A Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of a Ramipril Oral Solution versus Tablet in Healthy Adult Volunteers

Marie-Chantal Bonhomme[1], Nadia Cardillo Marricco[1], Mike Di Spirito[1], Elliot M. Offman[1], Stephen P. Smith[2] and M. Kevan Cassidy[3]
[1]Celerion, Montreal, Canada; [2]Belfast, Northern Ireland; [3]Rosemont Pharmaceuticals Ltd, Leeds, UK.

BACKGROUND

Ramipril is a potent, long-acting, angiotensin-converting enzyme (ACE) inhibitor and its effect on hypertension appears to result at least in part from inhibition of both tissue and circulating ACE activity, thereby reducing angiotensin-II formation in tissue and plasma.

Ramipril tablet is indicated in the treatment of hypertension; cardiovascular prevention for reducing cardiovascular morbidity and mortality; treatment of renal disease; and treatment of symptomatic heart failure. The recommended initial dose of ramipril is usually of 2.5 mg administered once daily. The dose adjustment and maintenance dose vary upon indication and ranges from 2.5 to 10 mg per day administered as a single dose or in two equally divided doses.

Following oral administration, ramipril is rapidly absorbed from the gastrointestinal tract with an absolute bioavailability of 50 to 60%. Cleavage of the ester group, primarily by esterases in the liver, converts ramipril to its active diacid metabolite, ramiprilat. The parent drug is almost completely metabolized to ramiprilat, which has about 6 times the ACE inhibitory activity of the parent ramipril, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat, all of which are inactive metabolites.

An oral solution was developed with the intention of improving treatment compliance in patients who struggle swallowing solid oral dosage forms. In addition, the oral solution allows for individualized dosing, improving dose adjustment to achieve target blood pressure.

OBJECTIVE

The primary objective of this study was to assess the single-dose relative bioavailability of a test 2.5 mg/ 5 mL ramipril oral solution and a marketed reference 2.5 mg ramipril tablet, under fasting conditions.

METHODS

- This was an open-label, randomized, 2-way crossover, 2-sequence, single-dose comparative bioavailability study.
- A total of 36 healthy adult subjects (32 males and 4 females) were enrolled in the study and were randomized to study treatments.
- In each study period, subjects received a single 2.5 mg oral dose of one of the following treatments following an overnight fast:
  - Test: 2.5 mg/ 5 mL ramipril oral solution
  - Reference: marketed 2.5 mg ramipril tablet
- The washout period was 35 days between doses which covered more than 5 times the mean half-life of the metabolite ramiprilat.
- Serial blood samples drawn from predose through 72 hours postdose were quantified for plasma ramipril (up to 12 hours) and ramiprilat using a validated LC-MS/MS method with a lower limit of quantification of 0.100 ng/mL for both analytes.
- A noncompartmental analysis was performed on the plasma ramipril and ramiprilat concentrations to derive the pharmacokinetic (PK) parameters of interest using PhAST 2.3-001 (Celerion, Lincoln, Nebraska). The maximum plasma concentration (C_{max}), area under the curve from time 0 to the last measureable concentration (AUC_{0-t}), area under the curve from time 0 to infinity ($AUC_{0-\infty}$), time to reach C_{max} (t_{max}), apparent elimination rate constant (kel), apparent terminal elimination half-life ($t_{1/2}$) were calculated for ramipril in plasma. The C_{max}, area under the curve from time 0 to 72 hours post-dose (AUC_{0-72}), AUC_{0-t} and t_{max} PK parameters were calculated for ramiprilat in plasma. Below limit of quantitation (BLQ) values were set to missing for statistical analyses when flanked by two measurable concentrations. Otherwise, BLQ values were set to zero.
- Analyses of variance were performed on the ln-transformed C_{max}, AUC_{0-72}, AUC_{0-t} and $AUC_{0-\infty}$, as applicable, using the GLM procedure (SAS® version 6.12, SAS Institute, Cary, North Carolina).
- The following standards were used to determine bioequivalence:
  - The 90% confidence interval of the ratios of least-squares means of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of the oral solution to the tablet formulation for ramipril should be within 80 - 125%. (The data for ramiprilat were presented for supportive information purposes.)
- A non-parametric analysis was performed on t_{max} using SAS® version 9.1.3 (SAS Institute, Cary, North Carolina).
- Safety assessments included vital signs, clinical laboratory evaluations, 12-lead ECG and adverse event monitoring.

