Information Meeting on Bonviva®

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

August 30, 2013

Although this presentation includes information regarding pharmaceuticals (including products under development), the information is not intended as any advertisement and/or medical advice.
Forward-Looking Statements

This presentation may include forward-looking statements pertaining to the business and prospects. These statements reflect the current analysis of existing information and trends. Actual results may differ from expectations based on risks and uncertainties.
Once-a-month Encouragement to Bone
New Option, One-shot Intravenous Injection

Yoshiomi Morishita
Bonviva Product Manager
Chugai Pharmaceutical Co., Ltd.

© Registered trademark of F. Hoffmann-La Roche, Ltd (Switzerland)
Epidemiology and Market of Osteoporosis

- The number of Japanese patients with osteoporosis is about 12.8 million, of which about 2.4 million patients* are estimated to be under medical treatment.

- The possibility of vertebral fracture in 50-year-old Japanese women is estimated to be about 37% in their lifetime.

- The market size reached about 220 billion yen in Japan and bisphosphonates and active vitamin D3 products occupy a significant share.

- Recently, bone formation agents have experienced remarkable growth.

*Copyright 2013 IMS Japan K.K. Source: JPM 2012. Reprinted with permission. The scope of the market is defined by Chugai.
### History of bisphosphonate development in Japan

- **Launch year of bisphosphonate formulations indicated for osteoporosis**

<table>
<thead>
<tr>
<th>Year</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>Etidronate Intermittent cyclic Oral formulation</td>
</tr>
<tr>
<td>2001</td>
<td>Alendronate Daily Oral formulation</td>
</tr>
<tr>
<td>2002</td>
<td>Risedronate Daily Oral formulation</td>
</tr>
<tr>
<td>2006</td>
<td>Minodronate Daily Oral formulation</td>
</tr>
<tr>
<td>2007</td>
<td>Alendronate Weekly Oral formulation</td>
</tr>
<tr>
<td>2009</td>
<td>Risedronate Weekly Oral formulation</td>
</tr>
<tr>
<td>2011</td>
<td>Minodronate Every four weeks Oral formulation</td>
</tr>
<tr>
<td>2012</td>
<td>Risedronate Monthly Oral formulation</td>
</tr>
<tr>
<td>2013</td>
<td>Alendronate Every four weeks Oral formulation</td>
</tr>
<tr>
<td></td>
<td>Ibandronate Monthly i.v. infusion formulation</td>
</tr>
</tbody>
</table>
Bonviva intravenous injection is a new bisphosphonate for the treatment of osteoporosis by one-shot monthly intravenous injection

Brand name: Bonviva i.v. injection 1mg syringe
Nonproprietary name: Ibandronate Sodium Hydrate
Dosage form: Injection (prefilled syringe)
Indications: Osteoporosis
Dosage and administration:
- The usual adult dosage is 1 mg as ibandronic acid by intravenous injection once a month.
Advantage of 1mL One-shot Monthly Intravenous Formulation

Bonviva intravenous formulation ensures delivery of the drug into the blood stream and expressing the effects directly.

- Bioavailability 100%
- Adherence improvement can be expected as it is a one-shot monthly administration for the long-term treatment of osteoporosis
- Applicable to patients with difficulty in oral administration or those who sometimes forget taking the drug

Prefilled syringe

1mL one-shot intravenous injection

Adminstration once a month in a hospital/clinic

Blood stream
**Phase II/III Study (MOVER Study)**

**Study Overview**  [Non-inferiority Study]

### Study design

- **Primary Osteoporosis patients** (n=1,265)
  - Randomization

#### Treatment: 3 years

- **Ibandronate injection 0.5mg/month group**
  - Ibandronate 0.5mg monthly injection + Risedronate placebo daily oral

- **Ibandronate injection 1mg/month group**
  - Ibandronate 1mg monthly injection + Risedronate placebo daily oral

- **Risedronate oral tablet 2.5mg/day group**
  - Ibandronate placebo monthly injection + Risedronate 2.5mg daily oral

