Information Meeting on Bonviva® Tablet

CHUGAI PHARMACEUTICAL CO., LTD.
TAISHO TOYAMA PHARMACEUTICAL CO., LTD.

April 5, 2016
Forward-Looking Statements

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. and Taisho Pharmaceutical Holdings Co., Ltd. (the “Companies”). These statements reflect the Companies’ current analysis of existing information and trends. Actual results may differ from expectations based on risks and uncertainties that may affect the Companies’ businesses.

Although this presentation includes information regarding pharmaceuticals (including products under development), the information is not intended as any advertisement and/or medical advice.
Once monthly, alternative treatment option for your life

Chugai Pharmaceutical Co., Ltd.
Bonviva Product Manager, Takeshi Sakaguchi

THERAPEUTIC AGENT FOR OSTEOPOROSIS
Powerful drug and Prescription drug†
BONVIVA® Tablet 100 mg
Ibandronate Sodium Hydrate Tablet
†Caution: Use only as prescribed by physician, etc.

BONVIVA is a trademark of F. HOFFMANN-LA ROCHE AG (SWITZERLAND)
[NAME]  
Generic name: Ibandronate Sodium Hydrate  
Brand name: BONVIVA Tablet 100 mg

[INDICATIONS]  
Osteoporosis

[DOSAGE AND ADMINISTRATION ]  
The usual adult dosage is 100 mg as ibandronic acid once a month, taken by mouth with plenty of plain water (approximately 180 mL) when the patient gets out of bed.  
For at least 60 minutes after taking BONVIVA, patients should not lie down and should avoid food or drink (except water) and other oral drugs.
Profiles of BONVIVA® Tablet 100 mg

- Once monthly oral bisphosphonate drug
- Two different monthly forms, BONVIVA tablet and BONVIVA IV injection, provide suitable treatment opportunities according to osteoporotic patients’ lifestyle.
- BONVIVA tablet proved non-inferiority to BONVIVA IV injection in lumbar spine BMD gains in Japanese patients with osteoporosis.
- BONVIVA tablet demonstrated BMD gains at femur sites (proximal femur, femoral neck).
- BONVIVA tablet suppressed bone turnover markers from early phase (one month after treatment).
- In total, 141 adverse reactions occurred in 86 out of 311 patients (27.7%) evaluated for safety assessment in Japanese clinical trials. The most common adverse events included diarrhea (14 reports, 4.5%), back pain (13 reports, 4.2%), headache (9 reports, 2.9%), arthralgia (9 reports, 2.9%) and malaise (9 reports, 2.9%) [at approval].
Phase III (MOVEST Study)  
Study design, materials and methods

**Objective**  
To examine the efficacy and safety of monthly oral ibandronate 100mg versus monthly intravenous ibandronate 1mg

**Patients**  
Japanese patients aged ≥ 55 years with primary osteoporosis  
- BMD of lumber spine (L2-L4) < 70% YAM; BMD of lumber spine (L2-L4) < 80% YAM with fragile bone fracture; BMD of total hip < 70% YAM

**Study design**  
Prospective, multicenter, randomized, double-blind, double-dummy comparative study

**Primary endpoint**  
The percentage change from baseline in lumbar spine (L2–L4) BMD at 12 months

**Secondary endpoints**  
The percentage change from baseline in total hip, femoral neck, and trochanter BMD; change from baseline in bone turnover markers; incidences of non-traumatic new vertebral or non-vertebral fractures.

※All patients received supplementary calcium 610mg and vitamin D₃ 400IU/day.

The study was supported by Chugai Pharmaceutical Co. Ltd. and Taisho Pharmaceutical Co. Ltd.
For missing values, LOCF (Last Observation Carried Forward) approach was used.


The study was supported by Chugai Pharmaceutical Co. Ltd. and Taisho Pharmaceutical Co. Ltd.
CONTRAINDICATIONS

[CONTRAINDICATIONS (BONVIVA is contraindicated in the following patients.)]

