=6 |
| Day 1 | 0.35 | 1.2 | 0.60 | 1.2 | 1.7 |
| Day 2 | 0.046 | 0.29 | 0.48 | 1.1 | 0.86 |
| Day 3 | 0.31 | 0.19 ^b | 0.26 | 0.63 | 4.5 |
| Day 4 | 0.16 ^b | 0.59 ^b | 0.25 | 0.33 | 2.0 ^b |

^a only data with n ≥ 5 considered ^b n=5

Mean Change from Baseline (Placebo Corrected) in 24 h Urine Excretion Rate over 4 Days

| Study Day | Mean Change from Baseline in 24 Urine Excretion Rate (Placebo Corrected), mL/min ^{a,b} | | | | |
|-----------|--|------------------|--------------|--------------|------------------|
| | Dose Level of OPC-41061 | | | | |
| | 5 mg n=6 | 10 mg n=6 | 15 mg n=6 | 30 mg n=6 | 60 mg n=6 |
| Day 1 | 1.4 | 2.3 | 1.7 | 2.3 | 2.8 |
| Day 2 | 1.2 | 1.5 | 1.6 | 2.3 | 2.0 |
| Day 3 | 1.6 | 1.4 ^c | 1.5 | 1.9 | 5.7 |
| Day 4 | 1.4 ^c | 1.8 ^c | 1.5 | 1.6 | 3.2 ^c |

^a Pooled placebo corrected ^b only data with n ≥ 5 considered ^c n=5

The baseline and placebo corrected data give higher values than the baseline corrected data. Both data sets indicate that all dose levels of OPC-41061 induce a net increase in the 24 h urine excretion rate on Days 1-4. Because of the significant decrease of the urine volumes/excretion rates compared to baseline in the patients on placebo, the baseline and placebo corrected volumes/excretion rates are systematically greater than the baseline corrected values. The largest net mean 24 h excretion rates are seen with the 30 mg and 60 mg doses of OPC-41061. With the baseline and placebo corrected data a systematic rebound effect is not seen in the patients with liver disease associated hyponatremia.

The next two tables glist the mean change from baseline (with/out placebo correction) in the urine excretion rates in the individual collection intervals:

Mean Change from Baseline in Urine Excretion Rate

| Dose Level, mg | Mean Change from Baseline in Urine Excretion Rate, mL/min | | | | |
|-------------------|---|------|------|------|-----|
| | 5 | 10 | 15 | 30 | 60 |
| Time Post-dose, h | | | | | |
| 0-4 | 0.98 | 2.1 | 0 | 1.3 | 1.5 |
| 4-8 | 0 | 1.7 | 1.4 | 2.6 | 2.8 |
| 8-12 | 0.71 | 1.9 | 0.68 | 1.7 | 2.2 |
| 12-24 | 0.21 | 0.50 | 0.55 | 0.56 | 1.3 |

Mean Change from Baseline (Placebo Corrected) in Urine Excretion Rate

| Dose Level, mg | Mean Change from Baseline (Placebo Corrected) in Urine Excretion Rate ^a , mL/min | | | | |
|-------------------|---|-----|-----|-----|-----|
| | 5 | 10 | 15 | 30 | 60 |
| Time Post-dose, h | | | | | |
| 0-4 | 2.2 | 3.3 | 1.1 | 2.5 | 2.7 |
| 4-8 | 1.9 | 3.9 | 3.6 | 4.7 | 4.9 |
| 8-12 | 1.5 | 2.6 | 1.5 | 2.5 | 2.9 |
| 12-24 | 1.0 | 1.3 | 1.3 | 1.3 | 2.1 |

^a Pooled placebo corrected

The baseline and placebo corrected data give systematically higher values for the urine excretion rate than the baseline only corrected data. The former dataset indicates that the onset of aquaretic activity (net excretion rate ≥ 1 mL/min) occurs in the first collection interval of 0-4 h post-dose. Peak rates ranging between 1.9 and 4.9 mL/min occurring at 6 h post-dose are observed. The aquaretic effect appears to last ≥ 18 h at all dose levels.

Fluid Balance

The below table lists the mean change from baseline in fluid balance in the 5 dose groups on Days 1-4:

TABLE 6.4-8 MEAN \pm SD CHANGES FROM BASELINE IN 24-HOUR FLUID BALANCE (mL): OBSERVED-CASE ANALYSIS

| Study Day | OPC-41061 | | | | | Pooled Placebo |
|----------------------------|------------------------------------|-------------------------------------|------------------------|-------------------------|--------------------------------------|-------------------------------------|
| | 5 mg n = 6 | 10 mg n = 6 | 15 mg n = 6 | 30 mg n = 6 | 60 mg n = 6 | |
| 24-h Baseline ^a | 410.5 \pm 971.6 | 628.7 \pm 1161.5 | 275.5 \pm 1447.6 | 1013.7 \pm 1611.0 | 409.7 \pm 1032.2 | 471.8 \pm 4199.9 |
| Day 1 | -1045.7 \pm 980.4 | 1732.0 \pm 1282.2 | 672.7 \pm 1852.5 | -2631.2 \pm 1167.1 | -2743.7 \pm 1225.0 | 1118.3 \pm 4354.5 |
| Day 2 | -803.3 \pm 903.7 | -156.7 \pm 1419.0 | 529.7 \pm 2389.4 | -1157.3 \pm 1555.9 | -1047.2 \pm 1356.9 | 990.7 \pm 4230.9 |
| Day 3 | -545.5 \pm 1699.4 | -447.0 \pm 1825.0 ^b | 450.7 \pm 1920.6 | -1021.3 \pm 1718.6 | -6619.4 \pm 7896.3 | 930.8 \pm 4443.7 |
| Day 4 | -416.4 \pm 934.9 ^c | -898.0 \pm 1114.7 ^c | -502.2 \pm 1937.6 | -767.8 \pm 1018.2 | -3393.0 \pm 4478.0 ^c | 1600.5 \pm 4896.3 ^b |

^a: Measurement on day 0.
^b: n=5.
^c: n=13.

Treatment with OPC-41061 at all tested dose levels results in a negative mean change from baseline in the 24 h fluid balance on Days 1-4. In contrast, placebo treatment is associated with a positive mean change from baseline in fluid balance.

24 h Urine Excretion of Na⁺

The below table lists the mean change in 24 h urine Na⁺ excretion for 4 days after initiation of the treatments:

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TABLE 6.4-6 MEAN±SD CHANGES FROM BASELINE IN 24-HOUR URINE SODIUM EXCRETION (mEq): OBSERVED-CASE ANALYSIS

| Study Day | OPC-41061 | | | | | Placebo n=15 |
|----------------------------|-------------------------|--------------------------|---------------|--------------|---------------------------|----------------------------|
| | 5 mg n=6 | 10 mg n=6 | 15 mg n=6 | 30 mg n=6 | 60 mg n=6 | |
| 24-h Baseline ^a | 94.1 ± 48.0 | 71.2 ± 71.9 | 110.3 ± 100.1 | 88.4 ± 51.7 | 110.4 ± 79.6 | 145.1 ± 135.7 |
| Day 1 | 9.6 ± 70.8 | 8.5 ± 58.9 | 44.3 ± 61.2 | 8.2 ± 30.0 | 13.0 ± 55.3 | -12.1 ± 129.0 |
| Day 2 | -10.6 ± 39.2 | -9.0 ± 41.3 | -26.6 ± 57.7 | -14.0 ± 43.1 | -14.3 ± 91.4 | -31.9 ± 123.9 |
| Day 3 | 32.7 ± 47.6 | -9.3 ± 59.0 ^b | -14.2 ± 69.8 | -20.0 ± 65.4 | 96.4 ± 152.9 | -60.6 ± 136.8 |
| Day 4 | 7.3 ± 52.3 ^a | -6.6 ± 53.4 ^a | -86.2 ± 106.0 | -19.0 ± 54.3 | 49.6 ± 170.2 ^a | -47.7 ± 154.9 ^b |

^a Measurement on day 0.
^a n=5.
^b n=13.

It appears that the OPC-41061 treatments on Days 1-4 are associated with a smaller reduction in the 24 h urine excretion of Na⁺ than placebo.

The following table tabulates the mean change from baseline (placebo corrected) in the 24 h urine excretion of Na⁺:

Mean Change from Baseline (Placebo Corrected) over 4 Days Na⁺ Excretion

| Study Day | Mean Change from Baseline (Placebo Corrected) in the 24 h Excretion of Na ⁺ , mEq ^{a,b} | | | | |
|-----------|---|-----------------|--------------|--------------|-----------------|
| | Dose Level of OPC-41061 | | | | |
| | 5 mg n=6 | 10 mg n=6 | 15 mg n=6 | 30 mg n=6 | 60 mg n=6 |
| Day 1 | 22 | 21 | -32 | 20 | 25 |
| Day 2 | 41 | 43 | 25 | 38 | 38 |
| Day 3 | 93 | 51 ^c | 46 | 40 | 157 |
| Day 4 | 55 ^c | 41 ^c | -39 | 29 | 97 ^c |

^a Pooled placebo corrected ^b only data with n ≥ 5 considered ^c n=5

OPC-41061 at all dose levels and throughout the 4 day observation period appears to increase mean net Na⁺ urine excretion with no discernable impact of dose size. The net Na⁺ excretion ranges between 20 and 157 mEq.

24 h Urine Excretion of K⁺

The following table lists the mean change from baseline in the 24 h urine excretion of K⁺ for 4 days after initiation of the treatments:

TABLE 6.4-7 MEAN±SD CHANGES FROM BASELINE IN 24-HOUR URINE POTASSIUM EXCRETION (mEq): OBSERVED-CASE ANALYSIS

| Study Day | OPC-41061 | | | | | Placebo n=15 |
|----------------------------|-------------------------|--------------------------|--------------|--------------|---------------------------|-----------------|
| | 5 mg n=6 | 10 mg n=6 | 15 mg n=6 | 30 mg n=6 | 60 mg n=6 | |
| 24-h Baseline ^a | 64.2 ± 29.1 | 65.6 ± 45.5 | 69.0 ± 66.9 | 57.8 ± 24.6 | 51.3 ± 19.3 | 127.7 ± 252.2 |
| Day 1 | 25.3 ± 57.7 | 24.9 ± 45.5 | 10.9 ± 43.1 | 0.3 ± 11.7 | 8.2 ± 29.8 | -61.7 ± 233.2 |
| Day 2 | 12.7 ± 40.4 | 0.6 ± 39.8 | -12.0 ± 49.3 | 5.4 ± 16.9 | -3.3 ± 16.4 | -57.9 ± 123.4 |
| Day 3 | 36.8 ± 51.5 | 29.2 ± 67.1 ^b | -23.5 ± 56.1 | 4.9 ± 18.6 | 77.1 ± 128.3 | -67.7 ± 240.5 |
| Day 4 | 1.3 ± 28.1 ^a | 59.3 ± 29.3 ^a | -37.6 ± 62.8 | -2.2 ± 10.6 | 60.0 ± 139.5 ^a | 79.9 ± 217.5 |

^a Measurement on day 0.
^a n=5.
^b n=13.

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The mean change from baseline in K⁺ excretion appears to be less negative with the OPC-41061 treatments than with the placebo treatment.

The below table lists the mean change from baseline (placebo corrected) in K⁺ urine excretion:

Mean Change from Baseline (Placebo Corrected) in 24 h K⁺ Excretion over a Period of 4 Days

| Study Day | Mean Change from Baseline (Placebo Corrected) in 24 h K ⁺ Excretion, mEq ^a | | | | |
|-----------|--|------------------|--------------|--------------|------------------|
| | Dose Level of OPC-41061 | | | | |
| | 5 mg n=6 | 10 mg n=6 | 15 mg n=6 | 30 mg n=6 | 60 mg n=6 |
| Day 1 | 84 | 87 | 51 | 62 | 70 |
| Day 2 | 71 | 59 | 46 | 63 | 55 |
| Day 3 | 99 | 97 ^b | 44 | 73 | 145 |
| Day 4 | 81 ^b | 119 ^b | 42 | 78 | 140 ^b |

^a Pooled placebo corrected ^b only data with n ≥ 5 considered ^c n=5

OPC-41061 at all dose levels and throughout the 4 day observation period appears to increase mean net K⁺ urine excretion with no discernable impact of dose size. The net K⁺ excretion ranges between 42-145 mEq.

Pharmacokinetic-Pharmacodynamic Correlations

The below tables list the mean change from baseline (with/out placebo correction) in urine excretion rate and the corresponding mean mid time plasma concentrations on Day 1 in the 5 groups of patients receiving OPC-41061:

Mean Change from Baseline in Urine Excretion Rate and Plasma Concentration of OPC-41061 on Day 1

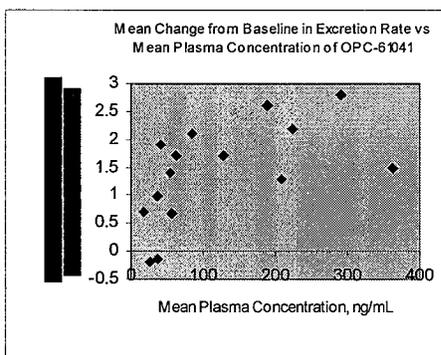
| Dose mg | Interval h | Mean Change from Baseline in Urine Excretion Rate mL/min | Time Post-Dose h | Mean Mid Time Plasma Concentration ng/mL |
|---------|------------|--|------------------|--|
| 5 | 0-4 | 0.98 | 2 | 36 |
| | 4-8 | 0 | 6 | 27 |
| | 8-12 | 0.71 | 10 | 18 |
| 10 | 0-4 | 2.1 | 2 | 84 |
| | 4-8 | 1.7 | 6 | 64 |
| | 8-12 | 1.9 | 10 | 41 |
| 15 | 0-4 | 0 | 2 | 36 |
| | 4-8 | 1.4 | 6 | 54 |
| | 8-12 | 0.68 | 10 | 56 |
| 30 | 0-4 | 1.3 | 2 | 208 |
| | 4-8 | 2.6 | 6 | 190 |
| | 8-12 | 1.7 | 10 | 129 |
| 60 | 0-4 | 1.5 | 2 | 363 |
| | 4-8 | 2.8 | 6 | 291 |
| | 8-12 | 2.2 | 10 | 223 |

Mean Change from Baseline (Placebo Corrected) in Urine Excretion Rate and Plasma Concentration of OPC-41061 on Day 1

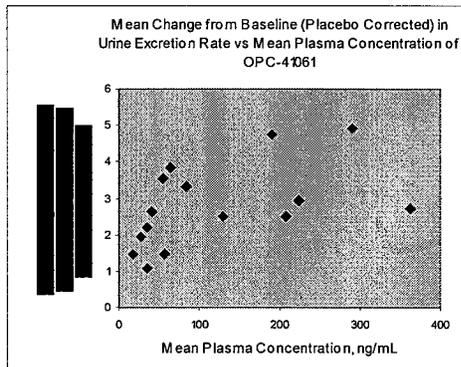
| Dose mg | Interval h | Mean Change from Baseline (Placebo Corrected) in Urine Excretion Rate ^a mL/min | Time Post-Dose h | Mean Mid Time Plasma Concentration ng/mL |
|---------|------------|--|---------------------|---|
| 5 | 0-4 | 2.2 | 2 | 36 |
| | 4-8 | 1.9 | 6 | 27 |
| | 8-12 | 1.5 | 10 | 18 |
| 10 | 0-4 | 3.3 | 2 | 84 |
| | 4-8 | 3.9 | 6 | 64 |
| | 8-12 | 2.6 | 10 | 41 |
| 15 | 0-4 | 1.1 | 2 | 36 |
| | 4-8 | 3.6 | 6 | 54 |
| | 8-12 | 1.5 | 10 | 56 |
| 30 | 0-4 | 2.5 | 2 | 208 |
| | 4-8 | 4.7 | 6 | 190 |
| | 8-12 | 2.5 | 10 | 129 |
| 60 | 0-4 | 2.7 | 2 | 363 |
| | 4-8 | 4.9 | 6 | 291 |
| | 8-12 | 2.9 | 10 | 223 |

^a Pooled placebo corrected

The below figures show plots of the mean change from baseline (with/out placebo correction) in urine excretion rate vs the corresponding mid mean plasma concentrations of OPC-41061 in the 5 dose groups on Day 1:



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The plots show that the mean net urine excretion rate increases with an increase in exposure. The relationship between net excretion rate and plasma concentration of OPC-41061 is saturable. It should be noted that the lagging of the aquaretic effect behind the plasma concentration of OPC-41061 (counter-clockwise hysteresis) contributes to the variability of the data.

The below table lists the mean change from baseline in the area under the plasma Na⁺ concentration time curve, AUC₀₋₂₄ Na⁺ and AUC₀₋₂₃ of OPC-41061 on Day 1:

| Dose, mg | Mean AUC ₀₋₂₃ Na ⁺ ^a mEq • h | Mean AUC ₀₋₂₃ Na ⁺ ^b mEq • h | Mean AUC ₀₋₂₃ OPC-41061 ng • h/mL |
|----------|--|--|---|
| 5 | 39.8 | 21.8 | 424 |
| 10 | 81.3 | 52.7 | 964 |
| 15 | 51.2 | 33.2 | 965 |
| 30 | 73.6 | 55.6 | 2850 |
| 60 | 78.4 | 62.6 | 5136 |

^a Pooled placebo corrected ^b Uncorrected for pooled placebo

There is no relationship between mean change from baseline (with/out correction for placebo) in AUC₀₋₂₃ Na⁺ and mean AUC₀₋₂₃ of OPC-41061 apparent.

