

6. On pp. 9 and 10 of the Bioanalytical Summary (Appendix III 1) the report lists results on precision and accuracy for tolvaptan and metabolites during analysis of the samples from the present study. The source of these results cannot be found in the Bioanalytical Report (Appendix II 2).

Study Report No. 156-95-305: "A Study to Investigate the Safety and Tolerability of OPC-41061, Administered Once Daily for 28 Days in Healthy Male Caucasian Subjects"

Investigator and Study Site

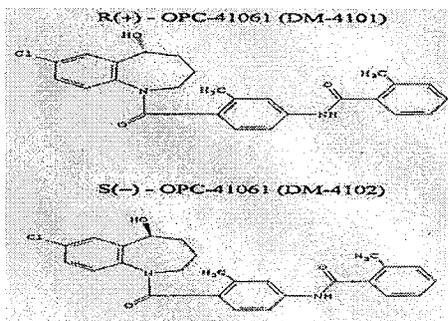
[REDACTED]

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Objectives

To determine the safety and tolerability of multiple doses of [REDACTED] OPC-41061 or placebo in normal subjects. In addition, some limited pharmacokinetic and pharmacodynamic data was collected to assess changes over the duration of the dosing period.

The sponsor added later an additional objective, namely to determine the serum concentrations of the S(-) and R(+) enantiomers to assess a potential stereo-specificity of the PK of OPC-41061. OPC-41061 is (±)-7-chloro-5-hydroxy-1-{2-methyl-4-(2-methylbenzoylamino) benzoyl}-2,3,4,5-tetrahydro-1*H*-benzazepine. The S(-) and R(+) enantiomers are shown below:



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Investigational Drugs and Formulations

Gelatine capsule containing a [REDACTED] formulation of 30 mg OPC-41061 (Lot No. 5J82A030) and similarly appearing placebo gelatine capsules [REDACTED] (Lot No. 5J81P) were provided by the sponsor.

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Design

This was a double-blind, parallel placebo-controlled study using multiple doses of 30 mg or 60 mg OPC-41061 or placebo administered once daily for 28 days in 24 healthy Caucasian, male subjects. The three dose groups were run in parallel in one center. Each subject received two capsules. The subjects entered the Clinic on Day -1 and remained on site until the morning of Day 8. They received the study medication at approximately the same time each morning, 2 h before breakfast. No breakfast was given on days when PK parameters were assessed (Days 1 and 28). Fluid intake and urine output were monitored for the 24 h period after dosing on Days 1, 7 and 28. After

administration of the dose on the morning of Day 8, subjects were discharged from the unit and returned every morning for dosing. On the evening of Day 27, the subjects entered the unit for the second pharmacokinetic assessment on Day 28 after the final dose of the drug. The subjects were discharged 24 h after the last dose on the morning of Day 29. They returned on Days 30 and 31 for pharmacokinetic blood sampling. A follow-up visit occurred on Day 35.

On Days 1, 7 and 28, subjects were allowed to consume water *ad libitum*. Medication was taken with 240 mL of non-carbonated water. A buccal inspection followed. Subjects were *npo* for 1 h post-dose, at which time they were to consume 240 ml of water. After 2 h post-dose water was allowed *ad libitum*. On all other days, the subjects received the dose with 240 mL non-carbonated water with subsequent fluid intake unrestricted.

The inclusion and exclusion criteria are listed below:

3.3.1 Inclusion Criteria

All subjects were male, non-smokers, or smokers who smoked less than 10 cigarettes/day; smokers agreed not to smoke while they were in the unit.

All subjects were in good health in the opinion of the Investigator.

Subjects were Caucasian, between the ages of 18 and 40 years, weighing between 60 and 100 kg and within 15% of ideal body weight (Metropolitan Life Insurance tables).

All subjects were able to understand and willing to comply with the study requirements.

Subjects were capable of giving and gave written informed consent prior to enrollment into the study.

Subjects had not used a prescribed drug within 4 weeks prior to the beginning of the study or an over-the-counter (OTC) medication within 14 days of the beginning of the study.

Subjects' medical history did not reveal any evidence of renal, hepatic, cardiovascular, or metabolic dysfunction.

Intake of prescription drugs was prohibited for 4 weeks prior to study initiation. Intake of OTC medications was prohibited in the previous 14 days. Subjects were not allowed any concomitant medication, either prescribed or OTC at any time during the study unless the sponsor gave prior approval, except in case of emergency.

The scheduled study activities are provided in the below scheme:

A HPLC method with internal standard and UV detection was used. The coefficient of correlation of the 1/y weighted standards was 0.998. The accuracy ranged between -0.1% and 1.8% and the precision was $\leq 9.5\%$. The measurements were performed by _____

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Enantiomers of OPC-41061

The study was completed in January 1996. After completion of the measurements of racemic OPC-41061 the sponsor in February 97 decided to determine the serum concentration of the R(+) and S(-)-enantiomers. The samples containing the remainder serum were shipped to _____. Only samples collected in the intervals of 0-24 h post-dose on Day 1 and 0-72 h on Day 28 were analyzed. No samples for 2 subjects in the 60 mg dose group were analyzed. For an additional subject in the 60 mg dose group who was withdrawn from the study on Day 8 no samples were available on Day 28. Only 2 subjects had measurable concentrations of the enantiomers 48 h or 72 h post dose on Day 28 and these time points were not included in the analysis.

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The LC/MS/MS assay method used a HPLC chiral separation for the determination of the S(-) and R(+) enantiomers. The calibration curve is linear over the range of 2.5-1000 ng/mL and the correlation coefficient of linear regressions of the 1/y weighted concentration standards is ≥ 0.996 . Using QC samples the accuracy for S(-) OPC-41061 ranges between -16.6% and 16.0% and the mean precision is $\leq 11.2\%$. The accuracy for R(+) OPC ranges between -19.0% and 14.7% and the mean precision is $\leq 12.9\%$.

Sample stability was confirmed for the following conditions: 24 h at ambient temperature and normal benchtop lighting, 3 freeze/thaw cycles after storage at -20°C , and 2 weeks after storage at -20°C .

AVP

The assays of AVP in serum were performed by the _____ An RIA method was used. The report does not state sensitivity, precision and accuracy and specificity of the assay used.

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Pharmacokinetic Data Analysis

Racemic OPC-41061

The following PK parameters were obtained on Days 1 and 28 for racemic OPC-41061 on Day 1: C_{max}, t_{max}, AUC_{0-t} and on Day 28 AUC_{0-∞}, CL/F and V_d/F, and Rac (accumulation factor). C_{max} and t_{max} were obtained by direct observation. Compartment-model independent methods were used employing WINNONLIN (Version 1.2). AUC_{0-tlast} was estimated by the linear trapezoidal rule. The λ_z was estimated by log-linear regression using at least three non-zero serum concentrations. The interval between 8 h and 24 h after administration of OPC-41061 was used to estimate λ_z . The report does not state how Rac was computed.

Enantiomers of OPC-41061

Individual and mean serum concentrations of the enantiomers were reported, but no PK parameters were obtained.

Pharmacodynamic Profiling

Urine Volume

Complete urine volumes were collected in the following intervals on:
Days 1, 7 and 28: 0-4, 4-8, 8-12, and 12-24 h post-dose

Body Weight

Body weight (indoor clothing with shoes) was recorded at screening, on Days -1, 2, 3, 5, 7, 8, 14, 21, 27, 28, 29, 30 and at follow-up on Day 35.

Serum AVP

Blood samples for the determination of AVP in serum were collected at the following times:

Days 1, 7 and 28: pre-dose, and 4, 8 and 12 h after dosing

Days 2, 8, 14, 21: pre-dose

Days 29: 24, 48 (Day 30), and 72 h (Day 31) post-dose

Statistical Analysis

Mean, SD and coefficient of variation about the mean, and standard error of the mean were calculated for OPC-41061 parameters and AVP concentrations. For urine volume and fluid intake an Analysis of Variance (ANOVA) using PROC GLM with treatment and day, with and without treatment-by-day interaction, was initially performed to test for significant difference in urine volume. An analysis of Covariance using PROC GLM was performed to account for differences in fluid intake. Pair-wise comparisons between different treatments used ESTIMATE statements. The difference in AVP concentrations among the three treatment groups was tested by an analysis of covariance model with treatment as a factor and baseline (pre-dose on Day 1) as covariate.

RESULTS

The demographics of the subjects enrolled in the study are shown in the below table:

Summary of Demographic Information					
Variable	Summary	Category	30 mg	60 mg	Placebo
Age (yrs)	MEAN		24.56	31.50	27.00
	STD		3.47	5.15	5.60
	MIN		20.00	22.00	20.00
	MAX		31.00	39.00	33.00
Height (cms)	MEAN		179.96	176.13	176.63
	STD		5.78	7.17	4.60
	MIN		172.70	165.50	169.00
	MAX		188.50	186.50	182.70
Weight (kgs)	MEAN		72.06	71.54	73.31
	STD		6.83	9.04	6.31
	MIN		61.10	62.00	65.60
	MAX		81.00	90.00	82.40
Frame	FREQ	Small	1.00	2.00	1.00
	FREQ	Medium	8.00	6.00	6.00
Smoke	FREQ	Yes	7.00	6.00	4.00
	FREQ	No	2.00	2.00	3.00
Smoke (1)	MEAN		9.14	8.50	9.25
	STD		1.21	1.97	1.50
	MIN		7.00	5.00	7.00
	MAX		10.00	10.00	10.00
Drink	FREQ	Yes	7.00	7.00	3.00
	FREQ	No	2.00	1.00	4.00
Drink (2)	MEAN		7.57	7.14	4.00
	STD		6.02	3.18	0.00
	MIN		3.00	2.00	4.00
	MAX		20.00	12.00	4.00

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(1): Mean number of cigarettes consumed per day for those subjects that smoke
 (2): Mean number of units consumed per week for those subjects that drink

The disposition of the subjects is shown in the below table:

Table 1
Disposition of Subjects

Treatment	Enrolled in study	Completed All Study Events	Completed Study Events through Study Day 7
30 mg	9	9	9
60 mg	8	7	8
Placebo	7	7	7

Of the 24 subjects enrolled in the study, 23 completed the study as per protocol. One subject was discontinued from the study by the Investigator on Day 8 because of rectal bleeding on Day 7. One subject developed a dental abscess and received a local anesthetic during dental extraction and subsequent penicillin.

Safety

No death or serious adverse events occurred. The most commonly reported adverse events were dry mouth, headache and thirst.

Pharmacokinetics

Racemic OPC-41061

Semi-logarithmic plots of the mean serum concentrations of racemic OPC-41061 on Days 1 and 28 after administration of 30 mg or 60 mg OPC-41061 qd to the healthy male Caucasian subjects are shown in the below 2 figures:

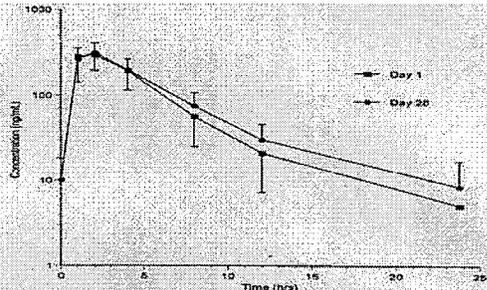


Fig. 6.6.2-1. Mean \pm SD serum concentration-time profile on semi-log scale following administration of 30 mg of OPC-41061 on Day 1 and Day 28

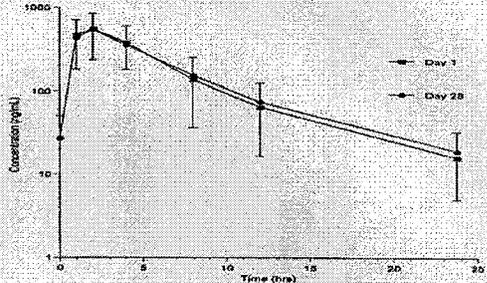


Fig. 6.6.2-4. Mean \pm SD serum concentration-time profile on semi-log scale following administration of 60 mg of OPC-41061 on Day 1 and Day 28

It should be noted that the plasma concentrations of OPC-41061 on Days 1 and 28 at both dose levels in some of the subjects are measurable only up to 12 h after administration. Hence, reliable estimates for λ_z , $t_{1/2z}$, AUC_{0-24} (Day

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1), AUC_{τ} (Day 28) and AUC_{∞} (Day 1) and derived parameters such as CL/F and V_{ss}/F cannot be obtained for racemic OPC-41061.

The below table summarizes PK parameters for OPC-41061 that can be considered reliable:

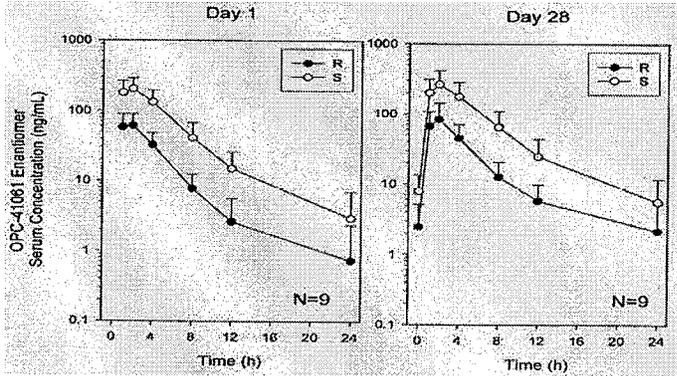
Mean (SD) Cmax and tmax of Racemic OPC-41061 after Doses of 30 mg or 60 mg OPC-41061

Dose, mg	Day	Cmax, ng/mL	tmax, h
30	1	308(127)	1.8 (0.46)
	28	327(88)	1.8 (0.46)
60	1	560 (249)	2.3 (1.2)
	28	548 (249)	1.9 (0.38)

At both dose levels peak concentrations on Days 1 and 28 are attained about 2 h after administration. The mean Cmax values on Days 1 and 28 at the 60 mg dose level are slightly less than twice those after 30 mg OPC-41061. At both dose levels the Cmax values on Day 1 and Day 28 are similar suggesting no important accumulation of OPC-41061 occurs with the qd regimens. The coefficient of variation about the mean Cmax ranges between 27%-45%. The mean tmax ranges between 1.8 and 2.3 h.

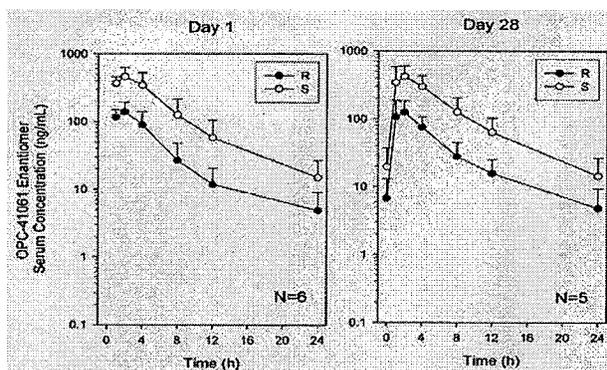
S(-) and R(+) Enantiomers of OPC-41061

Semi-logarithmic plots of the mean serum concentration profiles of R(+) and S(-) OPC-41061 on Days 1 and 28 after administration of 30 mg and 60 mg OPC-41061 are shown in the below figures:



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The results indicate consistently greater serum concentrations of the S(-) enantiomer compared to the R(+) enantiomer after single or multiple doses at both dose levels.

The below table lists the C_{max} and t_{max} values of the S(-) and R(+) enantiomers:

Mean (SD) C_{max} and t_{max} of S(-) and R(+) OPC-41061 after Doses of 30 mg and 60 mg OPC-041061

Dose, mg	Day	S(-) Enantiomer		R(+) Enantiomer	
		C _{max} , ng/mL	t _{max} , h	C _{max} , ng/mL	t _{max} , h
30	1	229 (75)	1.8 (0.44)	71 (29)	1.7 (0.50)
	28	295 (155)	1.8 (0.44)	96 (58)	1.7 (0.50)
60	1	471 (146)	1.8 (0.41)	142 (50)	1.8 (0.41)
	28	424 (188)	1.6 (0.55)	130 (59)	1.6 (0.49)

C_{max} of the S(-) enantiomer is on average about 3 times greater than C_{max} of the R(+) enantiomer indicating stereo-specificity of the pharmacokinetics of the OPC-41061. The peak concentrations of both enantiomers on Days 1 and 28 are attained at about 2 h after dosing. The ratios of the concentration of the S(-) enantiomer to the R(+) enantiomer if measured in the subjects at different times during the 24 h dose interval on Days 1 and 28 range between about 2 and 5 with lower ratios in the beginning and towards the end of the dose interval. Based on the available information it appears that absorption most likely is responsible for the stereospecific kinetics of OPC-41061.

Pharmacodynamics

Urine Volume

The below table lists the mean change from placebo in urine volumes excreted on Days 1, 7 and 28 by subjects receiving 30 mg or 60 mg OPC-41061 qd for 28 days:

Mean Change from Placebo in 24 h Urine Excretion Rates on Days 1, 7 and 28 in Subjects Receiving 30 mg or 60 mg OPC-41061 qd

Time Post-Dose	Mean Change from Placebo in Excretion Rate, mL/min ^a	
	30 mg n=9	60 mg n=8
Day 1		
0-4	5.6	4.7
4-8	5.1	6.0
8-12	2.4	3.0
12-24	0.61	1.2
0-24	2.5	2.9
Day 7		
0-4	2.6	3.2
4-8	3.7	4.0
8-12	1.9	2.6
12-24	0.95	1.6
0-24	1.8	2.4
Day 28		
0-4	2.2	4.4
4-8	3.8	5.8
8-12	1.1	2.0
12-24	0.17	0.74
0-24	1.3	2.4

^a Placebo group n=7

The regimens with 30 mg or 60 mg OPC-41061 qd induce a net increase in mean urine excretion rate over the entire 28 day treatment period. The 60 mg regimen has a greater aquaretic effect than the 30 mg regimen. The onset of the aquaretic effect (palcebo corrected net urine excretion rate ≥ 1 mL/min) occurs in the first collection interval 0-4 h post-dose. Peak excretion rates are seen predominantly in the 4-8 h interval. The duration of the aquaretic effect (palcebo corrected net urine excretion rate ≥ 1 mL/min) appears to be about 10 h and 10-18 h at the 30 and 60 mg dose levels, respectively. The 0-24 mean placebo corrected urine excretion volumes/rates on Day 28 decrease to between 51% and 83% those on Day 1 suggesting a rebound effect with more fluid retention and/or less fluid ingestion.

