1 STUDY SYNOPSIS

Name of Sponsor/Company: Ono Pharmaceutical Co., Ltd.	**Individual Study Table Referring to Part of the Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Finished Product: ONO-5334		
Name of Active Ingredient:		

Title of study:
A multi-centre randomised double-blind, placebo and active controlled parallel group study to investigate efficacy and safety of ONO-5334 in post menopausal women with osteopenia or osteoporosis.

Study centre(s):
A total of 17 centres were actually initiated in six countries (Czech Republic, Denmark, Estonia, Hungary, Lithuania and the Netherlands).

Publication(s): Eastell R, Nagase S, Ohyama M, Small M, Sawyer J, Boonen S, Spector T, Kuwayama T, Deacon S. Safety and efficacy of the cathepsin K inhibitor, ONO-5334, on postmenopausal osteopenia or osteoporosis – The OCEAN study. JBMR 26(6):1303-1312. Epub ahead of print 1 Feb 2011.	**Development Phase:** Phase II

Study period:
Initial 12-Month treatment phase: 11 Dec 2007 to 04 Aug 2009
12-Month extension phase: 15 Dec 2008 to 12 Sep 2010

Objectives:

PRIMARY OBJECTIVE OF THE INITIAL 12-Month TREATMENT PHASE
The primary objective of the initial 12-Month treatment phase was to compare the percentage change in Dual X-Ray Absorptiometry (DXA) Bone Mineral Density (BMD) of the lumbar spine between baseline and 12 months following treatment with ONO-5334 or placebo.

SECONDARY OBJECTIVES OF THE INITIAL 12-Month TREATMENT PHASE
The secondary objectives of the initial 12-Month treatment phase were:

- To compare the effect of ONO-5334 or once weekly alendronate (Fosamax Once Weekly®) versus placebo on DXA BMD and Bone Mineral Content (BMC) (Lumbar spine, Total hip, Femoral neck and Trochanter) and biochemical markers of bone turnover from baseline during the course of treatment.
- To compare the proportions of responders to ONO-5334 or alendronate therapy at the end of 12 months' treatment compared with placebo.
- To compare the safety and tolerability of ONO-5334 or alendronate versus placebo.
- To compare compliance with treatment with ONO-5334 or alendronate versus placebo.
- To compare the efficacy and safety of ONO-5334 versus alendronate.
- To investigate the efficacy and safety of three different doses of ONO-5334 (50mg twice daily [BID], 100mg daily [QD], 300mg QD).

EXPLORATORY OBJECTIVES OF THE INITAL 12-Month TREATMENT PHASE
In addition, the exploratory objectives of the initial 12-Month treatment phase were:

- To compare the effect of ONO-5334, alendronate or placebo on BMD, BMC and bone volume from baseline to 12 months, using Quantitative Computed Tomography (QCT) measurement of the lumbar spine and femur.
- To investigate the plasma concentrations of ONO-5334 and its metabolite ONO-KK1-420 at 1.5, 6 and 12 months.

Name of Sponsor/Company: Ono Pharmaceutical Co., Ltd.	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Finished Product: ONO-5334	**Volume:**	
Name of Active Ingredient:	**Page:**	

- To investigate the association between the changes in parameters using DXA or QCT and baseline level of biochemical markers of bone turnover.
- To investigate the association between the changes in parameters using DXA or QCT and change in level of biochemical markers of bone turnover.
- To undertake subgroup analyses using clinical and biological factors.

STUDY OBJECTIVES OF THE 12-Month EXTENDED TREATMENT PHASE

The primary objective of the 12-Month extension of the study was to evaluate the long-term safety of ONO-5334. The secondary objectives were to assess the long-term efficacy of ONO-5334 on DXA BMD and biochemical markers of bone turnover. The long-term efficacy of ONO-5334 on QCT BMD was to be investigated as an exploratory objective.

