TAISHO PHARMACEUTICAL GROUP
TAISHO TOYAMA PHARMACEUTICAL CO., LTD.

CHUGAI PHARMACEUTICAL CO., LTD.
Roche Group

Information Meeting on Bonviva®

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

August 30, 2013

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.

Therapeutic agent for osteoporosis
Powerful drug and Prescription drug (note)

National health insurance drug price listed

Bonviva® IV injection 1mg syringe

Ibandronate Sodium Hydrate (JAN)

Note) Caution – Use only as prescribed by physician

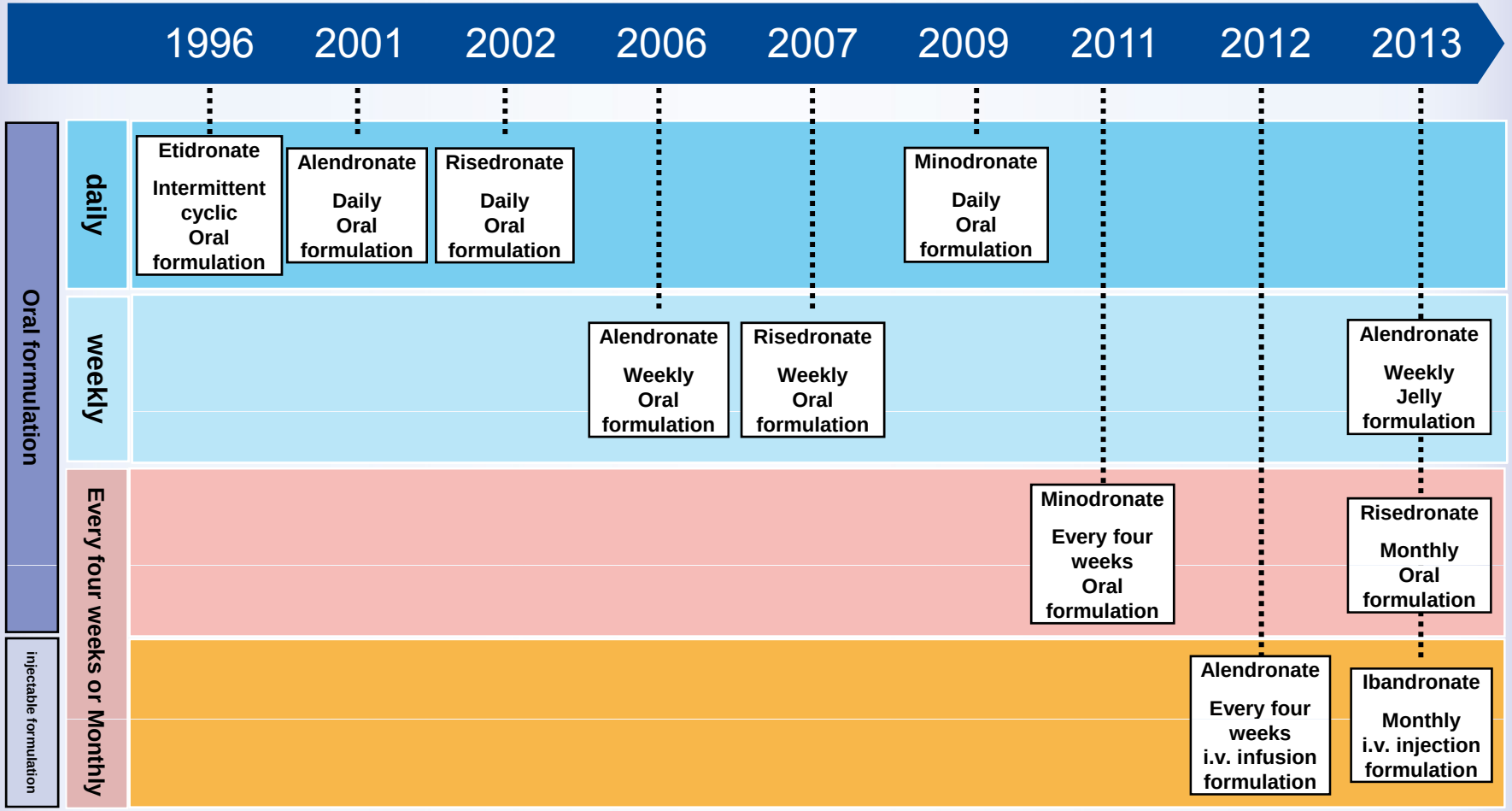
Epidemiology and Market of Osteoporosis

- **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 D_3 products occupy a significant share**
- **Recently, bone formation agents have experienced remarkable growth**

The scope of the market is defined by Chugai.

History of bisphosphonate development in Japan

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



Product Summary

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 ibandronate

Administration once a month in a hospital/clinic

1mL one-shot intravenous injection

Prefilled syringe

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

Bioavailability 100%

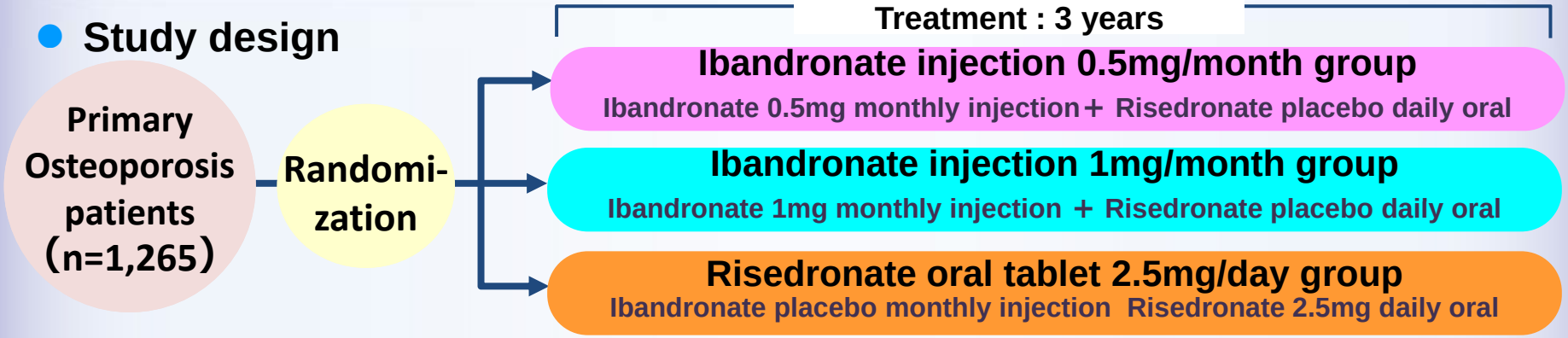
- **Adherence improvement can be expected as it is a one-shot monthly administration for the long-term treatment of osteoporosis**
- **Applicable to patients with difficulty in oral administration or those who sometimes forget taking the drug**

Phase II/III Study（MOVER Study）

Study Overview [Non-inferiority Study]

Bonviva ibandronate

● Study design



※All patients received supplementary calcium 305mg/day and vitamin D_3 200IU/day throughout the study period

● 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

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
Nakamura T, et al, Calcif Tissue Int 2013; 93: 137-146

CONTRAINDICATIONS

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]

Adverse Reactions

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

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Bonviva® IV injection 1mg syringe

Ibandronate Sodium Hydrate (JAN)

Note) Caution – Use only as prescribed by physician

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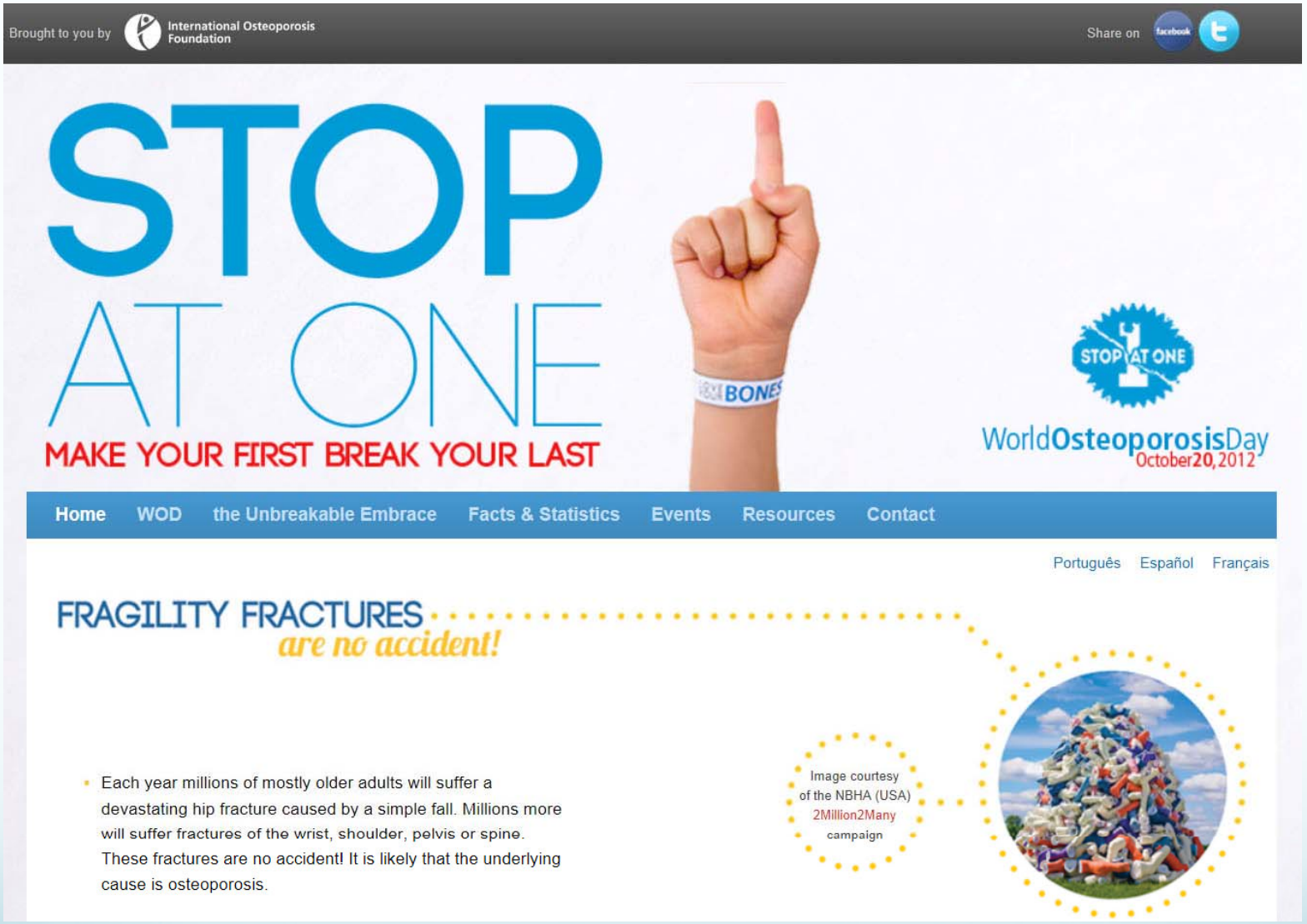
Clinical Usefulness and Our Expectation

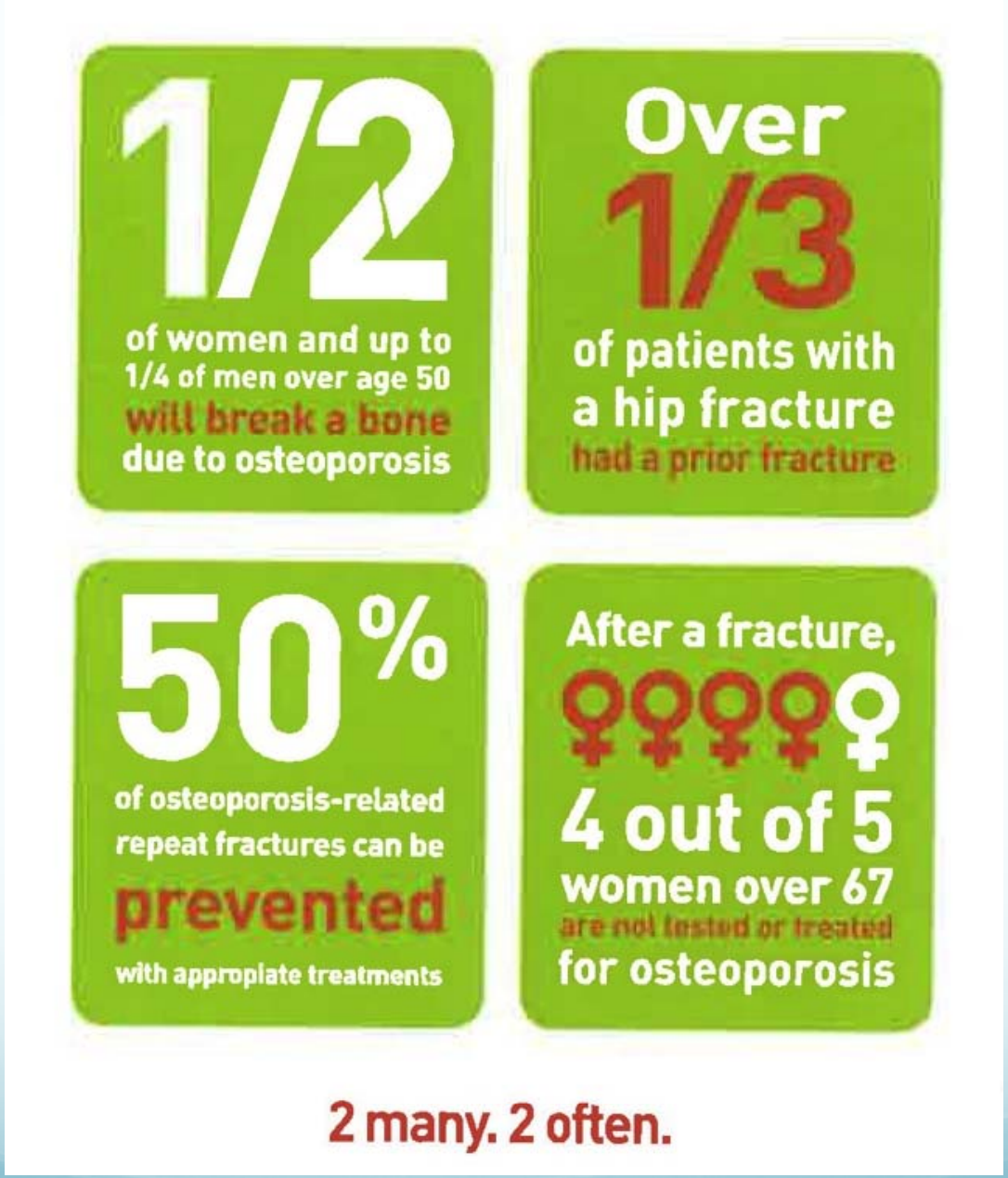
Masako Ito
Medical Work-Life-Balance Center
Nagasaki University Hospital