1. Patients with abnormalities that delay oesophageal transit such as oesophageal stricture or achalasia [Delayed oesophageal transit of BONVIVA increases the risk of local oesophageal adverse reactions.]
2. Patients who are unable to stand or sit upright for at least 60 minutes after taking BONVIVA
3. Patients with a history of hypersensitivity to the ingredients of BONVIVA or other bisphosphonates
4. Patients with hypocalcaemia [Serum calcium levels may decrease and symptoms of hypocalcaemia may worsen (see Important Precautions and Adverse Reactions: Clinically Significant Adverse Reactions (Similar Drugs))]
5. Women who are pregnant or may be pregnant (see Use During Pregnancy, Delivery or Lactation)
INDICATIONS

Osteoporosis

Precautions Related to INDICATIONS

BONVIVA should only be administered to patients with an established diagnosis of osteoporosis with reference to the guidelines of the Japanese Society for Bone and Mineral Research.
The usual adult dosage is 100 mg as ibandronic acid once a month, taken by mouth with plenty of plain water (approximately 180 mL) when the patient gets out of bed. For at least 60 minutes after taking BONVIVA, patients should not lie down and should avoid food or drink (except water) and other oral drugs.

**Precautions Related to DOSAGE AND ADMINISTRATION**

Patients should be given the following instructions before taking BONVIVA.

1. BONVIVA should be taken with water. Taking BONVIVA with drinks other than water (including mineral water containing particularly high levels of calcium, magnesium, etc.), food or other medication may interfere with absorption. Therefore, BONVIVA should be taken after getting out of bed, before the first food or drink of the day, and food or drink other than water should be avoided for at least 60 minutes after taking BONVIVA.

2. To reduce the possibility of oesophageal or local adverse reactions, it is important that BONVIVA reaches the stomach quickly. When taking BONVIVA, patients should take the following precautions.
   1) Patients should not chew or suck BONVIVA because of a potential for oropharyngeal ulceration.
   2) Patients should take BONVIVA in an upright position with plenty of water (approximately 180 mL) and should not lie down for 60 minutes after taking BONVIVA.
   3) Patients should not take BONVIVA at bedtime or before getting out of bed.

3. BONVIVA should be taken once a month. If patients forget to take a dose, one BONVIVA tablet should be taken the following day after it is remembered, and then once a month from that point onward.
PRECAUTIONS

Careful Administration (BONVIVA should be administered with care in the following patients.)

(1) Patients with upper gastrointestinal disorders such as dysphagia, oesophagitis, gastritis, duodenitis or ulcers [Possible irritant effects on the upper gastrointestinal mucosa may lead to worsening of the underlying disease.]

(2) Patients with severe renal disorders [Excretion may be delayed. No clinical data are available, and safety has not been established. (See PHARMACOKINETICS in the Package Insert)]
In total, 141 adverse reactions (ARs) occurred in 86 out of 311 patients (27.7%) evaluated for safety in Japanese clinical trials. The most frequent ARs included diarrhea (14 reports, 4.5%), back pain (13 reports, 4.2%), headache (9 reports, 2.9%), arthralgia (9 reports, 2.9%) and malaise (9 reports, 2.9%) [at approval].

The clinically significant ARs may occur, such as upper gastrointestinal disorders, anaphylactic shock/reaction, osteonecrosis/osteomyelitis of the jaw, and atypical fractures of the subtrochanteric and proximal diaphyseal femur.

Hypocalcemia was also reported as the clinically significant ARs in similar drugs.

* Because similar ARs occurred in a single patient were counted as one AR, the above-mentioned number of ARs are different from that in Summary of ARs.

### Summary of ARs

<table>
<thead>
<tr>
<th>Safety population</th>
<th>311 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patient with ARs</td>
<td>86 patients</td>
</tr>
<tr>
<td>No. of ARs</td>
<td>142</td>
</tr>
<tr>
<td>Incidence of ARs in Safety population</td>
<td>27.7%</td>
</tr>
</tbody>
</table>
PACKAGES

Record the date of taking BONVIVA tablet
Put the seal on your calendar
Roll-type Package

In addition to the description emphasizing that BONVIVA tablet is taken “once a month”, icons and explanations; “how to take the tablet” is placed on the package.

Easy-to-open, easy-to-fold, and convenient to bring it with you!