Conclusions

PK

The pharmacokinetics of OPC-41061 in patients with liver disease associated hyponatremia receiving qd regimens of 5, 10, 15, 30 and 60 mg are compatible with first order kinetics. On Day 1 the percent coefficient of variation (CV) about mean C_{max} and AUC₀₋₂₃ ranges between 44 % and 57 % and 26 % and 45 %, respectively, indicating marked intersubject variation. On Day 13 the respective CV about C_{max} and AUC₀₋₂₄ ranges between 23 % and 56 % and 5 % and 49 %. The median oral clearance ranges between 1.41 and 1.63 ml/min/kg and is smaller in the patients with moderate to severe liver impairment than in healthy subjects as observed in other studies. The median accumulation factor of OPC-41061 in assessable patients is 2.0 and increases with increasing Child-Pugh scores. The plasma protein binding of OPC-41061 in patients with liver impairment shows an unbound fraction ranging between 0.0128 and 0.0237.

PD

There is a net increase in the mean plasma Na⁺ concentrations on Days 1 through 5 at all dose levels of OPC-41061. The increase in serum Na⁺ is greatest at the 60 mg dose level. The increase in plasma Na⁺ can be seen at about 8 h after the first dose of OPC-41061. The mean net plasma K⁺ concentrations do not show a consistent change suggesting that OPC-41061 regimens of 5-60 mg qd have no discernible impact on serum K⁺ during the observation period of 5 days.

b(4)

The baseline and placebo corrected data give systematically higher values for the urine excretion rate than the baseline corrected data. The former dataset indicates that the onset of aquaretic activity occurs in the first collection interval of 0-4 h post-dose. Peak rates ranging between 1.9 and 4.9 mL/min occurring at 6 h post-dose are observed. The aquaretic effect appears to last \geq 18 h at all dose levels. The net 24 h urine volumes/rates do not decrease during the first 4 days of treatment in the patients with hyponatremia secondary to liver disease. The fluid balance is consistently negative on Days 1-4 at all OPC-41061 dose levels and is most negative with the 30 mg and 60 mg qd regimens. The fluid balance is positive in the patients receiving placebo.

OPC-41061 at all dose levels and throughout the 4 day observation period increases mean net Na⁺ urine excretion with no discernible impact of dose size. The net Na⁺ excretion ranges between 20 and 157 mEq.

OPC-41061 at all dose levels and throughout the 4 day observation period increases mean net K⁺ urine excretion with no discernible impact of dose size. The net K⁺ excretion ranges between 42-145 mEq.

PK-PD

The net mean urine excretion rate increases with an increase in exposure. The relationship between excretion rate and plasma concentration of OPC-41061 is saturable. At high plasma concentrations of OPC-41061 the increments in the excretion rate are less than proportional to the concentration.

Comments

1. The conclusion of the sponsor that the oral clearance of OPC-41061 in the patient population with hyponatremia secondary to liver disease is similar to that in healthy subjects is not supported by the data. The oral clearance values are smaller and the accumulation factor of OPC-41061 is greater in the patient population with assessable data than in healthy subjects.
2. A control group of healthy volunteers should have been included in this study.
3. The plasma protein binding of OPC-41061 in control samples containing plasma from healthy subjects should have been measured along with the plasma from patients.
4. Blood samples were collected over a 24 h time interval following single and multiple dose administration of OPC-41061. The t_{1/2z} is estimated during an approximate 12 h interval (12-23 h after administration) too short for determining reliably t_{1/2z} for OPC-41061 ranging between 7-31 h (estimated median values).
5. Contrary to the stipulation of the protocol V_z/F is not determined for OPC-41061.
6. The radiochemical purity of the ¹⁴C-OPC-41061 used should be indicated in the plasma protein binding study.
7. The Lot Nos. of the investigational drugs and formulations should be indicated.

Study Report No. 156-00-221: "An Open-Label, Randomized, Placebo-Controlled, Crossover Study to Assess the Effects of Tolvaptan (OPC-41061) Oral Tablets and Furosemide (Lasix®) Oral Tablets on Renal Function and Renal Hemodynamics in Patients with Mild to Moderate Congestive Heart Failure"

Investigator and Study Site

b(4)

Objectives

To determine the effects of a single dose of OPC-41061 (tolvaptan) and furosemide (Lasix®) on renal function and renal hemodynamics in subjects with mild to moderate congestive heart failure, New York Heart Association (NYHA) Class II-III.

Investigational Drugs and Formulations

Tolvaptan (OPC-41061), 30 mg tablets (Lot No. 99E87A030A, Otsuka Pharmaceuticals, Co., Ltd)
Furosemide, 80 mg oral tablets (Lot No. 3011287, Hoechst-Roussel Pharmaceuticals); Captopril, 12.5 mg oral tablets (Lot No. 0K972 and 1H345, Mylan Pharmaceuticals); Captopril, 25 mg oral tablets (Lot. No. 0K992, 1D426 and 1A668, Mylan Pharmaceuticals); Lithium carbonate, 600 mg oral capsules (Lot No. 991904A, Roxane Laboratories, Inc.); Matching placebo oral tablets (Lot No. 99D96P000 (Otsuka Pharmaceuticals Co.,Ltd)

Design

This was a single center, open-label, randomized, single-dose, placebo controlled, cross-over design study. Subjects were screened on Day -15 and therapy with ACE- inhibitors (other than captopril) was withdrawn and replaced by captopril (dose was determined by the Principal Investigator), and a 2 g/day NYHA low sodium diet started. On Day -3, subjects discontinued captopril, all diuretics, beta-blockers, and aspirin and they entered the hospital for 9 days. Study drug dosing occurred on Days 1, 3 and 5, with a wash-out period occurring on Days 2 and 4. On Days -1, 2 and 4, subjects received lithium carbonate at 10 PM. On Day 1 all subjects were randomized in a cross-over fashion and received OPC-41061 30 mg or placebo treatment. On Day 3, these same subjects received the opposite treatment they received on Day 1 (OPC-41061 or placebo). On Day 5, all subjects received open-label furosemide 80 mg. Subjects could then resume any medications they were taking prior to screening after the completion of testing on Day 5 or as determined by the Principal Investigator. Subjects were discharged on Day 6. A follow-up call was made to each subject on Day 30 to check for adverse events. Fourteen subjects were to be enrolled in the study. The study design is shown in the below scheme:

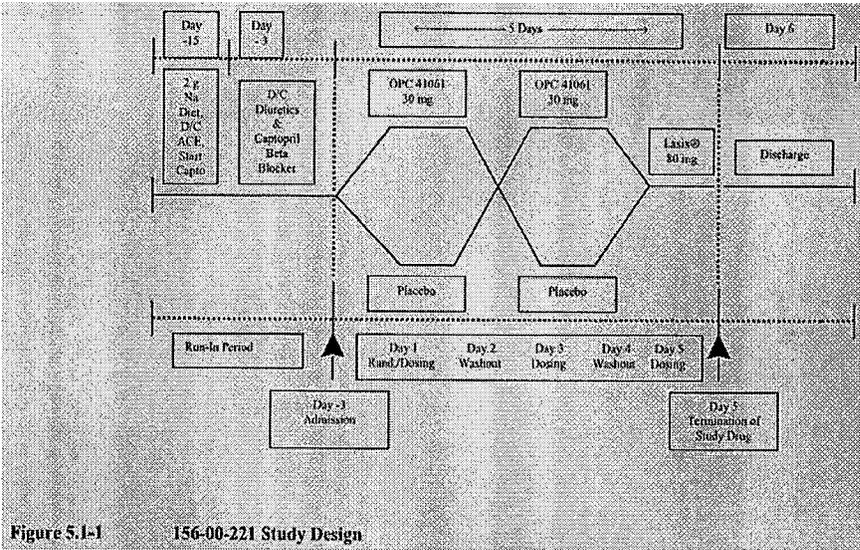


Figure 5.1-1 156-00-221 Study Design

The rationale for the 30 mg dose of OPC-41061 and 80 mg furoseamide is that 30 mg OPC-41061 is likely the therapeutic effective dose for CHF patients. The 80 mg dose for furoseamide is the usual adult dose when used as a diuretic.

The inclusion and exclusion criteria are defined in the below tables:

| Table 5.2.1-1 Inclusion Criteria | |
|----------------------------------|--|
| 1. | ≥ 18 and ≤ 80 years of age. |
| 2. | History of chronic congestive heart failure and symptoms classified as NYHA Class II-III for at least 30 days prior to Screening and on Day 1. |
| 3. | ≤ 40% ejection fraction within one year assessed by 2D echo, radionuclide ventriculogram, or angiography. |

Source: Appendix I-1.

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| | |
|-------------------|----------------------------------|
| 1. Diuretics | 17. Gestodene |
| 2. ACE inhibitors | 18. Indinavir |
| 3. Azithromycin | 19. Itraconazole |
| 4. Benemid | 20. Triacetyl |
| 5. Beta-blockers | 21. Oleandomycin |
| 6. Ketoconazole | 22. Procaine |
| 7. Troleandomycin | 23. Quinine |
| 8. Miconazole | 24. Quinine |
| 9. Amiodarone | 25. Ritonavir |
| 10. Cimetidine | 26. Saquinavir |
| 11. Clotrimazole | 27. Sulfa containing medications |
| 12. Danazol | 28. Thiazolesulfone |
| 13. Dexamethazone | 29. Verapamil |
| 14. Diltiazem | 30. Zafirlukast |
| 15. Erythromycin | 31. Lithium |
| 16. Fluconazole | |

Source: Appendix I-1.

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Grapefruit containing products were prohibited during the study and 48 h prior to screening. Subjects were also advised to abstain from xanthine containing products and alcohol for 72 h prior to entry into the hospital and during the in-hospital phase of the study. The use of tobacco containing products was also prohibited during the duration of the study from Day-15 to Day 6. Subjects were only allowed distilled water during the in-hospital phase of the study. Subjects received 4 glasses of purified water 1.5 h before receiving their dose of medication. All fluid intake and urine output were monitored and recorded on each dosing day. Subjects were encouraged to replace fluid lost from urine output prior to each clearance period.

The scheduled study activities are shown in the below scheme:

Table S.5-1 Schedule of Assessments

| Day | -16 | -3 | -1 | -2 | -1.5 | -1 | -0.5 | 0 | 0.5 | 1 | Days 1, 3, and 5 | | | | | | | | | |
|---|----------------|----------------|-----------------|----|------|----|------|-----------------|-----------------|-----------------|------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Hours | | | | | | | | | | | 1.5 | 2 | 2.5 | 3 | 3.5 | 4 | 4.5 | 5 | 5.5 | |
| Study Procedures | | | | | | | | | | | | | | | | | | | | |
| Medical history and previous med | x | | | | | | | | | | | | | | | | | | | |
| Informed consent/study procedures | x | | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | x | | | | | | | | | | | | | | | | | | | |
| Hepatitis B and HIV screen | x | | | | | | | | | | | | | | | | | | | |
| Urine drug, urine alcohol screen | x | x | | | | | | | | | | | | | | | | | | |
| Urine pregnancy | x ¹ | x ¹ | | | | | | | | | | | | | | | | | | |
| Physical exam w/NVHA class | x | | | | | | | | | | | | | | | | | | | |
| Cardiovascular exam | x | x | | x | | | | | | | | | | | | | | | | |
| D/C ACE, start captopril & Na ⁺ diet | x | | | | | | | | | | | | | | | | | | | |
| D/C captopril, diuretics, ASA, BB | | x | | | | | | | | | | | | | | | | | | |
| Bladder ultrasound (BUS) | x ² | | | | | | | | | | | | | | | | | | | |
| Admission/discharge | | | Adm | | | | | | | | | | | | | | | | | |
| Vital signs (HR, BP, temp & weight) | x | x | | | | | | | | | | | | | | | | | | |
| BP and HR (supine for 20 min) | | | x | | | x | | x ³ | | x ⁴ | | | | x ⁵ | | | | x | | x |
| Serum chemistry | x | | | x | | | | | | | | | | | | | | | | |
| Serum chemistry: Na ⁺ , K ⁺ , and Cl ⁻ | x ⁶ | | | | | | | | | x | | | | | x | | | | x | |
| Serum K ⁺ | | x | | | | | | | | | | | | | | | | | | |
| Hematology | x | | | x | | | | | | | | | | | | | | | | |
| Urinalysis | x | | | x | | | | | | | | | | | | | | | | |
| EKG (12 lead) | x | | | x | | | | | | | | | | | | | | | | |
| Lithium carbonate @ 10 PM | | | x ⁷ | | | | | | | | | | | | | | | | | |
| Urine lithium | x | | | | | | | | | | | | | | | | | | | |
| Administer study medication | | | | | | | | x | | | | | | | | | | | | |
| Pl. supine (except for voiding) | | | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Insert 3 IV catheters | | | x ⁸ | | | | | | | | | | | | | | | | | |
| Insert urinary catheter | | | x ⁹ | | | | | | | | | | | | | | | | | |
| 4 glasses distilled H ₂ O (8 oz/glass) | | | | | | | | | | | | | | | | | | | | |
| Loading dose insulin/PAH | | | | | x | | | | | | | | | | | | | | | |
| Insulin/PAH infusion | | | | | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Urine aliquots/void bladder | | | | x | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Oral distilled H ₂ O replacement (1:1) | | | | x | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Insulin/PAH/LC plasma samples | | | x ¹⁰ | x | | | | x ¹¹ | x ¹² | x ¹³ | x ¹⁴ | x ¹⁵ | x ¹⁶ | x ¹⁷ | x ¹⁸ | x ¹⁹ | x ²⁰ | x ²¹ | x ²² | x ²³ |
| Plasma hormones | | | | | | | | x ²⁴ | | | | | | | | | | | | |
| OPC 41061 PK samples | | | | | | | | x ²⁵ | | | | | | | | | | | | |
| Meals | | | | | | | | | x | | | | | | | | | | | |
| Concomitant med and AEs | | | | | | | | | | | | | | | | | | | | |

Table S.5-1 Schedule of Assessments (continued)

| Day | Days 1, 3, and 5 | | | | | | | | | | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | | |
|---|------------------|--|--|--|--|--|--|--|--|--|---|---|---|---|----|----|----|----|----|----|----|----|--|--|
| Hours | | | | | | | | | | | | | | | | | | | | | | | | |
| Study Procedures | | | | | | | | | | | | | | | | | | | | | | | | |
| Medical history/previous med | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed consent/study procedures | | | | | | | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatitis B and HIV screen | | | | | | | | | | | | | | | | | | | | | | | | |
| Urine drug, urine alcohol screen | | | | | | | | | | | | | | | | | | | | | | | | |
| Urine pregnancy | | | | | | | | | | | | | | | | | | | | | | | | |
| Physical exam | | | | | | | | | | | | | | | | | | | | | | | | |
| Cardiovascular exam | | | | | | | | | | | | | | | | | | | | | | | | |
| D/C ACE, start captopril & Na ⁺ diet | | | | | | | | | | | | | | | | | | | | | | | | |
| D/C captopril, diuretics, ASA, BB | | | | | | | | | | | | | | | | | | | | | | | | |
| Bladder ultrasound (BUS) | | | | | | | | | | | | | | | | | | | | | | | | |
| Admission/discharge | | | | | | | | | | | | | | | | | | | | | | | | |
| Vital signs (HR, BP, temp, weight) | | | | | | | | | | | | | | | | | | | | | | | | |
| BP and HR (supine for 20 min) | | | | | | | | | | | | | | | | | | | | | | | | |
| Serum chemistry | | | | | | | | | | | | | | | | | | | | | | | | |
| Serum chemistry: Na ⁺ , K ⁺ , Cl ⁻ | | | | | | | | | | | | | | | | | | | | | | | | |
| Hematology | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinalysis | | | | | | | | | | | | | | | | | | | | | | | | |
| EKG (12 lead) | | | | | | | | | | | | | | | | | | | | | | | | |
| Lithium carbonate @ 10 PM | | | | | | | | | | | | | | | | | | | | | | | | |
| Administer study medication | | | | | | | | | | | | | | | | | | | | | | | | |
| Subject supine (except for voiding) | | | | | | | | | | | | | | | | | | | | | | | | |
| Insert 3 IV catheters | | | | | | | | | | | | | | | | | | | | | | | | |
| Insert urinary catheter | | | | | | | | | | | | | | | | | | | | | | | | |
| 4 glasses distilled H ₂ O (8 oz/glass) | | | | | | | | | | | | | | | | | | | | | | | | |
| Loading dose insulin/PAH | | | | | | | | | | | | | | | | | | | | | | | | |
| Insulin/PAH infusion | | | | | | | | | | | | | | | | | | | | | | | | |
| Urine aliquots/void bladder | | | | | | | | | | | | | | | | | | | | | | | | |
| Oral distilled H ₂ O replacement (1:1) | | | | | | | | | | | | | | | | | | | | | | | | |
| Insulin/PAH/LC plasma samples | | | | | | | | | | | | | | | | | | | | | | | | |
| Plasma hormones | | | | | | | | | | | | | | | | | | | | | | | | |
| OPC 41061 PK samples | | | | | | | | | | | | | | | | | | | | | | | | |
| Meals | | | | | | | | | | | | | | | | | | | | | | | | |
| Concomitant med and AEs | | | | | | | | | | | | | | | | | | | | | | | | |
| 30 day follow-up phone call | | | | | | | | | | | | | | | | | | | | | | | | |

1. Women of childbearing potential. 2. Admission. 3. If requested by PI. 4. Obtain after blood draw. 5. On day subject takes OPC 41061 only. 6. Day -15 only. 7. Before eating. 8. Before subject stands to void. 9. Days -1, 2, and 4. 10. Day 5 or 6. 11. Prior to dosing. 12. Day 1 and maintain. 13. For K⁺ only. 14. If patient was unable to void for half-hour (same sample, a plasma sample at that interval was not to be obtained). 15. Lithium carbonate sample only on Days -1, 2, and 4. Draw prior to administering dose of lithium carbonate.