### Study information

#### Objective

1. To evaluate the efficacy inferiority to Residronate and safety of Ibandronate injection
2. To investigate the optimal dose of Ibandronate injection

#### Patients

- Primary osteoporosis (enrolled patients 1265, target number: 1182)
  - with one to five fractures in the fourth thoracic spine-fourth lumbar spine (Th4-L4) confirmed radiographically
  - aged 60 years and more

#### Method

- Multicenter, randomized, double-blinded, active drug-controlled study

#### Primary endpoint

- Incidence of non-traumatic morphometric vertebral fractures including worsening of prevalent fractures
  - Incidence of osteoporotic non-vertebral fracture
  - Change from baseline of bone density of lumbar spine (L2-L4) and proximal part of femur
  - Change from baseline of bone absorption marker (urine CTX and urine NTX) and bone formation marker (BAP and osteocalcin)

---

*Ito M, et al. Osteoporosis Int 2013;24 (Issue 1 Supplement), abst P396*

*Nakamura T, et al, Calcif Tissue Int 2013; 93: 137-146*
CONTRAINDICATIONS (BONVIVA is contraindicated in the following patients.)

1. Patients with a history of hypersensitivity to the ingredients of BONVIVA or other bisphosphonates

2. 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))]

3. 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.
DOSAGE AND ADMINISTRATION

The usual adult dosage is 1 mg as ibandronic acid by intravenous injection once a month.

Precautions Related to DOSAGE AND ADMINISTRATION

1. BONVIVA should be intravenously administered as slowly as possible.
2. Administration frequency of BONVIVA is once a month. If a scheduled dose is missed, BONVIVA should be administered as soon as possible and then once a month from that point onward.
PRECAUTIONS

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

Patients with severe renal disorders [No clinical data are available, and safety has not been established]
A total 353※ adverse reactions occurred in 239 of 979 patients (24.4%) evaluated for safety in Japanese clinical trials. The most frequent adverse reactions included back pain (25 reports, 2.6%), myalgia (21 reports, 2.1%) and arthralgia (20 reports, 2.0%) (at approval).

Clinically significant adverse reactions such as anaphylactic reaction/shock, osteonecrosis/osteomyelitis of the jaw, atypical fractures of the subtrochanteric and proximal diaphyseal femur were included in overseas spontaneous reports (frequency unknown Note).

Hypocalcemia was reported as a clinically significant adverse reactions of similar drugs.

※The number is different from that described in the Summary of Adverse reactions since the number of the multiple similar side effects observed in the same subject is counted as one.

### Summary of Adverse reactions

| Number of patients evaluated for safety | 979 |
| Number of patients with adverse reactions | 239 |
| Number of adverse reactions | 362 |
| Incidence rate of adverse reactions (%) | 24.4 |

Note) Frequency of adverse reactions spontaneously reported overseas is unknown.
Once-a-month Encouragement to Bone
New Option, One-shot Intravenous Injection

Bonviva® IV injection
1mg syringe
Ibandronate Sodium Hydrate (JAN)

Therapeutic agent for osteoporosis
Powerful drug and Prescription drug

Note) Caution – Use only as prescribed by physician

® Registered trademark of F. Hoffmann-La Roche, Ltd (Switzerland)
Today’s Topics

1. Current status of fracture incidence in Japan and foreign countries, and Osteoporosis treatment
2. Effect of Bisphosphonate on Bone Quality
3. Clinical Trial of Ibandronate Phase II/III
   (MOVER study)
FRAGILITY FRACTURES are no accident!

- Each year millions of mostly older adults will suffer a devastating hip fracture caused by a simple fall. Millions more will suffer fractures of the wrist, shoulder, pelvic or spine. These fractures are no accident! It is likely that the underlying cause is osteoporosis.

Image courtesy of the NOHA (USA) 2Million2Many campaign
1/2 of women and up to 1/4 of men over age 50 will break a bone due to osteoporosis.

Over 1/3 of patients with a hip fracture had a prior fracture.

50% of osteoporosis-related repeat fractures can be prevented with appropriate treatments.

After a fracture, 4 out of 5 women over 67 are not tested or treated for osteoporosis.

