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Evaluation of the Safety and Patient Satisfaction with GLASH VISTA™ (Bimatoprost 0.03%) in the Treatment of Hypotrichosis of Eyelashes. A Post-marketing Surveillance Study in Japan

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Phase:	Post-marketing Surveillance Study
Name of Investigational Product:	Bimatoprost 0.03% Cutaneous Solution (GLASH VISTA)
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List of Abbreviations and Definition of Terms

Abbreviation/Term	Definition
ADR	adverse drug reaction
AE	adverse event
CI	confidence interval
CRF	case report form
MedDRA	Medical Dictionary for Regulatory Activities
PMDA	Pharmaceutical and Medical Device Agency
SAE	serious adverse event

1. Study Drug and Indication

1.1 Study Drug

GLASH VISTA (Bimatoprost cutaneous solution 0.03%) for the upper eyelid henceforth referred to as GLASH VISTA.

1.2 Target Indication

The treatment of adults ≥18 years of age with idiopathic hypotrichosis of the eyelashes and hypotrichosis of the eyelashes due to chemotherapy for cancer.

2. Study Title

Evaluation of the Safety and Patient Satisfaction with GLASH VISTA (Bimatoprost 0.03%) in the Treatment of Hypotrichosis of the Eyelashes. A Post-marketing Surveillance in Japan.

3. Research objectives

The purpose of this post-marketing surveillance study is to evaluate the safety and patient satisfaction with GLASH VISTA in the treatment of hypotrichosis of the eyelash through active surveillance under routine clinical practice after the launch of GLASH VISTA in Japan.

The specific aims are to report on the:

1) Safety of GLASH VISTA treatment in patients with hypotrichosis of the eyelashes by identifying and evaluating adverse events (AEs) and rates of these events, including serious adverse events (SAEs) and non-serious AEs
2) Patient satisfaction with GLASH VISTA in the treatment of patients with hypotrichosis of the eyelashes by evaluating pre- and post-treatment patient satisfaction surveys

4. Study Design

This will be a prospective longitudinal observational study of patients with eyelash hypotrichosis treated with GLASH VISTA in Japan with follow-up for up to one year.

4.1 Study Population

Patients who have been prescribed GLASH VISTA in select clinical settings and filled at least one prescription for GLASH VISTA, regardless of age, gender or treatment indication.

4.2 Surveillance Sites and Physician Recruitment

GLASH VISTA in the treatment of hypotrichosis of the eyelashes is expected to be prescribed mainly in hospitals and clinics with departments of dermatology, cosmetic surgery or ophthalmology where treatment for eyelash hypotrichosis is available in Japan. Efforts will be

made to recruit oncologists if they prescribe GLASH VISTA, though patients are more likely treated by dermatologists, ophthalmologists or aesthetic plastic surgeons because the drug is not on the National Health Insurance Drug Price list. Therefore the surveillance sites will be the hospitals or clinics with relevant departments where physicians treat eligible patients with GLASH VISTA and are willing to participate as investigators in this post-marketing surveillance study. Approximately 75-150 sites are expected to participate.

The sponsor will contract with the relevant departments or institution to collect post-marketing data on the use of GLASH VISTA for the treatment of hypotrichosis.

The active surveillance study will begin after the product is launched in Japan and a contract has been executed between the institution and Allergan. In the event that a contracted principal investigator is changed during the agreed surveillance period, a replacement (eg, co-investigator) from the same study site will be identified, if possible, to assume the role of principal investigator to ensure continuity of the surveillance study. For this purpose, a separate contract or an amendment to the contract will be executed with the new principal investigator and the regulatory authority will be notified of changes.

4.3 Patient Recruitment

Each contracted institutions will consecutively enroll 10 to 20 eligible patients who have been prescribed GLASH VISTA at each surveillance site to ensure unbiased enrollment of patients during the agreed surveillance period. The decision to treat a patient with GLASH VISTA is to be determined by the physician and the patient, and is separate from the decision to include the patient in the study.

