TRELEGY ELLIPTA
General Drug Use Investigation
(asthma)

Protocol

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1. Objectives

The objective of this investigation is to collect and assess information regarding the safety and effectiveness of Trelegy Ellipta (hereinafter referred to as “Trelegy”) in asthma patients under the actual use conditions.

2. Safety Specifications

In this investigation, the safety specification will be defined as follows;

- Cardiovascular events

3. Target Population

This investigation will include patients who are prescribed Trelegy for the first time for the treatment of diagnosed bronchial asthma, which is one of the indications of Trelegy.

4. Target Sample Size and Rationale

Target number of patients: 300 (as patient registration)

1) Rationale:

Cardiovascular events are important identified risk in RMP and the proportion of patients experiencing any cardiovascular events in the Japanese long-term clinical trial (12 months) was 4.5%. To confirm the frequency of occurrence of cardiovascular events with estimation accuracy that enables a power of ≥80% for the 4.5% threshold in case the real risk exists at 2 times or more than the threshold, sample size of 222 subject for safety analysis will be required. Therefore, a Drug Use Investigation (DUI) of 300 subjects considered enough to confirm it.

5. Planned Number of Medical Institutions by Department

Approximately 60 medical institutions, mainly the departments of internal medicine and respiratory medicine

6. Investigation Period

1) Implementation of the investigation

Investigation period: June 2021 - November 2023

Observation period:

The observation period per patient will be 1 year from the first ever initiation date of Trelegy treatment. If a patient has withdrawn from /terminated administration of Trelegy, it will be until the withdrawal/termination date.

Planned registration period: June 2021 - August 2022

If the number of enrolled patients has reached the target sample size, registration may be terminated even prior to the end of the above-mentioned planned registration period.

2) End of the investigation

Final Statistical Analysis Completed: July 2024

Final Report Completed: January 2025

7. Investigation Methods

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

1) Request and contract for the investigation
   (1) The medical representative (MR) will explain the objectives, target population, investigation items, investigation methods, etc. to the physicians expected to be investigator of the investigation, etc. at the medical institutions where Trelegy has been adopted or delivered, and MR will request them to cooperate with the investigation.
   (2) When cooperation to the investigation has been obtained, the written contract should be concluded with the heads (e.g. directors, etc.) of the medical institutions before starting the investigation.
2) Issuance of user ID and password
   The investigator will receive user ID and the password which needed to enter data to the EDC system, after the contract.
3) Obtaining consent
   The investigator will conduct informed consent to the patient after the own decision of prescribing Trelegy under usual clinical practice.
   The investigator will explain about participation in the investigation and publication of the investigation results sufficiently to a patient (and/or patient's representative) using the Informed Consent Form (ICF) and obtain his/her (and/or person's representative's) signature or name/seal and date of consent. Once consent is obtained from a patient (and/or patient's representative), investigator will put that information into the Registration Form by marking in a checkbox for consent "Yes". The obtained ICF should not be submitted to MR.
   If a patient (and/or patient's representative) withdraws his/her consent during the investigation period, the investigator will fill in necessary information in a notification form of consent withdrawal which prepared by the sponsor and submits it to MR.
4) Registration of target population
   The investigation will be conducted using a central registration method.
   (1) The investigator will enter patient information, etc. into the registration form for "3. Target Population" who initiate Trelegy treatment after making a contract, and then register patient via the EDC system within 14 days from the prescription date of Trelegy treatment (the prescription date of the treatment will be regarded as Day 1). The personal information such as patient's name, address, date of birth, number of medical chart, patient initials should not be entered in the registration form.
   (2) When the number of registered patients has reached to the contracted number of patients with the medical institution, the investigator will stop further patient registration for the investigation.
5) Data collection and data entry in the EDC system
   (1) The investigator will confirm for the investigation items, such as the characteristics of registered patient etc.
   (2) The investigator will confirm data of Asthma Control Test (ACT) at the initiation of Trelegy treatment*, at the timing of 1, 3, and 6 months after the initiation of treatment and at the end of observation period (1 year after the initiation of treatment or at the withdrawal/termination of treatment if treatment with Trelegy is withdrawn/terminated) and enter those information to the EDC system, if tests are performed.
   * at the initiation of Trelegy: the day of starting Trelegy or the last visit before starting Trelegy.
   (3) The investigator will confirm the course of clinical symptoms and assess overall effectiveness at the end of observation period (1 year after the initiation of treatment or at

the withdrawal/termination of treatment if treatment with Trelegy is withdrawn/terminated).

(4) The investigator will review the information regarding safety and enter all adverse events (AEs) (e.g., a disease, symptom, abnormal laboratory value) and pregnancy, etc. observed during the observation period in EDC system.

