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

NCT Number: NCT02106442

Statistical analysis plan Approve Date: 17-Nov-2017

Certain information within this statistical analysis plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

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

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

Note; This document was translated into English as the language on original version was Japanese.

Benet 75 mg Tablets Special Drug Use Surveillance

Actonel 75 mg Tablets Special Drug Use Surveillance

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

Statistical Analysis Plan

Version 5.1

PPD

Takeda Pharmaceutical Co., Ltd.

PPD

PPD

PPD

History of amendments

Version number	Date of preparation	Preparator	Amendment/reason, etc.
1.0	7 March 2014	PPD	New document
2.0	29 September 2014		Thorough revision for the fourth periodic safety update report
2.1	8 October 2014		Correction made to Section 4.3, “Patients Included in Safety Analysis”
3.0	26 March 2015		Correction made to Section 3.3. 2), “Number of digits to be displayed” Addition to Section 5.4, “Handling of Time Points of Assessment” Addition to Section 5.5, “Derived Variables” Addition of Section 6.2.4, “Occurrence of Acute Phase Reaction”
4.0	6 January 2016		Thorough revision for the sixth periodic safety update report
4.1	27 May 2016		Standardization of expression: patients included in analysis→patients evaluated, patients excluded from analysis→patients not evaluated Correction made to Section 3.2, “Definitions of Terms” Addition to Section 4.3, “Patients Evaluated for Safety” Correction made to Section 5.5, “Derived Variables” Addition to Section 6.1.2, “Patient Baseline Characteristics” Addition to Section 6.3.6, “Percent Change in Bone Mineral Density”
5.0	22 November 2016		Thorough revision for the re-examination
5.1	17 November 2017		Revision to a list of serious adverse events only in the fracture surveillance for additional

			reporting

Table of Contents

1. Objectives

This document is intended to describe the details of statistical analyses in a special drug use surveillance on fracture incidence during 36-month treatment with Benet 75 mg Tablets and Actonel 75 mg Tablets (hereinafter referred to as the surveillance). The chart layout for analysis results will be specified in a separately prepared chart plan.

2. Synopsis

Surveillance drug	Benet 75 mg Tablets/Actonel 75 mg Tablets (hereinafter referred to as Benet/Actonel)
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/Actonel in osteoporotic patients in clinical settings
Planned sample size	250 patients/250 patients A total of 500 patients
Registration method	Central registration method
Planned surveillance period	Surveillance period: From May 2013 to April 2018 Registration period: From May 2013 to October 2014

3. Definitions

3.1. Definitions of Abbreviations

Abbreviation	Description
PMS system	CCI [redacted] (name of the system supplied by PPD [redacted] for managing the progression of post-marketing surveillances)
BMI	Body Mass Index
AE	Adverse Event
SOC	System Organ Class
PT	Preferred Term
LLT	Low Level Term

3.2. Definitions of Terms

Term	Description
Finalized patient	For Benet Tablets, a finalized patient is defined as a patient who has the date of CRF approval in the PMS system. For Actonel Tablets, a finalized patient is defined as a patient who has the date of temporary finalization in the business management system.
Adverse event (AE)	All events entered into the column of [Adverse event] or [Assessment of non-vertebral fracture] in the case report form (CRF) Any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of Benet/Actonel, whether or not it is considered related to Benet/Actonel
Adverse drug reaction (ADR)	All adverse events except those not related to Benet/Actonel according to "Causal relationship to Benet/Actonel" both in the column of [Adverse event] or [Assessment of non-vertebral fracture] in the CRF and determined by the company If either assessment is missing, non-missing assessment of causal relationship is confirmed to determine the adverse event as an adverse drug reaction unless not related to Benet/Actonel.
Serious adverse event (SAE)	Adverse event assessed as serious according to "Seriousness" at least either in the column of [Adverse event] or [Assessment of non-vertebral fracture] in the CRF or determined by the company, including "AEs that must always be assessed as serious" in the implementation guidelines and AEs in Takeda Medically Significant AE List

3.3. Statistical Arrangements

1) Summary statistics

For quantitative variables, summary statistics are number of relevant patients, mean, standard deviation, minimum, quartile points (25 percentile, 50 percentile, and 75 percentile), and maximum.

2) Number of digits to be displayed

Proportions and rates will be expressed as percentage (%) and displayed to two decimal places by rounding.

Minimum and maximum will be displayed with the same number of digits as raw data, and the other

summary statistics will be displayed to one lower digit than raw data by rounding.
Ninety-five percent confidence interval will be displayed with the same number of digits as the relevant statistics.
Statistical p-value will be displayed to four decimal places by rounding. P-value less than 0.0001 will be displayed as <0.0001. Infeasibility of testing will be indicated as "-."

3) 95% confidence interval
All confidence intervals will be presented as two-sided confidence intervals.

4) Rules of statistical testing
One-sample t-test or one-sample Wilcoxon test will be used for pre- and post-treatment comparison of continuous variables.
McNemar test will be used for pre- and post-treatment comparison in shift tables.
A two-sided 5% level of significance will be used.
The category of "unknown" will be excluded from statistical testing.

4. Analysis Sets

4.1. Enrolled Patients

All patients for whom the patient registration form has been accepted

4.2. Patients with the CRF Collected

Patients for whom the CRF has been collected and finalized

4.3. Patients Evaluated for Safety

All patients with the CRF collected, excluding those who meet any of the following criteria:
1) Not treated with Benet/Actonel
2) Unknown whether an AE occurred
3) Deviated from the registration criteria
• Treated before conclusion of a contract
• Not registered in the registration period
• Failed to fax the patient registration form within 15 days after the first prescription of Benet/Actonel
• Other (assessed as deviated from the registration criteria due to any reason not listed above)

4.4. Patients Evaluated for Efficacy

All patients evaluated for safety, excluding those who meet the following criterion:

Pre- and post-baseline values of all efficacy endpoints (bone turnover markers, bone mineral density, vertebral fracture, non-vertebral fracture, height, and low back pain) are unknown, including incalculable values

4.5. Patients Evaluated for Vertebral Fracture

All patients evaluated for efficacy, excluding those who meet any of the following criteria:

1) No evidence of 1 to 4 fractures from the fourth thoracic vertebra to the fourth lumbar vertebra provided by thoracic and lumbar spinal radiography performed before the start of the surveillance*

* The permissible range before the start of the surveillance is Days -90 to 1.

2) Not 50 years or older

3) Not an outpatient who can walk

4) No known date of pre- or post-treatment* radiography for assessment of vertebral fracture

* For the permissible range before or after treatment, refer to *1 in Section 6.3.1.

5. Handling of Data

Handling of data for analysis is described below. Details of processing will be specified in separately prepared analysis data set specifications.

5.1. Handling of Dichotomous Variables

For dichotomous variables, the presence or absence will be determined as described below when there is a column for details to be specified for "Yes."

1) "Yes" when details are specified

2) "No" when no details are specified and "No" is checked

3) "Unknown" when neither 1 nor 2) is applicable

5.2. Handling of Adverse Events

Multiple episodes of the same AE/ADR (SOC) in the same patient will be tabulated as 1 patient.

Multiple episodes of the same AE/ADR (PT) in the same patient will be tabulated as 1 event.

For tabulation by type (seriousness, time of onset, outcome), multiple episodes of the same AE/ADR (PT) in the same patient will be tabulated as 1 event on a PT basis according to the following order of precedence:

Seriousness: serious > not serious

Time of onset: chronological order

Outcome: death > recovered with sequelae > not recovered > recovering > recovered > unknown

5.3. Handling of Missing Data

In principle, no missing data will be imputed.

For frequency tabulation of qualitative variables, missing data will be handled as "unknown," and the column of "unknown" will not be presented if there is no relevant patient. For summary statistics of quantitative variables, missing data will be excluded.

5.4. Handling of Time Points of Assessment

Data within the permissible range as shown below will be employed.*

If there are multiple pieces of data within the permissible range, data on the day closest to the nominal day will be employed. If deviation is the same before and after the nominal day, the latest data will be employed.

Data collected up to the end date of Benet/Actonel treatment* + 30 days will be employed for bone

turnover markers and low back pain, and data collected up to the end date of Benet/Actonel treatment* + 90 days will be employed for the other endpoints. For patients with interruption of treatment, no data collected after 3 consecutive months (90 days) of interruption will be used for (efficacy) analysis.

At the final assessment, the latest available data (excluding data before the start of treatment) will be employed.

The start day of Benet/Actonel treatment is designated as Day 1, and the previous day as Day -1.

* Specified in Section 5.5, "Derived Variables"

<Time points of assessment of bone turnover markers and low back pain>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -30 to 1	Day 1
Month 3	Days 2 to 135	Day 90
Month 6	Days 136 to 270	Day 180
Month 12	Days 271 to 450	Day 360
Month 18	Days 451 to 630	Day 540
Month 24	Days 631 to 810	Day 720
Month 30	Days 811 to 990	Day 900
Month 36	Days 991 to 1170	Day 1096
Final assessment	Days 2 to 1170	-

<Time points of assessment of bone mineral density>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -90 to 30	Day 1
Month 3	Days 31 to 135	Day 90
Month 6	Days 136 to 270	Day 180
Month 12	Days 271 to 450	Day 360
Month 18	Days 451 to 630	Day 540
Month 24	Days 631 to 810	Day 720
Month 30	Days 811 to 990	Day 900
Month 36	Days 991 to 1170	Day 1096
Final assessment	Days 31 to 1170	-

<Time points of assessment of height>

Time point of assessment	Permissible range	Nominal day

Before the start of treatment	Days -90 to 1	Day 1
Month 12	Days 2 to 450	Day 360
Month 24	Days 451 to 900	Day 720
Month 36	Days 901 to 1170	Day 1096
Final assessment	Days 2 to 1170	-

5.5. Derived Variables

Derived variable	Description
Flag for enrollment	It is identified whether a patient is enrolled.
Flag for CRF collection	It is identified whether the CRF for a patient is collected.
Flag for inclusion in/exclusion from safety	It is identified whether a patient is evaluated for safety.
Flag for inclusion in/exclusion from efficacy	It is identified whether a patient is evaluated for efficacy.
Flag for inclusion in/exclusion from vertebral fracture	It is identified whether a patient is evaluated for vertebral fracture.
Age (years)	Age on the start day of Benet/Actonel treatment; or age described on the [Cover] in the CRF for Actonel Tablets if age cannot be calculated due to missing data on date of birth
BMI (kg/m^2)	Body mass index calculated as body weight (kg) ÷ height $(m)^2$
Duration of disease (years)	Number of years from diagnosis of osteoporosis to the start date of Benet/Actonel treatment (by rounding down)
Start date of Benet/Actonel treatment	The earliest (smallest) date among dates described in the [Treatment status of Benet/Actonel] in the CRF and when a patient appears to have taken the drug
End date of Benet/Actonel treatment	30 days after the latest (largest) date among dates described in the [Treatment status of Benet/Actonel] in the CRF and when a patient appears to have taken the drug
Duration of Benet/Actonel treatment (days)	Number of days from the start date of Benet/Actonel treatment to the end date of Benet/Actonel treatment "End date of Benet/Actonel treatment" - "start date of Benet/Actonel treatment" + 1
Duration of Benet/Actonel treatment (months)	Number of months from the start date of Benet/Actonel treatment to the end date of Benet/Actonel treatment "Duration of Benet/Actonel treatment (days)" ÷ 30

Derived variable	Description
Number of doses of Benet/Actonel	Number of doses during Benet/Actonel treatment counted as the number of checks made to "Took the drug on the day indicated by a physician" or "Took the drug on a different day from instructed by a physician" for patient's treatment status in the [Treatment status of Benet/Actonel] in the CRF Data are collected in the [Treatment status of Benet/Actonel] in the CRF on a dose basis (first dose, second dose, third dose,……) for Benet and on a monthly basis (Month 1, Month 2, Month 3,……) for Actonel. For tabulation, data of Actonel will be handled on a dose basis in line with data of Benet. No month with blank will be counted.
Amount of Benet/Actonel administered (mg)	Total dose during Benet/Actonel treatment calculated as number of doses of Benet/Actonel × 75 mg
Treatment rate (%)	Number of doses of Benet/Actonel ÷ number of entered "date indicated by a physician"
Treatment compliance rate (%)	Percentage of the number of doses taken as instructed by a physician relative to the number of doses indicated by the physician calculated as the number of checks made to "Took the drug on the day indicated by a physician" ÷ number of entered "date indicated by a physician"
Dosing interval (days)	Number of days from the date of a certain dosing to the date of the next dosing "Date of the next dosing" - "date of a certain dosing" Date of dosing refers to date when a patient took the drug (records of "Took no dose" for patient's treatment status are excluded to identify "date of a certain dosing" and "date of the next dosing"). Dosing interval is missing if either date of dosing is missing.
Duration of use (days)	Number of days from the start date of Benet/Actonel treatment to the end date of Benet/Actonel treatment "End date of Benet/Actonel treatment" - "start date of Benet/Actonel treatment" + 1
Duration of interruption of treatment (days)	Number of days from the date of a certain dosing to the date of the next dosing "Date of the next dosing" - "date of a certain dosing"

Derived variable	Description
	Date of dosing refers to date when a patient took the drug (records of "Took no dose" for patient's treatment status are excluded to identify "date of a certain dosing" and "date of the next dosing"). Dosing interval is missing if either date of dosing is missing.
Flag for previous treatment	A drug deemed as previous treatment is identified. Previous treatment being used after the start of Benet/Actonel treatment is also identified with a flag for concomitant medication.
Flag for concomitant medication	A drug deemed as concomitant medication is identified. Concomitant medication that has been used since before the start of Benet/Actonel treatment is also identified with a flag for previous treatment.
Flag for osteoporosis drug	An osteoporosis drug is identified.
Flag for anti-inflammatory analgesic	An anti-inflammatory analgesic is identified.
Flag for cardiovascular drug	A cardiovascular drug is identified.
Flag for central nervous system drug	A central nervous system drug is identified.
Flag for antidiabetic	An antidiabetic is identified.
Flag for digestive system drug	A digestive system drug is identified.
Flag for other drug	Other drug not listed above is identified.
Flag for Benet/Actonel 2.5 mg	A drug that is Benet/Actonel 2.5 mg is identified.
Flag for Benet/Actonel 17.5 mg	A drug that is Benet/Actonel 17.5 mg is identified.
Flag for bisphosphonate other than Benet/Actonel	A bisphosphonate other than Benet/Actonel is identified.
Flag for calcium	A drug that is calcium is identified.
Flag for vitamin D	A drug that is vitamin D is identified.
Flag for osteoporosis drug not listed above	A drug that is an osteoporosis drug not listed above is identified.
Flag for steroid	A drug that is a steroid is identified.
Flag for parathyroid hormone	A drug that is a parathyroid hormone is identified.
Flag for anti-RANKL	A drug that is an anti-RANKL monoclonal antibody is

Derived variable	Description
monoclonal antibody	identified.
Number of days to measurement (days)	Number of days from the start date of Benet/Actonel treatment to the date of measurement of the relevant endpoint "Date of measurement" - "start date of Benet/Actonel treatment" + 1; or "date of measurement" - "start date of Benet/Actonel treatment" if the date of measurement is earlier than the start date of Benet/Actonel treatment
Time point of assessment (for analysis)	Time points of assessment of bone turnover markers, low back pain, bone mineral density, and height are reallocated for analysis as specified in Section 5.4, "Handling of Time Points of Assessment."
Flag for employment of data	It is identified whether measurement data are employed.
Flag for event	A patient with event is defined as a patient who experienced at least one event such as vertebral fracture. A patient with no event is defined as a patient who experienced no event.
Time point of event onset	Time point of event onset is defined as the first onset of event such as vertebral fracture. Patients with no event are censored at the final assessment.
Measured value before the start of treatment	The measured value before the start of treatment is identified.
Change	Value obtained by deducting the measured value before the start of treatment from a measured value at each time point
Percent change (%)	Value obtained by dividing a change by the measured value before the start of treatment and then multiplying the division by 100
Time of onset (days)	Number of days from the start date of Benet/Actonel treatment to the date of onset of AE "Date of onset" - "start date of Benet/Actonel treatment" + 1
Flag for inclusion/exclusion as an AE	It is identified whether an event is an AE.
Relationship (for analysis)	It is identified whether an AE is related to Benet/Actonel. The causal relationship is handled as specified for "Adverse drug reaction" in Section 3.2.
Seriousness (for analysis)	It is identified whether an AE is serious. The seriousness is

Derived variable	Description
	handled as specified for “Serious adverse event” in Section 3.2.
Novelty	It is identified whether an AE is expected (known) or unexpected (unknown) based on the precautions for Benet/Actonel.
Presence or absence of an AE	It is identified whether there is an AE (including “unknown”).
Presence or absence of an ADR	It is identified whether there is an ADR (including “unknown”).
Presence or absence of a SAE	It is identified whether there is a SAE (including “unknown”).

6. Analysis Plan

Analysis sets, analysis items, and analysis methods are shown below. Details of variables for analysis and display will be specified in separately prepared statistical analysis specifications.

6.1. Analysis of Patients

6.1.1. Patient Composition Diagram

1) Analysis set: Enrolled patients

2) Chart plan: Figure 1-1

3) Analysis items:
- Number of registration sites
- Number of enrolled patients
- Number of patients with no CRF collected (including reasons for collecting no CRF)
- Number of patients with the CRF collected
- Number of patients not evaluated for safety (including reasons for exclusion)
- Number of patients evaluated for safety
- Number of patients not evaluated for efficacy (including reasons for exclusion)
- Number of patients evaluated for efficacy
- Number of patients not evaluated for vertebral fracture (including reasons for exclusion)
- Number of patients evaluated for vertebral fracture

4) Analysis methods: The number of patients (number of sites) will be calculated for the analysis item, and a composition diagram will be prepared.

6.1.2. Patient Baseline Characteristics

1) Analysis set: Patients evaluated for safety

Patients evaluated for vertebral fracture

2) Chart plan: Table 1-2

3) Analysis items: Sex [male, female, unknown]

Age (years)[*1] [<65 years, ≥65 years, unknown], [<75 years, ≥75 years, unknown]

Height before the start of treatment (cm)[*1]

Body weight (kg)[*1] [<50.0 kg, ≥50.0 kg, unknown]

BMI (kg/m^2)[*1] [<18.5 kg/m^2, ≥18.5 kg/m^2 to <25.0 kg/m^2, ≥25.0 kg/m^2, unknown]

Disease to be treated/diagnosis [primary, secondary, unknown]

Duration of disease (years)[*1] [<1 year, ≥1 year to <5 years, ≥5 years, unknown]

Predisposition to hypersensitivity [no, yes, unknown]

Presence or absence of concurrent illness[*2] [no, yes, unknown]

Disposition of concurrent illness [locomotor/spine disease other than osteoporosis (spinal osteoarthritis, lumbago, spinal column stenosis, osteoarthritis, other), rheumatoid arthritis, lifestyle-related disease (diabetes, hypertension, dyslipidemia, chronic obstructive pulmonary disease, other), cardiac disease (angina pectoris, myocardial infarction, arrhythmia, other), renal disease (diabetic nephropathy, nephrotic syndrome, glomerulonephritis, other), hepatic disease (chronic hepatitis, hepatic cirrhosis, hepatic steatosis, other), digestive disease (esophageal ulcer, gastric ulcer, duodenal ulcer, esophagitis, other), other]

Presence or absence of medical history (except previous fracture)[*2] [no, yes, unknown]

Disposition of medical history [cerebral infarction, myocardial infarction, thromboembolism, other]

Risk factors for fracture

Presence or absence of medical history (previous fracture)[*2] [no, yes, unknown]

Disposition of medical history (previous fracture) [vertebra, femur, wrist, forearm, upper arm, pelvis, lower limb, other]

Previous steroid use (except topical preparations) [no, yes, unknown]

Disposition of previous steroid use [at least 3 months at a prednisolone

equivalent dose of 5 mg/day or more, otherwise, unknown dose]

Parental history of femur fracture [no, yes, unknown]

Drinking history (≥3 units per day) [no, yes, unknown]

Smoking history [never smoked, current smoker, past smoker, unknown]

Previous osteoporosis drug [no, yes]

Previous treatment group [Benet/Actonel (risedronate), bisphosphonate other than Benet/Actonel, calcium, vitamin D, osteoporosis drug not listed above (parathyroid hormone, anti-RANKL monoclonal antibody, other), steroid]

Presence or absence of concomitant medication [no, yes]

Disposition of concomitant medication [osteoporosis drug, anti-inflammatory analgesic, cardiovascular drug, central nervous system drug, antidiabetic, digestive system drug, other]

Combination therapy group [calcium, vitamin D, osteoporosis drug not listed above (parathyroid hormone, anti-RANKL monoclonal antibody, other), steroid]

Presence or absence of physical therapy [no, yes, unknown]

Presence or absence of other concomitant therapy (e.g., diet therapy, exercise therapy, block therapy) [no, yes, unknown]

Presence or absence of low back pain before the start of treatment [no, yes, unknown]

4) Analysis methods: The number and proportion of patients will be calculated for the analysis item. Summary statistics will be calculated for analysis items with *1. Analysis items with *2 will be processed as specified in Section 5.1, "Handling of Dichotomous Variables."

6.1.3. Treatment Compliance Status

1) Analysis set: Patients evaluated for safety

2) Chart plan: Table 1-3

3) Analysis item: Treatment status [took the drug as instructed by a physician, took the drug on a different day from instructed by a physician, took no dose, unknown]

4) Analysis methods: The number and proportion of patients will be calculated for the analysis item by the number of doses indicated by a physician. In addition, a stacked bar chart will be plotted with the percentage of number of patients on the vertical axis and the number of doses on the horizontal axis.

6.1.4. Changes in Dosing Interval over Time

1) Analysis set	Patients evaluated for safety
2) Chart plan	Table 1-4
3) Analysis item	Dosing interval
4) Analysis methods	Summary statistics will be calculated for the analysis item by the number of doses of Benet/Actonel.

6.1.5. Number of Doses of Benet/Actonel

1) Analysis set	Patients evaluated for safety
2) Chart plan	Table 1-5
3) Analysis item	Number of doses of Benet/Actonel [1-6 doses, 7-9 doses, 10-12 doses, 13-24 doses, 25-36 doses, ≥37 doses]
4) Analysis methods	For the number of doses of Benet/Actonel, the number and proportion of patients in each category will be calculated, and summary statistics will be calculated.

6.2. Analysis of Safety

The safety will be analyzed in patients evaluated for safety.

6.2.1. List of Occurrence of Adverse Drug Reactions/Infections in the Special Drug Use Surveillance (Attachment Style 2)

1) Analysis set	Patients evaluated for safety
2) Chart plan	Table 2-1
3) Analysis items	Number of surveillance sites Number of surveyed patients Number of patients with an ADR, etc. Number of ADRs, etc. Proportion of patients with an ADR, etc. Proportion of patients with an ADR, etc. (number of ADRs, etc.) by type (SOC, PT)
4) Analysis methods	The number and proportion of patients (number of events) will be calculated for the analysis item, and a list of occurrence of ADRs/infections will be prepared.

6.2.2. List of Occurrence of Serious Adverse Events in Drug Use Surveillance/Special Drug Use Surveillance/Post-Marketing Clinical Study (Attachment Style 2-2, Attachment Style 10)

1) Analysis set	Patients evaluated for safety
2) Chart plan	Table 2-2
3) Analysis items	Number of surveillance sites Number of surveyed patients Number of patients with a SAE Number of SAEs Proportion of patients with a SAE Proportion of patients with a SAE (number of SAEs) by type (SOC, PT)
4) Analysis methods	The number and proportion of patients (number of events) will be calculated for the analysis item, and a list of occurrence of SAEs will be prepared.

6.2.3. Occurrence of Adverse Drug Reactions by Type

1) Analysis set	Patients evaluated for safety
2) Chart plan	Table 2-3
3) Analysis item	ADR type (SOC, PT)
4) Classification factors	Seriousness [serious, not serious] Time of onset [Days 1-7, Days 8-14, Days 15-21, Days 22-28, Days 29-56, Days 57-84, Days 85-180, Days 181-210, Days 211-360, Day 361 or later, unknown] Outcome [recovered, recovering, not recovered, recovered with sequelae, death, unknown]
5) Analysis methods	The number of ADRs by PT will be calculated for each category of classification. The number of patients with an ADR by SOC will be calculated only as the total.

6.2.4. List of Occurrence of Adverse Drug Reactions in Patients Not Evaluated for Safety

1) Analysis set	Patients not evaluated for safety
2) Chart plan	Table 2-4
3) Analysis items	Number of surveillance sites Number of surveyed patients Number of patients with an ADR, etc. Number of ADRs, etc. Proportion of patients with an ADR, etc.

	Proportion of patients with an ADR, etc. (number of ADRs, etc.) by type (SOC, PT)
4) Analysis methods	The number and proportion of patients (number of events) will be calculated for the analysis item, and a list of occurrence of ADRs will be prepared.

6.3. Analysis of Efficacy

The efficacy will be analyzed in patients evaluated for efficacy. Patients with no pre- or post-baseline data on the relevant efficacy endpoint will be excluded from analysis.