4.4 Study size

To estimate the onset of safety events in the real world setting, Allergan plans to enroll 1,500 patients with hypotrichosis of the eyelashes who have been prescribed and have used GLASH VISTA at least once and also have completed at least one follow-up visit. Enrollment will stop once 1500 patients have completed first follow-up visit.

The sample size calculation is based on the assumptions of 1 case of iris hyperpigmentation per 541 Latisse- (brand name of Bimatoprost outside of Japan) treated patients (0.2%) and 0 cases in vehicle-treated patients observed in the eyelash hypotrichosis clinical trials conducted outside of Japan.

A sample size of 1,500 patients would have an 95% power to observe adverse event occurring at least as frequent as the observed incidence of the iris hyperpigmentation in the Latisse clinical trials (ie, 0.2%).

The power calculation was conducted using the 'Cohort-no background incidence' design in PASS version 2008 (www.ncss.com).

4.5 Data Sources and Collection

4.5.1 Data Source

The investigators will collect the required information on enrolled patients utilizing study case report forms (CRFs) once the investigator site contract has been executed.

For this non-interventional surveillance study, safety and patient satisfaction data will be collected at approximately 1, 4 and 12 months after the first prescription of GLASH VISTA during one-year follow up period. If a patient has not scheduled a follow-up visit a month after initiating GLASH VISTA treatment, the investigator or his/her designate is required to contact the patient by telephone to collect follow-up safety and satisfaction information. If a patient has discontinued the treatment, the safety data collection from this patient will be terminated at three months post the last treatment. If a patient cannot be reached or does not wish to respond, this patient will be considered to be lost to follow up.

Investigators will collect all safety and satisfaction data at each follow-up visit or phone call during the study period by interviewing patients and/or reviewing medical charts.

Investigators will be instructed to report all AEs (serious and non-serious) or pregnancy exposed to GLASH VISTA to Allergan or its representatives according to Allergan's AE reporting policy to ensure no delays in reporting AEs to Health Authorities in accordance with local regulatory requirements.

4.5.2 Data Items on Case Report Forms

4.5.2.1 Data collected at enrollment

A. Basic information about the surveillance site (hospital/clinic name, department, prescriber name, specialty)

B. Patient background information such as patient initials, gender, date of birth, ocular medical history, concomitant ocular medications including previous usage of GLASH VISTA, allergy history, self-reported current pregnancy status (for females) and reason for prescribing GLASH VISTA,

C. GLASH VISTA prescription such as prescription date, bottle size, dosing schedule, and treatment duration

E. Baseline patient eyelash satisfaction survey.

4.5.2.2 Data collected at follow up visits

At each follow-up visit at approximately 1, 4 and 12 months after enrolment, actual usage of GLASH VISTA since receiving the most recent prescription will be collected along with the safety and satisfaction measures. Information on whether patients followed instruction found in the medication guide on the use of GLASH VISTA will be collected and physicians will re-educate patients who report not to be using GLASH VISTA according to the medication guide.

Patient Satisfaction Measure

Patient eyelash satisfaction survey post-GLASH VISTA use will be collected at approximately 1, 4 and 12 months after patient enrolment.

Safety Measures

All AEs(serious and non-serious) that occur during the follow-up period will be collected regardless of causal relationship to GLASH VISTA. The following adverse events will be monitored during follow up visits at approximately 1, 4 and 12 months after patient enrolment and discussed in the report:

- Iridal hyperpigmentation
- Enophthalmos (deepened eyelid sulcus)
- Periorbital tissue hyperpigmentation
- Punctate Keratitis

If an AE is reported by the patient, the following detailed information about the event will be collected using Allergan's Non-interventional Study Adverse Event Form

- Description of adverse event
- Site (body part) affected
- Start and stop date of adverse event
- Seriousness
- For SAE, specific type such as death, hospitalization, etc.
- Outcome of adverse event
- Causal relationship to GLASH VISTA

- Action regarding GLASH VISTA treatment
- Date of last GLASH VISTA application
- Relevant medical history
- Relevant concomitant medications
- Physician's comments on reported AE, including treatment given for AE

Any pregnancy reported by a study participant will be recorded as a pregnancy for the study and it is not part of the study to confirm pregnancies by a laboratory test. Pregnancies will be collected and reported in a manner similar to AE reporting, although pregnancy is not considered an AE by definition. If a pregnancy is reported, information regarding pregnancy will be reported using the Allergan Pregnancy Data Communication Form-Pre-Delivery (Initial) Information and/or the Allergan Pregnancy Data Communication Form- Post-Delivery (Follow-Up) Information. Pregnancy will be recorded in a separate category in the Allergan safety database. Pregnancies will be reported in a separate table from AEs in the study reports.

