For re-examination

Protocol No. 202029

Zagallo® Capsules
Drug Use Investigation

Implementation Plan

GlaxoSmithKline K.K.

Prepared on November 10, 2015 (Version 2.0)

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1. Purpose of investigation

This investigation is implemented to collect and evaluate the information on safety and effectiveness of Zagallo ® Capsules (hereinafter referred to as “Zagallo”) in male patients with androgenetic alopecia in daily clinical practice.

2. Safety specifications

In this investigation, the following items are handled as the safety investigation items.

- Sexual dysfunction (altered libido, impotence, ejaculation disorder) including its persistency
- Breast tenderness and enlargement
- Depressed mood
- Hepatic function disorder and jaundice

In this connection, the following item is the event of particular concern in the age group of androgenetic alopecia male patients, and this is set as the priority investigation matters, for which the information on incidence, seriousness and outcome will be collected to analyze the risk factors, etc.

- Sexual dysfunction (altered libido, impotence, ejaculation disorder) including its persistency

3. Patients targeted in investigation

The target patients are male patients with androgenetic alopecia using Zagallo for the first time for hair growth, hair restoration and prevention of hair loss indicated for Zagallo.

4. Planned number of patients to be investigated and rationale therefor

1) Target number of patients: 4,000 (3,000 as the number of patients to be included in the safety analysis set)

2) Rationale for setting:

In Study ARI114263 including 200 Japanese patients (557 patients were administered Zagallo), the incidence of an adverse reaction noted in 1 patient was 0.17%. Since about 3,000 patients are necessary to detect an adverse reaction appearing with an incidence of at least 0.1% in 1 patient with a probability of 95%, the target number of patients to be registered has been set at 4,000 in consideration of discontinuations and dropouts.

On assuming that the incidence of sexual function abnormality caused by Zagallo is 10% and the threshold incidence value of sexual function abnormality is 10% making

reference to Study ARI114263 including 200 Japanese patients, in a case where the true risk is not less than 1.2 times the threshold value, it is necessary to include 2,554 patients in the safety analysis set to confirm the incidence in the post-marketing surveillance with assuring the estimation precision so that the difference from the threshold value10% can be detected with a power of test being not less than 90%. It is therefore considered possible to implement the drug use investigation with 4,000 patients.

5. Number of medical institutions participating in investigation (by department)

About 800 medical institutions (mainly department of dermatology)

6. Investigation period

Investigation period: May 2016 to January 2019

Observation period: The observation period in each patient will be one year from the start of treatment with Zagallo.

Planned registration period: May 2016 to October 2017

But, when the planned number of patients to be registered is reached, registration may be finished even before the end of the above registration period.

7. Investigation methods

In this investigation, patient registration and data collection will be performed using the electronic data capture (hereinafter abbreviated into “EDC”) system.

1) Request and contract for investigation

(1) The medical representative (hereinafter abbreviated into “MR”) shall explain the purpose of this investigation, target patients, investigation items, investigation methods, etc. to the physician to be in charge of investigation at the medical institution where Zagallo is adopted and delivered and shall request the physician to cooperate to this investigation.

(2) When cooperation to this investigation is obtained, written contract shall be finalized with the head of the medical institution before the start of investigation.

2) Registration of patients to be investigated

This investigation shall be implemented by the central registration system.

(1) After the contract is finalized, the physician in charge of investigation shall input the patient information etc. of the patients described in “3. Patients targeted in investigation” to whom Zagallo is prescribed into the EDC system for registration within 14 days after the start of prescription (the day of starting prescription of

Zagallo is counted as Day 1).

(2) When the number of registered patients reaches the contracted number, the registration into this investigation shall be finished.

3) Data collection and inputting into EDC system

(1) The physician in charge of investigation shall check the investigation items such as backgrounds of registered patients.

(2) During the observation period, the physician in charge of investigation shall check the information on safety and effectiveness. When the patient does not visit the medical institution during the observation period, the information on adverse events, etc. shall be checked as far as possible by telephone, etc.

(3) At the end of observation period of each registered patient (or at the time of termination or discontinuation of Zagallo treatment), the physician in charge of investigation shall input the obtained information into the EDC system for transmission. input the obtained information into the EDC system for transmission.