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)

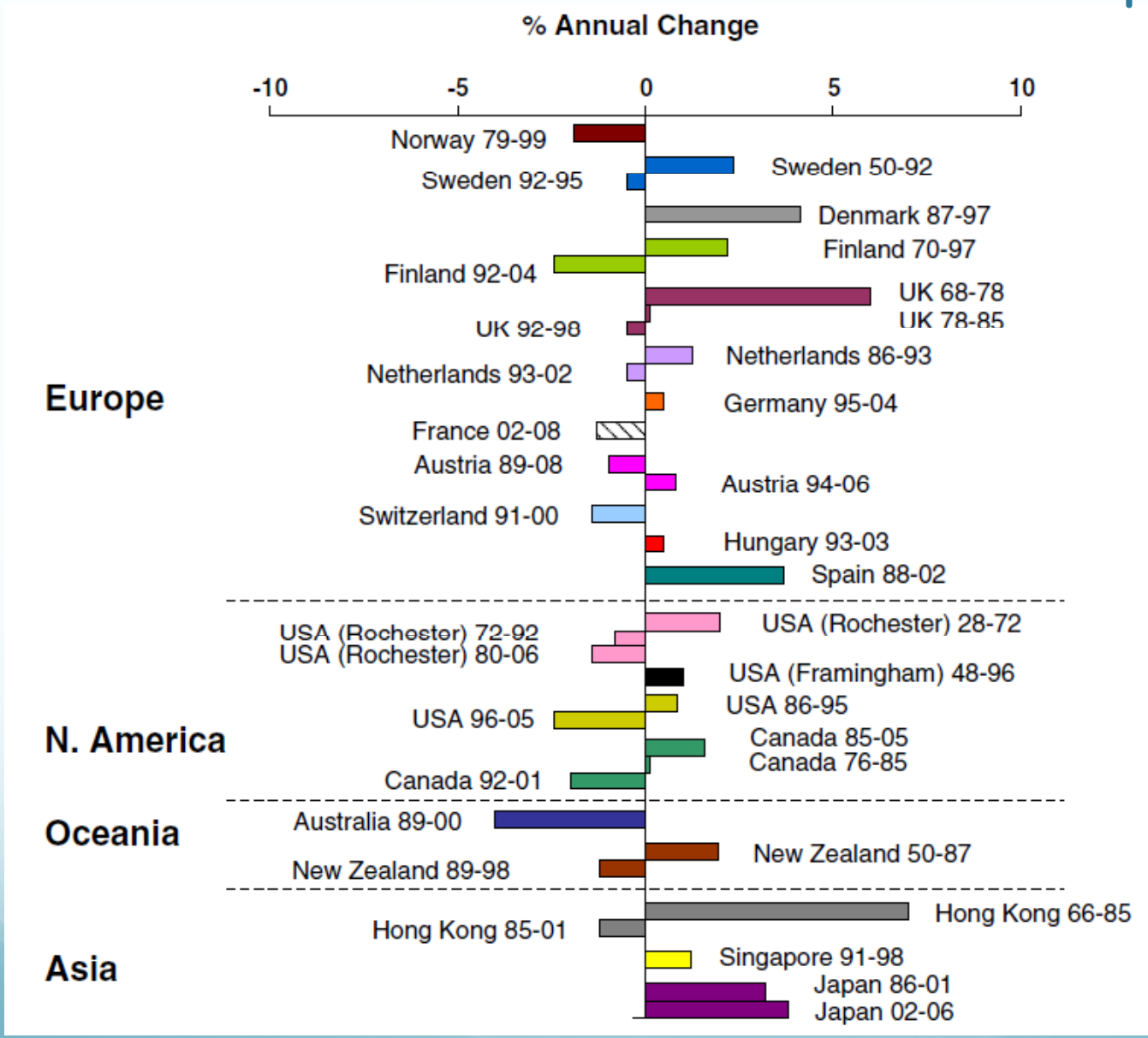


http://www.iofbonehealth.org



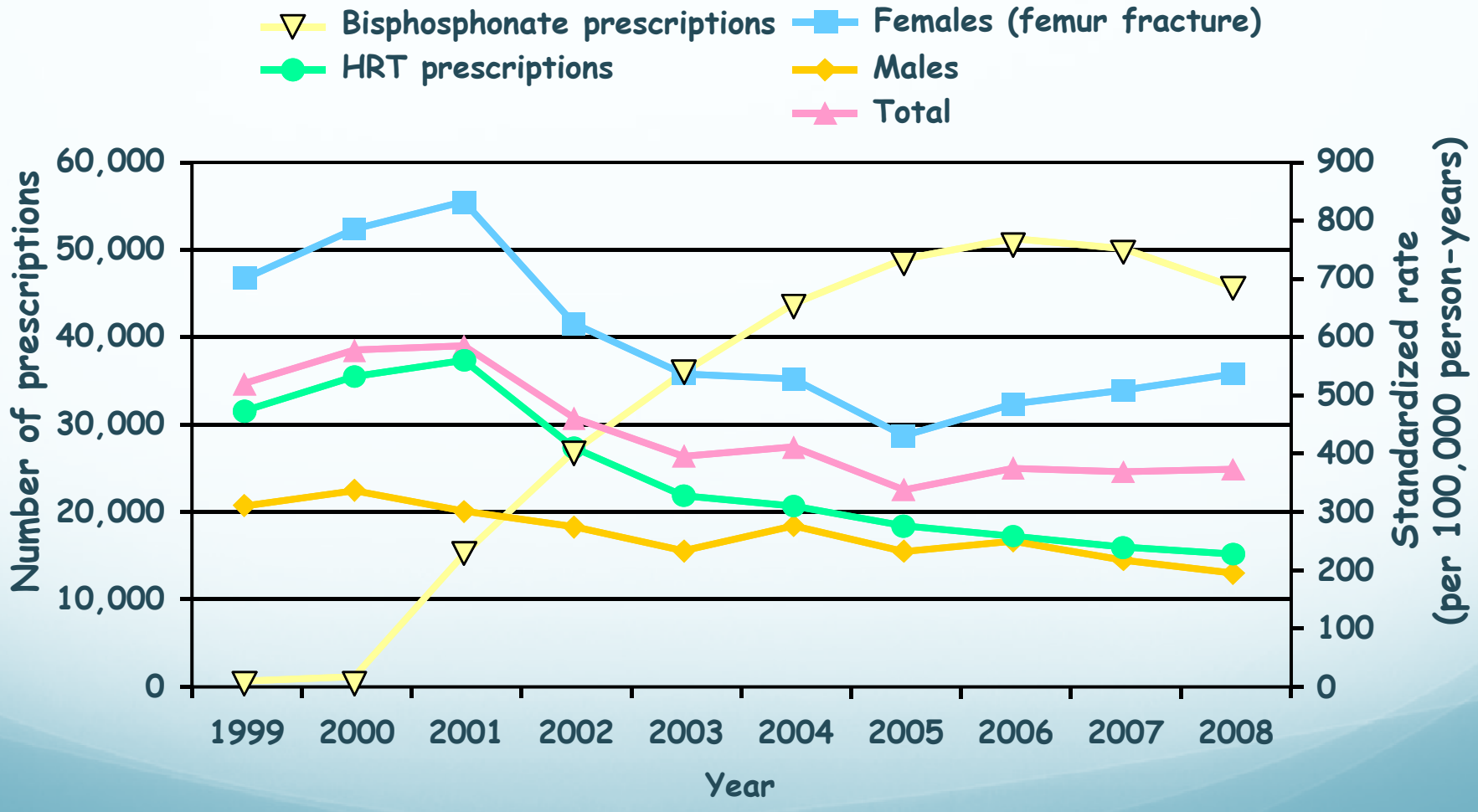
http://www.iofbonehealth.org

Secular trends in the incidence of hip fracture



Cooper C, et al, Osteoporos Int. 2011; 22: 1277-1288.

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



Fisher et al.:Clinical Interventions in Aging 2010,:5 :355 362

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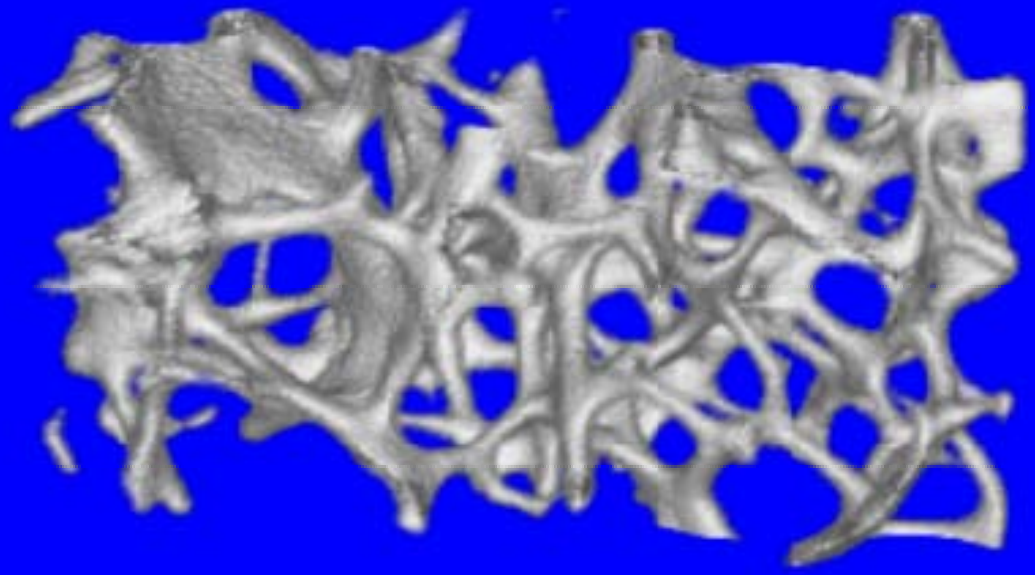
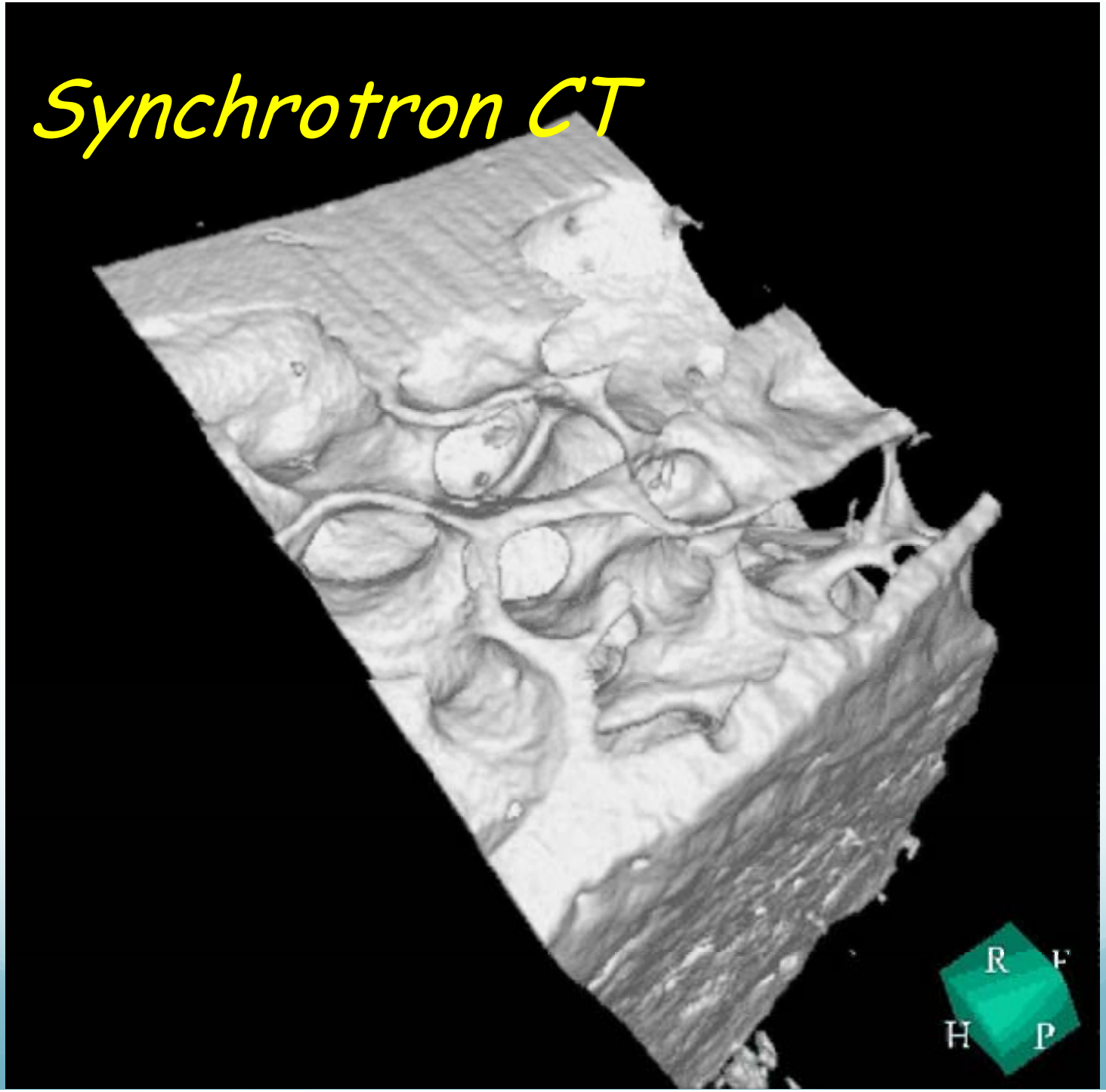
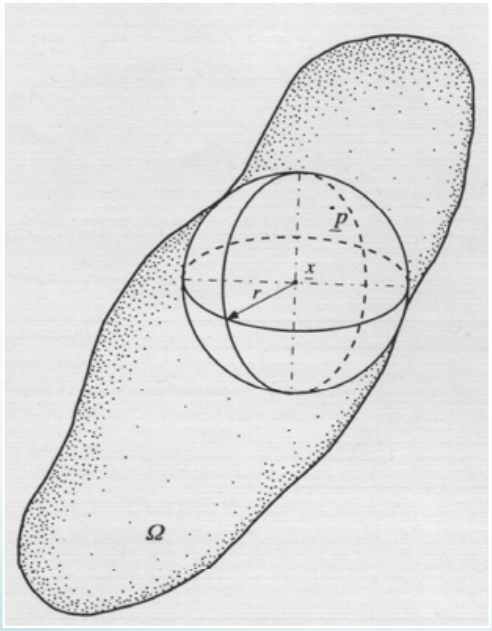
micro CT



