Genotropin
Special Investigation
– SGA long-term follow-up investigation –

Protocol

SGA (small-for-gestational age) dwarfism

without epiphyseal closure

[redacted]

Pfizer Japan Inc.

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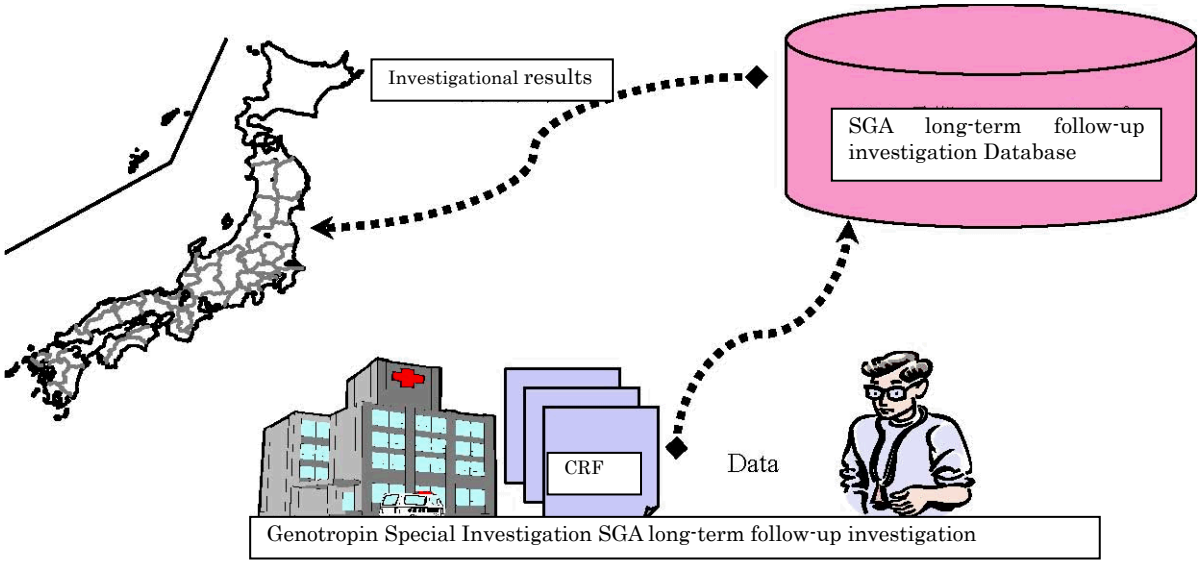
Ver.2

[redacted]

Summary

Genotropin Special Investigation - SGA long-term follow-up investigation - is a post-marketing database of children receiving Genotropin for the treatment of SGA (small-for-gestational age) dwarfism without epiphyseal closure. The outcome of this database is intended for public release at academic conferences and in scientific journals, and to contribute to the growth hormone treatment of patients with SGA dwarfism.



Ver.2

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Introduction

Genotropin Special Investigation - SGA long-term follow-up investigation - (hereinafter, this investigation) is an investigation intended to evaluate the long-term efficacy and safety of Genotropin in children with SGA dwarfism without epiphyseal closure. This investigation will be commenced upon consent of each relevant patient to receive a long-term Genotropin therapy.

The information collected in this investigation will be used to provide proper drug use and as part of safety information to be provided. Therefore, this investigation must be conducted with "Good Post-Marketing Study Practice" [Ministry of Health, Labour and Welfare (MHLW) Ordinance No. 171, December 20, 2004].

Data obtained from the patients enrolled in this investigation will be reported to regulatory authorities pursuant to the Pharmaceutical Affairs Law. Also, the data reported to regulatory authorities may be publicly posted in MHLW's "Pharmaceuticals and Medical Devices Safety Information" and "Pharmaceuticals and Medical Devices Information Website (http://www.info.pmda.go.jp)" as a listing of patients, which will present the names of drugs, adverse reactions, gender, age (increment of 10 years), and other relevant information. Furthermore, the data collected may also be disclosed if the MHLW is inquired to disclose such data in accordance with "Act on Access to Information Held by Administrative Organs" (Law No. 42 of May 14, 1999); provided that in no event will the names of investigators, hospitals and other personal information be made subject to such reporting, nor will it be posted or disclosed in any form or shape.

Meanwhile, the data collected from this investigation shall be anonymized, compiled, and used as evidence for mechanisms and causes of poor physical growth in children with SGA dwarfism without epiphyseal closure, as well as response of such children to growth hormone treatment, and to facilitate new findings and discovery concerning poor physical growth in children.