4) Regarding patients who experience sexual dysfunction (altered libido, impotence, ejaculation disorder) and thereafter terminate or discontinue Zagallo treatment during the observation period, the outcome, etc. after termination or discontinuation will be monitered(until recovery or possibly 6 months if they do not recover) regardless of the reason for termination or discontinuation. If patients do not visit the hospital/clinic, the investigator will monitor the information about AEs and others by telephone, etc. as far as possible.

8. Investigation items

The physician in charge of investigation shall collect information on the following items as far as possible and input the information into the EDC system.

1) Information on medical institution

Name of medical institution, name of department, name of physician in charge of investigation

2) Patient backgrounds (at the start of Zagallo treatment)

ID No., gender, age or birth year, date of starting Zagallo prescription, reason for using Zagallo, Norwood-Hamilton classification (see p. 6), presence/absence of complication (renal dysfunction, hepatic dysfunction, other) and disease name

ID No.: The specific No. assigned to each patient by the physician in charge of investigation to protect confidential personal information

Complication: The disease or symptom other than androgenetic alopecia existing before the start of Zagallo treatment is handled as “complication” in this

investigation.

3) Pretreatment medications used against androgenetic alopecia (drug used within 3 months before the start of Zagallo treatment)

Presence/absence of pretreatment medications used against androgenetic alopecia within 3 months before the start of Zagallo treatment, name of drug, use period, status at the start of Zagallo treatment and reason of discontinuation if a patient has discontinued from the administration before it started

4) Zagallo treatment status

Single dose and dose unit (mg/day), daily doze frequency (times/day), date of starting treatment, date of finishing treatment, reason for dosage regimen change

5) Concomitant drug

Presence/absence of concomitant drug used during the observation period, name of drug, reason for use

6) Global assessment of effectiveness

At one year after the start of Zagallo treatment or at the time of termination or discontinuation of treatment, the effectiveness shall be evaluated comprehensively from the changes in hair amount, hair thickness and hair loss amount and the change in Norwood-Hamilton classification from the start of Zagallo treatment to the end of observation period on the 7-grade scale of “Marked increase”, “Moderate increase”, “Mild increase”, “No change”, “Mild decrease”, “Moderate decrease” and “Marked decrease”. “No change” means the state in which hair loss is less-advanced. In a case where judgment cannot be made for some reason, the patient concerned shall be handled as “Indeterminate”, and the reason for such handling shall be inputted into the EDC system.

7) Zagallo treatment status at the end of observation period

The date when physician confirmed the treatment status if a patient has continued his/her administration, and the reason if a patient has terminataed /discontinued administration, will be inputted into the EDC system.

8) Adverse events

Presence/absence of adverse event after the start of Zagallo treatment, diagnosis name or symptom name, date of onset, outcome, date of outcome, seriousness, reason for judging as serious, causal relationship with Zagallo, factors other than Zagallo suspected to be relevant, measure taken against adverse event

(1) In this investigation, the following item shall be handled as the priority investigation matters.

- Sexual dysfunction (altered libido, impotence, ejaculation disorder) including its

persistency

(2) In order to grasp the priority investigation matters and adverse reaction, the physician in charge of investigation shall input all adverse events (disease, symptom, abnormal laboratory test value, etc.) noted after the start of Zagallo treatment into the EDC system irrespective of the causal relationship with Zagallo. The causal relationship with Zagallo shall be judged on the 2-grade scale of “Presence” and “Absence” of possible rational relationship, etc., and shall be inputted into the EDC system.

(3) The adverse event for which the causal relationship with Zagallo is judged as “Presence” shall be handled as a suspected “adverse reaction” to Zagallo.

9) Monitoring of sexual dysfunction (altered libido, impotence, ejaculation disorder)

Regarding patients who experience sexual dysfunction (altered libido, impotence, ejaculation disorder) and thereafter terminate or discontinue Zagallo treatment during the observation period, the outcome, outcome date (until recovery or possibly 6 months if they do not recover), presence/absence of readministration of Zagallo up to that point, presence/absence of therapeutically equivalent drugs and presence/absence of treatment intended for sexual dysfunction (altered libido, impotence, ejaculation disorder) will be inputted into the EDC system regardless of the reason for termination or discontinuation.