If the outcome of a pregnancy is an AE (eg, spontaneous abortion or congenital anomaly) the event will be considered an AE. Maternal events, such as spontaneous abortions, will be reported as an AE for the mother, and congenital anomalies will be reported as an AE for the child.

4.5.2.3 Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

Serious Adverse Event

A serious adverse event (SAE) is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Allergan considers all new or reoccurring cancer adverse events as serious adverse events. In addition, Allergan considers any abortion (spontaneous or non-spontaneous) as a serious adverse event.

Prior cancer diagnosis, pre-planned surgeries or procedures for pre-existing, known medical conditions for which a patient requires hospitalization are not reportable as serious adverse events.

Pregnancy

Pregnancy includes pregnancies occurring in female patients following exposure to GLASH VISTA or pregnancies occurring in the female partners of male patients exposed to GLASH VISTA. It also includes the pregnant women who are exposed to GLASH VISTA.

Causality of Adverse Event

Physician investigators will assess the relationship between GLASH VISTA and an AE using the following definitions below. Decisive factors for the assessment of causal relationship of an AE to GLASH VISTA include, but may not be limited to, temporal relationship between the AE and GLASH VISTA application, known side effects of bimatoprost (the active ingredient in GLASH VISTA), medical history, concomitant medication, and course of underlying disease.

- **Not related:** Not suspected to be reasonably related to GLASH VISTA application. The AE could not medically (pharmacologically/clinically) be attributed to GLASH VISTA application. An alternative explanation will be reported if possible.

- **Related:** Suspected to be reasonably related to the application of GLASH VISTA. The AE could medically (pharmacologically/clinically) be attributed to the application of GLASH VISTA.

The investigators will report AEs to Allergan or its representatives, including the requirement to notify Allergan immediately, but no later than 24 hours, after learning of all SAEs identified during the study.

4.6 Study Duration

The total duration of the study will be 3.5 years. Patient enrollment will start after the product launch and will be completed in 2.5 years. Each enrolled patient who have applied GLASH VISTA at least once will be followed for 1 year after enrollment or until they discontinue from the study, whichever comes first.

4.7 Data Management and Retention

Paper CRFs will be used to record all information in the study. Only de-identified data on these patients will be captured and used in study analyses

The documents prepared during this study including post-marketing surveillance protocol, post-marketing surveillance contract, and CRFs will be filed promptly after retrieving and retained for 5 years after submission of the surveillance report and reexamination by the Pharmaceutical and Medical Device Agency (PMDA).

4.8 Data Analysis Variables and Analysis Methods

4.8.1 Analysis Variables

4.8.1.1 Composition of Patients

Disposition of the surveillance patients will be generated to provide the following information:

- Number of patients enrolled
- Number of patients who dropped out and reasons for dropout
- Number of patients whose CRFs were collected (or entered into database)
- Number of patients who met the safety evaluation selection criteria
- Number of patients who met the patient satisfaction evaluation selection criteria

Patients will be included in the safety analyses if they used GLASH VISTA at least once and have safety data collected at least 1 post-treatment visit or via phone call during the 1 year follow-up period.

Patients will be included in the evaluation of patient satisfaction analyses if they used GLASH VISTA and had completed the pre- GLASH VISTA patient satisfaction survey and at least the 4 month follow-up patient satisfaction survey.

4.8.2 Analysis Methods

The analyses will be descriptive in nature, and there are no plans for formal statistical hypothesis testing. Results will be displayed in tabular format (ie, summary statistics, frequency distribution of item responses, and incidence rates with corresponding 95% confidence intervals [CI]). No imputations for missing data are planned.

A detailed Statistical Analysis Plan will be prepared prior to data analysis. The key elements of analysis are summarized in this section.