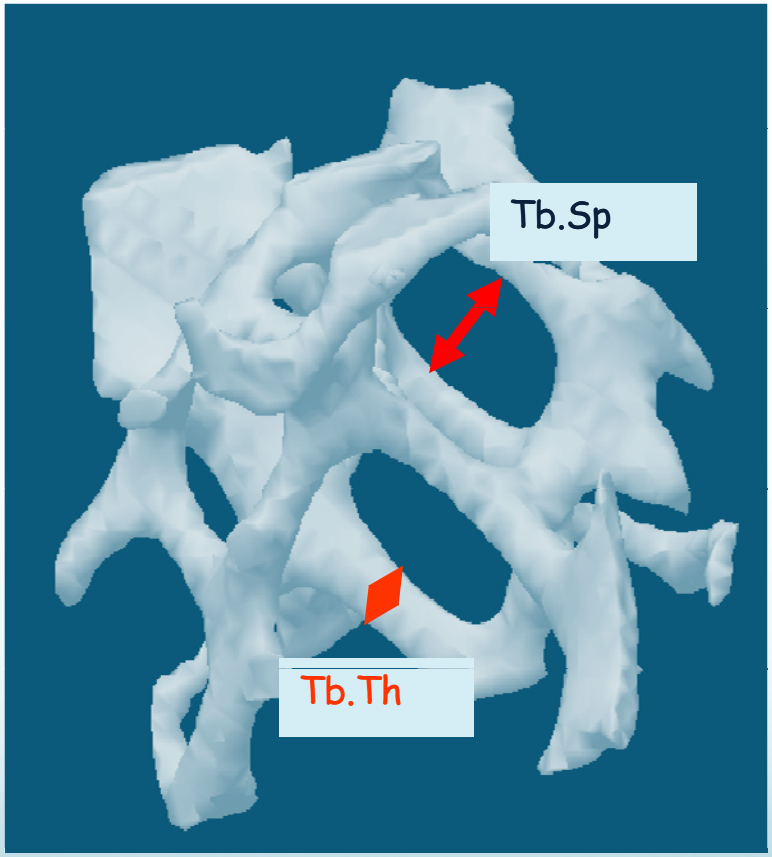
Synchrotron CT

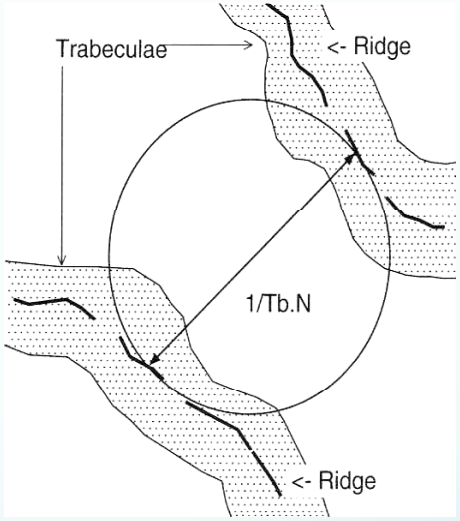


Morphometric parameters



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

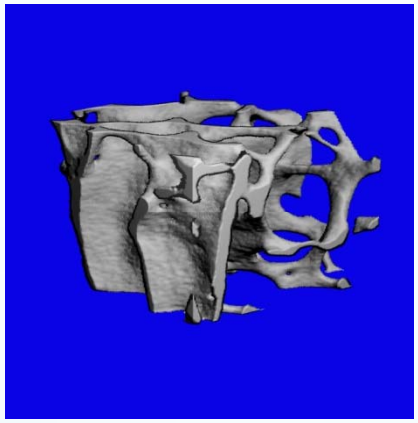


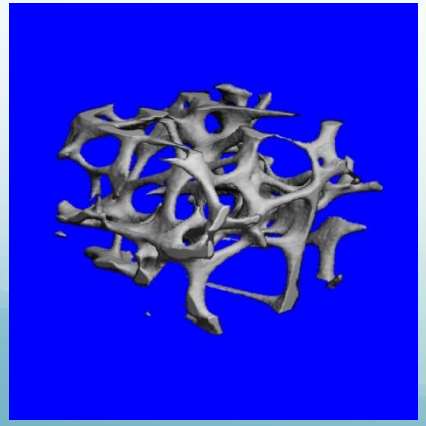


Direct 3D measurement: Tb.Th, Tb.Sp, Tb.N, etc

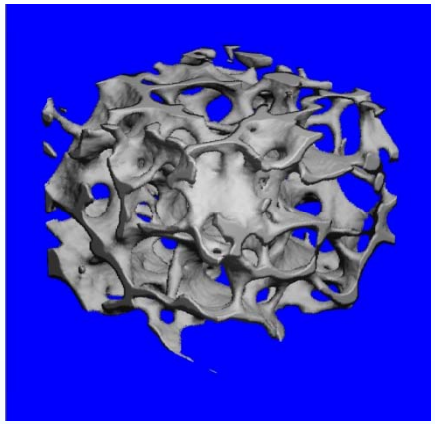
Non-metric parameters

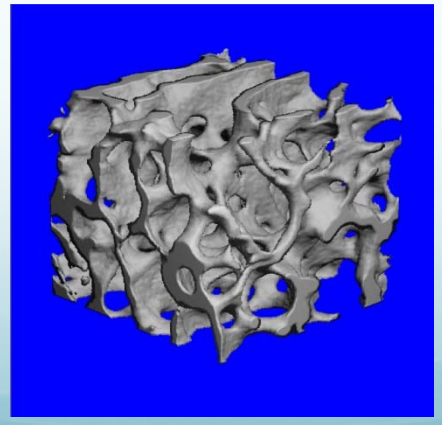
structure model index
(SMI)
Shape of trabeculae



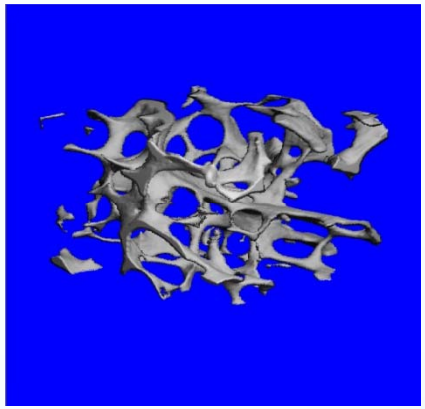


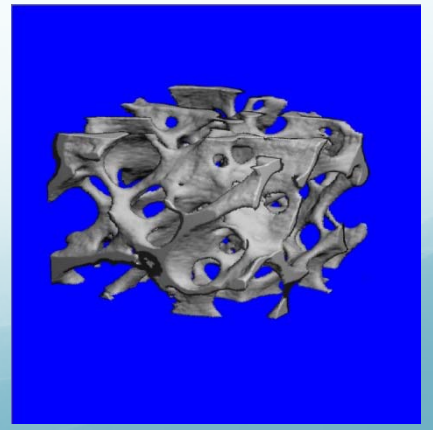
degree of anisotropy
(DA)
Orientation of trabeculae