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Safety

Safety assessments were completed through the evaluation of adverse events, and scheduled determinations of clinical laboratory, vital signs (blood pressure, heart rate, oral temperature, and weight), 12-Lead ECGs and physical examinations including a cardiovascular exam.

Pharmacokinetic Profiling

Blood samples for the determination of plasma concentrations of OPC-41061 were collected at pre-dose and 1, 2, 3, 4, 6, 8, 12, 16, and 24 h post-dose on Days 1 and 3.

Bioassay

Plasma samples were analyzed for OPC-41061 by a validated HPLC method with UV detection that used an internal standard. The method is linear (calibration standards weighted 1/y) over the range of between 5.00 and 1000 ng/mL OPC-41061 with a mean coefficient of correlation of 0.998. The accuracy of the method for OPC-41061 using QC samples ranges between -4.0 % and 0.9 % and the precision is ≤ 8.6 %. The stability of OPC-41061 in human plasma stored at -20 °C for 1 year and 9 months was confirmed. The impact of exposure to room temperature, freeze/thaw cycles, and light was not investigated. Therefore, the method cannot be considered fully validated.

The measurements were made by _____

b(4)

PK Data Analysis

C_{max}, t_{max}, λ_z and AUC_{0-tlast}, CL/F and V_z/F were determined. C_{max} and t_{max} were taken directly from the plasma concentration time data, λ_z was determined from log linear regressions of at least 3 non-zero concentrations. AUC_{0-tlast} was obtained by the linear trapezoidal rule. Parameters were not determined if the duration of measurable plasma concentrations was not sufficient. Non-compartmental methods were used. The calculations used WinNonlin Pro, Version 3.1 (Pharsight Corporation, Mountain View, CA).

Pharmacodynamic Profiling

Primary and Secondary Efficacy Variables

The primary efficacy variables and the assessment methods are listed below:

Glomerular Filtration Rate (GFR)
Proximal Fractional Reabsorption of Sodium (PFRNa⁺)
Distal Fractional Reabsorption of Sodium (DFRNa⁺)
Effective Renal Plasma Flow (ERPF)
Renal Blood Flow (RBF)
Renal Vascular Resistance (RVR)

The secondary efficacy variables are listed below:

Arginine Vasopressin (AVP)
Plasma Renin Activity (PRA)
Aldosterone
Atrial Natriuretic Peptide (ANP)
Brain Natriuretic Peptide (BNP)
Norepineprine

GFR was estimated by the plasma clearance of inulin. ERPF was estimated by the plasma clearance of PAH and RBF was computed from ERPF/1-Hc. Loading doses of inulin and PAH were administered at -1.5 h and maintenance infusions of 9 h duration were started at -1.0 h. Blood samples for the determination of inulin and PAH

were obtained at -2 and 0 h before administration of OPC-41061 and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, and 9 h after administration of OPC-41061.

Blood samples for the determination of AVP, PRA, aldosterone, ANP, BNP and norepinephrine were collected pre-dose and 2.5 h post dose of OPC-41061. The assay methods used for determining the plasma concentrations of the hormones are not indicated in the report.

Pharmacodynamic/Pharmacokinetic Correlations

Efficacy variables were correlated with AUC_{0-∞}.

Statistical Methods

Sample Size and Power

Sample size calculation for this protocol was based on the summary statistics of GFR (mL/min/1.73 m²) provided by Gottlieb et al.¹⁷ The means of GFR (mL/min/1.73 m²) for placebo and furosemide were respectively 81.5 and 63.4, with standard deviations of 23.5 and 18, and sample sizes of 12 and 11. These statistics were summarized from a crossover study with two sequences: placebo, test drug, furosemide and test drug, placebo, furosemide. No information on period was provided. However, the abstract stated that the p-value of GFR was less than 0.01 for intrasubject comparisons between furosemide and placebo.

In order to calculate sample size for a paired t-test, the standard deviation of GFR for intrasubject differences between furosemide and placebo was derived. To be conservative, the p-value of the intrasubject comparison between furosemide and placebo was assumed to be 0.025 instead of less than 0.01. This was because the 0.875 percentile of t-distribution with 10 degrees of freedom was 2.634, the equation was as follows:

$$(81.5 - 63.4)/(s^2/11)^{1/2} = 2.634$$

Thus, $s = 22.8$, which was an estimate of the standard deviation of the intrasubject difference between furosemide and placebo in GFR. Using an effect size of 18.1 ($= 81.5 - 63.4$) and standard deviation 22.8 to the sample size formula of one sample t-test, $n = 13$ was derived. Thus, 14 subjects were needed to get equal allocation to the two sequences of this crossover study.

Note that the intrasubject comparison between furosemide and placebo was used in the sample size calculation. Thus, the sample size of 14 subjects was for completers who had to finish all three treatment periods (OPC-41061-placebo, placebo-OPC-41061, and furosemide) specified in the protocol.

6.4 Efficacy Analyses

All statistical test procedures for the efficacy analysis were performed two-sided with a significance level of 0.05 unless otherwise specified. Baseline measurements of the efficacy variables were defined as the last measurements prior to dosing on Day 1, Day 3, and Day 5, respectively.

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6.4.1 Primary Efficacy Analysis

The primary efficacy variables were the changes from baseline in absolute values for glomerular filtration rate (GFR), proximal and distal fractional reabsorption of sodium ($PFRNa^+$ and $DFRNa^+$), effective renal plasma flow (ERPF), renal blood flow (RBF), and renal vascular resistance (RVR). Although the protocol stated that the primary time point of efficacy analysis was at 2 hours (when both OPC-41061 and furosemide approximately reached their C_{max}), no specific time point of focus was used in the analysis because measurements of these variables were contingent upon urine volume, which was unreliable due to combined timed-interval collections of less than 50 mL and adjusted start times.

The primary comparison was a by-time point comparison between OPC-41061 and placebo. The secondary comparison was a by-time point comparison between furosemide and placebo. In addition, even though it was not prespecified in the protocol, a by-time point comparison between OPC-41061 and furosemide was also conducted. Statistical significance tests were performed for these comparisons. No adjustment of the p-values was made for multiplicity.

To compare the means of a primary efficacy variable between OPC-41061 and placebo at a time point within a day, a two-sample t-test was applied to intra-subject differences in the variable of the two sequences (sequence OPC-41061, placebo and sequence placebo, OPC-41061). The intra-subject difference in the variable of a subject was defined as the value equal to the subject's observation of the variable from Day 1 minus the subject's observation of the variable from Day 3, at the same time point. All subjects who had observations of the variable at the same time point from Day 1 and Day 3 were included in this comparison. This approach is equivalent to an ANOVA with factors of sequence, subject with sequence, period and treatment for a 2 by 2 crossover study.

In order to validate this comparison, tests of equality of the carryover effects were performed. A two-sample t-test was applied to subjects' total changes from baseline in GFR over Day 1 and Day 3 of the two sequences in this protocol.

To compare the means of the observations in the variable between furosemide and placebo, a one-sample t-test was applied to the pooled (over the 2 sequences) intrasubject differences in the variable between furosemide and placebo by time point. The intra-subject difference of a subject was defined as the value equal to the subject's observation of the variable at a time point on Day 5 (after taking furosemide) minus the subject's observation of the variable at the same time point on Day 1 or Day 3 (after taking placebo). In this test, both period effect and carry-over effect were assumed to be zero. All subjects who finished three days of treatment were included in this comparison, if they had observations of the variable at the same time point within a day.

Statistical procedures for comparisons between OPC-41061 and furosemide were identical to the procedures for comparison between placebo and furosemide mentioned above.

Due to the nature of the analysis, i.e., the use of intrasubject difference in the analysis, subjects who did not have both observations of the two compared treatments at a time point were excluded from the analysis at the time point.

The analyses on $PFRNa^+$, $DFRNa^+$, ERPF, RBF, and RVR were similar to the analysis on GFR. Sample size was calculated only for GFR; therefore, statistical significance in comparisons between furosemide and placebo may not have been achieved for these primary efficacy variables. However, interpretations of the statistical procedure were to be carried out similarly.

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excretion rate. Thus derivations of these parameters are all dependent on the collection of urine volume.

In addition, all plasma concentrations of a substance that had greater than $\pm 50\%$ difference compared with their observations at adjacent time points were deleted. Also, negative values of PFRNa^+ and DFRNa^+ were excluded from the analysis.

6.4.2 Secondary Efficacy Analysis

The secondary efficacy variables in this protocol were arginine vasopressin (AVP), plasma renin activity (PRA), aldosterone (ALDO), atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and norepinephrine (NE). The statistical methods described in Section 6.4.1 were also applied to the analysis of the secondary efficacy variables.

6.4.3 Additional Efficacy Analyses

Additional efficacy analyses were conducted on the averages of GFR, ERPF, RBF, RVI, PFRNa^+ and DFRNa^+ over this 9-hour study using the analysis described in Section 6.4.1. These averages were derived from observations of these variables from each time interval within a day by using the lengths of the actual time intervals as weights to the observations.

Longitudinal analysis was also conducted on GFR, ERPF, RBF, MAP, RVR, PFRNa^+ and DFRNa^+ , clearance of Na^+ , clearance of K^+ , urine excretion rate, sodium excretion rate and potassium excretion rate. Negative values in PFRNa^+ and DFRNa^+ were converted to zero in this analysis. Mixed model with factors sequence, subject within sequence, treatment and period was used to compare OPC-41061 and placebo. Observations at different time intervals within a day were treated as repeated measures with autoregression(1) correlation structure. Comparisons between placebo and furosemide and OPC-41061 and furosemide were also conducted with the same autoregression(1) correlation structure, except factors used in the mixed model were subject and treatment only. Assumptions underlying this analysis were that observation of a variable on Day 1, Day 3, and Day 5 were independent, observations of a variable within a day had an autoregression(1) correlation structure, and observations of a variable within a day at time intervals were missing randomly.

The primary efficacy variables (GFR, PFRNa^+ , DFRNa^+ , ERPF, RBF and RVR) were determined by longitudinal analysis and correlated with $\text{AUC}_{0-\infty}$ for each individual.

RESULTS

Thirteen of the 14 enrolled subjects terminated the study per protocol. One subject withdrew consent in period 3 as shown in the below table:

| Subjects | OPC-41061/Placebo n | Placebo/OPC-41061 n | Total n |
|------------------------------------|------------------------|------------------------|------------|
| Randomized | 7 | 7 | 14 |
| Treated in Period 1 | 7 | 7 | 14 |
| Treated in Period 2 | 7 | 7 | 14 |
| Treated in Period 3 | 6 ^a | 7 | 13 |
| Completed ^b | 6 | 7 | 13 |
| Discontinued | 1 | 0 | 1 |
| Withdrew consent | 1 | 0 | 1 |
| Analyzed for efficacy ^c | 7 | 7 | 14 |
| Analyzed for safety ^d | 7 | 7 | 14 |

^a Subject 013, who discontinued on January 12, 2002, withdrew consent.

^b Subjects who completed corresponding period of the study.

^c Subjects who completed the first two study periods.

^d Subjects who received at least one dose of study medication.

Source: CST-1 and CST-2; Appendix IV-2.2.

The demographics and the baseline characteristics of the participating subjects are shown in the next 2 tables:

| | OPC-41061/Placebo N=7 | Placebo/OPC-41061 N=7 | Total N=14 |
|-------------------------------|--------------------------|--------------------------|---------------|
| Age (years) | | | |
| Mean (SD) | 58 (10.0) | 54 (7.0) | 56 (8.0) |
| Range | 45-70 | 46-65 | 45-70 |
| Gender, n (%) | | | |
| Male | 5 (71.4) | 5 (71.4) | 10 (71.4) |
| Female | 2 (28.6) | 2 (28.6) | 4 (28.6) |
| Race, n (%) | | | |
| Caucasian | 2 (28.6) | 5 (71.4) | 7 (50.0) |
| Black | 5 (71.4) | 2 (28.6) | 7 (50.0) |
| Smoking Status, n (%) | | | |
| Never smoked | 1 (14.3) | 2 (28.6) | 3 (21.4) |
| Smoker | 2 (28.6) | 2 (28.6) | 4 (28.6) |
| Ex-smoker | 4 (57.1) | 3 (42.9) | 7 (50.0) |
| Drinking Status, n (%) | | | |
| Drinker | 4 (57.1) | 4 (57.1) | 8 (57.1) |
| Ex-drinker | 3 (42.9) | 3 (42.9) | 6 (42.9) |

Source: CST- 3.1; Appendixes IV-3.1.1 through IV-3.1.2.

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| Table 8.2-2 Baseline Medical Characteristics | | | |
|--|--------------------------|--------------------------|---------------|
| Characteristic | OPC-41061/Placebo N=7 | Placebo/OPC-41061 N=7 | Total N=14 |
| Hypertension | 6 (86.0) | 6 (86.0) | 12 (86.0) |
| Hypertension treated | 6 (86.0) | 6 (86.0) | 12 (86.0) |
| Arrhythmias | 3 (43.0) | 5 (71.0) | 8 (57.0) |
| Atrial | 2 (29.0) | 2 (29.0) | 4 (29.0) |
| Ventricular | 1 (14.0) | 3 (43.0) | 4 (29.0) |
| Diabetes mellitus | 1 (14.0) | 5 (71.0) | 6 (43.0) |
| Insulin treated | 1 (14.0) | 1 (14.0) | 2 (14.0) |
| Hypercholesterolemia | 2 (29.0) | 2 (29.0) | 4 (29.0) |
| Hypercholesterolemia treated | 1 (14.0) | 2 (29.0) | 3 (21.0) |
| Cerebrovascular disease | 2 (29.0) | 0 (0.0) | 2 (14.0) |
| Stroke | 1 (14.0) | 0 (0.0) | 1 (7.0) |
| TIA | 1 (14.0) | 0 (0.0) | 1 (7.0) |
| Family history of CHD | 1 (14.0) | 2 (29.0) | 3 (21.0) |
| Peripheral vascular disease | 2 (29.0) | 2 (29.0) | 4 (29.0) |
| Severe COPD | 0 (0.0) | 1 (14.0) | 1 (7.0) |
| Valvular disease | 2 (29.0) | 0 (0.0) | 2 (14.0) |
| Mitral | 2 (29.0) | 0 (0.0) | 2 (14.0) |
| Aortic | 1 (14.0) | 0 (0.0) | 1 (7.0) |
| Previous CABG | 0 (0.0) | 2 (29.0) | 2 (14.0) |
| Previous PTCA | 1 (14.0) | 0 (0.0) | 1 (7.0) |
| Previous MI | 2 (29.0) | 3 (43.0) | 5 (36.0) |
| Unknown | 2 (29.0) | 3 (43.0) | 5 (36.0) |
| Previous angina | 3 (43.0) | 4 (57.0) | 7 (50.0) |
| At rest | 1 (14.0) | 1 (14.0) | 2 (14.0) |
| Exertional | 2 (29.0) | 3 (43.0) | 5 (36.0) |
| BP (%) | | | |
| Mean (SD) | 34 (4) | 33 (3) | 34 (3) |
| Range | 30-40 | 28-38 | 28-40 |

Source: CVT 3.2, Appendix IV.3.2

Safety

No serious adverse events or death occurred and no subject discontinued because of an adverse event.

