Title: Special Drug Use Surveillance on Fracture Incidence during 36-Month Treatment

NCT Number: NCT02106442

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This may include, but is not limited to, redaction of the following:

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- Patient identifiers within the text, tables, or figures or in by-patient data listings.
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Note; This document was translated into English as the language on original version was Japanese.

Special Drug Use Surveillance Protocol

Benet 75 mg Tablets

Special Drug Use Surveillance on Fracture Incidence during 36-Month Treatment

Version number	**4th version**
Date of preparation	**2 June 2017**
Sponsor	**Takeda Pharmaceutical Co., Ltd.**

Table of Contents

1.0 Background of the Surveillance

Data on the incidence of vertebral fracture during 96-week treatment with Benet 2.5 mg Tablets administered once daily were collected in a post-marketing clinical study. On the other hand, since the fracture prevention efficacy of Benet 75 mg Tablets (hereinafter referred to as Benet) has not been evaluated, a special drug use surveillance (hereinafter referred to as the surveillance) is planned to evaluate the efficacy (e.g., fracture incidence, percent change in bone mineral density) and safety of 36-month treatment with Benet in osteoporotic patients in clinical settings.

This surveillance will be conducted in compliance with the ministerial ordinance on Good Post-Marketing Study Practice (GPSP) and related regulatory requirements.

2.0 Objectives of the Surveillance

To evaluate the efficacy (e.g., fracture incidence, percent change in bone mineral density) and safety of 36-month treatment with Benet in osteoporotic patients in clinical settings

3.0 Planned Sample Size and Rationale

3.1 Planned Sample Size

250 patients treated with Benet

(PPD will collect another 250 patients treated with Actonel 75 mg Tablets, which contains the same active ingredient as Benet, resulting in a total of 500 patients.)

3.2 Rationale

In a Japanese clinical study of the approved formulation (2.5 mg tablets used on a daily basis) with the same active ingredient as Benet (study number: NE-58095/CCT-005) assessing fracture incidence, the number of subjects included in analysis was 273 with a treatment duration of 2 years and a discontinuation/dropout rate of 26.7%. Approximately 250 patients may be necessary to analyze data by reference to this clinical study.

Since fracture incidence will be assessed in clinical settingse during a 3-year observation period in the surveillance, the discontinuation/dropout rate is expected to be higher than in the clinical study. With an estimated dropout rate of 50%, therefore, the sample size of the surveillance is set at 500 patients, including those to be treated with Actonel Tablets.

4.0 Surveillance Population

Osteoporotic patients will be included in the surveillance. The selection criteria listed below should also be met, and the precautions concerning indications in the package insert should be referred to.

Selection criteria

Patients meeting all of the following criteria will be included in the surveillance:

1) A patient with evidence of 1 to 4 fractures from the fourth thoracic vertebra to the fourth lumbar vertebra (T_4 to L_4) provided by thoracic and lumbar spinal radiography performed before the start of the surveillance (within 3 months before the start of prescription of Benet)
2) A patient aged 50 years or older (menopausal if female)
3) An outpatient who can walk

5.0 Dosage and Administration in Surveillance Patients

Patients will orally receive 75 mg of sodium risedronate with sufficient water (approximately 180 mL) upon awakening once a month. They should not lie, consume food or beverages except water, or orally receive any other drugs for at least 30 minutes after dosing. In addition, the precautions concerning dosage and administration in the package insert should be referred to.

6.0 Planned Number of Medical Institutions by Department

Orthopedics, internal medicine, and other departments Approximately 50 to 85 medical institutions

7.0 Surveillance Method

7.1 Observation Period

36 months

7.2 Request to and Contract with the Study Site

This surveillance will be conducted using a paper case report form (CRF). A representative of Takeda Pharmaceutical Co., Ltd. (hereinafter referred to as Takeda's representative) will explain the objectives, contents, and methods of the surveillance to the investigator based on "Request for cooperation for special drug use surveillance," "Implementation outline," "Patient registration form (sample)," and "Case report form (sample)" to enter into a written contract with the study site and request the study site to conduct a surveillance within a specified period.

7.3 Method of Patient Registration

Patients will be registered using the central registration method via fax. After the start of the contract with the study site, the investigator shall register each surveillance patient for whom Benet is prescribed by faxing a patient registration form containing patient registration information (refer to Section 9.1) to the central registration center (refer to Section 11.3) within 15 days after the first prescription of Benet (day of the first prescription designated as day 1 and day following the day of the first prescription designated as 2 days after prescription). No patient can be registered before Benet is actually prescribed. Patients determined by the central registration center to be ineligible for any reason cannot be

registered. The investigator shall register a new patient using a new patient registration form supplied by Takeda's representative.

There are three CRFs per patient: CRF I (from the start of treatment to Month 12), CRF II (from Months 13 to 24), and CRF III (from Months 25 to 36).

Takeda's representative will supply a CRF I, which will be issued after the central registration center decides to register the relevant patient, to the investigator. A CRF II will be issued after completion of CRF I-related surveillance. Similarly, a CRF III will be issued after completion of CRF II-related surveillance.

7.4 Completion and Submission of Case Report Form

For each of all enrolled patients, the investigator shall complete and submit a CRF to Takeda Pharmaceutical within approximately 1 month after the end of the observation period (12 months after the start of Benet treatment for CRF I, 24 months after the start of Benet treatment for CRF II, and 36 months after the start of Benet treatment for CRF III).

For patients discontinued from Benet treatment for any reason during the observation period, the investigator shall complete and submit a CRF to Takeda Pharmaceutical within approximately 1 month after the end of required observation. For any patient discontinued from Benet treatment due to an adverse event, the investigator shall complete and submit a CRF to Takeda Pharmaceutical after monitoring the patient as long after discontinuation of treatment as possible until the adverse event is confirmed to have resolved or be resolving.

7.5 Actions to be Taken in Case of Serious Adverse Events

The investigator shall immediately communicate any serious adverse event in the observation period to Takeda's representative. In addition, the investigator shall provide detailed information at the request of Takeda's representative.

8.0 Planned Surveillance Period

Surveillance period: From May 2013 to 30 April 2018

Patient registration period: From May 2013 to 31 October 2014[Note)]

[Note)] Patient registration (receipt of a patient registration form via fax) will not be accepted on 1 November 2014 onwards even if Benet is prescribed by 31 October 2014.

If the total number of patients enrolled in the surveillance by Takeda Pharmaceutical Co., Ltd. and PPD reaches 500 before 31 October 2014, acceptance of registration may be terminated before the end of the patient registration period.

9.0 Surveillance Items

The investigator shall enter the items listed below into the patient registration form and the CRF. The surveillance schedule is presented in Appendix.

9.1 Entries into the Patient Registration Form

1) Surveillance items

Name of the medical institution, name of a physician who completes the patient registration form, date of the first prescription of Benet, date of the scheduled first dosing of Benet, patient identification number, patient initials, sex, date of birth, assessment based on the selection criteria

2) Time points of surveillance

At patient registration

9.2 Entries into the Case Report Form

9.2.1 Cover of the Case Report Form

Date of final entry into the CRF, name of a physician who completes the CRF

9.2.2 Patient Baseline Characteristics

1) Surveillance items

Disease to be treated, time of diagnosis of osteoporosis, body weight, predisposition to hypersensitivity (presence or absence and details), concurrent illness (presence or absence and details), medical history (except previous fracture) (presence or absence and details), risk factors for fracture [medical history (previous fracture), previous steroid use, parental history of femur fracture], drinking history, smoking history

2) Time points of surveillance

At the start of Benet treatment

9.2.3 Treatment Given

1) Surveillance items

Treatment status of Benet (date of dosing indicated by a prescribing physician, patient's treatment status, reason for discontinuation of treatment, and date of discontinuation), treatment status of osteoporosis drug (including calcium and vitamin D) other than Benet given from 3 months before the start of Benet treatment to 36 months after the start of treatment (or discontinuation of treatment) (presence or absence, name of the drug, daily dose, and duration of treatment), treatment status of steroid (presence or absence, name of the drug, daily dose, duration of treatment, and purpose of treatment), treatment status of concomitant medication other than osteoporosis drugs and steroids* (presence or absence, name of the drug, and purpose of treatment), presence or absence of concomitant therapy for osteoporosis (physical therapy, other concomitant therapy)

* The daily dose and duration of treatment will be confirmed in the following situations:

- An adverse event occurs; or
- The sponsor considers it necessary to collect this information.

2) Time points of surveillance

Period from the start of Benet treatment to 36 months after the start of treatment (or

discontinuation of treatment)

9.2.4 Tests/Observations

9.2.4.1 Laboratory Tests

1) Surveillance items

If laboratory testing such as hematology or blood chemistry is performed during Benet treatment, any abnormal change in laboratory parameter will be entered into the adverse event column in the CRF. In addition, only relevant laboratory values will be entered into the column for adverse event-related clinically significant change in laboratory parameter.