Fluid Balance

Mean urine volumes excreted and fluids ingested over 24 h on Days 1, 7 and 28 by the subjects treated with 30 mg, 60 mg OPC-41061 or placebo are depicted in the 3 figures below:

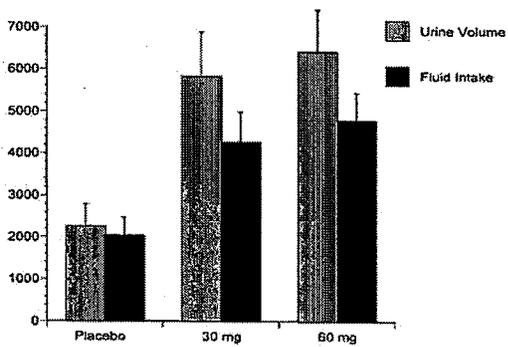


Fig. 6.5.8-1. Urine volume and fluid intake versus dose for Day 1

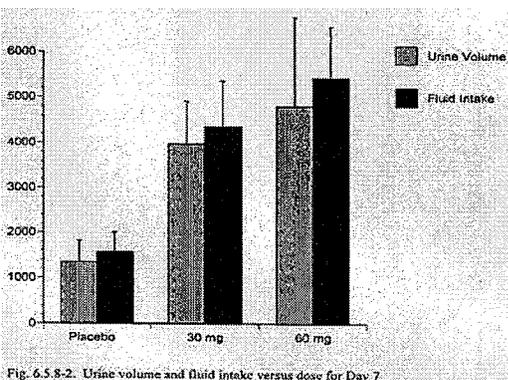


Fig. 6.5.8-2. Urine volume and fluid intake versus dose for Day 7

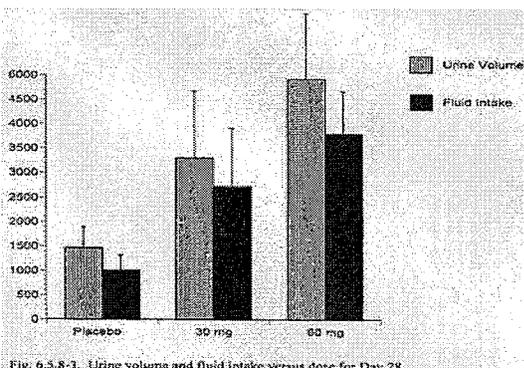


Fig. 6.5.8-3. Urine volume and fluid intake versus dose for Day 28

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The fluid balance on Days 1 and 28 appears to be negative, but positive on Day 7 in the OCP-41061 treated and placebo treated subjects. The mean urine volumes on Days 7 and 28 are smaller than on Day 1. The fluid intake on

Day 7 is greater than on Days 1 and 28. The fluid balance on Day 28 appears to be slightly more negative than on Day 1

Urine Osmolality

Mean urine osmolality (uncorrected for baseline and placebo) of the subjects on Days 1, 7 and 28 of the 28 day treatments is listed in the below table:

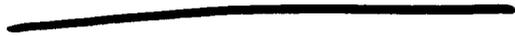
Table 6.5.3.3-2 Urine Osmolality Summary

Study Day	Collection Interval (hr)	Treatment		
		30 mg group (9 subjects) (Mean ± SD)	60 mg group (8 subjects)* (Mean ± SD)	Placebo group (7 subjects) (Mean ± SD)
Screening		775 ± 294	686 ± 360	644 ± 254
-1		853 ± 132	780 ± 223	628 ± 265
1	0-4	59 ± 18	52 ± 22	243 ± 191
	4-8	52 ± 15	50 ± 23	304 ± 229
	8-12	102 ± 42	99 ± 80	242 ± 149
	12-24	251 ± 134	162 ± 65	493 ± 93
7	Pre-dose	533 ± 146	374 ± 155	835 ± 138
7	0-4	116 ± 23	95 ± 37	464 ± 222
	4-8	93 ± 37	68 ± 37	307 ± 182
	8-12	233 ± 58	188 ± 80	628 ± 249
	12-24	329 ± 172	193 ± 89	682 ± 147
14	Pre-dose	484 ± 169	315 ± 154	866 ± 85
21	Pre-dose	542 ± 146	341 ± 228	725 ± 252
27	Pre-dose	538 ± 203	220 ± 127	825 ± 329
28	0-4	168 ± 58	93 ± 24	583 ± 292
	4-8	108 ± 32	75 ± 44	488 ± 206
	8-12	239 ± 86	133 ± 50	673 ± 211
	12-24	377 ± 212	171 ± 82	636 ± 218
Poststudy		655 ± 246	836 ± 156	847 ± 141

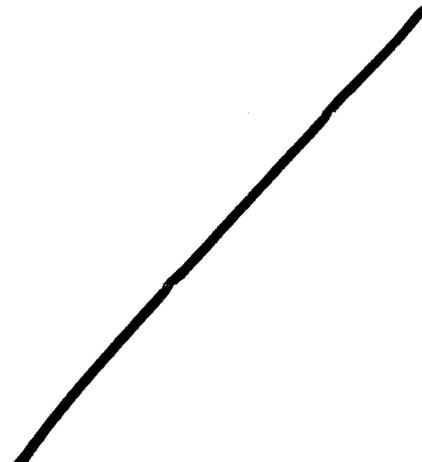
*Seven (7) subjects on Study Day 28 (Subject 20 was not dosed). All values are given in mOsm/kg.
Source: Summary Table 24.

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At both dose levels and throughout the treatment period OPC-41061 decreases urine osmolality relative to placebo. The decrease in mean urine osmolality by 60 mg OPC-41061 is greater than that by 30 mg. The effect in the early part of the dose interval is greater than in the later part. The time duration of the effect of OPC-41061 on osmolality at both dose levels exceeds 24 h, the length of the dose interval. The effect of OPC-41061 on urine osmolality appears to decline over the 28 day treatment period.



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Serum AVP

The serum concentrations of AVP are significantly higher in the 30 mg and 60 mg dose groups than in the placebo group with no significant difference in the AVP levels between the active treatment groups. It should be noted that body position and activity levels which were not defined in the protocol, may have impacted the results.

Conclusions

PK

Racemic OPC-41061

The respective dose normalized peak concentrations at the 60 mg dose level on Days 1 and 28 are 10 % and 16 % smaller than at the 30 mg dose level. The coefficient of variation about the mean C_{max} ranges between 27% and 45%. The mean t_{max} ranges between 1.8 and 2.3 h.

OPC-Enantiomers

The ratios of the mean C_{max} of the S(-) enantiomer to the R(+) enantiomer on Days 1 and 28 are at both dose levels about 3.0 indicating stereospecific kinetics of the enantiomers of OPC-41061. Absorption is most likely responsible for the observed stereo-specificity of the PK of OPC-41061

PD

The regimens with 30 mg or 60 mg OPC-41061 qd induce a net increase in urine volume/excretion rate over the entire 28 day treatment period. The 60 mg regimen exhibits a greater aquaretic effect than the 30 mg regimen. Peak volumes/excretion rates occur mainly in the 4-8 h interval. The onset of the aquaretic effect is seen in the first 0-4 h collection period. The duration of the aquaretic effect of OPC-4106 appears to be about 10 h at the 30 mg dose levels and 10-18 h at the 60 mg level. The mean 0-24 h urine volumes/excretion rate on Day 28 decreases to between 51% and 83% of the Day 1 values. The fluid intake is also smaller on Day 28 than on Day 1.

OPC-41061 decreases urine osmolality relative to placebo at both dose levels and throughout the treatment period. The decrease in mean urine osmolality by 60 mg OPC-41061 is greater than that by 30 mg. The effect on urine osmolality in the early part of the dose interval is greater than in the later part. The duration of the effect of OPC-41061 on urine osmolality at both dose levels exceeds 24 h, the length of the dose interval. The effect of OPC-41061 on urine osmolality appears to weaken over the 28 day treatment period.

and 2.0 kg.

The serum concentrations of AVP appear to be significantly higher in the 30 mg and 60 mg dose groups at most time points than in the placebo group with no significant difference in the AVP levels between the active treatment groups.

Comments

1. The report shows semi-logarithmic plots of the mean concentration profiles of the S(-) and R(+) enantiomers for 24 h on Days 1 and 28. At the 30 mg dose level the mean concentrations are from 9 subjects on Days 1 and 28. At the 60 mg dose level mean concentrations on Day 1 are from 6 subjects and on Day 28 from 5 subjects. The report in Amendment 2, pp.19-32 lists the individual concentrations of the enantiomers as well the concentration ratios. Data are reported on 22 subjects: for 7 subjects all concentrations were BLQ; 8 subjects had measurable concentrations of both enantiomers for 24 h on Day 1, 5 subjects had measurable concentrations of both enantiomers on Day 28 and 5 subjects had measurable concentrations during the 24 h dose interval on Day 1 and Day 28. The list does not provide the dose of OPC-41061 the subjects received. It is unclear why the concentrations of the enantiomers were BLQ in 7 subjects, in whom the concentrations of racemic OPC-41061 were previously measurable. It is unclear how the sponsor came up with 9 subjects who display measurable enantiomer concentrations over a period of 24 h. The plots of the time profiles of the enantiomers should consider only subjects who had measurable concentrations of the enantiomers both on Day 1 and Day 28. Also, time profiles of the enantiomer ratios should be provided.
2. The ratio of the S(-) enantiomer to the R(+) enantiomer during the dosing interval is not constant. Hence, stereospecific distribution or elimination kinetics of tolvaptan cannot be excluded.
3. The sensitivity of the HPLC-UV and LC/MS/MS assays are insufficient for determining AUC₀₋₂₄, λ_z and hence AUC_{0-∞}, CL/F, Vd/F, Rac for the racemic OPC -41061 and the individual enantiomers. As a result, only the respective C_{max} and t_{max} values can be considered unbiased among the parameters computed by the sponsor (see pp. 92-94 of the report for racemic OPC-41061). Assays are required that can measure racemic OPC 41061 and the individual enantiomers for sufficiently long periods ($\geq 3 \cdot t_{1/2z}$ in the terminal log linear phase) such that unbiased estimates for all relevant PK parameters are obtained.
4. The report should define the individual t_{last} for AUC_{tlast} for racemic OPC-41061.
5. In addition to simply listing the individual and mean concentrations, the report should show plots of the serum concentrations of AVP for a better understanding of the meaning of the aggregate data.
6. The sensitivity, specificity, accuracy and precision of the respective assays used is not provided.

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7. The method used for determining urine osmolality should be reported.

Study Report No. 156-98-210: "A Single Center, Placebo Controlled, Double-Blind, Crossover, Randomized, Ascending Single Dose Study to Determine the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Orally Administered OPC-41061 Tablets in Healthy Male and Female Adult Volunteers"

Investigator and Site

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Objectives

To determine the pharmacokinetics, pharmacodynamics, safety and tolerability of OPC-41061 administered to normal healthy male and female volunteers

Investigational Drugs and Formulations

OPC-41061 15 mg tablets (Lot No. 98D82A015A), placebo tablets (Lot No. 97B93P000) were provided by the sponsor.

Design

This was a single center, randomized, double-blind, placebo controlled, ascending single-dose study conducted in normal healthy male and female volunteers. Forty (40) subjects were enrolled in the study with five groups. Each group consisted of 6 subjects treated with a single dose of OPC-41061 (60, 90, 120, 180 or 240 mg) and 2 subjects treated with placebo on Days 1 and 8 under conditions of volumetric fluid replacement (Period 1) and no volumetric fluid replacement (Period 2), respectively. Dose escalation to the next dose level was determined after safety assessment of each dose administration.

Subjects who met the screening criteria entered the study site on the evening of Day-3. On Days -2 and 6, the subjects were kept in-house for having a controlled diet, including fluid intake, and timed collection periods for urine. All subjects received a single dose of OPC-41061 or placebo at about 8 AM on Days 1 and 8 with approximately 240 mL purified water. Subjects were required to consume approximately 1 to 1.5 L of clear fluid on Days -2, -1, and 7, prior to midnight. Subjects were abstained from food and beverages, other than water, from midnight on the evening before dose administration on Days 1 and 8 until lunch following drug administration. They were required to abstain from water for 2 h before dose administration through 2 h post-dose. During the volumetric fluid replacement period, subjects were required to consume the same amount of fluid as excreted during the previous time interval, beginning at 2 h post-dose. On Days 2 and 3, subjects were to have each urine void measured during the 24 h collection period in order to determine the amount of fluid that the subject had to consume throughout the day. During the non-volumetric fluid replacement period, subjects were allowed to consume water ad lib, beginning at 2 h post-dose. All fluid intake was to be monitored and recorded throughout the study. All meal provided by the site were low in sodium (approximately 2 g). Additionally, all meals provided were consistent in their composition between treatment groups. The subjects were allowed to consume only purified water during the study; no tap water was allowed.

During the study the subject were abstained from xanthine-, grapefruit- and alcohol containing products for 72 h before admission and for the duration of the study. Also, tobacco containing products were not to be used during the duration of the study.

The following prior or concomitant medications were prohibited: any recreational drugs in current use; any drug known to stimulate or inhibit drug metabolism within 30 days of dosing; and any over-the-counter, prescription, or herbal products (not including herbal teas) within two weeks of dosing.

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

TABLE 4.2-1 INCLUSION CRITERIA

1. Male and female subjects 18 to 45 years of age, inclusive. Females of childbearing potential had to be using two acceptable barrier contraceptive methods (such as a diaphragm and condom with spermicide). Females of non-childbearing potential are defined as surgically sterile or postmenopausal (menopausal for at least 12 months). Eligible subjects had to sign an informed consent form prior to the initiation of any study procedure.
2. Body weight had to be within $\pm 15\%$ of ideal body weight.
3. No clinically significant diseases or clinically significant abnormal laboratory values as assessed during the screening medical history, physical examination, and pretreatment laboratory evaluations.
4. Normal 12-lead electrocardiogram, or one with abnormalities considered to be clinically insignificant by the investigator.

Sources: Appendices 1-1 (Protocol) and 1-2 (Amendment 001).

TABLE 4.2-2 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 might place the volunteer at risk or interfere with outcome variables of the study including absorption, distribution, metabolism, and excretion of drug. This included, but was 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 (≥ 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. Use of caffeine-containing food or drinks, grapefruit, or grapefruit juice products within 72 hours of admission to the study unit and for the duration of the study.
5. Use of tobacco or tobacco products within 6 months prior to admission to the study unit.
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 that 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 carriage 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 to stimulate or inhibit drug metabolism within 30 days of dosing.
14. Use of any over-the-counter, prescription, or herbal products (not including herbal teas) within two weeks prior to dosing and for the duration of the study.
15. Pregnant or lactating women.
16. Volunteers who had sitting blood pressure, after resting for ≥ 3 minutes, higher than 150/90 mm Hg or lower than 100/50 mm Hg.
17. Volunteers who had a sitting pulse, after resting for ≥ 3 minutes, outside the range of 40 to 90 beats/minute.
18. Volunteers who had participated in any OPC-41061 clinical trial.

Sources: Appendices 1-1 (Protocol) and 1-2 (Amendment 001).

Subjects excluded for a positive reason for drugs of abuse were not re-screened for participation in the study. Subjects excluded for any of the other aforementioned reasons might be re-screened for participation at any time if the exclusion characteristic had changed.

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The scheduled study activities are shown in the below schemes:

TABLE 4.6-1 SCHEDULE OF ASSESSMENTS AND PROCEDURES

Day	-21	-1	0	2	4	6	8	12	23	23.5	24.0	0.5	1	1.5	2	3	4	5	6	7	8	10	12	16	
Medical history	X																								
Informed consent	X																								
Incl/Excl criteria	X	X																							
Phys exam (incl. Wt)	X ^a	X ^a																							
ECG (12-lead)	X	X								X					X		X						X		
Vital signs	X	X								X			X		X	X	X	X	X	X	X	X	X	X	X
Serum chemistry	X	X								X					X		X						X		
Hematology	X	X								X					X		X						X		
Hep. B & C, HIV Screen	X	X								X					X		X						X		
Urinary	X	X								X					X		X						X		
Drug & alcohol screen	X	X								X					X		X						X		
Serum pregnancy	X	X								X					X		X						X		
PK sampling										X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma AVP			X							X					X		X						X		
Serum electrolytes			X							X					X		X						X		
Plasma osmolality			X							X					X		X						X		
Plasma aldosterone			X							X					X		X						X		
Plasma catecholamines			X							X					X		X						X		
Urine creatinine										X					X		X						X		
Urea nitrogen										X					X		X						X		
Serum creatinine									X						X		X						X		
Plasma renin										X					X		X						X		
Coagulation panel	X	X ^b	X ^b																						
Lupus anticoagulant panel	X	X ^b	X ^b																						
Anticardiolipin panel	X	X ^b	X ^b																						
Urine collection			X ^c	X ^c						X		X			X		X						X		
Fluid intake			X ^d	X ^d						X		X			X		X						X		
1-1.5 L of water			X ^e	X ^e						X		X			X		X						X		
Disposition study																									X
Adverse events			X																						X
Discharge from study																									
30 Day follow-up																									

a = including height; b = all females; c = 0 hour equals 0800 hours; d = serious adverse events only; e = determined from 0-24 hour urine specimens beginning with previous 0 hour; f = including serum creatinine; h = procedure might be done on either Day -1 or Day -2; 1 = urine was collected at 0-2, 2-4, 4-6, 6-8, 8-12, 12-23, 23-24 hours; j = fluid intake was measured at 0-2, 2-4, 4-6, 6-8, 8-12, 12-23, 23-24 hours; k = urine was collected at 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-26, 26-28, 28-30, 30-32, 32-36, 36-48, 48-50, 50-52, 52-54, 54-56, 56-60 and 60-72 hours after dosing on Days 1 and 8; l = fluid intake was measured at 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-26, 26-28, 28-30, 30-32, 32-36, 36-48, 48-50, 50-52, 52-54, 54-56, 56-60 and 60-72 hours after dosing on Days 1 and 8; m = procedure might be done on either Day 4, 5, 6 or 7.

TABLE 4.6-1. SCHEDULE OF ASSESSMENTS AND PROCEDURES (Continued)

Day	2	3	3	5	6								
Hours	24	36	48	72	96	120/0	2	4	6	8	12	23	23.5
Medical history													
Informed consent													
Incl/Excl criteria													
Phys. exam (incl. Wt.)													
EKG (12-lead)	X												
Vital signs	X												
Serum Chemistry	X												
Hematology	X												
Hep. B & C, HIV Screen													
Urinalysis	X												
Drug & alcohol screen													
Serum pregnancy ^a													
PK sampling	X	X	X	X	X	X							
Plasma AVP													
Serum electrolytes	X												
Plasma osmolality	X												
Plasma aldosterone	X												
Plasma catecholamines	X												
Urine creatinine	X ^e												
Creatinine clearance	X ^e												
Plasma renin	X												
Coagulation panel	X ^g			X ^h	X ^h	X ^h							
Lupus anticoagulant panel	X ^g			X ^h	X ^h	X ^h							
Anticoagulant panel	X ^g			X ^h	X ^h	X ^h							
Urine collection	X	X ⁱ				X							X ^j
Fluid intake	X	X ⁱ				X							X ^j
1-1.5 L of water						X							X ^j
Dispense study meds						X							
Adverse events	X												
Discharge from study													

30 Day follow-up
 a = including height; b = all females; c = 0 hour equals 0800 hours; d = serious adverse events only; e = determined from 0-24 hour urine specimens beginning with previous 0 hour; f = including serum creatinine; g = procedure might be done on either Day -3 or Day -2; h = urine was collected at 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-26, 26-28, 28-30, 30-32, 32-36, 36-48, 48-50, 50-52, 52-54, 54-56, 56-60 and 60-72 hours after dosing on Days 1 and 8; i = fluid intake was measured at 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-26, 26-28, 28-30, 30-32, 32-36, 36-48, 48-50, 50-52, 52-54, 54-56, 56-60 and 60-72 hours after dosing on Days 1 and 8; j = fluid intake was measured at 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-26, 26-28, 28-30, 30-32, 32-36, 36-48, 48-50, 50-52, 52-54, 54-56, 56-60 and 60-72 hours after dosing on Days 1 and 8; m = procedure might be done on either Day 4, 5, 6 or 7.