Methodology:

This study consisted of a 2- to 6-week screening period followed by a randomised, double blind placebo and active controlled treatment phase initially of 12 months, followed by an optional 12-Month extended treatment phase. The treatment as assigned in the initial 12-Month treatment phase was continued in the extended treatment phase for each subject. Subjects were randomised to receive ONO-5334 300 mg QD, ONO-5334 100 mg QD, ONO-5334 50 mg BID, alendronate 70 mg once weekly (QW) or placebo in a 1:1:1:1:1 ratio and were treated in parallel groups. ONO-5334, and placebo were given after breakfast (1 tablet) and in the evening (3 tablets), with the composition of the tablets depending on the dose assigned. Alendronate or matching placebo was given QW in the morning after arising. Subjects were treated on an outpatient basis returning to the clinic at 1.5, 3, 6, 9 and 12 months in the initial 12-Month treatment phase and 15, 18, 21 and 24 months in the 12-Month extended treatment phase. An 8-week follow-up period followed.

Subjects took daily doses of calcium (at least 500 mg) and vitamin D (at least 400 international units [IU]) throughout the study.

Rescue medication was not permitted. Subjects had the right to withdraw from the study at any time without giving reason. Any subject who experienced an unacceptable serious adverse event (SAE) could be withdrawn from the study by the Investigator, who was to institute the appropriate follow-up investigations in accordance with accepted standards of medical care including performance of tests at the time of withdrawal. Subjects who withdrew from the study were not replaced.

Number of subjects (planned and analysed):

It was planned that a minimum of 265 subjects would be randomised into the initial 12-Month treatment phase of the study to ensure completion of 212 (80%) subjects. 928 subjects were actually screened, of whom 285 subjects were randomised and 246 subjects completed the initial 12-Month treatment phase of the study.

It was anticipated that a maximum of 250 subjects who had completed the initial 12-Month phase would meet the inclusion/exclusion criteria and be entered for the 12-Month extended treatment phase. 197 subjects actually entered the 12-Month extended treatment phase, and 186 subjects completed this phase of the study.

Diagnosis and main criteria for inclusion in the initial 12-Month treatment phase:

To qualify for participation in the study, post menopausal women with osteopenia or osteoporosis had to be aged between 55 and 75 years inclusive ($55 \leq age \leq 75$), and able and willing to give written informed consent. Post menopausal was defined as more than 5 years after menopause and with oestradiol and follicle stimulating hormone (FSH) levels consistent with menopause (FSH > 30 IU/L, oestradiol < 92 pmol/L). Osteoporosis was defined as a value of DXA BMD 2.5 standard deviations (SDs) or more below the young adult mean (T-score $\leq$ -2.5) at the lumbar spine (L1 to L4) or total hip. Osteopenia was defined as a value of DXA BMD more than 1 SD below the young adult mean, but less than 2.5 SDs below this value (T-score < -1 and > -2.5) at the lumbar spine (L1 to L4) or total hip. Subjects were also required to have a bone turnover defined as a urinary C-terminal telopeptide of type I collagen (CTX-I) above 200 μg/mmolCr at Screening.

Name of Sponsor/Company: Ono Pharmaceutical Co., Ltd.	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Finished Product: ONO-5334	**Volume:**	
Name of Active Ingredient:	**Page:**	

Subjects who met any of the exclusion criteria were not permitted to participate in the study. Exclusion criteria included:

1. Subjects with a value of DXA BMD more than 3.5 standard deviations below the young adult mean, (T-score < -3.5) at the lumbar spine (L1 to L4) or total hip.
2. Osteoporosis subjects (T-score ≤ -2.5) who had any vertebral fragility fracture between T4 and L4 inclusive.
3. Osteopenia subjects (T-score <-1 and >-2.5) who had no vertebral fragility fractures between T4 and L4 inclusive,