1. Objective

This investigation is intended to evaluate the long-term efficacy and safety of Genotropin in children with SGA dwarfism without epiphyseal closure. Responses of patients to Genotropin in relation to clinical conditions of patients, dose schedule, past history of growth hormone treatment, and other relevant factors will be investigated.

2. Study subjects

The indication for Genotropin in this investigation is as follows.

<Indication>

SGA (small-for-gestational age) dwarfism without epiphyseal closure

Subjects with the above disease who meet the following conditions will be enrolled in this investigation. In addition, the data in patients receiving Genotropin prior to the contract conclusion will also be included in this investigation.

[1] Patients receiving Genotropin and consenting in writing to take part in this investigation

[2] Newly enrolled patients who meet the following enrollment criteria

[3] Patients who have already been enrolled in "Genotropin Special Investigation - Investigation of Genotropin long-term use in patients with SGA dwarfism without epiphyseal closure."

<Enrollment criteria>

Patients who meet all of the following criteria

1) Patients whose height and weight at birth are both below the 10th percentile for patients of the same gestational age, and at the same time, either body weight or height is less than -2 SD compared to patients of the same gestational age. Neonates whose body height at birth were immeasurable and thus were not measured will be evaluated with birth weight.

2) Eligibility for the treatment

[1] Patients must be not younger than 3 years.

[2] The current body height must be less than -2.5 SD of the standard height.

[3] A pre-treatment height velocity within 1 year prior to the commencement of treatment must be less than 0 SD.

3) Patients whose poor physical growth after birth is attributable to disease other than intrauterine growth retardation cannot be enrolled in this investigation. Also patients who are currently receiving treatment that is known to cause poor physical growth cannot take part in this investigation.

3. Target sample size

The target number of subjects from which data will be collected is 400.

4. Duration of investigation

The duration will be from April 2013 to March 2016 (3 years); provided that it may be extended depending on the progress of the investigation.

The investigation will be continued as long as the subject is receiving Genotropin, or as determined appropriate by the investigator.

5. Investigation procedures

5.1. Investigation method

This is a multicenter open-label investigation to which subjects are enrolled with a central registration method.

5.2. Data collection method

In this investigation, data will be collected with case report/verification forms provided by Pfizer Japan, Inc. (hereinafter, "Sponsor"). Upon completion of the assessment period and height follow-up period, each investigator shall promptly complete the report/verification forms, and submit them to Sponsor.

5.3. Patient registration

Newly enrolled patients and ongoing patients*[1] will be included in this investigation. Before the commencement of investigation in each patient, the investigator shall obtain an informed consent of the patient or his/her parent (or a legally acceptable representative) in writing to take part in this investigation. If the subject meets all the enrollment criteria, the investigator shall complete the enrollment form with the name of sites, department, and attending doctor, ID number, patient's initials (not essential), gender, date of birth, and the status of informed consent.

5.3.1. Enrollment of new subjects

For the enrollment of a new subject, the investigator will, in addition to above information, complete an "Enrollment Form for New Subject" provided by Sponsor, in which, the date Genotropin therapy was commenced, the date the initial growth hormone therapy was commenced, and the eligibility to take part in this investigation should be recorded, and submitted to Sponsor. Subjects who have commenced on Genotropin therapy prior to the contract conclusion should be enrolled in this investigation promptly upon the contract conclusion.

5.3.2. Enrollment of ongoing patients*[1]

"Enrollment Form for Ongoing Subject" should be completed and submitted to Sponsor for all patients who are transferring from "Genotropin Special Investigation - Investigation of Genotropin long-term use in patients with SGA dwarfism without epiphyseal closure."

*[1]: Ongoing subjects are defined as patients in whom data was collected in "Genotropin Special Investigation - Investigation of Genotropin long-term use in patients with SGA dwarfism without epiphyseal closure."

5.3.3 Data to be provided to the Foundation for Growth Science in Japan

Investigator may provide the data recorded in the report forms to the Foundation for Growth Science in Japan; provided that the investigator is required to obtain consent of the patient or his/her parent (or a legally acceptable representative) for sharing such data with the foundation, and checkmark the relevant section concerning such consent in the enrollment form, and submit it to Sponsor.