TABLE 4.6-1. SCHEDULE OF ASSESSMENTS AND PROCEDURES (Continued)

Day	7								8														
Hours	144/0	2	4	6	8	12	23	23.5	240	0.5	1	1.5	2	3	4	5	6	7	8	10	12	16	
Medical history																							
Informed consent																							
Incl/Excl criteria																							
Phys. exam (incl. Wt.)																							
EKG (12-lead)								X				X		X		X						X	
Vital signs								X			X		X		X		X					X	
Serum Chemistry								X			X		X		X		X					X	
Hematology								X			X		X		X		X					X	
Hep. B & C, HIV Screen																							
Urinalysis								X								X						X	
Drug & alcohol screen																							
Serum pregnancy ^a																							
PK sampling	X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma AVP								X			X		X		X		X					X	
Serum electrolytes								X			X		X		X		X					X	
Plasma osmolality								X			X		X		X		X					X	
Plasma aldosterone								X			X		X		X		X					X	
Plasma catecholamines								X			X		X		X		X					X	
Urine creatinine								X			X		X		X		X					X	
Creatinine clearance								X			X		X		X		X					X	
Plasma renin								X			X		X		X		X					X	
Coagulation panel	X ^g							X			X		X		X		X					X	
Lupus anticoagulant panel	X ^g							X			X		X		X		X					X	
Anticoagulant panel	X ^g							X			X		X		X		X					X	
Urine collection	X							X ⁱ	X		X		X		X		X					X ^j	
Fluid intake	X							X ⁱ	X		X		X		X		X					X ^j	
1-1.5 L of water	X							X ⁱ	X		X		X		X		X					X ^j	
Dispense study meds								X			X		X		X		X					X	
Adverse events	X																						
Discharge from study																							X

30 Day follow-up
 a = including height; b = all females; c = 0 hour equals 0800 hours; d = serious adverse events only; e = determined from 0-24 hour urine specimens beginning with previous 0 hour; f = including serum creatinine; g = procedure might be done on either Day -3 or Day -2; h = urine was collected at 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-26, 26-28, 28-30, 30-32, 32-36, 36-48, 48-50, 50-52, 52-54, 54-56, 56-60 and 60-72 hours after dosing on Days 1 and 8; i = fluid intake was measured at 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-26, 26-28, 28-30, 30-32, 32-36, 36-48, 48-50, 50-52, 52-54, 54-56, 56-60 and 60-72 hours after dosing on Days 1 and 8; j = fluid intake was measured at 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-26, 26-28, 28-30, 30-32, 32-36, 36-48, 48-50, 50-52, 52-54, 54-56, 56-60 and 60-72 hours after dosing on Days 1 and 8; m = procedure might be done on either Day 4, 5, 6 or 7.

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TABLE 4.6-1 SCHEDULE OF ASSESSMENTS AND PROCEDURES (Continued)

Day	9	10	11	12	13	14	21	28	35	42	72
Hours	24	36	48	72	96	120	144	312	480	648	816
Medical history											
Informed consent											
Inclusion criteria											
Phys exam (incl. Wt)							X				
ECG (12-lead)	X					X					
Vital signs	X					X					
Serum Chemistry	X					X					
Hematology	X					X					
Hep. B & C, HIV Screen											
Urinalysis	X					X					
Drug & alcohol screen											
Serum pregnancy ^a						X					
PK sampling	X	X	X	X	X	X	X	X	X	X	X
Plasma AVP											
Serum electrolytes	X										
Plasma osmolality	X										
Plasma aldosterone	X										
Plasma catecholamines	X										
Urine creatinine	X										
Creatinine clearance	X ^b										
Plasma renin	X										
Coagulation panel	X					X				X	
Lupus anticoagulant panel	X					X				X	
Antinuclear panel	X					X				X	
Urine collection	X		X ^c								
Fluid intake	X		X ^d								
Dispense OPC-41061											
Adverse events	X		X	X	X	X	X	X	X	X	X ^e
Discharge from study											
30 Day follow-up											X

a = including height; b = all females; c = 0 hour equals 00:00 hours; d = serious adverse event only; e = determined from 0-24 hour urine specimens beginning with previous 0 hour; f = including serum creatinine; h = procedure might be done on either Day -1 or Day -2; i = urine was collected at 0-2, 3-4, 4-6, 6-8, 8-12, 12-23, 23-24 hours; j = fluid intake was measured at 0-2, 2-4, 4-6, 6-8, 8-12, 12-23, 23-24 hours; k = urine was collected at 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-26, 26-28, 28-30, 30-32, 32-36, 36-48, 48-50, 50-52, 52-54, 54-56, 56-60 and 60-72 hours after dosing on Days 1 and 8; l = fluid intake was measured at 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-26, 26-28, 28-30, 30-32, 32-36, 36-48, 48-50, 50-52, 52-54, 54-56, 56-60 and 60-72 hours after dosing on Days 1 and 8; m = procedure might be done on either Day 4, 5, 6, or 7.

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Pharmacokinetic Profiling

Blood samples for the determination of the plasma concentrations of OPC-41061 and the metabolites DM-4103, DM-4104, DM-4107, DM-4110, DM-4111, DM-4119 and MOP-21826 were collected at the following times on:

Days 1 and 8: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, and 120 h post-dose

Day 8: 144, 312, 480, 648 and 816 h post-dose

Bioassay

OPC-41061 and Metabolites

The plasma concentrations of OPC-41061 and its metabolites were determined by a LC/MS/MS method with an internal standard. The assay is linear in the range between 5.00 and 1000 ng/mL for OPC-41061 and six of the seven metabolites. DM-4103 has a linear range of the calibration curve between 12.5-2500 ng/mL. The respective correlation coefficients for OPC-41061 and the metabolites are ≥ 0.9957. Precision and accuracy of OPC-41061 and the metabolites was estimated with QC samples. For OPC-41061 the accuracy ranges between -5.2% and 5.5 % and the precision is 10.5%. For DM-4103 the accuracy ranges between -1.2 % and 5.4 % and the precision is ≤ 11.1 %. For DM-4104 the accuracy ranges between -5.6 % and 4.3 % and the precision is ≤ 9.5 %. For DM-4105 the accuracy ranges between -1.0 % and 7.4 % and the precision is ≤ 4.8 %. For DM-4107 the accuracy ranges between -5.1 % and 4.9 % and the precision is ≤ 12.3 %. For DM-4110 the accuracy ranges between -5.7 % and 7.1 % and the precision is ≤ 9.7 %. For DM-4111 the accuracy ranges between -6.1% and 7.1 % and the precision is ≤ 9.9 %. For DM-4119 the accuracy ranges between -6.1 % and 8.0% and the precision is ≤ 9.7 %. For MOP-21826 the accuracy ranges between -2.5 % and 8.0% and the precision is ≤ 5.2 %. The stability of the analytes in plasma was confirmed by exposure to 3 freeze/thaw cycles, long term freezer exposure at -80°C for 21 days. Also, the stability of the analytes in the extract was demonstrated for 24 h at room temperature. The measurements were performed by

b(4)

Plasma AVP, PRA, Aldosterone, Epinephrine and Osmolality

No information on the assays is provided.

PK Analysis

The following parameters were determined: C_{max}, t_{max}, AUC_t, AUC_∞, V_z/F, CL/F, λ_z and t_{1/2z}. In addition, all parameters with the exception of V_z/F and CL/F were determined for DM-4103, DM-4104, DM-4105, DM-4107, DM-4110, DM-4111, and DM-4119. No measurable plasma concentrations for MOP-21826 were observed. Standard compartment model independent methods were used. C_{max} and t_{max} were directly taken from the data sets. AUC_t was computed by using the linear trapezoidal rule. WinNonlin Professional (Version 3.01) was used. The time intervals used to measure λ_z and t_{1/2z} for OPC-41061 and the metabolites in the terminal log linear phase are not indicated.

Pharmacodynamic Profiling

Urine Volume

Urine volumes were collected during the following intervals on:

Days -2,-1, 6, 7: 0-2, 2-4, 4-6, 6-8, 8-12, 12-23, and 23-24 h

Days 1 and 8: 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-26, 26-28, 28-30, 30-32, 32-36, 36-48, 48-50, 50-52, 52-54, 54-56, 56-60 and 60-72 h post-dose

Fluid Intake

Fluid intake was measured during the following intervals on:

Days-2, -1, 6, 7: 0-2, 2-4, 4-6, 6-8, 8-12, 12-23, 23-24 h

Days 1 and 8: 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-26, 26-28, 28-30, 30-32, 32-36, 36-48, 48-50, 50-52, 52-54, 54-56, 56-60 and 60-72 h after dosing on Days 1 and 8

Serum Electrolytes and Plasma Osmolality

Serum concentrations of Na⁺, K⁺ and plasma osmolality were determined at the following times after drug administration on:

Day 1: -24 h pre-dose, 2, 4, 6, 8, 12, and 24 h post-dose

Day 8: pre-dose, 2, 4, 6, 8, 12, and 24 h post-dose

Plasma AVP

Plasma concentrations of AVP were collected at the following times after drug administration on:

Day 1: -24 h, pre-dose, 2, 4, 8, and 12 h post-dose

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

Plasma Renin Activity (PRA)

PRA was measured at the following times on:

Day 1: -24 h pre-dose, 2, 4, 8 and 24 h after dosing

Day 8: pre-dose, 2, 4, 8 and 24 h after dosing

Plasma Aldosterone and Catecholamines

Plasma aldosterone and catecholamines were measured at the following times after drug administration on:

Day 1: -24 h, pre-dose, 2, and 24 h post-dose

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

PD Data Analysis

Change from baseline of the values of urine volume excreted, urine osmolality, urine potassium, urine sodium, plasma AVP, plasma renin activity (PRA), plasma osmolality, serum potassium and sodium were summarized by treatment (with and without volumetric fluid replacement) within each dose group. Free water clearance, CH₂O, was calculated from:

$$CH_2O = V - Cosm$$

where Cosm is the osmolar clearance (mL/min) and V is the excretion rate of urine (mL/min). Cosm is obtained from $Cosm = Uosm \bullet V / Posm$, where Uosm (mOsm/kg H₂O) and Posm (mOsm/kg H₂O) is the respective osmolality in urine and plasma.

Statistical Analysis

Descriptive statistics were used to summarize the PK data. Regression analysis was used on log transformed AUC_∞ and C_{max} vs dose. Linear regression analysis was done on t_{1/2z} and CL/F vs dose. The 95% confidence intervals about the slope were calculated.

RESULTS

Demographics and Baseline Characteristics

The demographics and baseline characteristics of the subjects are listed in the below table:

TABLE 63-1. DEMOGRAPHICS AND BASELINE CHARACTERISTICS FOR ALL ENROLLED SUBJECTS

Characteristics	OPC 60 mg N = 6	OPC 90 mg N = 6	OPC 120 mg N = 6	OPC 180 mg N = 6	OPC 240 mg N = 6	Placebo N = 10
Age (years)						
Mean ± SD	29.2 ± 8.8	26.3 ± 7.4	25.7 ± 3.9	33.7 ± 7.4	26.5 ± 9.9	28.7 ± 8.1
Range	20-43	19-37	20-31	25-44	18-44	18-41
Height (cm)						
Mean ± SD	174.2 ± 5.3	172 ± 6.4	181.3 ± 6.3	175.8 ± 9.2	172 ± 13.7	174.3 ± 10.2
Range	168-183	165-180	170-189	160-186	134-186	160-187
Gender, n (%)						
Male	5 (83.3)	5 (83.3)	4 (66.6)	5 (83.3)	3 (50.0)	7 (70.0)
Female	1 (16.6)	1 (16.6)	2 (33.3)	1 (16.6)	3 (50.0)	3 (30.0)
Race, n (%)						
Caucasian	5 (83.3)	5 (83.3)	6 (100)	4 (66.6)	5 (83.3)	8 (80.0)
Black	0	1 (16.6)	0	2 (33.3)	1 (16.6)	2 (20.0)
Hispanic	1 (16.6)	0	0	0	0	0
Smoking status, n (%)						
Never	1 (16.6)	4 (66.6)	5 (83.3)	3 (50.0)	5 (83.3)	10 (100)
Ex-smoker	5 (83.3)	2 (33.3)	1 (16.6)	3 (50.0)	1 (16.6)	0
Drinking status, n (%)						
Never	0	2 (33.3)	3 (50.0)	0	2 (33.3)	3 (30.0)
Drinker	5 (83.3)	3 (50.0)	3 (50.0)	5 (83.3)	2 (33.3)	6 (60.0)
Ex-drinker	1 (16.6)	1 (16.6)	0	1 (16.6)	2 (33.3)	1 (10.0)

Source: Summary Table 4 and Appendix 11-3.1 to 3.3.

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Disposition of Subjects

Forty subjects were enrolled in the study with 30 subjects treated with OPC-41061 and 10 subjects treated with placebo. One subject receiving 180 mg OPC-41061 withdrew consent because of an adverse experience (delusions) after two days in the study. One subject receiving 240 mg OPC-41061 withdrew from the study because of personal reasons. One subject in the 240 mg group and another subject in the placebo group were lost to follow-up. A total of 27 OPC-41061 treated subjects and 9 placebo treated subjects completed the study.

Pharmacokinetics

Linear plots of the median plasma concentrations of OPC-41061 against time in the subjects during Period 1 with volumetric replacement and during Period 2 without volumetric replacement are shown in the below 2 figures and the median PK parameters estimated by the sponsor for OPC-41061 and metabolites are shown in the below 2 tables:

Figure 6.5-1: Median Plasma Concentration vs. Time Profiles of OPC-41061 Following Oral Administration of 60, 90, 120, 180 and 240 mg of OPC-41061 Dose in Subjects with Volumetric Fluid Replacement (Period 1)

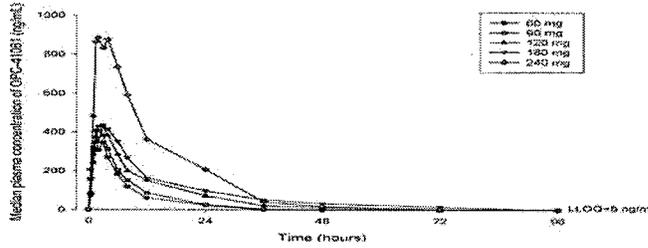
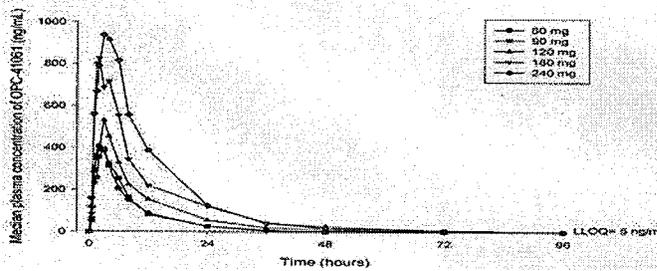


Figure 6.5-2: Median Plasma Concentration vs. Time Profiles of OPC-41061 Following Oral Administration of 60, 90, 120, 180 and 240 mg of OPC-41061 Dose in Subjects Without Volumetric Fluid Replacement (Period 2)



For most of the doses the plasma concentrations of OPC-41061 cannot be followed for a sufficient time interval ($\geq 2 \cdot t_{max} + 3 \cdot t_{1/2z}$) to reliably estimate λ_z and derived parameters. Plasma concentrations are measurable up to 24 h in all subjects of the 60 and 90 mg dose groups, up to 36 h in all subjects in the 120 and 180 mg dose groups and up to 48 h in all subjects of the 240 mg dose groups. The sponsor's estimates for $t_{1/2z}$ for tolvaptan vary between 6 h and 16 h and tend to increase with dose confirming that the assay used does not allow a follow-up of the plasma concentrations for a sufficiently long time interval. It appears though that the fraction of the AUC_{∞} determined by λ_z is relatively minor for OPC-41061 so that the bias in the estimates of AUC_{∞} and derived parameters (CL/F) is likely smaller than in the estimates for $t_{1/2z}$. The same limitation holds true for the sponsor's estimates for the parameters of the metabolites. As with the parent drug the sensitivity of the assay is insufficient for the metabolites. For tolvaptan and the metabolites DM-4107 and DM-4111 the parameters obtained at the 240 mg dose level only can be considered reliable. At dose levels < 240 mg the parameters other than C_{max} and t_{max} should be interpreted with caution. For the metabolites DM-4103, DM-4104, DM-4105, DM-4110, 4114 and DM-4119 this holds true for the parameters reported at all dose levels.

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The below tables summarize the main parameters for parent drug and metabolites estimated by the sponsor:

Median PK Parameters for OPC-41061 for Periods 1 (P1) and Period 2 (P2)

Dose mg	Cmax, ng/mL		tmax h		t1/2z h		AUC _∞ ng•h/mL		CL/F mL/min/kg	
	P 1	P2	P1	P2	P1	P2	P1	P2	P 1	P2
60	374	399	2.0	2.3	6.0	6.7	2789	3216	4.4	3.8
90	418	428	3.0	3.0	6.2	7.7	3113	3809	5.9	5.8
120	569	530	3.0	3.0	7.3	10	6245	5490	3.6	4.6
180	577	845	2.0	3.0	16	14	7528	9309	4.8	3.8
240	916	969	2.5	4.0	13	12	13181	13289	4.3	3.7

Median PK Parameters for DM-4103 for Period 1 (P1) and Period 2 (P2)

Dose mg	Cmax, ng/mL		tmax h		t1/2z h		AUC _∞ ng•h/mL	
	P 1	P2	P1	P2	P1	P2	P1	P2
60	282	337	24	12	125	184	49859	71541
90	322	447	16	10	134	138	60166	82817
120	470	651	24	24	124	171	88868	181449
180	649	1065	36	24	116	188	162562	259841
240	1009	1304	24	24	123	216	216345	505976

Median PK Parameters for DM-4104 for Period 1 (P1) and Period 2 (P2)

Dose mg	Cmax, ng/mL		tmax h		t1/2z h		AUC _∞ ng•h/mL	
	P 1	P2	P1	P2	P1	P1	P1	P2
60	141	121	2.5	3.0	6.2	6.2	1029	1010
90	241	160	3.0	3.0	5.6	6.1	1585	1433
120	226	185	3.5	4.0	7.2	7.3	2235	1750
180	242	276	2.5	3.0	8.7	9.2	3084	2819
240	374	252	3.0	3.0	7.2	11	4566	3818

Median PK Parameters for DM-4105 for Period 1 (P1) and Period 2 (P2)

Dose mg	Cmax, ng/mL		tmax h		t1/2z h		AUC _∞ ng•h/mL	
	P 1	P2	P1	P2	P1	P2	P1	P2
60	34.0	28.9	2.0	3.0	8.1	7.5	413	266
90	44.9	30.5	3.0	3.0	8.0	6.8	497	393
120	42.1	32.2	4.0	3.5	10	10	713	491
180	49.0	44.3	2.5	3.0	11	10	1039	778
240	65.0	45.7	3.5	3.0	11	12	1737	1352

Median PK Parameters for DM-4107 for Period 1 (P1) and Period 2 (P2)

Dose mg	Cmax, ng/mL		tmax h		t1/2z h		AUC _∞ ng•h/mL	
	P1	P2	P1	P2	P1	P2	P1	P2
60	156	124	3.5	5.0	11	11	2564	1915
90	234	173	4.0	4.2	19	12	3803	2832
120	199	184	5.0	6.0	17	18	4462	3929
180	344	334	4.0	6.0	18	16	7687	6924
240	353	315	5.0	6.2	16	17	9265	8900

Median PK Parameters for DM-4110 for Period 1 (P1) and Period 2 (P2)

Dose mg	Cmax, ng/mL		tmax h		t1/2z h		AUC _∞ ng•h/mL	
	P1	P2	P1	P2	P1	P2	P1	P2
60	43.1	43.8	2.5	3.0	11	11	717	761
90	82.8	70.8	2.5	3.5	11	11	1418	1230
120	84.2	78.6	3.5	4.0	13	12	1450	1506
180	105	99.2	2.0	3.0	15	13	2104	2106
240	145	131	4.0	4.0	12	15	3429	3206

Median PK Parameters for DM-4111 for Period 1 (P1) and Period 2(P2)

Dose mg	Cmax, ng/mL		tmax h		t1/2z h		AUC _∞ ng•h/mL	
	P1	P2	P1	P2	P1	P2	P1	P2
60	110	93.3	4.0	4.0	7.7	8.9	1693	1646
90	160	131	4.0	3.5	9.0	8.8	2896	2452
120	186	155	5.0	5.0	10	10	3759	3644
180	216	230	5.0	6.0	14	12	4880	5331
240	308	306	5.0	8.0	12	11	8554	7770

Median PK Parameters for DM-4119 for Period 1 (P1) and Period 2 (P2)