9. Analysis items and analysis methods

1) Analysis items

(1) Items related to patient structure

[1] Number of registered patients and number of patients from whom case report forms are retrieved

[2] Number of patients included in and excluded from safety and effectiveness analysis sets, and reason for exclusion

(2) Safety-related items

[1] Adverse reaction appearance status (type, severity and incidence of adverse reaction)

[2] Factors considered influential on safety (adverse reaction appearance status by patient background, odds ratio estimation by logistic regression, etc.)

[3] Appearance status of the event which is set as the priority investigation matters

(3) Effectiveness-related items

[1] Response rate based on the global assessment of effectiveness

The cases evaluated as “Marked increase”, “Moderate increase” and “Mild increase” are

defined as the effective cases, and the rate of effective cases is defined as the response rate.

[2] Factors considered influential on effectiveness (response rate by patient background, odds ratio estimation by logistic regression, etc.)

2) Analysis methods

Concerning the safety and effectiveness-related items, odds ratio and 95% confidence interval thereof shall be calculated for the factors considered influential. As necessary, forest plot figures, etc. shall be shown.

10. Organizational structure

The same as the organization system described in the drug risk management plan.

11. On consigning some of investigation operations, name and address of the person consigned the operation concerned and the range of the operation consigned

1) Enrollment
   Outsourcee : CMIC Co., Ltd. (1-1-1, Shibaura, Minato-ku, Tokyo)
   Scope : patient enrollment and other related operations
2) Data management
   Outsourcee : CMIC Co., Ltd. (1-1-1, Shibaura, Minato-ku, Tokyo)
   Scope : data management and other related operations
3) Statistical analysis
   Outsourcee: to be determined
   Scope : statistical analysis and other related operations
4) EDC system operarions
   Outsourcee : FUJITSU FIP Corporation (1-2-1, Shibaura, Minato-ku, Tokyo)
   Scope : development and operation of EDC system, and other related operations

12. Planned milestone time point of evaluating the investigation implementation status and obtained results or reporting to PMDA, and rationale therefor

・Time point of periodic safety reporting: The information on safety and effectiveness will be comprehensively evaluated.

・Time point of filing application for re-examination: The final report will be prepared and submitted based on the tabulation/analysis results of fixed data in all the retrieved case report forms.

13. Additional measures to be possibly taken based on the results of investigation and the standard to decide starting the measures

At the milestone time point, the drug risk management plan will be reviewed, including the review of the following.

・Concerning the sexual dysfunction (altered libido, impotence, ejaculation disorder) including its persistency, if the incidence and onset timing are clarified as an adverse reaction to Zagallo, whether it is necessary to revise the prescribing information and materials will be deliberated.

・Whether it is necessary to revise the contents of this investigation plan (including whether it is necessary to add new safety investigation items) will be deliberated.

・Whether it is necessary to prepare new risk-minimizing measures for the safety investigation items will be deliberated.

14. Publication of investigation results

The results of this investigation will be provided to the clinical practice sites as information provision in the form of interim report or final report by an appropriate method such as presentation at academic meeting or article publication for “proper use” and “safety securing” in consideration of the appropriate timing and the number of retrieved case report forms.

The investigation plan and the summary of results will be published in GSK Clinical Study Register.

15. Other necessary items

1) Revision of implementation plan

During the investigation period, the progress status, number of patients excluded from analysis, appearance of an unknown or serious adverse reaction, marked increase in incidence of a specific adverse reaction, reasonability of investigation items, etc. shall be grasped appropriately, and the implementation plan shall be reviewed and revised as necessary.

On changing the contents of implementation plan of this investigation, the change notification shall be submitted to the Pharmaceuticals and Medical Device Agency (hereinafter abbreviated into “PMDA”) except for minor changes.

