Morning Administration of the New Cathepsin K Inhibitor, ONO-5334, Causes Greater Suppression of Bone Resorption Markers Compared with Evening Administration

SU0390

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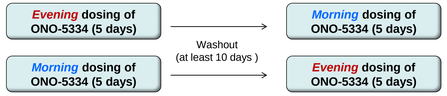
1 Introduction & Objectives

- Bone resorption is highest at night, thus it would seem preferable to administer anti-resorptive drugs in the evening.
- Evening administration of the cathepsin K inhibitor, ONO-5334, has been shown to increase bone mineral density (BMD) in patients with osteoporosis, and 300 mg of the immediate release tablet (IRT) was consistently the most efficacious dose overall on BMD and biochemical markers of bone resorption in the Phase II OCEAN study. [1,2] Another study in healthy post-menopausal women showed that 150 mg of the sustained release tablet (SRT) showed comparable suppression of biochemical markers with 300 mg IRT used in the OCEAN study. [3]
- The aim of this study was to investigate the effects of morning versus evening dosing on the pharmacodynamics and pharmacokinetics of multiple doses of ONO-5334 SRT in healthy post-menopausal women.

2 Methods

Study Design and Assessments

- Healthy post-menopausal women were enrolled in a single-blind, multiple-dose, randomised, two-period crossover study.
- Subjects were randomized to one of two different dosing sequences, either to Evening (8 pm) active dose in the first period and Morning (8 am) active dose in the second period, or to Morning active dose in the first period and Evening active dose in the second period as below. Subjects received 2 doses per day (one 150 mg SRT, one placebo tablet).



- A regular sleep/wake cycle (22:30-06:30) was scheduled for 7 days prior to and throughout the study period. Subjective sleep diaries and actigraphy were used to confirm compliance with sleep/wake cycle instructions and exercise restrictions.
- The timing of food intake and blood/urine sampling was consistent throughout the study. Breakfast, lunch, and dinner were served at 07:00, 13:00, and 19:00 respectively during the in-clinic period and water could be taken at other times.
- Breakfast had the same nutritional content as dinner since these times were considered to influence resorption the most. Lunch had a higher nutritional content to ensure daily nutritional status.
- Serum sampling was obtained ~ every 2h. A longline indwelling cannula was used for overnight sampling to minimise disturbance.
- Subjects were asked to void at 08:00 and the urine discarded. Subjects were then asked to void at the end of each 2h (or 4h) collection period with all urine collected within each period.
- CTX-I in serum and urine were measured throughout the study.
- CTX-I measurements in urine were adjusted for urine creatinine.

Main Inclusion Criteria

- Healthy post-menopausal women aged 55 to 75 years with body weight >50 kg and body mass index 19 to 30 kg/m^2.
- Subjects had a regular sleep history (for at least 1 month prior to screening) of bedtime between 21:30 to 00:00 on at least 5 nights per week, typical nightly sleep duration of 6.5 to 8.5 hours, typical night time awakening frequency for micturition of ≤2 and no habit of day time naps >1 hour.

Main Exclusion Criteria

- Subjects with serum CTX-I below the limit of quantification of the assay at time of predicted trough (14:00 – 16:00) following lunch.
- Subjects with sleep/wake disorders/complaints.

Statistical analysis

- The area under the pharmacodynamic effects time curve (AUE) for urine and serum CTX-I were compared using analysis of covariance (ANCOVA).
- Cmax, time to reach Cmax (Tmax) and area under the concentration-time curves (AUC) were compared between morning and evening dosing on Day 5. Geometric mean ratios (morning/evening) and 90% confidence intervals (CIs) of Pharmacokinetic (PK) parameters were calculated by ANOVA. Tmax was analyzed by Wilcoxon signed rank test at a two-sided significance level of 5%.

3 Results

Demographics and Baseline Characteristics

- 14 subjects were enrolled and 11 subjects were eligible for the per protocol analysis set.