   OR,

   Osteopenia subjects (T-score <-1 and >-2.5) who had two or more vertebral fragility fractures between T4 and L4 inclusive
4. Subjects who had experienced any non-vertebral fragility fractures after age of 50 years.
5. Subjects who had secondary causes of osteoporosis. e.g.,
   - A) Endocrine disorders: thyrotoxicosis, primary hyperparathyroidism, Cushing's syndrome
   - B) Rheumatologic conditions: rheumatoid arthritis, ankylosing spondylitis
   - C) Gastro-intestinal disorders: malabsorption partial gastrectomy
   - D) Malignancy: multiple myeloma, metatastic carcinoma
   - E) Drug treatment: systemic oral glucocorticoids, methotrexate, heparin, anti-convulsants
   - F) Genetic disorders: osteogenesis imperfecta
   - G) Nutritional deficiencies: osteomalacia or anorexia
   - H) Immobility
   - I) Other conditions: Diabetes (subjects with insulin dependent diabetes mellitus [IDDM], insulin treated or HbA1c ≥8.0%), hepatic impairment (defined by the exclusion criteria 8), alcohol intake (≥20 units per week)

Inclusion criteria for the 12-Month extended treatment phase:

Subjects were entered into the 12-Month extended treatment phase provided they had completed the initial 12-Month treatment phase of the study and were able and willing to give written informed consent for the extended treatment phase. Participation in the 12-month extended treatment phase was optional. Also, subjects for whom the Investigator had any safety concerns and judged it would not be in the best interest of the subject to continue with any of the study medications, or subjects whom, in the opinion of the Investigator, may not have been able to cooperate fully with the study requirements, were excluded from the 12-Month extended treatment phase.

Test product, dose and mode of administration, batch number:

ONO-5334 was administered orally as 50 mg or 100 mg tablets in doses of 50 mg BID, 100 mg QD or 300 mg QD, taken in the morning and/or evening according to treatment assignment. Morning and evening doses were taken at least 10 hours apart.

Duration of treatment:

Twenty-four months in total, comprising an initial 12-Month treatment phase, followed by an optional extended 12-Month treatment phase.

SUMMARY OF RESULTS

EFFICACY RESULTS:

Primary efficacy variable

The primary efficacy variable was the mean DXA BMD of the lumbar spine (L1-L4) at Month 12. The ONO-5334 and alendronate groups showed statistically significant greater least square mean increase from baseline

Name of Sponsor/Company: Ono Pharmaceutical Co., Ltd.	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use Only)
Name of Finished Product: ONO-5334	Volume:	
Name of Active Ingredient:	Page:	

in the mean DXA BMD of the lumbar spine (L1-L4) compared to placebo at Month 12 for the FAS (LOCF) population. A statistically significant number of lumbar spine (L1-L4) responders, when defined at a ≥ 3% improvement from baseline in DXA BMD at Month 12, were seen for all groups (ONO-5334 and alendronate) compared to placebo. This indicated an improvement in the subjects' condition in these groups, and was confirmed in the FAS (observed) and PPS populations, and was also supported by repeated measures analysis. The greatest improvement was seen in the alendronate and ONO-5334 300 mg QD groups followed by the ONO-5334 50 mg BID and then the ONO-5334 100 mg QD groups. The highest ONO-5334 dose group (300 mg QD) compared favourably with alendronate, currently one of the most commonly used bisphosphonate treatments for osteoporosis.

Neither pooled centre effect ($p = 0.877$), nor treatment by pooled centre interaction ($p = 0.662$) had a significant effect on the data, indicating the robustness of the results. Furthermore, the statistically significant LS mean increase from baseline in the mean DXA BMD of the lumbar spine (L1-L4) compared to placebo was maintained at Month 24 for the FAS (LOCF and observed) and PPS populations.

Secondary variables

In general, the secondary variable results followed similar trends to the primary variable, with alendronate and ONO-5334 300 mg QD giving the greatest improvement at the earliest visit followed by ONO-5334 50 mg BID and then ONO-5334 100 mg QD.