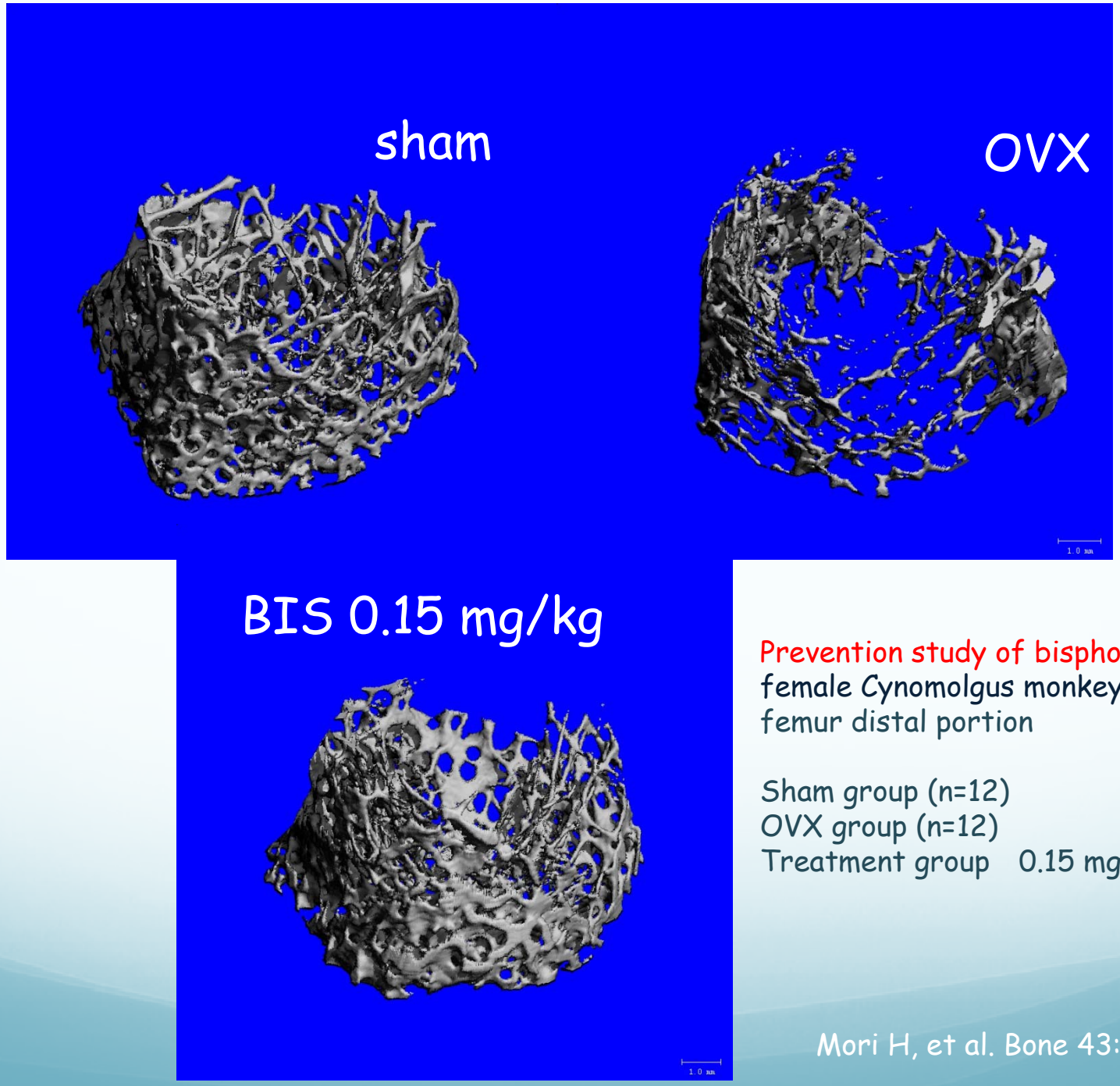




Connectivity density
Connectivity of trabeculae





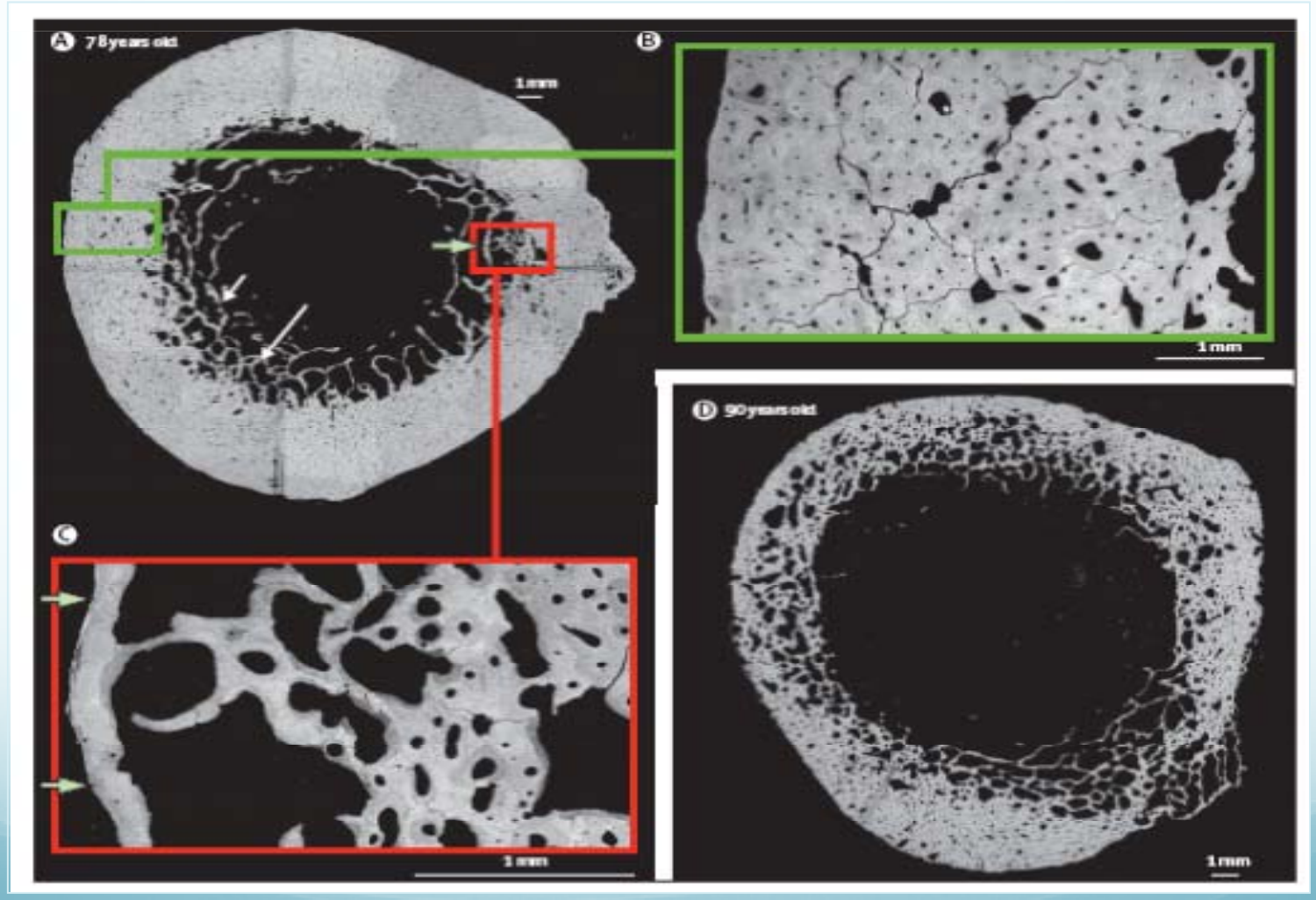


Prevention study of bisphosphonate
female Cynomolgus monkey ; 9-17 yo
femur distal portion

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

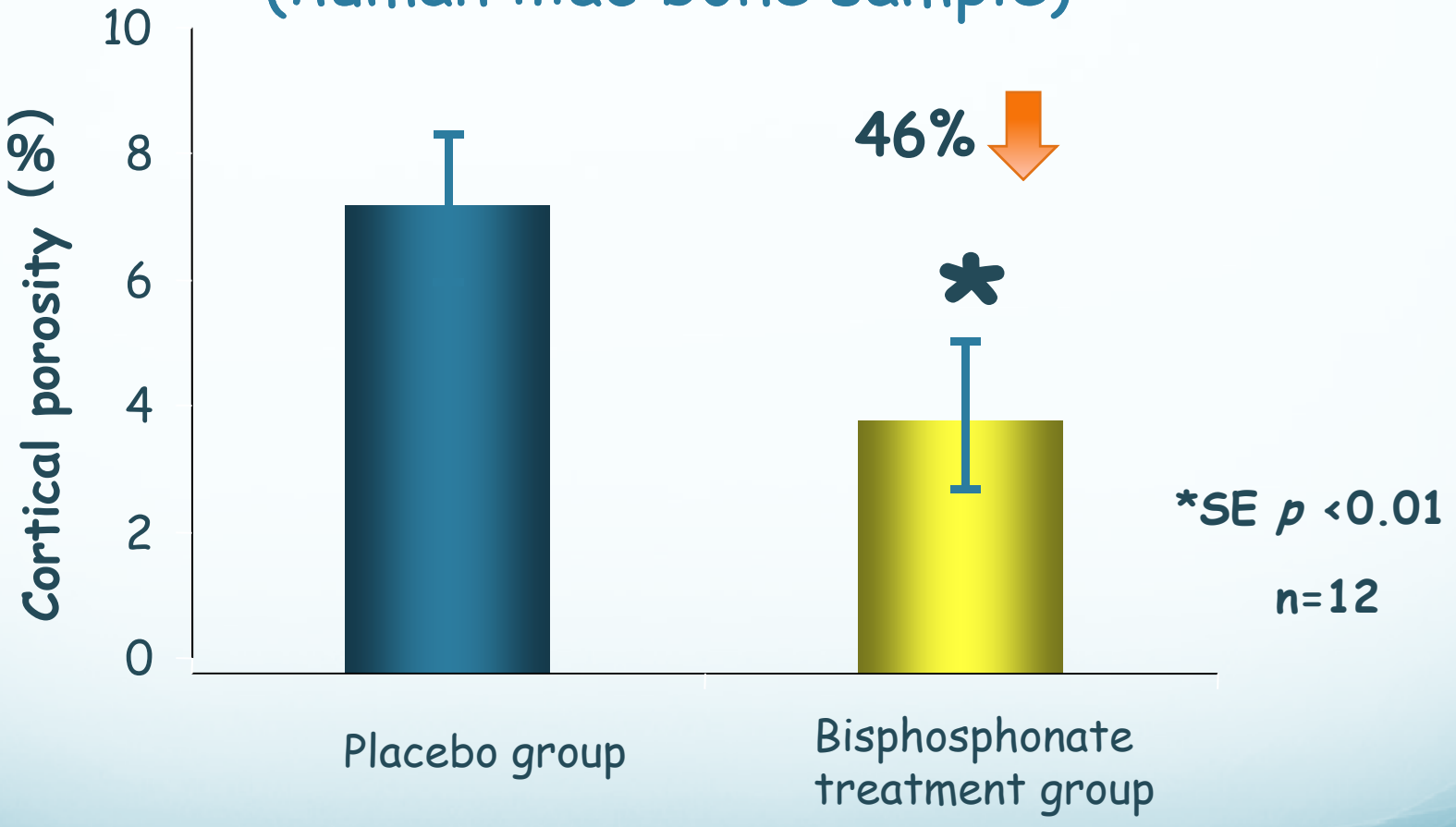
Mori H, et al. Bone 43:840-848, 2008

Increase in Cortical Porosity with Aging
Human cortical bone



Lancet 2010; 375: 1729–36

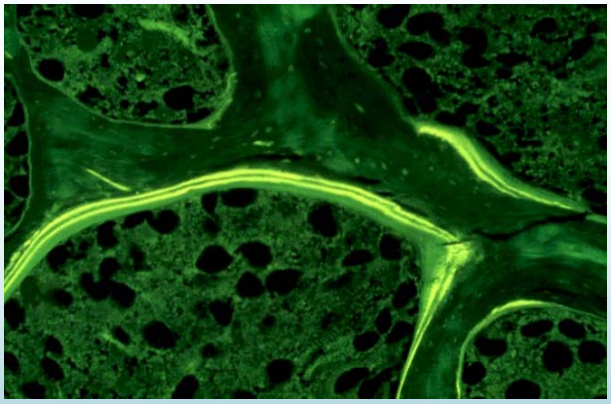
Bisphosphonate prevents increase in cortical porosity (human iliac bone sample)

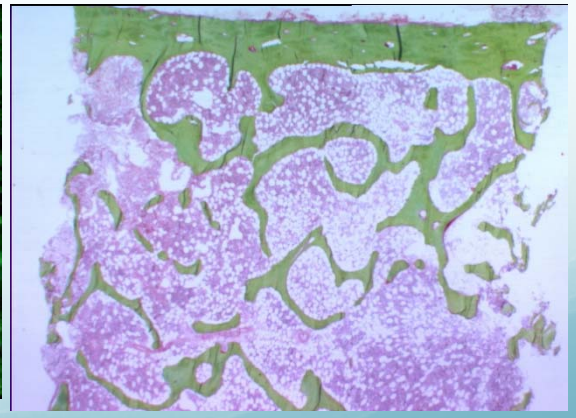


Roschger et al, Bone 29:185-191.2001

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





Recker RR, et al. Osteoporos Int 15:231-237, 2004

Today's Topics

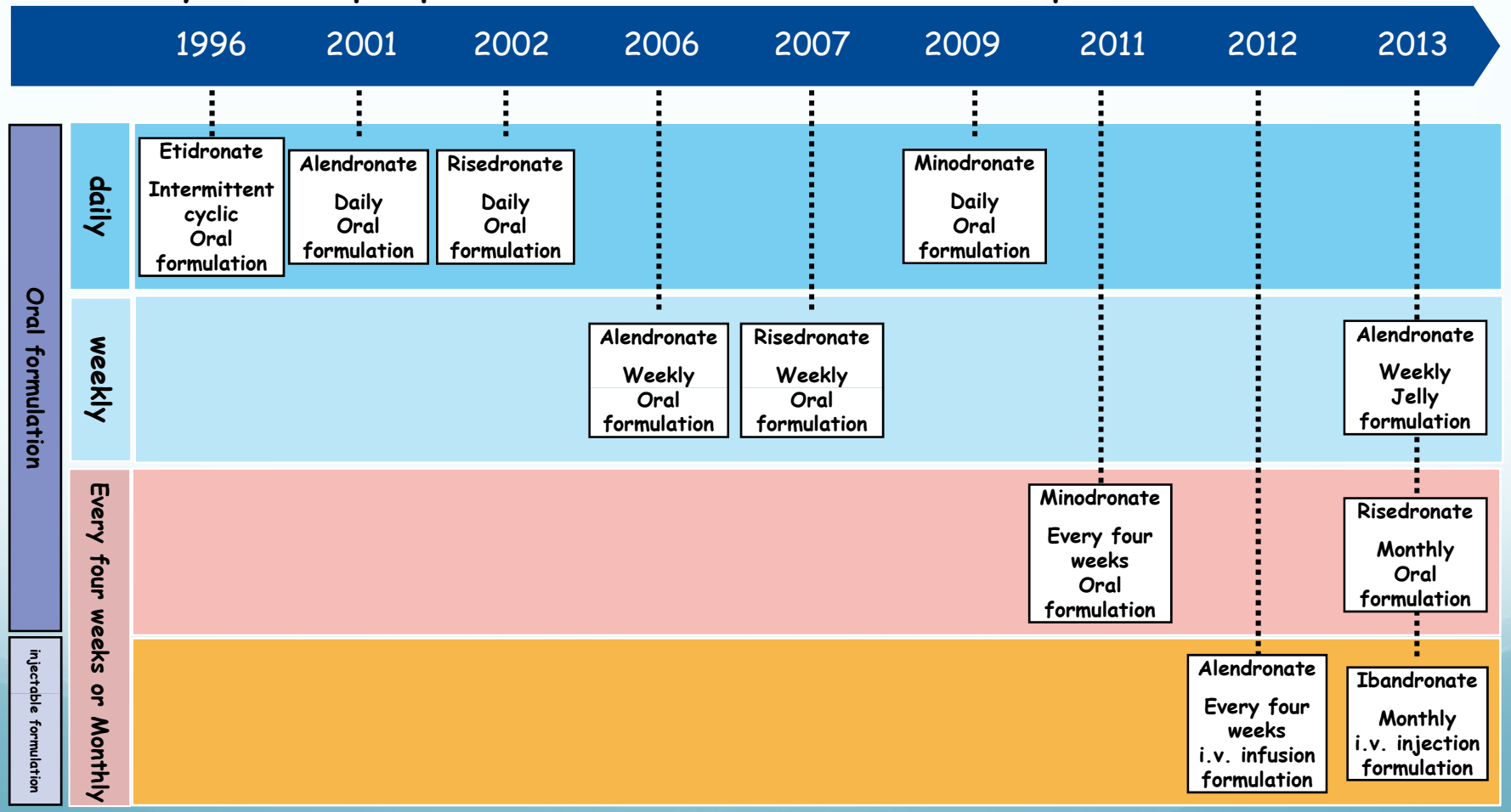
1. Current status of fracture incidence in Japan and foreign countries, and Osteoporosis treatment
2. Effect of Bisphosphonate on Bone Quality
3. Clinical Trial of Ibandronate Phase Ⅱ/Ⅲ (MOVER study)