6.3.1. Incidence of Vertebral Fracture

1) Analysis set	Patients evaluated for efficacy with dates of pre- and post-treatment[*1] radiography
	Patients evaluated for vertebral fracture
2) Chart plan	Table 3-1-1-1
	Table 3-1-1-2
	Table 3-1-1-3
	Table 3-1-1-4
	Table 3-1-1-5
	Table 3-1-1-6
	Table 3-1-2-1
	Table 3-1-2-2
	Table 3-1-2-3
	Table 3-1-2-4
	Table 3-1-2-5
	Table 3-1-2-6
3) Analysis items	New vertebral fracture or worsening of prevalent fracture
	New vertebral fracture or worsening of prevalent fracture <non-traumatic>
	New vertebral fracture
	New vertebral fracture <non-traumatic>
	Worsening of prevalent fracture
	Worsening of prevalent fracture <non-traumatic>
4) Analysis methods	For the time to the first onset of the analysis item, the point estimate of cumulative incidence, standard error, and 95% confidence interval will be calculated using the Kaplan-Meier method, and the number of relevant patients (number of patients at risk), cumulative number of patients with

the analysis item, and cumulative number of censored patients at Month 6 (Day 180), Month 12 (Day 360), Month 18 (Day 540), Month 24 (Day 720), Month 30 (Day 900), and Month 36 (Day 1096) will be calculated. In addition, a Kaplan-Meier curve will be plotted with the cumulative incidence (%) on the vertical axis and the time (months) on the horizontal axis. The number of relevant patients (number of patients at risk) will be presented under the time (months).

The time to the first onset of the analysis item is defined as time from the start date of Benet/Actonel treatment to the earliest date of radiography with a diagnosis of the analysis item. Patients with no analysis item will be censored at the latest date of radiography with no evidence of the analysis item.*2

No radiographic data collected after the end date of Benet/Actonel treatment + 90 days or after 3 consecutive months (90 days) of interruption in patients with interruption of treatment will be used for analysis.

*1 Range of assessment before and after treatment

- Before treatment: before the start of Benet/Actonel treatment defined as Days -90 to 1
- After treatment: before the end date of Benet/Actonel treatment + 90 days, and before 3 consecutive months (90 days) of interruption in patients with interruption of treatment

*2 The date of radiography with no evidence of the analysis item is defined as follows for each analysis set:

- Patients evaluated for efficacy with dates of pre- and post-treatment radiography: date when it is determined that the analysis item has not occurred
- Patients evaluated for vertebral fracture: date when it is determined that the analysis item has not occurred and radiography is performed on the same location (thoracic spine, lumbar spine) as before treatment (before the start of Benet/Actonel treatment defined as Days -90 to 1) (for instance, the day of lumbar spine radiography will not be handled as the date when it is determined that the analysis item has not occurred for patients with thoracic spine radiography before

treatment.)

6.3.2. Incidence of Non-vertebral Fracture

1) Analysis set	Patients evaluated for efficacy
2) Chart plan	Table 3-2-1 Table 3-2-2 Table 3-2-3 Table 3-2-4
3) Analysis items	Non-vertebral fracture Non-vertebral fracture <non-traumatic> Femur fracture Femur fracture <non-traumatic>
4) Analysis methods	Non-vertebral fracture will be analyzed in the same manner as described in Section 6.3.1, "Incidence of Vertebral Fracture." The time to the first onset of the analysis item is defined as time from the start date of Benet/Actonel treatment to the earliest date of diagnosis of the analysis item. Patients with no analysis item will be censored at the latest date of dosing, discontinuation, assessment of each efficacy endpoint, or onset/outcome of AE.

6.3.3. Incidence of Vertebral Fracture Event at Each Time Point of Assessment

1) Analysis set	Patients evaluated for vertebral fracture
2) Chart plan	Table 3-3-1 Table 3-3-2
3) Analysis items	New vertebral fracture or worsening of prevalent fracture New vertebral fracture or worsening of prevalent fracture <non-traumatic>
4) Analysis methods	The number of relevant patients, observed person·years, number of patients with the first onset of the analysis item, and incidence rate (number of patients with event/100 person·years) in the range of assessment at each time point of assessment (see below) will be calculated, and the ratio of incidence rate at each time point of assessment relative to Month 6 and its 95% confidence interval will be calculated. Handling of onset day of the analysis item and data for analysis will be as specified in Section 6.3.1, "Incidence of Vertebral Fracture." Observed person·years: (1)+2)) ÷ 12

1): (Number of patients with radiography, no event, and no censoring in the range of assessment at each time point of assessment) × 6

A patient with no radiography at the relevant time point of assessment, but with valid radiography at any later time point will be counted at the relevant time point of assessment.

2): Total time (months) from the start date of assessment to event or censoring in the range of assessment at each time point of assessment for patients with event or censoring

Incidence rate: (number of patients with event ÷ observed person·years) × 100

Range of assessment at each time point of assessment

Time point of assessment	Range of assessment
Month 6	Days 2 to 180
Month 12	Days 181 to 360
Month 18	Days 361 to 540
Month 24	Days 541 to 720
Month 30	Days 721 to 900
Month 36	Days 901 to 1096

No radiographic data collected after the end date of Benet/Actonel treatment + 90 days or after 3 consecutive months (90 days) of interruption in patients with interruption of treatment will be handled as data in the range of assessment (not used for analysis).

6.3.4. Percent Changes in Bone Turnover Markers

1) Analysis set — Patients evaluated for efficacy with pre- and post-treatment values of bone turnover markers

2) Chart plan — Table 3-4

3) Analysis items — Bone turnover markers

4) Analysis methods — For each bone turnover marker, summary statistics at each time point of assessment will be calculated for observed value and percent change. In addition, the 95% confidence interval for percent change will be calculated, and p-value will be calculated as specified in Section 3.3. 4), "Rules of statistical testing."

6.3.5. Percent Change in Bone Mineral Density

1) Analysis set	Patients evaluated for efficacy with pre- and post-treatment values of bone mineral density
2) Chart plan	Table 3-5
3) Analysis item	Bone mineral density
4) Analysis methods	For each bone mineral density, summary statistics at each time point of assessment will be calculated for observed value and percent change. In addition, the 95% confidence interval for percent change will be calculated, and p-value will be calculated as specified in Section 3.3. 4), "Rules of statistical testing." If a check is made to lumbar spines 2) to 4) in the "Location of vertebral fracture" in the CRF after the start of Benet/Actonel treatment, no data on lumbar spine (DXA) bone mineral density dated the relevant date or later will be employed.

6.3.6. Changes in Height over Time

1) Analysis set	Patients evaluated for efficacy with pre- and post-treatment values of height
2) Chart plan	Table 3-6
3) Analysis item	Height (cm)
4) Analysis methods	For height, summary statistics at each time point of assessment will be calculated for observed value and change. In addition, the 95% confidence interval for percent change will be calculated.

6.3.7. Changes in Low Back Pain over Time

1) Analysis set	Patients evaluated for efficacy with pre- and post-treatment values of low back pain
2) Chart plan	Table 3-7
3) Analysis item	Low back pain
4) Analysis methods	For low back pain, a shift table before the start of treatment versus at each time point of assessment will be prepared. In addition, p-value will be calculated as specified in Section 3.3. 4), "Rules of statistical testing."

6.4. Listing

6.4.1. List of Discontinued Patients

1) Analysis set	Discontinued patients

2) Chart plan Table 4-1

3) Analysis items Patient number, sex, age, included in or excluded from the analysis set, start date and discontinuation date of Benet/Actonel treatment, number of days from start to discontinuation of Benet/Actonel treatment, reason for discontinuation, presence or absence of an AE, AE term

4) Analysis methods A list with the analysis items will be prepared.

6.4.2. List of Patients Not Evaluated

1) Analysis set Patients not evaluated for safety
Patients not evaluated for efficacy
Patients not evaluated for vertebral fracture

2) Chart plan Table 4-2

3) Analysis items Patient number, sex, age, included in or excluded from the analysis set, start date of Benet/Actonel treatment, reason for exclusion, presence or absence of an AE, AE term

4) Analysis methods A list with the analysis items will be prepared.

6.4.3. Summary List of Surveyed Patients (Attachment Style 3)

1) Analysis set Patients with the CRF collected

2) Chart plan Table 4-3

3) Analysis items Patient number, name, founder/code, and location (prefecture) of the study site, patient abbreviation, sex, age, inpatient or outpatient, reason for use (disease code, disease name), severity at baseline, concurrent illness (presence or absence, number, name), route of administration, maximum dose (daily dose/single dose), mean dose (daily dose/single dose), units, daily number of doses (most common), duration of use, concomitant medication (drug code, representative drug name, number), degree of response, ADR (system organ code, ADR code, ADR term, presence or absence, number), outcome, CRF number, dropout

4) Analysis methods A list with the analysis items will be prepared.

Benet 75 mg Tablets Special Drug Use Surveillance

Actonel 75 mg Tablets Special Drug Use Surveillance

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

Statistical Analysis Plan

Version 5.0

PPD

Takeda Pharmaceutical Co., Ltd.

PPD

PPD

PPD

History of amendments

Version number	Date of preparation	Preparator	Amendment/reason, etc.
1.0	7 March 2014	PPD	New document
2.0	29 September 2014		Thorough revision for the fourth periodic safety update report
2.1	8 October 2014		Correction made to Section 4.3, “Patients Included in Safety Analysis”
3.0	26 March 2015		Correction made to Section 3.3. 2), “Number of digits to be displayed” Addition to Section 5.4, “Handling of Time Points of Assessment” Addition to Section 5.5, “Derived Variables” Addition of Section 6.2.4, “Occurrence of Acute Phase Reaction”
4.0	6 January 2016		Thorough revision for the sixth periodic safety update report
4.1	27 May 2016		Standardization of expression: patients included in analysis→patients evaluated, patients excluded from analysis→patients not evaluated Correction made to Section 3.2, “Definitions of Terms” Addition to Section 4.3, “Patients Evaluated for Safety” Correction made to Section 5.5, “Derived Variables” Addition to Section 6.1.2, “Patient Baseline Characteristics” Addition to Section 6.3.6, “Percent Change in Bone Mineral Density”
5.0	22 November 2016		Thorough revision for the re-examination

Table of Contents

1. Objectives

This document is intended to describe the details of statistical analyses in a special drug use surveillance on fracture incidence during 36-month treatment with Benet 75 mg Tablets and Actonel 75 mg Tablets (hereinafter referred to as the surveillance). The chart layout for analysis results will be specified in a separately prepared chart plan.

2. Synopsis

Surveillance drug	Benet 75 mg Tablets/Actonel 75 mg Tablets (hereinafter referred to as Benet/Actonel)
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/Actonel in osteoporotic patients in clinical settings
Planned sample size	250 patients/250 patients A total of 500 patients
Registration method	Central registration method
Planned surveillance period	Surveillance period: From May 2013 to April 2018 Registration period: From May 2013 to October 2014

3. Definitions

3.1. Definitions of Abbreviations

Abbreviation	Description
PMS system	CCI [redacted] (name of the system supplied by PPD [redacted] for managing the progression of post-marketing surveillances)
BMI	Body Mass Index
AE	Adverse Event
SOC	System Organ Class
PT	Preferred Term
LLT	Low Level Term

3.2. Definitions of Terms

Term	Description
Finalized patient	For Benet Tablets, a finalized patient is defined as a patient who has the date of CRF approval in the PMS system. For Actonel Tablets, a finalized patient is defined as a patient who has the date of temporary finalization in the business management system.
Adverse event (AE)	All events entered into the column of [Adverse event] in the case report form (CRF) Any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of Benet/Actonel, whether or not it is considered related to Benet/Actonel
Adverse drug reaction (ADR)	All adverse events except those not related to Benet/Actonel according to "Causal relationship to Benet/Actonel" both in the column of [Adverse event] in the CRF and determined by the company If either assessment is missing, non-missing assessment of causal relationship is confirmed to determine the adverse event as an adverse drug reaction unless not related to Benet/Actonel.
Serious adverse event (SAE)	Adverse event assessed as serious according to "Seriousness" at least either in the column of [Adverse event] in the CRF or determined by the company, including "AEs that must always be assessed as serious" in the implementation guidelines and AEs in Takeda Medically Significant AE List

3.3. Statistical Arrangements

1) Summary statistics

For quantitative variables, summary statistics are number of relevant patients, mean, standard deviation, minimum, quartile points (25 percentile, 50 percentile, and 75 percentile), and maximum.

2) Number of digits to be displayed

Proportions and rates will be expressed as percentage (%) and displayed to two decimal places by rounding.

Minimum and maximum will be displayed with the same number of digits as raw data, and the other summary statistics will be displayed to one lower digit than raw data by rounding.

Ninety-five percent confidence interval will be displayed with the same number of digits as the

relevant statistics.

Statistical p-value will be displayed to four decimal places by rounding. P-value less than 0.0001 will be displayed as <0.0001. Infeasibility of testing will be indicated as "-."

3) 95% confidence interval

All confidence intervals will be presented as two-sided confidence intervals.

4) Rules of statistical testing

One-sample t-test or one-sample Wilcoxon test will be used for pre- and post-treatment comparison of continuous variables.

McNemar test will be used for pre- and post-treatment comparison in shift tables.

A two-sided 5% level of significance will be used.

The category of "unknown" will be excluded from statistical testing.

4. Analysis Sets

4.1. Enrolled Patients

All patients for whom the patient registration form has been accepted

4.2. Patients with the CRF Collected

Patients for whom the CRF has been collected and finalized

4.3. Patients Evaluated for Safety

All patients with the CRF collected, excluding those who meet any of the following criteria:

1) Not treated with Benet/Actonel

2) Unknown whether an AE occurred

3) Deviated from the registration criteria

• Treated before conclusion of a contract

• Not registered in the registration period

• Failed to fax the patient registration form within 15 days after the first prescription of Benet/Actonel

• Other (assessed as deviated from the registration criteria due to any reason not listed above)

4.4. Patients Evaluated for Efficacy

All patients evaluated for safety, excluding those who meet the following criterion:

Pre- and post-baseline values of all efficacy endpoints (bone turnover markers, bone mineral density, vertebral fracture, non-vertebral fracture, height, and low back pain) are unknown, including incalculable values

4.5. Patients Evaluated for Vertebral Fracture

All patients evaluated for efficacy, excluding those who meet any of the following criteria:

1) No evidence of 1 to 4 fractures from the fourth thoracic vertebra to the fourth lumbar vertebra provided by thoracic and lumbar spinal radiography performed before the start of the surveillance*

* The permissible range before the start of the surveillance is Days -90 to 1.

2) Not 50 years or older

3) Not an outpatient who can walk

4) No known date of pre- or post-treatment* radiography for assessment of vertebral fracture

* For the permissible range before or after treatment, refer to *1 in Section 6.3.1.

5. Handling of Data

Handling of data for analysis is described below. Details of processing will be specified in separately prepared analysis data set specifications.

5.1. Handling of Dichotomous Variables

For dichotomous variables, the presence or absence will be determined as described below when there is a column for details to be specified for "Yes."

1) "Yes" when details are specified

2) "No" when no details are specified and "No" is checked

3) "Unknown" when neither 1 nor 2) is applicable

5.2. Handling of Adverse Events

Multiple episodes of the same AE/ADR (SOC) in the same patient will be tabulated as 1 patient.

Multiple episodes of the same AE/ADR (PT) in the same patient will be tabulated as 1 event.

For tabulation by type (seriousness, time of onset, outcome), multiple episodes of the same AE/ADR (PT) in the same patient will be tabulated as 1 event on a PT basis according to the following order of precedence:

Seriousness: serious > not serious

Time of onset: chronological order

Outcome: death > recovered with sequelae > not recovered > recovering > recovered > unknown

5.3. Handling of Missing Data

In principle, no missing data will be imputed.

For frequency tabulation of qualitative variables, missing data will be handled as "unknown," and the column of "unknown" will not be presented if there is no relevant patient. For summary statistics of quantitative variables, missing data will be excluded.

5.4. Handling of Time Points of Assessment

Data within the permissible range as shown below will be employed.*

If there are multiple pieces of data within the permissible range, data on the day closest to the nominal day will be employed. If deviation is the same before and after the nominal day, the latest data will be employed.

Data collected up to the end date of Benet/Actonel treatment* + 30 days will be employed for bone

turnover markers and low back pain, and data collected up to the end date of Benet/Actonel treatment* + 90 days will be employed for the other endpoints. For patients with interruption of treatment, no data collected after 3 consecutive months (90 days) of interruption will be used for (efficacy) analysis.

At the final assessment, the latest available data (excluding data before the start of treatment) will be employed.

The start day of Benet/Actonel treatment is designated as Day 1, and the previous day as Day -1.

* Specified in Section 5.5, "Derived Variables"

<Time points of assessment of bone turnover markers and low back pain>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -30 to 1	Day 1
Month 3	Days 2 to 135	Day 90
Month 6	Days 136 to 270	Day 180
Month 12	Days 271 to 450	Day 360
Month 18	Days 451 to 630	Day 540
Month 24	Days 631 to 810	Day 720
Month 30	Days 811 to 990	Day 900
Month 36	Days 991 to 1170	Day 1096
Final assessment	Days 2 to 1170	-

<Time points of assessment of bone mineral density>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -90 to 30	Day 1
Month 3	Days 31 to 135	Day 90
Month 6	Days 136 to 270	Day 180
Month 12	Days 271 to 450	Day 360
Month 18	Days 451 to 630	Day 540
Month 24	Days 631 to 810	Day 720
Month 30	Days 811 to 990	Day 900
Month 36	Days 991 to 1170	Day 1096
Final assessment	Days 31 to 1170	-

<Time points of assessment of height>

Time point of assessment	Permissible range	Nominal day

Before the start of treatment	Days -90 to 1	Day 1
Month 12	Days 2 to 450	Day 360
Month 24	Days 451 to 900	Day 720
Month 36	Days 901 to 1170	Day 1096
Final assessment	Days 2 to 1170	-

5.5. Derived Variables

Derived variable	Description
Flag for enrollment	It is identified whether a patient is enrolled.
Flag for CRF collection	It is identified whether the CRF for a patient is collected.
Flag for inclusion in/exclusion from safety	It is identified whether a patient is evaluated for safety.
Flag for inclusion in/exclusion from efficacy	It is identified whether a patient is evaluated for efficacy.
Flag for inclusion in/exclusion from vertebral fracture	It is identified whether a patient is evaluated for vertebral fracture.
Age (years)	Age on the start day of Benet/Actonel treatment; or age described on the [Cover] in the CRF for Actonel Tablets if age cannot be calculated due to missing data on date of birth
BMI (kg/m^2)	Body mass index calculated as body weight (kg) ÷ height $(m)^2$
Duration of disease (years)	Number of years from diagnosis of osteoporosis to the start date of Benet/Actonel treatment (by rounding down)
Start date of Benet/Actonel treatment	The earliest (smallest) date among dates described in the [Treatment status of Benet/Actonel] in the CRF and when a patient appears to have taken the drug
End date of Benet/Actonel treatment	30 days after the latest (largest) date among dates described in the [Treatment status of Benet/Actonel] in the CRF and when a patient appears to have taken the drug
Duration of Benet/Actonel treatment (days)	Number of days from the start date of Benet/Actonel treatment to the end date of Benet/Actonel treatment "End date of Benet/Actonel treatment" - "start date of Benet/Actonel treatment" + 1
Duration of Benet/Actonel treatment (months)	Number of months from the start date of Benet/Actonel treatment to the end date of Benet/Actonel treatment "Duration of Benet/Actonel treatment (days)" ÷ 30

Derived variable	Description
Number of doses of Benet/Actonel	Number of doses during Benet/Actonel treatment counted as the number of checks made to "Took the drug on the day indicated by a physician" or "Took the drug on a different day from instructed by a physician" for patient's treatment status in the [Treatment status of Benet/Actonel] in the CRF Data are collected in the [Treatment status of Benet/Actonel] in the CRF on a dose basis (first dose, second dose, third dose,……) for Benet and on a monthly basis (Month 1, Month 2, Month 3,……) for Actonel. For tabulation, data of Actonel will be handled on a dose basis in line with data of Benet. No month with blank will be counted.
Amount of Benet/Actonel administered (mg)	Total dose during Benet/Actonel treatment calculated as number of doses of Benet/Actonel × 75 mg
Treatment rate (%)	Number of doses of Benet/Actonel ÷ number of entered "date indicated by a physician"
Treatment compliance rate (%)	Percentage of the number of doses taken as instructed by a physician relative to the number of doses indicated by the physician calculated as the number of checks made to "Took the drug on the day indicated by a physician" ÷ number of entered "date indicated by a physician"
Dosing interval (days)	Number of days from the date of a certain dosing to the date of the next dosing "Date of the next dosing" - "date of a certain dosing" Date of dosing refers to date when a patient took the drug (records of "Took no dose" for patient's treatment status are excluded to identify "date of a certain dosing" and "date of the next dosing"). Dosing interval is missing if either date of dosing is missing.
Duration of use (days)	Number of days from the start date of Benet/Actonel treatment to the end date of Benet/Actonel treatment "End date of Benet/Actonel treatment" - "start date of Benet/Actonel treatment" + 1
Duration of interruption of treatment (days)	Number of days from the date of a certain dosing to the date of the next dosing "Date of the next dosing" - "date of a certain dosing"

Derived variable	Description
	Date of dosing refers to date when a patient took the drug (records of "Took no dose" for patient's treatment status are excluded to identify "date of a certain dosing" and "date of the next dosing"). Dosing interval is missing if either date of dosing is missing.
Flag for previous treatment	A drug deemed as previous treatment is identified. Previous treatment being used after the start of Benet/Actonel treatment is also identified with a flag for concomitant medication.
Flag for concomitant medication	A drug deemed as concomitant medication is identified. Concomitant medication that has been used since before the start of Benet/Actonel treatment is also identified with a flag for previous treatment.
Flag for osteoporosis drug	An osteoporosis drug is identified.
Flag for anti-inflammatory analgesic	An anti-inflammatory analgesic is identified.
Flag for cardiovascular drug	A cardiovascular drug is identified.
Flag for central nervous system drug	A central nervous system drug is identified.
Flag for antidiabetic	An antidiabetic is identified.
Flag for digestive system drug	A digestive system drug is identified.
Flag for other drug	Other drug not listed above is identified.
Flag for Benet/Actonel 2.5 mg	A drug that is Benet/Actonel 2.5 mg is identified.
Flag for Benet/Actonel 17.5 mg	A drug that is Benet/Actonel 17.5 mg is identified.
Flag for bisphosphonate other than Benet/Actonel	A bisphosphonate other than Benet/Actonel is identified.
Flag for calcium	A drug that is calcium is identified.
Flag for vitamin D	A drug that is vitamin D is identified.
Flag for osteoporosis drug not listed above	A drug that is an osteoporosis drug not listed above is identified.
Flag for steroid	A drug that is a steroid is identified.
Flag for parathyroid hormone	A drug that is a parathyroid hormone is identified.
Flag for anti-RANKL	A drug that is an anti-RANKL monoclonal antibody is

Derived variable	Description
monoclonal antibody	identified.
Number of days to measurement (days)	Number of days from the start date of Benet/Actonel treatment to the date of measurement of the relevant endpoint "Date of measurement" - "start date of Benet/Actonel treatment" + 1; or "date of measurement" - "start date of Benet/Actonel treatment" if the date of measurement is earlier than the start date of Benet/Actonel treatment
Time point of assessment (for analysis)	Time points of assessment of bone turnover markers, low back pain, bone mineral density, and height are reallocated for analysis as specified in Section 5.4, "Handling of Time Points of Assessment."
Flag for employment of data	It is identified whether measurement data are employed.
Flag for event	A patient with event is defined as a patient who experienced at least one event such as vertebral fracture. A patient with no event is defined as a patient who experienced no event.
Time point of event onset	Time point of event onset is defined as the first onset of event such as vertebral fracture. Patients with no event are censored at the final assessment.
Measured value before the start of treatment	The measured value before the start of treatment is identified.
Change	Value obtained by deducting the measured value before the start of treatment from a measured value at each time point
Percent change (%)	Value obtained by dividing a change by the measured value before the start of treatment and then multiplying the division by 100
Time of onset (days)	Number of days from the start date of Benet/Actonel treatment to the date of onset of AE "Date of onset" - "start date of Benet/Actonel treatment" + 1
Flag for inclusion/exclusion as an AE	It is identified whether an event is an AE.
Relationship (for analysis)	It is identified whether an AE is related to Benet/Actonel. The causal relationship is handled as specified for "Adverse drug reaction" in Section 3.2.
Seriousness (for analysis)	It is identified whether an AE is serious. The seriousness is

Derived variable	Description
	handled as specified for “Serious adverse event” in Section 3.2.
Novelty	It is identified whether an AE is expected (known) or unexpected (unknown) based on the precautions for Benet/Actonel.
Presence or absence of an AE	It is identified whether there is an AE (including “unknown”).
Presence or absence of an ADR	It is identified whether there is an ADR (including “unknown”).
Presence or absence of a SAE	It is identified whether there is a SAE (including “unknown”).

6. Analysis Plan

Analysis sets, analysis items, and analysis methods are shown below. Details of variables for analysis and display will be specified in separately prepared statistical analysis specifications.