(5) The investigator will enter the information of the registered patients obtained at the end of the observation period and send data via the EDC system. The personal information such as patient's name, address, date of birth, number of medical chart, patient initials should not be entered in the EDC system.

8. Investigation Items

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

1) Information regarding medical institutions
   Name of medical institution, department and investigator
2) Patient characteristics (at the initiation date of Trelegy treatment)
   Identification number, gender, year of birth or age, prescribed date for the treatment, confirmation of informed consent, reason for use of Trelegy, type of asthma, duration of asthma, severity* prior to start treatment, height, body weight, history of smoking, presence/absence and the name of comorbidities (renal function disorder, hepatic function disorder, cardiovascular disorder, COPD, and others) and medical history in the past.
   To protect the confidentiality of personal information of patient, the identification number should be a unique number assigned to an individual patient by the investigator, etc.
   In this investigation, the reason for use of Trelegy will be defined as a disease for which Trelegy is mainly used. Any disease/symptom except for asthma which is present before the initiation of Trelegy treatment will be handled as a “comorbidity”, had been cured before initiation will be handled as a “medical history in the past”.
   *Categorization of severity prior to start treatment follows "Asthma prevention and management guideline Japan 2018"
3) Pre-treatment medications for asthma (during 6 weeks prior to the initiation of Trelegy treatment)
   Presence or absence of medications for asthma during 6 weeks prior to the initiation of Trelegy treatment, name and category of medications, one day dose of Inhaled Corticosteroid (ICS) (if medicine contains ICS)
4) Administration status of Trelegy
   Unit dose and frequency of daily dose during the observation period, date of start and end of treatment, reason if dose and dosage changed, reasons if a patient has withdrawn from/terminated treatment
5) Concomitant medications
   Presence or absence of concomitant medications during the observation period, name of medications, and reason for the medications
6) Concomitant therapies for asthma (except for medications)
   Presence or absence of concomitant therapies for asthma, name of therapies
7) Asthma management status of a patient (course of clinical symptoms)
   (1) Respiratory Function Test (Peak Expiratory Flow [PEF])
   PEF result measured at the initiation of Trelegy treatment, at the timing of 1, 3, and 6 month after the initiation of treatment and at the end of observation period (1 year after the

initiation of treatment or at the withdrawal/termination of treatment if treatment with Trelegy is withdrawn/terminated), measurement date, measured timing of the day (morning/evening), presence and absence of use of short-acting beta 2 agonist (SABA) within 6 hours before measuring PEF score, type of peak flow meter used

(2) Respiratory Function Test (Spirometry)
Spirometry results performed at the initiation of treatment with Trelegy and during the observation period; the date of Spirometry performed, forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) , presence and absence of use of short-acting beta 2 agonist (SABA) within 6 hours before Spirometry

(3) Asthma Control Test (ACT)
The ACT score recorded by patients at the initiation of Trelegy treatment, at the timing of 1, 3, and 6 month after the initiation of treatment and at the end of observation period (1 year after the initiation of treatment or at the discontinuation of treatment if treatment with Trelegy is discontinued), the date of ACT performed

(4) Events related to exacerbation of asthma
Presence or absence of following events related to exacerbation of asthma for 1 year prior to the initiation of Trelegy treatment and 1 year after the initiating treatment (or to the time point of withdrawal/termination);

- Hospitalization due to exacerbation of asthma
- Treatment at emergency room due to exacerbation of asthma
- Oral corticosteroid use (3days or more) due to exacerbation of asthma
- Unscheduled visit to a medical institution due to exacerbation of asthma
- Experience of one day off from work (including home activities) or school due to exacerbation of asthma

The investigator enters the test results and details of above (1) to (3) in EDC system, if those tests are performed.

8) Overall assessment of effectiveness
Effectiveness will be comprehensively assessed by any of “effective” or “not effective” based on the course of subjective symptoms, and course of clinical symptoms (asthma management status), etc. from the initiation of Trelegy treatment to the end of the observation period. If effectiveness cannot be determined for some reasons, it should be assessed as “indeterminable”, and the reason should be entered in the EDC system.

9) Pregnancy
(For female patients) whether registered patient is pregnant during the observation period or not, and expected delivery date
In addition, the follow-up investigation will be conducted for a mother and her foetus as far as possible regarding the course of delivery, spontaneous abortion, elective abortion and AEs, etc.

