Drug Use Investigation of ANORO®ELLIPTA® inhaler

Protocol/Implementation Guidance

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Table of Contents

1. Objectives

This investigation will be conducted to collect and evaluate information regarding the safety and efficacy of ANORO®ELLIPTA® (hereinafter referred to as "Anoro Ellipta") under the actual post-marketing use conditions of the product.

2. Safety Considerations

・Cardiovascular events, and asthma-related intubation and death

3. Study Population

This investigation will be conducted in patients who are first prescribed Anoro Ellipta for the approved indication of the product, "Relief of symptoms of obstructive airway disorder due to chronic obstructive pulmonary disease (COPD) (chronic bronchitis and emphysema) (in the case that long-acting inhaled anticholinergic and long-acting inhaled beta$_2$-agonist combination is required)".

4. Planned Sample Size and Its Rationale

1) Target number of patients: 2000
2) Rationale:

The target number of patients in this investigation was set at 2000, taking the number of subjects necessary for safety and efficacy analyses as well as withdrawals/dropouts into consideration, based on the rationale for sample size determination shown below.

- To evaluate the change in FEV1 when treatment is switched from LAMA monotherapy to Anoro Ellipta, assuming that the mean change in FEV1 is 50 mL and the standard deviation (SD) is 150 mL with reference to the change in FEV1 observed in the previous medication LAMA group in a Japanese long-term study (DB2115362), with 80% power, the number of patients necessary as the efficacy analysis set is calculated to be 73. Based on the assumption that the number of patients whose FEV1 can be measured is 40% of the entire population and the number of patients whose treatment is switched from LAMA monotherapy in the subgroup according to previous medication is 50% of the entire population, the overall number of subjects necessary in the investigation is estimated to be 365.
- To evaluate the noninferiority in terms of the change in FEV1 when treatment is switched from LAMA/LABA combination to Anoro Ellipta, assuming that the expected change is 0 mL, the noninferiority margin is −25 mL, and the SD is 120 mL, with reference to the change in FEV1 observed in the previous medication LAMA/LABA combination group in the Japanese long-term study (DB2115362), with 80% power, the number of patients necessary as the efficacy analysis set is calculated to be 183. Based on the assumption that the number of patients whose FEV1 can be measured is 40% of the entire

population and the number of patients whose treatment is switched from LAMA/LABA combination in the subgroup according to previous medication is 25% of the entire population, the overall number of subjects necessary in the investigation is estimated to be 1830.

- Meanwhile, the incidence of adverse events (AEs) reported as serious cardiovascular events was approximately 1% (8 /842 subjects) in clinical studies of Anoro Ellipta in COPD patients. Assuming that the threshold incidence is 1% and securing at least 80% power to detect the threshold incidence of 1% in the case that the true risk is 2-fold or more than the threshold, the number of subjects necessary as the safety analysis set to confirm the incidence in the post-marketing surveillance is calculated to be 992.

5. Planned Number of Medical Institutions by Department

Approximately 400 medical institutions, primarily the department of respiratory medicine

6. Study Period

Study period: February 2015 to April 2018

Observation period: The observation period (duration of treatment with Anoro Ellipta) in each patient will be 1 year after the initiation of prescription of the product.

Planned registration period: February 2015 to January 2017

When the number of registered patients reaches the planned sample size, however, the registration may be discontinued before completion of the above-mentioned registration period.

7. Study Method

This investigation will be conducted by the central registration system.

In the investigation, the electronic data capture (EDC) system will be used for case registration and data collection.

1) Request for the investigation and contract
   (1) The medical representative (MR) will explain the study objectives, study population, study items, study method, etc. to the potential investigators, etc. of the medical institutions where Anoro Ellipta has been adopted and where the product is delivered, and request them to cooperate with the investigation.
   (2) Once agreement on cooperation with the investigation is obtained, a written contract should be concluded with the head (e.g., the director) of the medical institution prior to initiation of the investigation, and then the registration should be started.