Pharmacokinetics

Linear plots of the median and individual plasma concentrations of OPC-41061 in the subjects are shown in the below figures and the mean PK parameters are listed in the below table:

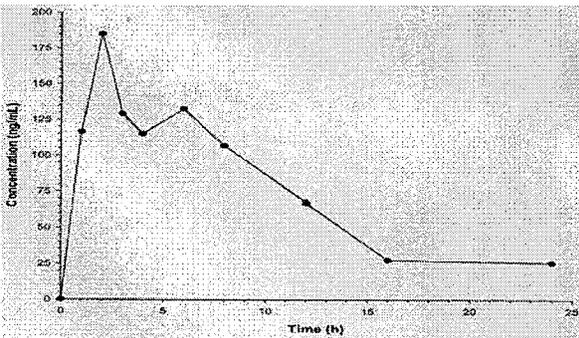
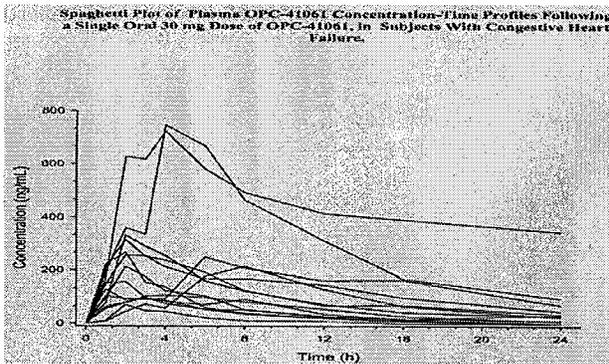


Figure 10.2.3-1 Median Plasma Concentration-time Profile Following a Single Oral 30 mg Dose of OPC-41061

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| Parameter | N | Mean | SD |
|-------------------------------|----|------|-----------|
| C_{max} (ng/mL) | 14 | 277 | 210 |
| t_{max} (h) ^a | 14 | 2.00 | 1.00-8.00 |
| AUC ₀₋₂₄ (ng·h/mL) | 14 | 2758 | 2833 |
| AUC _{0-∞} (ng·h/mL) | 11 | 5143 | 7502 |
| $t_{1/2}$ (h) | 11 | 9.4 | 8.2 |
| CL/F (mL/min/kg) | 11 | 2.66 | 2.04 |
| V_d/F (L/kg) | 11 | 1.41 | 0.68 |

^a Median and range presented for t_{max} .
Source: ST-3.

The individual plasma concentration profiles show significant inter-subject variation in peak and average exposure. Plasma concentrations were measured up to 24 h after administration. The sponsor used three non-zero plasma concentrations in the 12-16 h post-dose interval to estimate λ_z . As discussed in detail in the review of study report 156-98-202, this interval is not long enough to provide reliable estimates for λ_z and derived parameters and thus the above listed parameters with the exception of C_{max} and t_{max} are not reliable. Median C_{max} is 231 (range 70-746) ng/mL and median t_{max} is 2.0 (range 1.0-8.0) h, respectively, suggesting significant inter-subject variation of OPC-41061 in the subjects with mild to moderate congestive heart failure.

Pharmacodynamics

Impact of OPC-41061 Relative to Placebo

The below table summarizes the impact of a 30 mg treatment with OPC-41061 on the primary renal function parameters relative to placebo:

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| OPC-41061 and Placebo Treatment Comparisons ^a for the Renal Function Parameters | | | | | |
|--|-----------------|-----------------|-----------------|-----------------------|----------------------|
| | OPC-41061 | Placebo | | | |
| | LS Mean (SD) | LS Mean (SD) | Delta (SD) | % Change ^c | P-value ^d |
| GFR | 95.59 (49.35) | 94.22 (55.01) | 1.37 (69.19) | 1.45 | 0.7092 |
| ERPF | 315.38 (345.85) | 272.82 (269.78) | 42.56 (392.29) | 9.00 | 0.0437 |
| RBF | 854.96 (579.59) | 780.34 (461.71) | 74.62 (661.77) | 9.56 | 0.0362 |
| PFRNa ⁺ | 76.14 (72.67) | 76.76 (15.79) | -0.62 (73.84) | -0.81 | 0.8797 |
| DRFNa ⁺ | 93.15 (11.03) | 94.67 (6.75) | -1.53 (12.33) | -1.61 | 0.1404 |
| RVR ^b | 17.15 (13.89) | 18.69 (13.68) | -1.54 | -8.24 | 0.2382 ^e |
| MAP | 100.45 (14.30) | 100.25 (12.66) | 0.21 (18.67) | 0.20 | 0.8838 |
| Clearance of Na ⁺ | 0.88 (1.54) | 0.65 (0.63) | 0.22 (1.62) | 33.38 | 0.0880 |
| Clearance of K ⁺ | 11.86 (9.05) | 11.73 (11.71) | 0.14 (14.36) | 1.11 | 0.8967 |
| Urine Excretion Rate | 610.93 (720.14) | 358.70 (319.05) | 252.24 (778.25) | 33.19 | 0.0001 |
| Na ⁺ Excretion Rate | 6.82 (11.88) | 5.54 (5.22) | 1.28 (12.64) | 23.10 | 0.0705 |
| K ⁺ Excretion Rate | 3.33 (2.99) | 3.24 (3.39) | 0.09 (4.39) | 2.78 | 0.6975 |

^a Comparisons between OPC-41061 and placebo were made using sequence, subject within sequence, period, treatment as fixed effect, and time points within a day with autoregression(1) variance structure.
^b Based on the LS means of the daily averages. Daily average of RVR = 100*(daily average weighted average MAP)/(daily weighted average RBF).
^c Percent change = delta/LS mean of placebo*100.
^d Performed two-sided with a significance level of 0.05.
^e P-values were derived from ANOVA with factors sequence, subject (sequence), treatment, and period for comparison of OPC-41061 and placebo.
 Source: CST-5.7 and CST-5.8; Appendix IV-9.1, 9.2, 9.4, 10.1, and 14.

OPC-41061 increases statistically significantly ERPF, RBF and urine excretion rate. The respective mean increase in ERPF, RBF and urine excretion rate is 43 mL/min (9.0%), 75 mL/min (9.6%) and 2.5 mL/min (33%). OPC-41061 has no effect on PFRNa⁺, DRFNa⁺, RVR, mean arterial blood pressure (MAP), Na⁺ clearance, K⁺ clearance, Na⁺ excretion rate and K⁺ excretion rate. Also, the change from baseline 2.5 h after dosing is not statistically significant for any of the secondary efficacy parameters including AVP, aldosterone, PRA, ANP, BNP and norepinephrine.

Impact of OPC-41061 Relative to Furosemide

Statistically significant differences between the effects of OPC-41061 and furosemide are seen regarding ERPF, RBF, DRFNa⁺, Na⁺ clearance, K⁺ clearance, Na⁺ excretion and K⁺ excretion. OPC-41061 increases and furosemide decreases ERPF and RBF. Furosemide increases DRF Na⁺, Na⁺ clearance, K⁺ clearance, Na⁺ excretion and K⁺ excretion, whereas OPC-41061 has no impact. There is no statistically significant difference between the impact of OPC-41061 and furosemide on GFR, PFRNa⁺, MAP and urine excretion rate.

The below tables summarize the results on the renal function parameters for which the impact of OPC-41061 and furosemide is different:

ERPF

The comparative effects of OPC-41061, furosemide and placebo on ERPF are shown in the below table:

Table 9.3.2-1 Treatment Comparisons on Absolute Values of Effective Renal Plasma Flow (mL/min) Derived from Longitudinal Analysis

| Contrast | OPC-41061 | Placebo | Furosemide | | | |
|-----------------------|-----------------|-----------------|-----------------|----------------|---------------|----------------------|
| | LS Mean (SD) | LS Mean (SD) | LS Mean (SD) | Delta (SD) | 95% CI | P-value ^c |
| OPC vs Placebo | 515.38 (345.85) | 472.82 (269.78) | | 42.56 (392.24) | 1.21, 83.92 | 0.0437 |
| Placebo vs Furosemide | | 467.22 (258.04) | 432.55 (289.53) | 34.68 (325.74) | 0.03, 69.32 | 0.0498 |
| OPC vs Furosemide | 547.08 (348.43) | | 486.90 (333.22) | 60.18 (387.48) | 19.50, 100.85 | 0.0039 |

^a Comparisons between OPC-41061 and placebo were made using sequence, subject within sequence, period, treatment as fixed effect, and time points within a day with autoregression(1) variance structure.
^b Comparisons between OPC-41061/placebo and furosemide were made using subject, treatment as fixed effect, and time point within a day with autoregression(1) variance structure.
^c Performed two-sided with a significance level of 0.05.
 Source: CST-5.7; Appendices IV-9.1, 9.2, 9.4, 10.1, and 14.

OPC-41061 increases mean ERPF by 43 mL/min (9.0%) and furosemide decreases ERPF by 35 mL/min (-7.5%) relative to the respective placebo treatments. Both changes are statistically significant. The difference in the effect of ERPF between OPC-41061 and furosemide (60 mL/min) is statistically significant.

RBF

The comparative effects of the OPC-41061, furosemide and placebo treatments are shown in the next table:

Table 9.3.3-1 Treatment Comparisons on Absolute Values of Renal Blood Flow (mL/min) Derived from Longitudinal Analysis

| Contrast | OPC-41061 | Placebo | Furosemide | | | |
|-----------------------|-----------------|-----------------|-----------------|-----------------|---------------|----------------------|
| | LS Mean (SD) | LS Mean (SD) | LS Mean (SD) | Delta (SD) | 95% CI | P-value ^c |
| OPC vs Placebo | 854.96 (579.59) | 780.34 (461.71) | | 74.62 (661.77) | 4.84, 144.39 | 0.0362 |
| Placebo vs Furosemide | | 771.94 (442.83) | 674.61 (479.26) | 97.33 (544.04) | 39.47, 155.20 | 0.0010 |
| OPC vs Furosemide | 911.41 (581.80) | | 766.37 (554.36) | 145.05 (645.33) | 77.30, 212.79 | <0.0001 |

^a Comparisons between OPC-41061 and placebo were made using sequence, subject within sequence, period, treatment as fixed effect, and time points within a day with autoregression(1) variance structure.
^b Comparisons between OPC-41061/placebo and furosemide were made using subject, treatment as fixed effect, and time point within a day with autoregression(1) variance structure.
^c Performed two-sided with a significance level of 0.05.
 Source: CST-5.7; Appendices IV-9.1, 9.2, 9.4, 10.1, and 14.

OPC-41061 increases mean RBF by 75 mL/min (9.6%) and furosemide decreases RBF by 97 mL/min (-13%) relative to the respective placebo treatments. Both changes are statistically significant. The difference in RBF between OPC-41061 and furosemide (145 mL/min) is statistically significant.

The comparative effects of OPC-41061 and furosemide on DFRNa⁺ are shown in the next table:

Table 9.3.5-1 Treatment Comparisons on Absolute Values of Distal Fractional Reabsorption of Sodium (%) Derived from Longitudinal Analysis

| Contrast | OPC-41061 | Placebo | Furosemide | | | |
|------------------------------------|---------------|--------------|---------------|---------------|-------------|----------------------|
| | LS Mean (SD) | LS Mean (SD) | LS Mean (SD) | Delta (SD) | 95% CI | P-value ^c |
| OPC vs Placebo ^a | 93.15 (11.03) | 94.67 (6.75) | | -1.53 (12.33) | -3.57, 0.51 | 0.1304 |
| Placebo vs Furosemide ^b | | 94.56 (7.56) | 83.53 (46.08) | 11.03 (46.56) | 3.28, 18.78 | 0.0056 |
| OPC vs Furosemide ^b | 93.55 (12.11) | | 83.31 (52.76) | 10.23 (53.92) | 1.41, 19.05 | 0.0233 |

^a Comparisons between OPC-41061 and placebo were made using sequence, subject within sequence, period, treatment as fixed effect, and time points within a day with autoregression(1) variance structure.
^b Comparisons between OPC-41061/placebo and furosemide were made using subject, treatment as fixed effect, and time point within a day with autoregression(1) variance structure.
^c Performed two-sided with a significance level of 0.05.
Source: CST-5.7; Appendices IV-9.1, 9.2, 9.4, 10.1, and 14.

OPC-41061 decreases mean DFRNa⁺ not significantly by 1.5% and furosemide decreases DFRNa⁺ significantly by 11%. The difference in DFRNa⁺ between OPC-41061 and furosemide (10%) is statistically significant.

The comparative effects of OPC-41061 and furosemide on Na⁺ clearance are shown in the next table:

Table 9.3.7-2 Treatment Comparisons on Absolute Values of the Clearance of Na⁺ (mL/min) Derived from Longitudinal Analysis

| Contrast | OPC-41061 | Placebo | Furosemide | | | |
|------------------------------------|--------------|--------------|--------------|--------------|--------------|----------------------|
| | LS Mean (SD) | LS Mean (SD) | LS Mean (SD) | Delta (SD) | 95% CI | P-value ^c |
| OPC vs Placebo ^a | 0.88 (1.54) | 0.65 (0.63) | | 0.22 (1.62) | -0.03, 0.48 | 0.0880 |
| Placebo vs Furosemide ^b | | 0.65 (0.64) | 2.38 (6.99) | -1.73 (7.02) | -2.85, -0.61 | 0.0027 |
| OPC vs Furosemide ^b | 0.82 (1.68) | | 2.39 (7.89) | -1.56, 8.06 | -2.82, -0.30 | 0.0156 |

^a Comparisons between OPC-41061 and placebo were made using sequence, subject within sequence, period, treatment as fixed effect, and time points within a day with autoregression(1) variance structure.
^b Comparisons between OPC-41061/placebo and furosemide were made using subject, treatment as fixed effect, and time point within a day with autoregression(1) variance structure.
^c Performed two-sided with a significance level of 0.05.
Source: CST-5.7; Appendices IV-9.1, 9.2, 9.4, 10.1, and 14.

OPC-41061 increases the mean Na⁺ clearance not significantly by 0.22 mL/min, whereas furosemide increases Na⁺ clearance significantly by 1.7 mL/min. The difference in DFRNa⁺ between OPC-41061 and furosemide (1.56 mL/min) is statistically significant.

The comparative effects of OPC-41061 and furosemide on K⁺ clearance are shown in the next table:

Table 9.3.7-3 Treatment Comparisons on Absolute Values of the Clearance of K⁺ (mL/min) Derived from Longitudinal Analysis

| Contrast | OPC-41061 | Placebo | Furosemide | | | |
|------------------------------------|--------------|---------------|---------------|---------------|---------------|----------------------|
| | LS Mean (SD) | LS Mean (SD) | LS Mean (SD) | Delta (SD) | 95% CI | P-value ^c |
| OPC vs Placebo ^a | 11.86 (9.05) | 11.73 (11.71) | | 0.14 (14.36) | -1.92, 2.20 | 0.8967 |
| Placebo vs Furosemide ^b | | 12.28 (11.39) | 17.25 (31.84) | -4.97 (33.36) | -9.88, -0.07 | 0.0470 |
| OPC vs Furosemide ^b | 11.92 (9.13) | | 17.31 (36.32) | -5.39 (37.40) | -10.73, -0.05 | 0.0479 |

^a Comparisons between OPC-41061 and placebo were made using sequence, subject within sequence, period, treatment as fixed effect, and time points within a day with autoregression(1) variance structure.
^b Comparisons between OPC-41061/placebo and furosemide were made using subject, treatment as fixed effect, and time point within a day with autoregression(1) variance structure.
^c Performed two-sided with a significance level of 0.05.
Source: CST- 5.7; Appendices IV-9.1, 9.2, 9.4, 10.1, and 14.

OPC-41061 does not impact mean K⁺ clearance whereas furosemide increases K⁺ clearance significantly by 4.97 mL/min. The difference between OPC-41061 and furosemide in K⁺ clearance is statistically significant.

The comparative effects of OPC-41061 and furosemide on Na⁺ excretion rate are shown in the next table:

Table 9.3.7-5 Treatment Comparisons on Absolute Values of Na⁺ Excretion Rate (mmol/h) Derived from Longitudinal Analysis

| Contrast | OPC-41061 | Placebo | Furosemide | | | |
|------------------------------------|--------------|--------------|---------------|---------------|---------------|----------------------|
| | LS Mean (SD) | LS Mean (SD) | LS Mean (SD) | Delta (SD) | 95% CI | P-value ^c |
| OPC vs Placebo ^a | 6.82 (11.88) | 5.54 (5.22) | | 1.28 (12.64) | -0.11, 2.68 | 0.0705 |
| Placebo vs Furosemide ^b | | 5.56 (5.30) | 17.43 (57.60) | -11.88, 57.78 | -18.28, -5.47 | 0.0003 |
| OPC vs Furosemide ^b | 6.64 (12.79) | | 17.52 (63.05) | -10.88, 64.27 | -17.84, -3.92 | 0.0023 |

^a Comparisons between OPC-41061 and placebo were made using sequence, subject within sequence, period, treatment as fixed effect, and time points within a day with autoregression(1) variance structure.
^b Comparisons between OPC-41061/placebo and furosemide were made using subject, treatment as fixed effect, and time point within a day with autoregression(1) variance structure.
^c Performed two-sided with a significance level of 0.05.
Source: CST- 5.7; Appendices IV-9.1, 9.2, 9.4, 10.1, and 14.

Compared to placebo OPC-41061 does not impact Na⁺ excretion significantly, whereas furosemide increases Na⁺ excretion significantly by 17.43 mM/h. The difference between OPC-41061 and furosemide (10.88mM/h) is statistically significant.

