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

NCT Number: NCT03209518

Protocol Approve Date: 05-APR-2019

Certain information within this protocol 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.

Special Drug Use Surveillance Protocol

Special Drug Use Surveillance of Leuplin PRO for Injection Kit 22.5 mg for "Premenopausal Breast Cancer"

Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol number	**Leuprorelin-5003**
Version number	**5th version**
Date of preparation	**5 April 2019**

Table of Contents

1.0 Background of the Surveillance

Since the amount of leuprorelin acetate administered in a single dose of Leuplin PRO for Injection Kit 22.5 mg (hereinafter referred to as Leuplin PRO) is as high as twice that of Leuplin SR for Injection Kit 11.25 mg (hereinafter referred to as Leuplin SR), and the time profile of serum leuprorelin concentration after administration differs between the two formulations, a special drug use surveillance (hereinafter referred to as the surveillance) is planned to evaluate potential effects of the differences on the safety.

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

2.0 Objectives

To investigate the safety of Leuplin PRO in patients with premenopausal breast cancer in routine clinical settings in order to evaluate potential effects of differences between Leuplin PRO and Leuplin SR, including the higher amount administered in a single dose and differences in time profile of serum drug concentration after administration, on the safety

3.0 Planned Sample Size and Rationale

3.1 Planned Sample Size

300 patients

3.2 Rationale

To evaluate potential effects of differences between Leuplin PRO and Leuplin SR, that is, difference amounts of leuprorelin acetate administered in a single dose and different time profiles of serum drug concentration after administration, on the safety, it was decided to investigate the occurrence of injection site reaction and other adverse drug reactions (ADRs) with an incidence of 1% or higher, including the time of onset, incidence, and seriousness.

The sample size of 300 patients was determined to detect ADRs with an incidence of 1% or higher at a probability of 95% or higher.

4.0 Surveillance Population

Patients with premenopausal breast cancer will be included in the surveillance. Patients should not meet the exclusion criterion listed below. Refer to the Precautions section of the package insert.

<Exclusion criteria>

Patients who meet the following criterion will not be included:

- A history of hypersensitivity to any of the ingredients of Leuplin PRO or synthetic luteinizing hormone-releasing hormone (LH-RH) or LH-RH derivatives
- Pregnant or potentially pregnant patients and breastfeeding patients.

5.0 Dosage and Administration

The usual adult dosage is 22.5 mg of leuprorelin acetate administered subcutaneously once every 24 weeks. Refer to the Precautions section of the package insert.

6.0 Planned Number of Medical Institutions by Department

Breast surgery and other departments Approximately 60 medical institutions

7.0 Methodology

7.1 Observation Period

24 weeks

7.2 Request to and Contract with the Study Site

This surveillance will be conducted using a Web-based electronic data capture system (CCI [redacted]). A representative of Takeda Pharmaceutical Company Limited (hereinafter referred to as Takeda's representative) will explain the objectives and contents of the surveillance, operation method of CCI [redacted], and handling of electronic signature, user ID, and password to the investigator based on "Request for cooperation for special drug use surveillance," "Implementation outline," "Entry screen image," and "Operation manual of CCI [redacted] (brief version)" to enter into a written contract with the study site and request the study site to conduct a surveillance within a specified period.

7.3 Method of Patient Registration

Patients will be registered using the central registration method via CCI [redacted]. After the start of the contract with the study site, the investigator shall register each patient treated with Leuplin PRO by entering patient registration information (refer to Section 9.1) with his/her electronic signature within 14 days after administration of Leuplin PRO (day of administration designated as day 0 and day following the day of administration designated as 1 day post-dose).

7.4 Entry into the (Electronic) Case Report Form and Electronic Signature

The investigator or designee* shall enter patient baseline characteristics and treatment given into CCI [redacted] with the investigator's electronic signature within approximately 1 month after the end of required observation at 24 weeks after the

start of Leuplin PRO treatment.

For any patient with an adverse event, the investigator or designee shall enter observation results into CCI with the investigator's electronic signature after monitoring the patient as long after discontinuation of treatment as possible until the adverse event is confirmed to have resolved or be resolving.

* The investigator's designee should belong to the relevant medical institution (including those under contract with the medical institution such as temporary clinical research coordinators). Before the investigator's designee begins to enter data into CCI, a physician responsible for the surveillance (one physician per medical institution or department appointed at the time of contract) shall document the designation with the date of designation (no specific style), affix his/her signature or name and seal to the document, and submit it to Takeda's representative.

8.0 Planned Surveillance Period

Surveillance period: From March 2016 to 31 August 2017

Patient registration period: From April 2016 to 28 February 2017[Note)]

[Note)] Patient registration (entry into CCI) will not be accepted on 1 March 2018 onwards even if Leuplin PRO is administered by 28 February 2018.

If the number of patients enrolled in the surveillance reaches the planned sample size before 28 February 2018, acceptance of registration will be terminated before the end of the patient registration period. If the patient registration period is shortened, the surveillance period will be changed accordingly.

9.0 Surveillance Items

The investigator or designee shall enter the items listed below into CCI. The surveillance schedule is presented in Appendix.

9.1 Patient Registration

1) Surveillance items

Date of administration of Leuplin PRO, patient identification number, patient initials, date of birth, assessment based on the exclusion criteria

2) Time points of surveillance

At patient registration

9.2 Patient Baseline Characteristics

1) Surveillance items

Time of diagnosis of premenopausal breast cancer, ECOG Performance Status*, disease status, site of lesions before the start of Leuplin PRO treatment, presence or absence of hormone receptor expression, diagnostic category

(at the start of Leuplin PRO treatment), predisposition to hypersensitivity (presence or absence and details), concurrent illness (presence or absence and details), history of thromboembolism (presence or absence and details), height, body weight, treatment status of premenopausal breast cancer drug immediately before the start of Leuplin PRO treatment (presence or absence and name of the drug)

2) Time points of surveillance

At the start of Leuplin PRO treatment

* ECOG Performance Status

Score	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair

(Common Toxicity Criteria, Version 2.0 Published on April 30, 1999. Webpage of the JCOG at http://www.jcog.jp/)

9.3 Treatment Given

1) Surveillance items

Treatment status of Leuplin PRO (injection site* and full-treatment status of Leuplin PRO*), treatment status of premenopausal breast cancer drug other than Leuplin PRO (presence or absence and name of the drug), presence or absence of and reason for discontinuation of observation

2) Time points of surveillance

Period from the start of Leuplin PRO treatment to 24 weeks after the start of treatment (or discontinuation of observation)

* At the start of Leuplin PRO treatment

9.4 Assessments

1) Assessments

Pregnancy during the observation period (females only)

2) Outcome measure data collection timing

Period from the start of Leuplin PRO treatment to 24 weeks after the start of treatment (or discontinuation of observation)

9.5 Adverse Events (AEs)

1) Surveillance items

Presence or absence of injection site reaction, details of injection site reaction (specific symptom, date of onset, seriousness and reason for seriousness [refer to Table 2], cause of discontinuation of Leuplin PRO treatment, intervention (presence or absence and contents), date of outcome assessment, outcome, causal relationship to Leuplin PRO [refer to Table 3]).

Presence or absence of AE other than injection site reaction (refer to Table 1), AE term, date of onset, seriousness and reason for seriousness (refer to Table

2), cause of discontinuation of Leuplin PRO treatment, intervention (presence or absence and name of the drug/intervention), date of outcome assessment, outcome, causal relationship to Leuplin PRO* (refer to Table 3)
Patients with “not resolved” or “unknown” outcome or “unevaluable” causal relationship should be followed up wherever possible.

* For the causal relationship to Leuplin PRO, the rationale for “not related” and the reason for “unevaluable” shall be collected.

Note) Additional points to consider for AEs

Abnormal worsening of target disease, for instance, worsening beyond the expected natural course of the disease, will be handled as an AE.

2) Time points of surveillance

Period from the start of Leuplin PRO treatment to 24 weeks after the start of treatment (or discontinuation of observation)

Table 1 Definition of adverse events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.