4.8.2.1 Descriptive Statistics

Descriptive analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. Categorical variables (eg, gender) will be summarized by the number and percentage (%) of patients in each category. Any missing category included in the CRF or generated from data collection will be treated as an independent category. For describing the incidence of adverse events, the frequency, cumulative incidence proportion, patient-year incidence rate, and 95%CI for the cumulative incidence measures will be displayed. Unless otherwise specified, the 95% CI of the proportions will be calculated using the exact method, and the 95% CI of the incidence rates will be constructed assuming the frequency of a particular event in a given period of time follows a Poisson distribution.

Continuous variables (eg, age, treatment duration) will be summarized using descriptive statistics (number of non-missing values, mean, standard deviation, median, minimum, and maximum values).

4.8.2.2 Safety Analysis Methods

A frequency table by type of adverse event will be prepared for the study subjects as whole and by the following subgroups: age categories (<18 years, 18-64 years, and >=65 years), gender (male and female), treatment indication (idiopathic hypotrichosis, cancer chemotherapy related hypotrichosis of the eyelashes, others), and total follow-up time (may group it as 1 month, 4 months, 12 months according to the visit schedule). The causal relationship to GLASH VISTA will be described.

The frequency of SAEs and non-serious AEs will be tabulated in the study subjects as whole and by the same subgroups as above. The Medical Dictionary for Regulatory Activities (MedDRA) medical terminology will be used in data reporting at the level of Preferred Terms.

Pregnancy will be reported in a separate table from AEs

4.8.2.3 Patient Satisfaction Analysis Methods

The change from the baseline patient satisfaction (pre- GLASH VISTA use) and the 4 months follow-up visit patient satisfaction will be assessed for each patient. The results will be presented for the study subjects as whole and by the same subgroups for the safety.

5. Administrative Items

5.1 Protocol Amendment

When a significant change in the drug application, dosage, indications, or study conduct is required or anticipated during the active surveillance period of GLASH VISTA for the treatment of eyelash hypotrichosis, the protocol will be amended accordingly and submitted to the PMDA.

5.2 Reporting of Adverse Events

All adverse events that occurred during follow-up period regardless of causality to the surveillance drug will be recorded in the corresponding section of the CRF and/or the Allergan Non-interventional Study Adverse Event Form. The collected information includes seriousness, relatedness to the study drug, start and stop dates, actions taken, outcome, etc. A safety management plan, describing roles and responsibilities of identifying, collecting and reporting of adverse event data to Health Authorities as required, will be developed to inform the investigators on reporting AEs and SAEs.

In the event of an SAE, the investigator must:

1. Notify Allergan or its representatives immediately, but no later than 24 hours by fax or email using the PMS Adverse Event Form (contact details can be found on page 1 of Allergan Non-Interventional Study Adverse Event Form). Emergency phone numbers and relevant Allergan personnel contacts are also on the front page of protocol.

2. Obtain and maintain all pertinent medical records (hospital discharge summary, autopsy etc) , pertinent information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient. The investigator may be asked to provide this information to Allergan.

3. Provide Allergan with a complete, written description of the adverse event(s) on Allergan Non-interventional Study Adverse Event Form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the adverse event(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality which includes a statement as to whether the event was or was not related to the use of the investigational drug.

5.3 Human Patient Protection

The survey will be conducted in compliance with the Good Post-marketing Study Practice (GPSP) ["Ministerial Ordinance on Standards for Post-marketing Surveys and Studies on Medical Devices" (Ministry of Health, Labor and Welfare Ministerial Ordinance No. 38, 2005]) and the Personal Information Protection Act and other relevant law and regulations.

5.4 Reporting and Dissemination of Results

A final report will be compiled and submitted to PMDA during the reexamination period Periodic updates on the study status will be provided per the applicable local regulations.

6. Attachments

6.1 Case Report Form

6.2 Allergan Non-interventional Study Adverse Event Form

6.3 Pregnancy Data Communication Pre-delivery (initial) information

6.4 Pregnancy Data Communication Post-delivery (follow-up) information

6.5 Package Insert

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