The comparative effects of OPC-41061 and furosemide on the K⁺ excretion rate are shown in the next table:

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Table 9.3.7-6 Treatment Comparisons on Absolute Values of K⁺ Excretion Rate Derived from Longitudinal Analysis

| Contrast | OPC-41061 | Placebo | Furosemide | | | |
|------------------------------------|--------------|--------------|--------------|--------------|--------------|----------------------|
| | LS Mean (SD) | LS Mean (SD) | LS Mean (SD) | Delta (SD) | 95% CI | P-value ^c |
| OPC vs Placebo ^a | 3.33 (2.99) | 3.24 (3.39) | | 0.09 (4.39) | -0.35, 0.52 | 0.6975 |
| Placebo vs Furosemide ^b | | 3.32 (3.47) | 4.39 (7.30) | -1.07 (7.90) | -1.88, -0.27 | 0.0093 |
| OPC vs Furosemide ^b | 3.36 (3.01) | | 4.45 (7.47) | -1.09 (8.03) | -1.88, -0.30 | 0.0071 |

^a Comparisons between OPC-41061 and placebo were made using sequence, subject within sequence, period, treatment as fixed effect, and time points within a day with autoregression(1) variance structure.
^b Comparisons between OPC-41061/placebo and furosemide were made using subject, treatment as fixed effect, and time point within a day with autoregression(1) variance structure.
^c Performed two-sided with a significance level of 0.05.
Source: CST-5.7; Appendices IV-9.1, 9.2, 9.4, 10.1, and 14.

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Compared to placebo OPC-41061 increases mean K⁺ excretion not significantly by 0.09 mM/h, whereas furosemide increases K⁺ excretion significantly by 1.07 mM/h. The difference between OPC-41061 and furosemide (1.09) is statistically significant.

Conclusions

PK

C_{max} and t_{max} show important inter-subject variation.

PD

A single dose of 30 mg OPC-41061 increases statistically significantly ERPF, RBF and urine excretion rate. OPC-41061 has no effect on PFRNa⁺, DRFNa⁺, RVR, MAP, Na⁺ clearance, K⁺ clearance, Na⁺ excretion rate and K⁺ excretion rate. Also, the change from baseline 2.5 h after dosing is not statistically significant for any of the secondary efficacy parameters including AVP, aldosterone, PRA, ANP, BNP and norepinephrine suggesting no early impact of OPC-41061 on RAAS.

Safety

No serious adverse events or death occurred and no subject discontinued because of an adverse event.

Comments

1. The one day washout used in the present study may not be long enough to prevent carry-over effects.
2. Contrary to the statement made in the method section that parameters will be only be determined if the plasma concentrations of OPC-41061 are measurable during a sufficiently long period, the sponsor estimated λ_z from three non-zero plasma concentrations in intervals ranging from 8-24 h and 12-24 h which are clearly shorter than 3 times t_{1/2z} (estimated to be about 9 h). Hence λ_z and derived parameters including t_{1/2z}, AUC_{0-∞}, CL/F and Vz/F are likely biased.
3. The methods used for assessing the efficacy variables are not described in detail. Thus their adequacy cannot be judged. The assay methods used for inulin and PAH are not described and the plasma concentrations not reported.

4. The method section of the report states that correlations between primary efficacy variables and $AUC_{0-\infty}$ will be investigated. The results section of the report does not contain the results of these attempts.
5. The means of the efficacy parameters are reported to two digits after the comma. It is unclear how this precision is justified.
6. In Table 9.3.7-6 the unit for K^+ excretion rate should be added

Study Report No. 156-97-251: "Multi-center, Randomized, Double-Blind, Placebo Controlled, Oral, Dose-Ranging, Efficacy, Safety, and Pharmacokinetic Study of OPC-41061 Tablets in Patients with Congestive Heart Failure with Extracellular Volume Expansion"

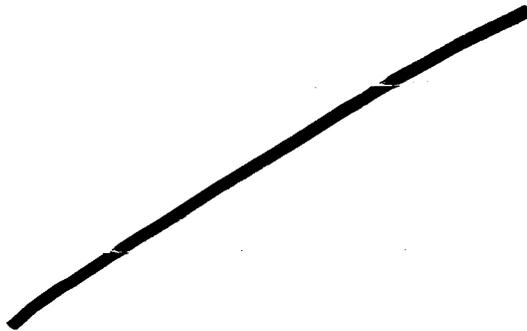
Objectives

To assess the efficacy, safety and pharmacokinetic characteristics of daily doses of up to six dosage levels of OPC-41061 in patients with congestive heart failure with extra-cellular volume expansion

Investigators and Study Sites

The eleven participating Investigator and Sites were the following:

.....



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Investigational Drugs and Formulations

OPC-41061 5 mg tablets (Lot No. 5L70A005) and 15 mg (Lot Nos. 98D82A015A, 5L70A015) and matching placebo tablets (Lot. Nos. 97B93P000 and 5L80P) were provided by the sponsor.

Design

This was a randomized, double-blind, placebo-controlled, dose ranging study in patients with congestive heart failure with extracellular volume expansion. The study consisted of a one-day baseline period (Day 0), a 13 day treatment period with study drug (patients were hospitalized during the first 3 days), a termination visit, and one follow-up evaluation on study Days 20 to 23. Six groups of patients were randomized on Day 1 in the following order: 10 mg, 15 mg, 30 mg, 60 mg, 90 mg, and 120 mg. The daily dose of 10 mg was administered as two 5 mg tablets, and the daily doses of 15, 30, 60, 90 and 120 mg were administered as one, two, four, six, and eight 15 mg tablets, respectively. In each treatment group 6 patients received OPC-41061 and 3 patients placebo, with the exception of the 10 mg dose group (5 OPC-41061 patients and 4 placebo patients) and the 120 mg dose group (7 OPC-41061 patients and 3 placebo patients). The patients returned to the clinic on Days 7, 10, 13, and 14. On Day 13 the subjects could volunteer for an extra-day of hospitalization so that additional blood and urine samples could be obtained for assessing the PK of OPC-41061.

_____ variables include urine osmolality, urine volume and urine sodium excretion. The safety outcome variables include adverse experiences, vital signs, ECGs and safety laboratory tests. The pharmacokinetics variables include measures of exposure including C_{max} and AUC.

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After patients in Groups 1, 2, 3, 4 or 5 had completed the follow-up visit on Day 20-23, the respective results after un-blinding were to be examined by the Sponsor. A decision was then to be made in consultation with the Investigator to proceed to the next dose. Individual patient dosing was to continue on Days 2 to 13, unless one of the following events occurred, at which time an assessment by the Investigator would be made regarding continuing the patient in the study:

At any time after dosing, the patient's plasma sodium ≥ 146 mEq/L

At any time after dosing, the patients plasma potassium ≥ 6 mEq/L

During the study patients were asked to refrain from ingesting food from 2400 the day before until 4 h post dose (1200) on Days 0-4, and until 2 h post-dose (1000) on all other days. The patients were required to remain on whatever oral diuretic they were on before entering the study. The diuretic dosing regimen was not to be changed in any other way. No new medications were to be added to the patients' treatment unless medically necessary. On Days 0-3 patients were given meals specified by a dietician to allow accurate estimation of the amount of fluid and sodium ingested. The dietary sodium was determined by the investigator, and remained relatively constant throughout the study. A standard 2 g/day was recommended unless a more restricted sodium diet was required. Fluid intake on Study Days 0-3 was recorded in intervals of 0800- 1200, 1200- 1600, 1600-2000, and 2000-0800. Fluid intake was also measured and recorded on patient diary cards during the outpatient period on Study Days 4-14. Fluid intake was not allowed for 1 h prior to the 0700 measurement of plasma sodium and prior to all 23 h post-dose measurements.

Patients were allowed to continue their medications (prescription and over-the counter) during the study except for NSAIDs or aspirin at a dose > 700 mg/day, ketoconazole, troleandomycin, and miconazole. Also, grapefruit containing products were prohibited.

Rationale for the Use of V₂ Antagonists

Fluid retention and extra-cellular volume expansion is a frequent complication of congestive heart failure causing morbidity and mortality. Standard therapy of extra-cellular volume expansion uses conventional diuretics which may cause electrolyte imbalance including hyponatremia inducing stupor, coma and death and hypokalemia inducing cardiac arrhythmias. Removal of excess water by V₂ receptor antagonists in volume expanded states could reduce the extra-cellular volume. Even though two thirds of water removed by V₂ antagonists would expected to be of intracellular origin, a reduction of the extra-cellular volume could help improve venous compliance, decrease systemic and pulmonary arterial resistance and thus ameliorate myocardial function. Addition of a V₂ antagonist may also allow reduction of the dose of conventional diuretics.

Rationale for the Dose Range of OPC-41061 Tested

The safety of OPC-41061 administered in a dose of 60 mg qd over a period of 28 days in healthy volunteers was demonstrated in Phase I studies.

The inclusion and exclusion criteria for the enrolled patients are listed in the below tables:

Table 4.1.1 INCLUSION CRITERIA

| | |
|----|---|
| 1. | Age greater than or equal to 18 years. |
| 2. | History of chronic congestive heart failure and symptoms classified as NYHA class I-III for at least 30 days prior to screening on Day 0. |
| 3. | In the judgment of the Investigator, the patient had extracellular volume expansion. |
| 4. | Patient had been on oral diuretic therapy at a controlled dose for at least 7 days with an inadequate reduction in volume load. |
| 5. | Current hepatojugular reflux, jugular venous distention, rales, or peripheral edema (pitting). |

Table 5.2.2-1 Exclusion Criteria

| | |
|-----|--|
| 1. | Clinically significant abnormality in past medical history or at the screening physical examination that in the investigator's or sponsor's opinion may place the volunteer at risk or interfere with outcome variables of the study including absorption, distribution, metabolism, and excretion of drug. This includes, but is not limited to, concurrent or history of cardiac, hepatic, renal, neurologic, gastrointestinal, respiratory, hematologic, and immunologic disease, or alcohol or drug abuse. |
| 2. | Current use of any recreational drugs or a history of drug addiction within one year. |
| 3. | History of alcoholism or of moderate (> or = to 24 oz of beer, 10 oz of wine, or 3 oz of distilled spirits) daily alcohol use, or use of alcohol within 72 hours of admission to the study unit and for the duration of the study. |
| 4. | Positive drug/alcohol test at screening. |
| 5. | Use of cranberry-containing food or drinks, grapefruit or grapefruit juice products, and Seville oranges within 72 hours of admission to the study unit and for the duration of the study. |
| 6. | History of serious mental disorders. |
| 7. | Any history of significant bleeding or hemorrhagic tendencies. |
| 8. | Volunteers having taken an investigational drug within the four weeks which precede study entry. |
| 9. | A history of difficulty in donating blood. |
| 10. | The donation of blood or plasma within 30 days prior to or during the study. |
| 11. | History of or current hepatitis or carriers of hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (anti-HCV), or HIV antibodies. |
| 12. | History of any significant drug allergy. |
| 13. | Use of any drug known (including codeine) to stimulate or inhibit drug metabolism within 30 days of dosing. |
| 14. | Use of any prescription (including hormonal contraceptives), over-the-counter, or herbal medication within 14 days prior to dosing and during the study; antibiotics within 30 days prior to dosing and during the study. Acceptance must be discussed with sponsor on a case-by-case basis and reasons documented. |
| 15. | Pregnant or lactating women. |
| 16. | Volunteers who have supine blood pressure, after resting for > or = to 3 minutes, higher than 150/90 mm Hg or lower than 100/50 mm Hg. |
| 17. | Volunteers who have a supine pulse, after resting for > or = to 3 minutes, outside the range of 40-90 beats/minute. |
| 18. | Volunteers who have participated in any OPC-41061 clinical trial. |
| 19. | History of AIDS. |
| 20. | Any subject who, in the opinion of the sponsor or the investigator, should not participate in the study. |

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The scheduled study activities are shown in the below scheme:

TABLE 4.3-1 SCHEDULE OF ASSESSMENTS

| Procedure | Baseline Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Days 7, 10, 13 | Day 13 | Follow-Up Day 20-23 |
|-----------------------------------|----------------|-------|-------|-------|-------|----------------|--------|---------------------|
| Informed Consent | X | | | | | | | |
| History | X | | | | | | | |
| Physical Examination | X | | | | | | X | X |
| Screen Pregnancy | X | | | | | | | |
| Vital Signs (Supine and Standing) | X | X | X | X | X | X | X | X |
| Temperature | X | X | X | X | X | X | X | X |
| Weight | X | X | X | X | X | X | X | X |
| Concomitant medications | | | | | | | | |
| Adverse Experiences | | | | | | | | |
| Administration of Diuretics | X | X | X | X | X | X | | |
| Previous Medications | X | | | | | | | |
| Plasma Sodium and Potassium | X | X | X | X | X | X | X | X |
| Urine Osmolality | X | X | X | X | X | X | | |
| Urine Sodium | X | X | X | X | X | X | X | X |
| Fluid Intake/Output Record | X | X | X | X | X | X | | |
| Dietary/ANZ Intake Record | X | X | X | X | X | X | | |
| Safety Laboratory Tests | X | | | | X | X | X | X |
| AVP measurement | X | X | | | | X | | |
| ET and apt | X | | | | | X | X | |
| 12-Lead ECG | X | X | X | X | X | X | X | X |
| OPC-41061 PK Urine samples | | X | | | | X | X | |
| OPC-41061 PK Plasma Samples | | X | X | X | X | X | X | |
| Study Drug Dosing | X | X | X | X | X | X | | |

These measures were only done on Day 7.
Adverse experiences were recorded on an ongoing basis following check-in on Day 0.
Concomitant medications were recorded on an ongoing basis.
Fluid output record on Study Days 0 through 3 only.
AVP measurement was to be done on Day 13 (2 hours post-dose).

Source: Appendix E-1 (Protocol and amendments)

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Safety

Vital signs (supine and standing blood pressure and heart rate) were measured at scheduled intervals on Days 0-3, once at each clinic visit on Days 4-14, and during the follow-up visit

Pharmacokinetic Profiling

Blood

Samples for the determination of plasma concentrations of OPC-41061 were collected at the following times on:
 Days 1 and 13: pre-dose, and 1, 2, 4, 6, 8, 10, 12, 16, and 23 h post-dose
 Days 2 and 3: 2 and 23 h post-dose
 Days 4, 7, 10, 13; pre-dose and 2 h post-dose

Urine

Total urine volumes were to be collected in the following intervals on:
 Day 1: 0-4, 4-8, 8-12 and 12-16 and 16-23 h post-dose
 Day 13: 0-4, 4-8, 8-12 and 16-23 h post-dose (patients volunteering for hospitalization on Day 13)

Bioassay

The plasma concentrations of OPC-41061 were measured by a HPLC method with UV detection using an internal standard. The assay is linear between 5.00 and 1000 ng/mL. The coefficient of correlation of standard samples (weighted 1/x) fitted to a straight line is 0.998. Using QC samples the accuracy ranges between -9.8 % and 2.3 % and the precision is ≤ 14.9 %. Stability of OPC-41061 in plasma was demonstrated by exposing samples to room temperature for 4 h and after extraction on the autosampler for 49 h. No information on the stability of OPC-41061 in plasma exposed to long term freezer conditions and freeze/thaw cycles is reported. The assay for OPC-41061 was performed by _____

b(4)

Pharmacodynamic Profiling

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Fluid Intake

Fluid intake was recorded in the following intervals on:

- Days 0-3: 0800-1200, 1200-1600, 1600-2000, and 2000-0800.

Administration of iv fluids was allowed, in which case the amount of iv solution administered was included in the daily intake of fluid and Na⁺. Fluid intake was also measured and recorded on patient diary cards on Days 4-14. Fluid intake was not allowed for 1 h prior to the 0700 measurements of Na⁺ and prior to all 23 h post-dose measurements.

Plasma Na⁺ and K⁺

Plasma sodium and potassium were measured at the following times on:

- Day 0 (at times corresponding to those on Day 1 after drug administration): 2, 4, 8, 12, and 23 h
- Day 1: 2, 4, 8, 12, and 23 h after dosing
- Days 2 and 3: 4, 8, and 23 h after dosing
- Days 4-14, and Days 20-23 (follow-up visit): at time corresponding to pre-dose time (0700-0800)

AVP

Plasma levels of AVP were to be measured at the following times on:

- Day 1: pre-dose and 2 h post-dose

Urine volume, Urine Osmolality and Urine Na⁺

Urine volume, osmolality and Na⁺ were measured by collecting total urine volumes during the following time intervals on:

- Days 0-3: 0800-1200, 1200-1600, 1600-2000, and 2000-0800
- Days 4, 7, 14 and at follow-up visit: from a single void

PK Data Analysis

The following parameters were determined: C_{max}, t_{max} (taken directly from the observed data) C_{max,ss}, λ_z, AUC_t, AUC_∞ (Day1), t_{1/2z}, AUC_{ss,τ}, CL/F, V_z/F, and Rac(AUC) = AUC_{ss,τ}/AUC_∞ and Rac(C_{max}) = C_{ss,max}/C_{1,max} were obtained by standard methods using WinNonlin™ Professional (Version 3.1) Linear regression of the log of the dose normalized C_{max}, C_{max,ss}, AUC_∞, or AUC_{ss,τ} versus the log dose were performed to test dose proportionality of the PK of OPC-41061. Slope and 95% CI about the slope were computed.

