Title: Benet 17.5 mg Tablets special drug use surveillance in patients with osseous Paget's disease (all-case surveillance) – 48-week surveillance –

NCT Number: NCT02106455

Protocol Approve Date: 02-Jun-2017

Certain information within this protocol/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 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease
(All-case Surveillance)
—48-week Surveillance—

Protocol Version 3

Prepared on June 2, 2017

1. Background and purpose of surveillance

Osseous Paget's disease is a very rare disease in Japan and available drugs are limited compared with Europe and the U.S. Benet 17.5 mg Tablets (this drug) was designated as an orphan drug and developed for treatment of osseous Paget's disease. During development, patients with osseous Paget's disease were surveyed for 40 weeks after oral administration of one tablet of this drug once daily for 8 consecutive weeks (total of 48 weeks). High level of serum alkaline phosphatase (serum ALP) that indicates abnormal acceleration of bone metabolism turnover, was lowered and maintained during the observation period. With respect to safety, a serious adverse event was observed in one patient (recurrent cholangiocarcinoma) but causal relationship was denied. However, osseous Paget's disease is rare disease in Japan and only a very limited number of patients (12 patients) were reviewed.

The purpose of this special drug use surveillance (8-week treatment period) is to evaluate the safety and efficacy of this drug administered once daily (one tablet per dose) in patients with osseous Paget's disease for 48 weeks from baseline in daily medical practice.

This surveillance is conducted as an all-case surveillance based on the approval conditions of this drug.

<Approval conditions>

"Given that the number of study patients is very limited in Japan, a drug use surveillance in all patients should be conducted after marketing until data are accumulated from a certain number of patients to understand the background information of the patients treated with this drug and to promptly collect the data of safety and efficacy of this drug, and to take necessary actions for ensuring appropriate use of this drug."

2. Scheduled number of patients and justification

(1) Scheduled number of patients

All patients (all patients administered this drug)

(2) Justification

This is an all-case surveillance in all patients administered this drug, and all patients are included in the survey without determining the number of patients.

3. Targeted patients

(1) Targeted patients

Osseous Paget's disease patients

(2) Dosage and administration in targeted patients

The usual dosage for adults is 17.5 mg of sodium risedronate administered orally with a sufficient volume (approximately 180 mL) of water once daily after waking for 8 consecutive weeks.

For at least 30 minutes after administration, patients should avoid lying in a supine position and taking food, drink (except for water) or other oral drugs.

4. Number of study sites to be surveyed by departments

This is an all-case surveillance and the number of sites is not determined irrespective of department.

5. Survey method

(1) Request to medical institutions and conclusion of contract

i) When requesting the surveillance, sufficient explanation on the summary and objective of this surveillance should be given to an investigator based on the "Request for Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)", "Guide for Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)", "Case Report Form for Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance) (sample)".

ii) An agreement will be concluded with a medical institution cooperating this surveillance, and surveillance will be requested in all patients with osseous Paget's disease who receive this drug during the specified survey period.

(2) Enrollment of targeted patients

The investigator will enroll patients for "all-case registration" according to the following procedures.

i) The investigator will enroll all patients with osseous Paget's disease who receive this drug packaged for osseous Paget's disease after the date of marketing on and after the date of concluding an agreement and within 14 days from the date of starting administration as best as possible.

A patient who was previously enrolled in this survey at the concerned site will be enrolled again when this drug is re-administered.

*Staff of Takeda should pay sufficient attention to the use state of packaging for osseous Paget's disease and promptly request for enrollment when a use is confirmed.

ii) The investigator will record the necessary items in the "patient enrollment information" section on the cover page of CRF for all patients administered this drug during the survey period, cut off a duplicate post card (enrollment postcard) bound in the back page, cover with a masking tape, and post it to the enrollment center within 14 days as best as possible from

the baseline.

iii) The investigator will submit CRF of all patients administered this drug. The investigator will sign and affix a seal on the "Confirmation form for all patients receiving administration" once a year after checking that the all patients are enrolled and their CRF was submitted.

(3) Observation period

Observation period will be 48 weeks from the baseline.

(4) Discontinuation/dropout of this drug

The investigator will record the reason and date of discontinuation/dropout for a patient who discontinued/dropped out during the treatment period of this drug (8 weeks). Details of observation period from the baseline up to Week 48 should be investigated as best as possible also for discontinued/dropped out patients.

6. Scheduled survey period

Scheduled survey period is from August 2008 to July 2017.

Survey period	August 2008 (scheduled) – July 2017 (9 years)
Patient enrollment period	August 2008 (scheduled) – January 2016 (7 years 6 months)

7. Survey items

(1) Items related to patient enrollment

Name of study site and department, address of study site, name of investigator, initials of patient, sex, date of birth, patient ID No., baseline serum ALP and date of test, date of starting administration, administration category (initial, re-administration)

(2) Demographic factors

Height, weight, pregnancy state (only for women), treatment category (inpatient/outpatient), diagnosis name, monoostotic/polyostotic and affected site, date of initial diagnosis of osseous Paget's disease*, complications, medical history, hypertensive disposition*, family history of osseous Paget's disease*, history of fracture at the affected site, previous drug therapy for osseous Paget's disease (if present, type of a drug, dose and dosing period)

Items with *: not to be recorded in case of re-administration

(3) Prior drugs for osseous Paget's disease before administration of this drug

Presence/absence of prior therapy discontinued within 8 weeks of baseline, drug name, administration method, dose, treatment period, therapeutic effect (record a therapeutic drug continued also after the start of administration of this drug only in the concomitant drug section)

(4) Details of treatment

i) Treatment period

Record the administration state during the survey period starting from the baseline (including

the case where administration was started after Week 8).

ii) Treatment compliance

Treatment compliance (4-step evaluation during treatment period), comments on treatment compliance (free comments section: record the comments of a patient on treatment compliance [reason, etc.] if any)

iii) Discontinuation/dropout concerning this drug administration

Reason for discontinuation/dropout, date of discontinuation/dropout

iv) Concomitant drugs and drugs used during the observation period

a) Drugs for osseous Paget's disease

Use of drugs, name of a drug, administration method, dose, dosing period, purpose of administration

b) Other drugs

Use of drugs, name of a drug, administration method, dosing period, purpose of administration

(5) Efficacy outcome items

[Primary endpoint]

i) Serum ALP

The investigator will record the serum ALP measured at baseline, Week 4, Week 8, during observation period, and Week 48 (at completion of observation period), date of test, reference value and unit.

[Secondary endpoint]

ii) Evaluation of pain associated with osseous Paget's disease

The investigator will evaluate presence/absence of pain at the affected site originating from osseous Paget's disease at baseline, Week 4, Week 8, during observation period, and Week 48 (at completion of observation period). When pain is present, record severity (not disturbing, tolerable, unbearable) and site.

iii) Bone metabolism markers <Record the data of tests conducted during the survey>

The investigator will record the measured values of bone metabolism markers (serum BAP, urine NTX, urine DPD, serum NTX, etc.) and date of test when they were measured at baseline, Week 4, Week 8, during observation period, and Week 48 (completion of observation period).

iv) Imaging findings (simple X-ray, bone scintigraphy, etc.) <Record the items conducted during the survey and findings>

The investigator will conduct simple X-ray at baseline and Week 48 (completion of observation period) as best as possible.

Assessment findings (abnormality of bone morphology and trabecular bone structure by simple X-ray, other abnormal findings) should be recorded based on the simple X-ray and bone scintigraphy conducted at baseline with a record of date of examination. When simple

X-ray is conducted at Week 4, or when simple X-ray and bone scintigraphy are conducted at Week 8, during observation period, and Week 48 (completion of observation period), date of examination and assessment findings (improvement, unchanged, aggravation of bone morphology, trabecular bone structure and other abnormal findings by simple X-ray, compared with baseline) should be recorded.

When CT and MRI is conducted at baseline, record the findings.

(6) Adverse events

Record the name of an adverse event that developed after the baseline and before completion of observation period, date of onset, seriousness, action taken, outcome, and causal relationship with this drug to be evaluated. Follow up adverse events until recovery as best as possible.

(7) Laboratory test

Conduct general hematology, blood chemistry, and urinalysis at baseline and during observation period and record the test item assessed as abnormal variation compared with baseline in the adverse events section of CRF. Record the laboratory test data of the item assessed as abnormal variation in "Variation of laboratory test data assessed as abnormal variation" section.

8. Items and method of analysis

(1) Analysis population

Conduct analysis for all patients administered this drug.

Conduct analysis of the patients above according to the baseline demographics and pathology.

(2) Demographic factors

Tabulate patients by sex, age, weight, morbid period, prior therapy, concomitant drugs.

(3) Efficacy endpoint

1) Serum ALP, bone metabolism markers

i) Serum ALP

Calculate summary statistics (mean, standard deviation, minimum, maximum) and 95% confidence interval for the excess serum ALP measured at baseline, Week 4, Week 8, during observation period, and Week 48. Conduct one-sample t-test for percent change in excess serum ALP. Show time-course of change at baseline, Week 4, Week 8, during observation period, and Week 48.

*Excess serum ALP: actual value of serum ALP — (maximum of reference value + minimum of reference value)/2

ii) Bone metabolism marker

Calculate the mean and standard deviation for the values measured before and after administration. Conduct one-sample t-test for percent change.

2) Tabulation of pain associated with osseous Paget's disease

Show distribution of pain severity at each time point of baseline, Week 4, Week 8, during observation period, and Week 48.

3) Treatment compliance

Conduct frequency tabulation for treatment compliance during treatment period.

(4) Safety endpoints

Conduct frequency tabulation for the type and seriousness of treatment-related adverse events.

9. Organization for conducting survey

Responsible person for surveillance

PPD

10. In case of contracting a part of survey duties, name and address of the party that contracted the concerned duty and scope of the contracted duty

PPD

11. Other necessary items

(1) Revision of survey plan

In case a partial change in Dosage and Administration or Indications is approved during the period of this surveillance, necessity for revision of the protocol should be reviewed when necessary.

(2) Actions taken in case of occurrence of a problem or question

In case any problem is found with safety or efficacy, implementation of a special drug use surveillance should be reviewed to detect or confirm the factor or to review a presumed item.

12. Reference

1) Jun Hashimoto, et al.: Prevalence and clinical characteristics of osseous Paget's disease in Japan Osteoporosis Japan 15 241-245, 2007

Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease
(All-case Surveillance)
—48-week Surveillance—

Protocol Version 2

Prepared on April 1, 2015

1. Background and purpose of surveillance

Osseous Paget's disease is a very rare disease in Japan and available drugs are limited compared with Europe and the U.S. Benet 17.5 mg Tablets (this drug) was designated as an orphan drug and developed for treatment of osseous Paget's disease. During development, patients with osseous Paget's disease were surveyed for 40 weeks after oral administration of one tablet of this drug once daily for 8 consecutive weeks (total of 48 weeks). High level of serum alkaline phosphatase (serum ALP) that indicates abnormal acceleration of bone metabolism turnover, was lowered and maintained during the observation period. With respect to safety, a serious adverse event was observed in one patient (recurrent cholangiocarcinoma) but causal relationship was denied. However, osseous Paget's disease is rare disease in Japan and only a very limited number of patients (12 patients) were reviewed.

The purpose of this special drug use surveillance (8-week treatment period) is to evaluate the safety and efficacy of this drug administered once daily (one tablet per dose) in patients with osseous Paget's disease for 48 weeks from baseline in daily medical practice.

This surveillance is conducted as an all-case surveillance based on the approval conditions of this drug.

<Approval conditions>

"Given that the number of study patients is very limited in Japan, a drug use surveillance in all patients should be conducted after marketing until data are accumulated from a certain number of patients to understand the background information of the patients treated with this drug and to promptly collect the data of safety and efficacy of this drug, and to take necessary actions for ensuring appropriate use of this drug."

2. Scheduled number of patients and justification

(1) Scheduled number of patients

All patients (all patients administered this drug)

(2) Justification

This is an all-case surveillance in all patients administered this drug, and all patients are included in the survey without determining the number of patients.

3. Targeted patients

(1) Targeted patients

Osseous Paget's disease patients

(2) Dosage and administration in targeted patients

The usual dosage for adults is 17.5 mg of sodium risedronate administered orally with a sufficient volume (approximately 180 mL) of water once daily after waking for 8 consecutive weeks.

For at least 30 minutes after administration, patients should avoid lying in a supine position and taking food, drink (except for water) or other oral drugs.

4. Number of study sites to be surveyed by departments

This is an all-case surveillance and the number of sites is not determined irrespective of department.

5. Survey method

(1) Request to medical institutions and conclusion of contract

i) When requesting the surveillance, sufficient explanation on the summary and objective of this surveillance should be given to an investigator based on the "Request for Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)", "Guide for Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)", "Case Report Form for Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance) (sample)".

ii) An agreement will be concluded with a medical institution cooperating this surveillance, and surveillance will be requested in all patients with osseous Paget's disease who receive this drug during the specified survey period.

(2) Enrollment of targeted patients

The investigator will enroll patients for "all-case registration" according to the following procedures.

i) The investigator will enroll all patients with osseous Paget's disease who receive this drug packaged for osseous Paget's disease after the date of marketing on and after the date of concluding an agreement and within 14 days from the date of starting administration as best as possible.

A patient who was previously enrolled in this survey at the concerned site will be enrolled again when this drug is re-administered.

*Staff of Takeda should pay sufficient attention to the use state of packaging for osseous Paget's disease and promptly request for enrollment when a use is confirmed.

ii) The investigator will record the necessary items in the "patient enrollment information" section on the cover page of CRF for all patients administered this drug during the survey period, cut off a duplicate post card (enrollment postcard) bound in the back page, cover with a masking tape, and post it to the enrollment center within 14 days as best as possible from

the baseline.

iii) The investigator will submit CRF of all patients administered this drug. The investigator will sign and affix a seal on the "Confirmation form for all patients receiving administration" once a year after checking that the all patients are enrolled and their CRF was submitted.

(3) Observation period

Observation period will be 48 weeks from the baseline.

(4) Discontinuation/dropout of this drug

The investigator will record the reason and date of discontinuation/dropout for a patient who discontinued/dropped out during the treatment period of this drug (8 weeks). Details of observation period from the baseline up to Week 48 should be investigated as best as possible also for discontinued/dropped out patients.

6. Scheduled survey period

Scheduled survey period is from August 2008 to July 2017.

Survey period	August 2008 (scheduled) – July 2017 (9 years)
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7. Survey items

(1) Items related to patient enrollment

Name of study site and department, address of study site, name of investigator, initials of patient, sex, date of birth, patient ID No., baseline serum ALP and date of test, date of starting administration, administration category (initial, re-administration)

(2) Demographic factors

Height, weight, pregnancy state (only for women), treatment category (inpatient/outpatient), diagnosis name, monoostotic/polyostotic and affected site, date of initial diagnosis of osseous Paget's disease*, complications, medical history, hypertensive disposition*, family history of osseous Paget's disease*, history of fracture at the affected site, previous drug therapy for osseous Paget's disease (if present, type of a drug, dose and dosing period)

Items with *: not to be recorded in case of re-administration

(3) Prior drugs for osseous Paget's disease before administration of this drug

Presence/absence of prior therapy discontinued within 8 weeks of baseline, drug name, administration method, dose, treatment period, therapeutic effect (record a therapeutic drug continued also after the start of administration of this drug only in the concomitant drug section)

(4) Details of treatment

i) Treatment period

Record the administration state during the survey period starting from the baseline (including

the case where administration was started after Week 8).

ii) Treatment compliance

Treatment compliance (4-step evaluation during treatment period), comments on treatment compliance (free comments section: record the comments of a patient on treatment compliance [reason, etc.] if any)

iii) Discontinuation/dropout concerning this drug administration

Reason for discontinuation/dropout, date of discontinuation/dropout

iv) Concomitant drugs and drugs used during the observation period

a) Drugs for osseous Paget's disease

Use of drugs, name of a drug, administration method, dose, dosing period, purpose of administration

b) Other drugs

Use of drugs, name of a drug, administration method, dosing period, purpose of administration

(5) Efficacy outcome items

[Primary endpoint]

i) Serum ALP

The investigator will record the serum ALP measured at baseline, Week 4, Week 8, during observation period, and Week 48 (at completion of observation period), date of test, reference value and unit.

[Secondary endpoint]

ii) Evaluation of pain associated with osseous Paget's disease

The investigator will evaluate presence/absence of pain at the affected site originating from osseous Paget's disease at baseline, Week 4, Week 8, during observation period, and Week 48 (at completion of observation period). When pain is present, record severity (not disturbing, tolerable, unbearable) and site.

iii) Bone metabolism markers <Record the data of tests conducted during the survey>

The investigator will record the measured values of bone metabolism markers (serum BAP, urine NTX, urine DPD, serum NTX, etc.) and date of test when they were measured at baseline, Week 4, Week 8, during observation period, and Week 48 (completion of observation period).

iv) Imaging findings (simple X-ray, bone scintigraphy, etc.) <Record the items conducted during the survey and findings>

The investigator will conduct simple X-ray at baseline and Week 48 (completion of observation period) as best as possible.

Assessment findings (abnormality of bone morphology and trabecular bone structure by simple X-ray, other abnormal findings) should be recorded based on the simple X-ray and bone scintigraphy conducted at baseline with a record of date of examination. When simple

X-ray is conducted at Week 4, or when simple X-ray and bone scintigraphy are conducted at Week 8, during observation period, and Week 48 (completion of observation period), date of examination and assessment findings (improvement, unchanged, aggravation of bone morphology, trabecular bone structure and other abnormal findings by simple X-ray, compared with baseline) should be recorded.

When CT and MRI is conducted at baseline, record the findings.

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Conduct general hematology, blood chemistry, and urinalysis at baseline and during observation period and record the test item assessed as abnormal variation compared with baseline in the adverse events section of CRF. Record the laboratory test data of the item assessed as abnormal variation in "Variation of laboratory test data assessed as abnormal variation" section.

8. Items and method of analysis

(1) Analysis population

Conduct analysis for all patients administered this drug.

Conduct analysis of the patients above according to the baseline demographics and pathology.

(2) Demographic factors

Tabulate patients by sex, age, weight, morbid period, prior therapy, concomitant drugs.

(3) Efficacy endpoint

1) Serum ALP, bone metabolism markers

i) Serum ALP

Calculate summary statistics (mean, standard deviation, minimum, maximum) and 95% confidence interval for the excess serum ALP measured at baseline, Week 4, Week 8, during observation period, and Week 48. Conduct one-sample t-test for percent change in excess serum ALP. Show time-course of change at baseline, Week 4, Week 8, during observation period, and Week 48.

*Excess serum ALP: actual value of serum ALP — (maximum of reference value + minimum of reference value)/2

ii) Bone metabolism marker

Calculate the mean and standard deviation for the values measured before and after administration. Conduct one-sample t-test for percent change.

2) Tabulation of pain associated with osseous Paget's disease

Show distribution of pain severity at each time point of baseline, Week 4, Week 8, during observation period, and Week 48.

3) Treatment compliance

Conduct frequency tabulation for treatment compliance during treatment period.

(4) Safety endpoints

Conduct frequency tabulation for the type and seriousness of treatment-related adverse events.

9. Organization for conducting survey

Responsible person for surveillance

PPD

10. In case of contracting a part of survey duties, name and address of the party that contracted the concerned duty and scope of the contracted duty

Contracted by: PPD

Contracted by: PPD

11. Other necessary items

(1) Revision of survey plan

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(All-case Surveillance)
—48-week Surveillance—

Protocol

Prepared on June 25, 2008

1. Background and purpose of surveillance

Osseous Paget's disease is a very rare disease in Japan and available drugs are limited compared with Europe and the U.S. Benet 17.5 mg Tablets (this drug) was designated as an orphan drug and developed for treatment of osseous Paget's disease. During development, patients with osseous Paget's disease were surveyed for 40 weeks after oral administration of one tablet of this drug once daily for 8 consecutive weeks (total of 48 weeks). High level of serum alkaline phosphatase (serum ALP) that indicates abnormal acceleration of bone metabolism turnover, was lowered and maintained during the observation period. With respect to safety, a serious adverse event was observed in one patient (recurrent cholangiocarcinoma) but causal relationship was denied. However, osseous Paget's disease is rare disease in Japan and only a very limited number of patients (12 patients) were reviewed.

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This surveillance is conducted as an all-case surveillance based on the approval conditions of this drug.

<Approval conditions>

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i) The investigator will enroll all patients with osseous Paget's disease who receive this drug packaged for osseous Paget's disease after the date of marketing on and after the date of concluding an agreement and within 14 days from the date of starting administration as best as possible.

A patient who was previously enrolled in this survey at the concerned site will be enrolled again when this drug is re-administered.

*The medical representative (MR) should pay sufficient attention to the use state of packaging for osseous Paget's disease and promptly request for enrollment when a use is confirmed.

ii) The investigator will record the necessary items in the "patient enrollment information" section on the cover page of CRF for all patients administered this drug during the survey period, cut off a duplicate post card (enrollment postcard) bound in the back page, cover with

a masking tape, and post it to the enrollment center within 14 days as best as possible from the baseline.

iii) The investigator will submit CRF of all patients administered this drug. The investigator will sign and affix a seal on the "Confirmation form for all patients receiving administration" once a year after checking that the all patients are enrolled and their CRF was submitted.

(3) Observation period

Observation period will be 48 weeks from the baseline.

(4) Discontinuation/dropout of this drug

The investigator will record the reason and date of discontinuation/dropout for a patient who discontinued/dropped out during the treatment period of this drug (8 weeks). Details of observation period from the baseline up to Week 48 should be investigated as best as possible also for discontinued/dropped out patients.

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(2) Demographic factors

Height, weight, pregnancy state (only for women), treatment category (inpatient/outpatient), diagnosis name, monoostotic/polyostotic and affected site, date of initial diagnosis of osseous Paget's disease*, complications, medical history, hypertensive disposition*, family history of osseous Paget's disease*, history of fracture at the affected site, previous drug therapy for osseous Paget's disease (if present, type of a drug, dose and dosing period)

Items with *: not to be recorded in case of re-administration

(3) Prior drugs for osseous Paget's disease before administration of this drug

Presence/absence of prior therapy discontinued within 8 weeks of baseline, drug name, administration method, dose, treatment period, therapeutic effect (record a therapeutic drug continued also after the start of administration of this drug only in the concomitant drug section)

(4) Details of treatment

i) Treatment period

Record the administration state during the survey period starting from the baseline (including the case where administration was started after Week 8).

ii) Treatment compliance

Treatment compliance (4-step evaluation during treatment period), comments on treatment compliance (free comments section: record the comments of a patient on treatment compliance [reason, etc.] if any)

iii) Discontinuation/dropout concerning this drug administration

Reason for discontinuation/dropout, date of discontinuation/dropout

iv) Concomitant drugs and drugs used during the observation period

a) Drugs for osseous Paget's disease

Use of drugs, name of a drug, administration method, dose, dosing period, purpose of administration

b) Other drugs

Use of drugs, name of a drug, administration method, dosing period, purpose of administration

(5) Efficacy outcome items

[Primary endpoint]

i) Serum ALP

The investigator will record the serum ALP measured at baseline, Week 4, Week 8, during observation period, and Week 48 (at completion of observation period), date of test, reference value and unit.

[Secondary endpoint]

ii) Evaluation of pain associated with osseous Paget's disease

The investigator will evaluate presence/absence of pain at the affected site originating from osseous Paget's disease at baseline, Week 4, Week 8, during observation period, and Week 48 (at completion of observation period). When pain is present, record severity (not disturbing, tolerable, unbearable) and site.

iii) Bone metabolism markers <Record the data of tests conducted during the survey>

The investigator will record the measured values of bone metabolism markers (serum BAP, urine NTX, urine DPD, serum NTX, etc.) and date of test when they were measured at baseline, Week 4, Week 8, during observation period, and Week 48 (completion of observation period).

iv) Imaging findings (simple X-ray, bone scintigraphy, etc.) <Record the items conducted during the survey and findings>

The investigator will conduct simple X-ray at baseline and Week 48 (completion of observation period) as best as possible.

Assessment findings (abnormality of bone morphology and trabecular bone structure by simple X-ray, other abnormal findings) should be recorded based on the simple X-ray and

bone scintigraphy conducted at baseline with a record of date of examination. When simple X-ray is conducted at Week 4, or when simple X-ray and bone scintigraphy are conducted at Week 8, during observation period, and Week 48 (completion of observation period), date of examination and assessment findings (improvement, unchanged, aggravation of bone morphology, trabecular bone structure and other abnormal findings by simple X-ray, compared with baseline) should be recorded.

When CT and MRI is conducted at baseline, record the findings.

(6) Adverse events

Record the name of an adverse event that developed after the baseline and before completion of observation period, date of onset, seriousness, action taken, outcome, and causal relationship with this drug to be evaluated. Follow up adverse events until recovery as best as possible.

(7) Laboratory test

Conduct general hematology, blood chemistry, and urinalysis at baseline and during observation period and record the test item assessed as abnormal variation compared with baseline in the adverse events section of CRF. Record the laboratory test data of the item assessed as abnormal variation in "Variation of laboratory test data assessed as abnormal variation" section.

8. Items and method of analysis

(1) Analysis population

Conduct analysis for all patients administered this drug.

Conduct analysis of the patients above according to the baseline demographics and pathology.

(2) Demographic factors

Tabulate patients by sex, age, weight, morbid period, prior therapy, concomitant drugs.

(3) Efficacy endpoint

1) Serum ALP, bone metabolism markers

i) Serum ALP

Calculate summary statistics (mean, standard deviation, minimum, maximum) and 95% confidence interval for the excess serum ALP measured at baseline, Week 4, Week 8, during observation period, and Week 48. Conduct one-sample t-test for percent change in excess serum ALP. Show time-course of change at baseline, Week 4, Week 8, during observation period, and Week 48.

*Excess serum ALP: actual value of serum ALP — (maximum of reference value + minimum of reference value)/2

ii) Bone metabolism marker

Calculate the mean and standard deviation for the values measured before and after administration. Conduct one-sample t-test for percent change.

2) Tabulation of pain associated with osseous Paget's disease

Show distribution of pain severity at each time point of baseline, Week 4, Week 8, during

observation period, and Week 48.

3) Treatment compliance

Conduct frequency tabulation for treatment compliance during treatment period.

(4) Safety endpoints

Conduct frequency tabulation for the type and seriousness of treatment-related adverse events.

9. Organization for conducting survey

Responsible person for surveillance

PPD

, Takeda Pharmaceutical Company Limited

10. In case of contracting a part of survey duties, name and address of the party that contracted the concerned duty and scope of the contracted duty

Not yet determined

11. Other necessary items

(1) Revision of survey plan

In case a partial change in Dosage and Administration or Indications is approved during the period of this surveillance, necessity for revision of the protocol should be reviewed when necessary.

(2) Actions taken in case of occurrence of a problem or question

In case any problem is found with safety or efficacy, implementation of a special drug use surveillance should be reviewed to detect or confirm the factor or to review a presumed item.

12. Reference

1) Jun Hashimoto, et al.: Prevalence and clinical characteristics of osseous Paget's disease in Japan Osteoporosis Japan 15 241-245, 2007