Easy-to-understand how to take the tablet
Once monthly, alternative treatment option for your life
Bonviva Tablet: Clinical Utility and Our Expectation

Univ. of Tottori
Hiroshi Hagino
Today’s topics

✓ Current status and issues of osteoporosis mediation in Japan

✓ New option for osteoporosis treatment

✓ Aiming to maintain a healthy life
Today’s topics

✓ Current status and issues of osteoporosis mediation in Japan

✓ New option for osteoporosis treatment

✓ Aiming to maintain a healthy life
Trends in hip fracture (worldwide)

% Annual Change

Europe
- Sweden '92-'95
- Finland '92-'04
- UK '92-'98
- Netherlands '93-'02
- UK '70-'97
- USA (Rochester) '72-'92
- USA (Rochester) '80-'06
- USA '86-'95
- Canada '92-'01
- Canada '76-'85
- New Zealand '89-'98
- Hong Kong '85-'01
- Japan '86-'01
- Japan '02-'06

North America
- USA (Rochester) '28-'72
- USA (Framingham) '48-'96
- USA '86-'95
- Canada '85-'05
- Hong Kong '66-'85

Oceania

Asia
Trends in estimated number of new hip fracture patients per year

Increasing No. of patients in each time point regardless of sex


Estimated number of new hip fracture patients per year

Male | Female
---|---
1987 | 53,200
1992 | 53,200
1997 | 53,200
2002 | 53,200
2007 | 175,700
2012 | 175,700

(people)
160,000
140,000
120,000
100,000
80,000
60,000
40,000
20,000
0
Proportions of major causes for being in need of care

- CVD: 21.7%
- Dementia: 21.4%
- Debilitation due to aging: 12.6%
- Fracture/fall: 10.9%
- Joint disease: 6.8%
- Others: 26.7%

Estimated number of annual new patients with hip fracture in Japan

Data are calculated by adjusting to the population structure (≥35 years old, 2012 Japan) based on the age- and gender-specific incidence of hip fracture in Tottori Prefecture (2004-2006).
POSHIP study  Prevention of Second Hip Fracture
～Number of 1st Hip Fracture～

2,663 pts

- 63 dead
- 276 excluded

2,324 pts

Average age 83.6 years (range 65-104)
Femoral neck fracture 1,019,
Trochanteric fracture 1,300 (unknown 5)

Risk of hip fracture after 1st hip fracture

/1000 person・yr

- after 1st hip fracture
- general population*

65-74 75-84 85-94 95-

Age group (in years)

18.6 3.4 1.5 1.9

* Data of Tottori prefecture from 2004 to 2006
(Hagino H, et al, Osteoporos Int 2009)

n = 2,324

## Associations between prior and subsequent fractures

<table>
<thead>
<tr>
<th>Location of prior fracture</th>
<th>Location of subsequent fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>wrist</td>
</tr>
<tr>
<td><strong>wrist</strong></td>
<td>3.3</td>
</tr>
<tr>
<td><strong>vertebra</strong></td>
<td>1.4</td>
</tr>
<tr>
<td><strong>hip</strong></td>
<td>-</td>
</tr>
</tbody>
</table>
Case finding & Fracture risk risk pyramid

Fracture Liaison Services secondary prevention

1.7 million women
50% of hip fractures from 16% of the population

Patients with new fragility fracture

Patients with prior fragility fracture

8.9 million women
50% of hip fractures from 84% of the population

Patients with high fracture risk

Patients with intermediate fracture risk

Patients with low fracture risk

Osteoporosis Treatment after Fragility Fractures

-POSHPH –

n=2,328 (1st hip fracture)

Today’s topics

✓ Current status and issues of osteoporosis mediation in Japan

✓ New option for osteoporosis treatment

✓ Aiming to maintain a healthy life
The history of developing bisphosphonate for treatment of osteoporosis represents the history of “extended dosing interval of oral formulation” & “development of injectable formulation.”

- **Launch of bisphosphonate products for treatment of osteoporosis**


<table>
<thead>
<tr>
<th>Oral</th>
<th>daily</th>
<th>alendronate daily oral tablet</th>
<th>risedronate daily oral tablet</th>
<th>minodronate daily oral tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>weekly</td>
<td></td>
<td>alendronate weekly oral tablet</td>
<td>risedronate weekly oral tablet</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>alendronate weekly oral jelly</td>
</tr>
<tr>
<td>every 4 weeks or monthly</td>
<td></td>
<td>minodronate every 4 weeks oral tablet</td>
<td></td>
<td>risedronate monthly oral tablet</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ibandronate monthly oral tablet</td>
</tr>
<tr>
<td>i.v.</td>
<td></td>
<td>alendronate monthly i.v. infusion</td>
<td></td>
<td>ibandronate monthly i.v. injection</td>
</tr>
</tbody>
</table>
MOVER study (i.v. Phase 2/3 study)