The following are also handled as AEs:

- Symptoms and so forth that occur in infants breast-fed by their mothers under treatment with a drug
- Untoward symptoms and so forth that occur in children treated with a drug
- Symptoms and so forth that occur as a result of occupational exposure to a drug
- Symptoms and so forth that occur after administration of counterfeit medicines of our ethical drugs
- Untoward symptoms that have become known to occur in drug users through lawsuits or other legal actions

Table 2 Criteria for assessing seriousness

An AE satisfying any of the following is assessed as serious:

1. Results in death (death)
2. Is life-threatening (risk of death)
3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization)
4. Results in persistent or significant disability/incapacity (disability)
5. Leads to a congenital anomaly/birth defect (congenital anomaly)
6. Is an important medical event according to 1 to 5 described above, including AEs in Takeda Medically Significant AE List

<u>Takeda Medically Significant AE List</u>

- Acute respiratory failure / acute respiratory distress syndrome (ARDS)
- Anaphylactic shock
- Torsade de pointes / ventricular fibrillation / ventricular tachycardia
- Acute renal failure
- Malignant hypertension
- Pulmonary hypertension
- Convulsive seizures (including convulsions and epilepsy)
- Pulmonary fibrosis (including interstitial pneumonia)
- Agranulocytosis
- Malignant syndrome / malignant hyperthermia

- Aplastic anemia
- Spontaneous abortion / stillbirth and fetal death
- Toxic epidermal necrolysis / mucocutaneous ocular syndrome (Stevens-Johnson syndrome)
- Confirmed or suspected transmission of infectious agent by a medicinal product
- Hepatic necrosis
- Confirmed or suspected endotoxin shock
- Acute liver failure

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

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

10.0 Analysis Items and Methods

10.1 Statistical Analysis Plan

A statistical analysis plan will be prepared before finalization of data. The statistical analysis plan will include definitions of endpoints and detailed analysis methods.

10.2 Analysis Sets

The analysis set is patients included in safety evaluation.

10.3 Matters on Patient Composition

The number of enrolled patients, number of patients with the (electronic) CRF collected, number of patients included in safety evaluation, number of patients excluded from safety evaluation, and reason for exclusion will be tabulated.

10.4 Patient Baseline Characteristics

Patient baseline characteristics, including age, predisposition to hypersensitivity, and concurrent illness, will be tabulated.

10.5 Treatment Given

The treatment status of Leuplin PRO and treatment status of premenopausal breast cancer drug other than Leuplin PRO will be tabulated.

10.6 Matters on Safety

For patients included in safety evaluation, data will be tabulated as described below. AEs will be coded according to the MedDRA/J and summarized using preferred term (PT) and system organ class (SOC).

10.6.1 Occurrence of Adverse Events

For AEs reported during the observation period, the incidence will be tabulated by type, time of onset, seriousness, and causal relationship to Leuplin PRO. In addition, events listed as the safety specifications for the surveillance in "2. Summary of Pharmacovigilance Plan" in the risk management plan will be tabulated separately.

10.6.2 Factors that May Affect the Safety

For ADRs reported during the observation period, the incidence will be tabulated by patient background factors (e.g., disease status, presence or absence of concurrent renal impairment, presence or absence of concurrent hepatic impairment) and treatment status of Leuplin PRO.

11.0 Posting of Surveillance Information

Surveillance information will be posted on the following open website before starting the surveillance:

- Japan Pharmaceutical Information Center-Clinical Trials Information

12.0 Surveillance Organization

12.1 Administrative Manager

PPD

Takeda Pharmaceutical Company Limited

13.0 Contract Research Organizations (CROs)

PPD

14.0 Other Necessary Matters

14.1 Revision of the Protocol

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

14.2 Actions to be Taken for Problems and Questions

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

Appendix　Observation schedule

Surveillance item \ Time point of surveillance		Observation period		
		At patient registration	At the start of treatment	After 24 weeks or at discontinuation of observation
Patient registration	Date of administration of Leuplin PRO	○		
	Patient identification number	○		
	Patient initials	○		
	Date of birth	○		
	Assessment based on the exclusion criteria	○		
Patient baseline characteristics	Time of diagnosis of premenopausal breast cancer		○	
	ECOG Performance Status		○	
	Disease status		○	
	Diagnostic category		○	
	Site of lesions before the start of Leuplin PRO treatment		○	
	Presence or absence of hormone receptor expression		○	
	Predisposition to hypersensitivity		○	
	Concurrent illness		○	
	History of thromboembolism		○	
	Height, body weight		○	
	Treatment status of premenopausal breast cancer drug immediately before the start of Leuplin PRO treatment		○	
Treatment given	Treatment status of Leuplin PRO		← ○ →	
	Treatment status of premenopausal breast cancer drug other than Leuplin PRO		← ○ →	
Assess-ments	Pregnancy during the observation period (females only)		← ○ →	
Adverse event	Injection site reaction		← ○ →	
	Adverse event other than injection site reaction		← ○ →	

○　: Performed

←○→: Performed throughout the period

Special Drug Use Surveillance Protocol

Special Drug Use Surveillance of Leuplin PRO for Injection Kit 22.5 mg for "Premenopausal Breast Cancer"

Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol number	**Leuprorelin-5003**
Version number	**4th version**
Date of preparation	**2 June 2017**

Table of Contents

1.0 Background of the Surveillance

Since the amount of leuprorelin acetate administered in a single dose of Leuplin PRO for Injection Kit 22.5 mg (hereinafter referred to as Leuplin PRO) is as high as twice that of Leuplin SR for Injection Kit 11.25 mg (hereinafter referred to as Leuplin SR), and the time profile of serum leuprorelin concentration after administration differs between the two formulations, a special drug use surveillance (hereinafter referred to as the surveillance) is planned to evaluate potential effects of the differences on the safety.

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

2.0 Objectives

To investigate the safety of Leuplin PRO in patients with premenopausal breast cancer in routine clinical settings in order to evaluate potential effects of differences between Leuplin PRO and Leuplin SR, including the higher amount administered in a single dose and differences in time profile of serum drug concentration after administration, on the safety

3.0 Planned Sample Size and Rationale

3.1 Planned Sample Size

300 patients

3.2 Rationale

To evaluate potential effects of differences between Leuplin PRO and Leuplin SR, that is, difference amounts of leuprorelin acetate administered in a single dose and different time profiles of serum drug concentration after administration, on the safety, it was decided to investigate the occurrence of injection site reaction and other adverse drug reactions (ADRs) with an incidence of 1% or higher, including the time of onset, incidence, and seriousness.

The sample size of 300 patients was determined to detect ADRs with an incidence of 1% or higher at a probability of 95% or higher.

4.0 Surveillance Population

Patients with premenopausal breast cancer will be included in the surveillance. Patients should not meet the exclusion criterion listed below. Refer to the Precautions section of the package insert.

<Exclusion criteria>

Patients who meet the following criterion will not be included:

- A history of hypersensitivity to any of the ingredients of Leuplin PRO or synthetic luteinizing hormone-releasing hormone (LH-RH) or LH-RH derivatives
- Pregnant or potentially pregnant patients and breastfeeding patients.

5.0 Dosage and Administration

The usual adult dosage is 22.5 mg of leuprorelin acetate administered subcutaneously once every 24 weeks. Refer to the Precautions section of the package insert.

6.0 Planned Number of Medical Institutions by Department

Breast surgery and other departments Approximately 60 medical institutions

7.0 Methodology

7.1 Observation Period

24 weeks

7.2 Request to and Contract with the Study Site

This surveillance will be conducted using a Web-based electronic data capture system (CCI [redacted]). A representative of Takeda Pharmaceutical Company Limited (hereinafter referred to as Takeda's representative) will explain the objectives and contents of the surveillance, operation method of CCI [redacted], and handling of electronic signature, user ID, and password to the investigator based on "Request for cooperation for special drug use surveillance," "Implementation outline," "Entry screen image," and "Operation manual of CCI [redacted] (brief version)" to enter into a written contract with the study site and request the study site to conduct a surveillance within a specified period.