10) Adverse Events (AEs)
Presence or absence of AEs after initiation of Trelegy treatment, diagnosis or symptoms, onset date, outcome of AEs, outcome date, seriousness, reason for assessing as serious, relationship with Trelegy, factors suspected of being related to AEs except for Trelegy

(1) To grasp the information of safety specification and ADRs, the investigator will enter the information of all AEs (e.g., a disease, symptom, abnormal laboratory value), seriousness and outcome of AEs occurring after the initiation of Trelegy treatment, regardless of whether or not the Trelegy is related. Please see "Adverse Event (p.8)" for the details of AE, ADR and seriousness. The relationship to Trelegy will be assessed by any of “related”

or “not related” by considering whether the possibility of a reasonable relationship to Trelegy is present or not.

Among the reported AEs, those corresponding to the events in the standard search formula (SMQ) [1] of “cardiovascular events” in the MedDRA[2] which introduced by ICH are handled as "safety specification".

AEs assessed as “related” to Trelegy will be handled as suspected “adverse drug reactions (ADRs)” that are caused by Trelegy.

9. Analysis Items and Methods

The detailed analysis plan will be stated in the Statistical Analysis Plan separately.

1) Analysis items
   (1) Patient composition-related matters
      i). Number of registered patients, number of patients whose Case Report Form (CRF) is collected and number of patients whose CRF data fixed
      ii). Numbers of patients included in the safety and effectiveness analysis sets, number of patients excluded from analysis and the reason for exclusion
   (2) Safety-related matters
      i). Occurrence of ADRs and infections (type, degrees and proportion of patients with ADRs, etc.)
      ii). Occurrence of events defined as safety specification
   (3) Effectiveness-related matters
      i). Responder rate based on the overall assessment of effectiveness
      The proportion of responders is the proportion of patients assessed as “effective”.
      ii). Distribution and changes of respiratory function test results
      iii). Distribution and changes of ACT score by each questionnaire items, total ACT score and changes in asthma control status
      iv). The proportion of events occurrence related to asthma exacerbation
2) Analysis methods
   (1) Safety
      i). Proportion of patients with ADRs will be calculated at 1-month, 3-month, 6-month and 1-year, and overall period.
      ii). Incidence rates per 100 Patient Years of follow-up will be calculated along with 95% exact Poisson confidence intervals using chi-square distribution around the estimate.
   (2) Effectiveness
      i). Proportion of responders in overall assessment will be calculated
      ii). For comparison of the scores, etc., the summary statistics for values at the time of measurement and changes from baseline, i.e. vs at 1-month, 3-month, 6-month and at the end of observation period (1 year after the initiation of treatment or at the discontinuation of treatment if treatment with Trelegy is discontinued) will be calculated.

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1 Standardised MedDRA Queries (SMQ) is standard search formula developed to retrieval data from a MedDRA-coded database. The group of related terms for defined medical condition or area of interest.

2 Medical Dictionary for Regulatory Activities (MedDRA). MedDRA is international medical terminology developed by International Council for Harmonisation of Technical. AEs are managed by cording into MedDRA terms (symptoms, diagnoses, physical signs, values of laboratory test, etc.).

(3) Consideration of covariates

i). Logistic regression model will be used to search for factors affecting safety (proportion of patients with ADRs) and effectiveness (proportion of responders).

10. Organizational Structure

Same as the one described in the Risk Management Plan (RMP)

11. Name, Address of the Outsourcees, and the Scope of Outsourced Operations

1) Registration, Data management

Outsourcee: CIMIC Co., Ltd

1-1-1 Shibaura, Minato-ku, Tokyo, Japan

Scope: patient registration, development of the EDC system, data cleaning and other related operations

Scope: data entry from CRFs, re-investigation, other related operations

2) Statistical analysis

Outsourcee: The Institute of Japanese Union of Scientists & Engineers

5-10-11 Sendagaya, Shibuya-ku, Tokyo, Japan

Scope: statistical analysis, other related operations

12. Scheduled Timing to Be a Milestone for Assessing the Status and Results of the Investigation, or Reporting to the Pharmaceuticals and Medical Devices Agency (PMDA) and Rationale

- At the time of Periodic Safety Reports: consideration will be comprehensively given to the safety and effectiveness information.
- At the time of re-examination application: the final report will be prepared/submitted, based on the results of tabulation and analysis obtained from the fixed data of all collected CRFs.

13. Additional Measures that Potentially to Be Taken Depending on the Investigation Results, and the Decision Criteria for the Commence

The RMP including the following, will be reviewed at the timings to be a milestone.

- Regarding the safety specification, if the proportion of occurrence, peak occurrence period and risk factors become visible as an ADR caused by Trelegy, the necessity for revising to the Package Insert and investigation materials will be considered as appropriate.
- Including whether a new issue in the safety specification is present or not, the necessity for changes in the content of plan in the present investigation will be considered.
- The necessity for creating the Risk Minimization Plan for a new issue in the safety specification will be considered.