Incidence of new or worsening vertebral fractures

- Risedronate oral 2.5mg / day (n=375)
- Ibandronate i.v. 1mg / month (n=381)

Relative change from baseline in lumbar spine (L2–L4) BMD

- (PPS)
  - Mean, 95%CI
  - * : p=0.005  ** : p=0.001
  - vs Risedronate oral 2.5mg / day
  - t-test

P3 with oral ibandronate
MOVEST study
Monthly Oral Versus intravenous ibandronate

Clinical efficacy and safety of monthly oral ibandronate 100mg versus monthly intravenous ibandronate 1mg in Japanese patients with primary osteoporosis


Osteoporos Int (2015) 26: 2685-2693
**Study design, Materials and methods**

**Objective**
To examine the efficacy and safety of monthly oral ibandronate 100mg versus monthly intravenous ibandronate 1mg in Japanese patients with primary osteoporosis.

**Patients**
Patients with Primary Osteoporosis

**Study design**
Prospective, Multicenter, Randomized, Double-blind, Double-dummy Comparative study (non-inferiority trial)

**Primary endpoint**
The percentage change from baseline in lumbar spine (L2–L4) BMD at 12 months

**Secondary endpoints**
The percentage change from baseline in femoral neck BMD at 12 months; change from baseline in BTMs; incidences of non-traumatic new fractures

※All patients received supplementary calcium 610mg and vitamin D₃ 400IU/day.

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**Phase III (MOVEST Study)**

**Patients with Primary Osteoporosis (n=422)**

1 years

- **Ibandronate oral**
  - Ibandronate oral 100mg / month + Ibandronate i.v. placebo / month

- **Ibandronate i.v.**
  - Ibandronate i.v. 1mg / month + Ibandronate oral placebo / month


The study was supported by Chugai Pharmaceutical Co. Ltd. and Taisho Pharmaceutical Co. Ltd.
Phase III (MOVEST Study)

Patient flow through the study

Enrolled (n=422)

Not treated (n=14)

Ibandronate oral (n=205)
- Completed (n=177)
  - Patient's choice (n=14)
  - Adverse event (n=4)
  - Did not meet eligibility criteria (n=2)
  - Personal reason (n=2)
  - Other reason (n=6)
- Withdrawn (n=28)
  - Patient's choice (n=14)
  - Adverse event (n=4)
  - Did not meet eligibility criteria (n=2)
  - Personal reason (n=2)
  - Other reason (n=6)

Ibandronate i.v. (n=203)
- Completed (n=184)
  - Patient's choice (n=9)
  - Adverse event (n=4)
  - Did not meet eligibility criteria (n=1)
  - Personal reason (n=1)
  - Other reason (n=4)
- Withdrawn (n=19)
  - Patient's choice (n=9)
  - Adverse event (n=4)
  - Did not meet eligibility criteria (n=1)
  - Personal reason (n=1)
  - Other reason (n=4)


The study was supported by Chugai Pharmaceutical Co. Ltd. and Taisho Pharmaceutical Co. Ltd.
### Baseline patient characteristics (PPS)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ibandronate oral (n=183)</th>
<th>Ibandronate i.v. (n=189)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, n (%)</td>
<td>177 (96.7%)</td>
<td>186 (98.4%)</td>
</tr>
<tr>
<td>Age, years (mean±SD)</td>
<td>68.8 ± 6.9</td>
<td>69.3 ± 6.0</td>
</tr>
<tr>
<td>Weight, kg (mean±SD)</td>
<td>49.5 ± 7.2</td>
<td>49.2 ± 6.7</td>
</tr>
<tr>
<td>Height, cm (mean±SD)</td>
<td>152.2 ± 6.5</td>
<td>151.6 ± 6.1</td>
</tr>
<tr>
<td>BMD T-score (mean±SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar spine (L2–L4)</td>
<td>−3.09 ± 0.58</td>
<td>−3.14 ± 0.60</td>
</tr>
<tr>
<td>Total hip</td>
<td>−2.41 ± 0.84</td>
<td>−2.47 ± 0.79</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>−2.98 ± 0.82</td>
<td>−2.99 ± 0.78</td>
</tr>
<tr>
<td>Prevalent vertebral fractures, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>124 (67.8%)</td>
<td>130 (68.8%)</td>
</tr>
<tr>
<td>1</td>
<td>34 (18.6%)</td>
<td>34 (18.0%)</td>
</tr>
<tr>
<td>≥2</td>
<td>25 (13.7%)</td>
<td>25 (13.2%)</td>
</tr>
<tr>
<td>Bone turnover markers (mean±SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>uCTX, μg/mmol CR</td>
<td>247.9 ± 138.8</td>
<td>249.4 ± 166.4</td>
</tr>
<tr>
<td>TRAP 5b, mU/dL</td>
<td>387.4 ± 131.6</td>
<td>389.2 ± 152.8</td>
</tr>
<tr>
<td>P1NP, μg/L</td>
<td>50.6 ± 21.4</td>
<td>49.0 ± 22.3</td>
</tr>
<tr>
<td>BALP, μg/L</td>
<td>17.1 ± 6.8</td>
<td>16.5 ± 6.9</td>
</tr>
<tr>
<td>25-OH(D), ng/mL</td>
<td>25.3 ± 6.3</td>
<td>25.3 ± 5.8</td>
</tr>
</tbody>
</table>