Statistical Analysis and Sample Size Considerations

Since this was an exploratory study no formal statistical analysis was performed. Also, the power of the study was not of concern.

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_____ variables urine Na⁺ excretion, urine osmolality, and urine volume for a period was defined as the observation on Day 0 in the same period. Baseline for additional _____ variables (including plasma Na⁺, plasma K⁺ concentration _____ was defined _____ For safety variables ECG

and laboratory tests, baseline was defined as the observation at time point Day 0. For vital signs baseline was defined as the observation at 0700 on Day 0. The intent to treat population was used in baseline comparisons for efficacy variables. No formal sample size determination was performed for this study.

RESULTS

The demographics of the enrolled patients are shown in the next table:

TABLE 7.3-1 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

| Parameter | OPC-41061 | | | | | | Placebo n = 19 |
|-------------------------------|----------------|----------------|----------------|----------------|----------------|-----------------|-------------------|
| | 10 mg n = 8 | 15 mg n = 6 | 30 mg n = 6 | 60 mg n = 6 | 90 mg n = 6 | 120 mg n = 7 | |
| Age (years) | | | | | | | |
| Mean | 74.8 | 62.5 | 70.8 | 58.0 | 69.0 | 60.7 | 62.1 |
| SD | 8.8 | 9.1 | 15.2 | 3.5 | 9.9 | 8.8 | 10.8 |
| Range | 62-86 | 51-76 | 49-84 | 54-63 | 55-84 | 50-77 | 44-81 |
| Height (cm) | | | | | | | |
| N | 5 | 6 | 6 | 6 | 6 | 7 | 18 |
| Mean | 170.9 | 169.8 | 165.7 | 160.3 | 164.7 | 169.4 | 172.5 |
| SD | 12.7 | 9.0 | 12.6 | 13.6 | 10.5 | 12.6 | 7.3 |
| Range | 152.0- | 160.0- | 147.4- | 151.3- | 149.9- | 152.4- | 162.6- |
| | 182.5 | 180.0 | 186.6 | 182.9 | 175.8 | 182.9 | 188.0 |
| Gender, n (%) | | | | | | | |
| Male | 3 (50) | 3 (50) | 4 (66.7) | 4 (50) | 3 (50) | 5 (71.4) | 13 (68.4) |
| Female | 2 (40) | 3 (50) | 2 (33.3) | 3 (50) | 3 (50) | 2 (28.6) | 6 (31.6) |
| Race, n (%) | | | | | | | |
| Caucasian | 4 (80) | 5 (83.3) | 6 (100) | 4 (66.7) | 5 (83.3) | 3 (42.9) | 18 (94.7) |
| Black | 1 (20) | 1 (16.7) | 0 | 2 (33.3) | 1 (16.7) | 3 (42.9) | 1 (5.3) |
| Other | 0 | 0 | 0 | 0 | 0 | 1 (14.3) | 0 |
| Smoking status, n (%) | | | | | | | |
| Never | 1 (20) | 1 (16.7) | 3 (50) | 2 (33.3) | 4 (66.7) | 2 (28.6) | 9 (47.4) |
| Smoker | 0 | 2 (33.3) | 0 | 2 (33.3) | 0 | 1 (14.3) | 0 |
| Ex-smoker | 4 (80) | 3 (50) | 3 (50) | 2 (33.3) | 2 (33.3) | 4 (57.1) | 10 (52.6) |
| Drinking status, n (%) | | | | | | | |
| Never | 1 (20) | 1 (16.7) | 5 (83.3) | 4 (66.7) | 3 (50) | 4 (57.1) | 8 (42.1) |
| Drinker | 2 (40) | 2 (33.3) | 1 (16.7) | 1 (16.7) | 2 (33.3) | 2 (28.6) | 5 (26.3) |
| Ex-drinker | 2 (40) | 3 (50) | 0 | 1 (16.7) | 1 (16.7) | 1 (14.3) | 6 (31.8) |

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The disposition of the patients enrolled in the study is summarized in the below table:

TABLE 7.1-1 DISPOSITION OF PATIENTS

| Patient Status | OPC-41061 | | | | | | Placebo N(%) | Total N(%) |
|--------------------------------|----------------|----------------|----------------|----------------|----------------|-----------------|-----------------|---------------|
| | 10 mg n (%) | 15 mg n (%) | 30 mg n (%) | 60 mg n (%) | 90 mg n (%) | 120 mg n (%) | | |
| Randomized | 5 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 7 (100) | 19 (100) | 55 (100) |
| Completed per protocol | 4 (80) | 6 (100) | 6 (100) | 5 (83.3) | 6 (100) | 7 (100) | 16 (84.2) | 50 (90.9) |
| Withdrawn | 1 (20) | 0 | 0 | 1 (16.7) | 0 | 0 | 3 (15.8) | 5 (9.1) |
| Adverse experience | 1 (20) | 0 | 0 | 1 (16.7) | 0 | 0 | 1 (5.3) | 3 (5.3) |
| Insufficient clinical response | 0 | 0 | 0 | 0 | 0 | 0 | 2 (10.5) | 2 (3.6) |
| Analyzed for efficacy* | 5 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 7 (100) | 19 (100) | 55 (100) |
| Analyzed for safety* | 5 (100) | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 7 (100) | 19 (100) | 55 (100) |

*Source: Summary Tables 1 and 4; Appendix IV.18

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Safety

Of the 55 patients enrolled and randomized, 50 patients completed the study per protocol. Five (5) patients were withdrawn from the study, 3 for adverse events and 2 because of an insufficient response. The 3 adverse events included ascites at the 30 mg dose level, aggravated congestive heart failure, and respiratory failure after 60 mg OPC-41061. The aggravated congestive heart failure and respiratory failure were reported as continuing. One subject on 10 mg OPC-41061 was withdrawn because of increased creatinine- and BUN levels. A subject receiving placebo was also withdrawn because of an increase in creatinine-level. One placebo-treated patient was incorrectly reported as withdrawn due to an adverse event (congestive heart failure aggravated). This patient actually withdrew because of an insufficient response. Two placebo treated patients died. One 64 year old male patient died of congestive heart failure 62 days after the last dose of study medication. Another 48 year old male died of cor pulmonale 18 days after the last dose of study medication. In the 120 mg group the mean values for ALT and AST at the follow-up meeting were 57.4 (normal range 0-47) U/L and 54.7 (normal range 0-37 U/L) U/L, respectively. The elevation in the mean LFT values were driven mainly by one patient whose AST and ALT values were 137 U/L and 123 U/L, respectively, at the first follow-up visit. No further follow-up visits with additional LFT values occurred. Thirst and dizziness were the most often reported adverse events.

Pharmacokinetics

Linear plots of the median plasma concentration time profiles of OPC-41061 on Days 1 and 13 are shown in the below 2 figures:

Figure 2.3-1: Median plasma concentration vs. time profiles of OPC-41061 following oral administration of 10, 15, 30, 60, 90 and 120 mg of OPC-41061 doses in CHF patients with extracellular volume expansion on Day 1.

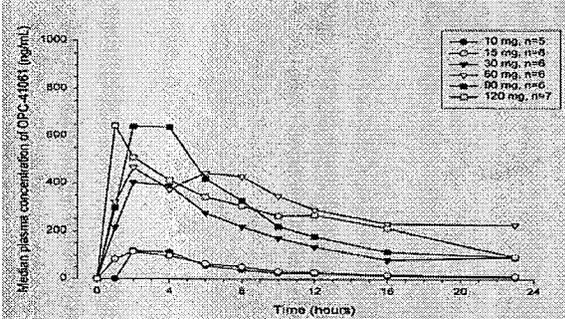
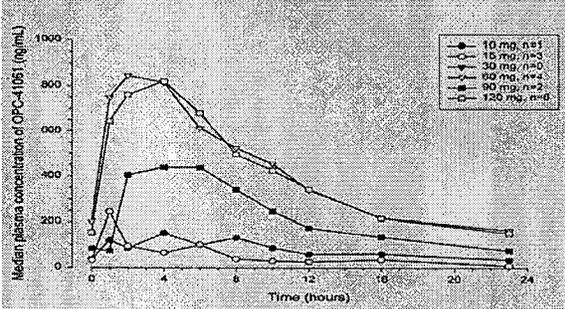


Figure 2.3-2: Median plasma concentration vs. time profiles of OPC-41061 following oral administration of 10, 15, 60, 90 and 120 mg of OPC-41061 dose in CHF patients with extracellular volume expansion on Day 13.



The plots indicate substantial inter-subject variation in peak and trough concentrations and average exposure of OPC-41061 in patients with mild to moderate CHF.

The median values of the PK parameters estimated by the sponsor for OPC-41061 on Days 1 and 13 are shown in the 2 below tables:

TABLE 7.6-1 MEDIAN PHARMACOKINETIC PARAMETERS OF OPC-41061 IN CHF PATIENTS WITH EXTRACELLULAR VOLUME EXPANSION ON DAY 1

| Dose (n) (mg) | t_{max} (h) | C_{max} (ng/mL) | $t_{1/2}$ ^a (h) | AUC ₀₋₂₄ ^a (ng h/mL) | CL/F ^a (mL/min/kg) |
|------------------|------------------|----------------------|-------------------------------|---|----------------------------------|
| 10 [5] | 3.42 | 82.22 | 9.15 | 1665 | 1.68 |
| 15 [6] | 2.08 | 120.37 | 9.07 | 1205 | 2.05 |
| 30 [6] | 2.92 | 494.15 | 10.19 | 5155 | 1.26 |
| 60 [8] | 3.00 | 772.87 | 10.28 | 9247 | 0.98 |
| 90 [6] | 2.04 | 785.70 | 10.91 | 8430 | 2.32 |
| 120 [7] | 3.93 | 650.87 | 9.73 | 8815 | 2.48 |

^a N=4 for the 10 mg group.
Source: Appendix V-3 (Pharmacokinetic Report)

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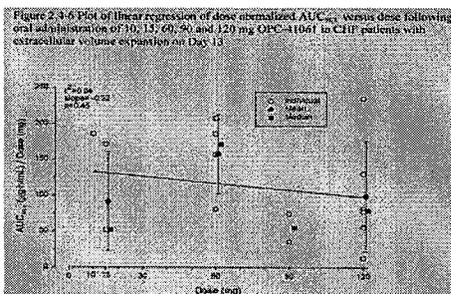
TABLE 7.6-2. MEDIAN PHARMACOKINETIC PARAMETERS OF OPC-41061 IN CHF PATIENTS WITH EXTRACELLULAR VOLUME EXPANSION ON DAY 13

| Dose (mg) | t _{max} (h) | C _{max} (ng/mL) | t _{1/2} (h) | AUC ₀₋₂₃ (ng·h/mL) | CL/F (mL/min/kg) |
|---------------------|----------------------|--------------------------|----------------------|-------------------------------|------------------|
| 10 [1] ^a | 3.75 | 152.19 | 13.12 | 1855 | 1.07 |
| 15 [3] | 1.25 | 125.65 | 7.78 | 783 | 2.96 |
| 60 [4] | 2.00 | 920.51 | 11.10 | 10271 | 0.93 |
| 90 [2] | 3.00 | 478.93 | 8.21 | 4972 | 3.69 |
| 120 [6] | 3.09 | 920.94 | 9.06 | 9516 | 2.61 |

^a Only individual data are presented since n = 1.

It should be noted that on Day 13 no data are reported on the PK parameters of the subjects receiving 30 mg OPC-41061 qd. Also, the number of subjects with plasma concentration information on Day 13 varies among the groups from n=1 in the 10 mg group to n=6 in the 120 mg group. Except for the 10 mg group on Day 1 the plasma concentrations of OPC-41061 are measurable for 23 post-dose on Days 1 and 13. The sponsor estimated λz from 3 non-zero concentrations measured in the 12-16 h post-dose interval. As discussed in detail in the review of report 156-98-202 this is a too short time interval to estimate λz and derived parameters reliably. Hence, only C_{max} and t_{max} for OPC-41061 on Days 1 and 13 and AUC₀₋₂₃ and CL/F on Day 13 for subjects receiving doses ≥ 15 mg qd in the above listed table can be considered unbiased.

Median t_{max} varies between 2.0 h and 3.9 h on Day 1 and between 1.3 h and 3.8 h on Day 13 suggesting significant inter-subject variation in absorption rate. The percent coefficient of variation about the mean C_{max} and AUC₀₋₂₃ on Days 1 and Day 13 ranges between 36 % and 74 % and 39 % and 100 %, respectively, indicating marked inter-subject variation. The increase in C_{max} appears to be less than proportional to dose. Oral clearance in the subjects with mild to moderate CHF ranges between 0.93 and 3.69 mL/min/kg. As shown in the below plot the slope of a linear regression of the dose normalized AUC₀₋₂₃ vs dose is not significantly different from zero and hence the kinetics of OPC-41061 in patients with hypervolemic CHF can be considered dose proportional:



The below tables list the median plasma concentrations of OPC-41061 at 2 h post-dose and at trough:

Median Plasma Concentrations of OPC-41061 at 2 h Post-Dose on Days 1, 2, 3, 4, 7 and 10 in the CHF Patients

| Day | Median Plasma Concentrations at 2 h Post-Dose, ng/mL | | | | | | |
|----------|--|-----|-----|-----|-----|-----|-----|
| | | 1 | 2 | 3 | 4 | 7 | 10 |
| Dose, mg | n | | | | | | |
| 10 | 3-4 | 119 | 113 | 91 | 93 | 127 | 133 |
| 15 | 6 | 115 | 134 | 125 | 118 | 135 | 134 |
| 30 | 6 | 404 | 355 | 293 | 264 | 539 | 568 |
| 60 | 6 | 472 | 382 | 308 | 352 | 547 | 570 |
| 90 | 6 | 642 | 807 | 852 | 824 | 881 | 762 |

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| | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|
| 120 | 6-7 | 510 | 490 | 427 | 637 | 659 | 628 |
|-----|-----|-----|-----|-----|-----|-----|-----|

Median Plasma Concentrations of OPC-41061 at Trough on Days 4, 7 and 10 in the CHF Patients

| Day | Median Plasma Concentrations at Trough, ng/mL | | | |
|----------|---|-----|-----|-----|
| | n | 4 | 7 | 10 |
| Dose, mg | | | | |
| 10 | 3 | 6.2 | 192 | 44 |
| 15 | 5-6 | 7.8 | 11 | 7 |
| 30 | 6 | 106 | 106 | 75 |
| 60 | 5-6 | 463 | 65 | 107 |
| 90 | 6 | 114 | 129 | 256 |
| 120 | 6-7 | 165 | 208 | 200 |

The median plasma concentrations at 2 h post-dose and trough show significant variation and the values at the different dose levels overlap. Cmax during the 13 day treatment period remains similar. Ctrough on Day 10 is not systematically greater than on Days 4 and 7 suggesting absence of significant accumulation.

The below table summarizes the peak plasma concentrations and the plasma concentrations 23 h post-dose of OPC-41061 and their ratio in the individual CHF patients:

Individual Plasma Concentrations of OPC-41061 at Peak and 23 h Post-Dose and their Ratio on Days 1 and 13 in the CHF Patients

| Dose | Individual Plasma Concentrations, ng/mL ^a | | | | | | |
|--------|--|------|-----|--------|------|-----|-------|
| | Day 1 | | | Day 13 | | | |
| | Subject No. | Cmax | C23 | Ratio | Cmax | C23 | Ratio |
| 10 mg | | | | | | | |
| 6002 | | | | 5.2 | | | 4.3 |
| 15 mg | | | | | | | |
| 60004 | | | | 11 | | | 14 |
| 100001 | | | | 8.8 | | | 9.7 |
| 60 mg | | | | | | | |
| 140001 | | | | 4.9 | | | 6.7 |
| 140004 | | | | 3.2 | | | 3.4 |
| 150001 | | | | 6.5 | | | 5.5 |
| 150003 | | | | 8.9 | | | 6.7 |
| 90 mg | | | | | | | |
| 140005 | | | | 22 | | | 24 |
| 140010 | | | | 10 | | | 4.6 |
| 120 mg | | | | | | | |
| 100002 | | | | 2.0 | | | 2.6 |
| 100003 | | | | 3.1 | | | 5.9 |
| 140013 | | | | 7.6 | | | 6.0 |
| 140014 | | | | 4.6 | | | 5.3 |
| 150007 | | | | 20 | | | 13 |
| 150008 | | | | 9.0 | | | 6.8 |

^a only subjects considered in whom this information is available

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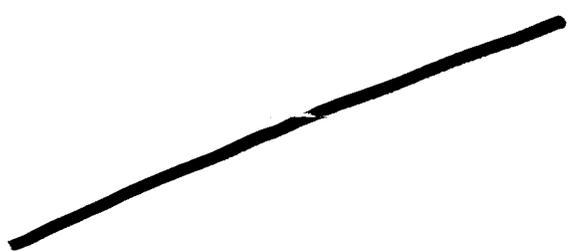
The individual plasma concentrations of OPC-41061 at peak and 23 h post-dose vary significantly among the subjects in the dose groups 60, 90 and 120 mg. The C_{max}/C₂₃ ratio on Day 1 varies between 2.0 and 20 and between 2.6 and 24 on Day 13. However, the respective values of C_{max}, C₂₃ and their ratio on Days 1 and 13 in the individual patients are remarkably similar indicating small intra-subject variability. The results suggest that variable absorption determines the C_{max} to C₂₃ ratio and the initial decline of the post C_{max} concentrations of OPC-41061. It should be noted that the peak to trough ratio are to be obtained from C_{max}/C₂₄, however C₂₄ values were not available.