2) Time points of surveillance

Time points of test from the start of Benet treatment to 36 months after the start of treatment (or discontinuation of treatment)

9.2.4.2 Bone Mineral Density

1) Surveillance items

Lumbar dual-energy x-ray absorptiometry (DXA), proximal femur DXA, radius DXA/peripheral quantitative computed tomography (pQCT), calcaneal DXA/quantitative ultrasound (QUS), second metacarpal bone microdensitometry (MD)/computed x-ray densitometry (CXD)/digital image processing (DIP)

2) Time points of surveillance

At the start of Benet treatment (within 3 months before the start of Benet treatment), 6*, 12, 18*, 24, 30*, and 36 months after the start of treatment (or discontinuation of treatment), and time points of test during the observation period

* Performed if necessary

9.2.4.3 Bone Turnover Markers

1) Surveillance items

Bone resorption markers:

Serum N-telopeptide of type I collagen (NTX), serum C-telopeptide of type I collagen (CTX), serum tartrate-resistant acid phosphatase (TRACP-5b), urinary NTX, urinary CTX, urinary deoxypyridinoline (DPD)

Bone formation markers:

Serum bone-specific alkaline phosphatase (BAP), serum N-propeptide of type I procollagen (P1NP)

Bone matrix-related marker:

Serum undercarboxylated osteocalcin (ucOC)

2) Time points of surveillance

At the start of Benet treatment (within 1 month before the start of Benet treatment), 6*, 12, 18*, 24, 30*, and 36 months after the start of treatment (or discontinuation of treatment), and time points of test during the observation period

* Performed if necessary

9.2.5 Assessment of Vertebral Fracture

1) Surveillance items

Vertebral fracture before the start of Benet treatment (baseline) will be confirmed, and the date of radiography, radiographic location, and location of vertebral fracture will be entered into the CRF. Then, the presence or absence and location of new vertebral fracture, presence or absence of worsening of prevalent vertebral fracture, and presence or absence of apparent trauma during treatment and at the end of the observation period (or discontinuation of treatment) relative to baseline will be entered into the CRF.

2) Time points of surveillance

At the start of Benet treatment, 12, 24, and 36 months after the start of treatment (or discontinuation of treatment), and when vertebral fracture is suspected during the observation period

9.2.6 Assessment of Non-vertebral Fracture

1) Surveillance items

Non-vertebral fracture during Benet treatment involving the femur, wrist, forearm, upper arm, pelvis, lower limb, etc. will be entered into the CRF. Confirmed non-vertebral fracture will be handled as an adverse event, and the fracture site, date of fracture (date of onset), presence or absence and details of apparent trauma, seriousness, reason for seriousness, presence or absence of discontinuation of Benet treatment, date of outcome assessment, outcome, and causal relationship to Benet will be entered into the CRF.

2) Time points of surveillance

12, 24, and 36 months after the start of Benet treatment (or discontinuation of treatment) and when non-vertebral fracture is confirmed during the observation period

9.2.7 Clinical Findings

1) Surveillance items

Height, low back pain

2) Time points of surveillance

Time points of medical examination at the start of treatment and 3, 6, 12, 18, 24, 30, and 36 months after the start of treatment (or discontinuation of treatment)

Only at the start of treatment and 12, 24, and 36 months after the start of treatment (or discontinuation of treatment) for height

9.3 Adverse Events (AEs)

1) Surveillance items

Presence or absence of AE (refer to Table 1), AE term, date of onset, seriousness and reason for seriousness (refer to Table 2), presence or absence of discontinuation of Benet treatment, date of outcome assessment, outcome, causal relationship to Benet* (refer to Table 3)

Patients with "not resolved" or "unknown" outcome or "unevaluable" causal relationship should be followed up wherever possible.

Any new vertebral fracture or worsening of prevalent fracture during treatment will be entered into the adverse event column.

The following events will also be entered into the adverse event column: upper gastrointestinal disorder, hepatic function disorder/jaundice, osteonecrosis of jaw/osteomyelitis of jaw, atypical fracture of subtrochanteric section of femur or shaft of proximal femur, musculoskeletal pain, atrial fibrillation, esophageal carcinoma, and gastrointestinal disorders including diarrhea.

* For the causal relationship to Benet, the rationale for "not related" and the reason for "unevaluable" shall be collected.

2) Time points of surveillance

12, 24, and 36 months after the start of Benet treatment (or discontinuation of treatment) and when an AE is confirmed during the observation period

Table 1 Definition of adverse events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug. The following are also handled as AEs: • Symptoms and so forth that occur in infants breast-fed by their mothers under treatment with a drug • Symptoms and so forth that occur in children treated with a drug • Symptoms and so forth that occur after administration or self-administration of a drug at higher doses than the approved dose

Table 2 Criteria for assessing seriousness

An AE satisfying any of the following is assessed as serious: 1. Results in death (death) 2. Is life-threatening (risk of death) 3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization) 4. Results in persistent or significant disability/incapacity (disability) 5. Leads to a congenital anomaly/birth defect (congenital anomaly) 6. Otherwise, is an important medical event (for instance, bronchospasm requiring short-term intensive care in an emergency room), including AEs in Takeda Medically Significant AE List <u>Takeda Medically Significant AE List</u> • Acute respiratory failure / acute respiratory distress syndrome (ARDS) • Anaphylactic shock

• Torsade de pointes / ventricular fibrillation / ventricular tachycardia
• Acute renal failure
• Malignant hypertension • Pulmonary hypertension
• Convulsive seizures (including convulsions and epilepsy)
• Pulmonary fibrosis (including interstitial pneumonia)
• Agranulocytosis
• Malignant syndrome / malignant hyperthermia
• Aplastic anemia
• Spontaneous abortion / stillbirth and fetal death
• Toxic epidermal necrolysis / mucocutaneous ocular syndrome (Stevens-Johnson syndrome)
• Confirmed or suspected transmission of infectious agent by a medicinal product
• Hepatic necrosis • Confirmed or suspected endotoxin shock
• Acute liver failure

Table 3 Criteria for assessing the relationship of each adverse event to Benet

Assessment	Criteria for assessment
Related	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments, may also be responsible
Not related	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments
Unevaluable	Information necessary for evaluation, including temporal sequence from administration of a drug (including the course after withdrawal of the drug), underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments, is not sufficient.

10.0 Analysis Items and Methods

Data from patients enrolled for Benet and Actonel 75 mg Tablets will be combined for analysis.

10.1 Matters on Patient Composition

The number of enrolled patients, number of patients for whom the CRF is collected, number of patients included in safety/efficacy analysis, number of patients excluded from analysis, and reason for exclusion will be tabulated.

10.2 Patient Baseline Characteristics

Patient baseline characteristics, including age, sex, duration of disease, height, body weight,

predisposition to hypersensitivity, and concurrent illness, will be tabulated.

10.3 Treatment Compliance Status

The treatment compliance status will be tabulated based on the date of dosing indicated by a prescribing physician and patient's treatment status (date of dosing).

10.4 Matters on Safety

For the safety population, the incidence of AEs reported during the observation period will be tabulated by causal relationship to Benet, type, seriousness, and time of onset.

10.5 Matters on Efficacy

For the efficacy population, data will be tabulated as described below.

10.5.1 Primary Endpoint

Incidence of vertebral fracture

10.5.2 Secondary Endpoints

Incidence of non-vertebral fracture, percent change in bone mineral density, percent changes in bone turnover markers, changes in height and low back pain over time

10.6 Analysis Methods

1) For vertebral fracture and non-vertebral fracture, the number and proportion of patients with fracture and cumulative incidence at each time point, including the final time point, will be calculated.
2) For the other endpoints, significance test will be performed by one-sample t-test, one-sample Wilcoxon test, or chi-square test, depending on the nature of the analysis item.

11.0 Surveillance Organization

11.1 Surveillance Administrative Manager

PPD

11.2 Medical Expert

To give advice on surveillance planning, publication of results, etc.

PPD

11.3 Central Registration Center

PPD

12.0 Name, Address, and Scope of Operations of Contract Research Organizations (CROs)

13.0 Other Necessary Matters

13.1 Revision of the Protocol

During the surveillance, attention will be paid to comprehend the status of progression of the surveillance, presence or absence of adverse drug reactions (ADRs) that are unexpected based on the precautions/serious ADRs, presence or absence of increased incidence of certain ADRs, and appropriateness of surveillance items, and this protocol will be reviewed and revised if necessary. If partial change to dosage and administration or indications is approved during the surveillance, the necessity of revising the protocol will be discussed if necessary, and the protocol will be revised as needed.

13.2 Actions to be Taken for Problems and Questions

If any safety or efficacy problem is detected, data will be carefully examined to discuss measures.