Dose mg	Cmax, ng/mL		tmax h		t1/2z h		AUC _∞ ng•h/mL	
	P1	P2	P1	P2	P1	P2	P1	P2
60	15.1	13.9	2.5	3.0	7.1	5.8	205	204
90	39.3	30.9	3.5	3.0	6.8	8.0	402	437
120	23.8	26.0	3.5	4.0	10	10	447	399
180	31.9	36.1	2.5	3.0	11	14	517	564
240	43.9	43.0	3.5	3.0	12	11	781	854

Linear regressions of the dose normalized Cmax and AUC_∞ of OPC-41061 on dose are shown below:

Figure 6.5-3: Plot of dose normalized C_{max} vs. dose following oral administration of 60, 90, 120, 180 and 240 mg of OPC-41061 dose in subjects with volumetric fluid replacement (Period 1)

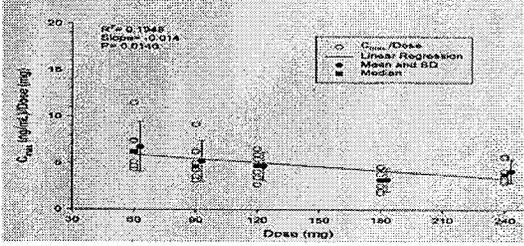


Figure 6.5-4: Plot of dose normalized AUC_∞ vs. dose following oral administration of 60, 90, 120, 180 and 240 mg of OPC-41061 dose in subjects with volumetric fluid replacement (Period 1)

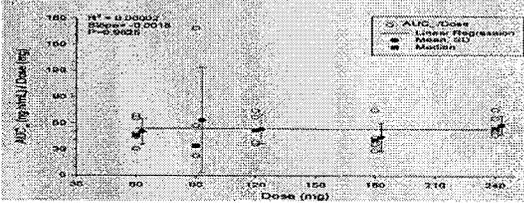


Figure 6.5-5: Plot of dose normalized C_{max} vs. dose following oral administration of 60, 90, 120, 180 and 240 mg of OPC-41061 dose in subjects without volumetric fluid replacement (Period 2)

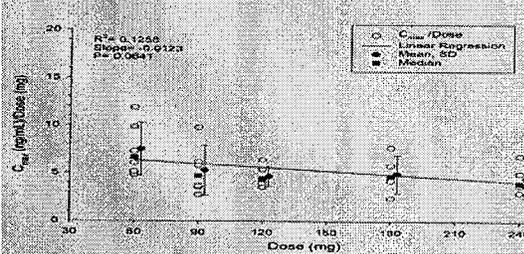
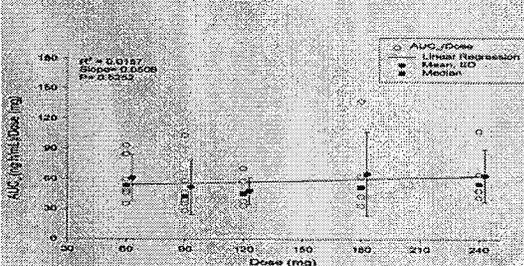


Figure 6.5-6: Plot of dose normalized AUC_∞ vs. dose following oral administration of 60, 90, 120, 180 and 240 mg of OPC-41061 dose in subjects without volumetric fluid replacement (Period 2)



The results indicate that the slope for C_{max} in Periods 1 and 2 is negative and statistically significantly different from zero indicating that the absorption kinetics of OPC-41061 are less than dose proportionate. The corresponding slope in the regressions of the dose normalized AUC_{∞} on dose is not significantly different from zero suggesting linear elimination PK of OPC-41061. T_{max} of OPC-41061 appears not to be impacted by the dose level. Taken together the results suggest a slowed but not diminished absorption of OPC-41061 as the dose is increased. The

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percent coefficient of variation about mean C_{max} and AUC_t ranges between 30 % and 48 % and 18 % and 92 %, respectively, indicating marked inter-subject variation.

The median C_{max} for OPC-41061 and the metabolites, with the exception of DM-4103, is similar in Periods 1 and 2. With DM-4103 C_{max} of Period 2 is consistently greater than in Period 1. The plasma concentration-time curve of DM-4103 decays at a much slower rate than the profiles of OPC-41061 and the other metabolites, so that at the end of the 7 day washout period observed in this study, significant amounts of DM-4103 remain in the circulation and contribute to C_{max} in Period 2. The dose normalized C_{max} values in Period 1 of DM-4103 at the 5 dose levels are comparable suggesting dose proportional kinetics of the metabolite.

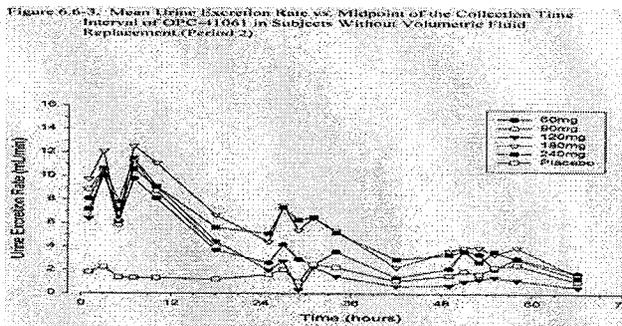
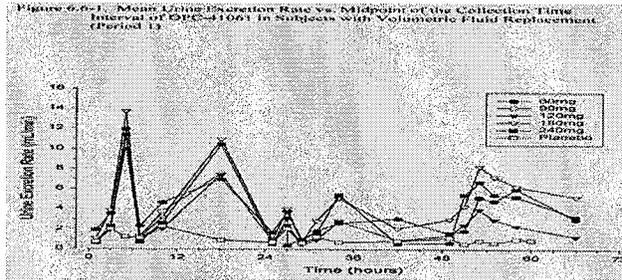
The median t_{max} values of OPC-41061 and the metabolites, except for DM-4103, are in a range between 2 h to 6 h suggesting that the kinetics of the metabolites, except for DM-4103, are formation limited. The t_{max} of DM-4103 ranges between 10 h and 36 h suggesting that elimination is the rate limiting step for the kinetics of DM-4103.

The parameter estimates of OPC-41061 and the metabolites, with the exception of DM-4103 in Periods 1 and 2 are comparable.

Pharmacodynamics

Urine Excretion Rate

Linear plots of the time profiles of the mean urinary excretion rates (uncorrected for baseline and placebo) in Periods 1 and 2 are shown in the below figures:



The time profile of the mean urine excretion rate in Period 2 appears to be smoother than in Period 1 suggesting possibly that fluid replacement in Period 2 (subject controlled) was more efficient than in Period 1 (volumetric replacement)

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The mean changes from baseline (with/out placebo correction) in urine excretion rate in Period 1 are shown in the below 2 tables:

Mean Change from Baseline in Urine Excretion Rate in Period 1 in Healthy Subjects

Collection Interval, h	Mean Change from Baseline in Urine Excretion Rate in Period 1, mL/min					Placebo
	OPC-41061 Dose Level, mg					
	60	90	120	180	240	
0-2	6.2	6.1	5.7	7.6	5.5	0.98
2-4	7.3	9.1	9.6	11.0	9.7	0.98
4-6	4.6	5.6	5.5	7.5	7.1	-0.33
6-8	9.6	9.1	10.3	12.7	10.6	0.092
8-12	5.3	6.9	6.7	10.0	9.9	0.21
12-24	1.5*	2.3	2.3	4.2	5.0	0.095
24-26	-0.60	na	2.0	3.0	5.0	0.31
26-28	2.7	na	3.5	7.1	6.0	0.20
28-30	2.9	na	2.7	6.1	4.8	-0.020
30-32	3.7	na	2.0*	5.1	4.5	0.14
32-36	1.3	na	0.54	4.3	2.7	0.38
36-48	-0.066	na	0.0078	1.8	1.0*	0
48-50	-0.22	na	0.23	2.7	1.5	0.87
50-52	1.9	na	0.19	4.9	2.2	0.42
52-54	0.01	na	0.23	3.9	1.4	0.75
54-56	1.3	na	0.11	5.7	1.7	0.48
56-60	0.84	na	-0.16	3.0	0.75	0.43
60-72	-0.29	na	-0.069	1.2	0.23	0.11
0-24	3.9	4.8	4.8	7.0	6.9	0.27
24-48	0.91	na	0.95	3.4	2.7	0.11
48-72	0.24	na	0	2.5	0.80	0.34

*last measured mean net excretion rate \geq 1.0 mL/min na=not available

Mean Change from Baseline (Placebo Corrected) in Urine Excretion Rate in Period 1 in Healthy Subjects

Collection Interval, h	Mean Change in Urine Excretion Rate (Placebo Corrected) from Baseline in Period 1, mL/min ^a				
	OPC-41061 Dose Level, mg				
	60	90	120	180	240
0-2	5.2	5.1	4.8	6.6	4.6
2-4	6.3	8.1	8.6	10.0	7.8
4-6	4.9	4.9	5.8	7.8	7.4
6-8	9.5	8.9	10.2	12.6	10.5
8-12	5.1	6.7	6.5	9.8	9.7
12-24	1.4*	2.2	2.2	4.1	4.9
24-26	-0.91	na	1.7	2.7	4.6
26-28	2.5	na	3.3	6.9	5.8
28-30	2.9	na	2.7	6.1	4.8

30-32	3.5	na	1.9*	5.0	4.4
32-36	0.95	na	0.16	3.9	2.3
36-48	-0.066	na	0.0078	1.8	1.0*
48-50	-0.99	na	-0.64	1.8	0.59
50-52	1.5	na	-0.23	4.5	1.8
52-54	-0.74	na	-0.53	3.1	0.60
54-56	0.83	na	-0.38	5.2	1.2
56-60	0.81	na	-0.60	2.6	0.32
60-72	-0.34	na	-0.12	1.2	0.18
0-24	3.7	4.5	4.6	6.7	6.6
24-48	0.79	na	0.83	3.3	2.5
48-72	-0.096	na	-0.27	2.2	0.46

^a pooled placebo corrected *last measured mean net excretion rate \geq 1.0 mL/min na= not available

Mean Change from Baseline in Urine Excretion Rate in Period 2 in Healthy Subjects

Collection Interval, h	Mean Change from Baseline in Urine Excretion Rate in Period 2, mL/min					Placebo
	OPC-41061 Dose Level, mg					
	60	90	120	180	240	
0-2	3.6	6.8	4.5	4.3	5.8	0.27
2-4	7.0	8.9	8.5	8.4	8.6	-0.51
4-6	2.6	3.5	6.0	2.4	4.9	-0.61
6-8	5.2	7.6	9.5	9.3	8.0	-0.95
8-12	4.3	5.6	6.7	7.1	6.0	-0.73
12-24	1.9*	2.3	3.5*	3.8*	4.2	0.003
24-26	-1.9	na	0.33	-0.98	3.7	0.28
26-28	0.62	na	1.1	3.8	5.9	-1.1
28-30	-0.60	na	-0.70	1.5	4.1	-1.3
30-32	-2.2	na	1.2	3.3	3.9	0.14
32-36	-0.21	na	-0.43	1.4	2.1	0.051
36-48	-0.44	na	-0.12	-0.62	1.4	-0.48
48-50	-2.4	na	-0.95	-1.8	1.9	0.19
50-52	0.09	na	0.66	0.22	2.2 *	-1.3
52-54	-0.18	na	0.23	0.075	0.44	-0.61
54-56	-2.5	na	0.35	0.18	0.94	-0.11
56-60	-0.75	na	-0.72	-0.079	-0.18	0.26
60-72	-0.063	na	-0.20	-1.3	-0.21	-0.53
0-24	3.2	4.3	5.2	5.1	5.3	-0.27
24-48	-0.59	na	-0.022	0.56	2.5	-0.40
48-72	-0.57	na	-0.31	-0.77	0.32	-0.37

*last measured mean net excretion rate \geq 1.0 mL/min na= not available

Mean Change from Baseline (Placebo Corrected) in Urine Excretion Rate in Period 2 in Healthy Subjects

Mean Change from Baseline (Placebo Corrected) in Urine Excretion Rate in Period 2, mL/min ^a					
Tolvaptan Dose Level, mg					
Collection Interval, h	60	90	120	180	240
0-2	3.3	6.6	4.2	4.1	5.5
2-4	7.5	9.4	9.0	8.9	9.1
4-6	3.2	4.1	6.6	3.0	5.5
6-8	6.1	8.6	10.5	10.3	9.0
8-12	5.0	6.3	7.5	7.8	6.7
12-24	1.9*	2.3	3.5*	3.8*	4.2
24-26	-2.2	na	0.05	-1.3	3.4
26-28	1.8	na	2.2	4.9	7.0
28-30	0.67	na	0.57	2.8	5.4
30-32	-2.4	na	1.0	3.1	3.7
32-36	-0.26	na	-0.48	1.3	2.0
36-48	0.035	na	0.36	-0.14	1.8
48-50	-2.6	na	-1.1	-2.0	1.7
50-52	1.4	na	2.0	1.5	3.5
52-54	0.43	na	0.83	0.68	1.1
54-56	-2.4	na	0.36	0.29	1.1*
56-60	-1.0	na	-1.0	-0.34	-0.44
60-72	-0.47	na	0.33	-0.77	-0.32
0-24	3.5	4.5	5.5	5.4	5.6
24-48	-0.20	na	0.37	0.95	2.9
48-72	-0.20	na	0.057	-0.40	0.69

^a pooled placebo corrected *last measured mean net excretion rate ≥ 1.0 mL/min
na=not available

There are no systematic differences in the aquaretic activity of OPC-41061 between the the 2 periods. Both data sets indicate a fast onset of the aquaretic activity of OPC-41061 in the first 0-2 h collection interval in both periods. Peak rates are observed in the 2-4, 4-6 or 6-8 h collection intervals suggesting a possible lagging of the aquaretic effect behind the plasma concentrations. The peak excretion rates are less than dose proportional indicating a nonlinear dose-effect relationship. Most of the net 24 h urine excretion rates on Days 2 and/or 3 are negative suggesting a rebound effect with increased retention of fluid. If a mean net excretion rate of ≥ 1.0 mL/min is considered a lower threshold value for aquaretic activity of OPC-41061 (corresponding to ≥ 100 % increase of the normal urine excretion rate of about 1 mL/min), estimates of the duration of the effect of OPC-41061 can be obtained by determining the last time point at which the mean net excretion rate is ≥ 1.0 mL/min.

The estimates for the duration of the aquaretic effect are provided in the below table:

Mean Time Duration of Aquaretic Effect of OPC-41061 in Healthy Subjects

Time Duration of Aquaretic Effect, h									
OPC-41061 Dose Level, mg									
60		90		120		180		240	
P 1	P 2	P 1	P 2	P 1	P 2	P 1	P 2	P 1	P 2
18 ^a	18 ^a	na	na	31 ^a	18 ^a	>72 ^a	18 ^a	42 ^a	51 ^a

18 ^b	18 ^b	na	na	31 ^b	18 ^b	>72 ^b	18 ^b	42 ^b	55 ^b
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^abaseline corrected ^bbaseline and placebo corrected na= not available

Both data sets provide similar estimates for the time duration of the aquaretic effect of OPC-41061 in both periods. There is considerable variability in the estimates. There appears to be a trend for a longer time duration of the effect with an increase in dose. At the 60 mg level the offset time is at 18 h and increases to between 42 and 55 h at the 240 mg dose level.

Free Water Clearance

Mean free water clearance profiles over 24 h after dosing in Periods 1 and 2 are shown in the below 2 figures:

Figure 6.6-2. Mean Free Water Clearance Over Time Profile of OPC-41061 for Subjects With Volumetric Fluid Replacement (Period 1)

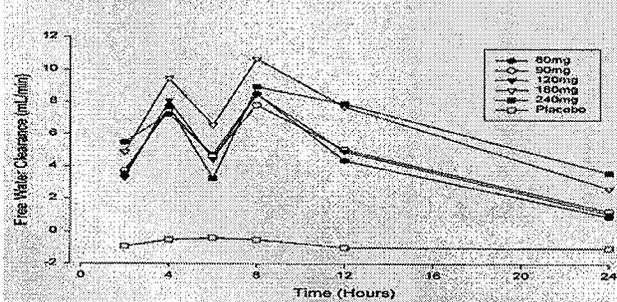
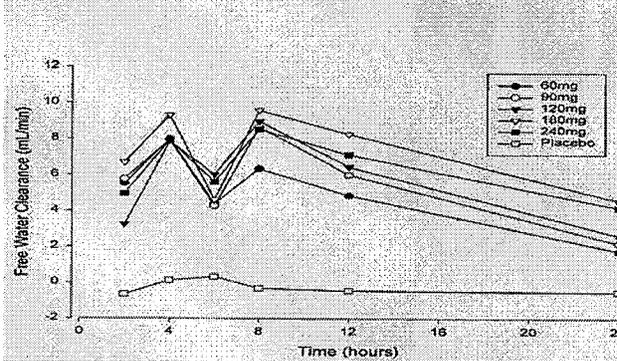


Figure 6.6-4. Mean Free Water Clearance Over Time Profile of OPC-41061 for Subjects Without Volumetric Fluid Replacement (Period 2)



The plots indicate a clear increase in free water clearance with all doses of OPC-41061 compared to placebo in both periods. The clearance values at the different dose levels of OPC-41061 are overlapping.

The mean free water clearance listed in the below table:

Mean Free Water Clearance Values in Periods 1 and 2

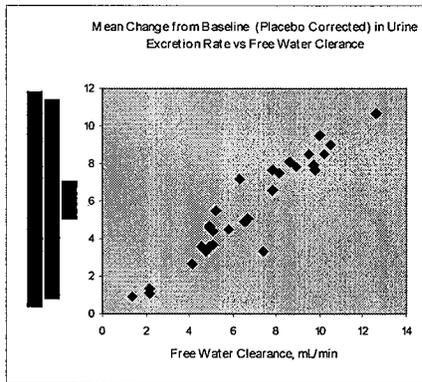
	Mean Free Water Clearance, mL/min					
	Collection Interval, h					
	0-2	2-4	4-6	6-8	8-12	12-24

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Dose, mg	P1	P2	P1	P2	P1	P2	P1	P2	P1	P2	P1	P2
Placebo	-0.91	-0.64	-0.51	0.13	-0.39	0.34	-0.50	-0.31	-0.98	-0.44	-1.02	-0.51
60	5.5	5.5	7.2	8.0	4.7	4.4	8.5	6.3	4.4	4.9	0.91	1.8
90	3.7	5.8	7.5	7.9	4.6	4.3	7.8	8.6	5.1	6.0	1.3	2.2
120	3.3	3.2	8.1	7.9	4.5	6.0	8.5	9.0	4.9	6.5	1.1	2.6
180	4.9	6.7	9.5	9.3	6.6	4.6	11	9.6	7.7	8.3	2.7	4.6
240	3.6	5.0	7.7	7.9	3.3	5.6	9.0	8.5	7.9	7.1	3.6	4.2

The free water clearance time profiles in the subjects receiving placebo show no time dependence and most of the values are slightly negative in both periods. The free water clearance profiles in the subjects receiving OPC-41061 during Periods 1 and 2 are similar. The increase in free water clearance is observable in the first collection interval of 0-2 h post-dose. Peak increases of the free water clearance are observed at 4 h to 8 h after dosing. At 18 h after administration the mean free water clearance in the subjects receiving OPC-41061 is still greater than in the subjects receiving placebo indicating that the aquoretic effect persists for ≥ 18 h. The effects of OPC-41061 on free water clearance at the different dose levels appear to overlap.