2 many. 2 often.

http://www.iofbonehealth.org
Secular trends in the incidence of hip fracture

Incidence of Hip fracture and Number of Prescriptions of Osteoporotic Agents in Australia

Fisher et al.: Clinical Interventions in Aging 2010; 5: 355-362
Today’s Topics

1. Current status of fracture incidence in Japan and foreign countries, and Osteoporosis treatment
2. Effect of Bisphosphonate on Bone Quality
3. Clinical Trial of Ibandronate Phase II/III (MOVER study)
micro CT
Synchrotron CT
Morphometric parameters

Direct 3D measurement: Tb.Th, Tb.Sp, Tb.N, etc

Hildebrand T, Ruegsegger P
J Microscopy 185:67-75, 1997
Non-metric parameters

- Structure model index (SMI)
  - Shape of trabeculae

- Degree of anisotropy (DA)
  - Orientation of trabeculae

- Connectivity density
  - Connectivity of trabeculae
Prevention study of bisphosphonate
female Cynomolgus monkey; 9-17 yo femur distal portion

Sham group (n=12)
OVX group (n=12)
Treatment group 0.15 mg/kg/day (n=12)

Increase in Cortical Porosity with Aging
Human cortical bone

_Lancet_ 2010; 375: 1729–36
Bisphosphonate prevents increase in cortical porosity (human iliac bone sample)

Roschger et al, Bone 29:185-191.2001
Qualitative histological analysis after 3 years treatment by Ibandronate

- Newly formed bone retained its normal lamellar structure, without signs of woven bone
- No marrow fibrosis or signs of cellular toxicity
- No indicators of osteomalacia, such as excessive osteoid

Today’s Topics

1. Current status of fracture incidence in Japan and foreign countries, and Osteoporosis treatment
2. Effect of Bisphosphonate on Bone Quality
3. Clinical Trial of Ibandronate Phase II/III (MOVER study)

MOVER: MOnthly intraVenous ibandronatE versus daily oral Risedronate
### History of Bisphosphonate Development in Japan

Transition of bisphosphonates in osteoporosis treatment are histories of “extension of dosing interval in oral formulation” and “development of formulation for injection”

- **Launch year of bisphosphonate formulations indicated for osteoporosis**

<table>
<thead>
<tr>
<th>Year</th>
<th>Bisphosphonate</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>Etidronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2001</td>
<td>Alendronate</td>
<td>Intermittent cyclic Oral formulation</td>
</tr>
<tr>
<td>2002</td>
<td>Alendronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2006</td>
<td>Risedronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2007</td>
<td>Minodronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2009</td>
<td>Alendronate</td>
<td>Weekly Oral formulation</td>
</tr>
<tr>
<td>2011</td>
<td>Risedronate</td>
<td>Weekly Oral formulation</td>
</tr>
<tr>
<td>2012</td>
<td>Alendronate</td>
<td>Every four weeks Oral formulation</td>
</tr>
<tr>
<td>2013</td>
<td>Ibandronate</td>
<td>Monthly Oral formulation</td>
</tr>
</tbody>
</table>

- **Launch year of bisphosphonate formulations indicated for osteoporosis**

<table>
<thead>
<tr>
<th>Year</th>
<th>Bisphosphonate</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>Etidronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2001</td>
<td>Alendronate</td>
<td>Intermittent cyclic Oral formulation</td>
</tr>
<tr>
<td>2002</td>
<td>Alendronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2006</td>
<td>Risedronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2007</td>
<td>Minodronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2009</td>
<td>Alendronate</td>
<td>Weekly Oral formulation</td>
</tr>
<tr>
<td>2011</td>
<td>Risedronate</td>
<td>Weekly Oral formulation</td>
</tr>
<tr>
<td>2012</td>
<td>Alendronate</td>
<td>Every four weeks Oral formulation</td>
</tr>
<tr>
<td>2013</td>
<td>Ibandronate</td>
<td>Monthly Oral formulation</td>
</tr>
</tbody>
</table>