Appendix　Surveillance schedule

Surveillance item \ Time point of surveillance		Observation period									
		At patient registration	At the start of treatment	After 3 months of treatment	After 6 months of treatment	After 12 months of treatment	After 18 months of treatment	After 24 months of treatment	After 30 months of treatment	After 36 months of treatment	At discontinuation of treatment
Patient registration	Date of the first prescription of Benet	○									
	Date of the scheduled first dosing of Benet	○									
	Patient identification number	○									
	Patient initials	○									
	Sex	○									
	Date of birth	○									
	Assessment based on the selection criteria	○									
Patient baseline characteristics	Disease to be treated		○								
	Time of diagnosis of osteoporosis		○								
	Body weight		○								
	Predisposition to hypersensitivity		○								
	Concurrent illness		○								
	Medical history		○								
	Risk factors for fracture		○								
Treatment given	Treatment status of Benet		←			○				→	○
	Treatment status of concomitant medication		←			○				→	○
	Concomitant therapy for osteoporosis		←			○				→	○
Tests/observations	Bone mineral density		○		(○)	○	(○)	○	(○)	○	○
	Bone turnover markers		○		(○)	○	(○)	○	(○)	○	○
	Assessment of vertebral fracture		○			○		○		○	○
	Assessment of non-vertebral fracture		←			○				→	○
	Clinical findings (height*, low back pain)		○	○	○	○	○	○	○	○	○
	Adverse event		←			○				→	○

○: Surveyed/examined/observed

(○): Examined if necessary

←—— ○ ——→: Surveyed/examined/observed throughout the period

* Height will be measured at the start of treatment and 12, 24, and 36 months after the start of treatment (or discontinuation of treatment).

Special Drug Use Surveillance Protocol

Benet 75 mg Tablets

Special Drug Use Surveillance on Fracture Incidence during 36-Month Treatment

Version number	**3rd version**
Date of preparation	**1 April 2015**
Sponsor	**Takeda Pharmaceutical Co., Ltd.**

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2) A patient aged 50 years or older (menopausal if female)
3) An outpatient who can walk

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Patients will be registered using the central registration method via fax. After the start of the contract with the study site, the investigator shall register each surveillance patient for whom Benet is prescribed by faxing a patient registration form containing patient registration information (refer to Section 9.1) to the central registration center (refer to Section 11.3) within 15 days after the first prescription of Benet (day of the first prescription designated as day 1 and day following the day of the first prescription designated as 2 days after prescription). No patient can be registered before Benet is actually prescribed. Patients determined by the central registration center to be ineligible for any reason cannot be

registered. The investigator shall register a new patient using a new patient registration form supplied by Takeda's representative.

There are three CRFs per patient: CRF I (from the start of treatment to Month 12), CRF II (from Months 13 to 24), and CRF III (from Months 25 to 36).

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7.4 Completion and Submission of Case Report Form

For each of all enrolled patients, the investigator shall complete and submit a CRF to Takeda Pharmaceutical within approximately 1 month after the end of the observation period (12 months after the start of Benet treatment for CRF I, 24 months after the start of Benet treatment for CRF II, and 36 months after the start of Benet treatment for CRF III).

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The investigator shall immediately communicate any serious adverse event in the observation period to Takeda's representative. In addition, the investigator shall provide detailed information at the request of Takeda's representative.

8.0 Planned Surveillance Period

Surveillance period: From May 2013 to 30 April 2018

Patient registration period: From May 2013 to 31 October 2014[Note)]

[Note)] Patient registration (receipt of a patient registration form via fax) will not be accepted on 1 November 2014 onwards even if Benet is prescribed by 31 October 2014.

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9.0 Surveillance Items

The investigator shall enter the items listed below into the patient registration form and the CRF. The surveillance schedule is presented in Appendix.

9.1 Entries into the Patient Registration Form

1) Surveillance items

Name of the medical institution, name of a physician who completes the patient registration form, date of the first prescription of Benet, date of the scheduled first dosing of Benet, patient identification number, patient initials, sex, date of birth, assessment based on the selection criteria

2) Time points of surveillance

At patient registration

9.2 Entries into the Case Report Form

9.2.1 Cover of the Case Report Form

Date of final entry into the CRF, name of a physician who completes the CRF

9.2.2 Patient Baseline Characteristics

1) Surveillance items

Disease to be treated, time of diagnosis of osteoporosis, body weight, predisposition to hypersensitivity (presence or absence and details), concurrent illness (presence or absence and details), medical history (except previous fracture) (presence or absence and details), risk factors for fracture [medical history (previous fracture), previous steroid use, parental history of femur fracture], drinking history, smoking history

2) Time points of surveillance

At the start of Benet treatment

9.2.3 Treatment Given

1) Surveillance items

Treatment status of Benet (date of dosing indicated by a prescribing physician, patient's treatment status, reason for discontinuation of treatment, and date of discontinuation), treatment status of osteoporosis drug (including calcium and vitamin D) other than Benet given from 3 months before the start of Benet treatment to 36 months after the start of treatment (or discontinuation of treatment) (presence or absence, name of the drug, daily dose, and duration of treatment), treatment status of steroid (presence or absence, name of the drug, daily dose, duration of treatment, and purpose of treatment), treatment status of concomitant medication other than osteoporosis drugs and steroids* (presence or absence, name of the drug, and purpose of treatment), presence or absence of concomitant therapy for osteoporosis (physical therapy, other concomitant therapy)

* The daily dose and duration of treatment will be confirmed in the following situations:

- An adverse event occurs; or
- The sponsor considers it necessary to collect this information.

2) Time points of surveillance

Period from the start of Benet treatment to 36 months after the start of treatment (or

discontinuation of treatment)

9.2.4 Tests/Observations

9.2.4.1 Laboratory Tests

1) Surveillance items

If laboratory testing such as hematology or blood chemistry is performed during Benet treatment, any abnormal change in laboratory parameter will be entered into the adverse event column in the CRF. In addition, only relevant laboratory values will be entered into the column for adverse event-related clinically significant change in laboratory parameter.

2) Time points of surveillance

Time points of test from the start of Benet treatment to 36 months after the start of treatment (or discontinuation of treatment)

9.2.4.2 Bone Mineral Density

1) Surveillance items

Lumbar dual-energy x-ray absorptiometry (DXA), proximal femur DXA, radius DXA/peripheral quantitative computed tomography (pQCT), calcaneal DXA/quantitative ultrasound (QUS), second metacarpal bone microdensitometry (MD)/computed x-ray densitometry (CXD)/digital image processing (DIP)

2) Time points of surveillance

At the start of Benet treatment (within 3 months before the start of Benet treatment), 6*, 12, 18*, 24, 30*, and 36 months after the start of treatment (or discontinuation of treatment), and time points of test during the observation period

* Performed if necessary

9.2.4.3 Bone Turnover Markers

1) Surveillance items

Bone resorption markers:

Serum N-telopeptide of type I collagen (NTX), serum C-telopeptide of type I collagen (CTX), serum tartrate-resistant acid phosphatase (TRACP-5b), urinary NTX, urinary CTX, urinary deoxypyridinoline (DPD)

Bone formation markers:

Serum bone-specific alkaline phosphatase (BAP), serum N-propeptide of type I procollagen (P1NP)

Bone matrix-related marker:

Serum undercarboxylated osteocalcin (ucOC)

2) Time points of surveillance

At the start of Benet treatment (within 1 month before the start of Benet treatment), 6*, 12, 18*, 24, 30*, and 36 months after the start of treatment (or discontinuation of treatment), and time points of test during the observation period

* Performed if necessary

9.2.5 Assessment of Vertebral Fracture

1) Surveillance items

Vertebral fracture before the start of Benet treatment (baseline) will be confirmed, and the date of radiography, radiographic location, and location of vertebral fracture will be entered into the CRF. Then, the presence or absence and location of new vertebral fracture, presence or absence of worsening of prevalent vertebral fracture, and presence or absence of apparent trauma during treatment and at the end of the observation period (or discontinuation of treatment) relative to baseline will be entered into the CRF.

2) Time points of surveillance

At the start of Benet treatment, 12, 24, and 36 months after the start of treatment (or discontinuation of treatment), and when vertebral fracture is suspected during the observation period

9.2.6 Assessment of Non-vertebral Fracture

1) Surveillance items

Non-vertebral fracture during Benet treatment involving the femur, wrist, forearm, upper arm, pelvis, lower limb, etc. will be entered into the CRF. Confirmed non-vertebral fracture will be handled as an adverse event, and the fracture site, date of fracture (date of onset), presence or absence and details of apparent trauma, seriousness, reason for seriousness, presence or absence of discontinuation of Benet treatment, date of outcome assessment, outcome, and causal relationship to Benet will be entered into the CRF.

2) Time points of surveillance

12, 24, and 36 months after the start of Benet treatment (or discontinuation of treatment) and when non-vertebral fracture is confirmed during the observation period

9.2.7 Clinical Findings

1) Surveillance items

Height, low back pain

2) Time points of surveillance

Time points of medical examination at the start of treatment and 3, 6, 12, 18, 24, 30, and 36 months after the start of treatment (or discontinuation of treatment)

Only at the start of treatment and 12, 24, and 36 months after the start of treatment (or discontinuation of treatment) for height

9.3 Adverse Events (AEs)

1) Surveillance items

Presence or absence of AE (refer to Table 1), AE term, date of onset, seriousness and reason for seriousness (refer to Table 2), presence or absence of discontinuation of Benet treatment, date of outcome assessment, outcome, causal relationship to Benet* (refer to Table 3)

Patients with "not resolved" or "unknown" outcome or "unevaluable" causal relationship should be followed up wherever possible.