5.4. Assessment period

5.4.1. Assessment period for newly-enrolled subjects

The fiscal assessment period of the year in which subject is enrolled will be defined as a period starting with the commencement of Genotropin therapy (which may be tracked back) and ending with the fiscal end. The fiscal assessment period of each subsequent year will be defined as the corresponding annual fiscal period.

5.4.2. Assessment period for ongoing subjects

For patients transferring from "Genotropin Special Investigation - Investigation of Genotropin long-term use in patients with SGA dwarfism without epiphyseal closure," the initial fiscal assessment period will be defined as a period starting on the day following the final assessment of data recorded in the last booklet for "Genotropin Special Investigation - Investigation of Genotropin long-term use in patients with SGA dwarfism without epiphyseal closure" and ending with the fiscal end of the applicable year. The fiscal assessment period of each subsequent year will be defined as the corresponding annual fiscal period.

5.4.3 Height follow-up period

Patients completing or discontinuing Genotropin therapy will be followed up to document body heights from the completion or discontinuation of Genotropin therapy to the completion of investigation or until reaching adult height (final assessment). The follow-up period for each booklet will correspond to each fiscal year.

Note: "The date of final assessment" in each booklet of case report will be the date of final assessment in the corresponding fiscal year.

Note: The completion of treatment is defined as the completion of Genotropin therapy for the therapeutic objective initially intended at the commencement of treatment being judged as cured etc.

5.5. Types of report/verification forms

Booklet-type report forms will be used for this investigation.

Report/verification forms to be used in this investigation include "Report Forms for Newly-enrolled Subjects (Booklet 01)," "Follow-up Report Form (Booklet 02 and thereafter)," and "Height Follow-up Form."

5.5.1. Report Forms for Newly-enrolled Subjects (Booklet 01)

"Report Forms for Newly-enrolled Subjects (Booklet 01)" will be used for collecting the data during the assessment year in which the subject is enrolled.

5.5.2. Follow-up Report Form (Booklet 02 and thereafter)

"Follow-up Report Form (Booklet 02 and thereafter)" will be used for collecting the data during the fiscal year following the assessment year in which the subject is enrolled, and each subsequent year thereafter; provided that "Follow-up Report Form (Booklet 02 and thereafter)" will be used from the year of enrollment for patients transferring from "Genotropin Special Investigation - Investigation of Genotropin long-term use in patients with SGA dwarfism without epiphyseal closure."

5.5.3. Height Follow-up Form

"Height Follow-up Form" will be used to collect data concerning body height in patients completing or discontinuing Genotropin therapy, and meeting the following criteria.

- Patients not switching to other drug product
- Patients not reaching adult height (final height)

5.6. Notes concerning completion, correction, and reviewing of report/verification forms

(1) Completion procedures

Investigator will, upon confirming the survey items, complete the report/verification forms with data based on medical record including laboratory data; a pen, ballpoint pen, or other inerasable means should be used to complete the forms. The data after the completion of Genotropin therapy may be collected through telephone or other verbal means.

(2) Data correction

Any corrections on the report to be made by the investigator will be struck out with a double line so that the original description can be legible, and put on a "correction seal". Upon receiving Sponsor's inquiry on the content of report form, the investigator will review the medical record described earlier, and as required, correct relevant sections and resubmit the forms.

(3) Data verification

Upon completion of all entries and corrections in the report/verification forms, the investigator will once again review the information on the forms and associated query forms, and sign or seal/name the relevant sections on the forms.

(4) Submission of report forms

Investigators must prepare a report/verification form and submit it to Sponsor promptly upon the completion of the assessment period and height follow-up period.

6. Assessment variables and time points

Investigator will conduct this investigation in accordance with the following assessment schedule. After the contract is concluded, the investigator shall enroll patients who meet the eligibility criteria, and complete the report/verification form upon confirming the baseline patient characteristics and other relevant data. The data will be collected from the birth of the subject to the completion of investigation (which will be determined by the subject, his/her parent [or a legally acceptable representative], or the attending doctor).