7.3 Method of Patient Registration

Patients will be registered using the central registration method via CCI [redacted]. After the start of the contract with the study site, the investigator shall register each patient treated with Leuplin PRO by entering patient registration information (refer to Section 9.1) with his/her electronic signature within 14 days after administration of Leuplin PRO (day of administration designated as day 0 and day following the day of administration designated as 1 day post-dose).

7.4 Entry into the (Electronic) Case Report Form and Electronic Signature

The investigator or designee* shall enter patient baseline characteristics and treatment given into CCI [redacted] with the investigator's electronic signature within approximately 1 month after the end of required observation at 24 weeks after the

start of Leuplin PRO treatment.

For any patient with an adverse event, the investigator or designee shall enter observation results into CCI with the investigator's electronic signature after monitoring the patient as long after discontinuation of treatment as possible until the adverse event is confirmed to have resolved or be resolving.

* The investigator's designee should belong to the relevant medical institution (including those under contract with the medical institution such as temporary clinical research coordinators). Before the investigator's designee begins to enter data into CCI, a physician responsible for the surveillance (one physician per medical institution or department appointed at the time of contract) shall document the designation with the date of designation (no specific style), affix his/her signature or name and seal to the document, and submit it to Takeda's representative.

8.0 Planned Surveillance Period

Surveillance period: From March 2016 to 31 August 2017

Patient registration period: From April 2016 to 28 February 2017[Note)]

[Note)] Patient registration (entry into CCI) will not be accepted on 1 March 2018 onwards even if Leuplin PRO is administered by 28 February 2018.

If the number of patients enrolled in the surveillance reaches the planned sample size before 28 February 2018, acceptance of registration will be terminated before the end of the patient registration period. If the patient registration period is shortened, the surveillance period will be changed accordingly.

9.0 Surveillance Items

The investigator or designee shall enter the items listed below into CCI. The surveillance schedule is presented in Appendix.

9.1 Patient Registration

1) Surveillance items

Date of administration of Leuplin PRO, patient identification number, patient initials, date of birth, assessment based on the exclusion criteria

2) Time points of surveillance

At patient registration

9.2 Patient Baseline Characteristics

1) Surveillance items

Time of diagnosis of premenopausal breast cancer, ECOG Performance Status*, disease status, site of lesions before the start of Leuplin PRO treatment, presence or absence of hormone receptor expression, diagnostic category

(at the start of Leuplin PRO treatment), predisposition to hypersensitivity (presence or absence and details), concurrent illness (presence or absence and details), history of thromboembolism (presence or absence and details), height, body weight, treatment status of premenopausal breast cancer drug immediately before the start of Leuplin PRO treatment (presence or absence and name of the drug)

2) Time points of surveillance

At the start of Leuplin PRO treatment

* ECOG Performance Status

Score	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair

(Common Toxicity Criteria, Version 2.0 Published on April 30, 1999. Webpage of the JCOG at http://www.jcog.jp/)

9.3 Treatment Given

1) Surveillance items

Treatment status of Leuplin PRO (injection site* and full-treatment status of Leuplin PRO*), treatment status of premenopausal breast cancer drug other than Leuplin PRO (presence or absence and name of the drug), presence or absence of and reason for discontinuation of observation

2) Time points of surveillance

Period from the start of Leuplin PRO treatment to 24 weeks after the start of treatment (or discontinuation of observation)

* At the start of Leuplin PRO treatment

9.4 Assessments

1) Assessments

Pregnancy during the observation period (females only)

2) Outcome measure data collection timing

Period from the start of Leuplin PRO treatment to 24 weeks after the start of treatment (or discontinuation of observation)

9.5 Adverse Events (AEs)

1) Surveillance items

Presence or absence of injection site reaction, details of injection site reaction (specific symptom, date of onset, seriousness and reason for seriousness [refer to Table 2], cause of discontinuation of Leuplin PRO treatment, intervention (presence or absence and contents), date of outcome assessment, outcome, causal relationship to Leuplin PRO [refer to Table 3]).

Presence or absence of AE other than injection site reaction (refer to Table 1), AE term, date of onset, seriousness and reason for seriousness (refer to Table

2), cause of discontinuation of Leuplin PRO treatment, intervention (presence or absence and name of the drug/intervention), date of outcome assessment, outcome, causal relationship to Leuplin PRO* (refer to Table 3)
Patients with “not resolved” or “unknown” outcome or “unevaluable” causal relationship should be followed up wherever possible.

* For the causal relationship to Leuplin PRO, the rationale for “not related” and the reason for “unevaluable” shall be collected.

Note) Additional points to consider for AEs

Abnormal worsening of target disease, for instance, worsening beyond the expected natural course of the disease, will be handled as an AE.

2) Time points of surveillance

Period from the start of Leuplin PRO treatment to 24 weeks after the start of treatment (or discontinuation of observation)

Table 1 Definition of adverse events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.

The following are also handled as AEs:

- Symptoms and so forth that occur in infants breast-fed by their mothers under treatment with a drug
- Untoward symptoms and so forth that occur in children treated with a drug
- Symptoms and so forth that occur as a result of occupational exposure to a drug
- Symptoms and so forth that occur after administration of counterfeit medicines of our ethical drugs
- Untoward symptoms that have become known to occur in drug users through lawsuits or other legal actions

Table 2 Criteria for assessing seriousness

An AE satisfying any of the following is assessed as serious:

1. Results in death (death)
2. Is life-threatening (risk of death)
3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization)
4. Results in persistent or significant disability/incapacity (disability)
5. Leads to a congenital anomaly/birth defect (congenital anomaly)
6. Is an important medical event according to 1 to 5 described above, including AEs in Takeda Medically Significant AE List

<u>Takeda Medically Significant AE List</u>

- Acute respiratory failure / acute respiratory distress syndrome (ARDS)
- Anaphylactic shock
- Torsade de pointes / ventricular fibrillation / ventricular tachycardia
- Acute renal failure
- Malignant hypertension
- Pulmonary hypertension
- Convulsive seizures (including convulsions and epilepsy)
- Pulmonary fibrosis (including interstitial pneumonia)
- Agranulocytosis
- Malignant syndrome / malignant hyperthermia

- Aplastic anemia
- Spontaneous abortion / stillbirth and fetal death
- Toxic epidermal necrolysis / mucocutaneous ocular syndrome (Stevens-Johnson syndrome)
- Confirmed or suspected transmission of infectious agent by a medicinal product
- Hepatic necrosis
- Confirmed or suspected endotoxin shock
- Acute liver failure

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

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

10.0 Analysis Items and Methods

10.1 Statistical Analysis Plan

A statistical analysis plan will be prepared before finalization of data. The statistical analysis plan will include definitions of endpoints and detailed analysis methods.

10.2 Analysis Sets

The analysis set is patients included in safety evaluation.

10.3 Matters on Patient Composition

The number of enrolled patients, number of patients with the (electronic) CRF collected, number of patients included in safety evaluation, number of patients excluded from safety evaluation, and reason for exclusion will be tabulated.

10.4 Patient Baseline Characteristics

Patient baseline characteristics, including age, predisposition to hypersensitivity, and concurrent illness, will be tabulated.

10.5 Treatment Given

The treatment status of Leuplin PRO and treatment status of premenopausal breast cancer drug other than Leuplin PRO will be tabulated.

10.6 Matters on Safety

For patients included in safety evaluation, data will be tabulated as described below. AEs will be coded according to the MedDRA/J and summarized using preferred term (PT) and system organ class (SOC).

10.6.1 Occurrence of Adverse Events

For AEs reported during the observation period, the incidence will be tabulated by type, time of onset, seriousness, and causal relationship to Leuplin PRO. In addition, events listed as the safety specifications for the surveillance in "2. Summary of Pharmacovigilance Plan" in the risk management plan will be tabulated separately.

10.6.2 Factors that May Affect the Safety

For ADRs reported during the observation period, the incidence will be tabulated by patient background factors (e.g., disease status, presence or absence of concurrent renal impairment, presence or absence of concurrent hepatic impairment) and treatment status of Leuplin PRO.