Any new vertebral fracture or worsening of prevalent fracture during treatment will be entered into the adverse event column.

The following events will also be entered into the adverse event column: upper gastrointestinal disorder, hepatic function disorder/jaundice, osteonecrosis of jaw/osteomyelitis of jaw, atypical fracture of subtrochanteric section of femur or shaft of proximal femur, musculoskeletal pain, atrial fibrillation, esophageal carcinoma, and gastrointestinal disorders including diarrhea.

* For the causal relationship to Benet, the rationale for "not related" and the reason for "unevaluable" shall be collected.

2) Time points of surveillance

12, 24, and 36 months after the start of Benet treatment (or discontinuation of treatment) and when an AE is confirmed during the observation period

Table 1 Definition of adverse events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug. The following are also handled as AEs: • Symptoms and so forth that occur in infants breast-fed by their mothers under treatment with a drug • Symptoms and so forth that occur in children treated with a drug • Symptoms and so forth that occur after administration or self-administration of a drug at higher doses than the approved dose

Table 2 Criteria for assessing seriousness

An AE satisfying any of the following is assessed as serious: 1. Results in death (death) 2. Is life-threatening (risk of death) 3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization) 4. Results in persistent or significant disability/incapacity (disability) 5. Leads to a congenital anomaly/birth defect (congenital anomaly) 6. Otherwise, is an important medical event (for instance, bronchospasm requiring short-term intensive care in an emergency room), including AEs in Takeda Medically Significant AE List <u>Takeda Medically Significant AE List</u> • Acute respiratory failure / acute respiratory distress syndrome (ARDS) • Anaphylactic shock

• Torsade de pointes / ventricular fibrillation / ventricular tachycardia
• Acute renal failure
• Malignant hypertension • Pulmonary hypertension
• Convulsive seizures (including convulsions and epilepsy)
• Pulmonary fibrosis (including interstitial pneumonia)
• Agranulocytosis
• Malignant syndrome / malignant hyperthermia
• Aplastic anemia
• Spontaneous abortion / stillbirth and fetal death
• Toxic epidermal necrolysis / mucocutaneous ocular syndrome (Stevens-Johnson syndrome)
• Confirmed or suspected transmission of infectious agent by a medicinal product
• Hepatic necrosis • Confirmed or suspected endotoxin shock
• Acute liver failure

Table 3 Criteria for assessing the relationship of each adverse event to Benet

Assessment	Criteria for assessment
Related	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments, may also be responsible
Not related	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments
Unevaluable	Information necessary for evaluation, including temporal sequence from administration of a drug (including the course after withdrawal of the drug), underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments, is not sufficient.

10.0 Analysis Items and Methods

Data from patients enrolled for Benet and Actonel 75 mg Tablets will be combined for analysis.

10.1 Matters on Patient Composition

The number of enrolled patients, number of patients for whom the CRF is collected, number of patients included in safety/efficacy analysis, number of patients excluded from analysis, and reason for exclusion will be tabulated.

10.2 Patient Baseline Characteristics

Patient baseline characteristics, including age, sex, duration of disease, height, body weight,

predisposition to hypersensitivity, and concurrent illness, will be tabulated.

10.3 Treatment Compliance Status

The treatment compliance status will be tabulated based on the date of dosing indicated by a prescribing physician and patient's treatment status (date of dosing).

10.4 Matters on Safety

For the safety population, the incidence of AEs reported during the observation period will be tabulated by causal relationship to Benet, type, seriousness, and time of onset.

10.5 Matters on Efficacy

For the efficacy population, data will be tabulated as described below.

10.5.1 Primary Endpoint

Incidence of vertebral fracture

10.5.2 Secondary Endpoints

Incidence of non-vertebral fracture, percent change in bone mineral density, percent changes in bone turnover markers, changes in height and low back pain over time

10.6 Analysis Methods

1) For vertebral fracture and non-vertebral fracture, the number and proportion of patients with fracture and cumulative incidence at each time point, including the final time point, will be calculated.
2) For the other endpoints, significance test will be performed by one-sample t-test, one-sample Wilcoxon test, or chi-square test, depending on the nature of the analysis item.

11.0 Surveillance Organization

11.1 Surveillance Administrative Manager

PPD

11.2 Medical Expert

To give advice on surveillance planning, publication of results, etc.

PPD

11.3 Central Registration Center

PPD

12.0 Name, Address, and Scope of Operations of Contract Research Organizations (CROs)

13.0 Other Necessary Matters

13.1 Revision of the Protocol

During the surveillance, attention will be paid to comprehend the status of progression of the surveillance, presence or absence of adverse drug reactions (ADRs) that are unexpected based on the precautions/serious ADRs, presence or absence of increased incidence of certain ADRs, and appropriateness of surveillance items, and this protocol will be reviewed and revised if necessary. If partial change to dosage and administration or indications is approved during the surveillance, the necessity of revising the protocol will be discussed if necessary, and the protocol will be revised as needed.

13.2 Actions to be Taken for Problems and Questions

If any safety or efficacy problem is detected, data will be carefully examined to discuss measures.

Appendix　Surveillance schedule

Surveillance item \ Time point of surveillance		Observation period									
		At patient registration	At the start of treatment	After 3 months of treatment	After 6 months of treatment	After 12 months of treatment	After 18 months of treatment	After 24 months of treatment	After 30 months of treatment	After 36 months of treatment	At discontinuation of treatment
Patient registration	Date of the first prescription of Benet	○									
	Date of the scheduled first dosing of Benet	○									
	Patient identification number	○									
	Patient initials	○									
	Sex	○									
	Date of birth	○									
	Assessment based on the selection criteria	○									
Patient baseline characteristics	Disease to be treated		○								
	Time of diagnosis of osteoporosis		○								
	Body weight		○								
	Predisposition to hypersensitivity		○								
	Concurrent illness		○								
	Medical history		○								
	Risk factors for fracture		○								
Treatment given	Treatment status of Benet		←			○				→	○
	Treatment status of concomitant medication		←			○				→	○
	Concomitant therapy for osteoporosis		←			○				→	○
Tests/observations	Bone mineral density		○		(○)	○	(○)	○	(○)	○	○
	Bone turnover markers		○		(○)	○	(○)	○	(○)	○	○
	Assessment of vertebral fracture		○			○		○		○	○
	Assessment of non-vertebral fracture		←			○				→	○
	Clinical findings (height*, low back pain)		○	○	○	○	○	○	○	○	○
	Adverse event		←			○				→	○

○: Surveyed/examined/observed

(○): Examined if necessary

←—— ○ ——→: Surveyed/examined/observed throughout the period

* Height will be measured at the start of treatment and 12, 24, and 36 months after the start of treatment (or discontinuation of treatment).

Special Drug Use Surveillance Protocol

Benet 75 mg Tablets

Special Drug Use Surveillance on Fracture Incidence during 36-Month Treatment

Version number	**2nd version**
Date of preparation	**16 April 2013**
Sponsor	**Takeda Pharmaceutical Co., Ltd.**

Table of Contents

1.0 Background of the Surveillance

Data on the incidence of vertebral fracture during 96-week treatment with Benet 2.5 mg Tablets administered once daily were collected in a post-marketing clinical study. On the other hand, since the fracture prevention efficacy of Benet 75 mg Tablets (hereinafter referred to as Benet) has not been evaluated, a special drug use surveillance (hereinafter referred to as the surveillance) is planned to evaluate the efficacy (e.g., fracture incidence, percent change in bone mineral density) and safety of 36-month treatment with Benet in osteoporotic patients in clinical settings.

This surveillance will be conducted in compliance with the ministerial ordinance on Good Post-Marketing Study Practice (GPSP) and related regulatory requirements.

2.0 Objectives of the Surveillance

To evaluate the efficacy (e.g., fracture incidence, percent change in bone mineral density) and safety of 36-month treatment with Benet in osteoporotic patients in clinical settings

3.0 Planned Sample Size and Rationale

3.1 Planned Sample Size

250 patients treated with Benet

(PPD will collect another 250 patients treated with Actonel 75 mg Tablets, which contains the same active ingredient as Benet, resulting in a total of 500 patients.)

3.2 Rationale

In a Japanese clinical study of the approved formulation (2.5 mg tablets used on a daily basis) with the same active ingredient as Benet (study number: NE-58095/CCT-005) assessing fracture incidence, the number of subjects included in analysis was 273 with a treatment duration of 2 years and a discontinuation/dropout rate of 26.7%. Approximately 250 patients may be necessary to analyze data by reference to this clinical study.

Since fracture incidence will be assessed in clinical settingse during a 3-year observation period in the surveillance, the discontinuation/dropout rate is expected to be higher than in the clinical study. With an estimated dropout rate of 50%, therefore, the sample size of the surveillance is set at 500 patients, including those to be treated with Actonel Tablets.