※n=181

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The study was supported by Chugai Pharmaceutical Co. Ltd. and Taisho Pharmaceutical Co. Ltd.
Phase III (MOVEST Study)

Relative change from baseline in lumbar spine (L2–L4) BMD (Primary endpoint)

For missing values, LOCF (Last Observation Carried Forward) approach was used.


The study was supported by Chugai Pharmaceutical Co. Ltd. and Taisho Pharmaceutical Co. Ltd.
### Relative change from baseline in hip BMD

#### Phase III (MOVEST Study)

**Relative change from baseline (%)**

<table>
<thead>
<tr>
<th>Time (month)</th>
<th>Ibandronate oral ( (n=183) )</th>
<th>Ibandronate i.v. ( (n=189) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.86</td>
<td>1.54</td>
</tr>
<tr>
<td>4</td>
<td>2.19</td>
<td>1.87</td>
</tr>
<tr>
<td>6</td>
<td>2.76</td>
<td>2.41</td>
</tr>
<tr>
<td>12</td>
<td>(PPS) Mean, 95%CI</td>
<td>(PPS) Mean, 95%CI</td>
</tr>
</tbody>
</table>

**Femoral neck**

<table>
<thead>
<tr>
<th>Time (month)</th>
<th>Ibandronate oral ( (n=183) )</th>
<th>Ibandronate i.v. ( (n=189) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.00</td>
<td>1.95</td>
</tr>
<tr>
<td>4</td>
<td>2.17</td>
<td>1.88</td>
</tr>
<tr>
<td>6</td>
<td>2.64</td>
<td>2.58</td>
</tr>
<tr>
<td>12</td>
<td>(PPS) Mean, 95%CI</td>
<td>(PPS) Mean, 95%CI</td>
</tr>
</tbody>
</table>

For missing values, LOCF (Last Observation Carried Forward) approach was used.


The study was supported by Chugai Pharmaceutical Co. Ltd. and Taisho Pharmaceutical Co. Ltd.
Phase III (MOVEST Study)

Relative change from baseline in bone turnover markers

Secondary endpoint

For missing values, LOCF (Last Observation Carried Forward) approach was used.

The study was supported by Chugai Pharmaceutical Co. Ltd. and Taisho Pharmaceutical Co. Ltd.
# Incidences of osteoporotic fractures

## Secondary endpoint (PPS)

<table>
<thead>
<tr>
<th>Sites of Fracture</th>
<th>Ibandronate Oral (n=183)</th>
<th>Ibandronate i.v. (n=189)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vertebral Fracture</strong></td>
<td>2 (1.1%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td><strong>Non-Vertebral Fractures</strong></td>
<td>2 (1.1%)</td>
<td>5 (2.6%)</td>
</tr>
<tr>
<td><strong>Radius Fracture</strong></td>
<td></td>
<td>Radius fracture (n=3)</td>
</tr>
<tr>
<td><strong>Wrist Joint Fracture</strong></td>
<td></td>
<td>Hand fracture</td>
</tr>
</tbody>
</table>

Evaluation data at approval and Nakamura T, et al, Osteoporos Int 2015; 26: 2685-2693. The study was supported by Chugai Pharmaceutical Co. Ltd. and Taisho Pharmaceutical Co. Ltd.
Responder rates (with 95 % CI) after 12 months of treatment

Phase III (MOVEST Study)