- **Launch year of bisphosphonate formulations indicated for osteoporosis**

<table>
<thead>
<tr>
<th>Year</th>
<th>Bisphosphonate</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>Etidronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2001</td>
<td>Alendronate</td>
<td>Intermittent cyclic Oral formulation</td>
</tr>
<tr>
<td>2002</td>
<td>Alendronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2006</td>
<td>Risedronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2007</td>
<td>Minodronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2009</td>
<td>Alendronate</td>
<td>Weekly Oral formulation</td>
</tr>
<tr>
<td>2011</td>
<td>Risedronate</td>
<td>Weekly Oral formulation</td>
</tr>
<tr>
<td>2012</td>
<td>Alendronate</td>
<td>Every four weeks Oral formulation</td>
</tr>
<tr>
<td>2013</td>
<td>Ibandronate</td>
<td>Monthly Oral formulation</td>
</tr>
</tbody>
</table>

- **Launch year of bisphosphonate formulations indicated for osteoporosis**

<table>
<thead>
<tr>
<th>Year</th>
<th>Bisphosphonate</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>Etidronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2001</td>
<td>Alendronate</td>
<td>Intermittent cyclic Oral formulation</td>
</tr>
<tr>
<td>2002</td>
<td>Alendronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2006</td>
<td>Risedronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2007</td>
<td>Minodronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2009</td>
<td>Alendronate</td>
<td>Weekly Oral formulation</td>
</tr>
<tr>
<td>2011</td>
<td>Risedronate</td>
<td>Weekly Oral formulation</td>
</tr>
<tr>
<td>2012</td>
<td>Alendronate</td>
<td>Every four weeks Oral formulation</td>
</tr>
<tr>
<td>2013</td>
<td>Ibandronate</td>
<td>Monthly Oral formulation</td>
</tr>
</tbody>
</table>

- **Launch year of bisphosphonate formulations indicated for osteoporosis**

<table>
<thead>
<tr>
<th>Year</th>
<th>Bisphosphonate</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>Etidronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2001</td>
<td>Alendronate</td>
<td>Intermittent cyclic Oral formulation</td>
</tr>
<tr>
<td>2002</td>
<td>Alendronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2006</td>
<td>Risedronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2007</td>
<td>Minodronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2009</td>
<td>Alendronate</td>
<td>Weekly Oral formulation</td>
</tr>
<tr>
<td>2011</td>
<td>Risedronate</td>
<td>Weekly Oral formulation</td>
</tr>
<tr>
<td>2012</td>
<td>Alendronate</td>
<td>Every four weeks Oral formulation</td>
</tr>
<tr>
<td>2013</td>
<td>Ibandronate</td>
<td>Monthly Oral formulation</td>
</tr>
</tbody>
</table>

- **Launch year of bisphosphonate formulations indicated for osteoporosis**

<table>
<thead>
<tr>
<th>Year</th>
<th>Bisphosphonate</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>Etidronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2001</td>
<td>Alendronate</td>
<td>Intermittent cyclic Oral formulation</td>
</tr>
<tr>
<td>2002</td>
<td>Alendronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2006</td>
<td>Risedronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2007</td>
<td>Minodronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2009</td>
<td>Alendronate</td>
<td>Weekly Oral formulation</td>
</tr>
<tr>
<td>2011</td>
<td>Risedronate</td>
<td>Weekly Oral formulation</td>
</tr>
<tr>
<td>2012</td>
<td>Alendronate</td>
<td>Every four weeks Oral formulation</td>
</tr>
<tr>
<td>2013</td>
<td>Ibandronate</td>
<td>Monthly Oral formulation</td>
</tr>
</tbody>
</table>