4.0 Surveillance Population

Osteoporotic patients will be included in the surveillance. The selection criteria listed below should also be met, and the precautions concerning indications in the package insert should be referred to.

Selection criteria

Patients meeting all of the following criteria will be included in the surveillance:

1) A patient with evidence of 1 to 4 fractures from the fourth thoracic vertebra to the fourth lumbar vertebra (T_4 to L_4) provided by thoracic and lumbar spinal radiography performed before the start of the surveillance (within 3 months before the start of prescription of Benet)
2) A patient aged 50 years or older (menopausal if female)
3) An outpatient who can walk

5.0 Dosage and Administration in Surveillance Patients

Patients will orally receive 75 mg of sodium risedronate with sufficient water (approximately 180 mL) upon awakening once a month. They should not lie, consume food or beverages except water, or orally receive any other drugs for at least 30 minutes after dosing. In addition, the precautions concerning dosage and administration in the package insert should be referred to.

6.0 Planned Number of Medical Institutions by Department

Orthopedics, internal medicine, and other departments Approximately 50 to 85 medical institutions

7.0 Surveillance Method

7.1 Observation Period

36 months

7.2 Request to and Contract with the Study Site

This surveillance will be conducted using a paper case report form (CRF). A medical representative of Takeda Pharmaceutical Co., Ltd. (hereinafter referred to as Takeda's MR) will explain the objectives, contents, and methods of the surveillance to the investigator based on "Request for cooperation for special drug use surveillance," "Implementation outline," "Patient registration form (sample)," and "Case report form (sample)" to enter into a written contract with the study site and request the study site to conduct a surveillance within a specified period.

7.3 Method of Patient Registration

Patients will be registered using the central registration method via fax. After the start of the contract with the study site, the investigator shall register each surveillance patient for whom Benet is prescribed by faxing a patient registration form containing patient registration information (refer to Section 9.1) to the central registration center (refer to Section 11.3) within 15 days after the first prescription of Benet (day of the first prescription designated as day 1 and day following the day of the first prescription designated as 2 days after prescription). No patient can be registered before Benet is actually prescribed. Patients determined by the central registration center to be ineligible for any reason cannot be

registered. The investigator shall register a new patient using a new patient registration form supplied by Takeda's MR.

There are three CRFs per patient: CRF I (from the start of treatment to Month 12), CRF II (from Months 13 to 24), and CRF III (from Months 25 to 36).

Takeda's MR will supply a CRF I, which will be issued after the central registration center decides to register the relevant patient, to the investigator. A CRF II will be issued after completion of CRF I-related surveillance. Similarly, a CRF III will be issued after completion of CRF II-related surveillance.

7.4 Completion and Submission of Case Report Form

For each of all enrolled patients, the investigator shall complete and submit a CRF to Takeda's MR within approximately 1 month after the end of the observation period (12 months after the start of Benet treatment for CRF I, 24 months after the start of Benet treatment for CRF II, and 36 months after the start of Benet treatment for CRF III).

For patients discontinued from Benet treatment for any reason during the observation period, the investigator shall complete and submit a CRF to Takeda's MR within approximately 1 month after the end of required observation. For any patient discontinued from Benet treatment due to an adverse event, the investigator shall complete and submit a CRF to Takeda's MR after monitoring the patient as long after discontinuation of treatment as possible until the adverse event is confirmed to have resolved or be resolving.

7.5 Actions to be Taken in Case of Serious Adverse Events

The investigator shall immediately communicate any serious adverse event in the observation period to Takeda's MR. In addition, the investigator shall provide detailed information at the request of Takeda's MR.

8.0 Planned Surveillance Period

Surveillance period: From May 2013 to 30 April 2018

Patient registration period: From May 2013 to 31 October 2014[Note)]

[Note)] Patient registration (receipt of a patient registration form via fax) will not be accepted on 1 November 2014 onwards even if Benet is prescribed by 31 October 2014.

If the total number of patients enrolled in the surveillance by Takeda Pharmaceutical Co., Ltd. and PPD reaches 500 before 31 October 2014, acceptance of registration may be terminated before the end of the patient registration period.

9.0 Surveillance Items

The investigator shall enter the items listed below into the patient registration form and the CRF. The surveillance schedule is presented in Appendix.

9.1 Entries into the Patient Registration Form

1) Surveillance items

Name of the medical institution, name of a physician who completes the patient registration form, date of the first prescription of Benet, date of the scheduled first dosing of Benet, patient identification number, patient initials, sex, date of birth, assessment based on the selection criteria

2) Time points of surveillance

At patient registration

9.2 Entries into the Case Report Form

9.2.1 Cover of the Case Report Form

Date of final entry into the CRF, name of a physician who completes the CRF

9.2.2 Patient Baseline Characteristics

1) Surveillance items

Disease to be treated, time of diagnosis of osteoporosis, body weight, predisposition to hypersensitivity (presence or absence and details), concurrent illness (presence or absence and details), medical history (except previous fracture) (presence or absence and details), risk factors for fracture [medical history (previous fracture), previous steroid use, parental history of femur fracture], drinking history, smoking history

2) Time points of surveillance

At the start of Benet treatment

9.2.3 Treatment Given

1) Surveillance items

Treatment status of Benet (date of dosing indicated by a prescribing physician, patient's treatment status, reason for discontinuation of treatment, and date of discontinuation), treatment status of osteoporosis drug (including calcium and vitamin D) other than Benet given from 3 months before the start of Benet treatment to 36 months after the start of treatment (or discontinuation of treatment) (presence or absence, name of the drug, daily dose, and duration of treatment), treatment status of steroid (presence or absence, name of the drug, daily dose, duration of treatment, and purpose of treatment), treatment status of concomitant medication other than osteoporosis drugs and steroids* (presence or absence, name of the drug, and purpose of treatment), presence or absence of concomitant therapy for osteoporosis (physical therapy, other concomitant therapy)

* The daily dose and duration of treatment will be confirmed in the following situations:

- An adverse event occurs; or
- The sponsor considers it necessary to collect this information.

2) Time points of surveillance

Period from the start of Benet treatment to 36 months after the start of treatment (or

discontinuation of treatment)

9.2.4 Tests/Observations

9.2.4.1 Laboratory Tests

1) Surveillance items

If laboratory testing such as hematology or blood chemistry is performed during Benet treatment, any abnormal change in laboratory parameter will be entered into the adverse event column in the CRF. In addition, only relevant laboratory values will be entered into the column for adverse event-related clinically significant change in laboratory parameter.

2) Time points of surveillance

Time points of test from the start of Benet treatment to 36 months after the start of treatment (or discontinuation of treatment)

9.2.4.2 Bone Mineral Density

1) Surveillance items

Lumbar dual-energy x-ray absorptiometry (DXA), proximal femur DXA, radius DXA/peripheral quantitative computed tomography (pQCT), calcaneal DXA/quantitative ultrasound (QUS), second metacarpal bone microdensitometry (MD)/computed x-ray densitometry (CXD)/digital image processing (DIP)

2) Time points of surveillance

At the start of Benet treatment (within 3 months before the start of Benet treatment), 6*, 12, 18*, 24, 30*, and 36 months after the start of treatment (or discontinuation of treatment), and time points of test during the observation period

* Performed if necessary

9.2.4.3 Bone Turnover Markers

1) Surveillance items

Bone resorption markers:

Serum N-telopeptide of type I collagen (NTX), serum C-telopeptide of type I collagen (CTX), serum tartrate-resistant acid phosphatase (TRACP-5b), urinary NTX, urinary CTX, urinary deoxypyridinoline (DPD)

Bone formation markers:

Serum bone-specific alkaline phosphatase (BAP), serum N-propeptide of type I procollagen (P1NP)

Bone matrix-related marker:

Serum undercarboxylated osteocalcin (ucOC)

2) Time points of surveillance

At the start of Benet treatment (within 1 month before the start of Benet treatment), 6*, 12, 18*, 24, 30*, and 36 months after the start of treatment (or discontinuation of treatment), and time points of test during the observation period

* Performed if necessary

9.2.5 Assessment of Vertebral Fracture

1) Surveillance items

Vertebral fracture before the start of Benet treatment (baseline) will be confirmed, and the date of radiography, radiographic location, and location of vertebral fracture will be entered into the CRF. Then, the presence or absence and location of new vertebral fracture, presence or absence of worsening of prevalent vertebral fracture, and presence or absence of apparent trauma during treatment and at the end of the observation period (or discontinuation of treatment) relative to baseline will be entered into the CRF.

2) Time points of surveillance

At the start of Benet treatment, 12, 24, and 36 months after the start of treatment (or discontinuation of treatment), and when vertebral fracture is suspected during the observation period

9.2.6 Assessment of Non-vertebral Fracture

1) Surveillance items

Non-vertebral fracture during Benet treatment involving the femur, wrist, forearm, upper arm, pelvis, lower limb, etc. will be entered into the CRF. Confirmed non-vertebral fracture will be handled as an adverse event, and the fracture site, date of fracture (date of onset), presence or absence and details of apparent trauma, seriousness, reason for seriousness, presence or absence of discontinuation of Benet treatment, date of outcome assessment, outcome, and causal relationship to Benet will be entered into the CRF.