The mean change from baseline (placebo corrected) in urine excretion rate and free water clearance are correlated as shown below:



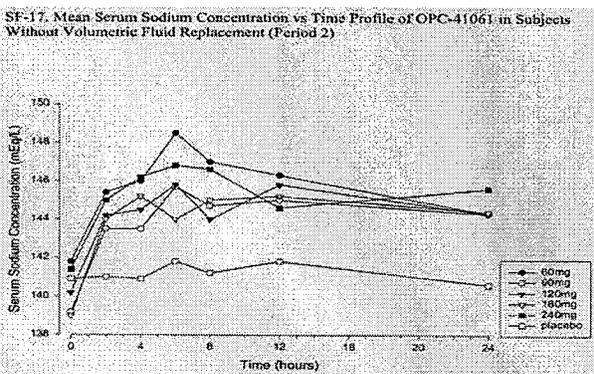
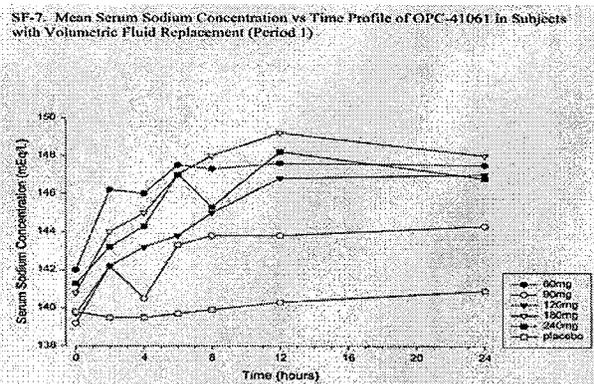
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$$y = -0.521 + 0.912 \cdot x, r^2 = 0.893$$

The data indicate good agreement between the baseline and placebo corrected urine excretion rate and free water clearance.

Serum Na⁺ Concentration

Linear plots of the serum sodium profiles over 24 h after placebo or OPC-41061 in Periods 1 and 2 are shown in the below 2 figures:



The baseline serum concentrations of Na^+ vary among the groups. The mean serum Na^+ profiles in the subjects receiving placebo show no significant time dependency in Periods 1 or 2. In both periods there is a clear time dependent increase in the sodium concentrations observable starting about 2 h after administration. The serum Na^+ levels appear to attain a plateau at about 12 post-dose in Period 1, whereas the peak increase in serum Na^+ is observed at about 6 h post-dose in Period 2. The offset of the effect of OPC-41061 on serum Na^+ exceeds 24 h. The effects on serum Na^+ exhibited by the different dose levels of tOPC-41061 are overlapping.

The below two tables list the mean change from baseline (with/out placebo correction) in serum Na^+ in Period 1:

Mean Change from Baseline in Serum Na^+ in Period 1

Time Post-Dose h	Mean Change from Baseline in Serum Na^+ Concentration ^a in Period 1 mEq				
	OPC-41061 Dose Levels, mg				
	60	90	120	180	240
2	4.2	3.0	2.5	3.2	1.8
4	4.0	1.3	3.5	4.2	3.0
6	5.5	4.2	4.2	6.2	5.7
8	5.3	4.7	5.3	7.2	4.0
12	5.4	4.7	7.2	8.3	6.8

24	5.5	5.2	7.3	7.2	5.5
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Mean Change from Baseline (Placebo Corrected) in Serum Na⁺ in Period 1

Time Post-Dose, h	Mean Change from Baseline (Placebo Corrected) in Serum Na ⁺ Concentration ^a in Period 1 mEq				
	OPC-41061 Dose Levels, mg				
	60	90	120	180	240
2	4.5	3.3	2.8	3.5	2.1
4	4.3	1.6	3.8	4.5	3.3
6	5.6	4.3	4.3	6.3	5.8
8	5.2	4.6	5.2	7.1	3.9
12	4.9	4.2	6.7	7.8	6.3
24	4.4	4.1	6.2	6.1	4.4

^a Corrected for pooled placebo

The below two tables list the mean change from baseline (with/out placebo correction) in serum Na⁺ in Period 2:

Mean Change from Baseline in Serum Na⁺ Rate in Period 2

Time Post-Dose h	Mean Change from Baseline in Serum Na ⁺ Concentration ^a in Period 2 mEq				
	OPC-41061 Dose Levels, mg				
	60	90	120	180	240
2	3.6	4.3	4.0	5.0	3.6
4	4.2	4.3	4.3	6.2	4.8
6	6.7	6.5	5.7	5.0	5.4
8	5.2	5.5	3.8	6.0	5.2
12	4.5	5.8	5.7	6.2	3.2
24	2.5	5.2	4.2	5.4	4.2

Mean Change from Baseline (Placebo Corrected) in Serum Na⁺ in Period 2

Time Post-Dose, h	Mean Change from Baseline (Placebo Corrected) in Serum Na ⁺ Concentration ^a in Period 2, mEq				
	OPC-41061 Dose Levels, mg				
	60	90	120	180	240
2	3.4	4.1	3.8	4.8	3.4
4	4.2	4.3	4.3	6.2	4.8
6	5.8	5.6	4.8	4.1	4.5
8	4.9	5.2	3.5	5.7	4.9
12	3.6	4.9	4.8	5.3	2.3
24	2.8	5.5	4.5	5.7	4.5

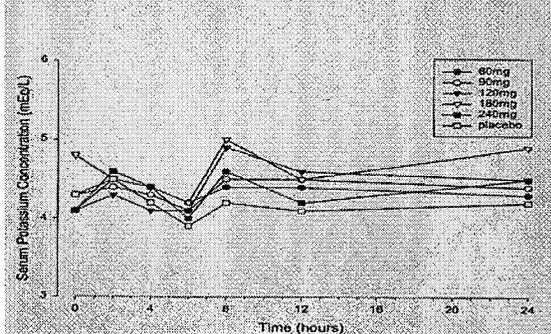
^a Corrected for pooled placebo

With both data sets a net increase of serum Na⁺ is seen with all tested doses of OPC-41061 in both periods. The effects of the different dose levels on serum Na⁺ are overlapping. The net increase in serum Na⁺ in both periods ranges between 1.6 and 7.8 mEq or 1.2% and 5.5%, respectively, with the placebo corrected data. The onset of the effect of OPC-41061 on serum Na⁺ is observable 2 h post-dose and the duration of the effect exceeds 24 h at all dose levels. The efficacy of single doses between 60 and 240 mg OPC-41061 on serum Na⁺ appears to be similar and reproducible suggesting that the impact of volumetric fluid replacement and fluid replacement controlled by the participants is not different.

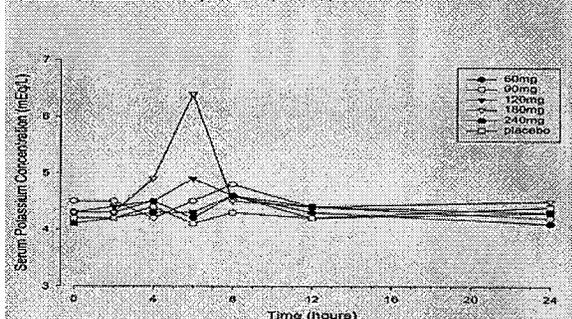
Serum Potassium Concentrations

The mean serum K⁺ concentrations in Periods 1 and 2 are shown in the below figures:

SF-8. Mean Serum Potassium Concentration vs Time Profile of OPC-41061 in Subjects with Volumetric Fluid Replacement (Period 1)



SF-18. Mean Serum Potassium Concentration vs Time Profile of OPC-41061 in Subject Without Volumetric Fluid Replacement (Period 2)



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The baseline values differ among the different groups. The mean K⁺ values of the placebo group are constant over the 24 h observation period. The mean K⁺ values in the OPC-41061 receiving groups appear to be higher than those of the placebo group. The mean serum K⁺ remains in the normal range for all groups at all dose levels of tolvaptan, except for the 6 h value in the group receiving 180 mg tolvaptan in Period 2. It is unlikely that the elevation is due to tolvaptan. The 4 h and 8 h serum K⁺ values in Period 1 and all serum K⁺ values during Period 2 are in the normal range for the group receiving 180 mg tolvaptan.

The below two tables list the mean change from baseline (placebo corrected) in serum K⁺ in Periods 1 and 2:

Mean Change from Baseline (Placebo Corrected) in Serum K⁺ in Period 1

Time Post-Dose, h	Mean Change from Baseline in Serum K ⁺ Concentration ^a in Period 1, mEq				
	OPC-41061 Dose Level, mg				
	60	90	120	180	240
2	0.1	-0.2	-0.1	-0.6	0.2
4	0.3	0.1	0.1	-0.3	0.4
6	0.5	0.2	0.4	-0.2	0.3
8	0.3	0.3	0.9	0.3	0.5
12	0.4	0.4	0.7	-0.1	0.3
24	0.3	0.2	0.4	0.2	0.5

^aPooled placebo corrected

Mean Change from Baseline (Placebo Corrected) of Serum K⁺ in Period 2

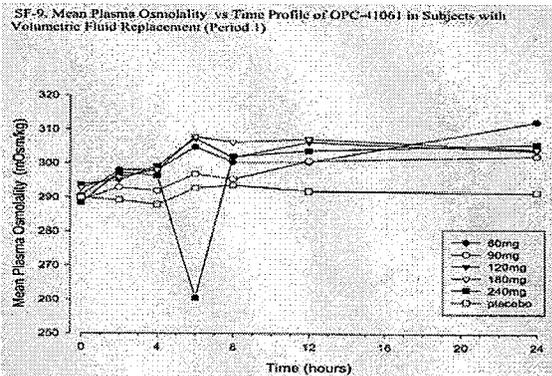
Time Post-Dose, h	Mean Change from Baseline in Serum K ⁺ Concentration ^a in Period 2, mEq				
	OPC-41061 Dose Level, mg				
	60	90	120	180	240
2	-0.1	-0.1	-0.1	0	0.1
4	0	-0.5	0	0.4	0
6	0	0.2	0.8	2.3	0.4
8	0.2	0.2	0.3	0.1	0.5
12	-0.1	-0.1	-0.1	0.1	0.3
24	-0.4	-0.5	-0.2	0	-0.1

^aPooled placebo corrected

The tabulated changes from baseline (placebo corrected) in the serum K⁺ values show significant variability among the OPC-41061 receiving groups. In Period 1, the serum K⁺ values appear to show a net increase at all dose levels of OPC-41061, except in the 180 mg group which exhibits a net decrease. In Period 2 there is no consistent net increase in K⁺ observable among the subjects on OPC-41061. Overall, no firm conclusion can be drawn.

Plasma Osmolality

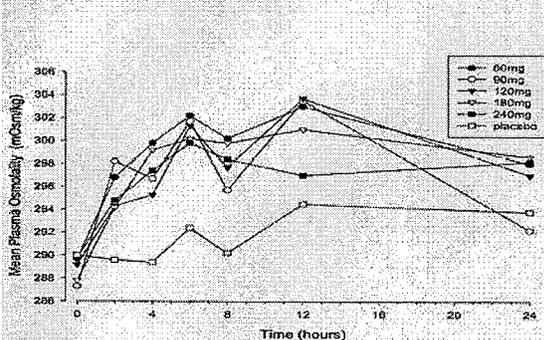
The mean plasma osmolality time curves (uncorrected for baseline and placebo) in Periods 1 and 2 are shown in the next 2 figures:



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SF-19. Mean Plasma Osmolality vs Time Profile of OPC-41061 in Subjects Without Volumetric Fluid Replacement (Period 2)



The baseline values for mean plasma osmolality vary among the different groups. In the subjects receiving OPC-41061 the mean plasma osmolality in Periods 1 and 2 increases over time and appears to reach a peak value between 6-12 h after administration. The 180 mg group shows a drop of the osmolality 6 h post-dose in Period 1 which is unlikely drug related.

Urine Na⁺ Excretion and Urine K⁺ Excretion

The below 2 tables list the mean change from baseline (placebo corrected) in Na⁺ urine excretion during Periods 1 and 2:

Mean Change from Baseline (Placebo Corrected) in Urine Na⁺ Excretion in Periods 1 and 2

Collection Interval, h	Mean Change from Baseline in Na ⁺ Excretion ^a , mEq				
	OPC-41061 Dose Level, mg				
	60	90	120	180	240
0-24 Period 1	24.7	20.3	36.4	52.5	53.6
24-48 Period 1	-13.9	na	-17.0	4.3	69.9
48-72 Period 1	-13.5	na	-6.8	7.7	6.6
0-24 Period 2	79.4	36.0	54.1	43.5	28.8
24-48 Period 2	4.3	na	-5.2	19.1	-24.1
48-72 Period 2	-16.8	na	-0.9	16.3	-5.9

^aPlacebo subtracted na= not available

The net Na⁺ excretion in urine during the 0-24 h collection interval appears to increase by between 20.3 and 79.4 mEq or 29 % and 124 %, respectively. There is no discernable dose effect.

The below 2 tables list the mean change from baseline (placebo corrected) in K⁺ urine excretion during Periods 1 and 2:

Mean Change from Baseline in Urine K⁺ Excretion in Periods 1 and 2

Collection Interval, h	Mean Change from Baseline in K ⁺ Excretion ^a , mEq				
	OPC-41061 Dose Level, mg				
	60	90	120	180	240

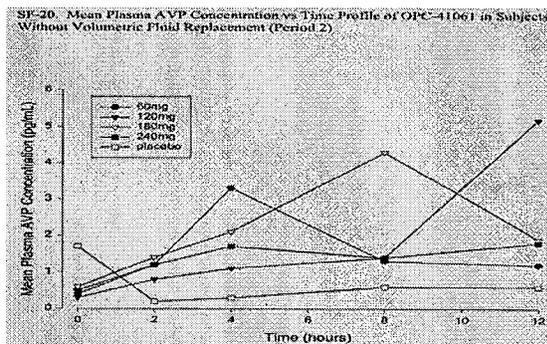
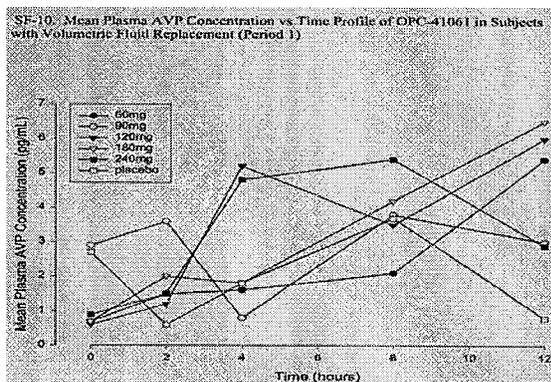
0-24 Period 1	63	na	75	80	101
24-48 Period 1	21	na	-5.3	-50	8.7
48-72 Period 1	37	na	1.1	-16	16
0-24 Period 2	8.8	61	27	-2.9	-11
24-48 Period 2	-13	na	-59	-73	-14
48-72 Period 2	2.1	na	-16	-41	-14

^aPooled placebo subtracted na=not available

The mean net urine excretion of K^+ appears to increase during the 0-24 h interval only in the first period with no discernable dose effect by OPC-41061.

Plasma AVP

The below 2 figures show the mean plasma concentration time profiles of AVP in Periods 1 and 2:



The baseline values differ among the different groups. There appears to be a trend for an increase in AVP in plasma AVP post-dose compared to placebo in the subjects on OPC-41061 with no consistent relationship to dose.

The below 2 tables list the mean percent change from baseline in the AVP levels in Periods 1 and 2:

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Mean Percent Change from Baseline in AVP Level in Period 1

Time after Administration, h	Mean Percent Change from Baseline (Placebo Corrected) in AVP Level ^a in Period 1, %				
	Dose Level of OPC-41061, mg				
	60	90	120	180	240
2	54	39	65	60*	90
4	198	20	44	80*	325
8	134	241	371	145*	879
12	432	187	211*	254*	238

^a Pooled placebo subtracted * <3 subjects

Mean Percent Change from Baseline in AVP Level in Period 2

Time after Administration, h	Mean Percent Change from Baseline in AVP Level ^a in Period 2, %				
	Dose Level of OPC-41061, mg				
	60	90	120	180	240
2	59	na	63*	158	169
4	41	na	112*	282	172
8	35	na	295*	197	166*
12	-22	na	969*	162	187*

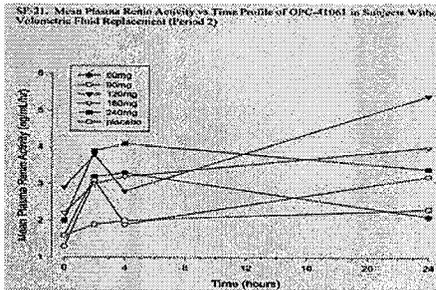
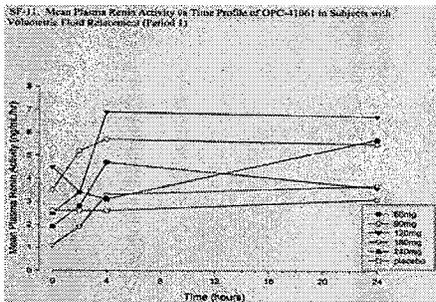
^a Pooled placebo subtracted * <3 subjects

There exist substantial differences in the baseline values of AVP among the groups. OPC-41061 increases the plasma concentrations of AVP more than placebo in both periods. The maximum effect of tolvaptan occurs 12 h after dosing with a mean net increase of 20% - 879 % in AVP. There is considerable overlap and fluctuation in the time profiles of AVP in the groups on OPC-41061. The data appear to show an effect on AVP levels by single OPC-41061 doses between 60 mg-240 mg.

Plasma PRA

The below 2 figures show the mean plasma concentration time profiles of PRA in Periods 1 and 2:

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The baseline values vary among the groups. It appears that PRA in the subjects on OPC-41061 is greater than in the subjects on placebo. There is no consistent relationship with dose.

The below 2 tables list the mean percent change from baseline (placebo corrected) in the PRA plasmas levels in Periods 1 and 2:

Mean Percent Change from Baseline (Placebo Corrected) of PRA in Period 1

Time after Administration, h	Mean Percent Change from Baseline in PRA Level ^a in Period 1, %				
	Dose Level of OPC-41061, mg				
	60	90	120	180	240
2	56	68	-50	54	81
4	146	128	159	217	51
24	75	121	83	218	162

^a Pooled placebo subtracted

Mean Percent Change from Baseline (Placebo Corrected) of PRA in Period 2

Time after Administration, h	Mean Percent Change from Baseline in PRA Level ^a in Period 2, %				
	Dose Level of OPC-41061, mg				
	60	90	120	180	240

2	69	103	14	0.5	73
4	33	-4.4	-73	-17	25
24	-52	48	9.6	8.9	-1.1

^a Pooled placebo subtracted

The mean net effect of OPC-41061 during Period 1 is an increase in the PRA levels at all three time points. The effect size is not related to the dose level. A consistent net increase of the plasma concentrations of PRA is only observable 2 h post-dose in Period 2.

Aldosterone in Plasma

The below 2 tables list the mean percent change from baseline (placebo corrected) in the aldosterone plasma levels in the subjects on OPC-41061 in Periods 1 and 2:

Mean Percent Change from Baseline in Aldosterone Level in Period 1

Time after Administration, h	Mean Percent Change from Baseline in Aldosterone Level ^a in Period 1, %				
	Dose Level of OPC-41061, mg				
	60	90	120	180	240
2	-11	-18	-4.4	17	10
24	3.4	-13	27	58	28

^a Pooled placebo subtracted

Mean Percent Change from Baseline in Aldosterone Level in Period 2

Time after Administration, h	Mean Percent Change from Baseline in Aldosterone Level ^a in Period 2, %				
	Dose Level of OPC-41061, mg				
	60	90	120	180	240
2	52	40	39	19	-3.1
24	30	5.2	32	86	-27

^a Pooled placebo subtracted

The mean percent change from baseline in aldosterone is difficult to interpret. There is no consistency in the net effects observed in Periods 1 and 2 at the two time points measured. Also, the net effect size is not related to the dose of OPC-41061.