- **Launch year of bisphosphonate formulations indicated for osteoporosis**

<table>
<thead>
<tr>
<th>Year</th>
<th>Bisphosphonate</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>Etidronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2001</td>
<td>Alendronate</td>
<td>Intermittent cyclic Oral formulation</td>
</tr>
<tr>
<td>2002</td>
<td>Alendronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2006</td>
<td>Risedronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2007</td>
<td>Minodronate</td>
<td>Daily Oral formulation</td>
</tr>
<tr>
<td>2009</td>
<td>Alendronate</td>
<td>Weekly Oral formulation</td>
</tr>
<tr>
<td>2011</td>
<td>Risedronate</td>
<td>Weekly Oral formulation</td>
</tr>
<tr>
<td>2012</td>
<td>Alendronate</td>
<td>Every four weeks Oral formulation</td>
</tr>
<tr>
<td>2013</td>
<td>Ibandronate</td>
<td>Monthly Oral formulation</td>
</tr>
</tbody>
</table>
Phase II/III study in Japan (MOVER study)

Study design

Treatment: 3 years

Primary osteoporosis patients (n=1,265)

Randomization

Ibandronate injection 0.5mg/month
- Ibandronate 0.5mg monthly injection
- + Risedronate placebo oral daily

Ibandronate injection 1mg/month
- Ibandronate 1mg monthly injection
- + Risedronate placebo oral daily

Risedronate oral tablet 2.5mg/day
- Ibandronate placebo monthly injection
- + Risedronate 2.5mg oral daily

※ All patients received supplementary calcium 305 mg/day and vitamin D₃ 200IU/day throughout the study period

Ito M, et al. Osteoporosis Int 2013:24 (Issue 1 Supplement), abst P396
Phase II/III study in Japan (MOVER study)

Overview of study

Objective

① To evaluate the efficacy (inferiority to oral daily Risedronate) and safety of Ibandronate injection (0.5 and 1 mg/month)
② To investigate the optimal dose of Ibandronate injection

Patients

Primary osteoporosis (enrolled patients 1265, target number: 1182)

● with one to five fractures in the fourth thoracic spine-fourth lumbar spine (Th4-L4) confirmed radiographically
● aged 60 years or older

Method

Multicenter, randomized, double-blinded, active drug-controlled study

Primary endpoints

Incidence of non-traumatic morphometric vertebral fractures including worsening of prevalent fractures

Secondary endpoints

● Incidence of osteoporotic non-vertebral fracture
● Change from baseline of bone density of lumbar spine (L2-L4) and proximal part of femur
● Change from baseline of bone absorption marker (urine CTX and urine NTX) and bone formation marker (BAP and osteocalcin)

Ito M, et al. Osteoporosis Int 2013;24 (Issue 1 Supplement), abst P396
Phase II/III study in Japan (MOVER study)

Patient flow through the study

Randomized
N=1,265

Not treated
N=37

IBN injection
0.5mg / month
N=411

Completed
N=305

Withdrawn
N=106

IBN injection
1mg / month
N=411

Completed
N=310

Withdrawn
N=101

RIS oral
2.5mg / day
N=406

Completed
N=294

Withdrawn
N=112

Ito M, et al. Osteoporosis Int 2013;24 (Issue 1 Supplement), abst P396
## Baseline patient characteristics