The below table lists the individual AUC₀₋₂₃ values on Days 1 and 13 and the accumulation factor, RAUC, in qualifying patients:

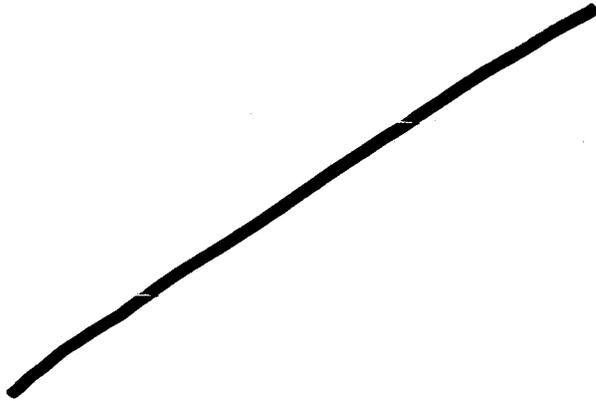
| Patient# | Dose, mg | AUC ₀₋₂₃ (Day13) | AUC ₀₋₂₃ (Day1) | RAUC |
|----------|----------|-----------------------------|----------------------------|------|
| 60004 | 15 | 768 | 965 | 0.80 |
| 70003 | | 2225 | 2316 | 0.96 |
| 100001 | | 774 | 952 | 0.81 |
| 140001 | 60 | 4772 | 4563 | 1.05 |
| 140004 | | 12204 | 10415 | 1.17 |
| 150001 | | 10971 | 9434 | 1.16 |
| 150003 | | 9261 | 5688 | 1.63 |
| 140005 | 90 | 3218 | 3138 | 1.03 |
| 140010 | | 6673 | 6271 | 1.06 |
| 100002 | 120 | 27337 | 26345 | 1.04 |
| 100003 | | 15368 | 10971 | 1.40 |
| 140013 | | 6655 | 7161 | 0.93 |
| 140014 | | 9628 | 5756 | 1.67 |
| 150007 | | 1511 | 1628 | 0.93 |
| 150008 | | 9114 | 6624 | 1.38 |
| Mean | | | | 1.13 |
| SD | | | | 0.27 |
| Median | | | | 1.05 |

The mean RAUC of 1.1 indicates small accumulation of tolvaptan given qd in patients with CHF NYHA Class I-III.

Pharmacodynamics



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Plasma Na⁺

The respective mean change from baseline in plasma sodium concentration is shown in the below table:

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TABLE 7.4-5 MEAN±SD CHANGES FROM BASELINE IN PLASMA SODIUM CONCENTRATION (mEq/L): OBSERVED-CASE ANALYSIS

| Post-Baseline Day Time Post-Dose | OPC-41061 | | | | | | Placebo |
|-------------------------------------|-----------------------|-----------------------|----------------------|-----------------------|--------------|-----------------------|-----------------------|
| | 10 mg n=5 | 15 mg n=6 | 30 mg n=6 | 60 mg n=6 | 90 mg n=7 | 120 mg n=18 | |
| Baseline mean | 133.4 | 137.8 | 137.3 | 135.3 | 138.8 | 135.0 | 135.1 |
| Day 1 | | | | | | | |
| 2 h | -0.8±1.3 ^a | -0.7±1.0 | 0.8±1.2 | -0.2±1.1 | -2.7±1.6 | -0.3±2.9 ^a | -1.5±1.2 ^a |
| 4 h | -0.8±1.0 ^a | 1.0±1.0 | 2.5±1.0 | 0.2±1.1 | 2.8±1.8 | 0.8±2.5 ^a | -1.1±1.7 ^a |
| 8 h | -0.4±1.6 | -0.3±1.8 | 2.2±2.0 | 1.0±1.3 | 1.3±1.8 | 1.8±2.0 ^a | 3.4±1.1 |
| 12 h | 2.0±1.1 | 1.6±2.0 ^a | 1.8±1.8 ^a | 0.2±1.2 | 0.2±1.6 | 3.4±1.0 | -2.2±1.1 |
| 23 h | 0.8±1.5 | 0.3±2.5 | 3.0±1.0 | 1.0±1.7 | 1.0±1.2 | 4.4±1.6 | 1.2±1.1 |
| Day 2 | | | | | | | |
| 4 h | -0.4±1.5 | -0.2±1.0 | 3.7±1.8 | 1.4±1.9 | 1.0±1.9 | 3.3±1.6 | -1.2±1.1 |
| 8 h | 1.2±1.2 | 0.2±1.0 | 3.8±1.7 | 2.2±1.2 | 1.6±1.8 | 1.9±2.0 | -2.5±1.1 |
| 23 h | 2.4±2.3 | 0.5±2.4 | 2.0±1.9 | -1.2±1.4 | 0.3±1.8 | 6.3±1.0 | -1.3±1.4 |
| Day 3 | | | | | | | |
| 4 h | 1.6±1.9 | 0.2±2.3 | 3.4±1.3 ^a | -1.6±1.5 ^a | -0.3±1.4 | 5.4±1.5 | -1.5±1.8 |
| 8 h | 3.0±1.2 | -0.2±1.7 | 2.2±1.3 ^a | 0.8±1.5 | 0.3±1.7 | 3.0±2.0 | -1.8±1.8 |
| 23 h | 2.8±1.6 ^a | -0.6±1.6 | 3.8±1.9 | -0.2±1.2 | -0.2±1.5 | 1.6±1.0 ^a | -1.2±1.8 ^a |
| Day 4 ^a | 1.0±1.9 ^a | -0.2±1.3 ^a | 2.3±1.6 | -0.6±1.0 ^a | 0.2±1.1 | 4.7±1.3 | -1.2±1.6 |
| Day 7 ^a | 2.0±2.1 | 1.5±1.9 | 3.5±1.1 | 0.2±1.4 ^a | 2.2±1.2 | 3.4±1.2 | 0.4±1.4 ^a |
| Day 10 ^a | 3.4±1.9 | 2.8±2.1 | 3.0±2.2 ^a | 1.8±1.6 ^a | 0.8±1.5 | 4.4±1.4 | -0.4±1.1 ^a |
| Day 13 ^a | 3.8±1.9 ^a | -0.6±2.7 ^a | 3.0±1.7 ^a | 0.9±1.7 ^a | 3.7±2.4 | 4.9±1.4 | -1.2±1.4 ^a |
| Day 14 ^a | 2.0±2.0 ^a | 1.3±1.8 | 2.3±1.0 | 1.6±1.0 ^a | 1.8±1.0 | 4.7±1.7 | -1.0±1.0 ^a |
| Follow-up ^a | 2.8±1.3 | 1.7±1.3 | 1.2±1.5 ^a | 2.8±1.2 | 0.0±1.7 | 0.2±1.5 | 0.2±1.1 ^a |

Source: Summary Table 7, Appendix B, b.

^a Plasma sodium concentrations were measured before dose administration on these days.

^b n=4; ^c n=6; ^d n=11.

^e n=5; ^f n=2; ^g n=16.

^h n=12; ⁱ n=3; ^j n=17.

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The mean baseline values for sodium among the 7 treatments groups range between 133.4 mEq/L and 138.8 mEq/L. The mean change from baseline exhibits a large inter-subject variation among the individuals of the different treatment groups. The placebo group tends to show a decrease in sodium plasma concentration relative to baseline during the treatment period, whereas the groups treated with OPC-41061 show a trend in the opposite direction.

The below table shows the mean change from baseline (placebo corrected) in the plasma Na⁺ concentrations:

Mean Change in Baseline (Placebo Corrected) in Plasma Na⁺ Concentration

| | Mean Change from Baseline in Plasma Na ⁺ , mEq/L ^{a,b,c} | | | | | |
|--|---|--------------|--------------|--------------|--------------|---------------|
| | 10 mg n=5 | 15 mg n=6 | 30 mg n=6 | 60 mg n=6 | 90 mg n=6 | 120 mg n=6 |
| Mean Baseline Na ⁺ Concentration ^b | 133.4 | 137.8 | 137.3 | 135.3 | 138.8 | 135.0 |
| Day Post-dose, h | | | | | | |
| Day 1 | | | | | | |
| 2 | na | 0.8 | 2.3 | 1.0 | -1.2 | 1.2 |
| 4 | na | 2.3 | 3.8 | 1.5 | -1.5 | 2.1 |
| 8 | 1.0 | 1.1 | 3.6 | 2.4 | 0.1 | 3.2 |
| 12 | 4.2 | 1.2 | 4.0 | 2.0 | 2.9 | 5.6 |
| 23 | 2.1 | 1.6 | 3.3 | 2.3 | 2.3 | 5.7 |
| Day 2 | | | | | | |
| 4 | 0.8 | 0.7 | 4.9 | -0.3 | 2.2 | 4.5 |
| 8 | 3.8 | 1.4 | 6.4 | 0.4 | 4.4 | 7.0 |
| 23 | 3.7 | 1.8 | 3.3 | 0.1 | 2.1 | 7.6 |
| Day 3 | | | | | | |
| 4 | 3.1 | 1.3 | 4.9 | -0.1 | 1.2 | 7.1 |
| 8 | 4.8 | 1.6 | 4.0 | -1.0 | 2.1 | 5.4 |
| 23 | na | 0.7 | 5.1 | 1.0 | 1.1 | 4.9 |
| Day 4 | na | 1.0 | 3.5 | 0.6 | 1.5 | 5.9 |
| Day 7 | 1.6 | 1.1 | 3.1 | -0.6 | 2.8 | 5.0 |
| Day 10 | 3.8 | 2.9 | 3.4 | 2.2 | 1.2 | 4.8 |
| Day 13 | na | 0.6 | 4.2 | na | 4.9 | 6.1 |
| Day 14 | na | -0.3 | 3.3 | 2.6 | 2.8 | 5.7 |
| Follow up | 1.9 | -3.1 | 0.3 | 2.1 | -0.9 | -0.2 |

^a Pooled placebo corrected ^b n≥5 at all time points na=not available

The net effect of OPC-41061 at the 30, 90 and 120 mg dose levels appears to be an increase in the Na⁺ plasma concentrations at trough which is greatest in the group receiving the 120 mg dose. The effect appears to be sustained for the duration of the 13 day treatment. The onset of the Na⁺ increasing effect of OPC-41061 appears to be at 8 h post-dose on Day 1.

Plasma K⁺

The next plot summarizes the mean change from baseline in the K⁺ plasma concentrations:

TABLE 7.4-6 MEAN±SD CHANGES FROM BASELINE IN PLASMA POTASSIUM CONCENTRATION (mEq/L): OBSERVED-CASE ANALYSIS

| Post-Baseline Day Time Post Dose | OPC-41061 | | | | | | Placebo n = 18 |
|-------------------------------------|-----------------------|----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| | 10 mg n = 5 | 15 mg n = 6 | 30 mg n = 6 | 60 mg n = 6 | 90 mg n = 6 | 120 mg n = 7 | |
| Baseline mean | 3.8 | 4.1 | 4.0 | 4.2 | 4.3 | 4.4 | 4.2 |
| Day 1 | | | | | | | |
| 2 h | 0.1±0.1 ^a | 0.1±0.2 | 0.2±0.3 | 0.1±0.3 | 0.1±0.6 | -0.4±0.6 ^c | 0.1±0.5 ^d |
| 4 h | 0.1±0.1 ^a | 0.1±0.4 | 0.1±0.4 | 0.2±0.3 | 0.2±0.3 | 0.4±1.0 ^b | 0.1±0.4 ^d |
| 8 h | -0.0±0.1 | 0.1±0.4 | 0.0±0.2 | 0.2±0.4 | -0.2±0.5 ^a | -0.2±0.7 ^b | 0.1±0.5 |
| 12 h | 0.1±0.2 | 0.2±0.5 ^b | 0.0±0.4 ^a | 0.2±0.4 | 0.2±0.3 ^a | -0.2±0.7 | -0.0±0.5 |
| 23 h | 0.1±0.3 | 0.2±0.5 | 0.0±0.4 | 0.0±0.4 | -0.0±0.6 | -0.3±0.9 | -0.2±0.3 |
| Day 2 | | | | | | | |
| 4 h | 0.4±0.6 | 0.1±0.5 | 0.1±0.5 | 0.3±0.4 | 0.1±0.5 ^b | -0.3±0.8 | -0.1±0.3 |
| 8 h | 0.7±0.8 | 0.1±0.3 | 0.0±0.2 | 0.1±0.4 | -0.1±0.5 | -0.5±0.8 | -0.0±0.4 |
| 23 h | -0.0±0.4 | 0.1±0.4 | -0.0±0.5 | 0.2±0.4 | 0.0±0.5 | -0.1±0.8 | -0.1±0.3 |
| Day 3 | | | | | | | |
| 4 h | -0.2±0.3 | 0.1±0.4 | 0.1±0.3 ^b | 0.0±0.5 ^b | 0.1±0.7 ^b | -0.0±0.8 | -0.1±0.3 |
| 8 h | -0.1±0.4 | 0.0±0.4 | 0.1±0.3 ^b | 0.0±0.4 | 0.1±0.4 | -0.0±1.0 | 0.1±0.5 |
| 23 h | -0.1±0.5 ^a | 0.1±0.4 ^a | 0.2±0.4 | 0.4±0.7 | -0.1±0.6 | 0.1±0.7 ^a | -0.1±0.4 ^a |
| Day 4 ^a | -0.1±0.5 ^a | 0.0±0.4 ^b | 0.2±0.3 | 0.3±0.8 ^a | 0.1±0.5 | 0.1±0.9 | -0.1±0.4 |
| Day 7 ^a | 0.2±0.7 | 0.1±0.9 | 0.1±0.6 | 0.2±0.7 ^b | 0.5±0.6 | -0.2±1.0 | 0.0±0.6 ^b |
| Day 10 ^a | 0.5±0.5 | 0.4±0.8 | 0.1±0.7 ^b | 0.1±0.4 ^a | 0.1±0.7 | -0.2±0.8 | -0.2±0.4 ^a |
| Day 13 ^a | 0.4±0.2 ^a | 0.0±0.9 ^b | -0.1±0.7 ^b | -0.2±0.2 ^a | -0.0±0.8 | -0.2±1.0 | -0.3±0.4 ^a |
| Day 14 ^a | 0.1±0.5 ^a | 0.2±0.3 | 0.1±0.7 | 0.0±0.5 ^a | 0.1±0.6 | -0.3±0.9 | 0.2±0.5 ^a |
| Follow-up ^a | 0.1±0.1 | 0.0±0.4 | 0.0±0.4 ^a | 0.0±0.4 | -0.1±0.7 | -0.0±0.9 | -0.2±0.5 ^a |

Source: Summary Table 8, Appendix IV-6.
 # Plasma potassium concentrations were measured before dose administration on these days.
 a: n = 4; b: n = 6; c: n = 11
 d: n = 5; e: n = 2; f: n = 16
 g: n = 15; h: n = 3; i: n = 17

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For potassium the mean baseline values for the 7 treatment groups range between 3.8 and 4.5 mEq/L and show significant inter-subject differences in the different treatment groups. There is no overt evidence for an impact of OPC-41061 on plasma potassium.

Urine Volume/Excretion Rate

The mean change from baseline in 24 h urine volume is shown in the table below:

TABLE 7.4-4 MEAN±SD CHANGES FROM BASELINE IN 24-HOUR URINE VOLUME (mL): OBSERVED-CASE ANALYSIS

| Post-Baseline Day | OPC-41061 | | | | | | Placebo n = 19 |
|--------------------|-----------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| | 10 mg n = 5 | 15 mg n = 6 | 30 mg n = 6 | 60 mg n = 6 | 90 mg n = 6 | 120 mg n = 7 | |
| 24-h Baseline mean | 1508.4 | 2943.7 | 3243.3 | 3597.5 | 2836.7 | 2948.6 | 2521.6 |
| Day 1 | 604.6 ±650.5 | 1166.3 ±1560.6 | 1069.2 ±1124.8 | 2985.0 ±1902.5 | 2105.0 ±1493.9 | 3750.0 ±2858.5 | 177.9 ±854.3 |
| Day 2 | 521.8 ±899.9 | 1217.2 ±1525.2 | 840.8 ±679.6 | 1794.2 ±1495.7 | 1509.7 ±1053.6 | 3615.0 ±2746.1 | 13.7 ±918.2 |
| Day 3 | 966.6 ±716.9 | 746.3 ±749.7 | 1046.7 ±1073.0 | 1900.8 ±1690.5 | 990.0 ±681.5 | 2312.1 ±1907.9 | 101.7 ±1262.1 |

Source: Summary Table 6.3; Appendix IV-9.