2) Time points of surveillance

12, 24, and 36 months after the start of Benet treatment (or discontinuation of treatment) and when non-vertebral fracture is confirmed during the observation period

9.2.7 Clinical Findings

1) Surveillance items

Height, low back pain

2) Time points of surveillance

Time points of medical examination at the start of treatment and 3, 6, 12, 18, 24, 30, and 36 months after the start of treatment (or discontinuation of treatment)

Only at the start of treatment and 12, 24, and 36 months after the start of treatment (or discontinuation of treatment) for height

9.3 Adverse Events (AEs)

1) Surveillance items

Presence or absence of AE (refer to Table 1), AE term, date of onset, seriousness and reason for seriousness (refer to Table 2), presence or absence of discontinuation of Benet treatment, date of outcome assessment, outcome, causal relationship to Benet* (refer to Table 3)

Patients with "not resolved" or "unknown" outcome or "unevaluable" causal relationship should be followed up wherever possible.

Any new vertebral fracture or worsening of prevalent fracture during treatment will be entered into the adverse event column.

The following events will also be entered into the adverse event column: upper gastrointestinal disorder, hepatic function disorder/jaundice, osteonecrosis of jaw/osteomyelitis of jaw, atypical fracture of subtrochanteric section of femur or shaft of proximal femur, musculoskeletal pain, atrial fibrillation, esophageal carcinoma, and gastrointestinal disorders including diarrhea.

* For the causal relationship to Benet, the rationale for "not related" and the reason for "unevaluable" shall be collected.

2) Time points of surveillance

12, 24, and 36 months after the start of Benet treatment (or discontinuation of treatment) and when an AE is confirmed during the observation period

Table 1 Definition of adverse events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug. The following are also handled as AEs: • Symptoms and so forth that occur in infants breast-fed by their mothers under treatment with a drug • Symptoms and so forth that occur in children treated with a drug • Symptoms and so forth that occur after administration or self-administration of a drug at higher doses than the approved dose

Table 2 Criteria for assessing seriousness

An AE satisfying any of the following is assessed as serious: 1. Results in death (death) 2. Is life-threatening (risk of death) 3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization) 4. Results in persistent or significant disability/incapacity (disability) 5. Leads to a congenital anomaly/birth defect (congenital anomaly) 6. Otherwise, is an important medical event (for instance, bronchospasm requiring short-term intensive care in an emergency room), including AEs in Takeda Medically Significant AE List <u>Takeda Medically Significant AE List</u> • Acute respiratory failure / acute respiratory distress syndrome (ARDS) • Anaphylactic shock

• Torsade de pointes / ventricular fibrillation / ventricular tachycardia
• Acute renal failure
• Malignant hypertension • Pulmonary hypertension
• Convulsive seizures (including convulsions and epilepsy)
• Pulmonary fibrosis (including interstitial pneumonia)
• Agranulocytosis
• Malignant syndrome / malignant hyperthermia
• Aplastic anemia
• Spontaneous abortion / stillbirth and fetal death
• Toxic epidermal necrolysis / mucocutaneous ocular syndrome (Stevens-Johnson syndrome)
• Confirmed or suspected transmission of infectious agent by a medicinal product
• Hepatic necrosis • Confirmed or suspected endotoxin shock
• Acute liver failure

Table 3 Criteria for assessing the relationship of each adverse event to Benet

Assessment	Criteria for assessment
Related	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments, may also be responsible
Not related	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments
Unevaluable	Information necessary for evaluation, including temporal sequence from administration of a drug (including the course after withdrawal of the drug), underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments, is not sufficient.

10.0 Analysis Items and Methods

Data from patients enrolled for Benet and Actonel 75 mg Tablets will be combined for analysis.

10.1 Matters on Patient Composition

The number of enrolled patients, number of patients for whom the CRF is collected, number of patients included in safety/efficacy analysis, number of patients excluded from analysis, and reason for exclusion will be tabulated.

10.2 Patient Baseline Characteristics

Patient baseline characteristics, including age, sex, duration of disease, height, body weight,

predisposition to hypersensitivity, and concurrent illness, will be tabulated.

10.3 Treatment Compliance Status

The treatment compliance status will be tabulated based on the date of dosing indicated by a prescribing physician and patient's treatment status (date of dosing).

10.4 Matters on Safety

For the safety population, the incidence of AEs reported during the observation period will be tabulated by causal relationship to Benet, type, seriousness, and time of onset.

10.5 Matters on Efficacy

For the efficacy population, data will be tabulated as described below.

10.5.1 Primary Endpoint

Incidence of vertebral fracture

10.5.2 Secondary Endpoints

Incidence of non-vertebral fracture, percent change in bone mineral density, percent changes in bone turnover markers, changes in height and low back pain over time

10.6 Analysis Methods

1) For vertebral fracture and non-vertebral fracture, the number and proportion of patients with fracture and cumulative incidence at each time point, including the final time point, will be calculated.
2) For the other endpoints, significance test will be performed by one-sample t-test, one-sample Wilcoxon test, or chi-square test, depending on the nature of the analysis item.

11.0 Surveillance Organization

11.1 Surveillance Administrative Manager

PPD

Takeda Pharmaceutical Co., Ltd.

11.2 Medical Expert

To give advice on surveillance planning, publication of results, etc.

PPD

11.3 Central Registration Center

PPD

PPD

12.0 Name, Address, and Scope of Operations of Contract Research Organizations (CROs)

PPD

13.0 Other Necessary Matters

13.1 Revision of the Protocol

During the surveillance, attention will be paid to comprehend the status of progression of the surveillance, presence or absence of adverse drug reactions (ADRs) that are unexpected based on the precautions/serious ADRs, presence or absence of increased incidence of certain ADRs, and appropriateness of surveillance items, and this protocol will be reviewed and revised if necessary. If partial change to dosage and administration or indications is approved during the surveillance, the necessity of revising the protocol will be discussed if necessary, and the protocol will be revised as needed.

13.2 Actions to be Taken for Problems and Questions

If any safety or efficacy problem is detected, data will be carefully examined to discuss measures.

Appendix　Surveillance schedule

Surveillance item \ Time point of surveillance		Observation period									
		At patient registration	At the start of treatment	After 3 months of treatment	After 6 months of treatment	After 12 months of treatment	After 18 months of treatment	After 24 months of treatment	After 30 months of treatment	After 36 months of treatment	At discontinuation of treatment
Patient registration	Date of the first prescription of Benet	○									
	Date of the scheduled first dosing of Benet	○									
	Patient identification number	○									
	Patient initials	○									
	Sex	○									
	Date of birth	○									
	Assessment based on the selection criteria	○									
Patient baseline characteristics	Disease to be treated		○								
	Time of diagnosis of osteoporosis		○								
	Body weight		○								
	Predisposition to hypersensitivity		○								
	Concurrent illness		○								
	Medical history		○								
	Risk factors for fracture		○								
Treatment given	Treatment status of Benet		←	―	―	○	―	―	―	→	○
	Treatment status of concomitant medication		←	―	―	○	―	―	―	→	○
	Concomitant therapy for osteoporosis		←	―	―	○	―	―	―	→	○
Tests/observations	Bone mineral density		○		(○)	○	(○)	○	(○)	○	○
	Bone turnover markers		○		(○)	○	(○)	○	(○)	○	○
	Assessment of vertebral fracture		○			○		○		○	○
	Assessment of non-vertebral fracture		←	―	―	○	―	―	―	→	○
	Clinical findings (height*, low back pain)		○	○	○	○	○	○	○	○	○
	Adverse event		←	―	―	○	―	―	―	→	○

○: Surveyed/examined/observed

(○): Examined if necessary

←—— ○ ——→: Surveyed/examined/observed throughout the period

* Height will be measured at the start of treatment and 12, 24, and 36 months after the start of treatment (or discontinuation of treatment).

Special Drug Use Surveillance Protocol

Benet 75 mg Tablets

Special Drug Use Surveillance on Fracture Incidence during 36-Month Treatment

Version number	**1st version**
Date of preparation	**27 February 2013**
Sponsor	**Takeda Pharmaceutical Co., Ltd.**

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1.0 Background of the Surveillance

Data on the incidence of vertebral fracture during 96-week treatment with Benet 2.5 mg Tablets administered once daily were collected in a post-marketing clinical study. On the other hand, since the fracture prevention efficacy of Benet 75 mg Tablets (hereinafter referred to as Benet) has not been evaluated, a special drug use surveillance (hereinafter referred to as the surveillance) is planned to evaluate the efficacy (e.g., fracture incidence, percent change in bone mineral density) and safety of 36-month treatment with Benet in osteoporotic patients in clinical settings.

This surveillance will be conducted in compliance with the ministerial ordinance on Good Post-Marketing Study Practice (GPSP) and related regulatory requirements.