<Examples of minor changes>

(1) Change of planned number of medical institutions participating in investigation (by department)

(2) EDC system-related changes

[1] Changes of layout of investigation items (position movement of described item, column enlargement or shrinkage)

[2] Changes of investigation item explanations

[3] Addition of example adverse reactions after revision of precautions or addition of noteworthy adverse reactions

(3) Addition, change or deletion of items not influential on the entire investigation (especially effectiveness/safety analysis)

(4) Investigation period-related changes

[1] Change of investigation initiation date due to delay of launch

[2] Prolongation of investigation period corresponding to necessary short prolongation of registration period (not longer than 3 months)

[3] Shortening of investigation period without changing the planned number of patients to be investigated

2) Measures to be taken on detecting a problematic or doubtful point

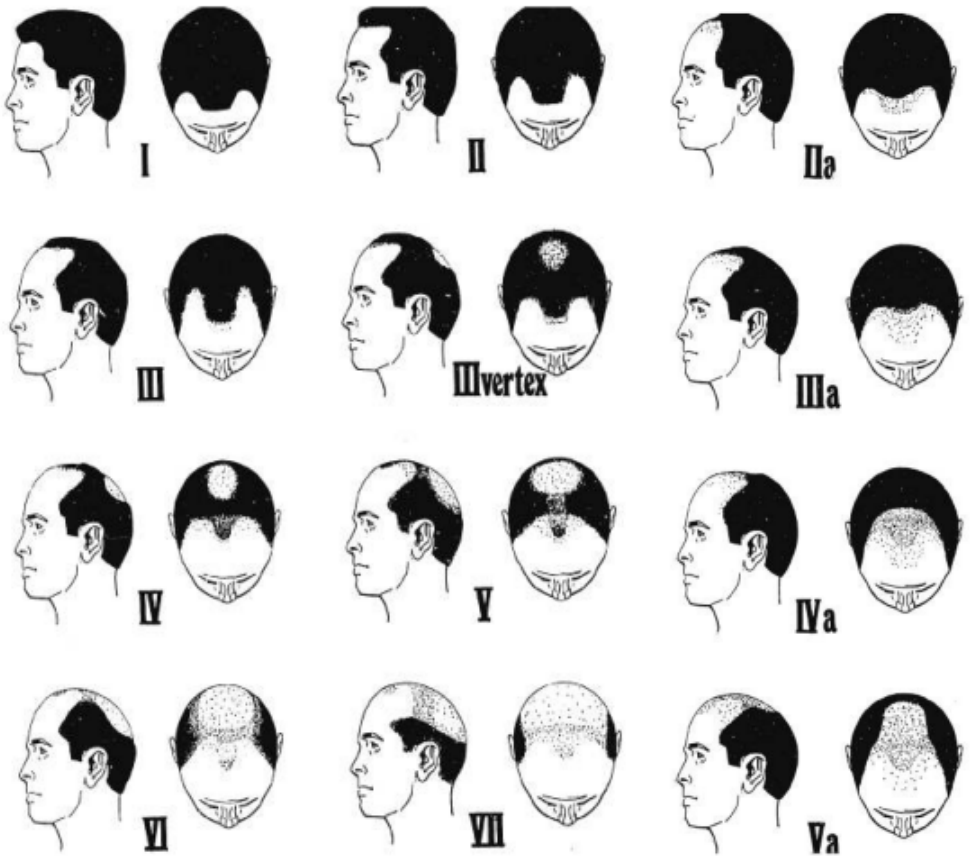
In a case where problematic points etc. have been detected in the evaluation/analysis results during or after the investigation period, implementation of a new special drug use investigation or a post-marketing clinical study shall be taken into consideration as necessary.

16. Attachments

1) Zagallo ® Capsule Drug Use Investigation Contract Form	Attachment 1
2) Zagallo ® Capsule Drug Use Investigation Implementation Guideline	Attachment 2
3) Zagallo ® Capsule Drug Use Investigation Registration Form	Attachment 3
4) Zagallo ® Capsule Drug Use Investigation Case Report Form	Attachment 4

17. Reference

Norwood-Hamilton classification of androgenetic alopecia



Cited from: Norwood OT. Male pattern baldness: classification and incidence. South Med J. 1975; 68(11): 1359-65.