[Assessment schedule]

		Enrollment Form for New Subject	Newly-enrolled subjects Report forms (Booklet 01)	Enrollment Form for Ongoing Subject	Report forms (Booklet 02) Follow up	Height Follow-up Form*
Assessment variables and time points		Enrollment	Assessment period From commencement of treatment to the fiscal end of the enrollment year	Enrollment	Assessment period Until the end of the fiscal year**	Height follow-up period From completion/discontinuation of treatment to each fiscal end
Patient identification	Identification number	●	●(Copy)	●	●	●
	Patient's initials (not essential)	●	●(Copy)	●	●	●
	Gender	●	●(Copy)	●	●	●
	Date of birth	●	●(Copy)	●	●	●
	Informed consent	●	●(Copy)	●		
	The date Genotropin therapy is commenced	●	●(Copy)	●		
	The date the initial growth hormone therapy was commenced	●	●(Copy)	●		
	Enrollment eligibility	●	●(Copy)			
Patient characteristics and family history	Height of parents		●			
	Mother's birth history		●			
	Presence/absence of family history of GHD		●			
	Twin/multiplets		●			
	Childbirth procedures		●			
	Fetus week number		●			
	Apgar score		●			
	Birth height		●			
	Birth weight		●			
	Birth head circumference		●			
	Body height at 1 year prior to the commencement of treatment		●			
	GH tolerance test		●			
	Clinical history		●			
	Past treatment history		●			
	Pregnancy status (Only for women)		●		●	
Dose record of Genotropin			●		●	
Concomitant therapy			●		●	
Examinations/tests			●		●	●***
Patient's profile			●		●	
Adverse events			●		●	

●: Variables to be recorded

*: The data after the completion of Genotropin therapy may be collected through telephone or other verbal means.

**: For the initial fiscal assessment period of patients transferring from "Genotropin Special Investigation - Investigation of Genotropin long-term use in patients with SGA (small-for-gestational age) dwarfism without epiphyseal closure," a "Follow-up Report Form (Booklet 02 and thereafter)" will be completed with data collected during a period starting on the day following the final assessment of data recorded in the last booklet of the previous investigation and ending with the fiscal end of the applicable year.

***: Height, weight, pubescence, and bone age

6.1. Patient identification

The following information should be recorded in the enrollment, report, and verification forms:

[1] Identification number

[2] Patient's initials (not essential)

[3] Gender

[4] Date of birth

[5] Informed consent

[6] The date Genotropin therapy is commenced

[7] The date the initial growth hormone therapy was commenced

[8] Enrollment eligibility

6.2. Family history and patient characteristics

(1) The following information obtained at the commencement of Genotropin therapy will be recorded:

[1] Height of parents (to the first decimal place)

[2] Mother's birth history (the first childbirth / multipara)

[3] Presence/absence of GHD family history

[4] Twin/multiplets

[5] Childbirth procedures

[6] Fetus week number

[7] Apgar score

[8] Birth height (to the first decimal place)

[9] Birth weight (to the first decimal place)

[10] Birth head circumference (to the first decimal place)

[11] Body height at 1 year prior to the commencement of treatment (to the first decimal place), and the date of measurement

[12] GH tolerance test

[13] Clinical history (past history and concurrent disease)

- Silver-Russell syndrome
- Name(s) of disease/syndrome
- Past or current regarding the following clinical history

  Chronic disease (including allergy), disease requiring medical treatment, disease/disorder accompanied by surgery, hospitalization, and/or subsequent complications, or any other

disease/syndrome determined problematic; of which, those occurred prior to the commencement of Genotropin therapy will be considered as "Past history", and those concurrent at the commencement of Genotropin therapy will be considered as "Concurrent disease".

[14] Prior medications

Presence/absence of growth hormone therapy intended for the treatment of SGA (small-for-gestational age) dwarfism without epiphyseal closure used until the day before the commencement of Genotropin therapy

(2) The following status will be recorded until the completion of assessment period for each booklet:

[1] Presence/absence of pregnancy, and the actual or expected date of birth [women only]

[2] Verification of revisits since the commencement of treatment (this checkmark is not required if not applicable)

6.3 Dose record of Genotropin

The following information concerning dose record of Genotropin will be recorded until the completion of assessment period for each booklet:

[1] Weekly dosage

[2] Dose frequency per week

[3] Preparation/dosage form

[4] Duration of treatment

[5] Reason for change

6.4 Concomitant therapies

(1) Concomitant medications

The following information concerning all concomitant medications used will be recorded until the completion of assessment period for each booklet. Information concerning drugs temporally associated with adverse events should also be collected, including all drugs used in such patients between the commencement of Genotropin therapy and the onset of each such adverse event, as well as drugs used for the treatment of the adverse event.

