Drug Use Investigation of Relvar® Ellipta® for Asthma Patients

Protocol

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1. **Objectives**
   This investigation will be conducted to collect and evaluate information regarding the safety and efficacy of Relvar® Ellipta® under the actual post-marketing use conditions of the product.

2. **Safety Specification**
   - Hypersensitivity
   - Serious cardiovascular events (cardiac arrhythmias (including QT prolongation and sudden death), cardiac ischemia, cardiac failure)
   - Systemic corticosteroid-related effects (suppression of adrenal cortical function, bone disorders, eye disorders, etc.)

3. **Study Population**
   This investigation will include patients who have been diagnosed with bronchial asthma, for which Relvar Ellipta is indicated, and to whom the product is prescribed for the first time.

4. **Planned Sample Size and Its Rationale**
   1) Target number of patients: 900 (750, as a safety analysis set)
   2) Rationale:
      In a clinical study in Japanese patients with bronchial asthma (214 patients), the incidence of adverse drug reactions (ADRs) occurring in one patient is 0.47%. The number of patients needed to allow detection of at least one case of each ADR occurring at an incidence of 0.4% or higher with a probability of at least 95% is 748. Therefore, the target number of patients was set at 900 in consideration of patients who may be withdrawn from, or who drop out of, the investigation.

5. **Planned Number of Medical Institutions by Department**
   Approximately 180 medical institutions, primarily the departments of internal medicine and respiratory medicine

6. **Investigation Period**
   Investigation period: December 2013 to November 2014
   Observation period: The observation period (duration of treatment with Relvar Ellipta) for each patient will be 12 weeks after the initiation of treatment with the product.
   Planned registration period: December 2013 to August 2014
   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. **Investigation Method**
   1) Request for the study 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 institution where Relvar 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) Registration of patients

This investigation will be conducted using a central registration method.

(1) The investigators will enter the patient information, etc. of patients to whom they started to prescribe Relvar Ellipta after concluding the contract (see “3. Study Population”) in the registration form, and send it to the Registration Center by FAX within 14 days after the initiation of prescription of Relvar Ellipta (the date of the initiation of prescription of the product should be regarded as Day 1).

Registration Center
ACRONET Corporation
FAX : (TEL : )

(2) When the number of registered patients reaches the contracted sample size, registration of patients at the study site will be stopped.

3) Collection of data and completion of the case report form (CRF)

(1) The investigator will confirm the study items such as the characteristics of the registered patients.

(2) At the initiation of treatment with Relvar Ellipta, the investigator will ask registered patients to enter necessary information in the “Asthma Control Test (ACT)” form 12 weeks after the initiation of treatment (or at the discontinuation/completion of treatment if treatment with Relvar Ellipta is discontinued/completed).

(3) The investigator will collect the ACT form from registered patients, review the content, and record it in the CRF.

(4) During the observation period, the investigator will review the information regarding the safety and efficacy, etc. If a registered patient does not visit the study site during the observation period, the investigator will obtain information regarding adverse events (AEs), etc. by telephone, etc. as far as possible.

(5) At the completion of the observation period (or at the discontinuation/completion of treatment if treatment with Relvar Ellipta is discontinued/completed) for a registered patient, the investigator will record the information obtained in the CRF and submit the completed CRF to the MR.

8. Investigation Items

The investigator will collect information regarding the following items, etc. as far as possible and record it in the CRF.

1) Information regarding the medical institution
   Names of the institution, department, and investigator

2) Patient characteristics (at the initiation of prescription of Relvar Ellipta)
   Identification number, sex, age or year of birth, date of the initiation of prescription of Relvar Ellipta, hospitalization status, body weight, reason for use of Relvar Ellipta, disease duration, severity prior to prescription of Relvar Ellipta, disease type, presence or absence of complications (renal impairment, hepatic impairment, etc.) and their names, and smoking history

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, symptoms, or allergies than bronchial asthma which have
existed prior to the initiation of treatment with Relvar Ellipta will be handled as a “complications.”

3) Prior medications for bronchial asthma (for 4 weeks prior to the initiation of treatment with Relvar Ellipta)
Presence or absence of prior medications for bronchial asthma for 4 weeks prior to the initiation of treatment with Relvar Ellipta, and the drug categories, names, and daily doses of long-term control medications (names and daily doses only of inhaled steroids and their combination medications will be necessary)

4) Status of treatment with Relvar Ellipta
Evaluation of Relvar Ellipta during the observation period in terms of the number of puffs per dose, treatment category, daily dose frequency, dates of initiation and completion of treatment, reason for change of the dosage regimen, treatment time zones, timing of treatment (relative to meals), status of the practice of pre- and post-treatment tooth brushing and gargling, treatment compliance, and usability of the inhaler