2) Issuance of user ID and password
   After conclusion of the contract, the ID and password necessary to log in the EDC system will be issued.
3) Registration of patients
   (1) The investigator will enter the information of patients for whom prescription of Anoro Ellipta is initiated after conclusion of the contract and who are listed in "3. Study Population" in the EDC system within 14 days after the initiation of prescription of Anoro Ellipta (the date of the initiation of prescription should be regarded as Day 1) to complete the registration of the patients.
   (2) When the number of registered patients reaches the contracted sample size, registration of patients at the study site will be stopped.
4) Collection of data and entry in the EDC system
   (1) The investigator will confirm the study items such as the characteristics of the registered patients.
   (2) The investigator will request the registered patients to fill out the "COPD Assessment Test (CAT)" at the initiation of treatment with Anoro Ellipta, and at 1 month and 1 year after the initiation of treatment (or at the discontinuation/completion of treatment if treatment with Anoro Ellipta is discontinued/completed).
   (3) The investigator will retrieve the CAT of the registered patients, check the content, and enter the information in the EDC system.
   (4) During the observation period, the investigator will review the information regarding the safety and efficacy, etc. If a patient does not visit the study site during the observation period, the investigator will obtain information regarding AEs, etc. by telephone, etc. as far as possible.
   (5) The investigator will enter the information of the registered patients obtained at 1 month and 1 year after the initiation of treatment with Anoro Ellipta (or at the discontinuation/completion of treatment if treatment with Anoro Ellipta is discontinued/completed), and send it.

8. Study Items

The investigator will collect information regarding the following items, etc. as far as possible and enter it in the EDC system.

1) Information regarding the medical institution
   Name of the institution, department, and investigator
2) Patient characteristics (at the initiation of prescription of Anoro Ellipta)
   Identification number, sex, age or year of birth, date of the initiation of prescription of Anoro Ellipta, hospitalization status, height, body weight, reason for use of Anoro Ellipta, type of COPD, stage classification, duration of COPD, history of cigarette smoking, Brinkman index, and presence or absence

of complications (bronchial asthma, cardiovascular disorder, renal impairment, hepatic impairment other than the primary disease, etc.) and their names
To protect the confidentiality of the identification of individual patients, the identification number will be a unique number assigned to each patient by the investigator, etc. In this investigation, any other diseases or symptoms than COPD that have existed prior to the initiation of treatment with Anoro Ellipta will be handled as "complications".

3) Prior medication for COPD (4 weeks before the initiation of treatment)
Presence or absence of prior medication for COPD 4 weeks before the initiation of treatment, and the category and product name of the medication
4) Status of treatment with Anoro Ellipta
Unit dose and daily dosing frequency of Anoro Ellipta, start and end dates of treatment, and reason for dosage modification during the observation period
5) Concomitant medications
Presence or absence of concomitant medications during the observation period, and the names and reasons for use of these medications
6) Concomitant therapies for COPD (other than medications)
Presence or absence of concomitant therapies for COPD during the observation period, and the name of the therapy
7) COPD exacerbations
Number of COPD exacerbations during the 1-year period before and after the initiation of treatment with Anoro Ellipta
8) Bronchial asthma-related intubation and death
Presence or absence of intubation due to an exacerbation of bronchial asthma and the presence or absence of bronchial asthma-related death during the observation period
Patients with COPD often concurrently have asthma, and "bronchial asthma-related intubation and death" are set as Safety Considerations in this investigation, and information regarding exacerbations of bronchial asthma during the observation period will be collected as AEs.
9) Respiratory function test (spirometry)
Presence or absence of use of short-acting beta$_2$-agonists, forced expiratory volume in one second (FEV_1), and forced vital capacity (FVC) at the initiation of treatment with Anoro Ellipta, at 1 month and 1 year after the initiation of treatment, on the day of assessment at the time of discontinuation/completion, and within 4 hours before measurement.
10) COPD assessment test (CAT)
Information in the "COPD Assessment Test (CAT)" filled out by patients at the initiation of treatment with Anoro Ellipta, at 1 month and 1 year after the initiation of treatment, and at the time of discontinuation/completion.
11) Global efficacy assessment

One year after the initiation of treatment with Anoro Ellipta or at the discontinuation/completion of treatment, the efficacy of the product will be assessed comprehensively on a scale of two categories, “effective” or “not effective”, based on the progress of subjective symptoms and clinical findings, changes in respiratory function test results, COPD exacerbations, changes in CAT scores, etc., from the initiation of treatment to the completion of the observation period. In case the efficacy cannot be determined for some reason, it will be considered as “indeterminable”, and the reason should be entered in the EDC system.