Pharmacodynamic-Pharmacokinetic Correlations

The mean change from baseline (placebo corrected) in urine excretion rates and the corresponding mid-time plasma concentrations of OPC-4106 in Periods 1 and 2 are listed in the below tables:

Mean Change from Baseline (Placebo Corrected) in Excretion Rates and Mid-Time Plasma Concentrations of OPC-41061 in Period 1

Dose mg	Urine Collection Interval mL	Mean Change from Baseline in Excretion ^a Rate, mL/min	Midpoint Time h	Mean Plasma ^b Concentration ng/mL
60	0-2	5.2	1	257
90		5.1		236
120		4.8		298
180		6.6		412
240		4.6		602
60	2-4	6.3	3	373
90		8.1		414
120		8.6		503
180		10.0		481
240		7.8		930
60	4-6	4.9	5	245
90		4.9		327
120		5.8		410
180		7.8		411
240		7.4		849
60	6-8	9.5	7	156
90		8.9		244
120		10.2		307
180		12.6		349
240		10.5		679
60	8-12	5.1	10	84
90		6.7		183
120		6.5		206
180		9.8		253
240		9.7		477
60	12-24	1.4	18	35
90		2.2		90
120		2.2		109
180		4.1		150
240		4.9		287
120	24-36	1.7	30	40
180		4.8		70
240		4.0		116
240	36-48	1.0	42	39

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

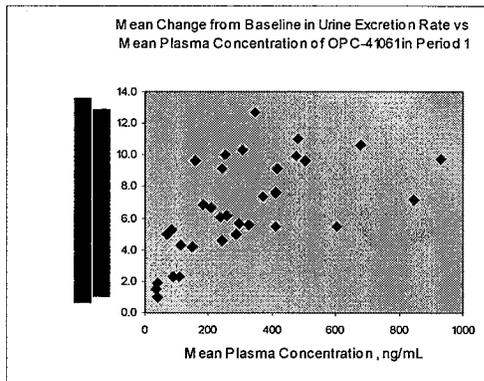
Mean Change from Baseline in Excretion Rates and Mid-Time Plasma Concentrations of OPC-41061 in Period 2

Dose mg	Urine Collection Interval mL	Mean Change from Baseline in Excretion ^a Rate, mL/min	Midpoint Time h	Mean Plasma ^b Concentration ng/mL
60	0-2	3.3	1	327
90		6.6		228
120		4.2		258
180		4.1		524
240		5.5		672

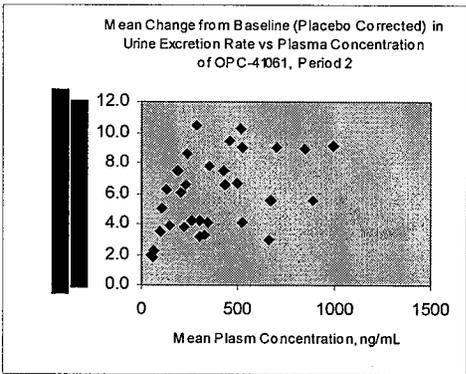
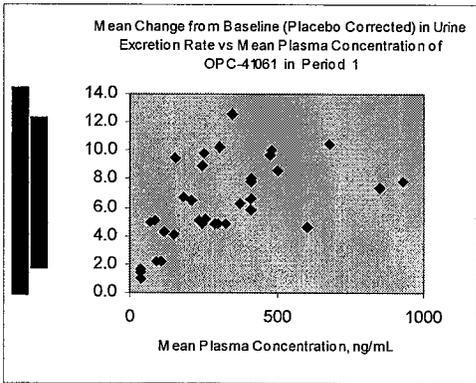
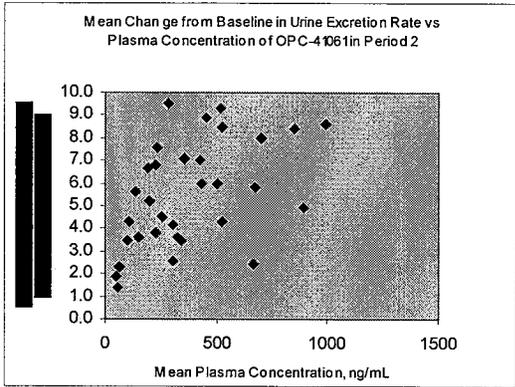
60	2-4	7.5	3	427
90		9.4		456
120		9.0		521
180		8.9		848
240		9.1		994
60	4-6	3.2	5	301
90		4.1		339
120		6.6		429
180		3.0		663
240		5.5		890
60	6-8	6.1	7	200
90		8.6		233
120		10.5		286
180		10.3		514
240		9.0		702
60	8-12	5.0	10	109
90		6.3		133
120		7.5		189
180		7.8		354
240		6.7		501
60	12-24	1.9	18	46
90		2.3		65
120		3.5		101
180		3.8		224
240		4.2		304
240	24-36	3.9	30	147
240	36-48	1.8	42	57

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

The below 4 figures show the relationship between mean change from baseline (with/out placebo correction) in urine excretion rate and mean plasma concentration of OPC-41061 in Periods 1 and 2:



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The relationship between mean net urine excretion rate and mid time plasma concentration of OPC-41061 in both periods shows significant variability. Both plots indicate that the relationship is saturable: the higher the plasma concentration the smaller the increments in the urine excretion rates. Similar results are obtained if the mean change from baseline (uncorrected for placebo) in the urine excretion rates are plotted against the midtime plasma concentrations of OPC-41061. 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.

Conclusions

PK

The sensitivity of the assay used by the sponsor does not allow a follow-up of the plasma concentrations of OPC-41061 and the metabolites for a sufficient time span to reliably estimate λ_z and derived parameters. Only at the highest 240 mg dose level reliable parameters estimates can be obtained for OPC-41061 and the metabolites DM-4107 and DM-4111. The PK parameters reported at dose levels < 240 mg for OPC-41061 and the metabolites must be interpreted with due caution. Because a relatively small percentage of OPC-41061 remains to be eliminated during the terminal phase determined by λ_z , the estimates for λ_z are more biased than those for AUC_{∞} and CL/F .

The pharmacokinetics of OPC-41061 appear to be dose proportional. The absorption is slowed when the dose of OPC-41061 is increased without affecting the bioavailability of the drug. The peak and average exposure measures of OPC-41061 indicate marked inter-subject variation.

The most prominent among the seven measured metabolites is DM-4103. It exhibits plasma concentrations that exceed those of the parent drug and the other metabolites. The elimination of DM-4103 is protracted and a reliable estimate for its terminal half-life is not available. It appears that the kinetics of DM-4103 are determined by its elimination in contrast to the other 6 metabolites which show formation limited kinetics. The PK of OPC-41061 and the metabolites are similar whether or not volumetric fluid replacement is provided or not.

PD

There are no systematic differences in the aquaretic activity of OPC-41061 between the the 2 periods. Both excredata sets on the net urine excretion rate indicate a fast onset of the aquaretic activity of OPC-41061 in the first 0-2 h collection interval in both periods. Peak rates are observed in the 2-4, 4-6 or 6-8 h collection intervals suggesting a possible lagging of the aquaretic effect behind the plasma concentrations. The offset of the aquaretic effect at the 60 mg level is at about 18 h post-dose and increases to between 42 and 55 h at the 240 mg level. The peak excretion rates are less than dose proportional indicating a nonlinear dose-effect relationship. Most of the net 24 h urine excretion rates on Days 2 and/or 3 are negative suggesting decreased fluid excretion because of more retention and/or decreased fluid ingestion.

The effect of OPC-41061 on the free water clearance is in accordance with the drug's impact on the urine excretion rates. The values of the baseline and placebo corrected urine excretion rate and free water clearance are similar. A net increase in the serum Na^+ concentrations is seen at all dose levels of OPC-41061. The effects of the different dose levels on serum Na^+ are overlapping and results a net increase ranging between 1.6 and 7.8 mEq. There is no overt evidence for a net increase in serum K^+ by OPC-41061.

OPC-41061 appears to increase the urine excretion of Na^+ on Day 1. In addition OPC-41061 appears to increase the levels of AVP and possibly aldosterone and PRA. However, body position and activity level of the subjects, known to affect the levels of AVP, aldosterone and PRA, were not defined by the protocol.

PK-PD

The relationship between mean net urine excretion rate and mid time plasma concentration is nonlinear with a saturation of the aquaretic effect at high OPC-41061 plasma concentrations.

Comments

1. The sponsor should explore the exposure response profile of OPC-41061 using baseline and placebo as covariates.
2. The sensitivity of the assay for OPC-41061 and metabolites is inadequate and does not allow determination of λ_z and derived parameters for OPC-41061 and for the metabolites.
3. The individual dose increments used in the study range between 33% and 50% and are too small to exert easily discernible effects
4. The level of AVP, PRA, aldosterone and norepinephrine levels vary with body position and activity level which were not defined in the protocol.
5. 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.
6. The washout interval between the repeat administrations of OPC-41061 is too short so that substantial amounts of DM-4103 remain in the circulation at the time of the administration of the second dose of OPC-41061. Thus, a comparison of the PK parameters is not appropriate.

Study Report 156-01-229: "A Single Center, Placebo-Controlled, Double-Blind, Randomized, Ascending Single Dose Study to Determine the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Orally Administered Tolvaptan (OPC-41061) Tablets in Healthy Male and Female Adult Volunteers"

Investigator and Study Site

b(4)

Objectives

Primary: To determine the maximum tolerated oral dose (MTD) of OPC-41061

Secondary: To characterize the pharmacokinetics of OPC-41061 and its metabolite, and the pharmacodynamic endpoints following OPC-41061 administration

Investigational Drugs and Formulations

Tolvaptan (OPC-41061) 60 mg oral tablets (Lot No. 99E87A060) and matching oral placebo tablets (Lot No. 99D96P000) were provided by the sponsor.

Design

This was a single center, double-blind, randomized, placebo controlled, ascending single dose study. Healthy males or females in the age between 18 and 55 years with a body weight within -15% to 35% of ideal were enrolled. Subjects had to be healthy as determined by medical history, physical examination, ECG, serum/urine biochemistry, hematology, and serology tests.

There were six treatment groups with 9 subjects per group, 6 subjects assigned to OPC-41061 and 3 subjects to placebo. The subjects received a single dose of 180, 240, 300, 360, 420, and 480 mg OPC-41061 or placebo on Day 1 without fluid restriction. All doses were administered with 240 mL purified water after an overnight fast of 10 h. Each subject participated in the study for a maximum of 35 days. Consumption of xanthine- alcohol and grapefruit or Seville orange containing products was prohibited for 72 h before study start and for the duration of the study.

The scheduled study activities are shown in the below schemes:

Day	Screening Period
Procedure	28 to -3 ^a
Informed consent ^b	X
Inclusion/exclusion criteria	X
Medical history	X
Physical examination (including height and weight)	X
Vital signs	X
Hepatitis B and C, HIV screen	X
Urine drug and alcohol screen	X
Hematology	X
Chemistry	X
Serum pregnancy (all females)	X
Urinalysis	X
Resting 12-lead ECG	X
Concomitant medications	X
Adverse event assessment	X

^a All eligible subjects arrived at the investigational site for screening procedures between Days -28 and -3. All screening tests were completed with the results available prior to admission to the clinic on Day -2. ^b Obtained prior to performing any study-related procedures.

Day	Check-In	Inpatient
Procedure	-2	-1
Admit to clinic in AM	X	
Verify inclusion/exclusion criteria ^a	X	
Physical examination (including body weight) ^a	X	
Vital signs ^b	X	X
12-lead electrocardiogram ^{c, d}	X	
Urine drug and alcohol screen ^e	X	
Safety labs ^{e, f}	X	
Serum pregnancy test (female subjects only) ^g	X	
Randomization		X
Urine collection ^h		X
Serum creatinine ⁱ		X
Meal ^j		X
Concomitant medications	X	X
Adverse event assessment	X	X
Begin fasting at 10 PM (2200 hours) ^k		X

^a Results were obtained prior to randomization. ^b Vital signs and the ECG were completed prior to lab draws. ^c Results were obtained prior to randomization. ^d Included hematology, chemistry, and urinalysis. ^e Timed urine intervals collection and measurements beginning with the morning void (0800 hours) and at 0-2, 2-4, 4-6, 6-8, 8-12, and 12-24 hours post morning void. Urine volume, osmolality, pH, sodium, and potassium and creatinine concentrations were recorded during each time interval. A 24-hour urine sample was also collected for the OPC-41061 bioequivalence study. ^f Serum creatinine was collected at 2, 4, 6, 8, 12, and 24 hours after the morning void (0800 hours). ^g Dinner and snack. ^h Fasting from 2200 hours on Day -1 through 2 hours post dosing on Day 1.

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

Day	Inpatients: Days 1 and 2	
	1 ^a	2
Procedures		
Vital signs ^b	X	X
Body weight ^c	X	X
Plasma protein binding ^d	X	
Administer study medication at 0800 ^e	X	
PK samples ^f	X	X
Plasma arginine vasopressin (AVP) ^g	X	
Plasma renin activity ^h	X	X
Serum electrolytes and plasma osmolality ⁱ	X	X
Plasma aldosterone and plasma catecholamines (norepinephrine) ^j	X	X
Urine collection ^k	X	X
24-hour urine OPC-41061 measurement ^l	X	X
Serum creatinine ^m	X	X
Safety labs ⁿ	X	X
12-lead ECG ^o	X	X
Meals	X ^p	
Concomitant medication	X	X
Adverse event assessment	X	X

^a Predose activities were performed within one hour prior to study drug administration, unless otherwise specified.

^b Day 1 vital signs immediately prior to dosing and at 1, 2, 3, 4, 6, 8, 10, and 12 hours post dose. Day 2 vital signs at 24 hours post Day 1 dose.

^c Body weight was obtained at the same time each day (0800 hours), using the same scale, prior to breakfast. Day 1 was obtained prior to dose.

^d Sample drawn at 0, 6, 8 hours.

^e Administered study medication with 240 mL of water at 0800 (a hand and mouth check was done to ensure that dose was ingested).

^f Day 1 PK samples at 0.5 hours predose, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post dose. Day 2 PK samples at 24 hours (prior to breakfast) and 36 hours post Day 1 dose.

^g Blood sample for AVP at predose and 2, 4, 8, and 12 hours post dose.

^h Blood sample for plasma renin activity at predose and at 2, 4, and 24 hours post dose.

ⁱ Blood sample for serum electrolytes and plasma osmolality at predose, 2, 4, 6, 8, 12 and 24 hours post dose.

^j Blood sample for plasma aldosterone and plasma catecholamines (norepinephrine) at predose, 2 and 24 hours post dose.

^k Timed urine interval collections and measurements at 0-2, 2-4, 4-6, 6-8, 8-12, and 12-24 hours post dose on Day 1 and beginning with the morning void (0800 hours) on Day 2. Urine volume, osmolality, pH, sodium and potassium concentrations were recorded during each timed interval. Urine creatinine concentration measurements were recorded during each timed interval on Day 1 only.

^l Urine OPC-41061 measurement.

^m Blood sample for serum creatinine at 2, 4, 6, 8, 12, and 24 hours post dose.

ⁿ Safety labs (hematology, chemistry, and urinalysis) at predose, 4, 12, and 24 hours post dose. The 12-hour post dose on Day 1 includes serum creatinine.

^o 12-lead ECG at predose, 2, 4, 12, and 24 hours post dose.

^p Lunch, dinner, and snack at 1, 10, and 13 hours after dosing, respectively.

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

Day	Inpatients: Days 3-7				
	3	4	5	6	7/EOT
Procedures					
PK samples ^a	X	X	X	X	X
Physical exam					X
Body weight ^b	X				X
Vital signs ^c	X	X	X	X	X
12-lead electrocardiogram ^d					X
Safety labs ^e					X
Serum pregnancy test for all females					X
Urine collection	X ^f	X ^f	X ^f	X ^f	
Urine OPC-41061 ^g	X	X	X	X	
Concomitant medication	X	X	X	X	
Adverse event assessment	X	X	X	X	
Discharged from study					X

^a PK samples: Day 3: 48 hours post dose; Day 4: 72 hours post dose; Day 5: 96 hours post dose; Day 6: 120 hours post dose; Day 7: 144 hours post dose. All PK samples were drawn before breakfast.

^b Body weight was obtained at the same time each day (0800 hours) using the same scale, prior to breakfast.

^c Completed vital signs and ECG prior to blood draws.

^d Safety labs (hematology, chemistry, and urinalysis).

^e Day 3: Timed urine interval collection and measurements beginning with the morning void (0800 hours) and at 0-2, 2-4, 4-6, 6-8, 8-12, 12-24 hours post dosing void. Urine volume, osmolality, pH, sodium and potassium concentrations will be recorded during each timed interval.

^f 24-hour urine collection in the 480 mg group only.

^g Urine OPC-41061 measurement.

Pharmacokinetic Profiling:

Blood

Blood samples for the determination of the plasma concentrations of OPC-41061 and the metabolite DM-4103 were obtained pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, and 144 h post-dose.

Urine

Total urine volumes on Days -1, 1, 2, and 3 for all dose groups and additionally on Days 4, 5 and 6 for the 480 mg group only were obtained.

Bioassay

Plasma

The plasma concentrations of OPC-41061 were determined by a HPLC/MS/MS method using an internal standard. QC samples were analyzed along plasma samples with unknown concentrations. The linear range of the method ranges between 5 ng/mL and 1000 ng/mL for OPC-41061 and 12.5 ng/mL and 2500 ng/mL for DM-4103. The correlation coefficient is ≥ 0.9977 . Using QC samples the accuracy of the method for OPC-41061 ranges between -2.82% and 0.28% and the precision is $\leq 6.23\%$. The accuracy of the method for DM-4103 ranges between 4.67% and 0.89% and the precision is $\leq 6.17\%$. Stability of the analytes in plasma was demonstrated by exposure of urine to 3 freeze/thaw cycles, long term freezer conditions at -20°C for 245 days and to short term room temperature.

Urine

The urine concentrations of OPC-41061 were measured by the same HPLC/MS/MS method using an internal standard. The linear range of the calibration curve for OPC-41061 is between 5.00 ng/mL and 1000 ng/mL. QC samples were analyzed along plasma samples with unknown concentrations. The accuracy ranges between 0.38% and 5.89% and the precision is $\leq 6.07\%$. Stability of the analytes in urine was tested by exposure to 3 freeze/thaw cycles, long term freezer conditions at -20°C for 245 days and short periods (sic) at room temperature. The recovery for OPC-41061 was decreased to 84 % after long term exposure to -20°C .

The assays in plasma and urine were performed by _____

b(4)

Pharmacodynamic Profiling:

Total urine volumes were collected during the following intervals: 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-48, 48-71, 72-96, 96-120 and 120-144 h on Days -1, 1, 2, and 3 for all dose groups and additionally on Days 4, 5 and 6 for the 480 mg dose group only. Collection began at 0800 on the day of dosing with the morning void. Urine volume, osmolality, pH, sodium and potassium concentrations were measured for each urine collection period. Urine creatinine was measured for each collection interval on Days -1 and 1. Serum Na^+ and K^+ , plasma aldosterone and norepinephrine, PRA and osmolality were measured on Days 1 and 2. Plasma AVP concentrations were measured on Day 1 pre-dose (-0.5 h) and 2, 4, 8, and 12 h post-dose. Blood samples for creatinine were collected at 2, 4, 6, 8, 12 and 24 h after the morning void (0800) on Days -1 and following dosing (0 h) on Days 1 and 2.

Data Analysis

PK

The following parameters were determined: C_{max} , t_{max} , λ_z , $t_{1/2z}$ (when possible), AUC_t , AUC_{∞} , V_z/F and CL/F , Ae_{72} and f_e . For DM-4103 only t_{max} , C_{max} and AUC_t was determined. Non-compartmental methods and the software WinNonlin Professional, Version 3.3 (Pharsight Corporation) were used. Estimates of λ_z were obtained from observation intervals in the apparent terminal log linear phase of ≥ 24 h at tolvaptan dose levels of 180-420 mg and of ≥ 36 h at the 480 mg dose level.