14. Publication of the Investigation Results

The information regarding the results of the investigation will be provided to clinical sites, including publication as a final report, and as an interim report as appropriate, for the purpose of “proper use” and “safety assurance.

Result which reported to PMDA will be disclosed when requested based on the Information Disclosure Law. In addition, the summaries of the results of the investigation will be disclosed in the websites designated by PMDA or international authorities, and in ClinicalTrials.gov, GSK Clinical Study Register and GSK homepage. In either case, no privacy information about patient or investigator will be disclosed.

15. Other Requirements

1) Protocol Revision
   In the progress of the investigation, the number of patients excluded from analysis, occurrence of unexpected/serious ADRs, large increase in occurrence of specific ADRs and validity of the investigation items, etc. will be timely grasped during the investigation period, and the protocol will be reviewed and revised if necessary.
   If the content of the protocol of the investigation has been changed, the written submission should be made to the PMDA in advance, except for minor changes.
2) Measures to be taken if issues and concerns are detected
   If issues, etc. have been detected from the results of assessment/analysis during the investigation period or after completion of the investigation, consideration will be given on whether or not the Post-marketing Studies should be newly conducted, as appropriate.

16. Attachments

1)	Trelegy Ellipta General DUI Implementation Guidance	Attachment1
2)	Trelegy Ellipta General DUI Registration Form	Attachment2
3)	Trelegy Ellipta General DUI Case Report Form (CRF)	Attachment3
4)	Asthma Control Test (ACT)	Attachment4

Requests when Adverse Events occur

- For patients who experienced AEs, further detailed investigation may be conducted, if necessary. In such a case, your cooperation would be appreciated.
- If you find your patient experience AEs, please contact to the medical representative (MR) of GlaxoSmithKline K.K. promptly.

Adverse Events (AEs)

1. Adverse Events (AEs)

The term "AE" means any untoward medical occurrence in a patient administered a medical product and which does not necessarily have to have a relationship to this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory value, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Examples regarded as an AE:

- Exacerbation of any chronic or intermittent symptom being present before the start of this investigation (including increase in frequency or severity of symptoms). Any case where a target disease and an underlying disease worsens **unexpectedly**.
- Any symptom being newly detected or diagnosed after the start of treatment (included as an AE if it has been detected or diagnosed after the treatment, even though it may have already been present before the start of the study).
- Any sign, symptom, or sequela originating from a suspected interaction.
- Any sign, symptom, or sequela originating from a suspected overdose of medical product or concomitant drugs (An overdose itself should not be reported as an AE or serious AE) However, a deliberate overdose intended for suicide/self-injury should be reported, regardless of the presence/absence of a sequela.
- Any abnormal laboratory value (haematological test, biochemical test, urine test) or any other abnormal safety assessment item (eg. electrocardiogram, X-ray test, measurement of vital signs) (including worsening from baseline) when an investigator judges a patient's condition as clinically significant **beyond the expectable range** based on medical and scientific judgment.

Examples not regarded as an AE:

- Any progress, sign or symptom of a target disease or disorder and an **expected** disease or disorder.
- Any medical or surgical treatment (eg. endoscopy, appendicectomy). The symptom which needs these treatments should be regarded as an AE.
- Any case where no unfavourable medical occurrence happens (social and /or hospitalisation in convenience, etc.).
- Any disease and condition, if identified or detected before the start of the study, the changes in them are within the expected range of daily changes or does not worsen.
- Any change in abnormal laboratory values and any other safety assessment items, etc. related to a target disease or an underlying disease.

2. Adverse Drug Reactions (ADRs)

All noxious and unintended responses to a medical product related to any dose should be considered ADRs. The phase "response to a medical product" means that a causal relationship between a medical product and an AE is at least a reasonable possibility. Unlike an AE, an ADR features the fact that a relationship between a medical product and occurrence of an AE is suspected.

3. Serious Adverse Events (SAEs) or Adverse Drug Reactions (SADRs)
   An SAE or SADR is any untoward medical occurrence that at any dose:
   1) results in death
   2) is life-threatening[3]
   3) requires inpatient hospitalisation or prolongation of existing hospitalisation
   4) results in persistent or significant disability/incapacity
   5) is a congenital anomaly/birth defect
   6) is another event or reaction, if judged to be a medically important[4]

3 The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

4 Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of other important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias; convulsions that do not result in an inpatient hospitalisation; the development of drug dependency; the development of drug abuse.