6.1. Analysis of Patients

6.1.1. Patient Composition Diagram

1) Analysis set: Enrolled patients

2) Chart plan: Figure 1-1

3) Analysis items:
- Number of registration sites
- Number of enrolled patients
- Number of patients with no CRF collected (including reasons for collecting no CRF)
- Number of patients with the CRF collected
- Number of patients not evaluated for safety (including reasons for exclusion)
- Number of patients evaluated for safety
- Number of patients not evaluated for efficacy (including reasons for exclusion)
- Number of patients evaluated for efficacy
- Number of patients not evaluated for vertebral fracture (including reasons for exclusion)
- Number of patients evaluated for vertebral fracture

4) Analysis methods: The number of patients (number of sites) will be calculated for the analysis item, and a composition diagram will be prepared.

6.1.2. Patient Baseline Characteristics

1) Analysis set: Patients evaluated for safety

Patients evaluated for vertebral fracture

2) Chart plan: Table 1-2

3) Analysis items: Sex [male, female, unknown]

Age (years)[*1] [<65 years, ≥65 years, unknown], [<75 years, ≥75 years, unknown]

Height before the start of treatment (cm)[*1]

Body weight (kg)[*1] [<50.0 kg, ≥50.0 kg, unknown]

BMI (kg/m^2)[*1] [<18.5 kg/m^2, ≥18.5 kg/m^2 to <25.0 kg/m^2, ≥25.0 kg/m^2, unknown]

Disease to be treated/diagnosis [primary, secondary, unknown]

Duration of disease (years)[*1] [<1 year, ≥1 year to <5 years, ≥5 years, unknown]

Predisposition to hypersensitivity [no, yes, unknown]

Presence or absence of concurrent illness[*2] [no, yes, unknown]

Disposition of concurrent illness [locomotor/spine disease other than osteoporosis (spinal osteoarthritis, lumbago, spinal column stenosis, osteoarthritis, other), rheumatoid arthritis, lifestyle-related disease (diabetes, hypertension, dyslipidemia, chronic obstructive pulmonary disease, other), cardiac disease (angina pectoris, myocardial infarction, arrhythmia, other), renal disease (diabetic nephropathy, nephrotic syndrome, glomerulonephritis, other), hepatic disease (chronic hepatitis, hepatic cirrhosis, hepatic steatosis, other), digestive disease (esophageal ulcer, gastric ulcer, duodenal ulcer, esophagitis, other), other]

Presence or absence of medical history (except previous fracture)[*2] [no, yes, unknown]

Disposition of medical history [cerebral infarction, myocardial infarction, thromboembolism, other]

Risk factors for fracture

Presence or absence of medical history (previous fracture)[*2] [no, yes, unknown]

Disposition of medical history (previous fracture) [vertebra, femur, wrist, forearm, upper arm, pelvis, lower limb, other]

Previous steroid use (except topical preparations) [no, yes, unknown]

Disposition of previous steroid use [at least 3 months at a prednisolone

equivalent dose of 5 mg/day or more, otherwise, unknown dose]

Parental history of femur fracture [no, yes, unknown]

Drinking history (≥3 units per day) [no, yes, unknown]

Smoking history [never smoked, current smoker, past smoker, unknown]

Previous osteoporosis drug [no, yes]

Previous treatment group [Benet/Actonel (risedronate), bisphosphonate other than Benet/Actonel, calcium, vitamin D, osteoporosis drug not listed above (parathyroid hormone, anti-RANKL monoclonal antibody, other), steroid]

Presence or absence of concomitant medication [no, yes]

Disposition of concomitant medication [osteoporosis drug, anti-inflammatory analgesic, cardiovascular drug, central nervous system drug, antidiabetic, digestive system drug, other]

Combination therapy group [calcium, vitamin D, osteoporosis drug not listed above (parathyroid hormone, anti-RANKL monoclonal antibody, other), steroid]

Presence or absence of physical therapy [no, yes, unknown]

Presence or absence of other concomitant therapy (e.g., diet therapy, exercise therapy, block therapy) [no, yes, unknown]

Presence or absence of low back pain before the start of treatment [no, yes, unknown]

4) Analysis methods: The number and proportion of patients will be calculated for the analysis item. Summary statistics will be calculated for analysis items with *1. Analysis items with *2 will be processed as specified in Section 5.1, "Handling of Dichotomous Variables."

6.1.3. Treatment Compliance Status

1) Analysis set: Patients evaluated for safety

2) Chart plan: Table 1-3

3) Analysis item: Treatment status [took the drug as instructed by a physician, took the drug on a different day from instructed by a physician, took no dose, unknown]

4) Analysis methods: The number and proportion of patients will be calculated for the analysis item by the number of doses indicated by a physician. In addition, a stacked bar chart will be plotted with the percentage of number of patients on the vertical axis and the number of doses on the horizontal axis.

6.1.4. Changes in Dosing Interval over Time

1) Analysis set	Patients evaluated for safety
2) Chart plan	Table 1-4
3) Analysis item	Dosing interval
4) Analysis methods	Summary statistics will be calculated for the analysis item by the number of doses of Benet/Actonel.

6.1.5. Number of Doses of Benet/Actonel

1) Analysis set	Patients evaluated for safety
2) Chart plan	Table 1-5
3) Analysis item	Number of doses of Benet/Actonel [1-6 doses, 7-9 doses, 10-12 doses, 13-24 doses, 25-36 doses, ≥37 doses]
4) Analysis methods	For the number of doses of Benet/Actonel, the number and proportion of patients in each category will be calculated, and summary statistics will be calculated.

6.2. Analysis of Safety

The safety will be analyzed in patients evaluated for safety.

6.2.1. List of Occurrence of Adverse Drug Reactions/Infections in the Special Drug Use Surveillance (Attachment Style 2)

1) Analysis set	Patients evaluated for safety
2) Chart plan	Table 2-1
3) Analysis items	Number of surveillance sites Number of surveyed patients Number of patients with an ADR, etc. Number of ADRs, etc. Proportion of patients with an ADR, etc. Proportion of patients with an ADR, etc. (number of ADRs, etc.) by type (SOC, PT)
4) Analysis methods	The number and proportion of patients (number of events) will be calculated for the analysis item, and a list of occurrence of ADRs/infections will be prepared.

6.2.2. List of Occurrence of Serious Adverse Events in Drug Use Surveillance/Special Drug Use Surveillance/Post-Marketing Clinical Study (Attachment Style 2-2, Attachment Style 10)

1) Analysis set	Patients evaluated for safety
2) Chart plan	Table 2-2
3) Analysis items	Number of surveillance sites Number of surveyed patients Number of patients with a SAE Number of SAEs Proportion of patients with a SAE Proportion of patients with a SAE (number of SAEs) by type (SOC, PT)
4) Analysis methods	The number and proportion of patients (number of events) will be calculated for the analysis item, and a list of occurrence of SAEs will be prepared. SAEs collected in a separate special drug use surveillance for long-term use of Benet/Actonel will be combined.

6.2.3. Occurrence of Adverse Drug Reactions by Type

1) Analysis set	Patients evaluated for safety
2) Chart plan	Table 2-3
3) Analysis item	ADR type (SOC, PT)
4) Classification factors	Seriousness [serious, not serious] Time of onset [Days 1-7, Days 8-14, Days 15-21, Days 22-28, Days 29-56, Days 57-84, Days 85-180, Days 181-210, Days 211-360, Day 361 or later, unknown] Outcome [recovered, recovering, not recovered, recovered with sequelae, death, unknown]
5) Analysis methods	The number of ADRs by PT will be calculated for each category of classification. The number of patients with an ADR by SOC will be calculated only as the total.

6.2.4. List of Occurrence of Adverse Drug Reactions in Patients Not Evaluated for Safety

1) Analysis set	Patients not evaluated for safety
2) Chart plan	Table 2-4
3) Analysis items	Number of surveillance sites Number of surveyed patients Number of patients with an ADR, etc.

	Number of ADRs, etc. Proportion of patients with an ADR, etc. Proportion of patients with an ADR, etc. (number of ADRs, etc.) by type (SOC, PT)
4) Analysis methods	The number and proportion of patients (number of events) will be calculated for the analysis item, and a list of occurrence of ADRs will be prepared.

6.3. Analysis of Efficacy

The efficacy will be analyzed in patients evaluated for efficacy. Patients with no pre- or post-baseline data on the relevant efficacy endpoint will be excluded from analysis.

6.3.1. Incidence of Vertebral Fracture

1) Analysis set	Patients evaluated for efficacy with dates of pre- and post-treatment[*1] radiography Patients evaluated for vertebral fracture
2) Chart plan	Table 3-1-1-1 Table 3-1-1-2 Table 3-1-1-3 Table 3-1-1-4 Table 3-1-1-5 Table 3-1-1-6 Table 3-1-2-1 Table 3-1-2-2 Table 3-1-2-3 Table 3-1-2-4 Table 3-1-2-5 Table 3-1-2-6
3) Analysis items	New vertebral fracture or worsening of prevalent fracture New vertebral fracture or worsening of prevalent fracture <non-traumatic> New vertebral fracture New vertebral fracture <non-traumatic> Worsening of prevalent fracture Worsening of prevalent fracture <non-traumatic>
4) Analysis methods	For the time to the first onset of the analysis item, the point estimate of cumulative incidence, standard error, and 95% confidence interval will be

calculated using the Kaplan-Meier method, and the number of relevant patients (number of patients at risk), cumulative number of patients with the analysis item, and cumulative number of censored patients at Month 6 (Day 180), Month 12 (Day 360), Month 18 (Day 540), Month 24 (Day 720), Month 30 (Day 900), and Month 36 (Day 1096) will be calculated. In addition, a Kaplan-Meier curve will be plotted with the cumulative incidence (%) on the vertical axis and the time (months) on the horizontal axis. The number of relevant patients (number of patients at risk) will be presented under the time (months).

The time to the first onset of the analysis item is defined as time from the start date of Benet/Actonel treatment to the earliest date of radiography with a diagnosis of the analysis item. Patients with no analysis item will be censored at the latest date of radiography with no evidence of the analysis item.*2

No radiographic data collected after the end date of Benet/Actonel treatment + 90 days or after 3 consecutive months (90 days) of interruption in patients with interruption of treatment will be used for analysis.

*1 Range of assessment before and after treatment

- Before treatment: before the start of Benet/Actonel treatment defined as Days -90 to 1
- After treatment: before the end date of Benet/Actonel treatment + 90 days, and before 3 consecutive months (90 days) of interruption in patients with interruption of treatment

*2 The date of radiography with no evidence of the analysis item is defined as follows for each analysis set:

- Patients evaluated for efficacy with dates of pre- and post-treatment radiography: date when it is determined that the analysis item has not occurred
- Patients evaluated for vertebral fracture: date when it is determined that the analysis item has not occurred and radiography is performed on the same location (thoracic spine, lumbar spine) as before treatment (before the start of Benet/Actonel treatment defined as Days -90 to 1) (for instance, the day of lumbar spine radiography will

not be handled as the date when it is determined that the analysis item has not occurred for patients with thoracic spine radiography before treatment.)

6.3.2. Incidence of Non-vertebral Fracture

1) Analysis set	Patients evaluated for efficacy
2) Chart plan	Table 3-2-1 Table 3-2-2 Table 3-2-3 Table 3-2-4
3) Analysis items	Non-vertebral fracture Non-vertebral fracture <non-traumatic> Femur fracture Femur fracture <non-traumatic>
4) Analysis methods	Non-vertebral fracture will be analyzed in the same manner as described in Section 6.3.1, "Incidence of Vertebral Fracture." The time to the first onset of the analysis item is defined as time from the start date of Benet/Actonel treatment to the earliest date of diagnosis of the analysis item. Patients with no analysis item will be censored at the latest date of dosing, discontinuation, assessment of each efficacy endpoint, or onset/outcome of AE.

6.3.3. Incidence of Vertebral Fracture Event at Each Time Point of Assessment

1) Analysis set	Patients evaluated for vertebral fracture
2) Chart plan	Table 3-3-1 Table 3-3-2
3) Analysis items	New vertebral fracture or worsening of prevalent fracture New vertebral fracture or worsening of prevalent fracture <non-traumatic>
4) Analysis methods	The number of relevant patients, observed person·years, number of patients with the first onset of the analysis item, and incidence rate (number of patients with event/100 person·years) in the range of assessment at each time point of assessment (see below) will be calculated, and the ratio of incidence rate at each time point of assessment relative to Month 6 and its 95% confidence interval will be calculated. Handling of onset day of the analysis item and data for analysis will be as specified in Section 6.3.1, "Incidence of Vertebral Fracture."

Observed person·years: (1)+2)) ÷ 12

1): (Number of patients with radiography, no event, and no censoring in the range of assessment at each time point of assessment) × 6

A patient with no radiography at the relevant time point of assessment, but with valid radiography at any later time point will be counted at the relevant time point of assessment.

2): Total time (months) from the start date of assessment to event or censoring in the range of assessment at each time point of assessment for patients with event or censoring

Incidence rate: (number of patients with event ÷ observed person·years) × 100

Range of assessment at each time point of assessment

Time point of assessment	Range of assessment
Month 6	Days 2 to 180
Month 12	Days 181 to 360
Month 18	Days 361 to 540
Month 24	Days 541 to 720
Month 30	Days 721 to 900
Month 36	Days 901 to 1096

No radiographic data collected after the end date of Benet/Actonel treatment + 90 days or after 3 consecutive months (90 days) of interruption in patients with interruption of treatment will be handled as data in the range of assessment (not used for analysis).

6.3.4. Percent Changes in Bone Turnover Markers

1) Analysis set — Patients evaluated for efficacy with pre- and post-treatment values of bone turnover markers

2) Chart plan — Table 3-4

3) Analysis items — Bone turnover markers

4) Analysis methods — For each bone turnover marker, summary statistics at each time point of assessment will be calculated for observed value and percent change. In addition, the 95% confidence interval for percent change will be calculated, and p-value will be calculated as specified in Section 3.3. 4),

"Rules of statistical testing."

6.3.5. Percent Change in Bone Mineral Density

1) Analysis set	Patients evaluated for efficacy with pre- and post-treatment values of bone mineral density
2) Chart plan	Table 3-5
3) Analysis item	Bone mineral density
4) Analysis methods	For each bone mineral density, summary statistics at each time point of assessment will be calculated for observed value and percent change. In addition, the 95% confidence interval for percent change will be calculated, and p-value will be calculated as specified in Section 3.3. 4), "Rules of statistical testing." If a check is made to lumbar spines 2) to 4) in the "Location of vertebral fracture" in the CRF after the start of Benet/Actonel treatment, no data on lumbar spine (DXA) bone mineral density dated the relevant date or later will be employed.

6.3.6. Changes in Height over Time

1) Analysis set	Patients evaluated for efficacy with pre- and post-treatment values of height
2) Chart plan	Table 3-6
3) Analysis item	Height (cm)
4) Analysis methods	For height, summary statistics at each time point of assessment will be calculated for observed value and change. In addition, the 95% confidence interval for percent change will be calculated.

6.3.7. Changes in Low Back Pain over Time

1) Analysis set	Patients evaluated for efficacy with pre- and post-treatment values of low back pain
2) Chart plan	Table 3-7
3) Analysis item	Low back pain
4) Analysis methods	For low back pain, a shift table before the start of treatment versus at each time point of assessment will be prepared. In addition, p-value will be calculated as specified in Section 3.3. 4), "Rules of statistical testing."

6.4. Listing

6.4.1. List of Discontinued Patients

1) Analysis set	Discontinued patients
2) Chart plan	Table 4-1
3) Analysis items	Patient number, sex, age, included in or excluded from the analysis set, start date and discontinuation date of Benet/Actonel treatment, number of days from start to discontinuation of Benet/Actonel treatment, reason for discontinuation, presence or absence of an AE, AE term
4) Analysis methods	A list with the analysis items will be prepared.

6.4.2. List of Patients Not Evaluated

1) Analysis set	Patients not evaluated for safety Patients not evaluated for efficacy Patients not evaluated for vertebral fracture
2) Chart plan	Table 4-2
3) Analysis items	Patient number, sex, age, included in or excluded from the analysis set, start date of Benet/Actonel treatment, reason for exclusion, presence or absence of an AE, AE term
4) Analysis methods	A list with the analysis items will be prepared.

6.4.3. Summary List of Surveyed Patients (Attachment Style 3)

1) Analysis set	Patients with the CRF collected
2) Chart plan	Table 4-3
3) Analysis items	Patient number, name, founder/code, and location (prefecture) of the study site, patient abbreviation, sex, age, inpatient or outpatient, reason for use (disease code, disease name), severity at baseline, concurrent illness (presence or absence, number, name), route of administration, maximum dose (daily dose/single dose), mean dose (daily dose/single dose), units, daily number of doses (most common), duration of use, concomitant medication (drug code, representative drug name, number), degree of response, ADR (system organ code, ADR code, ADR term, presence or absence, number), outcome, CRF number, dropout
4) Analysis methods	A list with the analysis items will be prepared.

Benet 75 mg Tablets Special Drug Use Surveillance

Actonel 75 mg Tablets Special Drug Use Surveillance

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

Statistical Analysis Plan

Version 4.1

PPD

Takeda Pharmaceutical Co., Ltd.

PPD

PPD

PPD

History of amendments

Version number	Date of preparation	Preparator	Amendment/reason, etc.
1.0	7 March 2014	PPD	New document
2.0	29 September 2014		Thorough revision for the fourth periodic safety update report
2.1	8 October 2014		Correction made to Section 4.3, “Patients Included in Safety Analysis”
3.0	26 March 2015		Correction made to Section 3.3. 2), “Number of digits to be displayed” Addition to Section 5.4, “Handling of Time Points of Assessment” Addition to Section 5.5, “Derived Variables” Addition of Section 6.2.4, “Occurrence of Acute Phase Reaction”
4.0	6 January 2016		Thorough revision for the sixth periodic safety update report
4.1	27 May 2016		Standardization of expression: patients included in analysis→patients evaluated, patients excluded from analysis→patients not evaluated Correction made to Section 3.2, “Definitions of Terms” Addition to Section 4.3, “Patients Evaluated for Safety” Correction made to Section 5.5, “Derived Variables” Addition to Section 6.1.2, “Patient Baseline Characteristics” Addition to Section 6.3.6, “Percent Change in Bone Mineral Density”

Table of Contents

1. Objectives

This document is intended to describe the details of statistical analyses in a special drug use surveillance on fracture incidence during 36-month treatment with Benet 75 mg Tablets and Actonel 75 mg Tablets (hereinafter referred to as the surveillance). The chart layout for analysis results will be specified in a separately prepared chart plan.

2. Synopsis

Surveillance drug	Benet 75 mg Tablets/Actonel 75 mg Tablets (hereinafter referred to as Benet/Actonel)
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/Actonel in osteoporotic patients in clinical settings
Planned sample size	250 patients/250 patients A total of 500 patients
Registration method	Central registration method
Planned surveillance period	Surveillance period: From May 2013 to April 2018 Registration period: From May 2013 to October 2014

3. Definitions

3.1. Definitions of Abbreviations

Abbreviation	Description
PMS system	CCI [redacted] (name of the system supplied by PPD [redacted] for managing the progression of post-marketing surveillances)
BMI	Body Mass Index
AE	Adverse Event
SOC	System Organ Class
PT	Preferred Term
LLT	Low Level Term

3.2. Definitions of Terms

Term	Description
Finalized patient	For Benet Tablets, a finalized patient is defined as a patient who has the date of CRF approval in the PMS system. For Actonel Tablets, a finalized patient is defined as a patient who has the date of temporary finalization in the business management system.
Adverse event (AE)	All events entered into the column of [Adverse event] in the case report form (CRF) Any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of Benet/Actonel, whether or not it is considered related to Benet/Actonel
Adverse drug reaction (ADR)	For Benet Tablets, all adverse events except those not related to Benet according to "Causal relationship to Benet" in the column of [Adverse event] in the CRF For Actonel Tablets, all adverse events except those not related to Actonel according to "Causal relationship to Actonel" both in the column of [Adverse event] in the CRF and determined by the company If either assessment is missing, non-missing assessment of causal relationship is confirmed to determine the adverse event as an adverse drug reaction unless not related to Actonel.
Serious adverse event (SAE)	Adverse event assessed as serious according to "Seriousness" at least either in the column of [Adverse event] in the CRF or determined by the company, including "AEs that must always be assessed as serious" in the implementation guidelines and AEs in Takeda Medically Significant AE List

3.3. Statistical Arrangements

1) Summary statistics

For quantitative variables, summary statistics are number of relevant patients, mean, standard deviation, minimum, quartile points (25 percentile, 50 percentile, and 75 percentile), and maximum.

2) Number of digits to be displayed

Proportions will be displayed to two decimal places by rounding.

Minimum and maximum will be displayed with the same number of digits as the number of

significant figures, and the other summary statistics will be displayed to one lower digit than raw data by rounding.
Statistical p-value will be displayed to four decimal places by rounding. P-value less than 0.0001 will be displayed as <0.0001. Infeasibility of testing will be indicated as "-."

3) 95% confidence interval
For continuous variables, 95% confidence interval for mean difference will be presented as confidence limits following t-distribution.

4) Rules of statistical testing
One-sample t-test or one-sample Wilcoxon test will be used for pre- and post-treatment comparison of continuous variables.
McNemar test will be used for pre- and post-treatment comparison of ratios.
For assessment of vertebral fracture, Poisson regression analysis will be used based on the assumption that the frequency follows the Poisson distribution, and there is a linear relationship between the expected value of frequency and the explanatory variable.
A two-sided 5% level of significance will be used.
The category of "unknown" will be excluded from statistical testing.

4. Analysis Sets

4.1. Enrolled Patients

All patients for whom the patient registration form has been accepted

4.2. Patients with the CRF Collected

Patients for whom the CRF has been collected and finalized

4.3. Patients Evaluated for Safety

All patients with the CRF collected, excluding those who meet any of the following criteria:
1) Not treated with Benet/Actonel
2) Unknown whether an AE occurred
3) Deviated from the registration criteria
• Treated before conclusion of a contract
• Not registered in the registration period
• Failed to fax the patient registration form within 15 days after the first prescription of Benet/Actonel

• Other (assessed as deviated from the registration criteria due to any reason not listed above)

4.4. Patients Evaluated for Efficacy

All patients evaluated for safety, excluding those who meet the following criterion:

Pre- and post-baseline values of all efficacy endpoints (bone turnover markers, bone mineral density, vertebral fracture, non-vertebral fracture, height, and low back pain) are unknown, including incalculable values

4.5. Patients Evaluated for Vertebral Fracture

All patients evaluated for efficacy, excluding those who meet any of the following criteria:

1) No evidence of 1 to 4 fractures from the fourth thoracic vertebra to the fourth lumbar vertebra provided by thoracic and lumbar spinal radiography performed before the start of the surveillance*

* The permissible range before the start of the surveillance is Days -90 to 1.

2) Not 50 years or older

3) Not an outpatient who can walk

4) Different radiographic location after treatment relative to baseline

5. Handling of Data

Handling of data for analysis is described below. Details of processing will be specified in separately prepared analysis data set specifications.

5.1. Handling of Dichotomous Variables

For dichotomous variables, the presence or absence will be determined as described below when there is a column for details to be specified for "Yes."

1) "Yes" when details are specified

2) "No" when no details are specified and "No" is checked

3) "Unknown" when neither 1 nor 2) is applicable

5.2. Handling of Adverse Events

When multiple AEs of the same LLT are reported in the same patient, an AE to be employed will be determined as described below.

1) AEs that differ in the causal relationship to Benet/Actonel will be handled separately.

2) When multiple AEs of the same causal relationship to Benet/Actonel are reported, the most serious AE will be employed.

3) When multiple AEs of the same seriousness are reported, the earliest AE will be employed.

4) When multiple AEs are reported on the same day, an AE with the latest outcome will be employed.

5.3. Handling of Missing Data

In principle, no missing data will be imputed.

For frequency tabulation of qualitative variables, missing data will be handled as "unknown." For summary statistics of quantitative variables, missing data will be excluded, and non-missing data will be used.

5.4. Handling of Time Points of Assessment

Data within the permissible range as shown below will be employed.

If there are multiple pieces of data within the permissible range, data on the day closest to the nominal day will be employed. If deviation is the same before and after the nominal day, the latest data will be employed.

Data collected up to the end date of Benet/Actonel treatment* + 90 days will be employed for bone

mineral density, and data collected up to the end date of Benet/Actonel treatment* + 30 days will be employed for the other endpoints. For patients with interruption of treatment, no data collected after 3 consecutive months (90 days) of interruption will be used for (efficacy) analysis.

* Specified in Section 5.5, "Derived Variables"

<Time points of assessment of vertebral fracture, non-vertebral fracture, and femur fracture>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -90 to 1	Day 1
Month 6	Days 2 to 180	Day 180
Month 12	Days 181 to 360	Day 360
Month 18	Days 361 to 540	Day 540
Month 24	Days 541 to 720	Day 720
Month 30	Days 721 to 900	Day 900
Month 36	Days 901 to 1096	Day 1096
Final assessment	Days 2 to 1096	-

<Time points of assessment of bone turnover markers and low back pain>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -30 to 3	Day 1
Month 3	Days 4 to 135	Day 90
Month 6	Days 136 to 270	Day 180
Month 12	Days 271 to 450	Day 360
Month 18	Days 451 to 630	Day 540
Month 24	Days 631 to 810	Day 720
Month 30	Days 811 to 990	Day 900
Month 36	Days 991 to 1170	Day 1096
Final assessment	Days 4 to 1170	-

<Time points of assessment of bone mineral density>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -30 to 1	Day 1
Month 3	Days 2 to 105	Day 90
Month 6	Days 106 to 270	Day 180
Month 12	Days 271 to 450	Day 360
Month 18	Days 451 to 630	Day 540

Month 24	Days 631 to 810	Day 720
Month 30	Days 811 to 990	Day 900
Month 36	Days 991 to 1170	Day 1096
Final assessment	Days 2 to 1170	-

<Time points of assessment of height>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -30 to 3	Day 1
Month 12	Days 4 to 540	Day 360
Month 24	Days 541 to 900	Day 720
Month 36	Days 901 to 1170	Day 1096
Final assessment	Days 4 to 1170	-

5.5. Derived Variables

Derived variable	Description
Flag for enrollment	It is identified whether a patient is enrolled.
Flag for CRF collection	It is identified whether the CRF for a patient is collected.
Flag for inclusion in/exclusion from safety	It is identified whether a patient is evaluated for safety.
Flag for inclusion in/exclusion from efficacy	It is identified whether a patient is evaluated for efficacy.
Flag for inclusion in/exclusion from vertebral fracture	It is identified whether a patient is evaluated for vertebral fracture.
Age (years)	Age on the start day of Benet/Actonel treatment; or age described on the [Cover] in the CRF if date of birth is missing
BMI (kg/m^2)	Body mass index calculated as body weight (kg) ÷ height $(m)^2$
Duration of disease (years)	Number of years from diagnosis of osteoporosis to the start date of Benet/Actonel treatment (by rounding down)
Start date of Benet/Actonel treatment	The earliest (smallest) date among dates described in the [Treatment status of Benet/Actonel] in the CRF and when a patient appears to have taken the drug
End date of Benet/Actonel treatment	30 days after the latest (largest) date among dates described in the [Treatment status of Benet/Actonel] in the CRF and when a patient appears to have taken the drug

Derived variable	Description
Duration of Benet/Actonel treatment (days)	Number of days from the start date of Benet/Actonel treatment to the end date of Benet/Actonel treatment
Duration of Benet/Actonel treatment (months)	Number of months from the start date of Benet/Actonel treatment to the end date of Benet/Actonel treatment
Number of doses of Benet/Actonel	Total number of doses during Benet/Actonel treatment counted as the number of checks made to "Took the drug on the day indicated by a physician" or "Took the drug on a different day from instructed by a physician" for patient's treatment status in the [Treatment status of Benet/Actonel] in the CRF Data are collected in the [Treatment status of Benet/Actonel] in the CRF on a dose basis (first dose, second dose, third dose,……) for Benet and on a monthly basis (Month 1, Month 2, Month 3,……) for Actonel. For tabulation, data of Actonel will be handled on a dose basis in line with data of Benet. No month with blank will be counted.
Amount of Benet/Actonel administered (mg)	Total dose during Benet/Actonel treatment calculated as number of doses of Benet/Actonel × 75 mg
Treatment rate (%)	Number of doses of Benet/Actonel ÷ number of entered "date indicated by a physician"
Treatment compliance rate (%)	Percentage of the number of doses taken as instructed by a physician relative to the number of doses indicated by the physician calculated as the number of checks made to "Took the drug on the day indicated by a physician" ÷ number of entered "date indicated by a physician"
Dosing interval (days)	Number of days from the date of a certain dosing to the date of the next dosing
Flag for previous treatment	A drug deemed as previous treatment is identified. Previous treatment being used after the start of Benet/Actonel treatment is also identified with a flag for concomitant medication.
Flag for concomitant medication	A drug deemed as concomitant medication is identified. Concomitant medication that has been used since before the start of Benet/Actonel treatment is also identified with a flag for previous treatment.
Flag for osteoporosis drug	An osteoporosis drug is identified.

Derived variable	Description
Flag for anti-inflammatory analgesic	An anti-inflammatory analgesic is identified.
Flag for cardiovascular drug	A cardiovascular drug is identified.
Flag for central nervous system drug	A central nervous system drug is identified.
Flag for antidiabetic	An antidiabetic is identified.
Flag for digestive system drug	A digestive system drug is identified.
Flag for other drug	Other drug not listed above is identified.
Flag for Benet/Actonel 2.5 mg	A drug that is Benet/Actonel 2.5 mg is identified.
Flag for Benet/Actonel 17.5 mg	A drug that is Benet/Actonel 17.5 mg is identified.
Flag for bisphosphonate other than Benet/Actonel	A bisphosphonate other than Benet/Actonel is identified.
Flag for calcium	A drug that is calcium is identified.
Flag for vitamin D	A drug that is vitamin D is identified.
Flag for osteoporosis drug not listed above	A drug that is an osteoporosis drug not listed above is identified.
Flag for steroid	A drug that is a steroid is identified.
Flag for parathyroid hormone	A drug that is a parathyroid hormone is identified.
Flag for anti-RANKL monoclonal antibody	A drug that is an anti-RANKL monoclonal antibody is identified.
Number of days to measurement (days)	Number of days from the start date of Benet/Actonel treatment to the date of measurement of the relevant endpoint
Time point of assessment (for analysis)	Time points of assessment are reallocated for analysis as specified in Section 5.4, “Handling of Time Points of Assessment.”
Flag for employment of data	It is identified whether measurement data are employed.
Flag for event	A patient with event is defined as a patient who experienced at least one event such as vertebral fracture. A patient with no event is defined as a patient who experienced no event.
Time point of event onset	Time point of event onset is defined as the first onset of event such as vertebral fracture. Time point of event onset is final assessment for patients with no event.
Measured value at the start of	The measured value at the start of treatment is identified.

Derived variable	Description
treatment	
Change	Value obtained by deducting the measured value at the start of treatment from a measured value at each time point
Percent change (%)	Value obtained by dividing a change by the measured value at the start of treatment and then multiplying the division by 100
Time of onset (days)	Number of days from the start date of Benet/Actonel treatment to the date of onset of AE
Flag for inclusion/exclusion as an AE	It is identified whether an event is an AE.
Relationship (for analysis)	It is identified whether an AE is related to Benet/Actonel.
Seriousness (for analysis)	It is identified whether an AE is serious.
Novelty	It is identified whether an AE is expected (known) or unexpected (unknown) based on the precautions for Benet/Actonel.
Presence or absence of an AE	It is identified whether there is an AE (including “unknown”).
Presence or absence of an ADR	It is identified whether there is an ADR (including “unknown”).
Presence or absence of a SAE	It is identified whether there is a SAE (including “unknown”).

6. Analysis Plan

Analysis sets, analysis items, and analysis methods are shown below. Details of variables for analysis and display will be specified in separately prepared statistical analysis specifications.

6.1. Analysis of Patients

6.1.1. Patient Composition Diagram

1) Analysis set　Enrolled patients

2) Chart plan　Figure 1-1

3) Analysis items　Number of registration sites

Number of enrolled patients

Number of patients with no CRF collected (including reasons for collecting no CRF)

Number of patients with the CRF collected

Number of patients not evaluated for safety (including reasons for exclusion)

Number of patients evaluated for safety
Number of patients not evaluated for efficacy (including reasons for exclusion)
Number of patients evaluated for efficacy
Number of patients not evaluated for vertebral fracture (including reasons for exclusion)
Number of patients evaluated for vertebral fracture

4) Analysis methods: The number of patients (number of sites) will be calculated for the analysis item, and a composition diagram will be prepared.

6.1.2. Patient Baseline Characteristics

1) Analysis set: Patients evaluated for safety
Patients evaluated for efficacy
Patients evaluated for vertebral fracture

2) Chart plan: Table 1-2

3) Analysis items: Sex [male, female]
Age (years)[*1] [<65 years, ≥65 years], [<75 years, ≥75 years]
Height at the start of treatment (cm)[*1]
Body weight (kg)[*1] [<50 kg, ≥50 kg]
BMI (kg/m^2)[*1] [<18.5 kg/m^2, ≥18.5 kg/m^2 to <25.0 kg/m^2, ≥25.0 kg/m^2]
Disease to be treated [osteoporosis: primary, osteoporosis: secondary]
Duration of disease (years)[*1] [<1 year, ≥1 year to <5 years, ≥5 years]
Predisposition to hypersensitivity [no, yes]
Presence or absence of concurrent illness[*2] [no, yes]
Disposition of concurrent illness [locomotor disease other than osteoporosis (spinal osteoarthritis, lumbago, spinal column stenosis, osteoarthritis), lifestyle-related disease (diabetes, hypertension, dyslipidemia, chronic obstructive pulmonary disease), cardiac disease, renal disease, hepatic disease, digestive disease (esophageal ulcer, gastric ulcer, duodenal ulcer, esophagitis), other (rheumatoid arthritis, other)]
Presence or absence of medical history (except previous fracture)[*2] [no, yes]
Presence or absence of medical history (previous fracture)[*2] [no, yes]
Disposition of medical history (previous fracture) [vertebra, femur, wrist, forearm, upper arm, pelvis, lower limb, other]
Previous steroid use [no, yes]

Disposition of previous steroid use [at least 3 months at a prednisolone equivalent dose of 5 mg/day or more, otherwise, unknown dose]
Parental history of femur fracture [no, yes]
Drinking history [no, yes]
Smoking history [never smoked, current smoker, past smoker]
Previous treatment [osteoporosis drug]
Previous treatment group [Benet/Actonel (risedronate), bisphosphonate other than Benet/Actonel, calcium, vitamin D, osteoporosis drug not listed above (parathyroid hormone, anti-RANKL monoclonal antibody, other), steroid]
Presence or absence of concomitant medication [no, yes]
Disposition of concomitant medication [osteoporosis drug, anti-inflammatory analgesic, cardiovascular drug, central nervous system drug, antidiabetic, digestive system drug, other]
Combination therapy group [calcium, vitamin D, osteoporosis drug not listed above (parathyroid hormone, anti-RANKL monoclonal antibody, other), steroid]
Presence or absence of physical therapy [no, yes]
Presence or absence of other concomitant therapy [no, yes]
Presence or absence of low back pain at the start of treatment [no, yes]

4) Analysis methods: The number and proportion of patients will be calculated for the analysis item. Summary statistics will be calculated for analysis items with *1. Analysis items with *2 will be processed as specified in Section 5.1, "Handling of Dichotomous Variables."

6.1.3. Treatment Compliance Status

1) Analysis set: Patients evaluated for safety
2) Chart plan: Table 1-3
3) Analysis item: Treatment status [took the drug as instructed by a physician, took the drug on a different day from instructed by a physician, took no dose, unknown]
4) Analysis methods: The number and proportion of patients will be calculated for the analysis item by the number of doses. In addition, a stacked bar chart will be plotted with the percentage of number of patients on the vertical axis and the number of doses on the horizontal axis.

6.1.4. Changes in Dosing Interval over Time

1) Analysis set	Patients evaluated for safety
2) Chart plan	Table 1-4
3) Analysis item	Dosing interval
4) Analysis methods	Summary statistics will be calculated for the analysis item by the number of doses.

6.2. Analysis of Safety

The safety will be analyzed in patients evaluated for safety.

6.2.1. List of Occurrence of Adverse Drug Reactions (Attachment Style 2)

1) Analysis set	Patients evaluated for safety
2) Chart plan	Table 2-1
3) Analysis items	Number of surveillance sites Number of surveyed patients Number of patients with an ADR, etc. Number of ADRs, etc. Proportion of patients with an ADR, etc. Proportion of patients with an ADR, etc. (number of ADRs, etc.) by type (PT)
4) Analysis methods	The number and proportion of patients (number of events) will be calculated for the analysis item, and a list of occurrence of ADRs will be prepared.

6.2.2. Occurrence of Adverse Drug Reactions by Type

1) Analysis set	Patients evaluated for safety
2) Chart plan	Table 2-2
3) Analysis item	ADR type (SOC, PT)
4) Classification factors	Seriousness [serious, not serious] Time of onset [Days 1-7, Days 8-14, Days 15-21, Days 22-28, Days 29-56, Days 57-84, Days 85-180, Days 181-210, Days 211-360, Day 361 or later] Presence or absence of discontinuation of Benet/Actonel treatment [yes, no] Outcome [recovered, recovering, not recovered, recovered with sequelae, death, unknown]

5) Analysis methods The number of patients will be calculated by ADR type for each category of classification.

6.2.3. List of Occurrence of Adverse Drug Reactions in Patients Not Evaluated for Safety

1) Analysis set Patients not evaluated for safety

2) Chart plan Table 2-3

3) Analysis items Number of surveillance sites
Number of surveyed patients
Number of patients with an ADR, etc.
Number of ADRs, etc.
Proportion of patients with an ADR, etc.
Proportion of patients with an ADR, etc. (number of ADRs, etc.) by type (PT)

4) Analysis methods The number and proportion of patients (number of events) will be calculated for the analysis item, and a list of occurrence of ADRs will be prepared.

6.3. Analysis of Efficacy

The efficacy will be analyzed in patients evaluated for efficacy. Patients with no pre- or post-baseline data on the relevant efficacy endpoint will be excluded from analysis.

6.3.1. Incidence of Vertebral Fracture

1) Analysis set Patients evaluated for efficacy
Patients evaluated for vertebral fracture

2) Chart plan Table 3-1-1-1
Table 3-1-1-2
Table 3-1-1-3
Table 3-1-1-4
Table 3-1-1-5
Table 3-1-1-6
Table 3-1-2-1
Table 3-1-2-2
Table 3-1-2-3
Table 3-1-2-4
Table 3-1-2-5
Table 3-1-2-6

3) Analysis items
New vertebral fracture or worsening of prevalent fracture
New vertebral fracture or worsening of prevalent fracture <non-traumatic>
New vertebral fracture
New vertebral fracture <non-traumatic>
Worsening of prevalent fracture
Worsening of prevalent fracture <non-traumatic>

4) Analysis methods
Using the Kaplan-Meier method with the first onset of the analysis item as the event, the number of relevant patients (risk population), number of censored patients, number and proportion of patients with event, as well as the point estimate of cumulative incidence, standard error, and 95% confidence interval, at each time point of assessment will be calculated. In addition, a Kaplan-Meier curve will be plotted with the cumulative incidence (%) on the vertical axis and the time (months) on the horizontal axis.

6.3.2. Incidence of Non-vertebral Fracture

1) Analysis set
Patients evaluated for efficacy

2) Chart plan
Table 3-2-1
Table 3-2-2
Table 3-2-3
Table 3-2-4

3) Analysis items
Non-vertebral fracture
Non-vertebral fracture <non-traumatic>
Femur fracture
Femur fracture <non-traumatic>

4) Analysis methods
Non-vertebral fracture will be analyzed in the same manner as described in Section 6.3.1, “Incidence of Vertebral Fracture.”

6.3.3. Poisson Regression Analysis of Vertebral Fracture

1) Analysis set
Patients evaluated for vertebral fracture

2) Chart plan
Table 3-3-1
Table 3-3-2

3) Analysis items
New vertebral fracture or worsening of prevalent fracture
New vertebral fracture or worsening of prevalent fracture <non-traumatic>

4) Analysis methods
With the first onset of the analysis item as the event, the number of relevant patients, risk population, number of patients with event, annual

number of patients with event, and incidence rate per risk population (number of patients with event/100 person·years) at each time point of assessment will be calculated. In addition, a curve of incidence rate estimated by Poisson regression will be plotted with the incidence rate on the vertical axis and the time (months) on the horizontal axis. In parallel, Poisson regression analysis will be performed with the incidence rate per risk population as the objective variable and the time point of assessment as the explanatory variable, and p-value at each time point of assessment will be presented in the figure.

Statistics will be calculated as specified in Section 6.3.1, "Incidence of Vertebral Fracture."

Risk population: mean number of relevant patients at the relevant time point and the previous time point

Annual number of patients with event: number of patients with event ÷ 6 months × 12 months

Incidence rate per risk population: (annual number of patients with event ÷ risk population) × 100

6.3.4. Risk Ratio of Vertebral Fracture

1) Analysis set	Patients evaluated for vertebral fracture
2) Chart plan	Table 3-4-1 Table 3-4-2
3) Analysis items	New vertebral fracture or worsening of prevalent fracture New vertebral fracture or worsening of prevalent fracture <non-traumatic>
4) Analysis methods	With the first onset of the analysis item as the event, the risk population, number of patients with event, and incidence rate per risk population (number of patients with event/100 person·years) at each time point of assessment will be calculated. In addition, the risk ratio of the event at each time point of assessment relative to Month 6 and its 95% confidence interval will be calculated. Statistics will be calculated as specified in Section 6.3.3, "Poisson Regression Analysis of Vertebral Fracture."

6.3.5. Percent Changes in Bone Turnover Markers

1) Analysis set	Patients evaluated for efficacy
2) Chart plan	Table 3-5

3) Analysis items Bone turnover markers

4) Analysis methods For each bone turnover marker, summary statistics at each time point of assessment will be calculated for observed value and percent change. In addition, the post-baseline difference in observed value and its 95% confidence interval will be calculated, and p-value will be calculated as specified in Section 3.3. 4), "Rules of statistical testing." One-sample Wilcoxon test will be used in an analysis report.

6.3.6. Percent Change in Bone Mineral Density

1) Analysis set Patients evaluated for efficacy

2) Chart plan Table 3-6

3) Analysis item Bone mineral density

4) Analysis methods For each bone mineral density, summary statistics at each time point of assessment will be calculated for observed value and percent change. In addition, the post-baseline difference in observed value and its 95% confidence interval will be calculated, and p-value will be calculated as specified in Section 3.3. 4), "Rules of statistical testing." One-sample t-test will be used in an analysis report.

If a check is made to lumbar spines 2) to 4) in the "Location of vertebral fracture" in the CRF after the start of Benet/Actonel treatment, no data on lumbar spine (DXA) bone mineral density dated the relevant date or later will be employed.

6.3.7. Changes in Height over Time

1) Analysis set Patients evaluated for efficacy

2) Chart plan Table 3-7

3) Analysis item Height (cm)

4) Analysis methods For height, summary statistics at each time point of assessment will be calculated for observed value and change. In addition, the post-baseline difference in observed value and its 95% confidence interval will be calculated.

6.3.8. Changes in Low Back Pain over Time

1) Analysis set Patients evaluated for efficacy

2) Chart plan Table 3-8

3) Analysis item Low back pain

4) Analysis methods For low back pain, a shift table at the start of treatment versus at each time point of assessment will be prepared. In addition, p-value will be calculated as specified in Section 3.3. 4), "Rules of statistical testing."

6.4. Listing

6.4.1. List of Discontinued Patients

1) Analysis set Discontinued patients

2) Chart plan Table 4-1

3) Analysis items Patient number, sex, age, included in or excluded from the analysis set, start date and discontinuation date of Benet/Actonel treatment, number of days from start to discontinuation of Benet/Actonel treatment, reason for discontinuation, presence or absence of an AE, AE term

4) Analysis methods A list with the analysis items will be prepared.

6.4.2. List of Patients Not Evaluated

1) Analysis set Patients not evaluated for safety
Patients not evaluated for efficacy
Patients not evaluated for vertebral fracture

2) Chart plan Table 4-2

3) Analysis items Patient number, sex, age, included in or excluded from the analysis set, start date of Benet/Actonel treatment, reason for exclusion, presence or absence of an AE, AE term

4) Analysis methods A list with the analysis items will be prepared.

6.4.3. List of Surveyed Patients (Attachment Style 3)

1) Analysis set Patients with the CRF collected

2) Chart plan Table 4-3

3) Analysis items Patient number, name, founder/code, and location (prefecture) of the study site, patient abbreviation, sex, age, inpatient or outpatient, reason for use (disease code, disease name), severity at baseline, concurrent illness (presence or absence, number, name), route of administration, maximum dose (daily dose/single dose), mean dose (daily dose/single dose), units, daily number of doses, duration of use, concomitant medication (drug code, representative drug name, number), degree of response, ADR (system organ code, ADR code, ADR term, presence or absence, number), outcome, CRF number, dropout

4) Analysis methods A list with the analysis items will be prepared.

Benet 75 mg Tablets Special Drug Use Surveillance

Actonel 75 mg Tablets Special Drug Use Surveillance

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

Statistical Analysis Plan

Version 4.0

PPD

Takeda Pharmaceutical Co., Ltd.

PPD

PPD

PPD

History of amendments

Version number	Date of preparation	Preparator	Amendment/reason, etc.
1.0	7 March 2014	PPD	New document
2.0	29 September 2014		Thorough revision for the fourth periodic safety update report
2.1	8 October 2014		Correction made to Section 4.3, “Patients Included in Safety Analysis”
3.0	26 March 2015		Correction made to Section 3.3. 2), “Number of digits to be displayed” Addition to Section 5.4, “Handling of Time Points of Assessment” Addition to Section 5.5, “Derived Variables” Addition of Section 6.2.4, “Occurrence of Acute Phase Reaction”
4.0	6 January 2016		Thorough revision for the sixth periodic safety update report

Table of Contents

1. Objectives

This document is intended to describe the details of statistical analyses in a special drug use surveillance on fracture incidence during 36-month treatment with Benet 75 mg Tablets and Actonel 75 mg Tablets (hereinafter referred to as the surveillance). The chart layout for analysis results will be specified in a separately prepared chart plan.

2. Synopsis

Surveillance drug	Benet 75 mg Tablets/Actonel 75 mg Tablets (hereinafter referred to as Benet/Actonel)
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/Actonel in osteoporotic patients in clinical settings
Planned sample size	250 patients/250 patients A total of 500 patients
Registration method	Central registration method
Planned surveillance period	Surveillance period: From May 2013 to April 2018 Registration period: From May 2013 to October 2014

3. Definitions

3.1. Definitions of Abbreviations

Abbreviation	Description
PMS system	CCI [redacted] (name of the system supplied by PPD [redacted] for managing the progression of post-marketing surveillances)
BMI	Body Mass Index
AE	Adverse Event
SOC	System Organ Class
PT	Preferred Term
LLT	Low Level Term

3.2. Definitions of Terms

Term	Description
Finalized patient	For Benet Tablets, a finalized patient is defined as a patient who has the date of CRF approval in the PMS system. For Actonel Tablets, a finalized patient is defined as a patient who has the date of temporary finalization in the business management system.
Adverse event (AE)	All events entered into the column of [Adverse event] in the case report form (CRF) Any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of Benet/Actonel, whether or not it is considered related to Benet/Actonel
Adverse drug reaction (ADR)	All adverse events except those not related to Benet/Actonel according to "Causal relationship to Benet/Actonel" both in the column of [Adverse event] in the CRF and determined by the company
Serious adverse event (SAE)	Adverse event assessed as serious according to "Seriousness" at least either in the column of [Adverse event] in the CRF or determined by the company, including "AEs that must always be assessed as serious" in the implementation guidelines and AEs in Takeda Medically Significant AE List

3.3. Statistical Arrangements

1) Summary statistics

For quantitative variables, summary statistics are number of relevant patients, mean, standard deviation, minimum, quartile points (25 percentile, 50 percentile, and 75 percentile), and maximum.

2) Number of digits to be displayed

Proportions will be displayed to two decimal places by rounding.

Minimum and maximum will be displayed with the same number of digits as the number of significant figures, and the other summary statistics will be displayed to one lower digit than raw data by rounding.

Statistical p-value will be displayed to four decimal places by rounding. P-value less than 0.0001 will be displayed as <0.0001. Infeasibility of testing will be indicated as "-."

3) 95% confidence interval

For continuous variables, 95% confidence interval for mean difference will be presented as confidence limits following t-distribution.

4) Rules of statistical testing

One-sample t-test or one-sample Wilcoxon test will be used for pre- and post-treatment comparison of continuous variables.

McNemar test will be used for pre- and post-treatment comparison of ratios.

For assessment of vertebral fracture, Poisson regression analysis will be used based on the assumption that the frequency follows the Poisson distribution, and there is a linear relationship between the expected value of frequency and the explanatory variable.

A two-sided 5% level of significance will be used.

The category of "unknown" will be excluded from statistical testing.

4. Analysis Sets

4.1. Enrolled Patients

All patients for whom the patient registration form has been accepted

4.2. Patients with the CRF Collected

Patients for whom the CRF has been collected and finalized

4.3. Patients Included in Safety Analysis

All patients with the CRF collected, excluding those who meet any of the following criteria:

1) Not treated with Benet/Actonel

2) Unknown whether an AE occurred

3) Deviated from the registration criteria

• Treated before conclusion of a contract

• Not registered in the registration period

• Failed to fax the patient registration form within 15 days after the first prescription of Benet/Actonel

4.4. Patients Included in Efficacy Analysis

All patients included in safety analysis, excluding those who meet the following criterion:

Pre- and post-baseline values of all efficacy endpoints (bone turnover markers, bone mineral density, vertebral fracture, non-vertebral fracture, height, and low back pain) are unknown, including

incalculable values

4.5. Patients Included in Analysis of Vertebral Fracture

All patients included in efficacy analysis, excluding those who meet any of the following criteria:

1) No evidence of 1 to 4 fractures from the fourth thoracic vertebra to the fourth lumbar vertebra provided by thoracic and lumbar spinal radiography performed before the start of the surveillance

2) Not 50 years or older

3) Not an outpatient who can walk

4) Different radiographic location after treatment relative to baseline

5. Handling of Data

Handling of data for analysis is described below. Details of processing will be specified in separately prepared analysis data set specifications.

5.1. Handling of Dichotomous Variables

For dichotomous variables, the presence or absence will be determined as described below when there is a column for details to be specified for "Yes."

1) "Yes" when details are specified

2) "No" when no details are specified and "No" is checked

3) "Unknown" when neither 1 nor 2) is applicable

5.2. Handling of Adverse Events

When multiple AEs of the same LLT are reported in the same patient, an AE to be employed will be determined as described below.

1) AEs that differ in the causal relationship to Benet/Actonel will be handled separately.

2) When multiple AEs of the same causal relationship to Benet/Actonel are reported, the most serious AE will be employed.

3) When multiple AEs of the same seriousness are reported, the earliest AE will be employed.

4) When multiple AEs are reported on the same day, an AE with the latest outcome will be employed.

5.3. Handling of Missing Data

In principle, no missing data will be imputed.

For frequency tabulation of qualitative variables, missing data will be handled as "unknown." For summary statistics of quantitative variables, missing data will be excluded, and non-missing data will be used.

5.4. Handling of Time Points of Assessment

Data within the permissible range as shown below will be employed.

If there are multiple pieces of data within the permissible range, data on the day closest to the nominal day will be employed. If deviation is the same before and after the nominal day, the latest data will be employed.

Data collected up to the end date of Benet/Actonel treatment* + 90 days will be employed for bone

mineral density, and data collected up to the end date of Benet/Actonel treatment* + 30 days will be employed for the other endpoints. For patients with interruption of treatment, no data collected after 3 consecutive months (90 days) of interruption will be used for (efficacy) analysis.

* Specified in Section 5.5, "Derived Variables"

<Time points of assessment of vertebral fracture, non-vertebral fracture, and femur fracture>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -90 to 1	Day 1
Month 6	Days 2 to 180	Day 180
Month 12	Days 181 to 360	Day 360
Month 18	Days 361 to 540	Day 540
Month 24	Days 541 to 720	Day 720
Month 30	Days 721 to 900	Day 900
Month 36	Days 901 to 1096	Day 1096
Final assessment	Days 2 to 1096	-

<Time points of assessment of bone turnover markers and low back pain>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -30 to 3	Day 1
Month 3	Days 4 to 135	Day 90
Month 6	Days 136 to 270	Day 180
Month 12	Days 271 to 450	Day 360
Month 18	Days 451 to 630	Day 540
Month 24	Days 631 to 810	Day 720
Month 30	Days 811 to 990	Day 900
Month 36	Days 991 to 1170	Day 1096
Final assessment	Days 4 to 1170	-

<Time points of assessment of bone mineral density>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -30 to 1	Day 1
Month 3	Days 2 to 105	Day 90
Month 6	Days 106 to 270	Day 180
Month 12	Days 271 to 450	Day 360
Month 18	Days 451 to 630	Day 540

Month 24	Days 631 to 810	Day 720
Month 30	Days 811 to 990	Day 900
Month 36	Days 991 to 1170	Day 1096
Final assessment	Days 2 to 1170	-

<Time points of assessment of height>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -30 to 3	Day 1
Month 12	Days 4 to 540	Day 360
Month 24	Days 541 to 900	Day 720
Month 36	Days 901 to 1170	Day 1096
Final assessment	Days 4 to 1170	-

5.5. Derived Variables

Derived variable	Description
Flag for enrollment	It is identified whether a patient is enrolled.
Flag for CRF collection	It is identified whether the CRF for a patient is collected.
Flag for inclusion in/exclusion from safety	It is identified whether a patient is included in safety analysis.
Flag for inclusion in/exclusion from efficacy	It is identified whether a patient is included in efficacy analysis.
Age (years)	Age on the start day of Benet/Actonel treatment; or age described on the [Cover] in the CRF if date of birth is missing
BMI (kg/m^2)	Body mass index calculated as body weight (kg) ÷ height $(m)^2$
Duration of disease (years)	Number of years from diagnosis of osteoporosis to the start date of Benet/Actonel treatment (by rounding down)
Start date of Benet/Actonel treatment	Date described as the date of the scheduled first dosing on the [Cover] in the CRF; or the earliest (smallest) date among dates described in the [Treatment status of Benet/Actonel] if the first dose is not given as scheduled
End date of Benet/Actonel treatment	30 days after the latest (largest) date among dates described in the [Treatment status of Benet/Actonel] in the CRF
Duration of Benet/Actonel treatment (days)	Number of days from the start date of Benet/Actonel treatment to the end date of Benet/Actonel treatment

Derived variable	Description
Duration of Benet/Actonel treatment (months)	Number of months from the start date of Benet/Actonel treatment to the end date of Benet/Actonel treatment
Number of doses of Benet/Actonel	Total number of doses during Benet/Actonel treatment counted as the number of checks made to "Took the drug on the day indicated by a physician" or "Took the drug on a different day from instructed by a physician" for patient's treatment status in the [Treatment status of Benet/Actonel] in the CRF Data are collected in the [Treatment status of Benet/Actonel] in the CRF on a dose basis (first dose, second dose, third dose,……) for Benet and on a monthly basis (Month 1, Month 2, Month 3,……) for Actonel. For tabulation, data of Actonel will be handled on a dose basis in line with data of Benet. No month with blank will be counted.
Amount of Benet/Actonel administered (mg)	Total dose during Benet/Actonel treatment calculated as number of doses of Benet/Actonel × 75 mg
Treatment rate (%)	Number of doses of Benet/Actonel ÷ number of entered "date indicated by a physician"
Treatment compliance rate (%)	Percentage of the number of doses taken as instructed by a physician relative to the number of doses indicated by the physician calculated as the number of checks made to "Took the drug on the day indicated by a physician" ÷ number of entered "date indicated by a physician"
Dosing interval (days)	Number of days from the date of a certain dosing to the date of the next dosing
Flag for previous treatment	A drug deemed as previous treatment is identified. Previous treatment being used after the start of Benet/Actonel treatment is also identified with a flag for concomitant medication.
Flag for concomitant medication	A drug deemed as concomitant medication is identified. Concomitant medication that has been used since before the start of Benet/Actonel treatment is also identified with a flag for previous treatment.
Flag for osteoporosis drug	An osteoporosis drug is identified.
Flag for anti-inflammatory analgesic	An anti-inflammatory analgesic is identified.

Derived variable	Description
Flag for cardiovascular drug	A cardiovascular drug is identified.
Flag for central nervous system drug	A central nervous system drug is identified.
Flag for antidiabetic	An antidiabetic is identified.
Flag for digestive system drug	A digestive system drug is identified.
Flag for other drug	Other drug not listed above is identified.
Flag for Benet/Actonel 2.5 mg	A drug that is Benet/Actonel 2.5 mg is identified.
Flag for Benet/Actonel 17.5 mg	A drug that is Benet/Actonel 17.5 mg is identified.
Flag for bisphosphonate other than Benet/Actonel	A bisphosphonate other than Benet/Actonel is identified.
Flag for calcium	A drug that is calcium is identified.
Flag for vitamin D	A drug that is vitamin D is identified.
Flag for osteoporosis drug not listed above	A drug that is an osteoporosis drug not listed above is identified.
Flag for steroid	A drug that is a steroid is identified.
Flag for parathyroid hormone	A drug that is a parathyroid hormone is identified.
Flag for anti-RANKL monoclonal antibody	A drug that is an anti-RANKL monoclonal antibody is identified.
Number of days to measurement (days)	Number of days from the start date of Benet/Actonel treatment to the date of measurement of the relevant endpoint
Time point of assessment (for analysis)	Time points of assessment are reallocated for analysis as specified in Section 5.4, “Handling of Time Points of Assessment.”
Flag for employment of data	It is identified whether measurement data are employed.
Flag for event	A patient with event is defined as a patient who experienced at least one event such as vertebral fracture. A patient with no event is defined as a patient who experienced no event.
Time point of event onset	Time point of event onset is defined as the first onset of event such as vertebral fracture. Time point of event onset is final assessment for patients with no event.
Measured value at the start of treatment	The measured value at the start of treatment is identified.
Change	Value obtained by deducting the measured value at the start of

Derived variable	Description
	treatment from a measured value at each time point
Percent change (%)	Value obtained by dividing a change by the measured value at the start of treatment and then multiplying the division by 100
Time of onset (days)	Number of days from the start date of Benet/Actonel treatment to the date of onset of AE
Flag for inclusion/exclusion as an AE	It is identified whether an event is an AE.
Relationship (for analysis)	It is identified whether an AE is related to Benet/Actonel.
Seriousness (for analysis)	It is identified whether an AE is serious.
Novelty	It is identified whether an AE is expected (known) or unexpected (unknown) based on the precautions for Benet/Actonel.
Presence or absence of an AE	It is identified whether there is an AE (including "unknown").
Presence or absence of an ADR	It is identified whether there is an ADR (including "unknown").
Presence or absence of a SAE	It is identified whether there is a SAE (including "unknown").

6. Analysis Plan

Analysis sets, analysis items, and analysis methods are shown below. Details of variables for analysis and display will be specified in separately prepared statistical analysis specifications.

6.1. Analysis of Patients

6.1.1. Patient Composition Diagram

1) Analysis set: Enrolled patients

2) Chart plan: Figure 1-1

3) Analysis items: Number of registration sites
Number of enrolled patients
Number of patients with no CRF collected (including reasons for collecting no CRF)
Number of patients with the CRF collected
Number of patients excluded from safety analysis (including reasons for exclusion)
Number of patients included in safety analysis
Number of patients excluded from efficacy analysis (including reasons for

exclusion)
Number of patients included in efficacy analysis
Number of patients excluded from analysis of vertebral fracture (including reasons for exclusion)
Number of patients included in analysis of vertebral fracture

4) Analysis methods: The number of patients (number of sites) will be calculated for the analysis item, and a composition diagram will be prepared.

6.1.2. Patient Baseline Characteristics

1) Analysis set: Patients included in safety analysis
Patients included in efficacy analysis
Patients included in analysis of vertebral fracture

2) Chart plan: Table 1-2

3) Analysis items: Sex [male, female]
Age (years)* [<65 years, ≥65 years], [<75 years, ≥75 years]
Height at the start of treatment (cm)*
Body weight (kg)* [<50 kg, ≥50 kg]
BMI (kg/m^2)* [<18.5 kg/m^2, ≥18.5 kg/m^2 to <25.0 kg/m^2, ≥25.0 kg/m^2]
Disease to be treated [osteoporosis: primary, osteoporosis: secondary]
Duration of disease (years)* [<1 year, ≥1 year to <5 years, ≥5 years]
Predisposition to hypersensitivity [no, yes]
Concurrent illness [no, yes]
Disposition of concurrent illness [locomotor disease other than osteoporosis (spinal osteoarthritis, lumbago, spinal column stenosis, osteoarthritis), lifestyle-related disease (diabetes, hypertension, dyslipidemia, chronic obstructive pulmonary disease), cardiac disease, renal disease, hepatic disease, digestive disease (esophageal ulcer, gastric ulcer, duodenal ulcer, esophagitis), other (rheumatoid arthritis, other)]
Medical history (except previous fracture) [no, yes]
Medical history (previous fracture) [no, yes]
Disposition of medical history (previous fracture) [vertebra, femur, wrist, forearm, upper arm, pelvis, lower limb, other]
Previous steroid use [no, yes]
Disposition of previous steroid use [at least 3 months at a prednisolone equivalent dose of 5 mg/day or more, otherwise, unknown dose]
Parental history of femur fracture [no, yes]

Drinking history [no, yes]
Smoking history [never smoked, current smoker, past smoker]
Previous treatment [osteoporosis drug]
Previous treatment group [Benet/Actonel (risedronate), bisphosphonate other than Benet/Actonel, calcium, vitamin D, osteoporosis drug not listed above (parathyroid hormone, anti-RANKL monoclonal antibody, other), steroid]
Presence or absence of concomitant medication [no, yes]
Disposition of concomitant medication [osteoporosis drug, anti-inflammatory analgesic, cardiovascular drug, central nervous system drug, antidiabetic, digestive system drug, other]
Combination therapy group [calcium, vitamin D, osteoporosis drug not listed above (parathyroid hormone, anti-RANKL monoclonal antibody, other), steroid]
Presence or absence of physical therapy [no, yes]
Presence or absence of other concomitant therapy [no, yes]
Presence or absence of low back pain at the start of treatment [no, yes]

4) Analysis methods The number and proportion of patients will be calculated for the analysis item. Summary statistics will be calculated for analysis items with *.

6.1.3. Treatment Compliance Status

1) Analysis set Patients included in safety analysis
2) Chart plan Table 1-3
3) Analysis item Treatment status [took the drug as instructed by a physician, took the drug on a different day from instructed by a physician, took no dose, unknown]
4) Analysis methods The number and proportion of patients will be calculated for the analysis item by the number of doses. In addition, a stacked bar chart will be plotted with the percentage of number of patients on the vertical axis and the number of doses on the horizontal axis.

6.1.4. Changes in Dosing Interval over Time

1) Analysis set Patients included in safety analysis
2) Chart plan Table 1-4
3) Analysis item Dosing interval
4) Analysis methods Summary statistics will be calculated for the analysis item by the number of doses.

6.2. Analysis of Safety

The safety will be analyzed in patients included in safety analysis.

6.2.1. List of Occurrence of Adverse Drug Reactions (Attachment Style 2)

1) Analysis set	Patients included in safety analysis
2) Chart plan	Table 2-1
3) Analysis items	Number of surveillance sites Number of surveyed patients Number of patients with an ADR, etc. Number of ADRs, etc. Proportion of patients with an ADR, etc. Proportion of patients with an ADR, etc. (number of ADRs, etc.) by type (PT)
4) Analysis methods	The number and proportion of patients (number of events) will be calculated for the analysis item, and a list of occurrence of ADRs will be prepared.

6.2.2. Occurrence of Adverse Drug Reactions by Type

1) Analysis set	Patients included in safety analysis
2) Chart plan	Table 2-2
3) Analysis item	ADR type (SOC, PT)
4) Classification factors	Seriousness [serious, not serious] Time of onset [Days 1-7, Days 8-14, Days 15-21, Days 22-28, Days 29-56, Days 57-84, Days 85-180, Days 181-210, Days 211-360, Day 361 or later] Presence or absence of discontinuation of Benet/Actonel treatment [yes, no] Outcome [recovered, recovering, not recovered, recovered with sequelae, death, unknown]
5) Analysis methods	The number of patients will be calculated by ADR type for each category of classification.

6.2.3. List of Occurrence of Adverse Drug Reactions in Patients Excluded from Safety Analysis

1) Analysis set	Patients excluded from safety analysis
2) Chart plan	Table 2-3

3) Analysis items	Number of surveillance sites
	Number of surveyed patients
	Number of patients with an ADR, etc.
	Number of ADRs, etc.
	Proportion of patients with an ADR, etc.
	Proportion of patients with an ADR, etc. (number of ADRs, etc.) by type (PT)
4) Analysis methods	The number and proportion of patients (number of events) will be calculated for the analysis item, and a list of occurrence of ADRs will be prepared.

6.3. Analysis of Efficacy

The efficacy will be analyzed in patients included in efficacy analysis. Patients with no pre- or post-baseline data on the relevant efficacy endpoint will be excluded from analysis.

6.3.1. Incidence of Vertebral Fracture

1) Analysis set	Patients included in efficacy analysis
	Patients included in analysis of vertebral fracture
2) Chart plan	Table 3-1-1-1
	Table 3-1-1-2
	Table 3-1-1-3
	Table 3-1-1-4
	Table 3-1-1-5
	Table 3-1-1-6
	Table 3-1-2-1
	Table 3-1-2-2
	Table 3-1-2-3
	Table 3-1-2-4
	Table 3-1-2-5
	Table 3-1-2-6
3) Analysis items	New vertebral fracture or worsening of prevalent fracture
	New vertebral fracture or worsening of prevalent fracture <non-traumatic>
	New vertebral fracture
	New vertebral fracture <non-traumatic>
	Worsening of prevalent fracture
	Worsening of prevalent fracture <non-traumatic>

4) Analysis methods Using the Kaplan-Meier method with the first onset of the analysis item as the event, the number of relevant patients (risk population), number of censored patients, number and proportion of patients with event, as well as the point estimate of cumulative incidence, standard error, and 95% confidence interval, at each time point of assessment will be calculated. In addition, a Kaplan-Meier curve will be plotted with the cumulative incidence (%) on the vertical axis and the time (months) on the horizontal axis.

6.3.2. Incidence of Non-vertebral Fracture

1) Analysis set Patients included in efficacy analysis

2) Chart plan Table 3-2-1
Table 3-2-2
Table 3-2-3
Table 3-2-4

3) Analysis items Non-vertebral fracture
Non-vertebral fracture <non-traumatic>
Femur fracture
Femur fracture <non-traumatic>

4) Analysis methods Non-vertebral fracture will be analyzed in the same manner as described in Section 6.3.1, “Incidence of Vertebral Fracture.”

6.3.3. Poisson Regression Analysis of Vertebral Fracture

1) Analysis set Patients included in analysis of vertebral fracture

2) Chart plan Table 3-3-1
Table 3-3-2

3) Analysis items New vertebral fracture or worsening of prevalent fracture
New vertebral fracture or worsening of prevalent fracture <non-traumatic>

4) Analysis methods With the first onset of the analysis item as the event, the number of relevant patients, risk population, number of patients with event, annual number of patients with event, and incidence rate per risk population (number of patients with event/100 person·years) at each time point of assessment will be calculated. In addition, a curve of incidence rate estimated by Poisson regression will be plotted with the incidence rate on the vertical axis and the time (months) on the horizontal axis. In parallel, Poisson regression analysis will be performed with the incidence rate per

risk population as the objective variable and the time point of assessment as the explanatory variable, and p-value at each time point of assessment will be presented in the figure.

Statistics will be calculated as specified in Section 6.3.1, "Incidence of Vertebral Fracture."

Risk population: mean number of relevant patients at the relevant time point and the previous time point

Annual number of patients with event: number of patients with event ÷ 6 months × 12 months

Incidence rate per risk population: (annual number of patients with event ÷ risk population) × 100

6.3.4. Risk Ratio of Vertebral Fracture

1) Analysis set	Patients included in analysis of vertebral fracture
2) Chart plan	Table 3-4-1 Table 3-4-2
3) Analysis items	New vertebral fracture or worsening of prevalent fracture New vertebral fracture or worsening of prevalent fracture <non-traumatic>
4) Analysis methods	With the first onset of the analysis item as the event, the risk population, number of patients with event, and incidence rate per risk population (number of patients with event/100 person·years) at each time point of assessment will be calculated. In addition, the risk ratio of the event at each time point of assessment relative to Month 6 and its 95% confidence interval will be calculated. Statistics will be calculated as specified in Section 6.3.3, "Poisson Regression Analysis of Vertebral Fracture."

6.3.5. Percent Changes in Bone Turnover Markers

1) Analysis set	Patients included in efficacy analysis
2) Chart plan	Table 3-5
3) Analysis items	Bone turnover markers
4) Analysis methods	For each bone turnover marker, summary statistics at each time point of assessment will be calculated for observed value and percent change. In addition, the post-baseline difference in observed value and its 95% confidence interval will be calculated, and p-value will be calculated as specified in Section 3.3. 4), "Rules of statistical testing." One-sample

Wilcoxon test will be used in an analysis report.

6.3.6. Percent Change in Bone Mineral Density

1) Analysis set: Patients included in efficacy analysis

2) Chart plan: Table 3-6

3) Analysis item: Bone mineral density

4) Analysis methods: For each bone mineral density, summary statistics at each time point of assessment will be calculated for observed value and percent change. In addition, the post-baseline difference in observed value and its 95% confidence interval will be calculated, and p-value will be calculated as specified in Section 3.3. 4), "Rules of statistical testing." One-sample t-test will be used in an analysis report.

If a check is made to lumbar spines 2) to 4) in the "Location of vertebral fracture" in the CRF, no data on lumbar spine (DXA) bone mineral density dated the relevant date or later will be employed.

6.3.7. Changes in Height over Time

1) Analysis set: Patients included in efficacy analysis

2) Chart plan: Table 3-7

3) Analysis item: Height (cm)

4) Analysis methods: For height, summary statistics at each time point of assessment will be calculated for observed value and change. In addition, the post-baseline difference in observed value and its 95% confidence interval will be calculated.

6.3.8. Changes in Low Back Pain over Time

1) Analysis set: Patients included in efficacy analysis

2) Chart plan: Table 3-8

3) Analysis item: Low back pain

4) Analysis methods: For low back pain, a shift table at the start of treatment versus at each time point of assessment will be prepared. In addition, p-value will be calculated as specified in Section 3.3. 4), "Rules of statistical testing."

6.4. Listing

6.4.1. List of Discontinued Patients

1) Analysis set: Discontinued patients

2) Chart plan Table 4-1

3) Analysis items Patient number, sex, age, included in or excluded from the analysis set, start date and discontinuation date of Benet/Actonel treatment, number of days from start to discontinuation of Benet/Actonel treatment, reason for discontinuation, presence or absence of an AE, AE term

4) Analysis methods A list with the analysis items will be prepared.

6.4.2. List of Patients Excluded from Analysis

1) Analysis set Patients excluded from safety analysis
Patients excluded from efficacy analysis
Patients excluded from analysis of vertebral fracture

2) Chart plan Table 4-2

3) Analysis items Patient number, sex, age, included in or excluded from the analysis set, start date of Benet/Actonel treatment, reason for exclusion, presence or absence of an AE, AE term

4) Analysis methods A list with the analysis items will be prepared.

6.4.3. List of Surveyed Patients (Attachment Style 3)

1) Analysis set Patients with the CRF collected

2) Chart plan Table 4-3

3) Analysis items Patient number, name, founder/code, and location (prefecture) of the study site, patient abbreviation, sex, age, inpatient or outpatient, reason for use (disease code, disease name), severity at baseline, concurrent illness (presence or absence, number, name), route of administration, maximum dose (daily dose/single dose), mean dose (daily dose/single dose), units, daily number of doses, duration of use, concomitant medication (drug code, representative drug name, number), degree of response, ADR (system organ code, ADR code, ADR term, presence or absence, number), outcome, CRF number, dropout

4) Analysis methods A list with the analysis items will be prepared.

Benet 75 mg Tablets Special Drug Use Surveillance

Actonel 75 mg Tablets Special Drug Use Surveillance

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

Statistical Analysis Plan

Version 3.0

PPD

Takeda Pharmaceutical Co., Ltd.

PPD

PPD

PPD

History of amendments

Version number	Date of preparation	Preparator	Amendment/reason, etc.
1.0	7 March 2014	PPD	New document
2.0	29 September 2014		Thorough revision for the fourth periodic safety update report
2.1	8 October 2014		Correction made to Section 4.3, “Patients Included in Safety Analysis”
3.0	26 March 2015		Correction made to Section 3.3. 2), “Number of digits to be displayed” Addition to Section 5.4, “Handling of Time Points of Assessment” Addition to Section 5.5, “Derived Variables” Addition of Section 6.2.4, “Occurrence of Acute Phase Reaction”

Table of Contents

1. Objectives

This document is intended to describe the details of statistical analyses in a special drug use surveillance on fracture incidence during 36-month treatment with Benet 75 mg Tablets and Actonel 75 mg Tablets (hereinafter referred to as the surveillance). The chart layout for analysis results will be specified in a separately prepared chart plan.

2. Synopsis

Surveillance drug	Benet 75 mg Tablets/Actonel 75 mg Tablets (hereinafter referred to as Benet/Actonel)
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/Actonel in osteoporotic patients in clinical settings
Planned sample size	250 patients/250 patients A total of 500 patients
Registration method	Central registration method
Planned surveillance period	Surveillance period: From May 2013 to April 2018 Registration period: From May 2013 to October 2014

3. Definitions

3.1. Definitions of Abbreviations

Abbreviation	Description
PMS system	CCI [redacted] (name of the system supplied by PPD [redacted] for managing the progression of post-marketing surveillances)
BMI	Body Mass Index
AE	Adverse Event
SOC	System Organ Class
PT	Preferred Term
LLT	Low Level Term

3.2. Definitions of Terms

Term	Description
Finalized patient	For Benet Tablets, a finalized patient is defined as a patient who has the date of CRF approval in the PMS system. For Actonel Tablets, a finalized patient is defined as a patient who has the date of temporary finalization in the business management system.
Adverse event (AE)	All events entered into the column of [Adverse event] in the case report form (CRF) Any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of Benet/Actonel, whether or not it is considered related to Benet/Actonel
Adverse drug reaction (ADR)	All adverse events except those not related to Benet/Actonel according to "Causal relationship to Benet/Actonel" both in the column of [Adverse event] in the CRF and determined by the company
Serious adverse event (SAE)	Adverse event assessed as serious according to "Seriousness" at least either in the column of [Adverse event] in the CRF or determined by the company, including AEs in Takeda Medically Significant AE List

3.3. Statistical Arrangements

1) Summary statistics

For quantitative variables, summary statistics are number of relevant patients, mean, standard deviation, minimum, median, and maximum.

2) Number of digits to be displayed

Proportions will be displayed to two decimal places by rounding.

Minimum and maximum will be displayed with the same number of digits as the number of significant figures, and the other summary statistics will be displayed to one lower digit than raw data by rounding.

Statistical p-value will be displayed to four decimal places by rounding. P-value less than 0.0001 will be displayed as <0.0001. Infeasibility of testing will be indicated as "-."

3) 95% confidence interval

For continuous variables, 95% confidence interval for mean difference will be presented as confidence limits following t-distribution.

4) Rules of statistical testing

One-sample t-test or one-sample Wilcoxon test will be used for pre- and post-treatment comparison of continuous variables.

McNemar test will be used for pre- and post-treatment comparison of ratios.

A two-sided 5% level of significance will be used.

The category of "unknown" will be excluded from statistical testing.

4. Analysis Sets

4.1. Enrolled Patients

All patients for whom the patient registration form has been accepted

4.2. Patients with the CRF Collected

Patients for whom the CRF has been collected before the end of the unit surveillance period and finalized

4.3. Patients Included in Safety Analysis

All patients with the CRF collected, excluding those who meet any of the following criteria:

1) Not treated with Benet/Actonel

2) Unknown whether an AE occurred

3) Deviated from the registration criteria

• Treated before conclusion of a contract

• Not registered in the registration period

• Failed to fax the patient registration form within 15 days after the first prescription of Benet/Actonel

4.4. Patients Included in Efficacy Analysis

All patients included in safety analysis, excluding those who meet any of the following criteria:

1) No evidence of 1 to 4 fractures from the fourth thoracic vertebra to the fourth lumbar vertebra provided by thoracic and lumbar spinal radiography performed before the start of the surveillance

2) Not 50 years or older

3) Not an outpatient who can walk

4) Pre- and post-baseline values of all efficacy endpoints (bone turnover markers, bone mineral density, vertebral fracture, non-vertebral fracture, height, and low back pain) are unknown, including

incalculable values

5. Handling of Data

Handling of data for analysis is described below. Details of processing will be specified in separately prepared analysis data set specifications.

5.1. Handling of Dichotomous Variables

For dichotomous variables, the presence or absence will be determined as described below when there is a column for details to be specified for "Yes."

1) "Yes" when details are specified

2) "No" when no details are specified and "No" is checked

3) "Unknown" when neither 1 nor 2) is applicable

5.2. Handling of Adverse Events

When multiple AEs of the same LLT are reported in the same patient, an AE to be employed will be determined as described below.

1) AEs that differ in the causal relationship to Benet/Actonel will be handled separately.

2) When multiple AEs of the same causal relationship to Benet/Actonel are reported, the most serious AE will be employed.

3) When multiple AEs of the same seriousness are reported, the earliest AE will be employed.

4) When multiple AEs are reported on the same day, an AE with the latest outcome will be employed.

5.3. Handling of Missing Data

In principle, no missing data will be imputed.

For frequency tabulation of qualitative variables, missing data will be handled as "unknown." For summary statistics of quantitative variables, missing data will be excluded, and non-missing data will be used.

5.4. Handling of Time Points of Assessment

Data within the permissible range as shown below will be employed.

If there are multiple pieces of data within the permissible range, data on the day closest to the nominal day will be employed. If deviation is the same before and after the nominal day, the latest data will be employed.

No data dated the end date of Benet/Actonel treatment + 30 days or later will be employed.

<Time points of assessment of vertebral fracture and non-vertebral fracture>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -90 to 1	Day 1
Month 6	Days 2 to 270	Day 180
Month 12	Days 271 to 540	Day 360
Month 24	Days 541 to 900	Day 720
Month 36	Days 901 to 1170	Day 1080
Final assessment	Days 2 to 1170	-

<Time points of assessment of bone turnover markers, bone mineral density, and low back pain>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -30 to 1	Day 1
Month 3	Days 2 to 105	Day 90
Month 6	Days 106 to 270	Day 180
Month 12	Days 271 to 450	Day 360
Month 18	Days 451 to 630	Day 540
Month 24	Days 631 to 810	Day 720
Month 30	Days 811 to 990	Day 900
Month 36	Days 991 to 1170	Day 1080
Final assessment	Days 2 to 1170	-

<Time points of assessment of height>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -30 to 1	Day 1
Month 12	Days 2 to 540	Day 360
Month 24	Days 541 to 900	Day 720
Month 36	Days 901 to 1170	Day 1080
Final assessment	Days 2 to 1170	-

5.5. Derived Variables

Derived variable	Description
Flag for enrollment	It is identified whether a patient is enrolled.
Flag for CRF collection	It is identified whether the CRF for a patient is collected.
Flag for inclusion in/exclusion from safety	It is identified whether a patient is included in safety analysis.

Derived variable	Description
Flag for inclusion in/exclusion from efficacy	It is identified whether a patient is included in efficacy analysis.
Age (years)	Age on the start day of Benet/Actonel treatment; or age described on the [Cover] in the CRF if date of birth is missing
BMI (kg/m^2)	Body mass index calculated as body weight (kg) ÷ height $(m)^2$
Duration of disease (years)	Number of years from diagnosis of osteoporosis to the start date of Benet/Actonel treatment (by rounding down)
Start date of Benet/Actonel treatment	Date described as the date of the scheduled first dosing on the [Cover] in the CRF; or the earliest (smallest) date among dates described in the [Treatment status of Benet/Actonel] if the first dose is not given as scheduled
End date of Benet/Actonel treatment	30 days after the latest (largest) date among dates described in the [Treatment status of Benet/Actonel] in the CRF
Duration of Benet/Actonel treatment (days)	Number of days from the start date of Benet/Actonel treatment to the end date of Benet/Actonel treatment
Duration of Benet/Actonel treatment (months)	Number of months from the start date of Benet/Actonel treatment to the end date of Benet/Actonel treatment
Number of doses of Benet/Actonel	Total number of doses during Benet/Actonel treatment counted as the number of checks made to "Took the drug" for patient's treatment status in the [Treatment status of Benet/Actonel] in the CRF
Amount of Benet/Actonel administered (mg)	Total dose during Benet/Actonel treatment calculated as number of doses of Benet/Actonel × 75 mg
Treatment compliance rate (%)	Percentage of the number of doses taken as instructed by a physician relative to the number of doses indicated by the physician
Dosing interval (days)	Number of days from the date of a certain dosing to the date of the next dosing
Flag for previous treatment	A drug deemed as previous treatment is identified.
Flag for concomitant medication	A drug deemed as concomitant medication is identified.
Flag for osteoporosis drug	An osteoporosis drug is identified.
Flag for anti-inflammatory	An anti-inflammatory analgesic is identified.

Derived variable	Description
analgesic	
Flag for cardiovascular drug	A cardiovascular drug is identified.
Flag for central nervous system drug	A central nervous system drug is identified.
Flag for antidiabetic	An antidiabetic is identified.
Flag for digestive system drug	A digestive system drug is identified.
Flag for other drug	Other drug not listed above is identified.
Flag for Benet/Actonel 2.5 mg	A drug that is Benet/Actonel 2.5 mg is identified.
Flag for Benet/Actonel 17.5 mg	A drug that is Benet/Actonel 17.5 mg is identified.
Flag for bisphosphonate other than Benet/Actonel	A bisphosphonate other than Benet/Actonel is identified.
Flag for calcium	A drug that is calcium is identified.
Flag for vitamin D	A drug that is vitamin D is identified.
Flag for osteoporosis drug not listed above	A drug that is an osteoporosis drug not listed above is identified.
Flag for steroid	A drug that is a steroid is identified.
Number of days to measurement (days)	Number of days from the start date of Benet/Actonel treatment to the date of measurement of the relevant endpoint
Time point of assessment (for analysis)	Time points of assessment are reallocated for analysis as specified in Section 5.4, “Handling of Time Points of Assessment.”
Flag for employment of data	It is identified whether measurement data are employed.
Flag for event	A patient with event is defined as a patient who experienced at least one event such as vertebral fracture. A patient with no event is defined as a patient who experienced no event.
Time point of event onset	Time point of event onset is defined as the first onset of event such as vertebral fracture. Time point of event onset is final assessment for patients with no event.
Measured value at the start of treatment	The measured value at the start of treatment is identified.
Change	Value obtained by deducting the measured value at the start of treatment from a measured value at each time point
Percent change (%)	Value obtained by dividing a change by the measured value at

Derived variable	Description
	the start of treatment and then multiplying the division by 100
Time of onset (days)	Number of days from the start date of Benet/Actonel treatment to the date of onset of AE
Flag for inclusion/exclusion as an AE	It is identified whether an event is an AE.
Relationship (for analysis)	It is identified whether an AE is related to Benet/Actonel.
Seriousness (for analysis)	It is identified whether an AE is serious.
Novelty	It is identified whether an AE is expected (known) or unexpected (unknown) based on the precautions for Benet/Actonel.
Presence or absence of an AE	It is identified whether there is an AE (including “unknown”).
Presence or absence of an ADR	It is identified whether there is an ADR (including “unknown”).
Presence or absence of a SAE	It is identified whether there is a SAE (including “unknown”).
Flag for acute phase reaction	Acute phase reaction is defined as an ADR that occurs within 3 days after administration of Benet/Actonel and persists for at most 7 days.

6. Analysis Plan

Analysis sets, analysis items, and analysis methods are shown below. Details of variables for analysis and display will be specified in separately prepared statistical analysis specifications.

6.1. Analysis of Patients

6.1.1. Patient Composition Diagram

1) Analysis set Enrolled patients

2) Chart plan Figure 1-1

3) Analysis items Number of registration sites
Number of enrolled patients
Number of patients with no CRF collected (including reasons for collecting no CRF)
Number of patients with the CRF collected
Number of patients excluded from safety analysis (including reasons for exclusion)
Number of patients included in safety analysis

Number of patients excluded from efficacy analysis (including reasons for exclusion)

Number of patients included in efficacy analysis

4) Analysis methods The number of patients (number of sites) will be calculated for the analysis item, and a composition diagram will be prepared.

6.1.2. Patient Baseline Characteristics

1) Analysis set Patients included in safety analysis

Patients included in efficacy analysis

2) Chart plan Table 1-2

3) Analysis items Sex [male, female]

Age (years)* [<50, ≥50 to <65, ≥65 to <75, ≥75], [<60, ≥60 to <70, ≥70 to <80, ≥80], [<65, ≥65]

Height at the start of treatment (cm)* [<140, ≥140 to <160, ≥160]

Body weight (kg)* [<40, ≥40 to <50, ≥50 to <60, ≥60]

BMI (kg/m^2)* [<18.5, ≥18.5 to <25.0, ≥25.0]

Disease to be treated [osteoporosis: primary, osteoporosis: secondary]

Duration of disease (years)* [<1, ≥1 to <5, ≥5]

Predisposition to hypersensitivity [no, yes]

Concurrent illness [no, yes]

Disposition of concurrent illness [locomotor disease other than osteoporosis (spinal osteoarthritis, lumbago, spinal column stenosis, osteoarthritis), lifestyle-related disease (diabetes, hypertension, dyslipidemia, chronic obstructive pulmonary disease), cardiac disease (angina pectoris, myocardial infarction, arrhythmia), renal disease (diabetic nephropathy, glomerulonephritis, nephrotic syndrome), hepatic disease (chronic hepatitis, hepatic steatosis, hepatic cirrhosis), digestive disease (esophageal ulcer, gastric ulcer, duodenal ulcer, esophagitis), other (rheumatoid arthritis, other)]

Medical history (except previous fracture) [no, yes]

Disposition of medical history [cerebral infarction, myocardial infarction, thromboembolism, other]

Medical history (previous fracture) [no, yes]

Disposition of medical history (previous fracture) [vertebra, femur, wrist,

forearm, upper arm, pelvis, lower limb, other]
Previous steroid use [no, yes]
Disposition of previous steroid use [at least 3 months at a prednisolone equivalent dose of 5 mg/day or more, otherwise, unknown dose]
Parental history of femur fracture [no, yes]
Drinking history [no, yes]
Smoking history [never smoked, current smoker, past smoker]
Duration of Benet/Actonel treatment (months)* [<12, ≥12 to <24, ≥24 to <36, ≥36]
Amount of Benet/Actonel administered (mg)* [<900, ≥900 to <1800, ≥1800 to <2700, ≥2700]
Presence or absence of previous treatment [no, yes]
Disposition of previous treatment [osteoporosis drug, anti-inflammatory analgesic, cardiovascular drug, central nervous system drug, antidiabetic, digestive system drug, other]
Switching group [Benet/Actonel 2.5 mg, Benet/Actonel 17.5 mg, bisphosphonate other than Benet/Actonel, calcium alone, vitamin D alone, combination of calcium and vitamin D, osteoporosis drug not listed above, steroid, other]
Presence or absence of concomitant medication [no, yes]
Disposition of concomitant medication [osteoporosis drug, anti-inflammatory analgesic, cardiovascular drug, central nervous system drug, antidiabetic, digestive system drug, other]
Combination therapy group [Benet/Actonel 75 mg alone, calcium, vitamin D, combination of calcium and vitamin D, osteoporosis drug not listed above, steroid, other]
Presence or absence of physical therapy [no, yes]
Presence or absence of other concomitant therapy [no, yes]
Presence or absence of low back pain at the start of treatment [no, yes]

4) Analysis methods: The number and proportion of patients will be calculated for the analysis item. Summary statistics will be calculated for analysis items with *.

6.1.3. Treatment Compliance Status

1) Analysis set: Patients included in safety analysis

2) Chart plan: Table 1-3

3) Analysis item: Treatment status [took the drug as instructed by a physician, took the drug

on a different day from instructed by a physician, took no dose, unknown]

4) Analysis methods: The number and proportion of patients will be calculated for the analysis item by the number of doses. In addition, a stacked bar chart will be plotted with the percentage of number of patients on the vertical axis and the number of doses on the horizontal axis.

6.1.4. Changes in Treatment Compliance Rate over Time

1) Analysis set: Patients included in safety analysis
2) Chart plan: Table 1-4
3) Analysis item: Treatment compliance rate
4) Analysis methods: Summary statistics will be calculated for the analysis item by the number of doses. In addition, a line chart will be plotted with the treatment compliance rate on the vertical axis and the number of doses on the horizontal axis.

6.1.5. Changes in Dosing Interval over Time

1) Analysis set: Patients included in safety analysis
2) Chart plan: Table 1-5
3) Analysis item: Dosing interval
4) Analysis methods: Summary statistics will be calculated for the analysis item by the number of doses. In addition, a line chart will be plotted with the dosing interval on the vertical axis and the number of doses on the horizontal axis.

6.2. Analysis of Safety

The safety will be analyzed in patients included in safety analysis.

6.2.1. List of Occurrence of Adverse Drug Reactions (Attachment Style 2)

1) Analysis set: Patients included in safety analysis
2) Chart plan: Table 2-1
3) Analysis items: Number of surveillance sites
Number of surveyed patients
Number of patients with an ADR, etc.
Number of ADRs, etc.
Proportion of patients with an ADR, etc.
Proportion of patients with an ADR, etc. (number of ADRs, etc.) by type (PT)

4) Analysis methods The number and proportion of patients (number of events) will be calculated for the analysis item, and a list of occurrence of ADRs will be prepared.

6.2.2. List of Occurrence of Serious Adverse Events (Attachment Style 2-2, Attachment Style 10)

1) Analysis set Patients included in safety analysis

2) Chart plan Table 2-2

3) Analysis items Number of surveillance sites
Number of surveyed patients
Number of patients with a SAE
Number of SAEs
Proportion of patients with a SAE
Proportion of patients with a SAE (number of SAEs) by type (PT)

4) Analysis methods The number and proportion of patients (number of events) will be calculated for the analysis item, and a list of occurrence of SAEs will be prepared.

6.2.3. Occurrence of Adverse Events by Type

1) Analysis set Patients included in safety analysis

2) Chart plan Table 2-3

3) Analysis item AE type (SOC, PT)

4) Classification factors Relationship [yes, no]
Seriousness [serious, not serious]
Time of onset [Days 1-7, Days 8-14, Days 15-21, Days 22-28, Days 29-56, Days 57-84, Days 85-180, Days 181-210, Days 211-360, Day 361 or later], [Days 1-3, Days 4-14, Days 15-30, Days 31-90, Days 91-180, Days 181-270, Days 271-360, Day 361 or later]
Presence or absence of discontinuation of Benet/Actonel treatment [yes, no]
Outcome [recovered, recovering, not recovered, recovered with sequelae, death, unknown]

5) Analysis methods The number of patients will be calculated by AE type for each category of classification.

6.2.4. Occurrence of Acute Phase Reaction

1) Analysis set Patients included in safety analysis

2) Chart plan	Table 2-4
3) Analysis item	Acute phase reaction (SOC, PT)
4) Analysis methods	The number and proportion of patients (number of events) will be calculated for the analysis item by the number of doses, and a list of occurrence of acute phase reaction will be prepared.

6.3. Analysis of Efficacy

The efficacy will be analyzed in patients included in efficacy analysis. Patients with no pre- or post-baseline data on the relevant efficacy endpoint will be excluded from analysis.

6.3.1. Incidence of Vertebral Fracture

1) Analysis set	Patients included in efficacy analysis
2) Chart plan	Table 3-1-1-1 Table 3-1-1-2 Table 3-1-2-1 Table 3-1-2-2 Table 3-1-3-1 Table 3-1-3-2
3) Analysis items	New vertebral fracture or worsening of prevalent fracture New vertebral fracture or worsening of prevalent fracture <non-traumatic> New vertebral fracture New vertebral fracture <non-traumatic> Worsening of prevalent fracture Worsening of prevalent fracture <non-traumatic>
4) Analysis methods	Using the Kaplan-Meier method with the first onset of the analysis item as the event, the number of relevant patients (risk population), number of censored patients, number and proportion of patients with event, as well as the point estimate of cumulative incidence, standard error, and 95% confidence interval, at each time point of assessment will be calculated. In addition, a Kaplan-Meier curve will be plotted with the cumulative incidence (%) on the vertical axis and the time (months) on the horizontal axis.

6.3.2. Incidence of Non-vertebral Fracture

1) Analysis set	Patients included in efficacy analysis
2) Chart plan	Table 3-2-1

Table 3-2-2

3) Analysis items: Non-vertebral fracture

Non-vertebral fracture <non-traumatic>

4) Analysis methods: Non-vertebral fracture will be analyzed in the same manner as described in Section 6.3.1, "Incidence of Vertebral Fracture."

6.3.3. Percent Changes in Bone Turnover Markers

1) Analysis set: Patients included in efficacy analysis

2) Chart plan: Table 3-3

3) Analysis items: Bone turnover markers

4) Analysis methods: For each bone turnover marker, summary statistics at each time point of assessment will be calculated for observed value and percent change. In addition, the post-baseline difference in observed value and its 95% confidence interval will be calculated, and p-value will be calculated as specified in Section 3.3. 4), "Rules of statistical testing."

6.3.4. Percent Change in Bone Mineral Density

1) Analysis set: Patients included in efficacy analysis

2) Chart plan: Table 3-4

3) Analysis item: Bone mineral density

4) Analysis methods: For each bone mineral density, summary statistics at each time point of assessment will be calculated for observed value and percent change. In addition, the post-baseline difference in observed value and its 95% confidence interval will be calculated, and p-value will be calculated as specified in Section 3.3. 4), "Rules of statistical testing."

6.3.5. Changes in Height over Time

1) Analysis set: Patients included in efficacy analysis

2) Chart plan: Table 3-5

3) Analysis item: Height (cm)

4) Analysis methods: For height, summary statistics at each time point of assessment will be calculated for observed value and change. In addition, the post-baseline difference in observed value and its 95% confidence interval will be calculated, and p-value will be calculated as specified in Section 3.3. 4), "Rules of statistical testing."

6.3.6. Changes in Low Back Pain over Time

1) Analysis set: Patients included in efficacy analysis

2) Chart plan: Table 3-6

3) Analysis item: Low back pain

4) Analysis methods: For low back pain, a shift table at the start of treatment versus at each time point of assessment will be prepared. In addition, p-value will be calculated as specified in Section 3.3. 4), "Rules of statistical testing."

6.4. Listing

6.4.1. List of Discontinued Patients

1) Analysis set: Discontinued patients

2) Chart plan: Table 4-1

3) Analysis items: Patient number, sex, age, included in or excluded from the analysis set, start date and discontinuation date of Benet/Actonel treatment, number of days from start to discontinuation of Benet/Actonel treatment, reason for discontinuation, presence or absence of an AE, AE term

4) Analysis methods: A list with the analysis items will be prepared.

6.4.2. List of Patients Excluded from Analysis

1) Analysis set: Patients excluded from safety analysis
Patients excluded from efficacy analysis

2) Chart plan: Table 4-2

3) Analysis items: Patient number, sex, age, included in or excluded from the analysis set, start date of Benet/Actonel treatment, reason for exclusion, presence or absence of an AE, AE term

4) Analysis methods: A list with the analysis items will be prepared.

6.4.3. List of Surveyed Patients (Attachment Style 3)

1) Analysis set: Patients with the CRF collected

2) Chart plan: Table 4-3

3) Analysis items: Patient number, name, founder/code, and location (prefecture) of the study site, patient abbreviation, sex, date of birth (or age), inpatient or outpatient, reason for use (disease code, disease name), severity at baseline, concurrent illness (presence or absence, number, name), route of administration, maximum dose (daily dose/single dose), mean dose (daily dose/single dose), units, daily number of doses, duration of use,

	concomitant medication (drug code, representative drug name, number), degree of response, ADR (system organ code, ADR code, ADR term, presence or absence, number), outcome, CRF number, dropout
4) Analysis methods	A list with the analysis items will be prepared.

Benet 75 mg Tablets Special Drug Use Surveillance

Actonel 75 mg Tablets Special Drug Use Surveillance

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

Statistical Analysis Plan

Version 2.1

PPD

Takeda Pharmaceutical Co., Ltd.

PPD

PPD

PPD

History of amendments

Version number	Date of preparation	Preparator	Amendment/reason, etc.
1.0	7 March 2014	PPD	New document
2.0	29 September 2014		Thorough revision for the fourth periodic safety update report
2.1	8 October 2014		Correction made to Section 4.3, “Patients Included in Safety Analysis”

Table of Contents

1. Objectives

This document is intended to describe the details of statistical analyses in a special drug use surveillance on fracture incidence during 36-month treatment with Benet 75 mg Tablets and Actonel 75 mg Tablets (hereinafter referred to as the surveillance). The chart layout for analysis results will be specified in a separately prepared chart plan.

2. Synopsis

Surveillance drug	Benet 75 mg Tablets/Actonel 75 mg Tablets (hereinafter referred to as Benet/Actonel)
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/Actonel in osteoporotic patients in clinical settings
Planned sample size	250 patients/250 patients A total of 500 patients
Registration method	Central registration method
Planned surveillance period	Surveillance period: From May 2013 to April 2018 Registration period: From May 2013 to October 2014

3. Definitions

3.1. Definitions of Abbreviations

Abbreviation	Description
PMS system	CCI [redacted] (name of the system supplied by PPD [redacted] for managing the progression of post-marketing surveillances)
BMI	Body Mass Index
AE	Adverse Event
SOC	System Organ Class
PT	Preferred Term
LLT	Low Level Term

3.2. Definitions of Terms

Term	Description
Finalized patient	For Benet Tablets, a finalized patient is defined as a patient who has the date of CRF approval in the PMS system. For Actonel Tablets, a finalized patient is defined as a patient who has the date of temporary finalization in the business management system.
Adverse event (AE)	All events entered into the column of [Adverse event] in the case report form (CRF) Any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of Benet/Actonel, whether or not it is considered related to Benet/Actonel
Adverse drug reaction (ADR)	All adverse events except those not related to Benet/Actonel according to "Causal relationship to Benet/Actonel" both in the column of [Adverse event] in the CRF and determined by the company
Serious adverse event (SAE)	Adverse event assessed as serious according to "Seriousness" at least either in the column of [Adverse event] in the CRF or determined by the company, including AEs in Takeda Medically Significant AE List

3.3. Statistical Arrangements

1) Summary statistics

For quantitative variables, summary statistics are number of relevant patients, mean, standard deviation, minimum, median, and maximum.

2) Number of digits to be displayed

Proportions will be displayed to one decimal place by rounding.

Minimum and maximum will be displayed with the same number of digits as the number of significant figures, and the other summary statistics will be displayed to one lower digit than raw data by rounding.

Statistical p-value will be displayed to four decimal places by rounding. P-value less than 0.0001 will be displayed as <0.0001. Infeasibility of testing will be indicated as "-."

3) 95% confidence interval

For continuous variables, 95% confidence interval for mean difference will be presented as confidence limits following t-distribution.

4) Rules of statistical testing

One-sample t-test or one-sample Wilcoxon test will be used for pre- and post-treatment comparison of continuous variables.

McNemar test will be used for pre- and post-treatment comparison of ratios.

A two-sided 5% level of significance will be used.

The category of "unknown" will be excluded from statistical testing.

4. Analysis Sets

4.1. Enrolled Patients

All patients for whom the patient registration form has been accepted

4.2. Patients with the CRF Collected

Patients for whom the CRF has been collected before the end of the unit surveillance period and finalized

4.3. Patients Included in Safety Analysis

All patients with the CRF collected, excluding those who meet any of the following criteria:

1) Not treated with Benet/Actonel

2) Unknown whether an AE occurred

3) Deviated from the registration criteria

• Treated before conclusion of a contract

• Not registered in the registration period

• Failed to fax the patient registration form within 15 days after the first prescription of Benet/Actonel

4.4. Patients Included in Efficacy Analysis

All patients included in safety analysis, excluding those who meet any of the following criteria:

1) No evidence of 1 to 4 fractures from the fourth thoracic vertebra to the fourth lumbar vertebra provided by thoracic and lumbar spinal radiography performed before the start of the surveillance

2) Not 50 years or older

3) Not an outpatient who can walk

4) Pre- and post-baseline values of all efficacy endpoints (bone turnover markers, bone mineral density, vertebral fracture, non-vertebral fracture, height, and low back pain) are unknown, including

incalculable values

5. Handling of Data

Handling of data for analysis is described below. Details of processing will be specified in separately prepared analysis data set specifications.

5.1. Handling of Dichotomous Variables

For dichotomous variables, the presence or absence will be determined as described below when there is a column for details to be specified for "Yes."

1) "Yes" when details are specified

2) "No" when no details are specified and "No" is checked

3) "Unknown" when neither 1 nor 2) is applicable

5.2. Handling of Adverse Events

When multiple AEs of the same LLT are reported in the same patient, an AE to be employed will be determined as described below.

1) AEs that differ in the causal relationship to Benet/Actonel will be handled separately.

2) When multiple AEs of the same causal relationship to Benet/Actonel are reported, the most serious AE will be employed.

3) When multiple AEs of the same seriousness are reported, the earliest AE will be employed.

4) When multiple AEs are reported on the same day, an AE with the latest outcome will be employed.

5.3. Handling of Missing Data

In principle, no missing data will be imputed.

For frequency tabulation of qualitative variables, missing data will be handled as "unknown." For summary statistics of quantitative variables, missing data will be excluded, and non-missing data will be used.

5.4. Handling of Time Points of Assessment

Data within the permissible range as shown below will be employed.

If there are multiple pieces of data within the permissible range, data on the day closest to the nominal day will be employed. If deviation is the same before and after the nominal day, the latest data will be employed.

<Time points of assessment of vertebral fracture and non-vertebral fracture>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -90 to 1	Day 1
Month 6	Days 2 to 270	Day 180
Month 12	Days 271 to 540	Day 360
Month 24	Days 541 to 900	Day 720
Month 36	Days 901 to 1170	Day 1080
Final assessment	Days 2 to 1170	-

<Time points of assessment of bone turnover markers, bone mineral density, and low back pain>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -30 to 1	Day 1
Month 3	Days 2 to 105	Day 90
Month 6	Days 106 to 270	Day 180
Month 12	Days 271 to 450	Day 360
Month 18	Days 451 to 630	Day 540
Month 24	Days 631 to 810	Day 720
Month 30	Days 811 to 990	Day 900
Month 36	Days 991 to 1170	Day 1080
Final assessment	Days 2 to 1170	-

<Time points of assessment of height>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -30 to 1	Day 1
Month 12	Days 2 to 540	Day 360
Month 24	Days 541 to 900	Day 720
Month 36	Days 901 to 1170	Day 1080
Final assessment	Days 2 to 1170	-

5.5. Derived Variables

Derived variable	Description
Flag for enrollment	It is identified whether a patient is enrolled.
Flag for CRF collection	It is identified whether the CRF for a patient is collected.
Flag for inclusion in/exclusion from safety	It is identified whether a patient is included in safety analysis.
Flag for inclusion in/exclusion	It is identified whether a patient is included in efficacy analysis.

Derived variable	Description
from efficacy	
Age (years)	Age on the start day of Benet/Actonel treatment; or age described on the [Cover] in the CRF if date of birth is missing
BMI (kg/m^2)	Body mass index calculated as body weight (kg) ÷ height $(m)^2$
Duration of disease (years)	Number of years from diagnosis of osteoporosis to the start date of Benet/Actonel treatment (by rounding down)
Start date of Benet/Actonel treatment	Date described as the date of the scheduled first dosing on the [Cover] in the CRF; or the earliest (smallest) date among dates described in the [Treatment status of Benet/Actonel] if the first dose is not given as scheduled
End date of Benet/Actonel treatment	30 days after the latest (largest) date among dates described in the [Treatment status of Benet/Actonel] in the CRF
Duration of Benet/Actonel treatment (days)	Number of days from the start date of Benet/Actonel treatment to the end date of Benet/Actonel treatment
Duration of Benet/Actonel treatment (months)	Number of months from the start date of Benet/Actonel treatment to the end date of Benet/Actonel treatment
Number of doses of Benet/Actonel	Total number of doses during Benet/Actonel treatment counted as the number of checks made to "Took the drug" for patient's treatment status in the [Treatment status of Benet/Actonel] in the CRF
Amount of Benet/Actonel administered (mg)	Total dose during Benet/Actonel treatment calculated as number of doses of Benet/Actonel × 75 mg
Treatment compliance rate (%)	Percentage of the number of doses taken as instructed by a physician relative to the number of doses indicated by the physician
Dosing interval (days)	Number of days from the date of a certain dosing to the date of the next dosing
Flag for previous treatment	A drug deemed as previous treatment is identified.
Flag for concomitant medication	A drug deemed as concomitant medication is identified.
Flag for osteoporosis drug	An osteoporosis drug is identified.
Flag for anti-inflammatory analgesic	An anti-inflammatory analgesic is identified.

Derived variable	Description
Flag for cardiovascular drug	A cardiovascular drug is identified.
Flag for central nervous system drug	A central nervous system drug is identified.
Flag for antidiabetic	An antidiabetic is identified.
Flag for digestive system drug	A digestive system drug is identified.
Flag for other drug	Other drug not listed above is identified.
Flag for Benet/Actonel 2.5 mg	A drug that is Benet/Actonel 2.5 mg is identified.
Flag for Benet/Actonel 17.5 mg	A drug that is Benet/Actonel 17.5 mg is identified.
Flag for bisphosphonate other than Benet/Actonel	A bisphosphonate other than Benet/Actonel is identified.
Flag for calcium	A drug that is calcium is identified.
Flag for vitamin D	A drug that is vitamin D is identified.
Flag for osteoporosis drug not listed above	A drug that is an osteoporosis drug not listed above is identified.
Flag for steroid	A drug that is a steroid is identified.
Number of days to measurement (days)	Number of days from the start date of Benet/Actonel treatment to the date of measurement of the relevant endpoint
Time point of assessment (for analysis)	Time points of assessment are reallocated for analysis as specified in Section 5.4, "Handling of Time Points of Assessment."
Flag for employment of data	It is identified whether measurement data are employed.
Flag for event	A patient with event is defined as a patient who experienced at least one event such as vertebral fracture. A patient with no event is defined as a patient who experienced no event.
Time point of event onset	Time point of event onset is defined as the first onset of event such as vertebral fracture. Time point of event onset is final assessment for patients with no event.
Measured value at the start of treatment	The measured value at the start of treatment is identified.
Change	Value obtained by deducting the measured value at the start of treatment from a measured value at each time point
Percent change (%)	Value obtained by dividing a change by the measured value at the start of treatment and then multiplying the division by 100

Derived variable	Description
Time of onset (days)	Number of days from the start date of Benet/Actonel treatment to the date of onset of AE
Flag for inclusion/exclusion as an AE	It is identified whether an event is an AE.
Relationship (for analysis)	It is identified whether an AE is related to Benet/Actonel.
Seriousness (for analysis)	It is identified whether an AE is serious.
Novelty	It is identified whether an AE is expected (known) or unexpected (unknown) based on the precautions for Benet/Actonel.
Presence or absence of an AE	It is identified whether there is an AE (including “unknown”).
Presence or absence of an ADR	It is identified whether there is an ADR (including “unknown”).
Presence or absence of a SAE	It is identified whether there is a SAE (including “unknown”).

6. Analysis Plan

Analysis sets, analysis items, and analysis methods are shown below. Details of variables for analysis and display will be specified in separately prepared statistical analysis specifications.

6.1. Analysis of Patients

6.1.1. Patient Composition Diagram

1) Analysis set: Enrolled patients

2) Chart plan: Figure 1-1

3) Analysis items:
- Number of registration sites
- Number of enrolled patients
- Number of patients with no CRF collected (including reasons for collecting no CRF)
- Number of patients with the CRF collected
- Number of patients excluded from safety analysis (including reasons for exclusion)
- Number of patients included in safety analysis
- Number of patients excluded from efficacy analysis (including reasons for exclusion)
- Number of patients included in efficacy analysis

4) Analysis methods: The number of patients (number of sites) will be calculated for the

analysis item, and a composition diagram will be prepared.

6.1.2. Patient Baseline Characteristics

1) Analysis set — Patients included in safety analysis
Patients included in efficacy analysis

2) Chart plan — Table 1-2

3) Analysis items — Sex [male, female]
Age (years)* [<50, ≥50 to <65, ≥65 to <75, ≥75], [<60, ≥60 to <70, ≥70 to <80, ≥80], [<65, ≥65]
Height at the start of treatment (cm)* [<140, ≥140 to <160, ≥160]
Body weight (kg)* [<40, ≥40 to <50, ≥50 to <60, ≥60]
BMI (kg/m^2)* [<18.5, ≥18.5 to <25.0, ≥25.0]
Disease to be treated [osteoporosis: primary, osteoporosis: secondary]
Duration of disease (years)* [<1, ≥1 to <5, ≥5]
Predisposition to hypersensitivity [no, yes]
Concurrent illness [no, yes]

Disposition of concurrent illness [locomotor disease other than osteoporosis (spinal osteoarthritis, lumbago, spinal column stenosis, osteoarthritis), lifestyle-related disease (diabetes, hypertension, dyslipidemia, chronic obstructive pulmonary disease), cardiac disease (angina pectoris, myocardial infarction, arrhythmia), renal disease (diabetic nephropathy, glomerulonephritis, nephrotic syndrome), hepatic disease (chronic hepatitis, hepatic steatosis, hepatic cirrhosis), digestive disease (esophageal ulcer, gastric ulcer, duodenal ulcer, esophagitis), other (rheumatoid arthritis, other)]
Medical history (except previous fracture) [no, yes]
Disposition of medical history [cerebral infarction, myocardial infarction, thromboembolism, other]
Medical history (previous fracture) [no, yes]
Disposition of medical history (previous fracture) [vertebra, femur, wrist, forearm, upper arm, pelvis, lower limb, other]
Previous steroid use [no, yes]
Disposition of previous steroid use [at least 3 months at a prednisolone equivalent dose of 5 mg/day or more, otherwise, unknown dose]

Parental history of femur fracture [no, yes]
Drinking history [no, yes]
Smoking history [never smoked, current smoker, past smoker]
Duration of Benet/Actonel treatment (months)* [<12, ≥12 to <24, ≥24 to <36, ≥36]
Amount of Benet/Actonel administered (mg)* [<900, ≥900 to <1800, ≥1800 to <2700, ≥2700]
Presence or absence of previous treatment [no, yes]
Disposition of previous treatment [osteoporosis drug, anti-inflammatory analgesic, cardiovascular drug, central nervous system drug, antidiabetic, digestive system drug, other]
Switching group [Benet/Actonel 2.5 mg, Benet/Actonel 17.5 mg, bisphosphonate other than Benet/Actonel, calcium alone, vitamin D alone, combination of calcium and vitamin D, osteoporosis drug not listed above, steroid, other]
Presence or absence of concomitant medication [no, yes]
Disposition of concomitant medication [osteoporosis drug, anti-inflammatory analgesic, cardiovascular drug, central nervous system drug, antidiabetic, digestive system drug, other]
Combination therapy group [Benet/Actonel 75 mg alone, calcium, vitamin D, combination of calcium and vitamin D, osteoporosis drug not listed above, steroid, other]
Presence or absence of physical therapy [no, yes]
Presence or absence of other concomitant therapy [no, yes]
Presence or absence of low back pain at the start of treatment [no, yes]

4) Analysis methods: The number and proportion of patients will be calculated for the analysis item. Summary statistics will be calculated for analysis items with *.

6.1.3. Treatment Compliance Status

1) Analysis set: Patients included in safety analysis
2) Chart plan: Table 1-3
3) Analysis item: Treatment status [took the drug as instructed by a physician, took the drug on a different day from instructed by a physician, took no dose, unknown]
4) Analysis methods: The number and proportion of patients will be calculated for the analysis item by the number of doses. In addition, a stacked bar chart will be plotted with the percentage of number of patients on the vertical axis and

the number of doses on the horizontal axis.

6.1.4. Changes in Treatment Compliance Rate over Time

1) Analysis set: Patients included in safety analysis
2) Chart plan: Table 1-4
3) Analysis item: Treatment compliance rate
4) Analysis methods: Summary statistics will be calculated for the analysis item by the number of doses. In addition, a line chart will be plotted with the treatment compliance rate on the vertical axis and the number of doses on the horizontal axis.

6.1.5. Changes in Dosing Interval over Time

1) Analysis set: Patients included in safety analysis
2) Chart plan: Table 1-5
3) Analysis item: Dosing interval
4) Analysis methods: Summary statistics will be calculated for the analysis item by the number of doses. In addition, a line chart will be plotted with the dosing interval on the vertical axis and the number of doses on the horizontal axis.

6.2. Analysis of Safety

The safety will be analyzed in patients included in safety analysis.

6.2.1. List of Occurrence of Adverse Drug Reactions (Attachment Style 2)

1) Analysis set: Patients included in safety analysis
2) Chart plan: Table 2-1
3) Analysis items: Number of surveillance sites
   Number of surveyed patients
   Number of patients with an ADR, etc.
   Number of ADRs, etc.
   Proportion of patients with an ADR, etc.
   Proportion of patients with an ADR, etc. (number of ADRs, etc.) by type (PT)
4) Analysis methods: The number and proportion of patients (number of events) will be calculated for the analysis item, and a list of occurrence of ADRs will be prepared.

6.2.2. List of Occurrence of Serious Adverse Events (Attachment Style 2-2, Attachment Style 10)

1) Analysis set	Patients included in safety analysis
2) Chart plan	Table 2-2
3) Analysis items	Number of surveillance sites Number of surveyed patients Number of patients with a SAE Number of SAEs Proportion of patients with a SAE Proportion of patients with a SAE (number of SAEs) by type (PT)
4) Analysis methods	The number and proportion of patients (number of events) will be calculated for the analysis item, and a list of occurrence of SAEs will be prepared.

6.2.3. Occurrence of Adverse Events by Type

1) Analysis set	Patients included in safety analysis
2) Chart plan	Table 2-3
3) Analysis item	AE type (SOC, PT)
4) Classification factors	Relationship [yes, no] Seriousness [serious, not serious] Time of onset [Days 1-7, Days 8-14, Days 15-21, Days 22-28, Days 29-56, Days 57-84, Days 85-180, Days 181-210, Days 211-360, Day 361 or later], [Days 1-3, Days 4-14, Days 15-30, Days 31-90, Days 91-180, Days 181-270, Days 271-360, Day 361 or later] Presence or absence of discontinuation of Benet/Actonel treatment [yes, no] Outcome [recovered, recovering, not recovered, recovered with sequelae, death, unknown]
5) Analysis methods	The number of patients will be calculated by AE type for each category of classification.

6.3. Analysis of Efficacy

The efficacy will be analyzed in patients included in efficacy analysis. Patients with no pre- or post-baseline data on the relevant efficacy endpoint will be excluded from analysis.

6.3.1. Incidence of Vertebral Fracture

1) Analysis set	Patients included in efficacy analysis

2) Chart plan	Table 3-1-1-1 Table 3-1-1-2 Table 3-1-2-1 Table 3-1-2-2 Table 3-1-3-1 Table 3-1-3-2
3) Analysis items	New vertebral fracture or worsening of prevalent fracture New vertebral fracture or worsening of prevalent fracture <non-traumatic> New vertebral fracture New vertebral fracture <non-traumatic> Worsening of prevalent fracture Worsening of prevalent fracture <non-traumatic>
4) Analysis methods	Using the Kaplan-Meier method with the first onset of the analysis item as the event, the number of relevant patients (risk population), number of censored patients, number and proportion of patients with event, as well as the point estimate of cumulative incidence, standard error, and 95% confidence interval, at each time point of assessment will be calculated. In addition, a Kaplan-Meier curve will be plotted with the cumulative incidence (%) on the vertical axis and the time (months) on the horizontal axis.

6.3.2. Incidence of Non-vertebral Fracture

1) Analysis set	Patients included in efficacy analysis
2) Chart plan	Table 3-2-1 Table 3-2-2
3) Analysis items	Non-vertebral fracture Non-vertebral fracture <non-traumatic>
4) Analysis methods	Non-vertebral fracture will be analyzed in the same manner as described in Section 6.3.1, “Incidence of Vertebral Fracture.”

6.3.3. Percent Changes in Bone Turnover Markers

1) Analysis set	Patients included in efficacy analysis
2) Chart plan	Table 3-3
3) Analysis items	Bone turnover markers
4) Analysis methods	For each bone turnover marker, summary statistics at each time point of assessment will be calculated for observed value and percent change. In

addition, the post-baseline difference in observed value and its 95% confidence interval will be calculated, and p-value will be calculated as specified in Section 3.3. 4), “Rules of statistical testing.”

6.3.4. Percent Change in Bone Mineral Density

1) Analysis set Patients included in efficacy analysis

2) Chart plan Table 3-4

3) Analysis item Bone mineral density

4) Analysis methods For each bone mineral density, summary statistics at each time point of assessment will be calculated for observed value and percent change. In addition, the post-baseline difference in observed value and its 95% confidence interval will be calculated, and p-value will be calculated as specified in Section 3.3. 4), “Rules of statistical testing.”

6.3.5. Changes in Height over Time

1) Analysis set Patients included in efficacy analysis

2) Chart plan Table 3-5

3) Analysis item Height (cm)

4) Analysis methods For height, summary statistics at each time point of assessment will be calculated for observed value and change. In addition, the post-baseline difference in observed value and its 95% confidence interval will be calculated, and p-value will be calculated as specified in Section 3.3. 4), “Rules of statistical testing.”

6.3.6. Changes in Low Back Pain over Time

1) Analysis set Patients included in efficacy analysis

2) Chart plan Table 3-6

3) Analysis item Low back pain

4) Analysis methods For low back pain, a shift table at the start of treatment versus at each time point of assessment will be prepared. In addition, p-value will be calculated as specified in Section 3.3. 4), “Rules of statistical testing.”

6.4. Listing

6.4.1. List of Discontinued Patients

1) Analysis set Discontinued patients

2) Chart plan Table 4-1

3) Analysis items　Patient number, sex, age, included in or excluded from the analysis set, start date and discontinuation date of Benet/Actonel treatment, number of days from start to discontinuation of Benet/Actonel treatment, reason for discontinuation, presence or absence of an AE, AE term

4) Analysis methods　A list with the analysis items will be prepared.

6.4.2. List of Patients Excluded from Analysis

1) Analysis set　Patients excluded from safety analysis
Patients excluded from efficacy analysis

2) Chart plan　Table 4-2

3) Analysis items　Patient number, sex, age, included in or excluded from the analysis set, start date of Benet/Actonel treatment, reason for exclusion, presence or absence of an AE, AE term

4) Analysis methods　A list with the analysis items will be prepared.

6.4.3. List of Surveyed Patients (Attachment Style 3)

1) Analysis set　Patients with the CRF collected

2) Chart plan　Table 4-3

3) Analysis items　Patient number, name, founder/code, and location (prefecture) of the study site, patient abbreviation, sex, date of birth (or age), inpatient or outpatient, reason for use (disease code, disease name), severity at baseline, concurrent illness (presence or absence, number, name), route of administration, maximum dose (daily dose/single dose), mean dose (daily dose/single dose), units, daily number of doses, duration of use, concomitant medication (drug code, representative drug name, number), degree of response, ADR (system organ code, ADR code, ADR term, presence or absence, number), outcome, CRF number, dropout

4) Analysis methods　A list with the analysis items will be prepared.

Benet 75 mg Tablets Special Drug Use Surveillance

Actonel 75 mg Tablets Special Drug Use Surveillance

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

Statistical Analysis Plan

Version 2.0

PPD

Takeda Pharmaceutical Co., Ltd.

PPD

PPD

PPD

History of amendments

Version number	Date of preparation	Preparator	Amendment/reason, etc.
1.0	7 March 2014	PPD	New document
2.0	29 September 2014		Thorough revision for the fourth periodic safety update report

Table of Contents

1. Objectives

This document is intended to describe the details of statistical analyses in a special drug use surveillance on fracture incidence during 36-month treatment with Benet 75 mg Tablets and Actonel 75 mg Tablets (hereinafter referred to as the surveillance). The chart layout for analysis results will be specified in a separately prepared chart plan.

2. Synopsis

Surveillance drug	Benet 75 mg Tablets/Actonel 75 mg Tablets (hereinafter referred to as Benet/Actonel)
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/Actonel in osteoporotic patients in clinical settings
Planned sample size	250 patients/250 patients A total of 500 patients
Registration method	Central registration method
Planned surveillance period	Surveillance period: From May 2013 to April 2018 Registration period: From May 2013 to October 2014

3. Definitions

3.1. Definitions of Abbreviations

Abbreviation	Description
PMS system	CCI [redacted] (name of the system supplied by PPD [redacted] for managing the progression of post-marketing surveillances)
BMI	Body Mass Index
AE	Adverse Event
SOC	System Organ Class
PT	Preferred Term
LLT	Low Level Term

3.2. Definitions of Terms

Term	Description
Finalized patient	For Benet Tablets, a finalized patient is defined as a patient who has the date of CRF approval in the PMS system. For Actonel Tablets, a finalized patient is defined as a patient who has the date of temporary finalization in the business management system.
Adverse event (AE)	All events entered into the column of [Adverse event] in the case report form (CRF) Any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of Benet/Actonel, whether or not it is considered related to Benet/Actonel
Adverse drug reaction (ADR)	All adverse events except those not related to Benet/Actonel according to "Causal relationship to Benet/Actonel" both in the column of [Adverse event] in the CRF and determined by the company
Serious adverse event (SAE)	Adverse event assessed as serious according to "Seriousness" at least either in the column of [Adverse event] in the CRF or determined by the company, including AEs in Takeda Medically Significant AE List

3.3. Statistical Arrangements

1) Summary statistics

For quantitative variables, summary statistics are number of relevant patients, mean, standard deviation, minimum, median, and maximum.

2) Number of digits to be displayed

Proportions will be displayed to one decimal place by rounding.

Minimum and maximum will be displayed with the same number of digits as the number of significant figures, and the other summary statistics will be displayed to one lower digit than raw data by rounding.

Statistical p-value will be displayed to four decimal places by rounding. P-value less than 0.0001 will be displayed as <0.0001. Infeasibility of testing will be indicated as "-."

3) 95% confidence interval

For continuous variables, 95% confidence interval for mean difference will be presented as confidence limits following t-distribution.

4) Rules of statistical testing

One-sample t-test or one-sample Wilcoxon test will be used for pre- and post-treatment comparison of continuous variables.

McNemar test will be used for pre- and post-treatment comparison of ratios.

A two-sided 5% level of significance will be used.

The category of "unknown" will be excluded from statistical testing.

4. Analysis Sets

4.1. Enrolled Patients

All patients for whom the patient registration form has been accepted

4.2. Patients with the CRF Collected

Patients for whom the CRF has been collected before the end of the unit surveillance period and finalized

4.3. Patients Included in Safety Analysis

All patients with the CRF collected, excluding those who meet any of the following criteria:

1) Not treated with Benet/Actonel

2) Unknown whether an AE occurred

3) Deviated from the registration criteria

• Treated before conclusion of a contract

• Not registered in the registration period

• Failed to fax the patient registration form within 15 days after the start of Benet/Actonel treatment

4.4. Patients Included in Efficacy Analysis

All patients included in safety analysis, excluding those who meet any of the following criteria:

1) No evidence of 1 to 4 fractures from the fourth thoracic vertebra to the fourth lumbar vertebra provided by thoracic and lumbar spinal radiography performed before the start of the surveillance

2) Not 50 years or older

3) Not an outpatient who can walk

4) Pre- and post-baseline values of all efficacy endpoints (bone turnover markers, bone mineral density, vertebral fracture, non-vertebral fracture, height, and low back pain) are unknown, including incalculable values

5. Handling of Data

Handling of data for analysis is described below. Details of processing will be specified in separately prepared analysis data set specifications.

5.1. Handling of Dichotomous Variables

For dichotomous variables, the presence or absence will be determined as described below when there is a column for details to be specified for "Yes."