Patients with >0 % increase in BMD

- Ibandronate oral (n=183)
- Ibandronate i.v. (n=189)

<table>
<thead>
<tr>
<th>Region</th>
<th>Ibandronate oral</th>
<th>Ibandronate i.v.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine (L2-L4)</td>
<td>91.8</td>
<td>92.1</td>
</tr>
<tr>
<td>Total hip</td>
<td>91.5</td>
<td>86.2</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>71.3</td>
<td>74.1</td>
</tr>
</tbody>
</table>

Patients with ≥3 % increase in BMD

- Ibandronate oral (n=183)
- Ibandronate i.v. (n=189)

<table>
<thead>
<tr>
<th>Region</th>
<th>Ibandronate oral</th>
<th>Ibandronate i.v.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine (L2-L4)</td>
<td>71.6</td>
<td>75.7</td>
</tr>
<tr>
<td>Total hip</td>
<td>71.6</td>
<td>75.7</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>39.2</td>
<td>43.4</td>
</tr>
</tbody>
</table>

The study was supported by Chugai Pharmaceutical Co. Ltd. and Taisho Pharmaceutical Co. Ltd.
### Summary of adverse events

**Phase III (MOVEST Study)**

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Ibandronate oral (n=205)</th>
<th>Ibandronate i.v. (n=203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>175 (85.4)</td>
<td>177 (87.2)</td>
</tr>
<tr>
<td>Drug-related AE</td>
<td>47 (22.9)</td>
<td>38 (18.7)</td>
</tr>
<tr>
<td>Severe intensity AE</td>
<td>2 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Serious AE</td>
<td>9 (4.4)</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td>AEs leading to death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AEs leading to treatment withdrawal</td>
<td>4 (2.0)</td>
<td>4 (2.0)</td>
</tr>
</tbody>
</table>

The study was supported by Chugai Pharmaceutical Co. Ltd. and Taisho Pharmaceutical Co. Ltd.
Oral bisphosphononats are absorbed from upper gastrointestinal tract

- Pharmacokinetics after oral administration of bisphosphononates

- Administration
  - GI
  - bioavailability (0.95%)

- Excretion (約99%)
  - Liver
  - Bloodstream
  - Kidney
  - Bone (distributed)
  - Urine (0.46%)

S. Wada, A. Suzuki: Bisphophonate wo tsukaikonasu Jissen Katsuyou Guidebook, 2011, p.9, Bunkoudou
### AUC\textsubscript{inf} for ibandronate in serum after oral and intravenous administration of ibandronate

<table>
<thead>
<tr>
<th>Population</th>
<th>Dose/route</th>
<th>Body weight (kg)</th>
<th>Creatinine clearance (mL/min)</th>
<th>AUC\textsubscript{inf} (ng h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal healthy women + postmenopausal women with osteoporosis (Domestic Study)</td>
<td>100mg/oral</td>
<td>53 ± 7 (n=14)</td>
<td>94 ± 20 (n=14)</td>
<td>219 ± 114 (n=14)</td>
</tr>
<tr>
<td>Postmenopausal women with osteopenia (Domestic Study)</td>
<td>1.0 mg/i.v.</td>
<td>57 ± 7 (n=10)</td>
<td>110 ± 29 (n=10)</td>
<td>240 ± 22.7 (n=10)</td>
</tr>
</tbody>
</table>

Values are mean ± SD

AUC\textsubscript{inf}: the area under the serum ibandronate concentration–time curve
### AUC\text{last} for ibandronate in serum fasting interval of 30 min vs. 60 min

<table>
<thead>
<tr>
<th>Study</th>
<th>Dosage</th>
<th>AUC\text{last} (ng\cdot h/mL)</th>
<th>fasting interval of 30 min</th>
<th>fasting interval of 60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study I</td>
<td>2.5mg ibandronate</td>
<td>1.12±0.950 (84.8%)</td>
<td>1.40±0.774 (55.3%)</td>
<td></td>
</tr>
<tr>
<td>(n=24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study II</td>
<td>50mg ibandronate</td>
<td>11.1±23.5 (212%)</td>
<td>16.0±15.6 (97.5%)</td>
<td></td>
</tr>
<tr>
<td>(n=24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD (coefficient of variation)

AUC\text{inf}: the area under the serum ibandronate concentration–time curve

AUC: fasting interval of 60 min after oral administration >30 min after oral administration

The mean percentage change in the lumbar spine (L1-L4) and hip BMD from baseline of 48-week oral ibandronate treatment in postmenopausal osteoporosis

Change in BMD:
fasting interval of 60 min > fasting interval of 60 min

Survey and analysis on fasting interval elongation in oral bisphosphonate therapies among patients with osteoporosis

Objective
To demonstrate what impacts on patient preference and what factor is related to the impact by elongating fasting interval from 30 min to 60 min in oral bisphosphonate (BP) therapies.