2.0 Objectives of the Surveillance

To evaluate the efficacy (e.g., fracture incidence, percent change in bone mineral density) and safety of 36-month treatment with Benet in osteoporotic patients in clinical settings

3.0 Planned Sample Size and Rationale

3.1 Planned Sample Size

250 patients treated with Benet

(PPD will collect another 250 patients treated with Actonel 75 mg Tablets, which contains the same active ingredient as Benet, resulting in a total of 500 patients.)

3.2 Rationale

In a Japanese clinical study of the approved formulation (2.5 mg tablets used on a daily basis) with the same active ingredient as Benet (study number: NE-58095/CCT-005) assessing fracture incidence, the number of subjects included in analysis was 273 with a treatment duration of 2 years and a discontinuation/dropout rate of 26.7%. Approximately 250 patients may be necessary to analyze data by reference to this clinical study.

Since fracture incidence will be assessed in clinical settingse during a 3-year observation period in the surveillance, the discontinuation/dropout rate is expected to be higher than in the clinical study. With an estimated dropout rate of 50%, therefore, the sample size of the surveillance is set at 500 patients, including those to be treated with Actonel Tablets.

4.0 Surveillance Population

Osteoporotic patients will be included in the surveillance. The selection criteria listed below should also be met, and the precautions concerning indications in the package insert should be referred to.

Selection criteria

Patients meeting all of the following criteria will be included in the surveillance:

1) A patient with evidence of 1 to 4 fractures from the fourth thoracic vertebra to the fourth lumbar vertebra (T_4 to L_4) provided by thoracic and lumbar spinal radiography performed before the start of the surveillance (within 3 months before the start of prescription of Benet)
2) A patient aged 50 years or older (menopausal if female)
3) An outpatient who can walk

5.0 Dosage and Administration in Surveillance Patients

Patients will orally receive 75 mg of sodium risedronate with sufficient water (approximately 180 mL) upon awakening once a month. They should not lie, consume food or beverages except water, or orally receive any other drugs for at least 30 minutes after dosing. In addition, the precautions concerning dosage and administration in the package insert should be referred to.

6.0 Planned Number of Medical Institutions by Department

Orthopedics, internal medicine, and other departments Approximately 50 to 85 medical institutions

7.0 Surveillance Method

7.1 Observation Period

36 months

7.2 Request to and Contract with the Study Site

This surveillance will be conducted using a paper case report form (CRF). A medical representative of Takeda Pharmaceutical Co., Ltd. (hereinafter referred to as Takeda's MR) will explain the objectives, contents, and methods of the surveillance to the investigator based on "Request for cooperation for special drug use surveillance," "Implementation outline," "Patient registration form (sample)," and "Case report form (sample)" to enter into a written contract with the study site and request the study site to conduct a surveillance within a specified period.

7.3 Method of Patient Registration

Patients will be registered using the central registration method via fax. After the start of the contract with the study site, the investigator shall register each surveillance patient for whom Benet is prescribed by faxing a patient registration form containing patient registration information (refer to Section 9.1) to the central registration center (refer to Section 11.3) within 15 days after the first prescription of Benet (day of the first prescription designated as day 1 and day following the day of the first prescription designated as 2 days after prescription). No patient can be registered before Benet is actually prescribed. Patients determined by the central registration center to be ineligible for any reason cannot be

registered. The investigator shall register a new patient using a new patient registration form supplied by Takeda's MR.

There are three CRFs per patient: CRF I (from the start of treatment to Month 12), CRF II (from Months 13 to 24), and CRF III (from Months 25 to 36).

Takeda's MR will supply a CRF I, which will be issued after the central registration center decides to register the relevant patient, to the investigator. A CRF II will be issued after completion of CRF I-related surveillance. Similarly, a CRF III will be issued after completion of CRF II-related surveillance.

7.4 Completion and Submission of Case Report Form

For each of all enrolled patients, the investigator shall complete and submit a CRF to Takeda's MR within approximately 1 month after the end of the observation period (12 months after the start of Benet treatment for CRF I, 24 months after the start of Benet treatment for CRF II, and 36 months after the start of Benet treatment for CRF III).

For patients discontinued from Benet treatment for any reason during the observation period, the investigator shall complete and submit a CRF to Takeda's MR within approximately 1 month after the end of required observation. For any patient discontinued from Benet treatment due to an adverse event, the investigator shall complete and submit a CRF to Takeda's MR after monitoring the patient as long after discontinuation of treatment as possible until the adverse event is confirmed to have resolved or be resolving.

7.5 Actions to be Taken in Case of Serious Adverse Events

The investigator shall immediately communicate any serious adverse event in the observation period to Takeda's MR. In addition, the investigator shall provide detailed information at the request of Takeda's MR.

8.0 Planned Surveillance Period

Surveillance period: From May 2013 to 30 April 2018

Patient registration period: From May 2013 to 31 October 2014[Note)]

[Note)] Patient registration (receipt of a patient registration form via fax) will not be accepted on 1 November 2014 onwards even if Benet is prescribed by 31 October 2014.

If the total number of patients enrolled in the surveillance by Takeda Pharmaceutical Co., Ltd. and PPD reaches 500 before 31 October 2014, acceptance of registration may be terminated before the end of the patient registration period.

9.0 Surveillance Items

The investigator shall enter the items listed below into the patient registration form and the CRF. The surveillance schedule is presented in Appendix.

9.1 Entries into the Patient Registration Form

1) Surveillance items

Name of the medical institution, name of a physician who completes the patient registration form, date of the first prescription of Benet, date of the scheduled first dosing of Benet, patient identification number, patient initials, sex, date of birth, assessment based on the selection criteria

2) Time points of surveillance

At patient registration

9.2 Entries into the Case Report Form

9.2.1 Cover of the Case Report Form

Date of final entry into the CRF, name of a physician who completes the CRF

9.2.2 Patient Baseline Characteristics

1) Surveillance items

Disease to be treated, time of diagnosis of osteoporosis, body weight, predisposition to hypersensitivity (presence or absence and details), concurrent illness (presence or absence and details), medical history (except previous fracture) (presence or absence and details), risk factors for fracture [medical history (previous fracture), previous steroid use, parental history of femur fracture], drinking history, smoking history

2) Time points of surveillance

At the start of Benet treatment

9.2.3 Treatment Given

1) Surveillance items

Treatment status of Benet (date of dosing indicated by a prescribing physician, patient's treatment status, reason for discontinuation of treatment, and date of discontinuation), treatment status of osteoporosis drug (including calcium and vitamin D) other than Benet given from 3 months before the start of Benet treatment to 36 months after the start of treatment (or discontinuation of treatment) (presence or absence, name of the drug, and date of completion of treatment), treatment status of concomitant medication other than osteoporosis drugs (presence or absence, name of the drug, and purpose of treatment), presence or absence of concomitant therapy for osteoporosis (physical therapy, other concomitant therapy)

2) Time points of surveillance

Period from the start of Benet treatment to 36 months after the start of treatment (or discontinuation of treatment)

9.2.4 Tests/Observations

9.2.4.1 Laboratory Tests

1) Surveillance items

If laboratory testing such as hematology or blood chemistry is performed during Benet treatment, any abnormal change in laboratory parameter will be entered into the adverse event column in the CRF. In addition, only relevant laboratory values will be entered into the column for adverse event-related clinically significant change in laboratory parameter.

2) Time points of surveillance

Time points of test from the start of Benet treatment to 36 months after the start of treatment (or discontinuation of treatment)

9.2.4.2 Bone Mineral Density

1) Surveillance items

Lumbar dual-energy x-ray absorptiometry (DXA), proximal femur DXA, radius DXA/peripheral quantitative computed tomography (pQCT), calcaneal DXA/quantitative ultrasound (QUS), second metacarpal bone microdensitometry (MD)/computed x-ray densitometry (CXD)/digital image processing (DIP)

2) Time points of surveillance

At the start of Benet treatment (within 3 months before the start of Benet treatment), 6*, 12, 18*, 24, 30*, and 36 months after the start of treatment (or discontinuation of treatment), and time points of test during the observation period

* Performed if necessary

9.2.4.3 Bone Turnover Markers

1) Surveillance items

Bone resorption markers:

Serum N-telopeptide of type I collagen (NTX), serum C-telopeptide of type I collagen (CTX), serum tartrate-resistant acid phosphatase (TRACP-5b), urinary NTX, urinary CTX, urinary deoxypyridinoline (DPD)

Bone formation markers:

Serum bone-specific alkaline phosphatase (BAP), serum N-propeptide of type I procollagen (P1NP)

Bone matrix-related marker:

Serum undercarboxylated osteocalcin (ucOC)

2) Time points of surveillance

At the start of Benet treatment (within 1 month before the start of Benet treatment), 6*, 12, 18*, 24, 30*, and 36 months after the start of treatment (or discontinuation of treatment), and time points of test during the observation period

* Performed if necessary

9.2.5 Assessment of Vertebral Fracture

1) Surveillance items

Vertebral fracture before the start of Benet treatment (baseline) will be confirmed, and the date of radiography, radiographic location, and location of vertebral fracture will be entered into the CRF. Then, the presence or absence and location of new vertebral fracture, presence or absence of worsening of prevalent vertebral fracture, and presence or absence of apparent trauma during treatment and at the end of the observation period (or discontinuation of treatment) relative to baseline will be entered into the CRF.