MOVER : MOnthly intraVenous ibandronatE versus daily oral Risedronate

History of bisphosphonate development in Japan

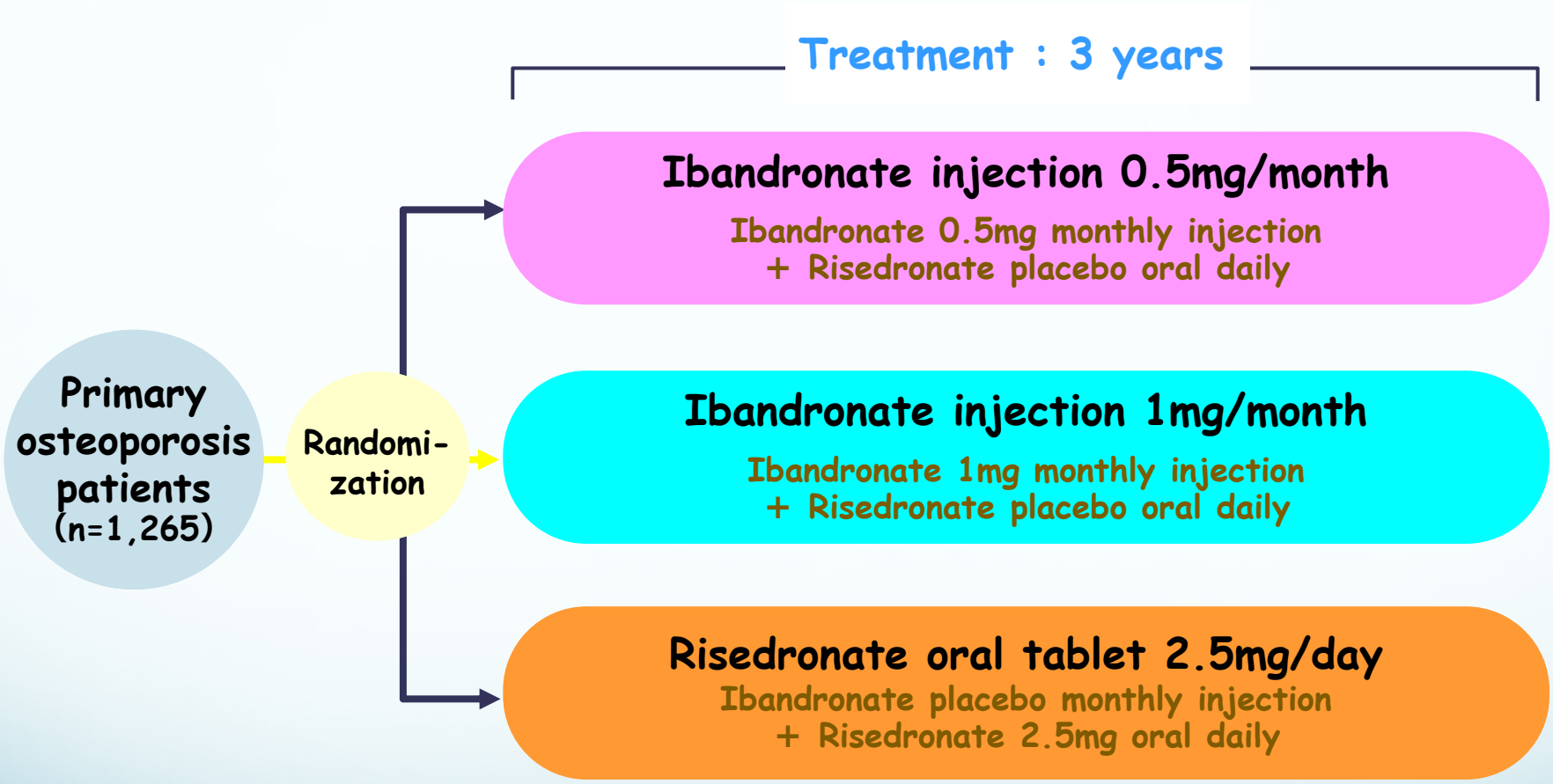
Transition of bisphosphonates in osteoporosis treatment are histories of "extension of dosing interval in oral formulation" and "development of formulation for injection"

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



Phase II/III study in Japan (MOVER study)

Study design



※All patients received supplementary calcium 305 mg/day and vitamin D_3 200IU/day throughout the study period

Ito M, et al. Osteoporosis Int 2013;24 (Issue 1 Supplement), abst P396
Nakamura T, et al, Calcif Tissue Int 2013; 93: 137-146

Phase II/III study in Japan (MOVER study)

Overview of study

Non-inferiority 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

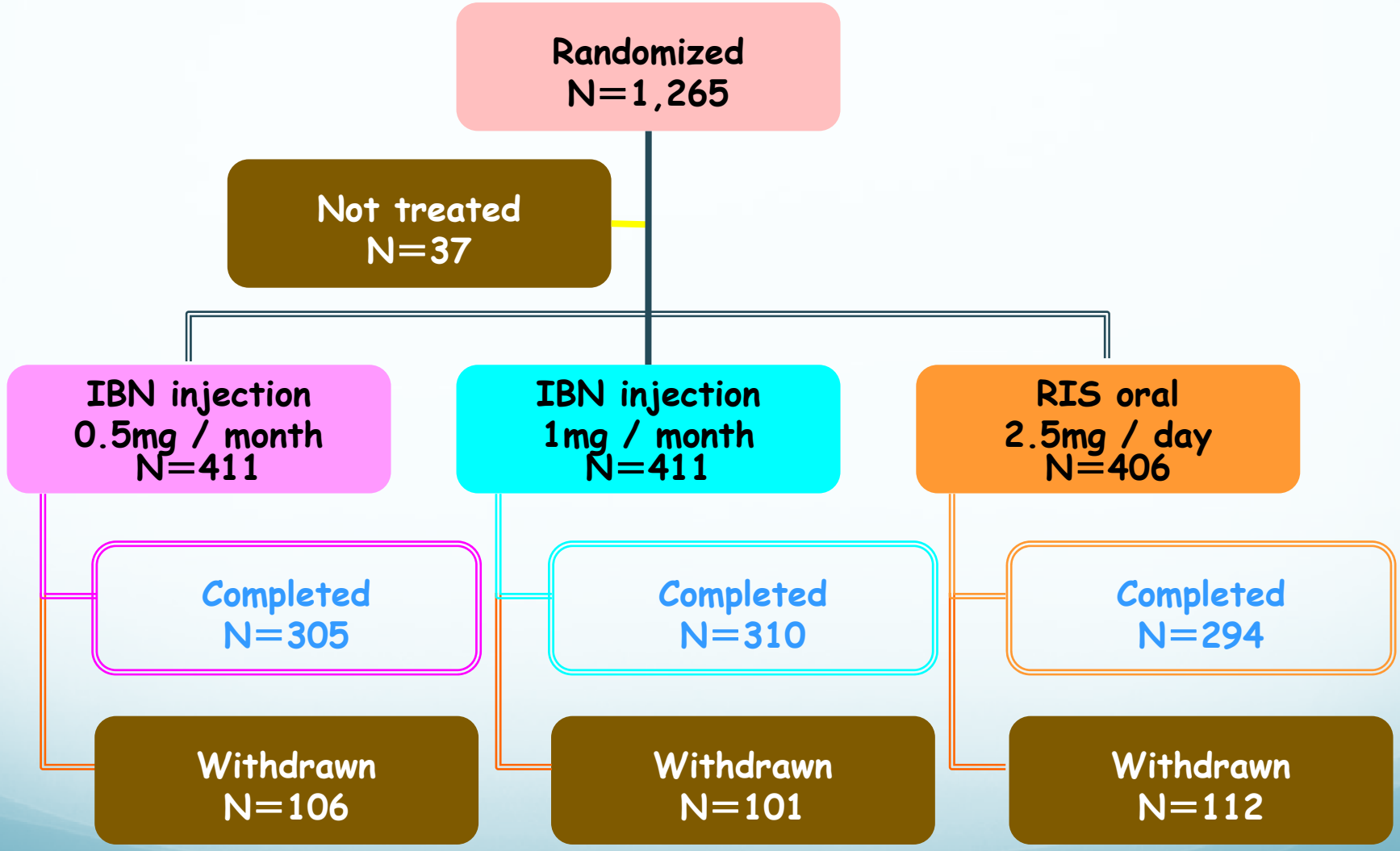
Secondary endpoints

- 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
Nakamura T, et al, Calcif Tissue Int 2013; 93: 137-146

Phase II/III study in Japan (MOVER study)

Patient flow through the study



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

Baseline patient characteristics

		RIS 2.5mg daily (n=376)	IBN 0.5mg monthly (n=376)	IBN 1mg monthly (n=382)
Sex	Women	343 (91.2%)	356 (94.7%)	354 (92.7%)
	Men	33 (8.8%)	20 (5.3%)	28 (7.3%)
Age [year]	60-74	227 (60.4%)	219 (58.2%)	245 (64.1%)
	75≦	149 (39.6%)	157 (41.8%)	137 (35.9%)
	mean±S.D.	73.0±6.3	72.9±6.3	72.2±6.4
Prevalent vertebral fracture	1	183 (48.7%)	186 (49.5%)	184 (48.2%)
	≧2	193 (51.3%)	190 (50.5%)	198 (51.8%)
SQ grade of vertebral fracture	Grade 1	88 (23.4%)	96 (25.5%)	81 (21.2%)
	Grade 2	147 (39.1%)	147 (39.1%)	161 (42.1%)
	Grade 3	141 (37.5%)	133 (35.4%)	140 (36.6%)
BMD (T-score) (mean±S.D.)	Lumbar spine (L2-L4)	−2.59±1.06	−2.71±1.01	−2.68±1.01
	Total hip	−2.18±0.86	−2.17±0.87	−2.09±0.86
BTM (mean±S.D.)	uCTX [μg/mmol・Cr]	373.2±261.0	382.4±226.2	368.6±209.9
	BAP [U/L]	32.4±12.0	33.6±13.2	33.9±13.1
25-OH Vitamin D [ng/mL] (mean±S.D.)		19.7±6.6	19.6±6.4	20.0±6.7

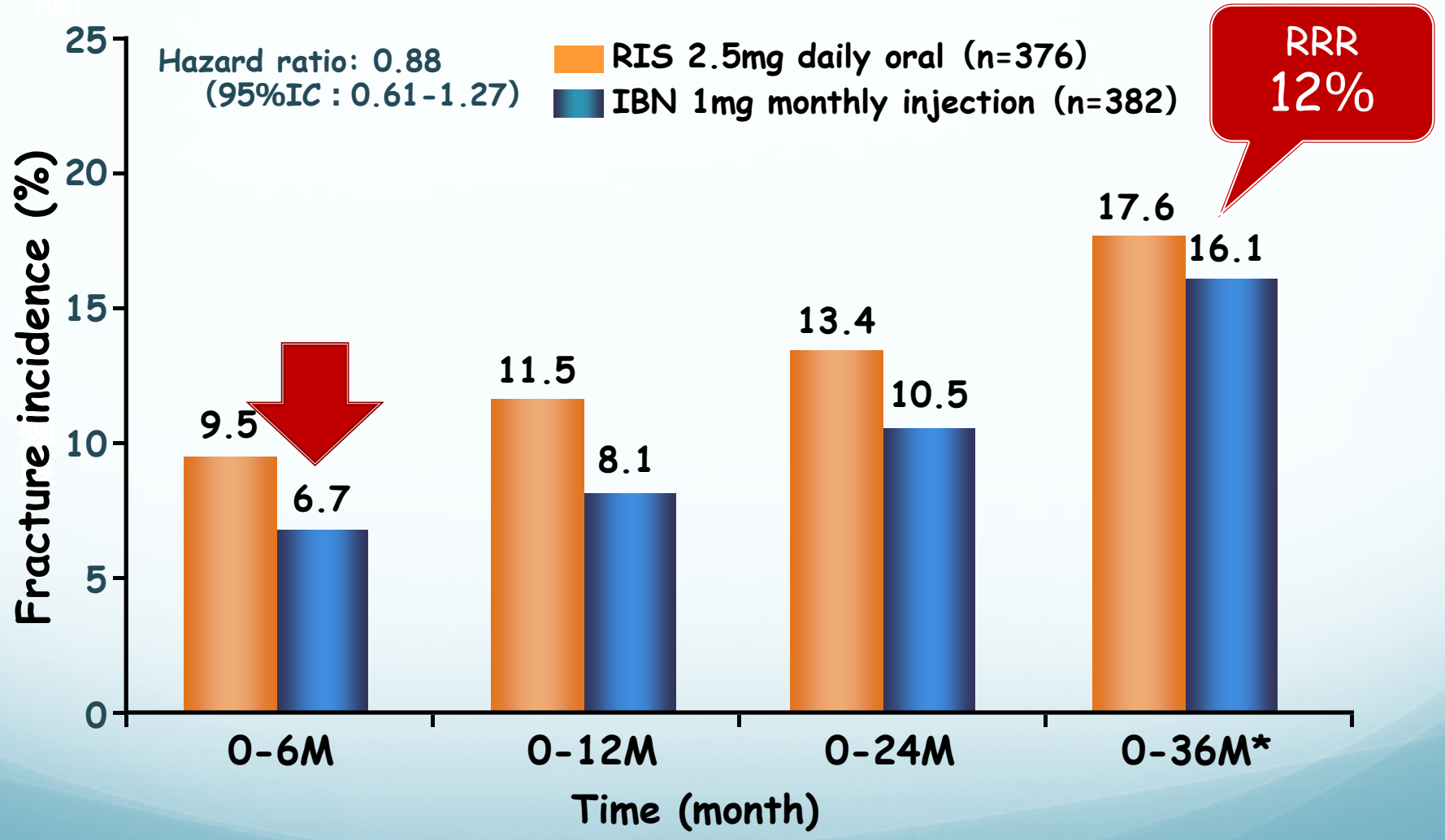
PPS : Per Protocol Set S.D. : standard deviation

Ito M, et al. Osteoporosis Int 2013;24 (Issue 1 Supplement), abst P396
Nakamura T, et al, Calcif Tissue Int 2013; 93: 137-146

Phase II/III study in Japan (MOVER study)

Incidence of vertebral fractures

- Non-traumatic vertebral fracture (incl. worsening)