Patients
148 orthopedic outpatients with osteoporosis visiting any of 4 institutions from March to November 2015 who received BP therapies (11 males and 137 females).

Method
We studied whether patients might get bothered by change in fasting interval of the currently taken BP agents from 30 min to 60 min by using a questionnaire.

Answers (bothered/not bothered) were defined as an objective variable in the multivariate analysis with gender, age, duration of BP therapies, BP dosing interval (daily, weekly, or monthly) and BP agent type as explanatory variables in order to explain what factor has an influence when choosing either “bothered” or “not bothered”.

Assessments on bisphosphonate therapies

”Do you get bothered?”

Duration of BP therapies

<table>
<thead>
<tr>
<th>Duration</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 year</td>
<td>n=2</td>
<td>n=34</td>
</tr>
<tr>
<td>&gt;1 to ≤3 years</td>
<td>n=22</td>
<td>n=49</td>
</tr>
<tr>
<td>&gt;3 years</td>
<td>n=11</td>
<td>n=30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BP dosing interval</th>
<th>Daily</th>
<th>Weekly</th>
<th>Monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>n=6</td>
<td>n=22</td>
<td>n=9</td>
</tr>
<tr>
<td>No</td>
<td>n=2</td>
<td>n=51</td>
<td>n=58</td>
</tr>
</tbody>
</table>

Wake-up Time And Breakfast Time Among Elderly People  
(The Survey on Time Use and Leisure Activities of Japan in 2011)

<table>
<thead>
<tr>
<th>Mean wake-up time*1</th>
<th>Male</th>
<th></th>
<th></th>
<th>Female</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weekdays</td>
<td>Saturday</td>
<td>Sunday</td>
<td>Weekdays</td>
<td>Saturday</td>
<td>Sunday</td>
</tr>
<tr>
<td>All</td>
<td>6:46</td>
<td>7:19</td>
<td>7:28</td>
<td>6:28</td>
<td>6:59</td>
<td>7:07</td>
</tr>
<tr>
<td>60-64 years</td>
<td>6:19</td>
<td>6:35</td>
<td>6:36</td>
<td>6:11</td>
<td>6:26</td>
<td>6:36</td>
</tr>
<tr>
<td>70-74 years</td>
<td>6:13</td>
<td>6:26</td>
<td>6:33</td>
<td>6:13</td>
<td>6:19</td>
<td>6:21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean breakfast time*2</th>
<th>Male</th>
<th></th>
<th></th>
<th>Female</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weekdays</td>
<td>Saturday</td>
<td>Sunday</td>
<td>Weekdays</td>
<td>Saturday</td>
<td>Sunday</td>
</tr>
<tr>
<td>All</td>
<td>7:05</td>
<td>7:31</td>
<td>7:38</td>
<td>7:15</td>
<td>7:35</td>
<td>7:43</td>
</tr>
<tr>
<td>60-64 years</td>
<td>7:00</td>
<td>7:16</td>
<td>7:18</td>
<td>7:11</td>
<td>7:22</td>
<td>7:29</td>
</tr>
<tr>
<td>65-69 years</td>
<td>7:08</td>
<td>7:14</td>
<td>7:23</td>
<td>7:13</td>
<td>7:21</td>
<td>7:23</td>
</tr>
<tr>
<td>70-74 years</td>
<td>7:10</td>
<td>7:17</td>
<td>7:20</td>
<td>7:17</td>
<td>7:19</td>
<td>7:19</td>
</tr>
<tr>
<td>≥75 years</td>
<td>7:19</td>
<td>7:23</td>
<td>7:23</td>
<td>7:25</td>
<td>7:27</td>
<td>7:29</td>
</tr>
</tbody>
</table>

*1: Finish time of the first sleep period starting from before 12:00 am lasting for >60 min  
*2: The first meal time after 4:00 am before 11:00 am