### Phase II/III study in Japan (MOVER study)

<table>
<thead>
<tr>
<th></th>
<th>RIS 2.5mg daily (n=376)</th>
<th>IBN 0.5mg monthly (n=376)</th>
<th>IBN 1mg monthly (n=382)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>343 (91.2%)</td>
<td>356 (94.7%)</td>
<td>354 (92.7%)</td>
</tr>
<tr>
<td>Men</td>
<td>33 (8.8%)</td>
<td>20 (5.3%)</td>
<td>28 (7.3%)</td>
</tr>
<tr>
<td><strong>Age [year]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-74</td>
<td>227 (60.4%)</td>
<td>219 (58.2%)</td>
<td>245 (64.1%)</td>
</tr>
<tr>
<td>75≤</td>
<td>149 (39.6%)</td>
<td>157 (41.8%)</td>
<td>137 (35.9%)</td>
</tr>
<tr>
<td>mean±S.D.</td>
<td>73.0±6.3</td>
<td>72.9±6.3</td>
<td>72.2±6.4</td>
</tr>
<tr>
<td><strong>Prevalent vertebral fracture</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>183 (48.7%)</td>
<td>186 (49.5%)</td>
<td>184 (48.2%)</td>
</tr>
<tr>
<td>≥2</td>
<td>193 (51.3%)</td>
<td>190 (50.5%)</td>
<td>198 (51.8%)</td>
</tr>
<tr>
<td><strong>SQ grade of vertebral fracture</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>88 (23.4%)</td>
<td>96 (25.5%)</td>
<td>81 (21.2%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>147 (39.1%)</td>
<td>147 (39.1%)</td>
<td>161 (42.1%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>141 (37.5%)</td>
<td>133 (35.4%)</td>
<td>140 (36.6%)</td>
</tr>
<tr>
<td><strong>BMD (T-score)</strong></td>
<td>Lumbar spine (L2-L4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>−2.59±1.06</td>
<td>−2.71±1.01</td>
<td>−2.68±1.01</td>
</tr>
<tr>
<td></td>
<td>Total hip</td>
<td>−2.18±0.86</td>
<td>−2.17±0.87</td>
</tr>
<tr>
<td><strong>BTM (mean±S.D.)</strong></td>
<td>uCTX [μg/mmol · Cr]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>373.2±261.0</td>
<td>382.4±226.2</td>
<td>368.6±209.9</td>
</tr>
<tr>
<td></td>
<td>BAP [U/L]</td>
<td>32.4±12.0</td>
<td>33.6±13.2</td>
</tr>
<tr>
<td><strong>25-OH Vitamin D [ng/mL]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19.7±6.6</td>
<td>19.6±6.4</td>
<td>20.0±6.7</td>
</tr>
</tbody>
</table>

**PPS**: Per Protocol Set  
S.D.: standard deviation

Ito M, et al. Osteoporosis Int 2013;24 (Issue 1 Supplement), abst P396
Incidence of vertebral fractures

Phase II/III study in Japan (MOVER study)

Non-traumatic vertebral fracture (incl. worsening)

Hazard ratio: 0.88 (95% IC: 0.61-1.27)  
RRR 12%  

Ito M, et al. Osteoporosis Int 2013;24 (Issue 1 Supplement), abst P396   
Phase II/III study in Japan (MOVER study)

Efficacy on vertebral fracture:

hazard ratios of non-traumatic vertebral fracture

(PPS)
Hazard ratio ± 95%CI

IBN 1mg monthly injection versus RIS 2.5mg daily oral

Hazard ratio

Parameter | Hazard ratio | 95% CI
---|---|---
IBN 1mg monthly injection versus RIS 2.5mg daily oral | 0.88 | 0.61-1.27

Ito M, et al. Osteoporosis Int 2013;24 (Issue 1 Supplement), abst P396
Phase II/III study in Japan (MOVER study)

Efficacy on non-vertebral fracture:
Estimated incidence of osteoporotic non-vertebral fractures

RIS 2.5mg daily oral (n=376)

Kaplan-Meier method

IBN 1mg monthly injection (n=382)

Chugai internal documents
Phase II/III study in Japan (MOVER study)

Efficacy on fracture:
Incidence of osteoporotic fractures through three years

Efficacy on Bone Mineral Density: Relative change from baseline in lumbar spine BMD

Phase II/III study in Japan (MOVER study)

(PPS)
Mean±95% CI
* : p=0.005  ** : p=0.001
(vs RIS 2.5mg daily oral)
t-test

IBN 1mg monthly injection (n=382)
RIS 2.5mg daily oral (n=376)

Ito M, et al. Osteoporosis Int 2013;24 (Issue 1 Supplement), abst P396
Phase II/III study in Japan (MOVER study)

Efficacy on Bone Mineral Density:
Relative change from baseline in total hip BMD

Ito M, et al. Osteoporosis Int 2013;24 (Issue 1 Supplement), abst P396
Phase II/III study in Japan (MOVER study)
Efficacy on bone absorption markers:
Relative change from baseline in urinary CTX and NTX

IBN 1mg monthly injection (n=382)
RIS 2.5mg daily oral (n=376)