PD

Mean urine excretion rate, Clcr, and free water clearance were determined. Clcr on Days -1 and 1 was obtained from $Clcr = (Ae_{24}/1440/Ccr)$, where Ae_{24} is the amount of creatinine excreted in 24 h, 1440 is the number of minutes in the 24 h collection interval and Ccr, is the creatinine concentration in serum at 12 h.

Free water clearance was obtained from:

$$CL_{H_2O} = V - Cosm$$

where Cosm is the osmolar clearance ($Uosm \bullet V/Posm$) and Uosm is the urine osmolality (mOsm/kg H₂O), V is the urine excretion rate (mL/min) and Posm is the plasma osmolality (mOsm/kg H₂O). Since urine was collected in time intervals, the upper time point of the collection interval was used in the calculation of CL_{H_2O} for urine volume and urine osmolality. For Day -1, a single CL_{H_2O} value was determined using the average 24 h urine excretion rate and the plasma osmolality at pre-dose on Day 1. This value was assumed to be representative of the average plasma osmolality for Day-1. For Day 1, CL_{H_2O} values were determined for each urine collection interval using the average plasma osmolality during the interval, where $Posm = (Posm_{,1} + Posm_{,2})/interval\ time\ in\ minutes$ and $Posm_{,1}$ and $Posm_{,2}$ are the plasma osmolality values at the beginning and end of the collection interval.

Mean values, and mean change from baseline were determined for serum Na⁺, serum K⁺, serum creatinine, plasma osmolality, urine Na⁺, urine K⁺, urine osmolality, plasma osmolality, urine volume and plasma AVP, plasma PRA, plasma norepinephrine and serum aldosterone. Baseline values of serum electrolytes and norepinephrine were defined as Day 1 pre-dose. Baseline values for other pharmacodynamic variables including urine volume, urine excretion rate, urine Na⁺, urine K⁺ and urine osmolality were defined as the collection intervals on Day-1.

PK-PD Correlations

No correlations were planned or performed.

Statistical Analysis

Regressions of log-transformed C_{max} and AUC_∞ on dose were done. Linear regressions of C_{max}, AUC_∞, t_{1/2z}, CL/F, C_{max}/Dose, and AUC_∞/Dose on dose were done and 95% CI computed.

RESULTS

Disposition of Subjects

The below table summarizes the disposition of the subjects:

Subjects	OPC-41061 180 mg	OPC-41061 240 mg	OPC-41061 300 mg	OPC-41061 360 mg	OPC-41061 420 mg	OPC-41061 480 mg	Placebo (Pooled)	Total
Screened								247
Randomized ^a	7	7	7	6	7	6	19	59
Treated	5	6	6	6	6	6	18	53
Completed	5	6	6	6	5	6	18	52
Discontinued	2	1	1	0	2	0	1	7
Before taking study drug	2	1	1	0	1	0	1	6
After taking study drug	0	0	0	0	1	0	0	1
Safety Analysis ^b	5	6	6	6	6	6	18	53

^a Number of subjects randomized to a treatment group.
^b Received at least one dose of study medication during the study.
Source: Table 1.

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Fifty-nine (59) subjects were randomized, 40 subjects to OPC-41061 treatment and 19 subjects to placebo treatment. Seven subjects were discontinued. A total of 52 out of the 53 subjects treated completed the study. Of the 7 subjects discontinued, 6 were assigned to OPC-41061. Of the 6 subjects, 5 met the withdrawal criteria and 1 was withdrawn because of concomitant use of medication. Two subjects withdrew consent, 2 subjects had non-qualifying pre-dose vital signs, 1 subject had a pre-dose blood pressure below protocol criteria and 1 subject developed an upper respiratory infection.

Demographics

The mean age of the subjects was 28.5 years (range 19-51 years) and the mean body weight 79.1 kg (range 52.1-115.8 kg). Eighty-five (85) % of the subjects were males and 83% Caucasian.

Safety

No subject was withdrawn because of treatment emergent events. There were no serious adverse events. The laboratory values, vital signs ECG, and physical examinations showed no clinically significant abnormalities.

Pharmacokinetics

OPC-41061

Linear and semi-logarithmic plots of the plasma concentration time profile of OPC-41061 are depicted in the below 2 figures:

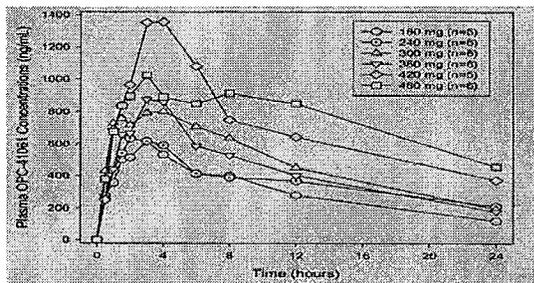


Figure 9.2.3.1 Median Plasma OPC-41061 Concentration-time Profiles for the First 24 Hours Post-dose Following a Single Oral Dose of 180, 240, 300, 360, 420, and 480 mg OPC-41061 in Healthy Male and Female Adult Subjects

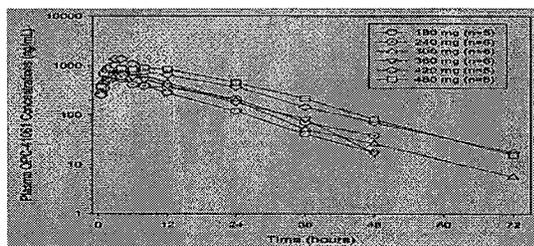


Figure 9.2.3.2 Median Plasma OPC-41061 Concentration-time Profiles Following a Single Oral Dose of 180, 240, 300, 360, 420, and 480 mg OPC-41061 in Healthy Male and Female Adult Subjects

The sponsor's estimated parameter values for OPC-41061 are listed in the below 2 tables:

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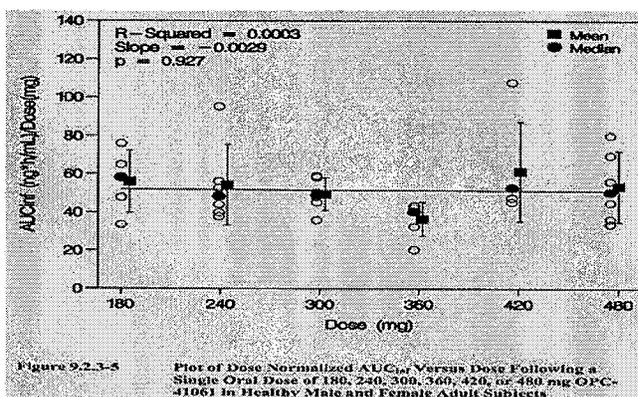
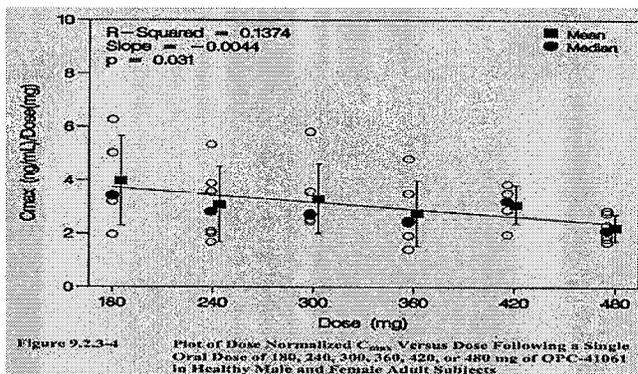
Table 9.2.3-1 Summary of OPC-41061 Pharmacokinetic Parameters Following a Single Oral Dose of 180, 240, 300, 360, 420, or 480 mg OPC-41061 in Healthy Male and Female Adult Subjects										
OPC-41061 Dose	t_{max} (h)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	AUC_{0-24} (ng·h/mL)	$t_{1/2}$ (h)	V_z/F (L/kg)	CL/F (mL/min/kg)	$t_{1/2}$ (%)	$C_{max}/Dose$ (ng/mL)/(mg)	$AUC_{0-\infty}/Dose$ (ng·h/mL)/(mg)
180 mg	N	5	5	5	5	5	5	5	5	5
Median	4.00	618	10300	10428	9.5	3.11	3.80	0.357	3.43	58.2
Mean	ND	717	9973	10099	9.7	3.44	4.10	0.374	3.98	56.1
SD	ND	302	2917	2923	5.0	1.55	0.96	0.071	1.68	16.3
%CV	ND	42.1	29.2	29.0	51.0	45.2	22.9	41.1	42.1	29.0
Minimum	1.00	156	6008	6050	5.0	1.43	3.32	0.100	1.98	13.6
Maximum	8.00	1179	13519	13689	17.1	5.10	5.52	0.287	6.27	76.0
240 mg	N	6	6	6	6	6	6	6	6	6
Median	2.75	582	11097	11625	10.5	3.28	4.27	0.138	2.84	48.4
Mean	ND	745	12503	13044	11.8	4.43	4.26	0.147	3.11	54.4
SD	ND	340	4748	5092	4.9	3.15	3.54	0.075	1.42	21.2
%CV	ND	45.6	38.0	39.0	42.1	71.3	36.2	51.2	45.6	39.0
Minimum	1.00	406	8315	9103	6.0	1.86	1.99	0.063	1.69	37.9
Maximum	12.00	1242	21461	22835	20.4	10.46	5.93	0.272	5.34	95.1
300 mg	N	6	6	6	6	6	6	6	6	6
Median	2.25	820	14509	14770	10.2	4.45	4.75	0.151	2.73	49.2
Mean	ND	794	14631	14861	14.1	6.16	4.86	0.171	2.31	49.5
SD	ND	368	2919	2583	9.8	4.87	6.02	0.061	1.29	8.7
%CV	ND	39.0	18.6	17.3	69.4	78.9	19.0	35.4	39.0	17.5
Minimum	1.00	742	10485	10890	6.0	2.21	3.70	0.083	2.47	36.0
Maximum	4.00	1737	17671	17737	12.1	15.13	6.21	0.256	5.82	59.1
Table 9.2.3-1 Summary of OPC-41061 Pharmacokinetic Parameters Following a Single Oral Dose of 180, 240, 300, 360, 420, or 480 mg OPC-41061 in Healthy Male and Female Adult Subjects (continued)										
OPC-41061 Dose	t_{max} (h)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	AUC_{0-24} (ng·h/mL)	$t_{1/2}$ (h)	V_z/F (L/kg)	CL/F (mL/min/kg)	$t_{1/2}$ (%)	$C_{max}/Dose$ (ng/mL)/(mg)	$AUC_{0-\infty}/Dose$ (ng·h/mL)/(mg)
360 mg	N	6	6	6	6	6	6	6	6	6
Median	3.50	957	14483	14579	8.9	5.38	6.43	0.130	2.46	40.5
Mean	ND	956	12962	13180	10.1	5.69	6.88	0.133	2.77	36.6
SD	ND	439	3194	3184	5.5	2.68	2.16	0.063	1.22	6.8
%CV	ND	44.1	24.6	24.2	54.4	47.1	31.4	41.0	44.1	24.2
Minimum	1.50	510	7023	7330	5.5	2.84	3.09	0.088	1.42	20.4
Maximum	12.00	1739	15419	15667	19.2	9.69	10.48	0.244	4.81	43.3
420 mg	N	5	5	5	5	5	5	5	5	5
Median	4.00	1357	21742	22202	10.8	3.51	3.99	0.230	3.23	52.9
Mean	ND	1301	23545	25777	12.5	4.10	3.72	0.212	3.10	61.4
SD	ND	301	11061	10995	6.8	2.60	1.27	0.098	0.72	26.2
%CV	ND	23.2	43.3	42.7	54.5	63.4	34.1	22.5	23.2	42.7
Minimum	3.00	831	18972	19069	5.4	1.01	1.68	0.141	1.98	45.4
Maximum	6.00	1617	45192	45282	19.9	6.80	5.37	0.257	3.85	107.8
480 mg	N	6	6	6	6	6	6	6	6	6
Median	3.50	1025	24121	24299	9.4	2.99	3.69	0.143	2.14	50.6
Mean	ND	1073	25501	25727	9.9	3.68	4.22	0.175	2.24	53.6
SD	ND	245	8889	8934	1.7	2.07	1.87	0.076	0.51	18.7
%CV	ND	22.8	34.9	34.8	17.3	36.3	44.3	43.2	22.8	34.8
Minimum	2.00	808	16902	16227	8.0	1.95	2.28	0.112	1.68	33.6
Maximum	6.00	1390	38316	38534	12.2	7.59	7.18	0.303	2.85	80.3

ND = not determined.

The plasma concentrations of OPC-41061 at all dose levels and in all subjects are measurable up to at least 48 h after administration and at the highest dose level of 480 mg up to 72 h after administration. The parameter estimates for OPC-41061 reported by the sponsor for the dose range 240-480 mg can be considered reliable. The respective mean values in the 5 dose groups for the main parameters CL/F , V_z/F , and $t_{1/2}$ range between 3.7 and 6.9 mL/min/kg, 3.7 and 6.2 L/kg and 9.9 and 14 h with no obvious dose dependency. Median t_{max} in the 6 dose groups ranges between 2.3 and 4.0 h and shows significant inter-subject variation, but no obvious trend to increase with increasing doses. The percent coefficient of variation about mean C_{max} and $AUC_{0-\infty}$ ranges between 23 % and 46 % and 19 % and 43 %, respectively. The median C_{max} (1025 ng/mL) in the group receiving the 480 mg dose is only 1.2 fold greater than C_{max} (618 ng/mL) in the group receiving the 180 mg dose, although the dose is 2.7 fold greater suggesting a dose dependent reduction in the peak concentration.

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Linear regressions of the dose normalized C_{max} and AUC_∞ on dose are shown in the below 2 figures:



The slope of the regression of the dose normalized C_{max} on dose is negative and statistically significantly different from zero indicating that the absorption kinetics of tolvaptan are less than dose proportionate without affecting bioavailability. In contrast, the slope of the linear regression of the dose normalized AUC_∞ on dose is not different from zero indicating that the elimination kinetics of tolvaptan are proportional to dose in the tested dose range.

The median amounts of unchanged tolvaptan in urine in % of the dose excreted over 72 h after administration are listed in the below table:

Median Amounts of Tolvaptan Excreted in Urine over 72 h after Administration Expressed in Percent of Dose

Median Amounts Excreted of Tolvaptan Excreted in Urine, % of Dose					
Dose Levels, mg					
180	240	300	360	420	480
0.15	0.14	0.18	0.13	0.23	0.14

The results indicate that negligible amounts of unchanged tolvaptan are excreted in urine.

A linear plot of the plasma concentrations of DM-4103 versus time is shown in the below figure and the sponsor's estimated parameter values are provided in the below table:

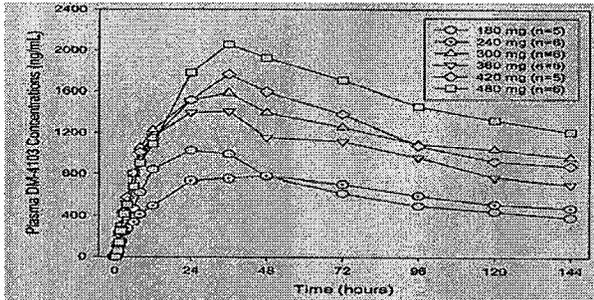


Figure 9.2.3-3 Median Plasma DM-4103 Concentration-time Profiles Following a Single Oral Dose of 180, 240, 300, 360, 420, and 480 mg OPC-41061 in Healthy Male and Female Adult Subjects

OPC-41061 Dose	n	t_{max} (h)	C_{max} (ng/mL)	AUC ₀₋₁₄₄ (ng·h/mL)
180 mg	N	5	5	5
	Median	24.23	1026	89917
	Mean	ND	813	86406
	SD	ND	260	21245
	%CV	ND	38.5	24.6
	Minimum	24.00	596	58393
	Maximum	36.00	1169	134211
240 mg	N	6	6	6
	Median	30.00	787	87145
	Mean	ND	804	88832
	SD	ND	143	18533
	%CV	ND	17.8	19.1
	Minimum	12.00	643	65077
	Maximum	48.00	997	105481
300 mg	N	6	6	6
	Median	30.00	1623	121312
	Mean	ND	1712	183125
	SD	ND	415	46667
	%CV	ND	24.3	25.6
	Minimum	24.00	1310	138374
	Maximum	36.00	2420	264019
360 mg	N	6	6	6
	Median	24.02	1487	144410
	Mean	ND	1566	153092
	SD	ND	393	38314
	%CV	ND	25.1	18.8
	Minimum	12.00	1201	112944
	Maximum	36.02	2258	201085

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420 mg	N	5	4	5
	Median	36.60	1763	180133
	Mean	ND	1859	189326
	SD	ND	330	46341
	%CV	ND	20.4	24.5
	Minimum	24.00	1499	150078
	Maximum	36.00	2373	266670
480 mg	N	6	6	6
	Median	36.00	2056	219288
	Mean	ND	2004	210106
	SD	ND	464	45380
	%CV	ND	23.1	26.4
	Minimum	24.00	1322	137184
	Maximum	48.00	2689	295831

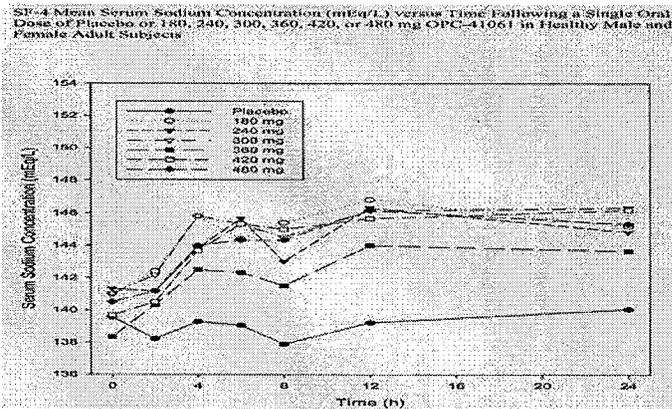
ND=not determined.

The plasma concentrations of DM-4103 were followed up to 144 h after administration. Given the very protracted decline of the plasma concentration time curve of DM-4103, it is uncertain whether the terminal log linear phase is attained at 144 h post-dose. Only C_{max} and t_{max} can be considered reliable with DM-4103. The dose normalized C_{max} values of DM-4103 at the 6 dose levels are comparable suggesting dose proportional kinetics of the metabolite.

Pharmacodynamics

Serum Na⁺ and K⁺

The mean serum Na⁺ profiles over 24 h is shown in the next figure:



The baseline values of the serum Na⁺ differ among the subject of the different groups. The mean serum Na⁺ concentrations increase with all dose of tolvaptan in comparison to placebo.

The below tables lists the mean change from baseline (with/out placebo correction) in serum Na⁺ concentration:

Mean Change from Baseline in Serum Na⁺

Mean Change from Baseline in Serum Na ⁺ , mEq ^a		
	Tolvaptan Dose Levels, mg	Placebo

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	180	240	300	360	420	480	
Time Post-Dose, h							
2	1.4	-0.17	1.2	2.0	0.83	0.67	-1.3
4	4.8	2.5	4.8	4.2	4.0	3.5	-0.28
6	3.4	4.3	4.3	4.0	5.7	3.8	-0.50
8	4.4	1.7	3.5	3.2	5.3	3.8	-1.7
12	5.8	5.0	5.2	5.7	6.0	5.7	-0.33
24	4.2	3.5	5.3	5.3	6.8	4.8	0.50
144	-0.60	0.67	0.17	1.8	1.6	1.7	2.1

Mean Change from Baseline (Placebo Corrected) in Serum Na⁺

Time Post-Dose, h	Mean Change from Baseline (Placebo Corrected) in Serum Na ⁺ , mEq ^a					
	Tolvaptan Dose Levels, mg					
	180	240	300	360	420	480
2	2.7	1.2	2.5	3.3	2.2	2.0
4	5.1	2.8	5.1	4.5	4.3	3.8
6	3.9	4.8	4.8	4.5	6.2	4.3
8	6.1	3.3	5.2	4.8	7.0	5.5
12	6.1	5.3	5.5	6.0	6.3	6.0
24	3.7	3.0	4.8	4.8	6.3	4.3
144	-2.7	-1.4	1.9	-0.28	-0.51	-0.44

^a Pooled placebo corrected

Both data sets suggest an net increase in serum Na⁺ at all dose levels of tolvaptan lasting at least 24 h post-dose. The placebo corrected data suggest a net increase in serum Na⁺ 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 2 h post-dose. Peak increases ranging between 5.3 mEq (3.8 %) and 7.0 mEq (5.0%) occur between 8 and 12 h after tolvaptan administration. Tolvaptan's effect on the serum Na⁺ lasts throughout the 24 h interval with all doses. By 144 h post-dose the net increase in serum Na⁺ is reversed.