RESULTS

- Data from 35 subjects who completed the study were included in the PK and statistical analyses. All 36 subjects dosed were included in the safety assessment. One subject withdrew from the study due to personal reasons.
- The arithmetic mean plasma ramipril and ramiprilat concentrations versus time plots following the administration of a single 2.5 mg oral dose of the ramipril oral solution and tablet, under fasting conditions, are presented in Figures 1 and 2, respectively.
- A summary of plasma ramipril and ramiprilat PK parameters following the administration of a single 2.5 mg oral dose of the ramipril oral solution and tablet, under fasting conditions, is presented in Table 1.
- Results from the ANOVA bioequivalence assessment are presented in Table 2.
- Peak and total exposure to ramipril and ramiprilat were comparable between the oral solution and tablet. The 90% confidence intervals of the ratios of least-square means for C_{max}, AUC_{0-t}, AUC_{0-72}, and $AUC_{0-\infty t}$, as applicable, were within the 80 – 125% acceptance range.
- The ramipril and ramiprilat intrasubject variability was low for the AUCs (< 15%) and slightly higher for C_{max} (22.7% and 14.6%, respectively).
- The $t_{1/2}$ and t_{max} values of ramipril were comparable between the oral solution and tablet. The t_{max} median difference (formulation effect, oral solution - tablet) and 90% confidence interval was 0.000 [-0.125; 0.000].
- The t_{max} values of ramiprilat were comparable between the oral solution and tablet. The t_{max} median difference (formulation effect, oral solution - tablet) and 90% confidence interval was 0.250 [-0.250; 0.750].
- All vital sign, 12-lead ECG and clinical laboratory results were judged by the Investigator as normal or not clinically significant.
- Overall, 1 subject (3% of the study population receiving the oral solution) and 1 subject (3% of the study population receiving the tablet) experienced adverse events possibly related to ramipril, consisting of reported headache, nausea, irritated area on the tongue and irritated throat.

CONCLUSIONS

The oral solution is bioequivalent to the marketed reference tablet under fasting conditions. Both the oral solution and the tablet products were equally well tolerated by all subjects. No serious or severe adverse events related to the study drug were observed.

Figure 1 Arithmetic Mean Plasma Ramipril Concentrations versus Time

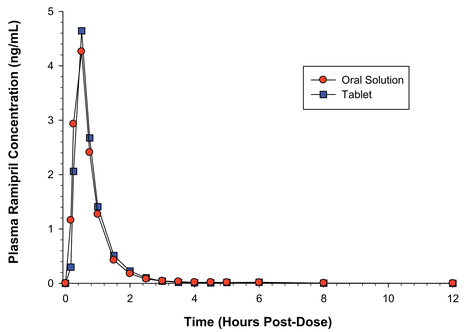

Figure 2 Arithmetic Mean Plasma Ramiprilat Concentrations versus Time

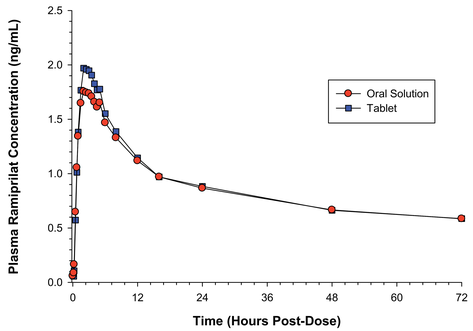

Table 1 Summary of Plasma Pharmacokinetic Parameters for Ramipril and Ramiprilat Following a Single 2.5 mg Dose of Ramipril

		Ramipril		Ramiprilat	
Pharmacokinetic Parameters	**Statistics**	**Oral Solution N= 35**	**Tablet N= 35**	**Oral Solution N= 35**	**Tablet N= 35**
C_{max} (ng/mL)	Arithmetic Mean (± SD) Geometric Mean	4.58 (2.54) 4.01	4.90 (3.09) 4.13	1.87 (0.76) 1.72	2.11 (1.21) 1.86
AUC_{0-t} (ng·hr/mL)	Arithmetic Mean (± SD) Geometric Mean	3.18 (1.99) 2.71	3.22 (1.96) 2.76	61.47 (15.68) 59.48	62.82 (18.25) 60.29
$AUC_{0-\infty}$ (ng·hr/mL)	Arithmetic Mean (± SD) Geometric Mean	3.11 (1.82)[1] 2.72[1]	2.95 (1.76)[1] 2.60[1]	NC	NC
AUC_{0-72} (ng·hr/mL)	Arithmetic Mean (± SD) Geometric Mean	NC	NC	61.47 (15.68) 59.48	62.82 (18.25) 60.29
t_{max} (hr)	Arithmetic Mean (± SD) Median (Min - Max)	0.47 (0.15) 0.50 (0.25 - 1.00)	0.51 (0.14) 0.50 (0.25 - 1.00)	3.27 (1.50) 2.50 (1.50 - 8.00)	2.97 (1.45) 2.50 (1.00 - 8.00)
$t_{1/2}$ (hr)	Arithmetic Mean (± SD)	0.560 (0.434)[1]	0.697 (1.385)[1]	NC	NC
k_{el} (1/hr)	Arithmetic Mean (± SD)	1.76 (0.81)[1]	1.72 (0.60)[1]	NC	NC

[1] N = 30
NC = Not Calculated

Table 2 Summary of the Statistical Comparison of Plasma Ramipril and Ramiprilat Pharmacokinetic Parameters: Test (2.5 mg/ 5 mL Oral Solution) Versus Reference (Marketed 2 mg Tablet)

	Ramipril		Ramiprilat	
PK Parameter	**Mean Ratio [90% Confidence Interval]**	**Intrasubject CV (%)**	**Mean Ratio [90% Confidence Interval]**	**Intrasubject CV (%)**
C_{max} (ng/mL)	97.1% [88.6-106.3%]	22.7	93.3 % [88.0-99.0%]	14.6
AUC_{0-t} (ng·h/mL)	98.0% [92.4-104.0%]	14.8	99.0% [96.3-101.8%]	6.9
$AUC_{0-\infty}$ (ng·h/mL)	96.0% [89.8-102.7%]	14.1	NC	NC
AUC_{0-72} (ng·h/mL)	NC	NC	99.0% [96.3-101.8%]	6.9

NC = Not Calculated