2) Time points of surveillance

At the start of Benet treatment, 12, 24, and 36 months after the start of treatment (or discontinuation of treatment), and when vertebral fracture is suspected during the observation period

9.2.6 Assessment of Non-vertebral Fracture

1) Surveillance items

Non-vertebral fracture during Benet treatment involving the femur, wrist, forearm, upper arm, pelvis, lower limb, etc. will be entered into the CRF. Confirmed non-vertebral fracture will be handled as an adverse event, and the fracture site, date of fracture (date of onset), presence or absence and details of apparent trauma, seriousness, reason for seriousness, presence or absence of discontinuation of Benet treatment, date of outcome assessment, outcome, and causal relationship to Benet will be entered into the CRF.

2) Time points of surveillance

12, 24, and 36 months after the start of Benet treatment (or discontinuation of treatment) and when non-vertebral fracture is confirmed during the observation period

9.2.7 Clinical Findings

1) Surveillance items

Height, low back pain

2) Time points of surveillance

Time points of medical examination at the start of treatment and 3, 6, 12, 18, 24, 30, and 36 months after the start of treatment (or discontinuation of treatment)

Only at the start of treatment and 12, 24, and 36 months after the start of treatment (or discontinuation of treatment) for height

9.3 Adverse Events (AEs)

1) Surveillance items

Presence or absence of AE (refer to Table 1), AE term, date of onset, seriousness and reason for seriousness (refer to Table 2), presence or absence of discontinuation of Benet treatment, date of outcome assessment, outcome, causal relationship to Benet* (refer to Table 3)

Patients with “not resolved” or “unknown” outcome or “unevaluable” causal relationship should be followed up wherever possible.

Any new vertebral fracture or worsening of prevalent fracture during treatment will be entered into the adverse event column.

The following events will also be entered into the adverse event column: upper gastrointestinal disorder, hepatic function disorder/jaundice, osteonecrosis of jaw/osteomyelitis of jaw, atypical fracture of subtrochanteric section of femur or shaft of proximal femur, musculoskeletal pain, atrial fibrillation, esophageal carcinoma, and gastrointestinal disorders including diarrhea.

* For the causal relationship to Benet, the rationale for "not related" and the reason for "unevaluable" shall be collected.

Clinical findings associated with progression of osteoporosis, such as decreased height and worsening of low back pain, should not be handled as AEs.

2) Time points of surveillance

12, 24, and 36 months after the start of Benet treatment (or discontinuation of treatment) and when an AE is confirmed during the observation period

Table 1 Definition of adverse events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug. The following are also handled as AEs: • Symptoms and so forth that occur in infants breast-fed by their mothers under treatment with a drug • Symptoms and so forth that occur in children treated with a drug • Symptoms and so forth that occur after administration or self-administration of a drug at higher doses than the approved dose

Table 2 Criteria for assessing seriousness

An AE satisfying any of the following is assessed as serious: 1. Results in death (death) 2. Is life-threatening (risk of death) 3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization) 4. Results in persistent or significant disability/incapacity (disability) 5. Leads to a congenital anomaly/birth defect (congenital anomaly) 6. Otherwise, is an important medical event (for instance, bronchospasm requiring short-term intensive care in an emergency room), including AEs in Takeda Medically Significant AE List <u>Takeda Medically Significant AE List</u> • Acute respiratory failure / acute respiratory distress syndrome (ARDS) • Anaphylactic shock

• Torsade de pointes / ventricular fibrillation / ventricular tachycardia
• Acute renal failure
• Malignant hypertension • Pulmonary hypertension
• Convulsive seizures (including convulsions and epilepsy)
• Pulmonary fibrosis (including interstitial pneumonia)
• Agranulocytosis
• Malignant syndrome / malignant hyperthermia
• Aplastic anemia
• Spontaneous abortion / stillbirth and fetal death
• Toxic epidermal necrolysis / mucocutaneous ocular syndrome (Stevens-Johnson syndrome)
• Confirmed or suspected transmission of infectious agent by a medicinal product
• Hepatic necrosis • Confirmed or suspected endotoxin shock
• Acute liver failure

Table 3 Criteria for assessing the relationship of each adverse event to Benet

Assessment	Criteria for assessment
Related (Involvement is suspected)	An AE that follows an apparently reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments, may also be responsible
Not related (Involvement is unlikely)	An AE that does not follow an apparently reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments
Unevaluable	Information necessary for evaluation, including temporal sequence from administration of a drug (including the course after withdrawal of the drug), underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments, is not sufficient.

10.0 Analysis Items and Methods

Data from patients enrolled for Benet and Actonel 75 mg Tablets will be combined for analysis.

10.1 Matters on Patient Composition

The number of enrolled patients, number of patients for whom the CRF is collected, number of patients included in safety/efficacy analysis, number of patients excluded from analysis, and reason for exclusion will be tabulated.

10.2 Patient Baseline Characteristics

Patient baseline characteristics, including age, sex, duration of disease, height, body weight,

predisposition to hypersensitivity, and concurrent illness, will be tabulated.

10.3 Treatment Compliance Status

The treatment compliance status will be tabulated based on the date of dosing indicated by a prescribing physician and patient's treatment status (date of dosing).

10.4 Matters on Safety

For the safety population, the incidence of AEs reported during the observation period will be tabulated by causal relationship to Benet, type, seriousness, and time of onset.

10.5 Matters on Efficacy

For the efficacy population, data will be tabulated as described below.

10.5.1 Primary Endpoint

Incidence of vertebral fracture

10.5.2 Secondary Endpoints

Incidence of non-vertebral fracture, percent change in bone mineral density, percent changes in bone turnover markers, changes in height and low back pain over time

10.6 Analysis Methods

1) For vertebral fracture and non-vertebral fracture, the number and proportion of patients with fracture and cumulative incidence at each time point, including the final time point, will be calculated.
2) For the other endpoints, significance test will be performed by one-sample t-test, one-sample Wilcoxon test, or chi-square test, depending on the nature of the analysis item.

11.0 Surveillance Organization

11.1 Surveillance Administrative Manager

PPD

Takeda Pharmaceutical Co., Ltd.

11.2 Medical Expert

To give advice on surveillance planning, publication of results, etc.

PPD

11.3 Central Registration Center

Not determined

12.0 Name, Address, and Scope of Operations of Contract Research Organizations (CROs)

Not determined

13.0 Other Necessary Matters

13.1 Revision of the Protocol

During the surveillance, attention will be paid to comprehend the status of progression of the surveillance, presence or absence of adverse drug reactions (ADRs) that are unexpected based on the precautions/serious ADRs, presence or absence of increased incidence of certain ADRs, and appropriateness of surveillance items, and this protocol will be reviewed and revised if necessary. If partial change to dosage and administration or indications is approved during the surveillance, the necessity of revising the protocol will be discussed if necessary, and the protocol will be revised as needed.

13.2 Actions to be Taken for Problems and Questions

If any safety or efficacy problem is detected, data will be carefully examined to discuss measures.

Appendix　Surveillance schedule

Surveillance item \ Time point of surveillance		Observation period									
		At patient registration	At the start of treatment	After 3 months of treatment	After 6 months of treatment	After 12 months of treatment	After 18 months of treatment	After 24 months of treatment	After 30 months of treatment	After 36 months of treatment	At discontinuation of treatment
Patient registration	Date of the first prescription of Benet	○									
	Date of the scheduled first dosing of Benet	○									
	Patient identification number	○									
	Patient initials	○									
	Sex	○									
	Date of birth	○									
	Assessment based on the selection criteria	○									
Patient baseline characteristics	Disease to be treated		○								
	Time of diagnosis of osteoporosis		○								
	Body weight		○								
	Predisposition to hypersensitivity		○								
	Concurrent illness		○								
	Medical history		○								
	Risk factors for fracture		○								
Treatment given	Treatment status of Benet		←			○				→	○
	Treatment status of concomitant medication		←			○				→	○
	Concomitant therapy for osteoporosis		←			○				→	○
Tests/observations	Bone mineral density		○		(○)	○	(○)	○	(○)	○	○
	Bone turnover markers		○		(○)	○	(○)	○	(○)	○	○
	Assessment of vertebral fracture		○			○		○		○	○
	Assessment of non-vertebral fracture		←			○				→	○
	Clinical findings (height*, low back pain)		○	○	○	○	○	○	○	○	○
	Adverse event		←			○				→	○

○: Surveyed/examined/observed

(○): Examined if necessary

←—— ○ ——→ : Surveyed/examined/observed throughout the period

* Height will be measured at the start of treatment and 12, 24, and 36 months after the start of treatment (or discontinuation of treatment).