[1] Name of drug (brand name)

[2] Route of administration

[3] Duration of treatment

[4] Reason for treatment

(2) Non-drug therapy

The following information concerning non-drug concomitant therapies used will be recorded until the

completion of assessment period for each booklet. Information concerning non-drug therapies temporally associated with adverse events should also be collected, including all non-drug therapies used in such patients between the commencement of Genotropin therapy and the onset of each such adverse event, as well as non-drug therapies used for the treatment of the adverse event.

[1] Name of therapy

[2] Duration of treatment

[3] Reason for treatment

6.5. Examinations/tests (clinical laboratory/clinical course)

Results of the following parameters tested will be recorded until the completion of assessment period for each booklet; provided that Booklet 01 should include the results prior to the commencement of Genotropin therapy. Of the results of examinations and tests performed prior to the commencement of Genotropin therapy, those within 1 month prior to the commencement of Genotropin therapy should be recorded (including the date the Genotropin therapy is commenced).

[1] Carbohydrate metabolism related tests (fasting or continuous glucose, HbA1c), serum lipid concentration (total cholesterol, triglyceride), thyroid function related tests (TSH, free T4), and IGF-I

[2] Height (to the first decimal place), weight (to the first decimal place), and head circumference (to the first decimal place)

[3] Pubescence

[4] Bone age

[5] Body composition

6.6 Patient's profile

Eligibility for further treatment with Genotropin will be evaluated at the completion of assessment period for each booklet. If further treatment with Genotropin is not indicated, a major reason for treatment discontinuation should be selected from among the following options. If "Adverse event", "Laboratory abnormal", or "Death" is selected, relevant data should also be recorded in the adverse event section.

[1] Reaching adult height (final height)

[2] Reaching the standard height

[3] Epiphyseal closure

[4] Growth rate

[5] Preference of patient/parent(s)

[6] Non-compliance

[7] Discontinuance of public funding

[8] Change in diagnosis

[9] Poor clinical response

[10] Adverse event

[11] Laboratory abnormal

[12] Death

[13] Lost to follow-up (specify "Names of center/department" if the reason for lost to follow-up is transfer to other hospital/department)

[14] Others (the reason should be specified if "Others" is selected)

Treatment strategy as well as presence of other medication which has been switched to after discontinuation of Genotropin therapy should also be described for subjects completing or discontinuing Genotropin therapy.

6.7. Adverse events

Pertinent to safety assessment, the status of adverse events after the commencement of Genotropin therapy should be verified and the following information should be recorded. Adverse events should be verified in principle until the assessment period for each booklet is completed. Upon occurrence of any adverse event, the investigator shall provide appropriate intervention, promptly report to Sponsor in accordance with "Adverse event reporting" (Attachment 1), and follow up on the progress and outcome in principle until the symptoms disappear. Also, the investigator shall quickly notify Sponsor, "if a patient or the patient's partner conceives, or it has been found out that a patient or the patient's partner has conceived, whether adverse event has occurred or not," "if a serious adverse event occurred," and if any follow-up information thereto related has been obtained. Refer to "Adverse event reporting" (Attachment 1) for the details of procedures.

Furthermore, any occurrence of intrauterine exposure, or a serious adverse drug reaction or an adverse reaction not described in the package insert should be separately investigated as determined necessary by Sponsor.

[1] Presence/absence of adverse event

[2] Name of adverse event

[3] Date of onset

[4] Intervention

[5] Seriousness

[6] Outcome

[7] Causal relation with Genotropin

[The following variables should be recorded if the adverse event is associated with abnormal test results, e.g., clinical laboratory]

[8] Laboratory parameter

[9] Site reference

[10] Unit

[11] Date of measurement

[12] Result

Note: An adverse event is any untoward medical occurrence in a subject following Genotropin dose (including clinically significant change in laboratory test results); the event needs not necessarily to have a causal relationship with the treatment. A serious adverse event is any untoward medical occurrence that; Results in death; Is life-threatening (immediate risk of death), Requires inpatient hospitalization or prolongation of existing hospitalization; Results in persistent or significant disability/incapacity; Results in congenital anomaly/birth defect; or otherwise may result in medically important event or disorder.

6.8. Height follow-up after completion or discontinuation of Genotropin therapy

"Height Follow-up Form" will be used to collect data concerning body height in patients completing or discontinuing Genotropin therapy, and meeting the following criteria.

・Patients not switching to other drug product

・Patients not reaching adult height (final height)

[1] Date on which height follow-up is completed

[2] Height (to the first decimal place), and weight (to the first decimal place)

[3] Bone age

[4] Pubescence

[5] Future treatment strategy

Note: Any occurrence of adverse event during the height follow-up period should be separately investigated in details as determined necessary by Sponsor.