Table 1. Baseline Demographics for the Safety Population

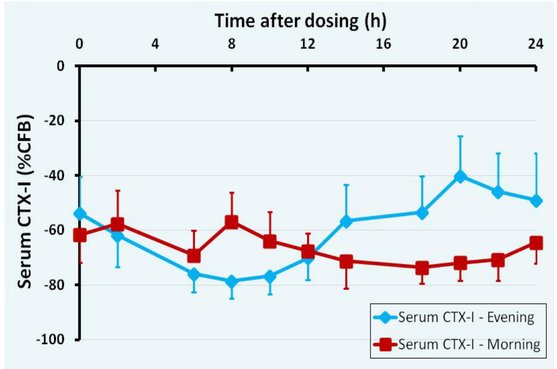
			All Subjects (N=14)
Age (years)			65.0 ± 7.74
Height (m)			1.63 ± 0.06
Weight (kg)			64.6 ± 7.1
Body Mass Index (kg/m^2)			24.5 ± 2.8
Serum CTX-I [a]	(μg/L)	08:00	0.50 ± 0.17
		20:00	0.35 ± 0.09
		Total 24h (AUE)	10.7 ± 2.9
Urine CTX-I/Cr [a]	(μg/mmol crea.*h)	08:00 - 10:30	70.5 ± 25.6
		20:00 - 22:30	69.3 ± 31.7
	(μg/mmol crea.)	Total 24h (AUE)	1651.9 ± 671.3

Expressed as Mean ± SD
[a]: CTX-I in serum and urine were measured on the previous day of the first dosing (Day -1, Period 1).

Pharmacodynamics Results

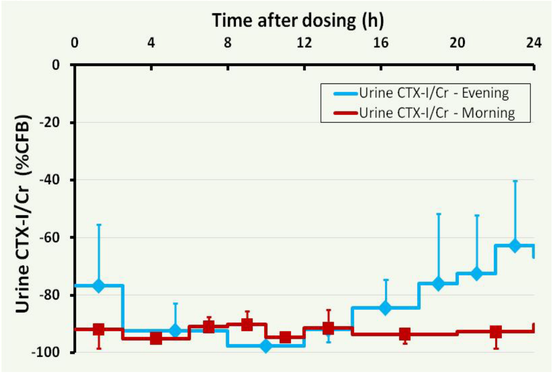
- On Day 5, there was a marked difference in effect between morning and evening administration on the serum CTX-I profile across 24h (time-matched against individual's own Day -1, 24h baselines), Figure 1.
- On Day 5, there was also a marked difference in effect between morning and evening administration on the urine CTX-I/Cr profile across 24h (time-matched against individual's own Day -1, 24h baselines), Figure 2.
- Although evening administration showed a larger suppressive effect this appeared less sustained.
- Morning dosing showed a more consistent suppressive effect across 24h.
- Summarising over the whole 24h using the area under the pharmacodynamic effects time curve (AUE) analyses, the differences between morning and evening appeared to be of a lesser magnitude although significant differences were still observed, Table 2.
- Morning dosing achieved greater suppression of serum CTX-I (24h AUE) compared with evening dosing.
- With urine CTX-I/Cr (24h AUE), morning dosing showed even greater suppression compared with evening dosing.

Figure 1. Serum CTX-I (Time-matched %CFB) after 5 days dosing



Values are expressed as Mean and SD. CFB: Change from baseline
N = 11

Figure 2. Urine CTX-I/Cr (Time-matched %CFB) after 5 days dosing



Values are expressed as Mean and SD. CFB: Change from baseline
N = 11

Table 2. CTX-I (Percent change from baseline) on Day 5 (N=11)