DXA BMD of the lumbar spine (L1-L4)

Significant improvement in DXA BMD of the lumbar spine (L1-L4) compared to placebo was seen at Month 3 for the alendronate, ONO-5334 300 mg QD and ONO-5334 50 mg BID dose groups. Over time, statistical significance improved in all treatment groups through to Month 24, with the ONO-5334 100 mg QD group achieving statistical significance by Month 12 (Month 3 in XPPS).

DXA BMD of the hip (total hip, femoral neck, trochanter, and intertrochanter)

A statistically significant improvement in DXA BMD of the hip compared to placebo was seen for the total hip, femoral neck and intertrochanter in the ONO-5334 50 mg BID, ONO-5334 300 mg QD and alendronate groups at Month 12. By Month 18, the ONO-5334 100 mg QD cohort had achieved statistical significance in the ONO-5334 50 mg, ONO-5334 300 mg and alendronate groups. By Month 24, significant improvement was seen in the intertrochanter in all treatment groups.

DXA BMC of the lumbar spine (L1-L4)

A statistically significant improvement in DXA BMC of the lumbar spine (L1-L4) compared to placebo was seen for the alendronate and ONO-5334 300 mg QD groups at Month 3. By Month 6 all treatment groups showed significant improvement, with the degree of statistical significance increasing over time to Month 24.

DXA BMC of the hip (total hip, femoral neck, trochanter, and intertrochanter)

For the hip, a statistically significant improvement in DXA BMC from baseline to Month 12 compared to placebo was seen for the total hip, femoral neck and intertrochanter for the ONO-5334 50 mg BID, ONO-5334 300 mg QD and alendronate groups. By Month 24 statistical significance was seen for the total hip, femoral neck, trochanter and intertrochanter in all treatment groups for LOCF data but not observed data.

DXA mean area of the lumbar spine

Significant increases in DXA mean area of the lumbar spine (L1-L4) compared to placebo were seen at Month 3 for the alendronate, ONO-5334 300 mg QD and ONO-5334 50 mg BID dose groups. Over time, statistical significance improved in all treatment groups through to Month 24, with the ONO-5334 100 mg QD group achieving statistical significance by Month 6.

DXA mean area of the hip

Name of Sponsor/Company: Ono Pharmaceutical Co., Ltd.	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Finished Product: ONO-5334	**Volume:**	
Name of Active Ingredient:	**Page:**	

In the early stages of the study (to Month 12), there were statistically significant decreases in DXA mean area of the hip compared to placebo, sporadically for the total hip, femoral neck and trochanter for all treatment groups. By Month 24, a statistically significant decrease was seen for the femoral neck only (in the ONO-5334 100 mg QD group).

Although there were isolated occurrences of statistically significant correlations between baseline bone turnover markers and DXA BMD of the lumbar spine and hip at Month 12, these results did not suggest any clinical correlation.

Bone Turnover Markers

- A decrease in the bone resorption markers, urine CTX-I and urine NTX-I was seen throughout the 24 months for all treatment groups, with the majority of the decrease occurring by Month 1.5.
- A decrease in serum CTX-I was seen from Month 1.5 through to Month 24 for the ONO-5334 300 mg QD and alendronate groups. Decreases were seen for the ONO-5334 100 mg QD groups up to and including Month 9 and for the ONO-5334 50 mg group up to and including Month 12.
- Up to Month 12, there were significant decreases in the following bone formation markers: serum PINP, B-ALP, and OC for the highest dose ONO-5334 and alendronate treatment groups. However, by Month 24, statistically significant decreases ($p \leq 0.001$) in B-ALP, PINP and OC were seen only in the alendronate group.
- FDPD increased significantly for the lower dose ONO-5334 groups to Month 24, and decreased in the alendronate group.
- By Month 3, TRAP5b decreased in all ONO-5334 treatment groups after which there was a progressive return towards baseline. The ONO-5334 100 mg QD dose group showed a statistically significant increase from baseline at Month 12, and the 50 mg BID dose showed a statistically significant increase from baseline at Month 24. TRAP5b concentration was suppressed throughout the 24 months of the study for the alendronate group.
- I-CTP increased significantly for the ONO-5334 groups for the 24 months of the study, with no change seen in the alendronate group.
- At Month 12, CTX-II decreased for the ONO-5334 and alendronate treatment groups.