Ito M, et al. Osteoporosis Int 2013;24 (Issue 1 Supplement), abst P396
Phase II/III study in Japan (MOVER study)
Efficacy on bone formation markers:
Relative change from baseline in serum BAP and OC

IBN 1mg monthly injection (n=382)
RIS 2.5mg daily oral (n=376)

Chugai internal documents
### Phase II/III study in Japan (MOVER study)

**Adverse events of interest**

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>RIS 2.5mg daily oral (n=406)</th>
<th>IBN 1mg monthly injection (n=411)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>393 (96.8)</td>
<td>401 (97.6)</td>
</tr>
<tr>
<td>GI related</td>
<td>108 (26.6)</td>
<td>120 (29.2)</td>
</tr>
<tr>
<td>Serious GI related</td>
<td>9 (2.2)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>APR related</td>
<td>20 (4.9)</td>
<td>46 (11.2)</td>
</tr>
<tr>
<td>Renal function related</td>
<td>8 (2.0)</td>
<td>11 (2.7)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atypical fracture of the femur</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

GI: gastrointestinal, APR: acute phase reaction

Phase II/III study in Japan (MOVER study)

Acute phase reaction (APR)

- Acute phase reaction was commonly experienced following administration of intermittent N-containing bisphosphonates.

- In this study, the symptoms with onset within 3 days after administration and duration within 7 days are regarded as APR.

**Adverse events**

<table>
<thead>
<tr>
<th></th>
<th>Risedronate 2.5mg daily oral (n=406)</th>
<th>Ibandonrate 1mg monthly injection (n=411)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APR related</td>
<td>20 (4.9)</td>
<td>46 (11.2)</td>
</tr>
</tbody>
</table>

n (%)  
※APR related AEs with causality linked to the study drugs;  
Risedronate 2.5mg daily oral: 3.0%, Ibandronate 1mg monthly oral: 7.1%.

Chugai internal documents
Phase II/III study in Japan (MOVER study)

Change in the incidence of acute phase reactions

![Graph showing the incidence of acute phase reactions over time.](image)

**Incidences of APRs decreased after 2\(^{nd}\) dosing.**

2\(^{nd}\) – 3\(^{rd}\): 0.5-2.2%, 4\(^{th}\) or more: 0-0.8%

Reports of Osteonecrosis of the Jaw (ONJ) (overseas: clinical trial/spontaneous reports/literature)

Maximally 5-year administration of Ibandronate

No cases meet ASBMR required conditions for ONJ (no reports in MOVER study)

Possible
n=176

Diagnosis of ONJ
n=49

ONJ fulfilled ASBMR conditions
n=34

“Roche Briefing Information for the September 9, 2011 Joint Meeting of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee.”
Atypical femoral fracture and ONJ (Ibandronate)

- ATF fulfilled all ASBMR conditions (n=8)
  - 0.3 / 1,000,000 patients
- ONJ fulfilled all ASBMR conditions (n=34)
  - 2.1 / 1,000,000 patients
Why we need monthly injection bisphosphonate?
Pharmacokinetics of Oral Bisphosphonate (Rats)

Oral administration

GI Resorption rate (0.95%)

Liver

Blood

Tissue

Bone (distribution)

Kidney

Urine (0.46%)

Fecal excretion (approximately 99%)

Wada S., A. Suzuki, Practical guidebook to use bisphosphonate efficiently, Koubundou, 2011; 9
Monthly one-shot intravenous injection

- Drug distribution and discharge of iv Ibandronate (rat, dog)
Contacts:

**Media Relations:**

Chugai Pharmaceutical Co., Ltd.
Corporate Communications Dept. Media Relations Group
Tel: +81 (0)3-3273-0881

Taisho Pharmaceutical Holdings Co., Ltd.
Public Relations Section, Media Relations Group
Tel: +81 (0)3-3985-1115

**Investor Relations:**

Chugai Pharmaceutical Co., Ltd.
Corporate Communications Dept. Investor Relations Group
Tel: +81 (0)3-3273-0554

Taisho Pharmaceutical Holdings Co., Ltd.
Public Relations Section, Investor Relations Group
Tel: +81 (0)3-3985-1115