● What is the Survey on Time Use and Leisure Activities of Japan?  
The purpose of the Survey on Time Use and Leisure Activities of Japan is to take a survey about the use of living hours and major activities in their free time among Japanese people for providing basic data for various kinds of administrative programs, conducted every 5 year since the first survey in fiscal 1976. In the Survey conducted in 2011, about 0.2 million members age 10 or older in about 83,000 families were randomly selected across the nation as of October 20 2011. After providing the initial result about time use, the detailed data on time use according to various activities were released in December 2012.
Today’s topics

✓ Current status and issues of osteoporosis mediation in Japan

✓ New option for osteoporosis treatment

✓ Aiming to maintain a healthy life
Three steps
- identification
- fracture risk assessment
- appropriate intervention

Identification of fracture (emergency, orthopedics)

New radiology report of fracture

Previous fragility fracture
- Referred by primary care physicians

High risk except previous fracture
- Referred by primary care physicians

Liaison
(Osteoporosis manager)

Liaison Service
(secondary prevention)
Not only “secondary prevention” but also “primary prevention” in Japan

FLS frequently used in UK and other countries is “Fracture Liaison Service” mainly for secondary prevention for fracture.

OLS in Japan is “Osteoporosis Liaison Service” including primary prevention for fracture.

IOF (International Osteoporosis Foundation) recommends secondary prevention.

Japan targets also primary prevention.

Liaison service reduces secondary fracture

Cumulative refracture incidence by age and group

MTF: minimal trauma fracture (intervention program)

骨の健康手帳
再骨折予防のための転ばぬ先の杖

骨折をしたあなたへ
骨がもろくなると骨折を繰り返す心配があります。
骨を丈夫にして再骨折を予防していくことが大切です。
元気で健やかな生活が送れるよう、お手伝いさせていただきます。

患者様名：
連絡先：
この手帳を受け取った日：年月日

骨相ぼう症は
骨折の原因となります

骨相ぼう症はどんな病気
骨の強度にかかわる2つの要素
骨折前にこんな症状はありませんでしたか？
骨相ぼう症になると
こんな部位が骨折しやすくなります

再骨折予防のポイント
骨を丈夫にする食事
骨を丈夫にするおすすめレシピ
転びにくい体づくりのための運動
転ばないための環境づくり
骨相ぼう症の治療法

最初の骨折を最後の骨折に！
JOS activities for OLS

To promote OLS (Osteoporosis Liaison Service), JOS (Japan Osteoporosis Society) implements:

- accreditation system for osteoporosis manager
- educational program (osteoporosis manager lecture course)

Osteoporosis Manager Accreditation System

**Eligible person**
Persons who belong to hospital/clinic/care service facility/pharmacy/clinical laboratory/local government/health center/educational institution, etc. and engage in medical/health/educational activities (health nurses, nurses, clinical radiologists, clinical laboratory technicians, PTs, OTs, clinical engineers, STs, pharmacists, registered dietitians, social workers, care workers)

**Validity**
5 years (from April 1st in the year accredited to March 31st after 5 years)

**Announcement**
Name and work site of OLS managers are published in the journal and homepage of JOS in principle.

Created based on data from the JOS website http://www.josteo.com/ja/liaison/index.html
Liaison conference / Regional alliance conference

osteoporosis manager
orthopedic chief nurse
clerk
research collaborator
orthopedist

In-house liaison conference

Regional alliance pathways conference
Community osteoporosis managers cooperate with hospital/clinic osteoporosis managers for treatment by sharing patient information.
OLS Provider

Physicians (certified osteoporosis specialists)

cooperation

Medical staff (osteoporosis manager)
health nurses, maternity nurses, nurses, clinical radiologists, clinical laboratory technicians, PTs, OTs, clinical engineers, STs, pharmacists, registered dietitians, social workers, care workers etc.

Prevention/improvement of osteoporosis and prevention of fracture

9th Osteoporosis manager lecture course
October 8th 2016, Sendai

3rd Osteoporosis manager accreditation exam
October 30th 2016, Tokyo

Qualifications of candidacy:
health nurse, nurse, clinical radiologist, clinical laboratory technicians, PTs, OTs, clinical engineers, STs, pharmacists, registered dietitians, social workers, care workers and other national qualified medical staff

680 candidates passed the 1st exam on April 1st 2015:
nurse 48%, pharmacist 19%, PT 19%, clinical radiologist 5%, registered dietitians 4%

For more details refer to the JOS homepage
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