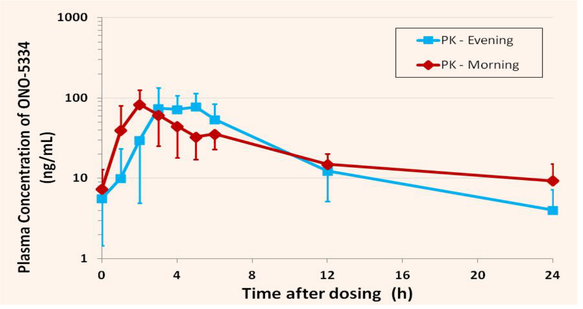
Parameter	Morning	Evening	M vs. E
Serum CTX-I: AUE	-68.8	-62.9	-5.9 *
Urine 24h CTX-I/Cr: AUE	-92.6	-85.8	-6.8 **

Expressed as Least Squares Means and p-values obtained from ANCOVA model including Regimen, Cohort, Period and Dosing Sequence as fixed effects, Baseline variable as a Covariate and subject within Sequence as a random effect. * p<0.05, ** p<0.01

Pharmacokinetics Results

- Figure 3 shows the mean plasma concentration-time profile of ONO-5334 on Day 5 for the per protocol analysis set.
- On Day 5, ONO-5334 in plasma reached Cmax at 2.0 and 5.0 h post-dose after morning and evening dosing, respectively, Table 3. A statistically significant difference was observed in Tmax between morning and evening dosing. Geometric mean ratios (Morning/Evening) of the Cmax and AUC24h and their 90% confidence intervals are presented in Table 3.

Figure 3. Mean Plasma concentration of ONO-5334



Expressed as Mean and SD
N = 11

Table 3. PK parameters of ONO-5334 on Day 5 (N=11)

Dose (mg)	Dosing	C_{max} (ng/mL)	T_{max} (h)	AUC_{24h} (ng•h/mL)
150	Morning	99.5 (45.3)	2.0 (1.0 - 3.0)	582 (196)
150	Evening	107 (52)	5.0 (2.0 - 6.0)	591 (204)
M/E[a] (90%CI[b])		0.91 (0.78 - 1.05)	P = 0.0020[c]	0.99 (0.88 - 1.11)

Cmax, AUC24h; Mean (SD), Tmax; Median (range)
M/E: Morning dosing / Evening dosing
[a]; Geometric mean ration, [b]; 90% confidence interval of the geometric mean ratio, [c]; Wilcoxon signed rank test

Safety Results

- In total 79 Treatment Emergent Adverse Events (TEAEs) were reported by 14/14 (100%) of subjects. The TEAEs reported by the greatest number of subjects were procedural site reaction (8 subjects [57.1%]), nausea (5 subjects [35.7%]) and back pain (4 subjects [28.6%]).
- Overall a similar number of subjects reported TEAEs after morning dosing (12/12 subjects [100%]) and after evening dosing (12/13 subjects [92.3%]). Procedural site reaction was more frequently reported after evening dosing (7/13 subjects [53.8%] compared to 4/12 subjects [33.3%] after morning dosing). Nausea was more frequently reported after morning dosing (4/12 subjects [33.3%] compared to 1/13 subjects [7.7%] after evening dosing).
- A greater number and subject incidence of treatment-related TEAEs were reported after morning dosing (17 TEAEs reported by 7/12 subjects [58.3%] compared to 7 TEAEs reported by 5/13 subjects [38.5%]. Nausea was the most frequently reported treatment-related TEAE (reported by 3/12 subjects [25.0%] following morning dosing and 1/13 subjects [7.7%] following evening dosing).
- There were no clinically relevant findings noted in clinical laboratory safety data, vital signs, ECGs or physical examinations following dosing with ONO-5334 for 5 days.

4 Discussion & Summary

- Morning administration of ONO-5334 shows greater suppression of CTX-I over 24-hours compared to evening administration at the dose of 150mg.
- The sustained CTX-I suppression in the second half of the day with morning administration may be related to higher plasma ONO-5334 levels.
- Evening administration of ONO-5334 has been shown to significantly improve BMD in the OCEAN study. [1, 2] It remains to be seen whether morning administration would show increased efficacy (on BMD) and whether the morning vs. evening effect is observed with higher doses of ONO-5334.

5 Acknowledgements

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6 References

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