The mean baseline 24 h urine volumes show significant inter-group differences. There is also substantial variation among the subjects of the groups. OPC-41061 administered in doses of 10-120 mg consistently increases the mean baseline corrected 24 h urine volume more than placebo. The increase in the baseline corrected mean 24 h urine volume tends to increase with increasing dose.

The mean change from baseline (with/out placebo correction) in the 24 h urine excretion rate is listed in the below 2 tables:

Mean Change from Baseline in 24 h Urine Excretion Rate

| Mean Change from Baseline in 24 h Urine Excretion Rate ^a , mL/min | | | | | | |
|--|-----------|-----------|-----------|-----------|-----------|------------|
| Dose, mg | 10 n=5 | 15 n=6 | 30 n=6 | 60 n=6 | 90 n=6 | 120 n=7 |
| Baseline | 1.0 | 2.0 | 2.3 | 2.5 | 2.0 | 2.0 |
| Post-Baseline Day | | | | | | |
| 1 | 0.42 | 0.81 | 0.74 | 2.1 | 1.5 | 2.6 |
| 2 | 0.36 | 0.85 | 0.58 | 1.2 | 1.0 | 2.5 |
| 3 | 0.67 | 0.52 | 0.73 | 1.3 | 0.69 | 1.6 |

^a Mean 24 h baseline excretion rate in placebo group=1.8 mL/min

Mean Change from Baseline (Placebo Corrected) in 24 h Urine Excretion Rate

| Mean Change from Baseline (Placebo Corrected) in 24 h Urine Excretion Rate ^{a,b} , mL/min | | | | | | |
|--|-----------|-----------|-----------|-----------|-----------|------------|
| Dose, mg | 10 n=5 | 15 n=6 | 30 n=6 | 60 n=6 | 90 n=6 | 120 n=7 |
| Baseline | 1.0 | 2.0 | 2.3 | 2.5 | 2.0 | 2.0 |
| Post-Baseline Day | | | | | | |
| 1 | 0.30 | 0.69 | 0.62 | 1.9 | 1.3 | 2.5 |
| 2 | 0.35 | 0.84 | 0.57 | 1.2 | 1.0 | 1.6 |
| 3 | 0.60 | 0.45 | 0.66 | 1.2 | 0.62 | 1.5 |

^aPooled placebo corrected ^b Mean 24 h baseline excretion rate in placebo group=1.8 mL/min

OPC-41061 induces a mean net increase in the respective 24 urine excretion rates at all dose levels. The respective net urine excretion rates on Days 1 and 2 increases with dose. In the groups receiving 60, 90 and 120 mg OPC-41061 the net excretion rates on Days 2 and 3 are smaller than on Day 1 indicating increased fluid retention and/or decreased fluid ingestion.

Fluid Balance



b(4)

b(4)

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Urine Sodium Excretion

The mean change from baseline in urine sodium excretion is shown in the table below:

TABLE 7.4-2. MEAN ±SD CHANGES FROM BASELINE IN 24-HOUR URINE SODIUM EXCRETION (mEq): OBSERVED-CASE ANALYSIS

| Post-Baseline Day | OPC-41061 | | | | | | Placebo n=19 |
|--------------------|----------------|-----------------|-----------------|------------------|----------------|-----------------|-----------------|
| | 10 mg n=5 | 15 mg n=6 | 30 mg n=6 | 60 mg n=5 | 90 mg n=6 | 120 mg n=7 | |
| 24-h Baseline mean | 112.8 | 210.8 | 201.5 | 223.7 | 165.8 | 220.1 | 158.0 |
| Day 1 | -22.7 ±19.5 | -34.2 ±85.4 | -65.5 ±47.4 | -27.4 ±119.0 | -38.0 ±28.1 | -91.3 ±107.9 | -0.1 ±81.8 |
| Day 2 | -31.4 ±64.0 | -39.2 ±105.2 | -99.0 ±71.5 | -122.0 ±81.5 | -23.3 ±81.1 | -92.8 ±68.0 | -34.9 ±97.2 |
| Day 3 | 3.4 ±58.4 | -60.7 ±105.8 | -113.1 ±67.1 | -111.6 ±141.1 | -68.2 ±77.6 | -128.9 ±84.9 | -35.0 ±135.6 |

The mean baseline values for sodium excretion show significant inter-group variation. There is also significant inter-subject variation within the groups for the mean change from baseline. Compared to baseline the reduction in sodium excretion in the patients receiving 15 mg to 120 mg OPC-41061 tends to be greater than in the patients receiving placebo.

The below table lists the mean change from baseline (placebo corrected) in the 24 h excretion of Na⁺:

Mean Change from Baseline (Placebo Corrected) in 24 h Na⁺ Excretion

| | Mean Change from Baseline (Placebo Corrected) in 24 h Na ⁺ Excretion ^{a,b} , mEq | | | | | |
|--|--|--------------|--------------|--------------|--------------|---------------|
| | 10 mg n=5 | 15 mg n=6 | 30 mg n=6 | 60 mg n=5 | 90 mg n=6 | 120 mg n=7 |
| Mean Baseline Na ⁺ Excretion ^b | 112.8 | 210.8 | 201.5 | 223.7 | 165.8 | 220.1 |
| Day Post-dose, h | | | | | | |
| Day 1 | -22.6 | -54.1 | -65.4 | -27.3 | -37.9 | -91.2 |
| Day 2 | 3.5 | -4.3 | -64.1 | -87.1 | 11.6 | -57.9 |
| Day 3 | 40.4 | -25.7 | -78.1 | -76.6 | -33.2 | -93.9 |

^a Pooled placebo corrected ^b mean baseline 24 h Na⁺ excretion of placebo group =158.0 mEq

The net effect of single doses of 15 mg to 120 mg OPC-41061 appears to be a reduction in the excretion of Na⁺.

The impact of OPC-41061 on urine osmolality is shown in the next table:

TABLE 7.4.3 MEAN±SD CHANGES FROM BASELINE IN URINE OSMOLALITY (mOsm/Kg): OBSERVED-CASE ANALYSIS

| Post-Baseline Day Time | OPC-41061 | | | | | | Placebo N=19 |
|------------------------|---------------------|--------------------|--------------------|--------------------|--------------|---------------------|---------------------|
| | 10 mg n=5 | 15 mg n=6 | 30 mg n=6 | 60 mg n=6 | 90 mg n=6 | 120 mg n=7 | |
| Baseline mean | | | | | | | |
| 0800-1200 | 398.7 ^a | 340.2 | 306.2 ^a | 323.0 | 530.5 | 351.4 | 442.4 ^d |
| 1200-1600 | 410.0 | 400.7 | 326.8 | 298.8 | 380.5 | 386.0 | 409.8 |
| 1600-2000 | 467.8 | 392.5 | 353.8 | 286.7 | 337.8 | 465.1 | 418.2 |
| 2000-0800 | 431.2 ^b | 381.3 | 370.0 | 271.0 | 379.5 | 416.3 | 450.9 |
| Day 1 | | | | | | | |
| 0800-1200 | -127.3 | -111.7 | -130.6 | -148.3 | -333.7 | -209.0 | -55.2 |
| 1200-1600 | ±131.5 ^c | ±67.2 | ±62.4 | ±94.8 | ±232.2 | ±101.7 | ±152.0 ^e |
| 1600-2000 | ±176.8 | ±28.7 | ±41.7 | ±133.0 | ±214.0 | ±268.9 | ±33.8 |
| 2000-0800 | ±201.3 ^a | ±122.4 | ±25.2 | ±117.9 | ±200.1 | ±40.3 | ±126.0 |
| Day 2 | | | | | | | |
| 0800-1200 | -193.8 | -167.6 | -133.8 | -149.8 | -172.5 | -325.9 | -24.4 |
| 1200-1600 | ±202.7 ^a | ±52.1 ^b | ±110.3 | ±93.4 | ±109.0 | ±71.2 | ±93.8 |
| 1600-2000 | ±50.5 | ±20.8 | ±15.8 | ±107.8 | ±64.7 | ±13.6 | ±34.8 |
| 2000-0800 | ±112.2 ^a | ±89.4 | ±172.8 | ±107.8 | ±143.2 | ±109.8 | ±121.5 |
| Day 3 | | | | | | | |
| 0800-1200 | -142.7 | -121.3 | -101.2 | -154.3 | -313.5 | -195.9 | -67.8 |
| 1200-1600 | ±152.7 | ±117.0 | ±59.6 ^c | ±84.8 | ±234.9 | ±113.1 | ±180.3 ^d |
| 1600-2000 | ±117.7 | ±145.0 | ±39.2 | ±187.7 | ±106.3 | ±57.0 | ±61.4 |
| 2000-0800 | ±154.0 | ±106.0 | ±66.5 | ±23.0 | ±120.3 | ±15.4 | ±126.6 |
| Day 1 | | | | | | | |
| 0800-1200 | -123.1 | -110.5 | -122.1 | -159.4 | -142.8 | -195.2 | -198.5 |
| 1200-1600 | ±63.8 | ±75.2 | ±118.3 | ±11.0 | ±124.8 | ±39.0 | ±43.5 |
| 1600-2000 | ±190.8 ^a | ±103.0 | ±137.5 | ±84.9 | ±132.1 | ±153.0 | ±102.6 |
| Day 2 | | | | | | | |
| 0800-1200 | -131.7 | -125.3 | -89.8 | -160.7 | -312.7 | -197.9 | -97.0 |
| 1200-1600 | ±133.9 ^b | ±111.0 | ±43.4 ^c | ±78.3 | ±231.4 | ±107.8 | ±150.0 ^d |
| 1600-2000 | ±157.6 | ±133.0 | ±42.8 | ±51.2 | ±179.3 | ±242.7 | ±53.7 |
| 2000-0800 | ±161.8 | ±110.0 | ±47.2 | ±54.4 | ±128.3 | ±14.6 | ±23.7 |
| Day 3 | | | | | | | |
| 0800-1200 | -196.6 | -100.0 | ±92.9 | ±93.4 ^a | ±121.7 | ±89.8 | ±124.2 ^b |
| 1200-1600 | ±124.0 | ±08.8 | ±03.2 | ±12.3 | ±17.2 | ±16.4 | ±4.6 |
| 1600-2000 | ±128.7 ^c | ±89.7 | ±35.6 | ±99.2 | ±135.5 | ±204.1 ^d | ±130.3 ^e |

Source: Summary Table 6.2, Appendix IV-8
a. n=5; b. n=4; c. n=5; d. n=6
d. n=18; e. n=17; f. n=16

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The mean baseline values of urine osmolality show significant variations among the different groups. There is also significant inter-subject variability in the mean change from baseline among the subjects within the groups. The mean reduction in urine osmolality in the patients receiving 10-120 mg OPC-41061 qd appears to be consistently greater than in the patients receiving placebo. The effect appears to last throughout the 24 h dose interval and not to vary between Days 1, 2 and 3. The effects of the tested OPC-41061 doses on urine osmolality are overlapping.

PK-PD Correlations

The below tables list the mean change from baseline (with/out placebo correction) in the urine excretion rates and the corresponding mid time plasma concentrations of OPC-41061 on Day 1:

Mean Change from Baseline in Urine Excretion Rates and Mean Plasma Concentrations Measured at Mid-Time for OPC-41061 on Day 1

| Mean Change from Baseline in Urine Excretion Rate and Plasma Concentration Measured at Mid-Time for OPC-41061 | | | | |
|---|------------------------|---|---------|--------------------------|
| Dose, mg | Collection Interval, h | Mean Change from Baseline in Excretion Rate, mL/min | Time, h | Mean Concentration ng/mL |
| 10 | 0-4 | 0.86 | 2 | 116 |
| | 4-8 | 1.1 | 6 | 86 |
| | 8-12 | -0.13 | 10 | 55 |

| | | | | |
|-----|-------|------|----|-----|
| | 12-24 | 0.23 | 18 | 28 |
| 15 | 0-4 | 0.63 | 2 | 135 |
| | 4-8 | 0.38 | 6 | 77 |
| | 8-12 | 1.3 | 10 | 48 |
| | 12-24 | 0.87 | 18 | 19 |
| 30 | 0-4 | 2.5 | 2 | 378 |
| | 4-8 | 0.82 | 6 | 306 |
| | 8-12 | 0.14 | 10 | 195 |
| | 12-24 | 0.53 | 18 | 100 |
| 60 | 0-4 | 3.6 | 2 | 526 |
| | 4-8 | 2.7 | 6 | 470 |
| | 8-12 | 3.2 | 10 | 338 |
| | 12-24 | 0.98 | 18 | 179 |
| 90 | 0-4 | 4.2 | 2 | 592 |
| | 4-8 | 0.91 | 6 | 423 |
| | 8-12 | 1.7 | 10 | 208 |
| | 12-24 | 0.66 | 18 | 101 |
| 120 | 0-4 | 4.4 | 2 | 505 |
| | 4-8 | 3.8 | 6 | 502 |
| | 8-12 | 2.9 | 10 | 392 |
| | 12-24 | 1.5 | 18 | 199 |

Mean Change from Baseline (Placebo Corrected) in Urine Excretion Rate and Mean Plasma Concentrations Measured at Mid-Time for OPC-41061 on Day 1

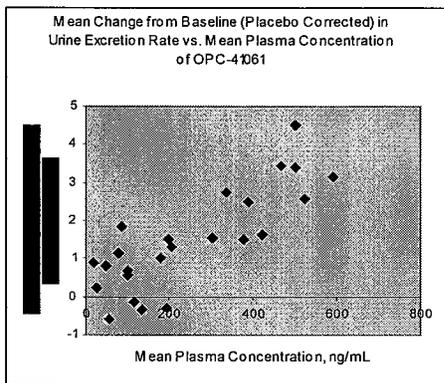
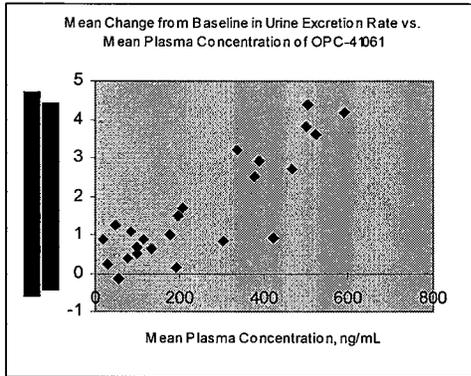
| Mean Change from Baseline (Placebo Corrected) Urine Excretion Rates and Plasma Concentrations Measured at Mid-Time for OPC-41061 | | | | |
|--|------------------------|---|---------|--------------------------|
| Dose, mg | Collection Interval, h | Mean Change from Baseline in Excretion Rate ^a , mL/min | Time, h | Mean Concentration ng/mL |
| 10 | 0-4 | -0.13 | 2 | 116 |
| | 4-8 | 1.8 | 6 | 86 |
| | 8-12 | -0.57 | 10 | 55 |
| | 12-24 | 0.25 | 18 | 28 |
| 15 | 0-4 | -0.36 | 2 | 135 |
| | 4-8 | 1.1 | 6 | 77 |
| | 8-12 | 0.80 | 10 | 48 |
| | 12-24 | 0.89 | 18 | 19 |
| 30 | 0-4 | 1.5 | 2 | 378 |
| | 4-8 | 1.6 | 6 | 306 |
| | 8-12 | -0.31 | 10 | 195 |
| | 12-24 | 0.55 | 18 | 100 |
| 60 | 0-4 | 2.6 | 2 | 526 |
| | 4-8 | 3.5 | 6 | 470 |
| | 8-12 | 2.8 | 10 | 338 |
| | 12-24 | 1.0 | 18 | 179 |
| 90 | 0-4 | 3.2 | 2 | 592 |
| | 4-8 | 1.7 | 6 | 423 |
| | 8-12 | 1.3 | 10 | 208 |
| | 12-24 | 0.68 | 18 | 101 |
| 120 | 0-4 | 3.4 | 2 | 505 |
| | 4-8 | 4.5 | 6 | 502 |
| | 8-12 | 2.5 | 10 | 392 |

| | | | | |
|--|-------|-----|----|-----|
| | 12-24 | 1.5 | 18 | 199 |
|--|-------|-----|----|-----|

^a Corrected for baseline and placebo

Both data sets indicate that a continuous aquaretic effect (net rate ≥ 1 mL/min) is attained on Day 1 with dose levels of ≥ 30 mg. At these dose levels the onset of aquaretic activity is observed in the first collection interval of 0-4 h post-dose. Peak rates are seen in the 0-4 or 4-8 h interval and the time duration of the aquaretic effect ranges between 6 and 18 h.

The below figures show plots of the mean change from baseline (with/out placebo correction) in 24 the h urine excretion rates vs the correspondng midtime mean plasma concentrations of OPC-41061 on Day 1:



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Both data sets suggest that the net urine excretion rate increases with increasing exposure to OPC-41061 on Day 1 in the patients with CHF NYHA Class I-III. It should be noted that the lagging of the aquaretic effect behind the plasma concentration of tolvaptan (counterclockwise hysteresis) contributes to the variability of the data.

The below table lists the mean change from baseline (with/out placebo correction) in AUC0-23 of plasma Na⁺ and the AUC0-23 of OPC-41061 on Day 1:

Mean Change from Baseline (with/out Placebo Correction) in AUC0-23Na⁺ and Mean AUC0-23 of OPC-41061