QCT spine and femur parameters

Most QCT spine and femur parameters showed a statistically significant greater LS mean increase from baseline compared to placebo at both Month 12 and Month 24 for all active treatment groups (ONO-5334 and alendronate).

SAFETY RESULTS:

The safety profile was generally similar across treatment groups for both the initial and extension treatment periods of this study.

During the initial treatment period, TEAEs were experienced by 71.9%, 82.5%, 89.5%, 77.2% and 71.9% of subjects in the placebo, ONO-5334 50 mg BID, 100 mg QD, 300 mg QD and alendronate groups, respectively. Individual TEAEs affected less than 13% of subjects in each group and there was no single TEAE that occurred most frequently in all groups. For the placebo group, the most frequent TEAEs were nasopharyngitis, nausea and headache, each affecting five subjects (8.8%). For the ONO-5334 groups, the most frequent TEAEs were dyspepsia, affecting a maximum of six subjects (10.5%) in the 50 mg BID group, and hypertension, affecting a maximum of seven subjects (12.3%) in the 100 mg QD group. No dose relationship was evident. The most frequent TEAE for the alendronate group was abdominal pain upper, affecting six subjects (10.5%).

Name of Sponsor/Company: Ono Pharmaceutical Co., Ltd.	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Finished Product: ONO-5334	**Volume:**	
Name of Active Ingredient:	**Page:**	

During the 24-month treatment period, TEAEs were experienced by 87.7%, 91.2%, 94.7%, 91.2% and 86.0% of subjects in the placebo, ONO-5334 50 mg BID, 100 mg QD, 300 mg QD and alendronate groups, respectively. Individual TEAEs affected less than 23% of subjects in each group and there was no single TEAE that occurred most frequently in all groups. For the placebo group, the most frequent TEAEs were nasopharyngitis (nine subjects; 15.8%), back pain (13 subjects; 22.8%) and headache (seven subjects; 12.3%). For the ONO-5334 groups, the most frequent TEAEs were arthralgia, affecting a maximum of eight subjects (14.0%) in the 50 mg BID group, and hypertension, affecting a maximum of ten subjects (17.5%) in the 100 mg QD group. No dose relationship was evident. The most frequent TEAE for the alendronate group was nasopharyngitis, affecting nine subjects (15.8%).

For the 24-month treatment period, most drug-related TEAEs occurred in no more than two subjects in any group, with the exception of dyspepsia, abdominal discomfort and abdominal pain, which occurred in a maximum of six subjects (8.8%) in any group. Nausea, flatulence and dysgeusia occurred in three subjects from the placebo group. No dose relationship was evident for the ONO-5334 groups. Severe TEAEs were experienced by 14 subjects.

Serious adverse events occurred in no more than 11 subjects (19.3%) in any group, with the most frequent incidence in the ONO-5334 50 mg BID group. Apart from tubulointerstitial nephritis and hypertension (two subjects each), no SAE occurred in more than one subject. No dose relationship was evident.

The most frequent TEAE that led to study discontinuation was dyspepsia; this occurred in a maximum of two subjects (3.5%) in the ONO-5334 50 mg BID group and one subject in the ONO-5334 300 mg QD and alendronate groups.

There was no notable difference across the groups in terms of fractures experienced during the study; one subject in the placebo group experienced a new vertebral fracture, and there was no worsening of existing fractures.

There was one death during the study, due to multiple myeloma, (subject 51095). This event was not considered to be related to the study medication. Laboratory data, physical examination, vital signs and ECG data were generally unremarkable with no major differences across the group.

CONCLUSIONS:

In conclusion, ONO-5334 appeared to be safe and well-tolerated during both the 12-Month and extension phases of this study, with a statistically significant positive effect on bone density of the lumbar spine (L1-L4) and hip compared to placebo.

Date of the report: 9 September 2011