11.0 Posting of Surveillance Information

Surveillance information will be posted on the following open website before starting the surveillance:

- Japan Pharmaceutical Information Center-Clinical Trials Information

12.0 Surveillance Organization

12.1 Administrative Manager

PPD

Takeda Pharmaceutical Company Limited

13.0 Contract Research Organizations (CROs)

PPD

PPD

14.0 Other Necessary Matters

14.1 Revision of the Protocol

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

14.2 Actions to be Taken for Problems and Questions

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

Appendix　Observation schedule

Surveillance item \ Time point of surveillance		Observation period		
		At patient registration	At the start of treatment	After 24 weeks or at discontinuation of observation
Patient registration	Date of administration of Leuplin PRO	○		
	Patient identification number	○		
	Patient initials	○		
	Date of birth	○		
	Assessment based on the exclusion criteria	○		
Patient baseline characteristics	Time of diagnosis of premenopausal breast cancer		○	
	ECOG Performance Status		○	
	Disease status		○	
	Diagnostic category		○	
	Site of lesions before the start of Leuplin PRO treatment		○	
	Presence or absence of hormone receptor expression		○	
	Predisposition to hypersensitivity		○	
	Concurrent illness		○	
	History of thromboembolism		○	
	Height, body weight		○	
	Treatment status of premenopausal breast cancer drug immediately before the start of Leuplin PRO treatment		○	
Treatment given	Treatment status of Leuplin PRO		← ○ →	
	Treatment status of premenopausal breast cancer drug other than Leuplin PRO		← ○ →	
Assess-ments	Pregnancy during the observation period (females only)		← ○ →	
Adverse event	Injection site reaction		← ○ →	
	Adverse event other than injection site reaction		← ○ →	

○　: Performed

←○→: Performed throughout the period

Special Drug Use Surveillance Protocol

Special Drug Use Surveillance of Leuplin PRO for Injection Kit 22.5 mg for "Premenopausal Breast Cancer"

Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol number	**Leuprorelin-5003**
Version number	**3rd version**
Date of preparation	**5 September 2016**

Table of Contents

1.0 Background of the Surveillance

Since the amount of leuprorelin acetate administered in a single dose of Leuplin PRO for Injection Kit 22.5 mg (hereinafter referred to as Leuplin PRO) is as high as twice that of Leuplin SR for Injection Kit 11.25 mg (hereinafter referred to as Leuplin SR), and the time profile of serum leuprorelin concentration after administration differs between the two formulations, a special drug use surveillance (hereinafter referred to as the surveillance) is planned to evaluate potential effects of the differences on the safety.

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

2.0 Objectives

To investigate the safety of Leuplin PRO in patients with premenopausal breast cancer in routine clinical settings in order to evaluate potential effects of differences between Leuplin PRO and Leuplin SR, including the higher amount administered in a single dose and differences in time profile of serum drug concentration after administration, on the safety

3.0 Planned Sample Size and Rationale

3.1 Planned Sample Size

300 patients

3.2 Rationale

To evaluate potential effects of differences between Leuplin PRO and Leuplin SR, that is, difference amounts of leuprorelin acetate administered in a single dose and different time profiles of serum drug concentration after administration, on the safety, it was decided to investigate the occurrence of injection site reaction and other adverse drug reactions (ADRs) with an incidence of 1% or higher, including the time of onset, incidence, and seriousness.

The sample size of 300 patients was determined to detect ADRs with an incidence of 1% or higher at a probability of 95% or higher.

4.0 Surveillance Population

Patients with premenopausal breast cancer will be included in the surveillance. Patients should not meet the exclusion criterion listed below. Refer to the Precautions section of the package insert.

<Exclusion criteria>

Patients who meet the following criterion will not be included:

- A history of hypersensitivity to any of the ingredients of Leuplin PRO or synthetic luteinizing hormone-releasing hormone (LH-RH) or LH-RH derivatives
- Pregnant or potentially pregnant patients and breastfeeding patients.

5.0 Dosage and Administration

The usual adult dosage is 22.5 mg of leuprorelin acetate administered subcutaneously once every 24 weeks. Refer to the Precautions section of the package insert.

6.0 Planned Number of Medical Institutions by Department

Breast surgery and other departments Approximately 60 medical institutions

7.0 Methodology

7.1 Observation Period

24 weeks

7.2 Request to and Contract with the Study Site

This surveillance will be conducted using a Web-based electronic data capture system (CCI [redacted]). A representative of Takeda Pharmaceutical Company Limited (hereinafter referred to as Takeda's representative) will explain the objectives and contents of the surveillance, operation method of CCI [redacted], and handling of electronic signature, user ID, and password to the investigator based on "Request for cooperation for special drug use surveillance," "Implementation outline," "Entry screen image," and "Operation manual of CCI [redacted] (brief version)" to enter into a written contract with the study site and request the study site to conduct a surveillance within a specified period.

7.3 Method of Patient Registration

Patients will be registered using the central registration method via CCI [redacted]. After the start of the contract with the study site, the investigator shall register each patient treated with Leuplin PRO by entering patient registration information (refer to Section 9.1) with his/her electronic signature within 14 days after administration of Leuplin PRO (day of administration designated as day 0 and day following the day of administration designated as 1 day post-dose).

* The investigator's designee should belong to the relevant medical institution (including those under contract with the medical institution such as temporary clinical research coordinators). Before the investigator's designee begins to enter data into CCI [redacted], a physician responsible for the surveillance (one physician per medical institution or department

appointed at the time of contract) shall document the designation with the date of designation (no specific style), affix his/her signature or name and seal to the document, and submit it to Takeda's representative.

7.4 Entry into the (Electronic) Case Report Form and Electronic Signature

The investigator or designee* shall enter patient baseline characteristics and treatment given into CCI with the investigator's electronic signature within approximately 1 month after the end of required observation at 24 weeks after the start of Leuplin PRO treatment.

For any patient with an adverse event, the investigator or designee shall enter observation results into CCI with the investigator's electronic signature after monitoring the patient as long after discontinuation of treatment as possible until the adverse event is confirmed to have resolved or be resolving.

* The investigator's designee should belong to the relevant medical institution (including those under contract with the medical institution such as temporary clinical research coordinators). Before the investigator's designee begins to enter data into CCI a physician responsible for the surveillance (one physician per medical institution or department appointed at the time of contract) shall document the designation with the date of designation (no specific style), affix his/her signature or name and seal to the document, and submit it to Takeda's representative.

8.0 Planned Surveillance Period

Surveillance period: From March 2016 to 31 August 2017

Patient registration period: From April 2016 to 28 February 2017[Note)]

[Note)] Patient registration (entry into CCI) will not be accepted on 1 March 2018 onwards even if Leuplin PRO is administered by 28 February 2018.

If the number of patients enrolled in the surveillance reaches the planned sample size before 28 February 2018, acceptance of registration will be terminated before the end of the patient registration period. If the patient registration period is shortened, the surveillance period will be changed accordingly.

9.0 Surveillance Items

The investigator or designee shall enter the items listed below into CCI. The surveillance schedule is presented in Appendix.