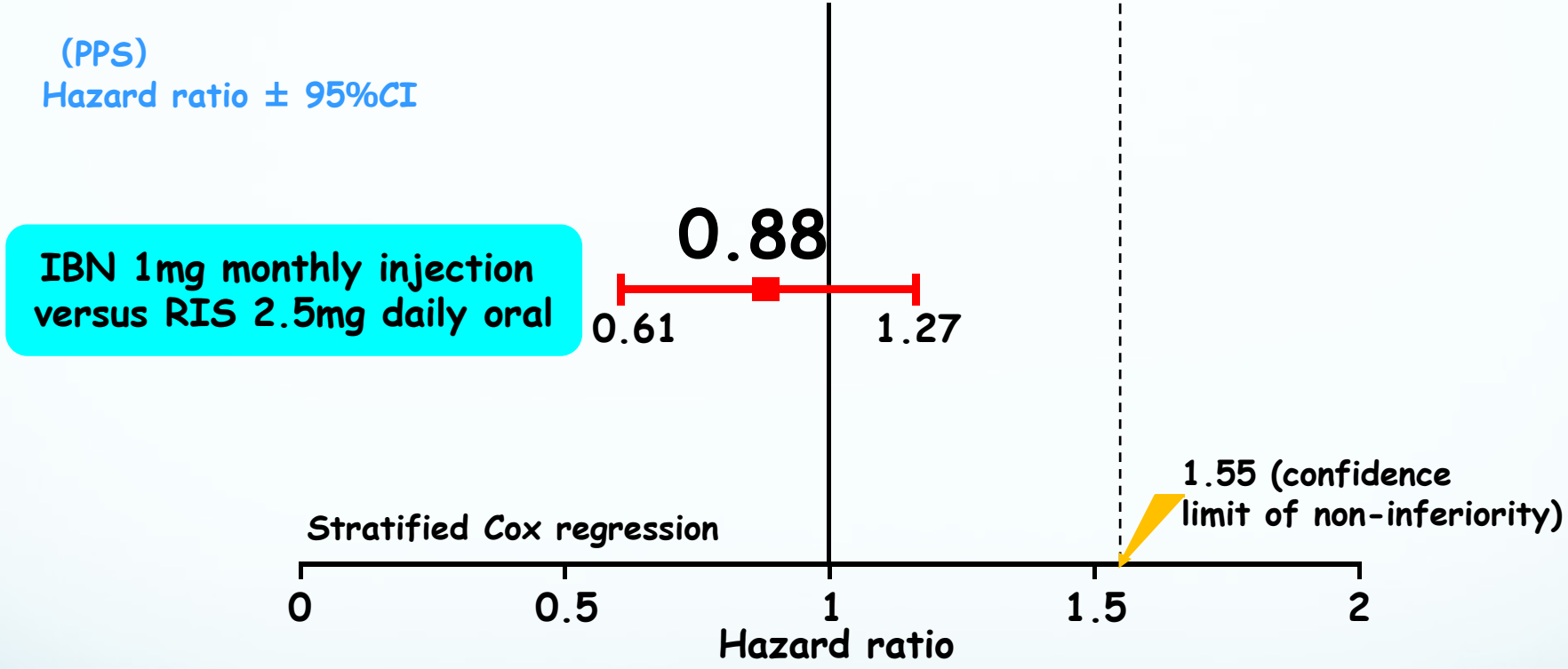


Ito M, et al. Osteoporosis Int 2013;24 (Issue 1 Supplement), abst P396
Nakamura T, et al, Calcif Tissue Int 2013; 93: 137-146

Phase II/III study in Japan (MOVER study)

Efficacy on vertebral fracture: hazard ratios of non-traumatic vertebral fracture

(PPS)
Hazard ratio ± 95%CI

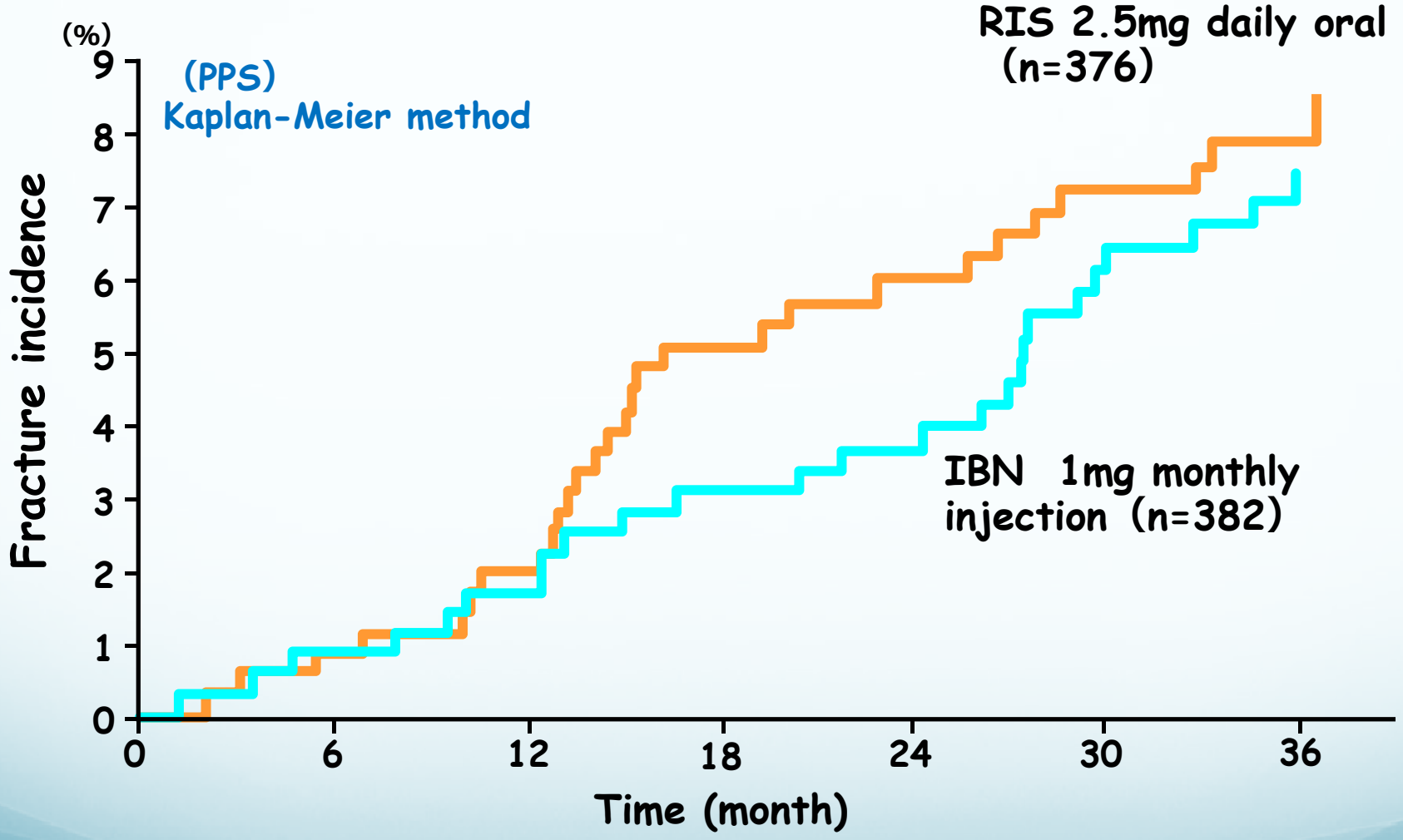


Parameter	Hazard ratio	95% CI
IBN 1mg monthly injection versus RIS 2.5mg daily oral	0.88	0.61-1.27

Ito M, et al. Osteoporosis Int 2013;24 (Issue 1 Supplement), abst P396
Nakamura T, et al, Calcif Tissue Int 2013; 93: 137-146

Phase II/III study in Japan (MOVER study)

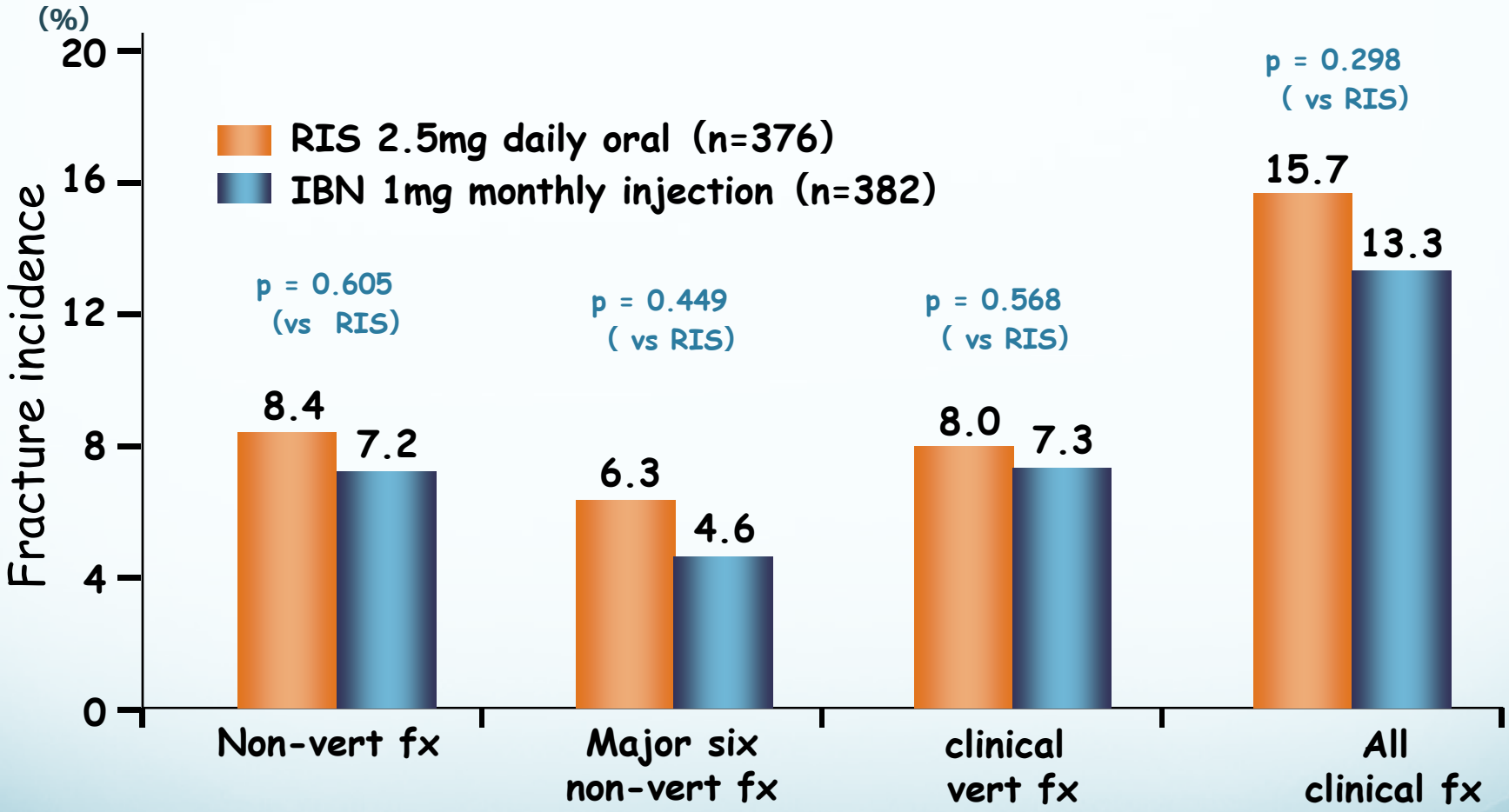
Efficacy on non-vertebral fracture: Estimated incidence of osteoporotic non-vertebral fractures



Nakamura T, et al, Calcif Tissue Int 2013; 93: 137-146
Chugai internal documents

Phase II/III study in Japan (MOVER study)

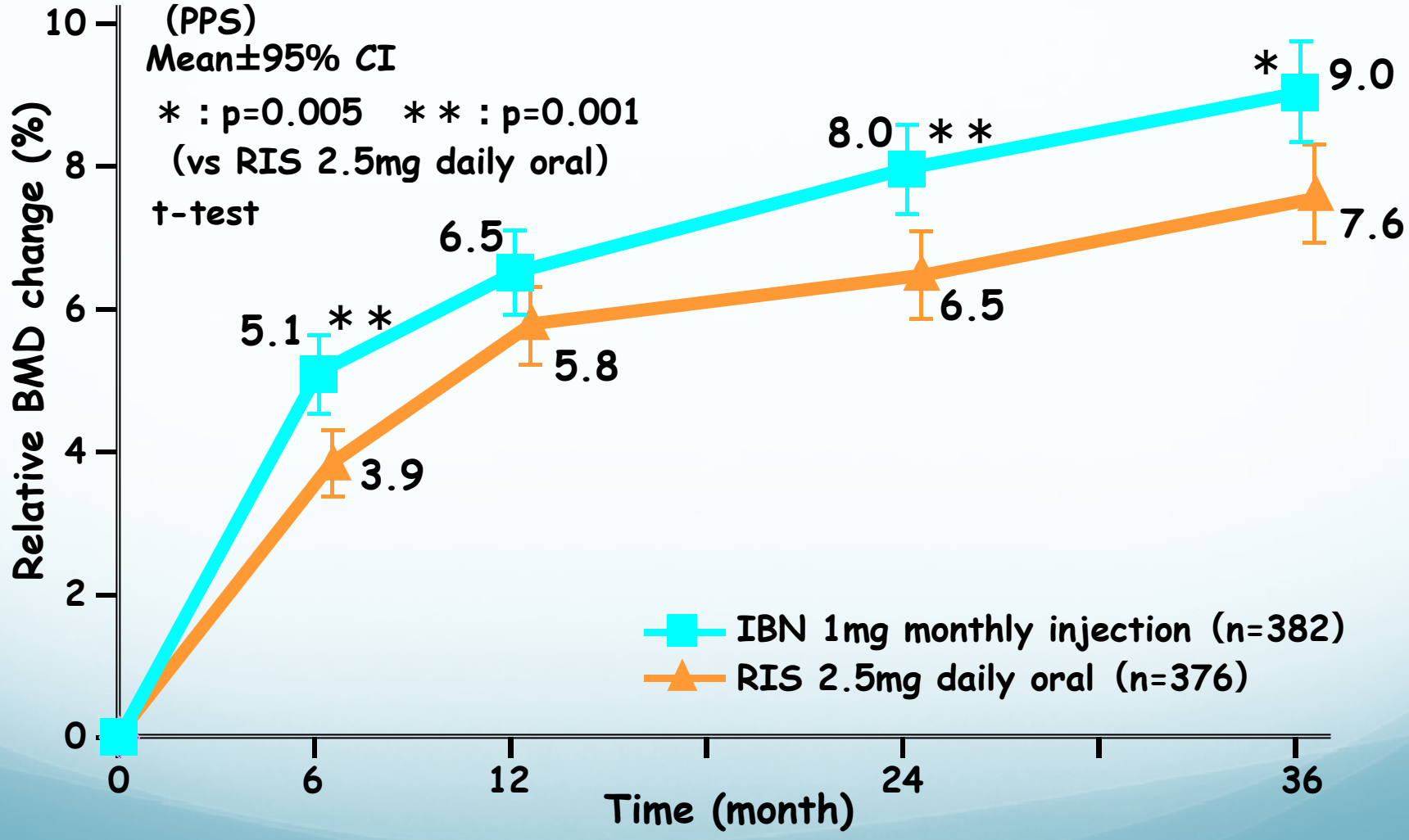
Efficacy on fracture:
Incidence of osteoporotic fractures through three years