5) Concomitant medications
Presence or absence of concomitant medications during the observation period, and the names, routes of administration, average daily doses (only for inhaled steroids), and reasons for use of these medications

6) Concomitant therapies for bronchial asthma (other than medications)
Presence or absence of concomitant therapies (other than medications) for bronchial asthma during the observation period and the names of these therapies

7) Asthma Control Test (ACT)
Information provided on the ACT form by patients at the initiation of treatment with Relvar Ellipta and at the completion of the observation period (or at discontinuation/completion of treatment if treatment is discontinued/completed)

8) Global efficacy assessment
At 12 weeks after the initiation of treatment with Relvar Ellipta or at discontinuation/completion of treatment, the efficacy will be globally assessed as either “effective” or “ineffective” based on the courses of the subjective and the clinical symptoms, change in ACT score, etc. during the period between the initiation of treatment with Relvar Ellipta and 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 recorded in the CRF.

9) The status of continuation of treatment with Relvar Ellipta at the completion of the observation period
Status of the continuation of treatment at 12 weeks after the initiation of treatment with Relvar Ellipta and the reason for the discontinuation/completion

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

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

(1) In this investigation, the following items are defined as priority investigation items in order to monitor occurrence of them, etc.

- Hypersensitivity
- $\beta_2$-receptor agonist-related ADRs: serious cardiovascular events (cardiac arrhythmias (including QT prolongation and sudden death), cardiac ischemia, cardiac failure), tremor, effects on serum potassium
- Systemic corticosteroid-related effects: suppression of adrenal cortical function, bone disorders (fracture, osteoporosis, etc.), eye disorders (cataract, glaucoma, etc.), effects on glucose (blood glucose increased, diabetes mellitus, etc.), pneumonia
- Local corticosteroid-related effects: dysphonia, oral candidiasis

(2) To capture the priority investigation items and ADRs, the investigator will record information regarding all AEs (e.g., diseases, symptoms, abnormal laboratory values) occurring after the initiation of treatment with Relvar Ellipta in the CRF, regardless of the presence or absence of a relationship with the product. The relationship with Relvar Ellipta will be assessed on a scale of two categories: “related” or “not related,” and it will be recorded in the CRF.

(3) AEs assessed as “related” to Relvar 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 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 ACT item analysis set, number of patients excluded from the analysis sets and the reason for exclusion

(2) Items related to safety
   [1] Status of occurrence of ADRs and infections (e.g., type, severity and incidence of ADRs, etc.)
   [2] Factors that may affect safety (e.g., status of occurrence of ADRs and infections by patient characteristics [e.g., by age])

(3) Items related to efficacy
   [1] Efficacy rate based on the global assessment of efficacy
      The efficacy rate is defined as the proportion of patients assessed as “effective.”
   [2] Factors that may affect efficacy (e.g., the efficacy rate by patient characteristics)
   [3] Comparison of the total ACT scores

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
10. Medical Expert and Its Roles

1) Medical Expert

2) Roles of the Medical Expert
   (1) To provide advice on the content of the protocol
   (2) To determine the handling of any suspected cases and to create criteria on the handling of cases (as appropriate)
   (3) To provide the necessary medical advice for the conduct of this investigation

11. Publication of Investigation Results

Regarding the results of this investigation, information will be provided, as appropriate, to clinical sites as an interim or 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.

12. Organization

1) Same as the Risk Management Plan

2) Person responsible for the investigation: Manager

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

1) Registration
   Contractor: person responsible for PMS implementation and GVP director
   ACRONET Corporation
   1-4-1, Koishikawa, Bunkyo-ku, Tokyo
   Scope: patient registration, self-inspection, and other related operations

2) Data management, tabulation, and analysis
   Contractor: person responsible for PMS implementation and GVP director
   ACRONET Corporation
   1-4-1, Koishikawa, Bunkyo-ku, Tokyo
   Scope: data management, statistical analysis, self-inspection, and other related operations

14. 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 completion of the investigation: A final report will be created based on the tabulated analysis results obtained at the completion of the data lock for 900 patients (the planned sample size).
15. Additional Measures That May Be Implemented Based on the Investigation 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.

- The safety and efficacy will be evaluated, and revision of the package insert and other materials will be considered, as appropriate.
- 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.

16. 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 Ministry of Health, Labour and Welfare 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) CRF
      [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.

17. Attachments

1) Contract Document Attachment 1
2) Implementation Guidance for the Drug Use Investigation of Relvar Ellipta Attachment 2
3) Registration Form for the Drug Use Investigation of Relvar Ellipta Attachment 3
4) Case Report Form for the Drug Use Investigation of Relvar Ellipta  Attachment 4
5) ACT Form for the Drug Use Investigation of Relvar Ellipta  Attachment 5