9.1 Patient Registration

1) Surveillance items

Date of administration of Leuplin PRO, patient identification number, patient

initials, date of birth, assessment based on the exclusion criteria

2) Time points of surveillance

At patient registration

9.2 Patient Baseline Characteristics

1) Surveillance items

Time of diagnosis of premenopausal breast cancer, ECOG Performance Status*, disease status, site of lesions before the start of Leuplin PRO treatment, presence or absence of hormone receptor expression, diagnostic category (at the start of Leuplin PRO treatment), predisposition to hypersensitivity (presence or absence and details), concurrent illness (presence or absence and details), history of thromboembolism (presence or absence and details), height, body weight, treatment status of premenopausal breast cancer drug immediately before the start of Leuplin PRO treatment (presence or absence and name of the drug)

2) Time points of surveillance

At the start of Leuplin PRO treatment

* ECOG Performance Status

Score	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair

(Common Toxicity Criteria, Version 2.0 Published on April 30, 1999. Webpage of the JCOG at http://www.jcog.jp/)

9.3 Treatment Given

1) Surveillance items

Treatment status of Leuplin PRO (injection site* and full-treatment status of Leuplin PRO*), treatment status of premenopausal breast cancer drug other than Leuplin PRO (presence or absence and name of the drug), presence or absence of and reason for discontinuation of observation

2) Time points of surveillance

Period from the start of Leuplin PRO treatment to 24 weeks after the start of treatment (or discontinuation of observation)

* At the start of Leuplin PRO treatment

9.4 Assessments

1) Assessments

Pregnancy during the observation period (females only)

2) Outcome measure data collection timing

Period from the start of Leuplin PRO treatment to 24 weeks after the start of treatment (or discontinuation of observation)

9.5 Adverse Events (AEs)

1) Surveillance items

Presence or absence of injection site reaction, details of injection site reaction (specific symptom, date of onset, seriousness and reason for seriousness [refer to Table 2], cause of discontinuation of Leuplin PRO treatment, intervention (presence or absence and contents), date of outcome assessment, outcome, causal relationship to Leuplin PRO [refer to Table 3]).

Presence or absence of AE other than injection site reaction (refer to Table 1), AE term, date of onset, seriousness and reason for seriousness (refer to Table 2), cause of discontinuation of Leuplin PRO treatment, intervention (presence or absence and name of the drug/intervention), date of outcome assessment, outcome, causal relationship to Leuplin PRO* (refer to Table 3)

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

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

Note) Additional points to consider for AEs

Abnormal worsening of target disease, for instance, worsening beyond the expected natural course of the disease, will be handled as an AE.

2) Time points of surveillance

Period from the start of Leuplin PRO treatment to 24 weeks after the start of treatment (or discontinuation of observation)

Table 1 Definition of adverse events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.

The following are also handled as AEs:

- Symptoms and so forth that occur in infants breast-fed by their mothers under treatment with a drug
- Untoward symptoms and so forth that occur in children treated with a drug
- Symptoms and so forth that occur as a result of occupational exposure to a drug
- Symptoms and so forth that occur after administration of counterfeit medicines of our ethical drugs
- Untoward symptoms that have become known to occur in drug users through lawsuits or other legal actions

Table 2 Criteria for assessing seriousness

An AE satisfying any of the following is assessed as serious:

1. Results in death (death)
2. Is life-threatening (risk of death)
3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization)
4. Results in persistent or significant disability/incapacity (disability)
5. Leads to a congenital anomaly/birth defect (congenital anomaly)
6. Is an important medical event according to 1 to 5 described above, including AEs in Takeda Medically Significant AE List

<u>Takeda Medically Significant AE List</u>

- Acute respiratory failure / acute respiratory distress syndrome (ARDS)
- Anaphylactic shock
- Torsade de pointes / ventricular fibrillation / ventricular tachycardia
- Acute renal failure
- Malignant hypertension
- Pulmonary hypertension
- Convulsive seizures (including convulsions and epilepsy)
- Pulmonary fibrosis (including interstitial pneumonia)
- Agranulocytosis
- Malignant syndrome / malignant hyperthermia

- Aplastic anemia
- Spontaneous abortion / stillbirth and fetal death
- Toxic epidermal necrolysis / mucocutaneous ocular syndrome (Stevens-Johnson syndrome)
- Confirmed or suspected transmission of infectious agent by a medicinal product
- Hepatic necrosis
- Confirmed or suspected endotoxin shock
- Acute liver failure

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

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

10.0 Analysis Items and Methods

10.1 Statistical Analysis Plan

A statistical analysis plan will be prepared before finalization of data. The statistical analysis plan will include definitions of endpoints and detailed analysis methods.

10.2 Analysis Sets

The analysis set is patients included in safety evaluation.

10.3 Matters on Patient Composition

The number of enrolled patients, number of patients with the (electronic) CRF collected, number of patients included in safety evaluation, number of patients excluded from safety evaluation, and reason for exclusion will be tabulated.

10.4 Patient Baseline Characteristics

Patient baseline characteristics, including age, predisposition to hypersensitivity, and concurrent illness, will be tabulated.

10.5 Treatment Given

The treatment status of Leuplin PRO and treatment status of premenopausal breast cancer drug other than Leuplin PRO will be tabulated.

10.6 Matters on Safety

For patients included in safety evaluation, data will be tabulated as described below. AEs will be coded according to the MedDRA/J and summarized using preferred term (PT) and system organ class (SOC).

10.6.1 Occurrence of Adverse Events

For AEs reported during the observation period, the incidence will be tabulated by type, time of onset, seriousness, and causal relationship to Leuplin PRO. In addition, events listed as the safety specifications for the surveillance in "2. Summary of Pharmacovigilance Plan" in the risk management plan will be tabulated separately.

10.6.2 Factors that May Affect the Safety

For ADRs reported during the observation period, the incidence will be tabulated by patient background factors (e.g., disease status, presence or absence of concurrent renal impairment, presence or absence of concurrent hepatic impairment) and treatment status of Leuplin PRO.

11.0 Posting of Surveillance Information

Surveillance information will be posted on the following open website before starting the surveillance:

- Japan Pharmaceutical Information Center-Clinical Trials Information

12.0 Surveillance Organization

12.1 Administrative Manager

PPD

Takeda Pharmaceutical Company Limited

13.0 Contract Research Organizations (CROs)

PPD

PPD

14.0 Other Necessary Matters

14.1 Revision of the Protocol

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

14.2 Actions to be Taken for Problems and Questions

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

Appendix　Observation schedule

Surveillance item \ Time point of surveillance		Observation period		
		At patient registration	At the start of treatment	After 24 weeks or at discontinuation of observation
Patient registration	Date of administration of Leuplin PRO	○		
	Patient identification number	○		
	Patient initials	○		
	Date of birth	○		
	Assessment based on the exclusion criteria	○		
Patient baseline characteristics	Time of diagnosis of premenopausal breast cancer		○	
	ECOG Performance Status		○	
	Disease status		○	
	Diagnostic category		○	
	Site of lesions before the start of Leuplin PRO treatment		○	
	Presence or absence of hormone receptor expression		○	
	Predisposition to hypersensitivity		○	
	Concurrent illness		○	
	History of thromboembolism		○	
	Height, body weight		○	
	Treatment status of premenopausal breast cancer drug immediately before the start of Leuplin PRO treatment		○	
Treatment given	Treatment status of Leuplin PRO		← ○ →	
	Treatment status of premenopausal breast cancer drug other than Leuplin PRO		← ○ →	
Assess-ments	Pregnancy during the observation period (females only)		← ○ →	
Adverse event	Injection site reaction		← ○ →	
	Adverse event other than injection site reaction		← ○ →	

○　: Performed

←○→: Performed throughout the period

Special Drug Use Surveillance Protocol

Special Drug Use Surveillance of Leuplin PRO for Injection Kit 22.5 mg for "Premenopausal Breast Cancer"

Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol number	**Leuprorelin-5003**
Version number	**2nd version**
Date of preparation	**25 February 2016**

Table of Contents

1.0 Background of the Surveillance

Since the amount of leuprorelin acetate administered in a single dose of Leuplin PRO for Injection Kit 22.5 mg (hereinafter referred to as Leuplin PRO) is as high as twice that of Leuplin SR for Injection Kit 11.25 mg (hereinafter referred to as Leuplin SR), and the time profile of serum leuprorelin concentration after administration differs between the two formulations, a special drug use surveillance (hereinafter referred to as the surveillance) is planned to evaluate potential effects of the differences on the safety.