Nakamura T, et al, Calcif Tissue Int 2013; 93: 137-146

Phase II/III study in Japan (MOVER study)

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



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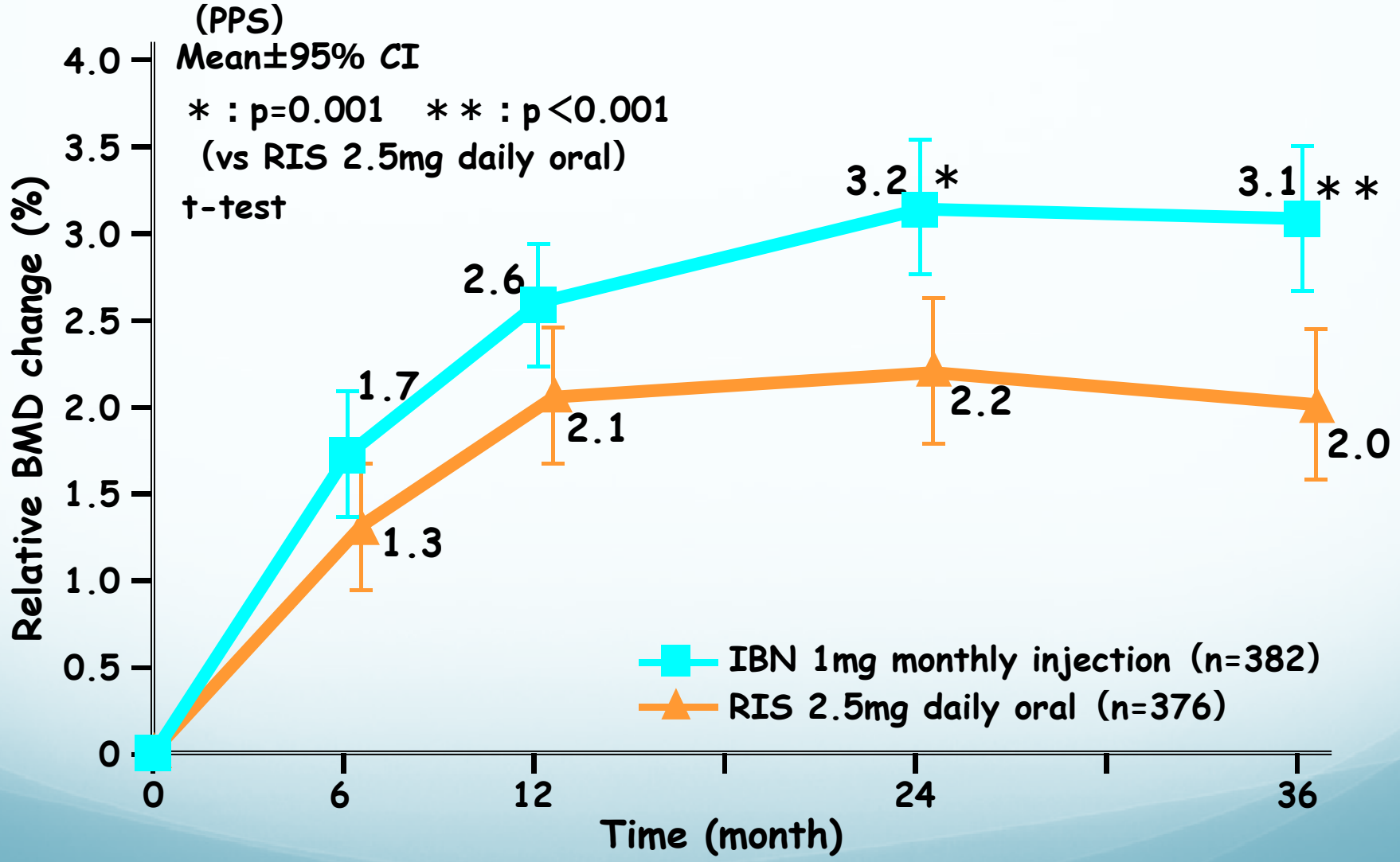
Phase II/III study in Japan (MOVER study)

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



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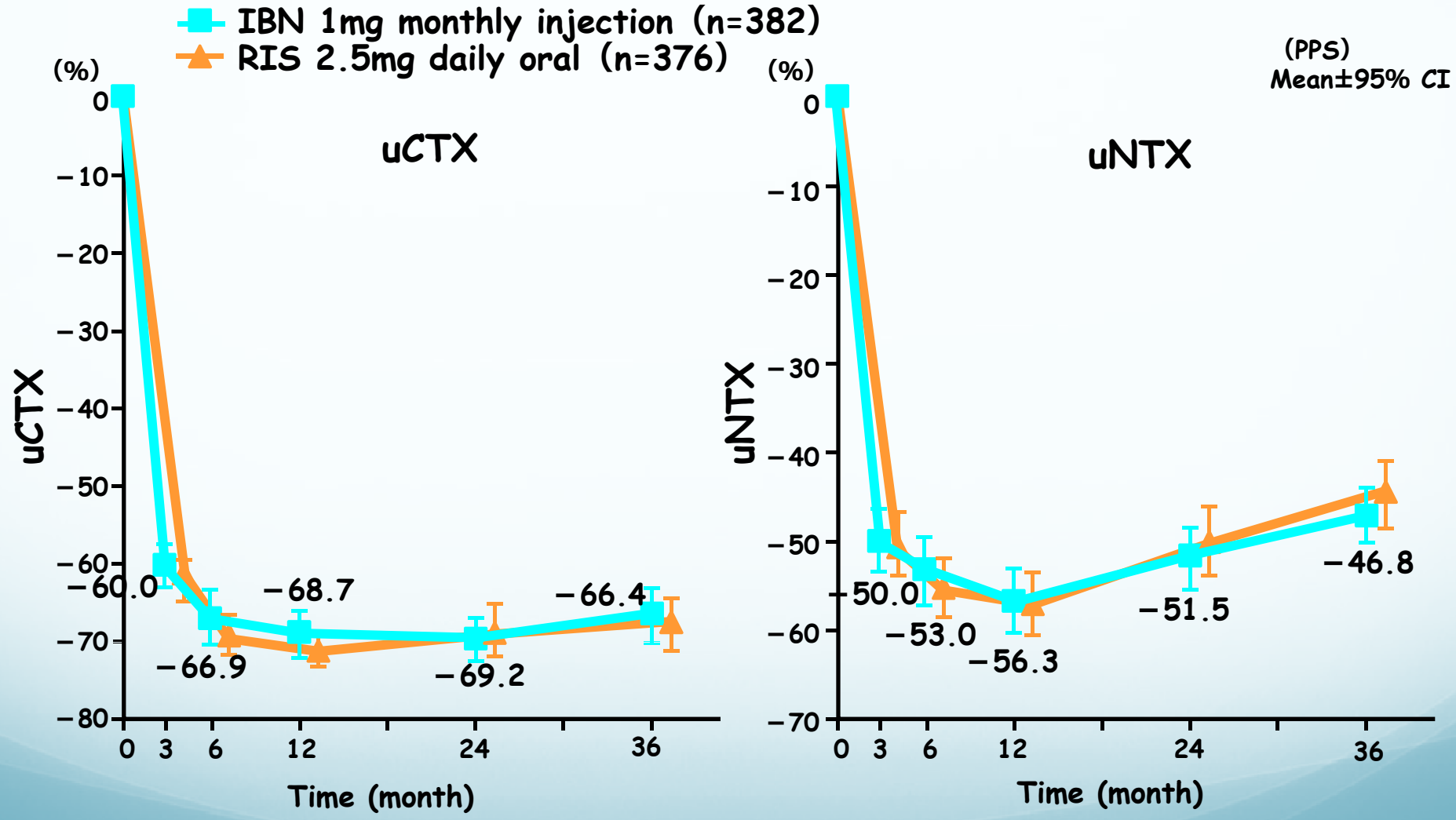
Nakamura T, et al, Calcif Tissue Int 2013; 93: 137-146

Phase II/III study in Japan (MOVER study)

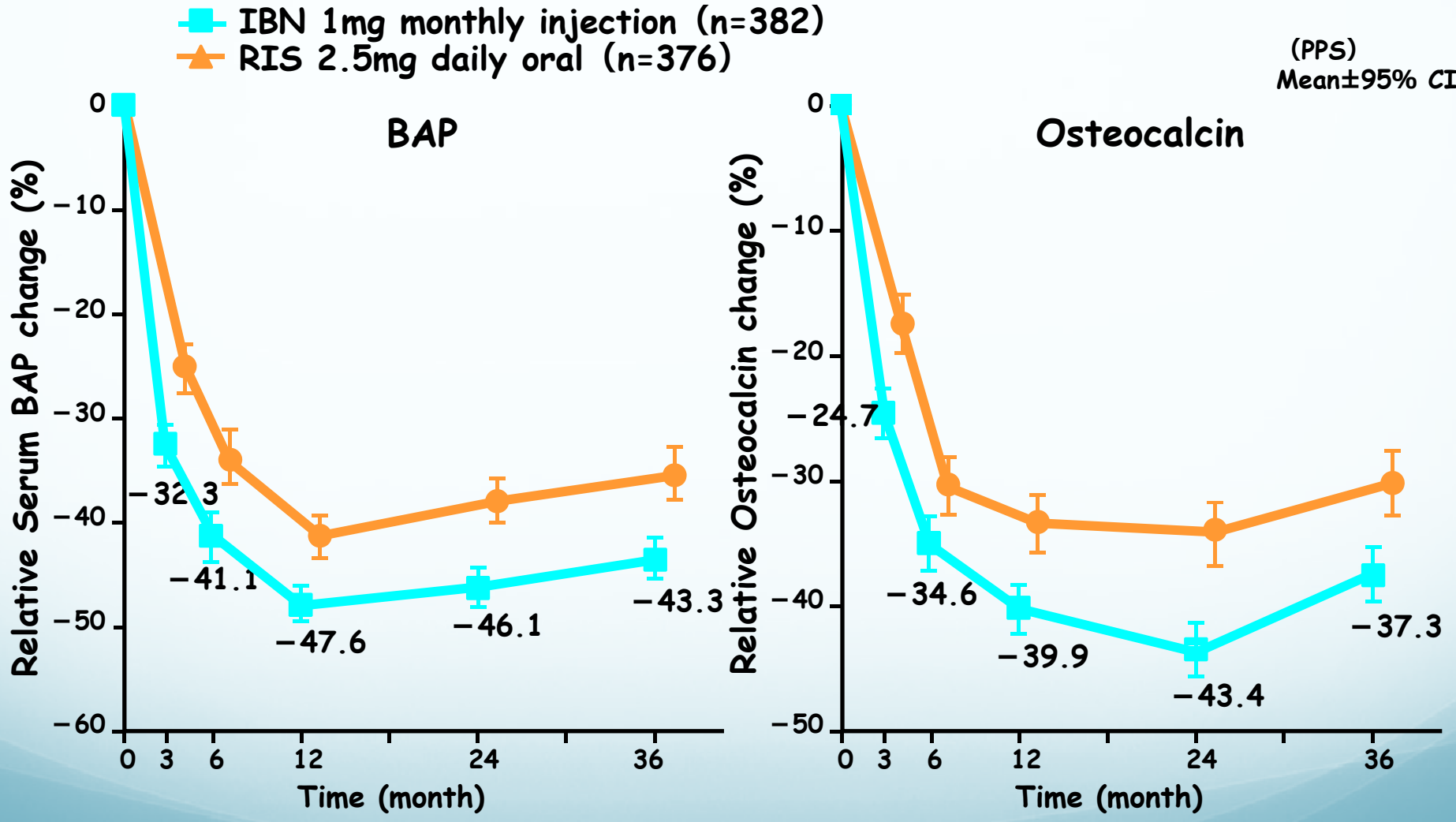
Efficacy on bone absorption markers: Relative change from baseline in urinary CTX and NTX



Ito M, et al. Osteoporosis Int 2013;24 (Issue 1 Supplement), abst P396
Nakamura T, et al, Calcif Tissue Int 2013; 93: 137-146

Phase II/III study in Japan (MOVER study)

Efficacy on bone formation markers: Relative change from baseline in serum BAP and OC



Nakamura T, et al, Calcif Tissue Int 2013; 93: 137-146
Chugai internal documents

Phase II/III study in Japan (MOVER study)

Adverse events of interest

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

GI : gastrointestinal, APR : acute phase reaction

Nakamura T, et al, Calcif Tissue Int 2013; 93: 137-146 (revised)

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

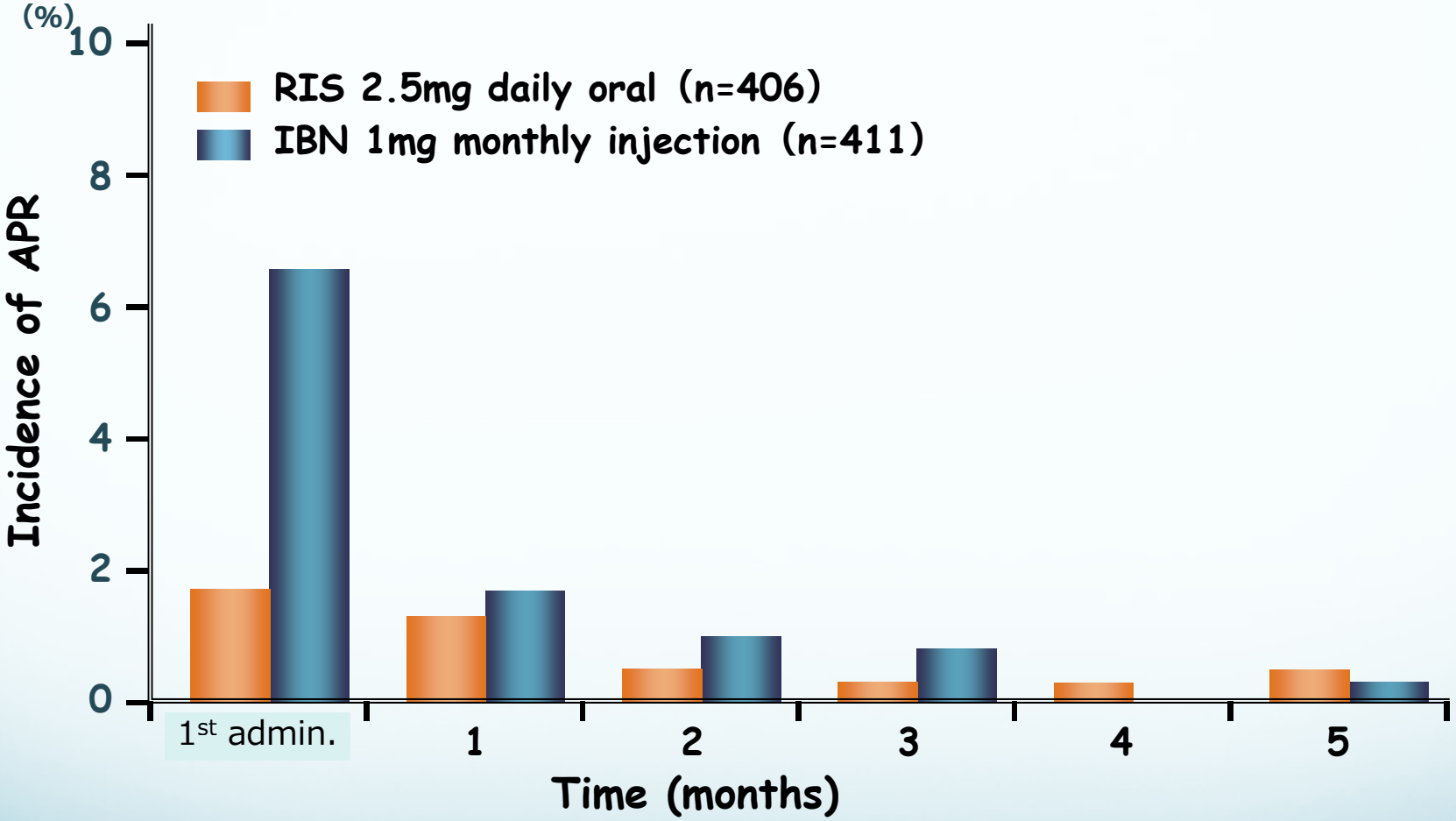
	Risedronate 2.5mg daily oral (n=406)	Ibandronate 1mg monthly injection (n=411)
APR related	20 (4.9)	46 (11.2)

n (%)

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

Nakamura T, et al, Calcif Tissue Int 2013; 93: 137-146
Chugai internal documents

Change in the incidence of acute phase reactions



Incidences of APRs decreased after 2nd dosing.
2nd – 3rd: 0.5-2.2%, 4th or more: 0-0.8%

Nakamura T, et al, Calcif Tissue Int 2013; 93: 137-146

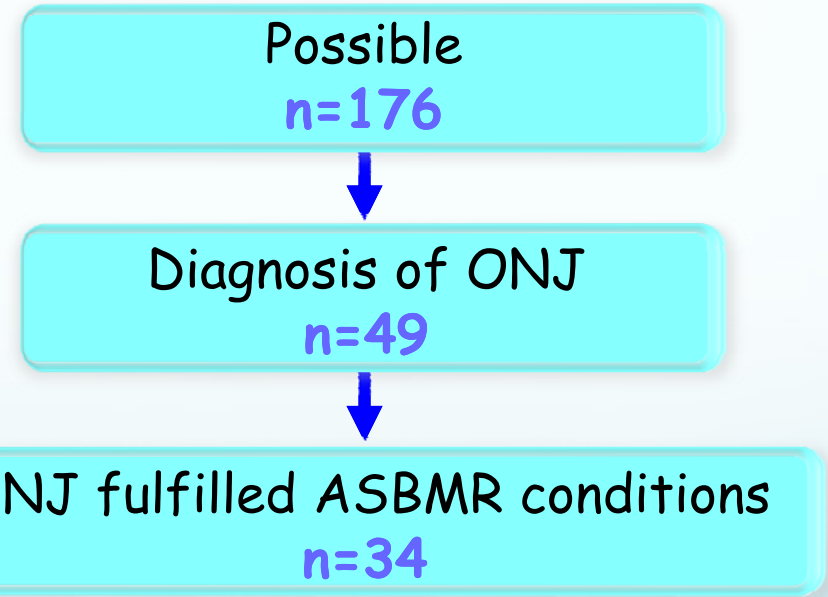
Reports of Osteonecrosis of the Jaw (ONJ) (overseas : clinical trial/spontaneous reports/literature)

Clinical trial

Maximally 5-year administration of Ibandronate

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

Spontaneous reports/ literature



"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."

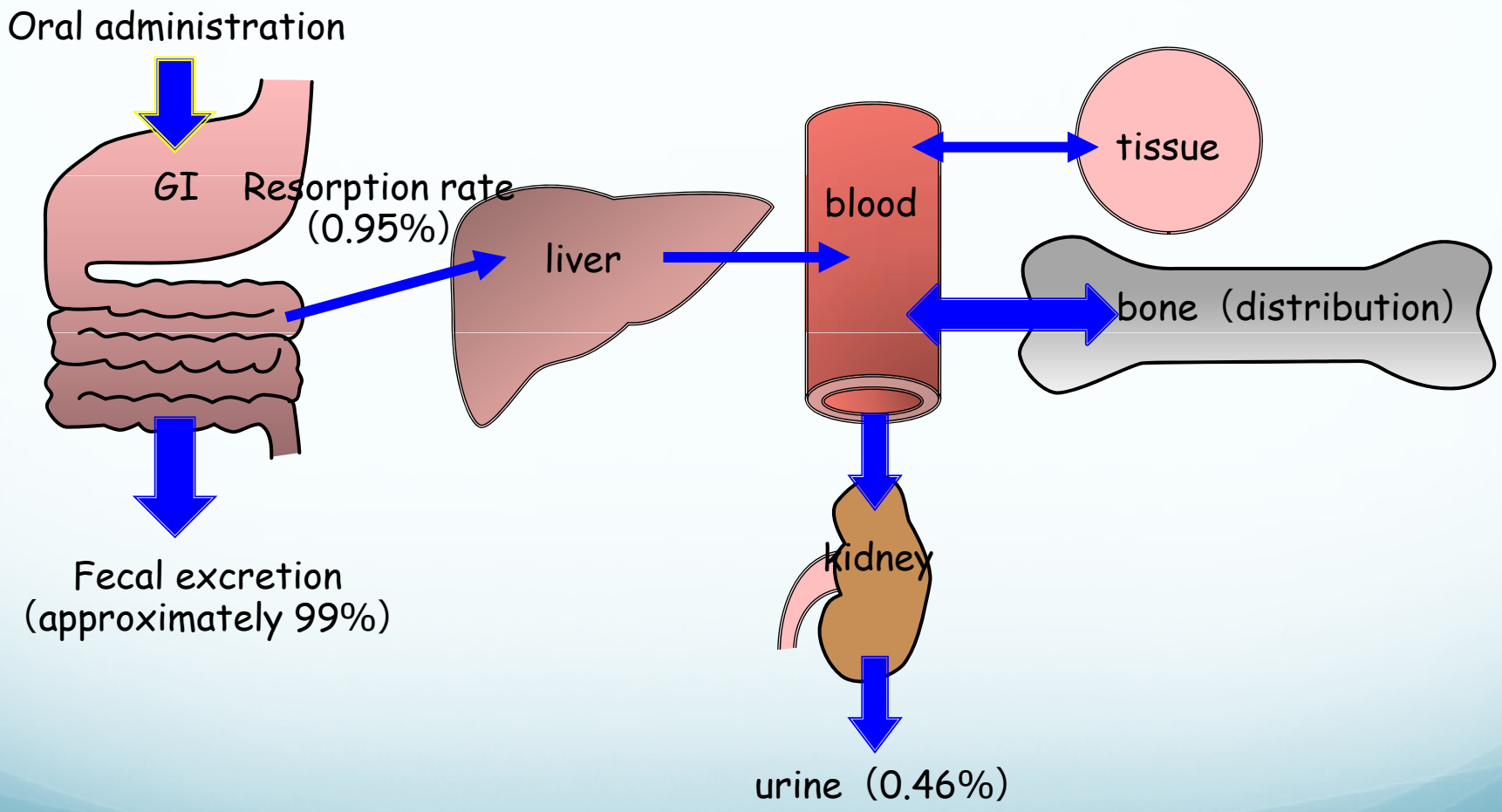
Atypical femoral fracture and ONJ (Ibandronate)

- ATF fullfiled all ASBMR conditions (n=8)
  - 0.3 / 1,000,000 patients
- ONJ fullfiled all ASBMR conditions (n=34)
  - 2.1 / 1,000,000 patients

"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."

Why we need monthly injection bisphosphonate?

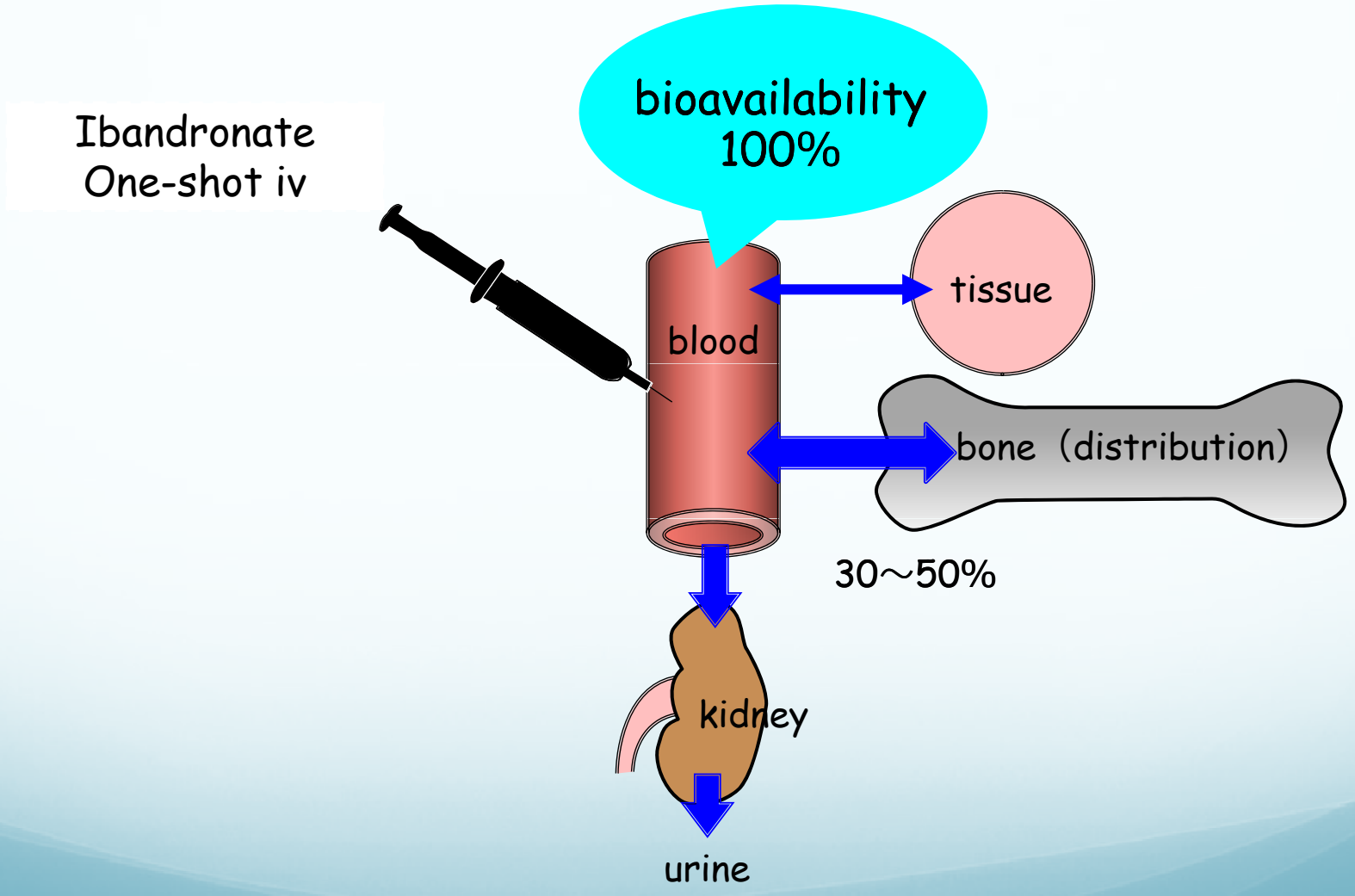
Pharmacokinetics of Oral Bisphosphonate (Rats)



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)



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