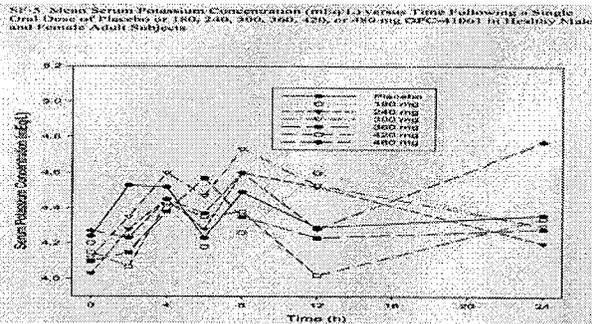
The below table lists the mean change from baseline (with/out placebo correction) in AUC0-24 Na⁺ at the different dose levels:

Dose, mg	Mean AUC0-24 Na ⁺ ^a mEq • h	Mean AUC0-24 Na ⁺ ^b mEq • h
180	104	113
240	52.7	88.2
300	105	113
360	107	116
420	126	135
480	102	115

^aUncorrected for pooled placebo ^b Pooled placebo corrected

The values for the mean change from baseline (with/out placebo correction) in AUC0-24 Na⁺ at the different dose levels are overlapping suggesting a ceiling effect on serum Na⁺ is attained with tolvaptan doses between 180 mg and 240 mg.

The below figure shows the mean serum K⁺ concentrations over a period of 24 h post-dose:



The baseline serum K⁺ concentrations differ among the different groups. The levels fluctuate over time in the placebo and tolvaptan receiving groups.

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

Mean Change from Baseline (Placebo Corrected) in Serum K⁺

Time Post-Dose, h	Mean Change from Baseline (Placebo Corrected) in Serum K ⁺ ^a					
	Tolvaptan Dose Levels, mg					
	180	240	300	360	420	480
2	-0.24	-0.03	-0.05	-0.23	-0.36	-0.31
4	-0.05	0.15	0.21	0.01	0.01	-0.09
6	-0.01	0.26	0.36	0.48	0.21	0.11
8	-0.19	0.32	0.37	0.00	-0.02	0.08
12	0.36	0.44	0.38	0.09	-0.17	0.02
24	-0.04	0.05	0.06	0.06	0.08	0.38
144	0.07	0.37	0.10	0.49	0.33	0.12

^aPooled placebo corrected

There appears to be a slight net increase of the serum K⁺ concentrations by tolvaptan in the 0-24 h post-dose interval on Day 1 which is not related to the dose of tolvaptan. The net increase in serum K⁺ appears to be maintained on Day 7 which is unexpected.

Urine Excretion Rate and 24 h Urine Volume

A plot of the mean 24 h urine volumes excreted after single doses of tolvaptan is shown in the below figure:

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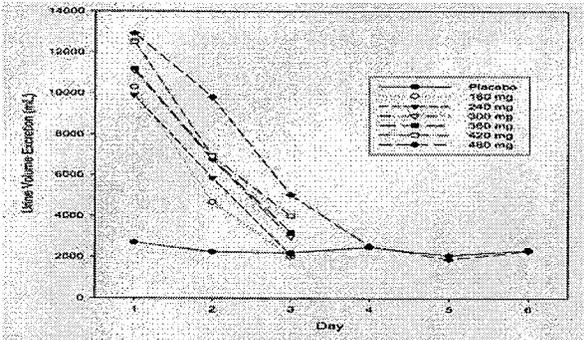


Figure 9.3.3-2 Mean Total Urine Excretion (mL) per Day Following a Single Oral Dose of Placebo or 180, 240, 300, 360, 420, or 480 mg OPC-41061 in Healthy Male and Female Adult Subjects

The effect of tolvaptan on the mean 24 h urine volume is in the order of the size of the dose.

A linear plot of the time profile of the mean urine excretion rates is shown in the below figure:

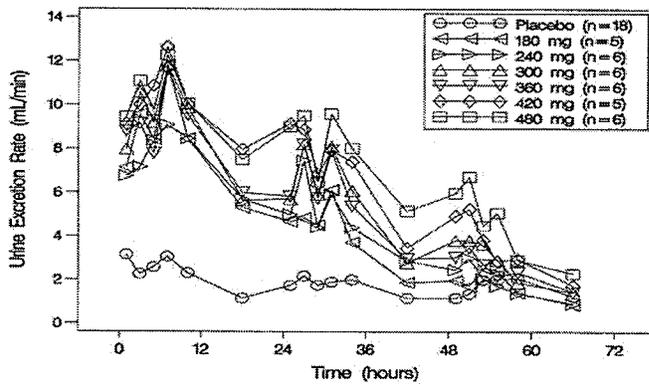


Figure 9.3.3-1 Mean Urine Excretion Rate Versus Midpoint of the Collection Interval on Days 1, 2, and 3 Following a Single Oral Dose of Placebo or 180, 240, 300, 360, 420, or 480 mg OPC-41061 in Healthy Male and Female Adult Subjects

The mean urine excretion rates after all doses of tolvaptan are greater than after placebo. It appears that the onset of the aquaretic activity is swiftest, the peak excretion rates highest and the duration of the effect longest with the two top doses of 480 mg and 420 mg.

The mean changes from baseline in the urine excretion rate are shown in the below table:

Mean Change from Baseline in Urine Excretion Rate in Healthy Subjects after Single Doses of 180, 240, 300, 360, 420 and 480 mg Tolvaptan

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Collection Interval, h	Mean Change from Baseline in Urine Excretion Rate, mL/min						
	Tolvaptan Dose Level, mg						Placebo
	180	240	300	360	420	480	
0-2	6.0	5.6	7.3	7.1	7.5	8.4	1.6
2-4	7.3	4.2	6.2	8.3	8.0	9.5	-0.17
4-6	7.0	6.1	5.6	7.4	8.9	6.6	-0.042
6-8	10.3	5.9	8.9	9.8	10.0	7.7	0.29
8-12	7.0	6.4	8.5	8.6	7.1	7.3	0.19
12-24	4.7	4.7	4.7	4.4	6.1	6.0	0.096
24-26	3.6	3.8	4.3	4.8	7.3	7.9	0.18
26-28	2.5	4.4	5.2	5.9	5.8	7.9	-0.25
28-30	3.1	2.1	3.6	4.3	5.3	3.4	-0.86
30-32	4.7	2.7	5.3	6.1	6.0	5.0	-0.86
32-36	2.2	2.3	4.4	4.8	4.7	5.1	-0.12
36-48	1.3*	1.9	1.7	1.5	1.9	3.7	0.11
48-50	0.88	1.3*	1.6*	2.9	3.7	4.8	-0.40
50-52	-0.59	-0.017	0.48	1.6	3.7	5.2	-1.1
52-54	-0.11	-0.19	0.55	1.9*	2.2*	1.3*	-0.60
54-56	0.99	-1.48	-0.46	0.91	0.93	0.52	-0.73
56-60	-0.071	0.70	1.3	0.59	0.30	0.15	-0.038
60-72	0.24	-0.051	0.14	0.19	0.20	0.79	0.099
0-24	6.1	5.2	6.1	6.4	7.1	6.9	0.22
24-48	2.2	2.4	3.1	3.3	3.2	4.7	-0.11
48-72	0.12	-0.17	0.47	0.80	1.0	1.4	-0.14
72-96						-0.32	0.26
96-120						-0.78	-0.019

* denotes last time point with mean net urine excretion rate ≥ 1.0 mL/min

The mean changes from baseline (placebo corrected) in the urine excretion rate are shown in the below table:

Mean Change from Baseline (Placebo Corrected) in Urine Excretion Rate in Healthy Subjects after Single Doses of 180, 240, 300, 360, 420 and 480 mg Tolvaptan

Collection Interval, h	Mean Change from Baseline in Urine Excretion Rate, mL/min ^a					
	Tolvaptan Dose Level, mg					480
	180	240	300	360	420	
0-2	4.4	4.0	5.7	5.5	5.9	6.8
2-4	7.5	4.4	6.4	8.5	8.2	9.7
4-6	7.0	6.1	5.6	7.4	8.9	6.6
6-8	10.0	5.6	8.6	9.5	9.7	7.4
8-12	6.8	6.2	8.3	8.4	6.9	7.1
12-24	4.6	4.6	4.6	4.3	6.0	5.9
24-26	3.4	3.6	4.1	4.6	7.1	7.7
26-28	2.8	4.7	5.5	6.2	6.1	8.2
28-30	4.0	3.0	4.5	5.2	6.2	4.3

30-32	5.6	3.6	6.2	7.0	6.9	5.9
32-36	2.3	2.4	4.5	4.9	4.8	5.2
36-48	1.2	1.8	1.6	1.4	1.8	3.6
48-50	1.3*	1.7	2.0	3.3	4.1	5.2
50-52	0.47	1.1*	1.6	2.7	4.8	6.3
52-54	0.49	0.41	1.2*	2.5	2.8	1.9
54-56	1.7	-0.80	0.27	1.6*	1.7*	1.3*
56-60	-0.043	0.74	1.3	0.63	0.34	0.19
60-72	0.14	-0.15	0.040	0.09	0.10	0.69
0-24	5.9	5.0	5.9	6.2	5.9	6.7
24-48	2.3	2.5	3.2	3.4	3.3	4.8
48-72	0.26	-0.03	0.61	0.94	1.1	1.5
72-96						-0.58
96-120						-0.76

^a Mean change from baseline corrected for pooled placebo * denotes last time point with net mean urine excretion rate ≥ 1.0 mL/min

The tabulated mean changes from baseline (with/out placebo correction) in urine excretion rate indicate that the onset of the aquarectic activity of tolvaptan occurs during the first collection 0-2 h post-dose. Peak rates are attained with the 480 mg dose during the 2-4 h collection interval and with the lower doses in the 6-8 h or 8-12 h collection interval. The fact that peak urine excretion rates are observed later than the peak plasma concentrations (median t_{max} 2.3-4 h) suggests a counterclockwise hysteresis of the aquarectic effect of tolvaptan. The net urine excretion rates measured in the 72-96 h and 96-120 h intervals in the group receiving the highest dose of 480 mg tolvaptan are negative, indicating a rebound effect with increased retention of water and/or decreased ingestion. Negative net urine excretion rates following cessation of the aquarectic activity of tolvaptan are also seen at the 180 mg and 240 mg dose levels.

If a net increase of ≥ 1.0 mL/min in the mean excretion rate is considered a lower threshold value for aquarectic activity of tolvaptan, estimates of the duration of the effect of tolvaptan can be obtained by determining the last collection interval after dosing at which the net mean excretion rate ≥ 1.0 mL/min. The so obtained estimates for the duration of the aquarectic effect are listed in the below table:

Time Duration of Aquarectic Effect, h					
Tolvaptan Dose Level, mg					
180	240	300	360	420	480
42 ^a	49 ^a	49 ^a	53 ^a	53 ^a	53 ^a
49 ^b	51 ^b	53 ^b	55 ^b	55 ^b	55 ^b

^a mean change from baseline in urine excretion rate ^b mean change from baseline (placebo corrected) in urine excretion rate

The results of both data sets indicate the aquarectic effect of tolvaptan to last between 42 h and 55 h post-dose at the tested dose levels.

Free Water Clearance

The next figure depicts the time profile of the mean free water clearance:

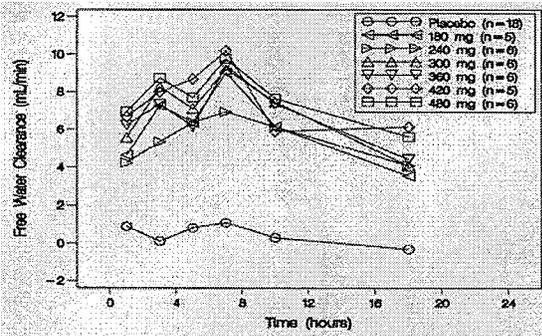


Figure 9.3.3-3 Mean Free Water Clearance Versus Midpoint of the Collection Interval on Day 1 Following a Single Oral Dose of Placebo or 180, 240, 300, 360, 420, or 480 mg OPC-11661 in Healthy Male and Female Adult Subjects

The corresponding values of the free water clearance are tabulated in the below table:

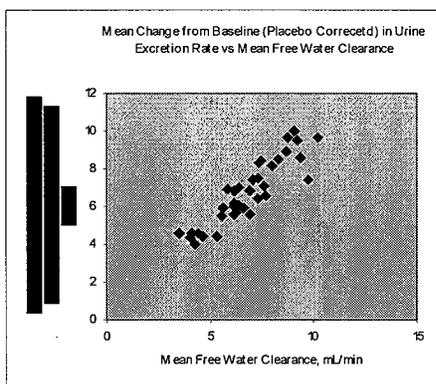
Mean Free Water Clearance, mL/min

Collection Interval, h	Mean Free Water Clearance, mL/min					
	0-2	2-4	4-6	6-8	8-12	12-24
Dose, mg						
Placebo	-0.24	-0.41	0.29	0.01	-0.38	-0.50
180	4.63	7.28	6.37	9.05	6.14	3.54
240	4.23	5.34	6.38	6.93	6.14	4.10
300	6.23	7.34	6.16	9.38	7.37	4.42
360	5.57	8.27	7.11	9.21	7.46	4.07
420	6.66	8.01	8.68	10.18	5.90	6.14
480	6.95	8.74	7.70	9.77	7.65	5.62

The free water clearance is greater with all doses of tolvaptan tested than with placebo. The top doses of 480 mg and 420 mg tolvaptan exhibit the greatest effects. The onset of the effect on free water clearance with all tested doses occurs in the first collection interval 0-2 h post-dose. The peak effect is observed in the 6- 8 h interval. The aquaretic effect lasts ≥ 18 h post-dose at all dose levels.

The mean change from baseline (placebo corrected) in urine excretion rate and the free water clearance are correlated as shown in the below plot:

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$$y = 0.630 + 0.901 \bullet x, r^2 = 0.812$$

The data indicate good agreement between baseline and placebo corrected urine excretion rate and free water clearance.

Urine Excretion of Sodium and Potassium

The below 2 tables lists the mean change from baseline (placebo corrected) in urine Na⁺ and K⁺ excretion over 24 h on Days 1-3 after dosing:

Mean Change from Baseline in Na⁺ Excretion

Collection Interval, h	Mean Change from Baseline in Na ⁺ Excretion ^a , mEq					
	Dose Level of Tolvaptan, mg					
	180	240	300	360	420	480
0-24	-37	-41	na	na	-106	37
24-48	-46	-29	na	-35	na	na
48-72	-18	-71	-42	22	-63	-40

^a Pooled placebo corrected na= not available

Single doses between 180 mg and 480 mg tolvaptan can decrease net 0-24 h Na⁺ excretion on Days 1-3 by between 18 and 71 mEq corresponding to between 14 % and 46 %.

Mean Change from Baseline in Urine Excretion of K⁺

Time after Administration, h	Mean Change from Baseline in K ⁺ Excretion ^a , %					
	Dose Level of Tolvaptan, mg					
	180	240	300	360	420	480
0-24	41	31	31	24	40	38
24-48	-1.2	-0.83	-0.88	-1.82	52	32
48-72	-15	-38	-23	-34	16	0.77

^a Pooled placebo corrected

Tolvaptan appears to increase net K^+ excretion at all dose levels on Day 1. The increase ranges between 24 and 41 mEq corresponding to between 28 % and 73 %.

Creatinine Clearance (CLcr)

The below table lists the CLcr values in the presence and absence of tolvaptan:

Table 9.3.3-1 Mean \pm SD Creatinine Clearance (mL/min) on Day -1 and on Day 1 Following a Single Oral Dose of Placebo or 180, 240, 300, 360, 420, or 480 mg OPC-41061 in Healthy Male and Female Adult Subjects

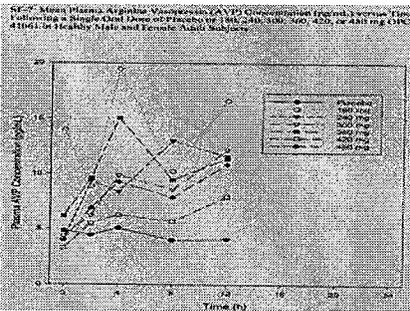
OPC-41061 Dose (n)	Day -1	Day 1
Placebo (18)	116 \pm 20	121 \pm 21
180 mg (5)	109 \pm 18	107 \pm 18
240 mg (6)	112 \pm 15	110 \pm 14
300 mg (6)	110 \pm 14	97 \pm 11
360 mg (6)	123 \pm 25	108 \pm 17
420 mg (5)	118 \pm 14	108 \pm 9
480 mg (6)	138 \pm 14	123 \pm 13

Source: ST-40 to ST-46.

The listed values of CLcr in the presence and absence of tolvaptan are not clinically significantly different from each other.

AVP, PRA and Norepinephrine Concentrations in Plasma

A linear plot of the time profiles of AVP measured over a period of 12 h after tolvaptan administration is shown below:



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

Mean Percentage Change from Baseline (Placebo Corrected) in AVP Level

Time after Administration, h	Mean Percent Change from Baseline in AVP Level ^a , %					
	Dose Level of Tolvaptan, mg					
	180	240	300	360	420	480

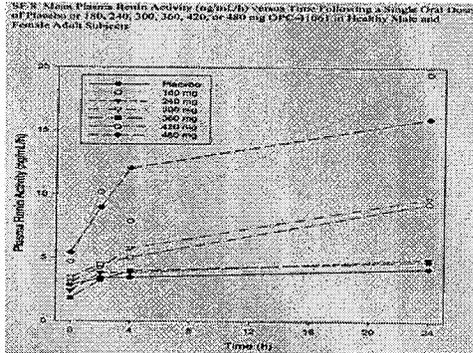
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2	16	117	49	46	79	80
4	113	114	121	137	105	139
8	65	242	114	77	108	125
12	108	204	169	107	161	183

^a Pooled placebo corrected

The net effect of tolvaptan at all dose levels and time points is an increase in the net plasma concentrations of AVP. The maximum effect of tolvaptan occurs 12 h after dosing with 108% to 204 % increases in net AVP levels.

The below figure shows the time profiles of PRA measured 2, 4, and 24 h after dosing:



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The baseline values for mean PRA vary among the groups. PRA of the placebo group shows a small increase over time. PRA in the groups receiving tolvaptan follows the same temporal pattern, but the values are substantially greater than those of the placebo group.

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

Time after Administration, h	Mean Percent Change from Baseline PRA Level ^a , %					
	Dose Level of Tolvaptan, mg					
	180	240	300	360	420	480
2	72	34	28	63	27	50
4	81	43	71	120	46	96
24	257	68	155	122	85	110

^a Pooled placebo subtracted

The effects of the different dose levels of tolvaptan on PRA are overlapping. The increase in baseline and placebo corrected PRA is greater 24 h after administration than 2 h and 4 h after dosing. The maximum increase of PRA ranges between 68 % and 257 %. The data are compatible with an increase in PRA by single tolvaptan in doses ranging between 180 mg and 480 mg.

Below are the time profiles of epinephrine measured 2 h and 24 h after dosing: