Title: Special drug use surveillance for “premenopausal breast cancer”

NCT Number: NCT03209518

Statistical analysis plan Approve Date: 04-APR-2019

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:

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- 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.
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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.

Statistical Analysis Plan

(Analyses for final tabulation)

Product name	: Leuplin PRO for Injection Kit 22.5 mg
Surveillance name	: Special drug use surveillance for “premenopausal breast cancer”
Protocol number	: Leuprorelin-5003
Sponsor	: Takeda Pharmaceutical Company Limited

PPD

PPD Takeda Pharmaceutical Company Limited

PPD

1st version prepared on 4 April 2019

Table of Contents

1 Definitions of Terms, etc.

1.1 List of Terms and Abbreviations

- Leuplin PRO: Leuplin PRO for Injection Kit 22.5 mg is abbreviated as Leuplin PRO.
- Adverse drug reaction (ADR), etc.: ADR, etc. is an abbreviation of ADR/infection. ADRs, etc. refer to all adverse events (AEs) other than those assessed by the investigator to be not related to Leuplin PRO. In this document, "adverse drug reactions/infections" is used in titles, and "ADRs, etc." is used in the text and tables.
- Serious adverse event (SAE): A SAE is an adverse event assessed by the investigator to be serious. Events included in the MedDRA code list in Takeda Medically Significant AE List will be handled as serious even if assessed by the investigator to be not serious.
- Causal relationship: An event assessed as not related to Leuplin PRO will be handled as "not related." Events not unrelated to Leuplin PRO in the text and tables refer to all events other than those assessed as not related to Leuplin PRO.
- Summary statistics: Collective term for number of patients, mean, standard deviation, maximum, minimum, and quartiles
- Patient with no CRF collected: Enrolled patient for whom the CRF has not been collected
- Patient with the CRF collected: Enrolled patient for whom the CRF has been collected
- Finalized patient: Patient for whom the CRF has been collected and finalized at least once by data lock point
- Non-finalized patient: Patient for whom the CRF has been collected, but has not been finalized by data lock point
- Age: If the month and day of starting Leuplin PRO treatment is smaller than the month and day of birth, age will be calculated as year of starting Leuplin PRO treatment - year of birth - 1. If the month and day of starting Leuplin PRO treatment is equal to or greater than the month and day of birth, age will be calculated as year of starting Leuplin PRO treatment - year of birth. If the day of birth is unknown, 1 will be used for calculation.
- Time from diagnosis of premenopausal breast cancer to patient registration (months):
  - Actual number (units: month) = ("date of patient registration" - "date of diagnosis" + 1)/30.44
- BMI (kg/m^2): Calculated as body weight (kg)/height $(m)^2$ (displayed to one decimal place by rounding)

- Induration: AE with “induration” selected for “Specific symptom (multiple answers allowed)” in the column of [Adverse event: Injection site reaction] in the CRF

1.2 Analysis Sets

The analysis set in this surveillance is safety population. This analysis set is defined as described below.

- Safety population

  In this document, the safety population is defined as all Leuplin PRO-treated patients evaluable for safety with no major protocol violation. Patients for whom the CRF has been collected will be excluded from the safety population if any of the following criteria is met:

  - Not treated with Leuplin PRO
  - Treatment before the contract period
  - Registration 15 days or more after Leuplin PRO treatment
  - It is unknown whether the patient experienced an AE
  - Three-month depot administered

1.3 Number of Digits to be Displayed

- Percentage (%)
  Proportion of patients with an AE or an ADR, etc. or number of AE or ADR, etc.:
  Displayed to two decimal places by rounding
  Other:
  Displayed to one decimal place by rounding

- Summary statistics
  Mean, median, first quartile, and third quartile:
  Displayed to one lower digit than raw data by rounding
  Standard deviation:
  Displayed to two lower digits than raw data by rounding
  Minimum and maximum:
  Displayed to the same number of digits as the relevant data

1.4 Important Identified Risks, Important Potential Risks, and Important Missing Information

- Important identified risks
  - Injection site reaction: Injection site reaction is defined as the following AEs:
    - HLT code 10022097 [Infusion site reactions]
    - HLT code 10057196 [Administration site reactions NEC]
    - PT code: Refer to [Attached table 1　PTs corresponding to risks].
  - Decreased bone mass density: Decreased bone mass density is defined as the following AEs:
    - SMQ code 20000178 [Osteoporosis/osteopenia (SMQ) narrow]
    - PT code: Refer to [Attached table 1　PTs corresponding to risks].
  - Diabetes mellitus: Diabetes mellitus is defined as the following AEs:
    - SMQ code 20000041 [Hyperglycemia/new onset diabetes mellitus (SMQ) broad]
  - Interstitial lung disease : Interstitial lung disease is defined as the following AEs:
    - SMQ code 20000042 [Interstitial lung disease (SMQ) narrow]
  - Depression: Depression is defined as the following AEs:
    - SMQ code 20000167 [Depression (excl suicide and self injury) (SMQ) narrow]
    - SMQ code 20000037 [Suicide/self-injury (SMQ) narrow]
  - Thromboembolism: Thromboembolism is defined as the following AEs:
    - SMQ code 20000004 [Cardiac failure (SMQ) narrow]
    - SMQ code 20000166 [Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ) narrow]
    - SMQ code 20000064 [Haemorrhagic cerebrovascular conditions (SMQ) narrow]
    - SMQ code 20000063 [Ischemic central nervous system vascular conditions (SMQ) narrow]
    - SMQ code 20000165 [Cerebrovascular disorders, not specified as haemorrhagic or ischaemic (SMQ) narrow]
    - SMQ code 20000082 [Embolic and thrombotic events, arterial (SMQ) narrow]
    - SMQ code 20000084 [Embolic and thrombotic events, venous (SMQ) narrow]
    - SMQ code 20000083 [Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ) narrow]
    - SMQ code 20000047 [Myocardial infarction (SMQ) broad]
    - SMQ code 20000168 [Other ischaemic heart disease (SMQ) broad]

- Pituitary apoplexy: Pituitary apoplexy is defined as the following AEs:
  - PT code: Refer to [Attached table 1　PTs corresponding to risks].
- Hepatic dysfunction/jaundice: Hepatic dysfunction/jaundice is defined as the following AEs:
  - SMQ code 20000009 [Cholestasis and jaundice of hepatic origin (SMQ) narrow]
  - SMQ code 20000013 [Hepatic failure, fibrosis, and cirrhosis and other liver damage-related conditions (SMQ) narrow]
  - SMQ code 20000010 [Hepatitis, non-infectious (SMQ) narrow]
  - SMQ code 20000008 [Liver related investigations, signs and symptoms (SMQ) narrow]

- Important potential risks
  - Anaphylaxis: Anaphylaxis is defined as the following AEs:
    - SMQ code 20000021 [Anaphylactic reaction (SMQ) narrow]
    - SMQ code 20000071 [Anaphylactic/anaphylactoid shock conditions (SMQ) narrow]
  - Hypertension: Hypertension is defined as the following AEs:
    - SMQ code 20000147 [Hypertension (SMQ) narrow]
- Important missing information: Not applicable

1.5 Other Handling

- Time of onset of AE (or ADR, etc.): Time of onset of AE (or ADR, etc.) will be calculated as date of onset of AE (or ADR, etc.) - start date of Leuplin PRO treatment + 1. If the day of AE (or ADR, etc.) is unknown, 1 will be used for calculation. If an AE (or ADR, etc.) occurs in the same year and month as Leuplin PRO treatment is started, the start date of Leuplin PRO treatment will be used for calculation.
- Premenopausal breast cancer drugs other than LH-RH agonists and premenopausal breast cancer drugs other than Leuplin PRO will be classified using drug codes according to Attached table 2.

2 Number of Surveillance Medical Institutions, Number of Enrolled Patients, and Patient Composition

2.1 Disposition of Patients

Patients included in analysis:	All enrolled patients (enrolled patients)	
Analysis items:	Enrolled patients	
	Number of surveillance medical institutions	
	Patients with no CRF collected	
	Reason for failure to collect	[Transfer of the investigator, medical reason for the investigator, other]
	Patients with the CRF collected	
	Non-finalized patients	
	Finalized patients	
	Patients excluded from safety evaluation*	
	Reason for exclusion (multiple tabulation)	[Not treated with Leuplin PRO, treatment before the contract period, registration 15 days or more after Leuplin PRO treatment, it is unknown whether the patient experienced an AE, 3-month depot administered]
	Patients included in safety evaluation*	
Analysis methods:	For the aforementioned analysis items, analysis will be performed as described below, and a patient composition diagram will be prepared.	
	For enrolled patients, the number of surveillance medical institutions will also be calculated. One medical institution with different departments will be counted as one medical institution.	
	* Patients included in safety evaluation refer to the safety population, and patients excluded from safety evaluation refer to patients excluded from the safety population (finalized patients excluded from the safety population here).	
	(1) Frequency tabulation	

3 Patient Baseline Characteristics

3.1 Patient Baseline Characteristics

Patients included in analysis:	Safety population	
Analysis items:	Age (years)	[<35 years, >=35 years, unknown]
	Time from diagnosis of premenopausal breast cancer to patient registration (months)	
	ECOG Performance Status	[0, 1, 2, 3, 4]
	Disease status	[Patient on preoperative adjuvant therapy, patient on postoperative adjuvant therapy, patient with advanced breast cancer, patient with recurrent breast cancer]
	Presence or absence of hormone receptor expression	[No, yes, unknown]
	Diagnostic category	[Outpatient, inpatient]
	Presence or absence of predisposition to hypersensitivity	[No, yes, unknown]
	Presence or absence of concurrent illness	[No, yes]
	Detail of concurrent illness (multiple tabulation)	[Lifestyle diseases, hepatic disease, renal disease, allergic disease, malignant tumor, other]
	Presence or absence of history of thromboembolism	[No, yes, unknown]
	Detailed history of thromboembolism (multiple tabulation)	[Myocardial infarction, cerebral infarction, venous thrombosis, pulmonary embolism, other]
	Height (cm)	
	Body weight (kg)	
	BMI (kg/m^2)	[<18.5, 18.5-<25.0, 25.0-<30.0, >=30.0, unknown]
	Presence or absence of treatment with LH-RH agonist immediately before the start of Leuplin PRO treatment	[No, yes]

	Disposition of treatment with LH-RH agonist immediately before the start of Leuplin PRO treatment	[Leuprorelin acetate 3.75 mg, leuprorelin acetate 11.25 mg, goserelin 3.6 mg, goserelin 10.8 mg]
	Presence or absence of treatment with premenopausal breast cancer drug other than LH-RH agonists immediately before the start of Leuplin PRO treatment	[No, yes]
	Disposition of treatment with premenopausal breast cancer drug other than LH-RH agonists immediately before the start of Leuplin PRO treatment (multiple tabulation)	[Adrenal hormone preparations, estrogen and gestagen preparations, oral anti-renal anemia agents/anti-mammary tumor agents, bone resorption inhibitors, alkylating agents, antimetabolic agents, antitumor antibiotics and preparations, antineoplastic preparations extracted from plants, antineoplastic agents]
Analysis methods:	For the aforementioned analysis items, frequency tabulation will be performed for discrete data, and summary statistics will be calculated for continuous data.	

4 Treatment Given

4.1 Treatment Status of Premenopausal Breast Cancer Drug Other Than Leuplin PRO

Patients included in analysis:	Safety population	
Analysis items:	Presence or absence of treatment with premenopausal breast cancer drug other than Leuplin PRO	[No, yes]
	Disposition of treatment with premenopausal breast cancer drug other than Leuplin PRO (multiple tabulation)	[Adrenal hormone preparations, estrogen and gestagen preparations, oral anti-renal anemia agents/anti-mammary tumor agents, bone resorption inhibitors, alkylating agents, antimetabolic agents, antitumor antibiotics and preparations, antineoplastic preparations extracted from plants, antineoplastic agents]
Analysis methods:	For the aforementioned analysis items, frequency tabulation will be performed.	

4.2 Treatment Status of Leuplin PRO

Patients included in analysis:	Safety population	
Analysis items:	Full-treatment status of Leuplin PRO	[Yes, no]
	Injection site	[Extensor surface of the upper arm, deltoid region of the upper arm, abdomen, buttocks, other]
Analysis methods:	For the aforementioned analysis items, frequency tabulation will be performed.	

4.3 Presence or Absence of and Reason for Discontinuation of Observation

Patients included in analysis:	Safety population	
Analysis items:	Presence or absence of discontinuation of observation	[No, yes]
	Reason for discontinuation of observation	[Patient's failure to visit the hospital such as transfer to another hospital, death, other]

Analysis methods:	For the aforementioned analysis items, frequency tabulation will be performed.

5 Matters on Safety

5.1 Occurrence of Adverse Events and Adverse Drug Reactions/Infections

5.1.1 Occurrence of Adverse Events

Patients included in analysis: Safety population

Analysis item: AEs

Analysis methods: For the aforementioned analysis item, analysis will be performed as described below.

(1) Number of patients with an AE

(2) Number of AE

(3) Proportion of patients with an AE

(4) Type of AE

For each analysis, events or patients will be counted as described below.

[Number of patients with an AE]

- Number of patients who experienced an AE

[Number of AE]

- Number of reported AE. Multiple episodes of the same AE in the same patient will be tabulated as the total number of episodes.

[Proportion of patients with an AE]

- The proportion of patients with an AE will be calculated as number of patients with an AE/number of patients included in safety evaluation × 100.

[Type of AE]

- AEs will be coded using the MedDRA/J. AEs will be classified by SOC and then tabulated by PT. For the SOC of investigations, AEs will be sorted by HLGT (lined up in ascending order of HLGT code, but not output) and then tabulated by PT.
- For SOC, the number and proportion of patients with an AE will be listed in internationally agreed SOC order. Multiple episodes of the same SOC in the same patient will be counted as 1 patient for the relevant SOC.
- For PT, the number and proportion of patients with an AE will be listed in ascending order of PT code. Multiple episodes of the same PT in the same patient will be counted as 1 patient for the relevant PT.

5.1.2 Occurrence of Adverse Drug Reactions/Infections

Patients included in analysis: Safety population

Analysis item: ADRs, etc.

Analysis methods: For the aforementioned analysis item, analysis will be performed as described below.

(1) Number of patients with an ADR, etc.

(2) Number of ADR, etc.

(3) Proportion of patients with an ADR, etc.

(4) Type of ADR, etc.

For each analysis, events or patients will be counted as described below.

[Number of patients with an ADR, etc.]

- Number of patients who experienced an ADR, etc.

[Number of ADR, etc.]

- Number of reported ADR, etc. Multiple episodes of the same ADR, etc. in the same patient will be tabulated as the total number of episodes.

[Proportion of patients with an ADR, etc.]

- The proportion of patients with an ADR, etc. will be calculated as number of patients with an ADR, etc./number of patients included in safety evaluation × 100.

[Type of ADR, etc.]

- ADRs, etc. will be coded using the MedDRA/J. ADRs, etc. will be classified by SOC and then tabulated by PT. For the SOC of investigations, ADRs, etc. will be sorted by HLGT (lined up in ascending order of HLGT code, but not output) and then tabulated by PT.
- For SOC, the number and proportion of patients with an ADR, etc. will be listed in internationally agreed SOC order. Multiple episodes of the same SOC in the same patient will be counted as 1 patient for the relevant SOC.
- For PT, the number and proportion of patients with an ADR, etc. will be listed in ascending order of PT code. Multiple episodes of the same PT in the same patient will be counted as 1 patient for the relevant PT.

5.1.3 Occurrence of Adverse Events Corresponding to Important Identified Risks (tabulation by risk)

Patients included in analysis:	Safety population
Analysis item:	AEs corresponding to important identified risks (described in Section 1.4 in Section 1, “Definitions of Terms, etc.”)
Stratification factors:	Seriousness [Serious, not serious]
Analysis methods:	For the aforementioned analysis item, analysis will be performed for each stratum by risk as described below. The risks to be analyzed are as described in Section 1.4 in Section 1, “Definitions of Terms, etc.”

[Type of AE]

- AEs will be coded using the MedDRA/J. AEs will be classified by SOC and then tabulated by PT. For the SOC of investigations, AEs will be sorted by HLGT (lined up in ascending order of HLGT code, but not output) and then tabulated by PT.
- For SOC, the number and proportion of patients with an AE will be listed in internationally agreed SOC order. Multiple episodes of the same SOC in the same patient will be counted as 1 patient for the relevant SOC. However, when these episodes differ in seriousness, they will be counted once each for “serious” and “not serious.”
- For PT, the number and proportion of patients with an AE will be listed in ascending order of PT code. Multiple episodes of the same PT in the same patient will be counted as 1 patient for the relevant PT. However, when these episodes differ in seriousness, they will be counted once each for “serious” and “not serious.”

5.1.4 Occurrence of Adverse Events Corresponding to Important Potential Risks (tabulation by risk)

Patients included in analysis:	Safety population	
Analysis item:	AEs corresponding to important potential risks (described in Section 1.4 in Section 1, "Definitions of Terms, etc.")	
Stratification factors:	Seriousness	[Serious, not serious]

Analysis methods: For the aforementioned analysis item, analysis will be performed for each stratum by risk as described below. The risks to be analyzed are as described in Section 1.4 in Section 1, "Definitions of Terms, etc."

[Type of AE]

- AEs will be coded using the MedDRA/J. AEs will be classified by SOC and then tabulated by PT. For the SOC of investigations, AEs will be sorted by HLGT (lined up in ascending order of HLGT code, but not output) and then tabulated by PT.
- For SOC, the number and proportion of patients with an AE will be listed in internationally agreed SOC order. Multiple episodes of the same SOC in the same patient will be counted as 1 patient for the relevant SOC. However, when these episodes differ in seriousness, they will be counted once each for "serious" and "not serious."
- For PT, the number and proportion of patients with an AE will be listed in ascending order of PT code. Multiple episodes of the same PT in the same patient will be counted as 1 patient for the relevant PT. However, when these episodes differ in seriousness, they will be counted once each for "serious" and "not serious."

5.1.5 Occurrence of Adverse Drug Reactions/Infections Corresponding to Important Identified Risks (tabulation by risk)

Patients included in analysis:	Safety population	
Analysis item:	ADRs, etc. corresponding to important identified risks (described in Section 1.4 in Section 1, "Definitions of Terms, etc.")	
Stratification factors:	Seriousness	[Serious, not serious]

Analysis methods: For the aforementioned analysis item, analysis will be performed for each stratum by risk as described below. The risks to be analyzed are as described in Section 1.4 in Section 1, "Definitions of Terms, etc."

[Type of ADR, etc.]

- ADRs, etc. will be coded using the MedDRA/J. ADRs, etc. will be classified by SOC and then tabulated by PT. For the SOC of investigations, ADRs, etc. will be sorted by HLGT (lined up in ascending order of HLGT code, but not output) and then tabulated by PT.
- For SOC, the number and proportion of patients with an ADR, etc. will be listed in internationally agreed SOC order. Multiple episodes of the same SOC in the same patient will be counted as 1 patient for the relevant SOC. However, when these episodes differ in seriousness, they will be counted once each for "serious" and "not serious."
- For PT, the number and proportion of patients with an ADR, etc. will be listed in ascending order of PT code. Multiple episodes of the same PT in the same patient will be counted as 1 patient for the relevant PT. However, when these episodes differ in seriousness, they will be counted once each for "serious" and "not serious."

5.1.6 Occurrence of Adverse Drug Reactions/Infections Corresponding to Important Potential Risks (tabulation by risk)

Patients included in analysis: Safety population

Analysis item: ADRs, etc. corresponding to important potential risks (described in Section 1.4 in Section 1, "Definitions of Terms, etc.")

Stratification factors: Seriousness [Serious, not serious]

Analysis methods: For the aforementioned analysis item, analysis will be performed for each stratum by risk as described below. The risks to be analyzed are as described in Section 1.4 in Section 1, "Definitions of Terms, etc."

[Type of ADR, etc.]

- ADRs, etc. will be coded using the MedDRA/J. ADRs, etc. will be classified by SOC and then tabulated by PT. For the SOC of investigations, ADRs, etc. will be sorted by HLGT (lined up in ascending order of HLGT code, but not output) and then tabulated by PT.
- For SOC, the number and proportion of patients with an ADR, etc. will be listed in internationally agreed SOC order. Multiple episodes of the same SOC in the same patient will be counted as 1 patient for the relevant SOC.

However, when these episodes differ in seriousness, they will be counted once each for “serious” and “not serious.”

- For PT, the number and proportion of patients with an ADR, etc. will be listed in ascending order of PT code. Multiple episodes of the same PT in the same patient will be counted as 1 patient for the relevant PT. However, when these episodes differ in seriousness, they will be counted once each for “serious” and “not serious.”

5.2 Occurrence of Adverse Events and Adverse Drug Reactions/Infections by Seriousness, Time of Onset, and Outcome

5.2.1 Occurrence of Adverse Events by Seriousness, Time of Onset, and Outcome

Patients included in analysis:	Safety population	
Analysis item:	AEs	
Stratification factors:	Total	
	Seriousness	[Serious, not serious]
	Time of onset	[<7 days, 7-<28 days, 28-<56 days, 56-<84 days, 84-<168 days, >=168 days]
	Outcome	[Recovered, recovering, not recovered, recovered with sequelae, died, unknown, unknown]

Analysis methods: For the aforementioned analysis item, analysis will be performed in each stratum of the stratification factor as described below.

(1) Number of patients with an AE
(2) Number of AE
(3) Proportion of patients with an AE
(4) Type of AE

For each analysis, events or patients will be counted as described below.

[Number of patients with an AE]

- Number of patients who experienced an AE

[Number of AE]

- Number of reported AE. Multiple episodes of the same AE in the same patient will be tabulated as the total number of episodes.

[Proportion of patients with an AE]

- The proportion of patients with an AE will be calculated as number of patients with an AE/number of patients included in safety evaluation × 100.

[Type of AE]

- AEs will be coded using the MedDRA/J. AEs will be classified by SOC and then tabulated by PT. For the SOC of investigations, AEs will be sorted by HLGT (lined up in ascending order of HLGT code, but not output) and then tabulated by PT.
- For SOC, the number and proportion of patients with an AE will be listed in internationally agreed SOC order. Multiple episodes of the same SOC in the same patient will be counted as 1 patient for the relevant SOC. Multiple

episodes of the same SOC will be employed as 1 event according to the order of precedence described at the end.

- For PT, the number and proportion of patients with an AE will be listed in ascending order of PT code. Multiple episodes of the same PT in the same patient will be counted as 1 patient for the relevant PT. Multiple episodes of the same PT will be employed as 1 event according to the following order of precedence:
  Seriousness: serious → not serious
  Time of onset: <7 days → 7-<28 days → 28-<56 days → 56-<84 days → 84-<168 days → >=168 days
  Outcome: died → recovered with sequelae → not recovered → recovering → recovered → unknown

5.2.2 Occurrence of Adverse Drug Reactions/Infections by Seriousness, Time of Onset, and Outcome

Patients included in analysis:	Safety population	
Analysis item:	ADRs, etc.	
Stratification factors:	Total	
	Seriousness	[Serious, not serious]
	Time of onset	[<7 days, 7-<28 days, 28-<56 days, 56-<84 days, 84-<168 days, >=168 days]
	Outcome	[Recovered, recovering, not recovered, recovered with sequelae, died, unknown, unknown]

Analysis methods: For the aforementioned analysis item, analysis will be performed in each stratum of the stratification factor as described below.

(1) Number of patients with an ADR, etc.
(2) Number of ADR, etc.
(3) Proportion of patients with an ADR, etc.
(4) Type of ADR, etc.

For each analysis, events or patients will be counted as described below.

[Number of patients with an ADR, etc.]

- Number of patients who experienced an ADR, etc.

[Number of ADR, etc.]

- Number of reported ADR, etc. Multiple episodes of the same ADR, etc. in the same patient will be tabulated as the total number of episodes.

[Proportion of patients with an ADR, etc.]

- The proportion of patients with an ADR, etc. will be calculated as number of patients with an ADR, etc./number of patients included in safety evaluation × 100.

[Type of ADR, etc.]

- ADRs, etc. will be coded using the MedDRA/J. ADRs, etc. will be classified by SOC and then tabulated by PT. For the SOC of investigations, ADRs, etc. will be sorted by HLGT (lined up in ascending order of HLGT code, but not output) and then tabulated by PT.
- For SOC, the number and proportion of patients with an ADR, etc. will be listed in internationally agreed SOC order. Multiple episodes of the same SOC in the same patient will be counted as 1 patient for the relevant SOC. Multiple episodes of the same SOC will be employed as 1 event according to the order of precedence described at the end.
- For PT, the number and proportion of patients with an ADR, etc. will be listed in ascending order of PT code. Multiple episodes of the same PT in the same patient will be counted as 1 patient for the relevant PT. Multiple episodes of the same PT will be employed as 1 event according to the following order of precedence:
  Seriousness: serious → not serious
  Time of onset: <7 days → 7-<28 days → 28-<56 days → 56-<84 days → 84-<168 days → >=168 days
  Outcome: died → recovered with sequelae → not recovered → recovering → recovered → unknown

5.3 Occurrence of Injection Site Reaction Not Unrelated to Leuplin PRO

5.3.1 Occurrence of Injection Site Reaction Not Unrelated to Leuplin PRO

Patients included in analysis:	Safety population	
Analysis item:	Injection site reaction not unrelated to Leuplin PRO	
Stratification factors:	Specific symptom (multiple answers allowed)	[Pain, pruritus, erythema, swelling, induration, abscess, ulcer, other]
Analysis methods:	For the aforementioned analysis item, frequency tabulation will be performed in each stratum of the stratification factor.	

5.3.2 Detail of Induration Not Unrelated to Leuplin PRO

Patients included in analysis:	Patients in the safety population who experienced induration not unrelated to Leuplin PRO	
Analysis items:	Seriousness	[Serious, not serious]
	Abscess/ulcer	[No, yes]
	Size of induration (longest diameter)	[-10 mm, 11-20 mm, 21-30 mm, 31-40 mm, 41 mm-, unknown]
	Number of days from Leuplin PRO treatment to the day of onset	[<7 days, 7-<28 days, 28-<56 days, 56-<84 days, 84-<168 days, >=168 days]
	Cause of discontinuation of Leuplin PRO treatment	[Yes, no]
	Presence or absence of intervention	[No, yes]
	Outcome	[Recovered, recovering, not recovered, recovered with sequelae, died, unknown, unknown]
	Number of days from the day of onset to “recovered” or “recovering” (frequency tabulation with only patients who recovered or were recovering as the denominator)	[<7 days, 7-<28 days, 28-<56 days, 56-<84 days, 84-<168 days, >=168 days]
Analysis methods:	For the aforementioned analysis items, frequency tabulation will be performed for discrete data, and summary statistics will be calculated for continuous data.	

5.3.3 Incidence of Induration Not Unrelated to Leuplin PRO by Factor

Patients included in analysis:	Safety population	
Analysis item:	Induration not unrelated to Leuplin PRO	
Stratification factors:	Age (years)	[<35 years, >=35 years, unknown]
	BMI (kg/m^2)	[<18.5, 18.5-<25.0, 25.0-<30.0, >=30.0, unknown]
	Full-treatment status of Leuplin PRO	[Yes, no]
	Injection site	[Extensor surface of the upper arm, deltoid region of the upper arm, abdomen, buttocks, other]
	Presence or absence of predisposition to hypersensitivity	[No, yes, unknown]
	Presence or absence of concurrent allergic disease	[No, yes]
	Disposition of allergic disease	[Bronchial asthma, pollinosis, allergic rhinitis, allergic dermatitis]
	Presence or absence of treatment with LH-RH agonist immediately before the start of Leuplin PRO treatment	[No, yes]
	Disposition of treatment with LH-RH agonist immediately before the start of Leuplin PRO treatment	[Leuprorelin acetate 3.75 mg, leuprorelin acetate 11.25 mg, goserelin 3.6 mg, goserelin 10.8 mg]
Analysis methods:	For the aforementioned analysis item, analysis will be performed in each stratum of the stratification factor as described below.	

(1) Number of patients with induration not unrelated to Leuplin PRO and incidence of induration not unrelated to Leuplin PRO

5.4 Occurrence of Adverse Drug Reactions/Infections by Baseline Characteristics and Treatment Given

5.4.1 Occurrence of Adverse Drug Reactions/Infections by Baseline Characteristics and Treatment Given

Patients included in analysis:	Safety population	
Analysis item:	ADRs, etc.	
Stratification factors:	Age (years)	[<35 years, >=35 years, unknown]
	ECOG Performance Status	[0, 1, 2, 3, 4]
	Full-treatment status of Leuplin PRO	[Yes, no]
	Injection site	[Extensor surface of the upper arm, deltoid region of the upper arm, abdomen, buttocks, other]
	Disease status	[Patient on preoperative adjuvant therapy, patient on postoperative adjuvant therapy, patient with advanced breast cancer, patient with recurrent breast cancer]
	Presence or absence of predisposition to hypersensitivity	[No, yes, unknown]
	Presence or absence of concurrent renal impairment	[No, yes]
	Presence or absence of concurrent hepatic impairment	[No, yes]
	Presence or absence of concurrent lifestyle diseases	[No, yes]
	Presence or absence of concurrent allergic disease	[No, yes]
	Presence or absence of history of thromboembolism	[No, yes, unknown]
	BMI (kg/m^2)	[<18.5, 18.5-<25.0, 25.0-<30.0, >=30.0, unknown]
	Presence or absence of treatment with LH-RH agonist immediately before the start of Leuplin PRO treatment	[No, yes]

	Presence or absence of treatment with premenopausal breast cancer drug other than LH-RH agonists immediately before the start of Leuplin PRO treatment	[No, yes]

Analysis methods: For the aforementioned analysis item, analysis will be performed in each stratum of the stratification factor as described below.

(1) Number of patients with an ADR, etc. and incidence of ADR, etc.

5.4.2 Occurrence of Adverse Drug Reactions/Infections by Age Group

Patients included in analysis:	Safety population	
Analysis item:	ADRs, etc.	
Stratification factor:	Age (years)	[<35 years, >=35 years, unknown]
Analysis methods:	For the aforementioned analysis item, analysis as described in Section 5.1.2 will be performed in each stratum of the stratification factor.	

5.4.3 Occurrence of Adverse Drug Reactions/Infections by ECOG Performance Status

Patients included in analysis:	Safety population	
Analysis item:	ADRs, etc.	
Stratification factor:	ECOG Performance Status	[0, 1, 2, 3, 4]
Analysis methods:	For the aforementioned analysis item, analysis as described in Section 5.1.2 will be performed in each stratum of the stratification factor.	

5.4.4 Occurrence of Adverse Drug Reactions/Infections by Full-Treatment Status of Leuplin PRO

Patients included in analysis:	Safety population	
Analysis item:	ADRs, etc.	
Stratification factor:	Full-treatment status of Leuplin PRO	[Yes, no]
Analysis methods:	For the aforementioned analysis item, analysis as described in Section 5.1.2 will be performed in each stratum of the stratification factor.	

5.4.5 Occurrence of Adverse Drug Reactions/Infections by Injection Site

Patients included in analysis:	Safety population	
Analysis item:	ADRs, etc.	
Stratification factor:	Injection site	[Extensor surface of the upper arm, deltoid region of the upper arm, abdomen, buttocks, other]
Analysis methods:	For the aforementioned analysis item, analysis as described in Section 5.1.2 will be performed in each stratum of the stratification factor.	

5.4.6 Occurrence of Adverse Drug Reactions/Infections by Disease Status

Patients included in analysis:	Safety population	
Analysis item:	ADRs, etc.	
Stratification factor:	Disease status	[Patient on premenopausal adjuvant therapy, patient on postoperative adjuvant therapy, patient with advanced breast cancer, patient with recurrent breast cancer]
Analysis methods:	For the aforementioned analysis item, analysis as described in Section 5.1.2 will be performed in each stratum of the stratification factor.	

5.4.7 Occurrence of Adverse Drug Reactions/Infections by Presence or Absence of Predisposition to Hypersensitivity

Patients included in analysis:	Safety population	
Analysis item:	ADRs, etc.	
Stratification factor:	Presence or absence of predisposition to hypersensitivity	[No, yes, unknown]
Analysis methods:	For the aforementioned analysis item, analysis as described in Section 5.1.2 will be performed in each stratum of the stratification factor.	

5.4.8 Occurrence of Adverse Drug Reactions/Infections by Presence or Absence of Concurrent Renal Impairment

Patients included in analysis:	Safety population	
Analysis item:	ADRs, etc.	
Stratification factor:	Presence or absence of concurrent renal impairment	[No, yes]
Analysis methods:	For the aforementioned analysis item, analysis as described in Section 5.1.2 will be performed in each stratum of the stratification factor.	

5.4.9 Occurrence of Adverse Drug Reactions/Infections by Presence or Absence of Concurrent Hepatic Impairment

Patients included in analysis:	Safety population
Analysis item:	ADRs, etc.

Stratification factor:	Presence or absence of concurrent hepatic impairment	[No, yes]
Analysis methods:	For the aforementioned analysis item, analysis as described in Section 5.1.2 will be performed in each stratum of the stratification factor.	

5.4.10 Occurrence of Adverse Drug Reactions/Infections by Presence or Absence of Concurrent Lifestyle Diseases

Patients included in analysis:	Safety population	
Analysis item:	ADRs, etc.	
Stratification factor:	Presence or absence of concurrent lifestyle diseases	[No, yes]
Analysis methods:	For the aforementioned analysis item, analysis as described in Section 5.1.2 will be performed in each stratum of the stratification factor.	

5.4.11 Occurrence of Adverse Drug Reactions/Infections by Presence or Absence of Concurrent Allergic Disease

Patients included in analysis:	Safety population	
Analysis item:	ADRs, etc.	
Stratification factor:	Presence or absence of concurrent allergic disease	[No, yes]
Analysis methods:	For the aforementioned analysis item, analysis as described in Section 5.1.2 will be performed in each stratum of the stratification factor.	

5.4.12 Occurrence of Adverse Drug Reactions/Infections by Presence or Absence of History of Thromboembolism

Patients included in analysis:	Safety population	
Analysis item:	ADRs, etc.	
Stratification factor:	Presence or absence of history of thromboembolism	[No, yes, unknown]
Analysis methods:	For the aforementioned analysis item, analysis as described in Section 5.1.2 will be performed in each stratum of the stratification factor.	

5.4.13 Occurrence of Adverse Drug Reactions/Infections by BMI

Patients included in analysis:	Safety population	
Analysis item:	ADRs, etc.	
Stratification factor:	BMI (kg/m^2)	[<18.5, 18.5-<25.0, 25.0-<30.0, >=30.0, unknown]
Analysis methods:	For the aforementioned analysis item, analysis as described in Section 5.1.2 will be performed in each stratum of the stratification factor.	

5.4.14 Occurrence of Adverse Drug Reactions/Infections by Presence or Absence of Treatment with LH-RH Agonist Immediately before the Start of Leuplin PRO Treatment

Patients included in analysis:	Safety population	
Analysis item:	ADRs, etc.	
Stratification factor:	Presence or absence of treatment with LH-RH agonist immediately before the start of Leuplin PRO treatment	[No, yes]
Analysis methods:	For the aforementioned analysis item, analysis as described in Section 5.1.2 will be performed in each stratum of the stratification factor.	

5.4.15 Occurrence of Adverse Drug Reactions/Infections by Presence or Absence of Treatment with Premenopausal Breast Cancer Drug Other Than LH-RH Agonists Immediately before the Start of Leuplin PRO Treatment

Patients included in analysis:	Safety population	
Analysis item:	ADRs, etc.	
Stratification factor:	Presence or absence of treatment with premenopausal breast cancer drug other than LH-RH agonists immediately before the start of Leuplin PRO treatment	[No, yes]
Analysis methods:	For the aforementioned analysis item, analysis as described in Section 5.1.2 will be performed in each stratum of the stratification factor.	

5.5 Occurrence of Adverse Drug Reactions/Infections in Additional Pharmacovigilance Plan (Attachment Style 12)

Patients included in analysis:	Safety population
Analysis item:	ADRs, etc. corresponding to important identified risks or important potential risks (described in Section 1.4 in Section 1, "Definitions of Terms, etc.")
Stratification factor:	Seriousness [Serious, non-serious]
Analysis methods:	For the aforementioned analysis item, analysis will be performed in each stratum of the stratification factor as described below in accordance with Notes 1 to 4 in Attachment style 12 in Notification concerning re-examination, PSEHB/PAB/ED Notification No. 1128-2 dated 28 November 2017. (1) Number and proportion of patients with an important identified risk (2) Number and proportion of patients with an important potential risk Risk terms and the order of risk terms are specified in Section 1.4 in Section 1, "Definitions of Terms, etc."

5.6 Summary of Patients in Post-Marketing Surveillance, etc. (Attachment Style 16)

Patients included in analysis:	Patients with the CRF collected
Analysis items:	Patient number Site name Sex Date of birth Reason for use (disease code, disease name) Concurrent illness (disease code, disease name) Route of administration Maximum dose Mean dose Units Duration of use Concomitant medication (NHI drug code, drug name) Degree of response ADR (disease code, disease name, outcome) CRF number Dropout
Analysis methods:	The aforementioned analysis items will be listed in accordance with Notes 1 to 3 in Attachment style 16 in Notification concerning re-examination, PSEHB/PAB/ED Notification No. 1128-2 dated 28 November 2017.

Attached table 1　PTs corresponding to risks

Risk	PT code	PT
Injection site reaction	10022044	Injection site abscess
	10068791	Administration site abscess
Decreased bone mass density	10000397	Acetabulum fracture
	10002544	Ankle fracture
	10009245	Clavicle fracture
	10009506	Closed fracture manipulation
	10010149	Complicated fracture
	10010214	Compression fracture
	10014487	Elevation skull fracture
	10015741	External fixation of fracture
	10016042	Facial bones fracture
	10016450	Femoral neck fracture
	10016454	Femur fracture
	10016667	Fibula fracture
	10016970	Foot fracture
	10016997	Forearm fracture
	10017076	Fracture
	10017081	Fracture delayed union
	10017085	Fracture malunion
	10017088	Fracture nonunion
	10017107	Fracture of clavicle due to birth trauma
	10017290	Fractured ischium
	10017296	Fractured maxilla elevation
	10017308	Fractured sacrum
	10017310	Fractured skull depressed
	10018720	Greenstick fracture
	10019114	Hand fracture
	10020100	Hip fracture
	10020462	Humerus fracture
	10021343	Ilium fracture
	10022576	Internal fixation of fracture
	10023149	Jaw fracture
	10028200	Multiple fractures
	10030527	Open fracture

Risk	PT code	PT
	10030682	Open reduction of fracture
	10030684	Open reduction of spinal fracture
	10031290	Osteoporotic fracture
	10034122	Patella fracture
	10034156	Pathological fracture
	10037802	Radius fracture
	10039117	Rib fracture
	10039579	Scapula fracture
	10040960	Skull fractured base
	10041541	Spinal compression fracture
	10041569	Spinal fracture
	10042015	Sternal fracture
	10042212	Stress fracture
	10043827	Tibia fracture
	10045375	Ulna fracture
	10048049	Wrist fracture
	10049164	Fractured coccyx
	10049514	Traumatic fracture
	10049946	Cervical vertebral fracture
	10049947	Lumbar vertebral fracture
	10049948	Thoracic vertebral fracture
	10052614	Comminuted fracture
	10053206	Fracture displacement
	10053962	Epiphyseal fracture
	10057147	Fracture debridement
	10057609	Fracture reduction
	10059362	Fractured zygomatic arch elevation
	10061161	Pelvic fracture
	10061365	Skull fracture
	10061394	Upper limb fracture
	10061599	Lower limb fracture
	10061959	Fracture treatment
	10066094	Torus fracture
	10066184	Avulsion fracture
	10066386	Impacted fracture
	10069135	Periprosthetic fracture

Risk	PT code	PT
	10069723	Loss of anatomical alignment after fracture reduction
	10070286	Pubis fracture
	10070884	Atypical femur fracture
	10072132	Fracture pain
	10072395	Atypical fracture
	10073162	Chance fracture
	10073853	Osteochondral fracture
	10074362	Sacroiliac fracture
	10074551	Limb fracture
	10074807	Spinal fusion fracture
	10077270	Surgical fixation of rib fracture
	10077603	Craniofacial fracture
	10078358	Costal cartilage fracture
	10078749	Lisfranc fracture
	10079423	Fracture blisters
	10079667	Metaphyseal corner fracture
	10079813	Fracture infection
	10079864	Subchondral insufficiency fracture
	10080404	Pseudofracture
	10080550	Osteophyte fracture
	10081343	Maisonneuve fracture
	10081442	Stapes fracture
Pituitary apoplexy	10035092	Pituitary infarction
	10049760	Pituitary haemorrhage
	10035104	Pituitary tumour

Attached table 2 Disposition of Premenopausal Breast Cancer Drugs Other Than LH-RH Agonists

Therapeutic category	Drug code	Nonproprietary name
Adrenal hormone preparations	2452002	Hydrocortisone
	2452400	Hydrocortisone Sodium Succinate
	2454002	Dexamethasone
	2454004	Betamethasone
	2454402	Triamcinolone Acetonide
	2454404	Betamethasone Sodium Phosphate
	2454405	Dexamethasone Sodium Phosphate
	2456001	Prednisolone
	2456003	Methylprednisolone
	2456405	Prednisolone Sodium Succinate
Estrogen and gestagen preparations	2478002	Medroxyprogesterone Acetate
Oral anti-renal anemia agents/anti-mammary tumor agents	2499003	Mepitiostane
Bone resorption inhibitors	3999418	Pamidronate Disodium Hydrate
	3999435	Denosumab (Genetical Recombination)
Alkylating agents	4211002	Cyclophosphamide Hydrate
	4211401	Cyclophosphamide Hydrate
Antimetabolic agents	4222400	Methotrexate
	4223002	Tegafur
	4223003	Fluorouracil
	4223004	Doxifluridine
	4223005	Capecitabine
	4223401	Fluorouracil
	4224401	Cytarabine
	4224403	Gemcitabine Hydrochloride
	4229100	Uracil Tegafur
	4229101	Oteracil Potassium Gimeracil Tegafur
Antitumor antibiotics and preparations	4231400	Mitomycin C
	4235400	Aclarubicin Hydrochloride
	4235402	Doxorubicin Hydrochloride
	4235403	Pirarubicin

Therapeutic category	Drug code	Nonproprietary name
	4235404	Epirubicin Hydrochloride
Antineoplastic preparations extracted from plants	4240404	Irinotecan Hydrochloride Hydrate
	4240490	Docetaxel
	4240406	Paclitaxel
	4240407	Vinorelbine Ditartrate
	4240409	Paclitaxel (albumin-bound)
Antineoplastic agents	4291003	Tamoxifen Citrate
	4291007	Toremifene Citrate
	4291022	Lapatinib Tosilate Hydrate
	4291023	Everolimus
	4291051	Palbociclib
	4291052	Olaparib
	4291054	Abemaciclib
	4291402	Mitoxantrone Hydrochloride
	4291403	Carboplatin
	4291406	Trastuzumab (Genetical Recombination)
	4291413	Bevacizumab (Genetical Recombination)
	4291420	Eribulin Mesilate
	4291421	Fulvestrant
	4291424	Pertuzumab (Genetical Recombination)
	4291426	Trastuzumab Emtansine (Genetical Recombination)
	4291010	Anastrozole
	4291012	Exemestane
	4291015	Letrozole

History of preparation (version control)

Version	Date	Person who prepared/changed the SAP	Comment
1st version	2019.4.4	PPD	The 1st version was prepared.