12) Status of continuation of treatment with Anoro Ellipta at the completion of the observation period

Status of the continuation of treatment at 1 year after the initiation of treatment with Anoro Ellipta and reason for the discontinuation/completion

13) Pregnancy

Whether Anoro Ellipta has been administered to a pregnant woman or not, presence or absence of pregnancy during the observation period, and expected delivery date (if the patient is a female)

If Anoro Ellipta is administered to a pregnant woman or a patient is found to be pregnant during the observation period, follow-up should be performed on the mother and her fetus/infant as far as possible regarding the pre- and post-pregnancy course, delivery, miscarriage, abortion, etc. and AEs, etc.

14) AEs

Presence or absence of AEs after the initiation of treatment with Anoro Ellipta, diagnosis or symptom(s), date of onset, outcome of the AEs, date of outcome, seriousness, reason for being considered as serious, relationship with Anoro Ellipta, and other suspected or related factor(s) than Anoro Ellipta

(1) Since Anoro Ellipta contains a long-acting muscarinic receptor antagonist and a long-acting $beta_2$-agonist, the following priority study item is set to check the occurrence, etc.

・Cardiovascular events, effects on glucose, effects on potassium, tremor, urinary retention, effects on eyes, gallbladder disorder, intestinal obstruction, anticholinergic effect, lower respiratory tract infection, and pneumonia

(2) To capture the priority study item and adverse drug reactions (ADRs), the investigator will enter information regarding all AEs (e.g., diseases, symptoms, abnormal laboratory values) occurring after the initiation of treatment with Anoro Ellipta in the EDC system, regardless of the presence or absence of a relationship with the product. The relationship with Anoro Ellipta will be assessed on a scale of two categories, “related” or “not related”, and it will be entered in the EDC system.

(3) AEs assessed as “related” to Anoro Ellipta will be handled as suspected “ADRs” that are caused by the product.

9. Analysis Items and Methods

1) Analysis items

(1) Items related to patient disposition

[1] Number of patients registered, number of patients whose case report form (CRF) was retrieved

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

[3] Number of patients included in the analysis set for Efficacy 1 (spirometry), number of patients excluded from the analysis set and the reason for exclusion

[4] Number of patients included in the analysis set for Efficacy 2 (global efficacy assessment and CAT score), number of patients excluded from the analysis set and the reason for exclusion

(2) Patient demographic and baseline characteristics

Distribution of patient demographic and baseline characteristics

- Stage classification, duration of COPD, past treatment history, type of concomitant medications/therapies, history of cigarette smoking, age, body weight, complications, presence or absence of bronchial asthma, etc.
- CAT scores, number of COPD exacerbations
- Spirometry

(3) Items related to safety

[1] Incidence of ADRs (including infections, hereinafter the same) by MedDRA SOC and PT

[2] Priority study item: MedDRA codes should be identified.

- Cardiovascular events, effects on glucose, effects on potassium, tremor, urinary retention, effects on eyes, gallbladder disorder, intestinal obstruction, anticholinergic effect, lower respiratory tract infection, and pneumonia

[3] Explorative assessment of factors (patient demographic and baseline characteristics) that may affect the presence or absence of ADRs and the presence or absence of ADRs set as the priority study item

[4] Subgroup analyses (elderly, etc.) by the presence or absence of ADRs and the presence or absence of ADRs set as the priority study item

(4) Items related to efficacy

[1] Efficacy 1

- Distribution of FEV1
- Explorative assessment of the effects of factors (patient demographic and baseline characteristics) that may affect FEV1
- Subgroup analyses (elderly etc.) by FEV1

[2] Efficacy 2

- Distribution of global efficacy assessment and CAT score
- Explorative assessment of the effects of factors (patient demographic and baseline characteristics) that may affect the efficacy and CAT score

2) Analysis methods

For factors that may affect the items related to the safety and efficacy, etc., the odds ratios and their 95% confidence intervals will be calculated, as appropriate. The results will be graphically presented using a forest plot, etc., as appropriate. For comparison of the scores, etc., the mean values and quartile points, etc. of the values at the measurement time points and the changes from baseline will be calculated and graphically presented using a boxplot, as appropriate.

10. Publication of Study Results

Regarding the results of this investigation, information will be provided, as appropriate, to clinical sites as a final report as presentations at conferences and published articles, etc. taking an appropriate timing and number of collected patients, etc. for “proper use” and to “ensure safety” into consideration.