7. Analysis plan

Statistical analysis on safety and efficacy shall be performed; the results of which shall be posted in scientific journal, and reported at academic conferences and through research activities. In no event shall the investigator inquire Sponsor to perform statistical analysis for this investigation without confirming with Japan Genotropin Advisory Board in advance.

8. Discontinuation

8.1 Discontinuation of investigation

This investigation may be discontinued any time upon decision of the Investigator, or preference of the patient or the

patient's parent (or legally acceptable representative).

8.2 Discontinuation of treatment

Upon discontinuing Genotropin therapy, the Investigator shall record the reason for such discontinuation in the designated section of case report forms. The assessment at the termination (or discontinuation) of GH therapy should be appropriately performed.

9. Reporting and sharing of Investigation outcome

9.1 Reporting of Investigation outcome

Investigator and Sponsor hereby agree that the data obtained by Sponsor from this investigation shall be provided to regulatory authorities upon their request.

9.2 Sharing of Investigation outcome

(1) Patient feedback report

As a reference for the treatment strategy of each patient taking part in this investigation, Sponsor shall provide Investigator with a feedback report for each patient at every time case report forms are retrieved. Patient feedback report presents auxanologic data, bone age, adolescent development, hormone replacement, target and anticipated height, and other relevant information calculated based on data reported through case report forms, which are laid out in tables and figures.

(2) Public release (scientific journal, academic conference, and presentation, etc.)

Of the research results based on this investigation, the information publicly released by Sponsor shall be provided to each Investigator. Such public release includes but not limited to academic paper.

An Investigator may release his/her own academic report based on the data he/she contributed to this investigation or using the database; provided that the Investigator shall submit a copy or abstract of the report to Sponsor and obtain prior approval of Sponsor.

(3) Queries concerning database for this Investigation

The data compiled in the database for this investigation may be shared by Investigator in a Q&A format. Upon receiving an Investigator's question concerning treatment and diagnosis pertinent to the database for this investigation, Sponsor shall respond to the Investigator within approximately 1 month. The response to the question may be used by the Investigator as a reference to support day-to-day treatment and therapeutic plan for patients.

10. Ethical requirements

10.1 Declaration of Helsinki

This investigation shall be conducted in compliance with Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects; including the amendment thereto) which was adopted by the 18th General Assembly of the World Medical Association (Helsinki, Finland) in 1964.

10.2 Approval of institutional review board

Where the approval of institutional review board*[2] is required for conducting this investigation, the Investigator, prior to the commencement of this investigation, shall obtain a written document signed and dated by the institutional review board for approving this investigation including the patient information and consent form.

*[2] Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

10.3 Data protection and patient's informed consent

Data concerning patients shall be handled with registration numbers and site ID. Investigator shall retain the patient identification log as required; provided that in no event shall Investigator disclose such information to any other person.

Before enrolling a patient to this investigation, the Investigator shall explain to the patient or his/her parent (or legally acceptable representative), verbally or in writing, the objective, contents, and that the patient or his/her parent (or legally acceptable representative) may discontinue this investigation any time they wish, and then shall obtain a written consent to take part in this study. Furthermore, a copy of such consent form shall be provide to the patient prior to enrollment, and the original consent form with signature shall be retained by the Investigator.

11. Others

11.1 Investigator and Japan Genotropin Advisory Board

(1) Investigator

Before taking part in this investigation, the Investigator shall review the protocol, enrollment form, and case report forms for this investigation, and shall be given Sponsor's adequate explanation on the objective and procedures of the investigation. Data collected for this investigation must be recorded in the case report forms by the Investigator.

(2) Japan Genotropin Advisory Board

Operation, organization, and management of this investigation shall be the responsibilities of Sponsor. Japan Genotropin Advisory Board is an organization comprising medical expertise selected by Sponsor, and its function is to provide its assessment and advice to Sponsor on the handling of data compiled for this investigation as well as the release of information contained in the database for academic papers, publications, and at academic conferences.

12. Amendment of this Protocol

Any change or amendment of procedures contained in this Protocol shall be reported to the institutional review board as required and/or in accordance with the on-site rules.

13. Contact for questions concerning this Investigation

PPD

Post-marketing Surveillance Division, Development Japan, Pfizer Japan Inc.

Email address: PPD

14. Reference materials

Attachment: Adverse event reporting