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

2.0 Objectives

To investigate the safety of Leuplin PRO in patients with premenopausal breast cancer in routine clinical settings in order to evaluate potential effects of differences between Leuplin PRO and Leuplin SR, including the higher amount administered in a single dose and differences in time profile of serum drug concentration after administration, on the safety

3.0 Planned Sample Size and Rationale

3.1 Planned Sample Size

300 patients

3.2 Rationale

To evaluate potential effects of differences between Leuplin PRO and Leuplin SR, that is, difference amounts of leuprorelin acetate administered in a single dose and different time profiles of serum drug concentration after administration, on the safety, it was decided to investigate the occurrence of injection site reaction and other adverse drug reactions (ADRs) with an incidence of 1% or higher, including the time of onset, incidence, and seriousness.

The sample size of 300 patients was determined to detect ADRs with an incidence of 1% or higher at a probability of 95% or higher.

4.0 Surveillance Population

Patients with premenopausal breast cancer will be included in the surveillance. Patients should not meet the exclusion criterion listed below. Refer to the Precautions section of the package insert.

<Exclusion criteria>

Patients who meet the following criterion will not be included:

- A history of hypersensitivity to any of the ingredients of Leuplin PRO or synthetic luteinizing hormone-releasing hormone (LH-RH) or LH-RH derivatives
- Pregnant or potentially pregnant patients and breastfeeding patients.

5.0 Dosage and Administration

The usual adult dosage is 22.5 mg of leuprorelin acetate administered subcutaneously once every 24 weeks. Refer to the Precautions section of the package insert.

6.0 Planned Number of Medical Institutions by Department

Breast surgery and other departments Approximately 60 medical institutions

7.0 Methodology

7.1 Observation Period

24 weeks

7.2 Request to and Contract with the Study Site

This surveillance will be conducted using a Web-based electronic data capture system (CCI [redacted]). A representative of Takeda Pharmaceutical Company Limited (hereinafter referred to as Takeda's representative) will explain the objectives and contents of the surveillance, operation method of CCI [redacted], and handling of electronic signature, user ID, and password to the investigator based on "Request for cooperation for special drug use surveillance," "Implementation outline," "Entry screen image," and "Operation manual of CCI [redacted] (brief version)" to enter into a written contract with the study site and request the study site to conduct a surveillance within a specified period.

7.3 Method of Patient Registration

Patients will be registered using the central registration method via CCI [redacted]. After the start of the contract with the study site, the investigator shall register each patient treated with Leuplin PRO by entering patient registration information (refer to Section 9.1) with his/her electronic signature within 14 days after administration of Leuplin PRO (day of administration designated as day 0 and day following the day of administration designated as 1 day post-dose).

* The investigator's designee should belong to the relevant medical institution (including those under contract with the medical institution such as temporary clinical research coordinators). Before the investigator's designee begins to enter data into CCI [redacted], a physician responsible for the surveillance (one physician per medical institution or department

appointed at the time of contract) shall document the designation with the date of designation (no specific style), affix his/her signature or name and seal to the document, and submit it to Takeda's representative.

7.4 Entry into the (Electronic) Case Report Form and Electronic Signature

The investigator or designee* shall enter patient baseline characteristics and treatment given into CCI with the investigator's electronic signature within approximately 1 month after the end of required observation at 24 weeks after the start of Leuplin PRO treatment.

For any patient with an adverse event, the investigator or designee shall enter observation results into CCI with the investigator's electronic signature after monitoring the patient as long after discontinuation of treatment as possible until the adverse event is confirmed to have resolved or be resolving.

8.0 Planned Surveillance Period

Surveillance period: From March 2016 to 31 August 2017

Patient registration period: From April 2016 to 28 February 2017[Note)]

[Note)] Patient registration (entry into CCI) will not be accepted on 1 March 2018 onwards even if Leuplin PRO is administered by 28 February 2018.

If the number of patients enrolled in the surveillance reaches the planned sample size before 28 February 2018, acceptance of registration will be terminated before the end of the patient registration period. If the patient registration period is shortened, the surveillance period will be changed accordingly.

9.0 Surveillance Items

The investigator or designee shall enter the items listed below into CCI. The surveillance schedule is presented in Appendix.

9.1 Patient Registration

1) Surveillance items

Date of administration of Leuplin PRO, patient identification number, patient initials, date of birth, assessment based on the exclusion criteria

2) Time points of surveillance

At patient registration

9.2 Patient Baseline Characteristics

1) Surveillance items

Time of diagnosis of premenopausal breast cancer, ECOG Performance Status*, disease status, site of lesions before the start of Leuplin PRO treatment, presence or absence of hormone receptor expression, diagnostic category

(at the start of Leuplin PRO treatment), predisposition to hypersensitivity (presence or absence and details), concurrent illness (presence or absence and details), history of thromboembolism (presence or absence and details), height, body weight, treatment status of premenopausal breast cancer drug immediately before the start of Leuplin PRO treatment (presence or absence and name of the drug)

2) Time points of surveillance

At the start of Leuplin PRO treatment

* ECOG Performance Status

Score	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair

(Common Toxicity Criteria, Version 2.0 Published on April 30, 1999. Webpage of the JCOG at http://www.jcog.jp/)

9.3 Treatment Given

1) Surveillance items

Treatment status of Leuplin PRO (injection site* and full-treatment status of Leuplin PRO*), treatment status of premenopausal breast cancer drug other than Leuplin PRO (presence or absence and name of the drug), presence or absence of and reason for discontinuation of observation

2) Time points of surveillance

Period from the start of Leuplin PRO treatment to 24 weeks after the start of treatment (or discontinuation of observation)

* At the start of Leuplin PRO treatment

9.4 Assessments

1) Assessments

Pregnancy during the observation period (females only)

2) Outcome measure data collection timing

Period from the start of Leuplin PRO treatment to 24 weeks after the start of treatment (or discontinuation of observation)

9.5 Adverse Events (AEs)

1) Surveillance items

Presence or absence of injection site reaction, details of injection site reaction (specific symptom, date of onset, seriousness and reason for seriousness [refer to Table 2], cause of discontinuation of Leuplin PRO treatment, intervention (presence or absence and contents), date of outcome assessment, outcome, causal relationship to Leuplin PRO [refer to Table 3]).

Presence or absence of AE other than injection site reaction (refer to Table 1), AE term, date of onset, seriousness and reason for seriousness (refer to Table

2), cause of discontinuation of Leuplin PRO treatment, intervention (presence or absence and name of the drug/intervention), date of outcome assessment, outcome, causal relationship to Leuplin PRO* (refer to Table 3)
Patients with “not resolved” or “unknown” outcome or “unevaluable” causal relationship should be followed up wherever possible.

* For the causal relationship to Leuplin PRO, the rationale for “not related” and the reason for “unevaluable” shall be collected.

Note) Additional points to consider for AEs

Abnormal worsening of target disease, for instance, worsening beyond the expected natural course of the disease, will be handled as an AE.

2) Time points of surveillance

Period from the start of Leuplin PRO treatment to 24 weeks after the start of treatment (or discontinuation of observation)

Table 1 Definition of adverse events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.

The following are also handled as AEs:

- Symptoms and so forth that occur in infants breast-fed by their mothers under treatment with a drug
- Untoward symptoms and so forth that occur in children treated with a drug
- Symptoms and so forth that occur as a result of occupational exposure to a drug
- Symptoms and so forth that occur after administration of counterfeit medicines of our ethical drugs
- Untoward symptoms that have become known to occur in drug users through lawsuits or other legal actions

Table 2 Criteria for assessing seriousness

An AE satisfying any of the following is assessed as serious:

1. Results in death (death)
2. Is life-threatening (risk of death)
3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization)
4. Results in persistent or significant disability/incapacity (disability)
5. Leads to a congenital anomaly/birth defect (congenital anomaly)
6. Is an important medical event according to 1 to 5 described above, including AEs in Takeda Medically Significant AE List

<u>Takeda Medically Significant AE List</u>

- Acute respiratory failure / acute respiratory distress syndrome (ARDS)
- Anaphylactic shock
- Torsade de pointes / ventricular fibrillation / ventricular tachycardia
- Acute renal failure
- Malignant hypertension
- Pulmonary hypertension
- Convulsive seizures (including convulsions and epilepsy)
- Pulmonary fibrosis (including interstitial pneumonia)
- Agranulocytosis
- Malignant syndrome / malignant hyperthermia

- Aplastic anemia
- Spontaneous abortion / stillbirth and fetal death
- Toxic epidermal necrolysis / mucocutaneous ocular syndrome (Stevens-Johnson syndrome)
- Confirmed or suspected transmission of infectious agent by a medicinal product
- Hepatic necrosis
- Confirmed or suspected endotoxin shock
- Acute liver failure

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

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

10.0 Analysis Items and Methods

10.1 Statistical Analysis Plan

A statistical analysis plan will be prepared before finalization of data. The statistical analysis plan will include definitions of endpoints and detailed analysis methods.