11. Organization

1) Same as the Risk Management Plan
2) Person responsible for the investigation: [redacted], Manager, Planning Group, PMS Department

12. Name and Address of the Contractor, and the Scope of Outsourced Operations

1) Registration operations
   Contractor: CMIC Co., Ltd.
   Scope of outsourced operations: patient registration, self-inspection, and other related operations
2) Data management operations
   Contractor: CMIC Co., Ltd.
   Scope of outsourced operations: CRF data entry, follow-up investigation, self-inspection, and other related operations
3) Data tabulation operations
   Contractor: CMIC Co., Ltd.
   Scope of outsourced operations: data tabulation, data analysis, self-inspection, and other related operations
4) Electronic data capture (EDC) operations
   Contractor: FUJITSU FIP CORPORATION
   Scope of outsourced operations: EDC system development, self-inspection, and other related operations

13. Progress of the Investigation and Evaluation of the Results Obtained or the Timing of Milestones for Reporting to the PMDA and Their Rationales

- At the time of a periodic safety report: To conduct a comprehensive review of the safety information
- At the time of submission of the application for re-examination: To prepare a final report based on the tabulation/analysis results obtained from fixed data in all retrieved CRFs.

14. Additional Measures That May Be Implemented Based on the Study Results and the Decision Criteria for the Initiation of These Measures

At the milestone time points, the Risk Management Plan, including the following contents, will be reviewed.

- Safety and efficacy evaluation will be performed, and the necessity of amendment to the prescribing information and/or packaging/labeling materials will be considered, if necessary.
- Necessity of any changes to the content of the plan for this investigation, including the presence or absence of new safety considerations, will be considered.

15. Other Necessary Matters

1) Protocol amendments

During the study period, the progress of the investigation, the number of patients excluded from the analysis sets, occurrence of unknown/serious ADRs, a significant increase in the incidence of specific ADRs, appropriateness of study items, etc. should be assessed at all times, and the study protocol should be reviewed and revised if necessary.

In case of making changes to the protocol for this investigation, a change notification should be submitted to the Pharmaceuticals and Medical Devices Agency in advance, except for minor changes.

<Examples of minor changes>

(1) Change of the organization or the person in charge for the conduct of the investigation
(2) Change of the planned number of medical institutions (by department)
(3) EDC system
    [1] Modifications to the layout of items (relocation of items, enlargement or reduction of sections)
    [2] Change in the explanation of items
    [3] Inclusion of additional examples of ADRs, in association with a revision of the Precautions or inclusion of noteworthy ADRs
(4) Addition, change, and deletion of items that have no impact on the entire investigation, particularly efficacy and safety analyses
(5) Study period
    [1] Change of the start day of the investigation due to a delay in the product launch
    [2] Prolongation of the study period to correspond to a short-term (within 3 months) prolongation, if necessary, of the registration period
    [3] Reduction of the study period in case no change has been made to the planned sample size

2) Handling of problems or questions detected

If any problem is found during the study period or in the evaluation and analysis results, etc. after completion of the investigation, implementation of an additional special drug use investigation or post-marketing clinical study will be considered according to need.

16. Attachments

1) Contract Document for the Drug Use Investigation of ANORO®ELLIPTA® Attachment 1
2) Implementation Guidance for the Drug Use Investigation of ANORO®ELLIPTA® Attachment 2

3) Registration Form for the Drug Use Investigation of ANORO®ELLIPTA®
Attachment 3

4) Case Report Form for the Drug Use Investigation of ANORO®ELLIPTA®
Attachment 4

5) CAT for the Drug Use Investigation of ANORO®ELLIPTA®
Attachment 5

17. Study Schedule

Preferable time points of observations and assessments of major study items are shown below.

Study item \ Study period	Day of the initiation of treatment with Anoro Ellipta[*1]	1 month after[*1]	1 year after[*1]	At discontin-uation/ completion
Patient characteristics	●	-	-	-
Prior medication	●	-	-	-
Status of treatment	←	—	→	●
Concomitant medications	←	—	→	●
Concomitant therapies[*2]	←	—	→	●
Respiratory function test	●	●	●	●
CAT	●	●	●	●
Global efficacy assessment	-	-	●	●
Status of continuation of treatment at the completion of the observation period	-	-	●	●
Pregnancy	←	—	→	●
AEs	←	—	→	●

*1: Permissible time ranges are as follows:
Day of the initiation of treatment with Anoro Ellipta: −1 month, 1 month after the initiation of treatment: −2 weeks to +1 month, 1 year after the initiation of treatment: ±1 month

*2: Concomitant therapies for COPD (other than medications)

18. Adverse Events

Requests in the Event of Adverse Events

- For patients who experienced AEs, further detailed investigation may be conducted, if necessary. In such a case, your cooperation would be appreciated.
- If the experience AE is an adverse reaction to Anoro Ellipta or a serious adverse event (SAE), contact the medical representative (MR) of GlaxoSmithKline K.K. promptly.