1) "Yes" when details are specified

2) "No" when no details are specified and "No" is checked

3) "Unknown" when neither 1 nor 2) is applicable

5.2. Handling of Adverse Events

When multiple AEs of the same LLT are reported in the same patient, an AE to be employed will be determined as described below.

1) AEs that differ in the causal relationship to Benet/Actonel will be handled separately.

2) When multiple AEs of the same causal relationship to Benet/Actonel are reported, the most serious AE will be employed.

3) When multiple AEs of the same seriousness are reported, the earliest AE will be employed.

4) When multiple AEs are reported on the same day, an AE with the latest outcome will be employed.

5.3. Handling of Missing Data

In principle, no missing data will be imputed.

For frequency tabulation of qualitative variables, missing data will be handled as "unknown." For summary statistics of quantitative variables, missing data will be excluded, and non-missing data will be used.

5.4. Handling of Time Points of Assessment

Data within the permissible range as shown below will be employed.

If there are multiple pieces of data within the permissible range, data on the day closest to the nominal day will be employed. If deviation is the same before and after the nominal day, the latest data will be employed.

<Time points of assessment of vertebral fracture and non-vertebral fracture>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -90 to 1	Day 1
Month 6	Days 2 to 270	Day 180
Month 12	Days 271 to 540	Day 360
Month 24	Days 541 to 900	Day 720
Month 36	Days 901 to 1170	Day 1080
Final assessment	Days 2 to 1170	-

<Time points of assessment of bone turnover markers, bone mineral density, and low back pain>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -30 to 1	Day 1
Month 3	Days 2 to 105	Day 90
Month 6	Days 106 to 270	Day 180
Month 12	Days 271 to 450	Day 360
Month 18	Days 451 to 630	Day 540
Month 24	Days 631 to 810	Day 720
Month 30	Days 811 to 990	Day 900
Month 36	Days 991 to 1170	Day 1080
Final assessment	Days 2 to 1170	-

<Time points of assessment of height>

Time point of assessment	Permissible range	Nominal day
Before the start of treatment	Days -30 to 1	Day 1
Month 12	Days 2 to 540	Day 360
Month 24	Days 541 to 900	Day 720
Month 36	Days 901 to 1170	Day 1080
Final assessment	Days 2 to 1170	-

5.5. Derived Variables

Derived variable	Description
Flag for enrollment	It is identified whether a patient is enrolled.
Flag for CRF collection	It is identified whether the CRF for a patient is collected.
Flag for inclusion in/exclusion from safety	It is identified whether a patient is included in safety analysis.
Flag for inclusion in/exclusion	It is identified whether a patient is included in efficacy analysis.

Derived variable	Description
from efficacy	
Age (years)	Age on the start day of Benet/Actonel treatment; or age described on the [Cover] in the CRF if date of birth is missing
BMI (kg/m^2)	Body mass index calculated as body weight (kg) ÷ height $(m)^2$
Duration of disease (years)	Number of years from diagnosis of osteoporosis to the start date of Benet/Actonel treatment (by rounding down)
Start date of Benet/Actonel treatment	Date described as the date of the scheduled first dosing on the [Cover] in the CRF; or the earliest (smallest) date among dates described in the [Treatment status of Benet/Actonel] if the first dose is not given as scheduled
End date of Benet/Actonel treatment	30 days after the latest (largest) date among dates described in the [Treatment status of Benet/Actonel] in the CRF
Duration of Benet/Actonel treatment (days)	Number of days from the start date of Benet/Actonel treatment to the end date of Benet/Actonel treatment
Duration of Benet/Actonel treatment (months)	Number of months from the start date of Benet/Actonel treatment to the end date of Benet/Actonel treatment
Number of doses of Benet/Actonel	Total number of doses during Benet/Actonel treatment counted as the number of checks made to "Took the drug" for patient's treatment status in the [Treatment status of Benet/Actonel] in the CRF
Amount of Benet/Actonel administered (mg)	Total dose during Benet/Actonel treatment calculated as number of doses of Benet/Actonel × 75 mg
Treatment compliance rate (%)	Percentage of the number of doses taken as instructed by a physician relative to the number of doses indicated by the physician
Dosing interval (days)	Number of days from the date of a certain dosing to the date of the next dosing
Flag for previous treatment	A drug deemed as previous treatment is identified.
Flag for concomitant medication	A drug deemed as concomitant medication is identified.
Flag for osteoporosis drug	An osteoporosis drug is identified.
Flag for anti-inflammatory analgesic	An anti-inflammatory analgesic is identified.

Derived variable	Description
Flag for cardiovascular drug	A cardiovascular drug is identified.
Flag for central nervous system drug	A central nervous system drug is identified.
Flag for antidiabetic	An antidiabetic is identified.
Flag for digestive system drug	A digestive system drug is identified.
Flag for other drug	Other drug not listed above is identified.
Flag for Benet/Actonel 2.5 mg	A drug that is Benet/Actonel 2.5 mg is identified.
Flag for Benet/Actonel 17.5 mg	A drug that is Benet/Actonel 17.5 mg is identified.
Flag for bisphosphonate other than Benet/Actonel	A bisphosphonate other than Benet/Actonel is identified.
Flag for calcium	A drug that is calcium is identified.
Flag for vitamin D	A drug that is vitamin D is identified.
Flag for osteoporosis drug not listed above	A drug that is an osteoporosis drug not listed above is identified.
Flag for steroid	A drug that is a steroid is identified.
Number of days to measurement (days)	Number of days from the start date of Benet/Actonel treatment to the date of measurement of the relevant endpoint
Time point of assessment (for analysis)	Time points of assessment are reallocated for analysis as specified in Section 5.4, "Handling of Time Points of Assessment."
Flag for employment of data	It is identified whether measurement data are employed.
Flag for event	A patient with event is defined as a patient who experienced at least one event such as vertebral fracture. A patient with no event is defined as a patient who experienced no event.
Time point of event onset	Time point of event onset is defined as the first onset of event such as vertebral fracture. Time point of event onset is final assessment for patients with no event.
Measured value at the start of treatment	The measured value at the start of treatment is identified.
Change	Value obtained by deducting the measured value at the start of treatment from a measured value at each time point
Percent change (%)	Value obtained by dividing a change by the measured value at the start of treatment and then multiplying the division by 100

Derived variable	Description
Time of onset (days)	Number of days from the start date of Benet/Actonel treatment to the date of onset of AE
Flag for inclusion/exclusion as an AE	It is identified whether an event is an AE.
Relationship (for analysis)	It is identified whether an AE is related to Benet/Actonel.
Seriousness (for analysis)	It is identified whether an AE is serious.
Novelty	It is identified whether an AE is expected (known) or unexpected (unknown) based on the precautions for Benet/Actonel.
Presence or absence of an AE	It is identified whether there is an AE (including “unknown”).
Presence or absence of an ADR	It is identified whether there is an ADR (including “unknown”).
Presence or absence of a SAE	It is identified whether there is a SAE (including “unknown”).

6. Analysis Plan

Analysis sets, analysis items, and analysis methods are shown below. Details of variables for analysis and display will be specified in separately prepared statistical analysis specifications.

6.1. Analysis of Patients

6.1.1. Patient Composition Diagram

1) Analysis set: Enrolled patients

2) Chart plan: Figure 1-1

3) Analysis items:
- Number of registration sites
- Number of enrolled patients
- Number of patients with no CRF collected (including reasons for collecting no CRF)
- Number of patients with the CRF collected
- Number of patients excluded from safety analysis (including reasons for exclusion)
- Number of patients included in safety analysis
- Number of patients excluded from efficacy analysis (including reasons for exclusion)
- Number of patients included in efficacy analysis

4) Analysis methods: The number of patients (number of sites) will be calculated for the

analysis item, and a composition diagram will be prepared.

6.1.2. Patient Baseline Characteristics

1) Analysis set — Patients included in safety analysis
Patients included in efficacy analysis

2) Chart plan — Table 1-2

3) Analysis items — Sex [male, female]
Age (years)* [<50, ≥50 to <65, ≥65 to <75, ≥75], [<60, ≥60 to <70, ≥70 to <80, ≥80], [<65, ≥65]
Height at the start of treatment (cm)* [<140, ≥140 to <160, ≥160]
Body weight (kg)* [<40, ≥40 to <50, ≥50 to <60, ≥60]
BMI (kg/m^2)* [<18.5, ≥18.5 to <25.0, ≥25.0]
Disease to be treated [osteoporosis: primary, osteoporosis: secondary]
Duration of disease (years)* [<1, ≥1 to <5, ≥5]
Predisposition to hypersensitivity [no, yes]
Concurrent illness [no, yes]

Disposition of concurrent illness [locomotor disease other than osteoporosis (spinal osteoarthritis, lumbago, spinal column stenosis, osteoarthritis), lifestyle-related disease (diabetes, hypertension, dyslipidemia, chronic obstructive pulmonary disease), cardiac disease (angina pectoris, myocardial infarction, arrhythmia), renal disease (diabetic nephropathy, glomerulonephritis, nephrotic syndrome), hepatic disease (chronic hepatitis, hepatic steatosis, hepatic cirrhosis), digestive disease (esophageal ulcer, gastric ulcer, duodenal ulcer, esophagitis), other (rheumatoid arthritis, other)]
Medical history (except previous fracture) [no, yes]
Disposition of medical history [cerebral infarction, myocardial infarction, thromboembolism, other]
Medical history (previous fracture) [no, yes]
Disposition of medical history (previous fracture) [vertebra, femur, wrist, forearm, upper arm, pelvis, lower limb, other]
Previous steroid use [no, yes]
Disposition of previous steroid use [at least 3 months at a prednisolone equivalent dose of 5 mg/day or more, otherwise, unknown dose]

Parental history of femur fracture [no, yes]
Drinking history [no, yes]
Smoking history [never smoked, current smoker, past smoker]
Duration of Benet/Actonel treatment (months)* [<12, ≥12 to <24, ≥24 to <36, ≥36]
Amount of Benet/Actonel administered (mg)* [<900, ≥900 to <1800, ≥1800 to <2700, ≥2700]
Presence or absence of previous treatment [no, yes]
Disposition of previous treatment [osteoporosis drug, anti-inflammatory analgesic, cardiovascular drug, central nervous system drug, antidiabetic, digestive system drug, other]
Switching group [Benet/Actonel 2.5 mg, Benet/Actonel 17.5 mg, bisphosphonate other than Benet/Actonel, calcium alone, vitamin D alone, combination of calcium and vitamin D, osteoporosis drug not listed above, steroid, other]
Presence or absence of concomitant medication [no, yes]
Disposition of concomitant medication [osteoporosis drug, anti-inflammatory analgesic, cardiovascular drug, central nervous system drug, antidiabetic, digestive system drug, other]
Combination therapy group [Benet/Actonel 75 mg alone, calcium, vitamin D, combination of calcium and vitamin D, osteoporosis drug not listed above, steroid, other]
Presence or absence of physical therapy [no, yes]
Presence or absence of other concomitant therapy [no, yes]
Presence or absence of low back pain at the start of treatment [no, yes]

4) Analysis methods: The number and proportion of patients will be calculated for the analysis item. Summary statistics will be calculated for analysis items with *.

6.1.3. Treatment Compliance Status

1) Analysis set: Patients included in safety analysis
2) Chart plan: Table 1-3
3) Analysis item: Treatment status [took the drug as instructed by a physician, took the drug on a different day from instructed by a physician, took no dose, unknown]
4) Analysis methods: The number and proportion of patients will be calculated for the analysis item by the number of doses. In addition, a stacked bar chart will be plotted with the percentage of number of patients on the vertical axis and

the number of doses on the horizontal axis.

6.1.4. Changes in Treatment Compliance Rate over Time

1) Analysis set: Patients included in safety analysis
2) Chart plan: Table 1-4
3) Analysis item: Treatment compliance rate
4) Analysis methods: Summary statistics will be calculated for the analysis item by the number of doses. In addition, a line chart will be plotted with the treatment compliance rate on the vertical axis and the number of doses on the horizontal axis.

6.1.5. Changes in Dosing Interval over Time

1) Analysis set: Patients included in safety analysis
2) Chart plan: Table 1-5
3) Analysis item: Dosing interval
4) Analysis methods: Summary statistics will be calculated for the analysis item by the number of doses. In addition, a line chart will be plotted with the dosing interval on the vertical axis and the number of doses on the horizontal axis.

6.2. Analysis of Safety

The safety will be analyzed in patients included in safety analysis.

6.2.1. List of Occurrence of Adverse Drug Reactions (Attachment Style 2)

1) Analysis set: Patients included in safety analysis
2) Chart plan: Table 2-1
3) Analysis items: Number of surveillance sites
   Number of surveyed patients
   Number of patients with an ADR, etc.
   Number of ADRs, etc.
   Proportion of patients with an ADR, etc.
   Proportion of patients with an ADR, etc. (number of ADRs, etc.) by type (PT)
4) Analysis methods: The number and proportion of patients (number of events) will be calculated for the analysis item, and a list of occurrence of ADRs will be prepared.

6.2.2. List of Occurrence of Serious Adverse Events (Attachment Style 2-2, Attachment Style 10)

1) Analysis set	Patients included in safety analysis
2) Chart plan	Table 2-2
3) Analysis items	Number of surveillance sites Number of surveyed patients Number of patients with a SAE Number of SAEs Proportion of patients with a SAE Proportion of patients with a SAE (number of SAEs) by type (PT)
4) Analysis methods	The number and proportion of patients (number of events) will be calculated for the analysis item, and a list of occurrence of SAEs will be prepared.

6.2.3. Occurrence of Adverse Events by Type

1) Analysis set	Patients included in safety analysis
2) Chart plan	Table 2-3
3) Analysis item	AE type (SOC, PT)
4) Classification factors	Relationship [yes, no] Seriousness [serious, not serious] Time of onset [Days 1-7, Days 8-14, Days 15-21, Days 22-28, Days 29-56, Days 57-84, Days 85-180, Days 181-210, Days 211-360, Day 361 or later], [Days 1-3, Days 4-14, Days 15-30, Days 31-90, Days 91-180, Days 181-270, Days 271-360, Day 361 or later] Presence or absence of discontinuation of Benet/Actonel treatment [yes, no] Outcome [recovered, recovering, not recovered, recovered with sequelae, death, unknown]
5) Analysis methods	The number of patients will be calculated by AE type for each category of classification.

6.3. Analysis of Efficacy

The efficacy will be analyzed in patients included in efficacy analysis. Patients with no pre- or post-baseline data on the relevant efficacy endpoint will be excluded from analysis.

6.3.1. Incidence of Vertebral Fracture

1) Analysis set	Patients included in efficacy analysis

2) Chart plan	Table 3-1-1-1 Table 3-1-1-2 Table 3-1-2-1 Table 3-1-2-2 Table 3-1-3-1 Table 3-1-3-2
3) Analysis items	New vertebral fracture or worsening of prevalent fracture New vertebral fracture or worsening of prevalent fracture <non-traumatic> New vertebral fracture New vertebral fracture <non-traumatic> Worsening of prevalent fracture Worsening of prevalent fracture <non-traumatic>
4) Analysis methods	Using the Kaplan-Meier method with the first onset of the analysis item as the event, the number of relevant patients (risk population), number of censored patients, number and proportion of patients with event, as well as the point estimate of cumulative incidence, standard error, and 95% confidence interval, at each time point of assessment will be calculated. In addition, a Kaplan-Meier curve will be plotted with the cumulative incidence (%) on the vertical axis and the time (months) on the horizontal axis.

6.3.2. Incidence of Non-vertebral Fracture

1) Analysis set	Patients included in efficacy analysis
2) Chart plan	Table 3-2-1 Table 3-2-2
3) Analysis items	Non-vertebral fracture Non-vertebral fracture <non-traumatic>
4) Analysis methods	Non-vertebral fracture will be analyzed in the same manner as described in Section 6.3.1, “Incidence of Vertebral Fracture.”

6.3.3. Percent Changes in Bone Turnover Markers

1) Analysis set	Patients included in efficacy analysis
2) Chart plan	Table 3-3
3) Analysis items	Bone turnover markers
4) Analysis methods	For each bone turnover marker, summary statistics at each time point of assessment will be calculated for observed value and percent change. In

addition, the post-baseline difference in observed value and its 95% confidence interval will be calculated, and p-value will be calculated as specified in Section 3.3. 4), “Rules of statistical testing.”

6.3.4. Percent Change in Bone Mineral Density

1) Analysis set Patients included in efficacy analysis

2) Chart plan Table 3-4

3) Analysis item Bone mineral density

4) Analysis methods For each bone mineral density, summary statistics at each time point of assessment will be calculated for observed value and percent change. In addition, the post-baseline difference in observed value and its 95% confidence interval will be calculated, and p-value will be calculated as specified in Section 3.3. 4), “Rules of statistical testing.”

6.3.5. Changes in Height over Time

1) Analysis set Patients included in efficacy analysis

2) Chart plan Table 3-5

3) Analysis item Height (cm)

4) Analysis methods For height, summary statistics at each time point of assessment will be calculated for observed value and change. In addition, the post-baseline difference in observed value and its 95% confidence interval will be calculated, and p-value will be calculated as specified in Section 3.3. 4), “Rules of statistical testing.”

6.3.6. Changes in Low Back Pain over Time

1) Analysis set Patients included in efficacy analysis

2) Chart plan Table 3-6

3) Analysis item Low back pain

4) Analysis methods For low back pain, a shift table at the start of treatment versus at each time point of assessment will be prepared. In addition, p-value will be calculated as specified in Section 3.3. 4), “Rules of statistical testing.”

6.4. Listing

6.4.1. List of Discontinued Patients

1) Analysis set Discontinued patients

2) Chart plan Table 4-1

3) Analysis items　Patient number, sex, age, included in or excluded from the analysis set, start date and discontinuation date of Benet/Actonel treatment, number of days from start to discontinuation of Benet/Actonel treatment, reason for discontinuation, presence or absence of an AE, AE term

4) Analysis methods　A list with the analysis items will be prepared.

6.4.2. List of Patients Excluded from Analysis

1) Analysis set　Patients excluded from safety analysis
Patients excluded from efficacy analysis

2) Chart plan　Table 4-2

3) Analysis items　Patient number, sex, age, included in or excluded from the analysis set, start date of Benet/Actonel treatment, reason for exclusion, presence or absence of an AE, AE term

4) Analysis methods　A list with the analysis items will be prepared.

6.4.3. List of Surveyed Patients (Attachment Style 3)

1) Analysis set　Patients with the CRF collected

2) Chart plan　Table 4-3

3) Analysis items　Patient number, name, founder/code, and location (prefecture) of the study site, patient abbreviation, sex, date of birth (or age), inpatient or outpatient, reason for use (disease code, disease name), severity at baseline, concurrent illness (presence or absence, number, name), route of administration, maximum dose (daily dose/single dose), mean dose (daily dose/single dose), units, daily number of doses, duration of use, concomitant medication (drug code, representative drug name, number), degree of response, ADR (system organ code, ADR code, ADR term, presence or absence, number), outcome, CRF number, dropout

4) Analysis methods　A list with the analysis items will be prepared.

Benet 75 mg Tablets Special Drug Use Surveillance

Actonel 75 mg Tablets Special Drug Use Surveillance

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

Statistical Analysis Plan

Version 1.0

PPD

Takeda Pharmaceutical Co., Ltd.

PPD

PPD

PPD

History of amendments

Version number	Date of preparation	Preparator	Amendment/reason, etc.
1.0	7 March 2014	PPD	New document

Table of Contents

1. Objectives

This document is intended to describe the details of statistical analyses in a special drug use surveillance on fracture incidence during 36-month treatment with Benet 75 mg Tablets and Actonel 75 mg Tablets (hereinafter referred to as the surveillance). The chart layout for analysis results will be specified in a separately prepared chart plan.

2. Synopsis

Surveillance drug	Benet 75 mg Tablets/Actonel 75 mg Tablets (hereinafter referred to as Benet/Actonel)
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/Actonel in osteoporotic patients in clinical settings
Planned sample size	250 patients/250 patients A total of 500 patients
Registration method	Central registration method
Planned surveillance period	Surveillance period: From May 2013 to April 2018 Registration period: From May 2013 to October 2014

3. Definitions

3.1. Definitions of Abbreviations

Abbreviation	Description
AE	Adverse Event
SOC	System Organ Class
PT	Preferred Term
LLT	Low Level Term

3.2. Definitions of Terms

Term	Description
Adverse event (AE)	All events entered into the column of [Adverse event] in the case report form (CRF) Any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of Benet/Actonel, whether or not it is considered related to Benet/Actonel
Adverse drug reaction (ADR)	All adverse events except those not related to Benet/Actonel according to "Causal relationship to Benet/Actonel" both in the column of [Adverse event] in the CRF and determined by the company
Serious adverse event (SAE)	Adverse event assessed as serious according to "Seriousness" at least either in the column of [Adverse event] in the CRF or determined by the company, including AEs in Takeda Medically Significant AE List

4. Analysis Sets

4.1. Enrolled Patients

Patients for whom the patient registration form has been accepted

4.2. Patients with the CRF Collected

Patients for whom the CRF has been collected before the end of the unit surveillance period and finalized

4.3. Patients Included in Safety Analysis

All patients with the CRF collected, excluding those who meet any of the following criteria:

1) Not treated with Benet/Actonel

2) Unknown whether an AE occurred

3) Deviated from the registration criteria

• Treated before conclusion of a contract

• Not registered in the registration period

• Failed to post the patient registration form within 15 days after the start of Benet/Actonel treatment

4.4. Patients Included in Efficacy Analysis

Not applicable

5. Handling of Data

Handling of data for analysis is described below. Details of processing will be specified in separately prepared analysis data set specifications.

5.1. Handling of Dichotomous Variables

For dichotomous variables, the presence or absence will be determined as described below when there is a column for details to be specified for "Yes."

1) "Yes" when details are specified

2) "No" when no details are specified and "No" is checked

3) "Unknown" when neither 1 nor 2) is applicable

5.2. Handling of Adverse Events

When multiple AEs of the same LLT are reported in the same patient, an AE to be employed will be determined as described below.

1) AEs that differ in the causal relationship to Benet/Actonel will be handled separately.

2) When multiple AEs of the same causal relationship to Benet/Actonel are reported, the most serious AE will be employed.

3) When multiple AEs of the same seriousness are reported, the earliest AE will be employed.

4) When multiple AEs are reported on the same day, an AE with the latest outcome will be employed.

5.3. Derived Variables

Derived variable	Description
Flag for enrollment	It is identified whether a patient is enrolled.
Flag for CRF collection	It is identified whether the CRF for a patient is collected.
Flag for inclusion in/exclusion from safety	It is identified whether a patient is included in safety analysis.
Flag for inclusion in/exclusion from efficacy	It is identified whether a patient is included in efficacy analysis.
Flag for inclusion/exclusion as an AE	It is identified whether an event is an AE.
Relationship	It is identified whether an AE is related to Benet/Actonel.
Seriousness	It is identified whether an AE is serious.
Novelty	It is identified whether an AE is expected (known) or

Derived variable	Description
	unexpected (unknown) based on the precautions for Benet/Actonel.
Presence or absence of an AE	It is identified whether there is an AE (including “unknown”).
Presence or absence of an ADR	It is identified whether there is an ADR (including “unknown”).
Presence or absence of a SAE	It is identified whether there is a SAE (including “unknown”).

6. Analysis Plan

Analysis sets, analysis items, and analysis methods are shown below. Details of variables for analysis and display will be specified in separately prepared statistical analysis specifications.

6.1. Analysis of Patients

6.1.1. Patient Composition Diagram

1) Analysis set: Enrolled patients

2) Chart plan: Figure 1-1

3) Analysis items:
- Number of registration sites
- Number of enrolled patients
- Number of patients with a failure to collect the CRF (including reasons for failing to collect the CRF)
- Number of patients with the CRF collected
- Number of patients excluded from safety analysis (including reasons for exclusion)
- Number of patients included in safety analysis
- Number of patients excluded from efficacy analysis (including reasons for exclusion)
- Number of patients included in efficacy analysis

4) Analysis methods: The number of patients (number of sites) will be calculated for the analysis item, and a composition diagram will be prepared.

6.2. Analysis of Safety

6.2.1. List of Occurrence of Adverse Drug Reactions (Attachment Style 2)

1) Analysis set: Patients included in safety analysis

2) Chart plan: Table 2-1

3) Analysis items: Number of surveillance sites

Number of surveyed patients
Number of patients with an ADR, etc.
Number of ADRs, etc.
Proportion of patients with an ADR, etc.
Proportion of patients with an ADR, etc. (number of ADRs, etc.) by type (PT)

4) Analysis methods: The number and proportion of patients (number of events) will be calculated for the analysis item, and a list of occurrence of ADRs will be prepared.

6.2.2. List of Occurrence of Serious Adverse Events (Attachment Style 2-2, Attachment Style 10)

1) Analysis set: Patients included in safety analysis

2) Chart plan: Table 2-2

3) Analysis items: Number of surveillance sites
Number of surveyed patients
Number of patients with a SAE
Number of SAEs
Proportion of patients with a SAE
Proportion of patients with a SAE (number of SAEs) by type (PT)

4) Analysis methods: The number and proportion of patients (number of events) will be calculated for the analysis item, and a list of occurrence of SAEs will be prepared.

6.3. Analysis of Efficacy

Not applicable