10.2 Analysis Sets

The analysis set is patients included in safety evaluation.

10.3 Matters on Patient Composition

The number of enrolled patients, number of patients with the (electronic) CRF collected, number of patients included in safety evaluation, number of patients excluded from safety evaluation, and reason for exclusion will be tabulated.

10.4 Patient Baseline Characteristics

Patient baseline characteristics, including age, predisposition to hypersensitivity, and concurrent illness, will be tabulated.

10.5 Treatment Given

The treatment status of Leuplin PRO and treatment status of premenopausal breast cancer drug other than Leuplin PRO will be tabulated.

10.6 Matters on Safety

For patients included in safety evaluation, data will be tabulated as described below. AEs will be coded according to the MedDRA/J and summarized using preferred term (PT) and system organ class (SOC).

10.6.1 Occurrence of Adverse Events

For AEs reported during the observation period, the incidence will be tabulated by type, time of onset, seriousness, and causal relationship to Leuplin PRO. In addition, events listed as the safety specifications for the surveillance in "2. Summary of Pharmacovigilance Plan" in the risk management plan will be tabulated separately.

10.6.2 Factors that May Affect the Safety

For ADRs reported during the observation period, the incidence will be tabulated by patient background factors (e.g., disease status, presence or absence of concurrent renal impairment, presence or absence of concurrent hepatic impairment) and treatment status of Leuplin PRO.

11.0 Posting of Surveillance Information

Surveillance information will be posted on the following open website before starting the surveillance:

- Japan Pharmaceutical Information Center-Clinical Trials Information

12.0 Surveillance Organization

12.1 Administrative Manager

PPD

Takeda Pharmaceutical Company Limited

13.0 Contract Research Organizations (CROs)

PPD

14.0 Other Necessary Matters

14.1 Revision of the Protocol

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

14.2 Actions to be Taken for Problems and Questions

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

Appendix　Observation schedule

Surveillance item \ Time point of surveillance		Observation period		
		At patient registration	At the start of treatment	After 24 weeks or at discontinuation of observation
Patient registration	Date of administration of Leuplin PRO	○		
	Patient identification number	○		
	Patient initials	○		
	Date of birth	○		
	Assessment based on the exclusion criteria	○		
Patient baseline characteristics	Time of diagnosis of premenopausal breast cancer		○	
	ECOG Performance Status		○	
	Disease status		○	
	Diagnostic category		○	
	Site of lesions before the start of Leuplin PRO treatment		○	
	Presence or absence of hormone receptor expression		○	
	Predisposition to hypersensitivity		○	
	Concurrent illness		○	
	History of thromboembolism		○	
	Height, body weight		○	
	Treatment status of premenopausal breast cancer drug immediately before the start of Leuplin PRO treatment		○	
Treatment given	Treatment status of Leuplin PRO		← ○ →	
	Treatment status of premenopausal breast cancer drug other than Leuplin PRO		← ○ →	
Assess-ments	Pregnancy during the observation period (females only)		← ○ →	
Adverse event	Injection site reaction		← ○ →	
	Adverse event other than injection site reaction		← ○ →	

○　: Performed

←○→: Performed throughout the period

Special Drug Use Surveillance Protocol

Special Drug Use Surveillance of Leuplin PRO for Injection Kit 22.5 mg for "Premenopausal Breast Cancer"

Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol number	**Leuprorelin-5003**
Version number	**1st version**
Date of preparation	**22 January 2016**

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1.0 Background of the Surveillance

Since the amount of leuprorelin acetate administered in a single dose of Leuplin PRO for Injection Kit 22.5 mg (hereinafter referred to as Leuplin PRO) is as high as twice that of Leuplin SR for Injection Kit 11.25 mg (hereinafter referred to as Leuplin SR), and the time profile of serum leuprorelin concentration after administration differs between the two formulations, a special drug use surveillance (hereinafter referred to as the surveillance) is planned to evaluate potential effects of the differences on the safety.

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

2.0 Objectives

To investigate the safety of Leuplin PRO in patients with premenopausal breast cancer in routine clinical settings in order to evaluate potential effects of differences between Leuplin PRO and Leuplin SR, including the higher amount administered in a single dose and differences in time profile of serum drug concentration after administration, on the safety

3.0 Planned Sample Size and Rationale

3.1 Planned Sample Size

300 patients

3.2 Rationale

To evaluate potential effects of differences between Leuplin PRO and Leuplin SR, that is, difference amounts of leuprorelin acetate administered in a single dose and different time profiles of serum drug concentration after administration, on the safety, it was decided to investigate the occurrence of injection site reaction and other adverse drug reactions (ADRs) with an incidence of 1% or higher, including the time of onset, incidence, and seriousness.

The sample size of 300 patients was determined to detect ADRs with an incidence of 1% or higher at a probability of 95% or higher.

4.0 Surveillance Population

Patients with premenopausal breast cancer will be included in the surveillance. Patients should not meet the exclusion criterion listed below. Refer to the Precautions section of the package insert.

<Exclusion criteria>

Patients who meet the following criterion will not be included:

- A history of hypersensitivity to any of the ingredients of Leuplin PRO or synthetic luteinizing hormone-releasing hormone (LH-RH) or LH-RH derivatives
- Pregnant or potentially pregnant patients and breastfeeding patients.

5.0 Dosage and Administration

The usual adult dosage is 22.5 mg of leuprorelin acetate administered subcutaneously once every 24 weeks. Refer to the Precautions section of the package insert.

6.0 Planned Number of Medical Institutions by Department

Breast surgery and other departments Approximately 60 medical institutions

7.0 Methodology

7.1 Observation Period

24 weeks

7.2 Request to and Contract with the Study Site

This surveillance will be conducted using a Web-based electronic data capture system ([redacted]). A representative of Takeda Pharmaceutical Company Limited (hereinafter referred to as Takeda's representative) will explain the objectives and contents of the surveillance, operation method of [redacted], and handling of electronic signature, user ID, and password to the investigator based on "Request for cooperation for special drug use surveillance," "Implementation outline," "Entry screen image," and "Operation manual of [redacted] (brief version)" to enter into a written contract with the study site and request the study site to conduct a surveillance within a specified period.

7.3 Method of Patient Registration

Patients will be registered using the central registration method via [redacted]. After the start of the contract with the study site, the investigator shall register each patient treated with Leuplin PRO by entering patient registration information (refer to Section 9.1) with his/her electronic signature within 14 days after administration of Leuplin PRO (day of administration designated as day 0 and day following the day of administration designated as 1 day post-dose).

7.4 Entry into the (Electronic) Case Report Form and Electronic Signature

The investigator or designee* shall enter patient baseline characteristics and treatment given into [redacted] with the investigator's electronic signature within approximately 1 month after the end of required observation at 24 weeks after the

start of Leuplin PRO treatment.

For any patient with an adverse event, the investigator or designee shall enter observation results into CCI with the investigator's electronic signature after monitoring the patient as long after discontinuation of treatment as possible until the adverse event is confirmed to have resolved or be resolving.

8.0 Planned Surveillance Period

Surveillance period: From March 2016 to 31 August 2017

Patient registration period: From April 2016 to 28 February 2017[Note)]

[Note)] Patient registration (entry into CCI) will not be accepted on 1 March 2018 onwards even if Leuplin PRO is administered by 28 February 2018.

If the number of patients enrolled in the surveillance reaches the planned sample size before 28 February 2018, acceptance of registration will be terminated before the end of the patient registration period. If the patient registration period is shortened, the surveillance period will be changed accordingly.