1) AEs

An AE is any untoward medical occurrence in a patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE could therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless of the presence or absence of a relationship with the product.

Events meeting the definition of an AE could include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after the initiation of treatment with Anoro Ellipta, even though it may have been present prior to the initiation of the investigation
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either Anoro Ellipta or a concomitant medication (overdose per se is not subject to AE/SAE reporting). However, deliberate overdose with the intent of suicide/self mutilation must be reported, regardless of the presence or absence of sequelae.

Events not meeting the definition of an AE could include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that led to the procedure is an AE
- Situations where an untoward medical occurrence do not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the initiation of the investigation that do not worsen

- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition

2) ADRs

An ADR is any noxious and unintended response to a medicinal product related to any dose. The phrase "response to a medicinal product" means that a relationship between a medicinal product and an AE is at least a reasonable possibility. Unlike AEs, ADRs are characterized by the fact that the relationship between the medicinal product and the AE is suspected.

3) SAEs/ADRs

An SAE or ADR is any untoward medical occurrence that, at any dose:

(1) Results in death
(2) Is life-threatening[1]
(3) Requires hospitalization or prolongation of existing hospitalization
(4) Results in persistent or significant disability/incapacity
(5) Is a congenital anomaly/birth defect
(6) Is an event or response that is otherwise judged to be medically significant[2]

[1] The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically may have caused death, if it were more severe.

[2] Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Handling of AEs

Information of patients who have experienced AEs may be reported to the Pharmaceuticals and Medical Devices Agency (PMDA) and GlaxoSmithKline in the UK. Also, if an inquiry about previous cases is received from healthcare professionals who have encountered similar ADRs, information of corresponding patients regarding clinical course of the ADR, actions taken for the ADR, and others may be provided as reference information. Moreover, the tabulation/analysis results in this investigation will be provided to medical institutions, etc. for "Proper Use" and "Safety Assurance".

ADR information reported from GlaxoSmithKline K.K. to the PMDA will be disclosed upon request in accordance with the Information Disclosure Law (It is specified under the Information Disclosure Law "Every person can request for disclosure of administrative documents…"; administrative documents mentioned therein include information reported from GlaxoSmithKline K.K. to the PMDA). Of these pieces of information, ADR information will be disclosed in the List of Cases or the List of Reported ADRs on the website via the PMDA's pharmaceuticals and medical devices information provision system. However, patient personal information contained in the reported information will never be disclosed. Information regarding reporting physicians, such as name of the medical institution or physician, will never be reported to the PMDA or medical institutions, etc. by GlaxoSmithKline K.K. Provided information will be strictly managed in accordance with the Personal Information Protection Law.

19. Publication of Study Results

Regarding the results of this investigation, information will be provided, as appropriate, to clinical sites as a final report as presentations at conferences and published articles, etc. taking an appropriate timing and number of collected patients, etc. for "proper use" and to "ensure safety" into consideration.

A summary of the study results will be published in the GSK Clinical Study Register.

20. Sponsor's Representative

[redacted]

Person responsible for the management of post-marketing surveillance etc.
GlaxoSmithKline K.K.

21. References

The stage classification of COPD given in the "Guidelines for the Diagnosis and Treatment of COPD (Chronic Obstructive Pulmonary Disease) 4th Edition" is shown below.

Guidelines for the Diagnosis and Treatment of COPD (Chronic Obstructive Pulmonary Disease) 4th Edition

Table 1 Stage Classification of COPD

Stage		$\%FEV_1$
Stage I:	Mild airflow obstruction	$\%FEV_1 \geq 80\%$
Stage II:	Moderate airflow obstruction	$50\% \leq \%FEV_1 < 80\%$
Stage III:	Severe airflow obstruction	$30\% \leq \%FEV_1 < 50\%$
Stage IV:	Very severe airflow obstruction	$\%FEV_1 < 30\%$

The FEV_1/FVC ratio of <70% after treatment with bronchodilators is a must.