9.0 Surveillance Items

The investigator or designee shall enter the items listed below into CCI. The surveillance schedule is presented in Appendix.

9.1 Patient Registration

1) Surveillance items

Date of administration of Leuplin PRO, patient identification number, patient initials, date of birth, assessment based on the exclusion criteria

2) Time points of surveillance

At patient registration

9.2 Patient Baseline Characteristics

1) Surveillance items

Time of diagnosis of premenopausal breast cancer, ECOG Performance Status*, disease status, site of lesions before the start of Leuplin PRO treatment, presence or absence of hormone receptor expression, diagnostic category (at the start of Leuplin PRO treatment), predisposition to hypersensitivity (presence or absence and details), concurrent illness (presence or absence and details), history of thromboembolism (presence or absence and details), height, body weight, treatment status of premenopausal breast cancer drug immediately before the start of Leuplin PRO treatment (presence or absence and name of the drug)

2) Time points of surveillance

At the start of Leuplin PRO treatment

* ECOG Performance Status

Score	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair

(Common Toxicity Criteria, Version 2.0 Published on April 30, 1999. Webpage of the JCOG at http://www.jcog.jp/)

9.3 Treatment Given

1) Surveillance items

Treatment status of Leuplin PRO (injection site* and full-treatment status of Leuplin PRO*), treatment status of premenopausal breast cancer drug other than Leuplin PRO (presence or absence and name of the drug), presence or absence of and reason for discontinuation of observation

2) Time points of surveillance

Period from the start of Leuplin PRO treatment to 24 weeks after the start of treatment (or discontinuation of observation)

* At the start of Leuplin PRO treatment

9.4 Assessments

1) Assessments

Pregnancy during the observation period (females only)

2) Outcome measure data collection timing

Period from the start of Leuplin PRO treatment to 24 weeks after the start of treatment (or discontinuation of observation)

9.5 Adverse Events (AEs)

1) Surveillance items

Presence or absence of injection site reaction, details of injection site reaction (specific symptom, date of onset, seriousness and reason for seriousness [refer to Table 2], cause of discontinuation of Leuplin PRO treatment, intervention (presence or absence and contents), date of outcome assessment, outcome, causal relationship to Leuplin PRO [refer to Table 3]).

Presence or absence of AE other than injection site reaction (refer to Table 1), AE term, date of onset, seriousness and reason for seriousness (refer to Table 2), cause of discontinuation of Leuplin PRO treatment, intervention (presence or absence and name of the drug/intervention), date of outcome assessment, outcome, causal relationship to Leuplin PRO* (refer to Table 3)

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

* For the causal relationship to Leuplin PRO, the rationale for “not related” and the reason for “unevaluable” shall be collected.

Note) Additional points to consider for AEs

Abnormal worsening of target disease, for instance, worsening beyond the expected natural course of the disease, will be handled as an AE.

2) Time points of surveillance
Period from the start of Leuplin PRO treatment to 24 weeks after the start of treatment (or discontinuation of observation)

Table 1 Definition of adverse events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.

The following are also handled as AEs:

- Symptoms and so forth that occur in infants breast-fed by their mothers under treatment with a drug
- Untoward symptoms and so forth that occur in children treated with a drug
- Symptoms and so forth that occur as a result of occupational exposure to a drug
- Symptoms and so forth that occur after administration of counterfeit medicines of our ethical drugs
- Untoward symptoms that have become known to occur in drug users through lawsuits or other legal actions

Table 2 Criteria for assessing seriousness

An AE satisfying any of the following is assessed as serious:

1. Results in death (death)
2. Is life-threatening (risk of death)
3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization)
4. Results in persistent or significant disability/incapacity (disability)
5. Leads to a congenital anomaly/birth defect (congenital anomaly)
6. Is an important medical event according to 1 to 5 described above, including AEs in Takeda Medically Significant AE List

<u>Takeda Medically Significant AE List</u>

- Acute respiratory failure / acute respiratory distress syndrome (ARDS)
- Anaphylactic shock
- Torsade de pointes / ventricular fibrillation / ventricular tachycardia
- Acute renal failure
- Malignant hypertension
- Pulmonary hypertension
- Convulsive seizures (including convulsions and epilepsy)
- Pulmonary fibrosis (including interstitial pneumonia)
- Agranulocytosis
- Malignant syndrome / malignant hyperthermia

- Aplastic anemia
- Spontaneous abortion / stillbirth and fetal death
- Toxic epidermal necrolysis / mucocutaneous ocular syndrome (Stevens-Johnson syndrome)
- Confirmed or suspected transmission of infectious agent by a medicinal product
- Hepatic necrosis
- Confirmed or suspected endotoxin shock
- Acute liver failure

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

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

10.0 Analysis Items and Methods

10.1 Statistical Analysis Plan

A statistical analysis plan will be prepared before finalization of data. The statistical analysis plan will include definitions of endpoints and detailed analysis methods.

10.2 Analysis Sets

The analysis set is patients included in safety evaluation.

10.3 Matters on Patient Composition

The number of enrolled patients, number of patients with the (electronic) CRF collected, number of patients included in safety evaluation, number of patients excluded from safety evaluation, and reason for exclusion will be tabulated.

10.4 Patient Baseline Characteristics

Patient baseline characteristics, including age, predisposition to hypersensitivity, and concurrent illness, will be tabulated.

10.5 Treatment Given

The treatment status of Leuplin PRO and treatment status of premenopausal breast cancer drug other than Leuplin PRO will be tabulated.

10.6 Matters on Safety

For patients included in safety evaluation, data will be tabulated as described below. AEs will be coded according to the MedDRA/J and summarized using preferred term (PT) and system organ class (SOC).

10.6.1 Occurrence of Adverse Events

For AEs reported during the observation period, the incidence will be tabulated by type, time of onset, seriousness, and causal relationship to Leuplin PRO. In addition, events listed as the safety specifications for the surveillance in "2. Summary of Pharmacovigilance Plan" in the risk management plan will be tabulated separately.

10.6.2 Factors that May Affect the Safety

For ADRs reported during the observation period, the incidence will be tabulated by patient background factors (e.g., disease status, presence or absence of concurrent renal impairment, presence or absence of concurrent hepatic impairment) and treatment status of Leuplin PRO.

11.0 Posting of Surveillance Information

Surveillance information will be posted on the following open website before starting the surveillance:

- Japan Pharmaceutical Information Center-Clinical Trials Information

12.0 Surveillance Organization

12.1 Administrative Manager

PPD

Takeda Pharmaceutical Company Limited

13.0 Contract Research Organizations (CROs)

PPD

14.0 Other Necessary Matters

14.1 Revision of the Protocol

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

14.2 Actions to be Taken for Problems and Questions

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

Appendix　Observation schedule

Surveillance item \ Time point of surveillance		Observation period		
		At patient registration	At the start of treatment	After 24 weeks or at discontinuation of observation
Patient registration	Date of administration of Leuplin PRO	○		
	Patient identification number	○		
	Patient initials	○		
	Date of birth	○		
	Assessment based on the exclusion criteria	○		
Patient baseline characteristics	Time of diagnosis of premenopausal breast cancer		○	
	ECOG Performance Status		○	
	Disease status		○	
	Diagnostic category		○	
	Site of lesions before the start of Leuplin PRO treatment		○	
	Presence or absence of hormone receptor expression		○	
	Predisposition to hypersensitivity		○	
	Concurrent illness		○	
	History of thromboembolism		○	
	Height, body weight		○	
	Treatment status of premenopausal breast cancer drug immediately before the start of Leuplin PRO treatment		○	
Treatment given	Treatment status of Leuplin PRO		← ○ →	
	Treatment status of premenopausal breast cancer drug other than Leuplin PRO		← ○ →	
Assess-ments	Pregnancy during the observation period (females only)		← ○ →	
Adverse event	Injection site reaction		← ○ →	
	Adverse event other than injection site reaction		← ○ →	

○　: Performed

←○→: Performed throughout the period