Symbicort Turbuhaler 30/60
Protocol of SCEI for long-term use for COPD patients

1. Purpose of the investigation:

The purpose of the investigation is to confirm the following items in long-term use of Symbicort Turbuhaler (hereinafter referred to as the drug) in patients with chronic obstructive pulmonary disease (hereinafter referred to as COPD) under actual drug use in the post-marketing phase.

(1) Development of ADR not listed in the Precautions for use

(2) Safety in long-term use

   1) Development of ADRs possibly related to the pharmacological class effects of beta2 stimulant (Palpitations, Tachycardia, Tremor, Muscle cramp, etc), aggravation of hyperthyroidism
   2) Development of ADRs possible related to the pharmacological effect of steroid (local effect and systemic effect)
   3) Serious cardiovascular adverse events (such as arrhythmia, atrial fibrillation, supraventricular tachycardia, extrasystole, and angina pectoris)
   4) Pneumonia-related adverse events (such as pneumonia, bacterial pneumonia, and bronchopneumonia)

(3) Efficacy in long-term use (respiratory function, change of the subjective symptoms, etc.)

2. Target number of patients and the basis

Target number of patients: 1000

Ground: Adverse events reported in the phase III international joint controlled-study for Symbicort and the study of long-term administration of Symbicort both in which Japanese patients with COPD enrolled, and the overseas clinical studies for Symbicort were considered as common health problems in patients with COPD and those expected with beta stimulants or inhalation steroids as class effect.

However, considering that the drug is used for more broadly in the post-marketing phase, and that the drug is expected to be used longer in the post-marketing phase for patients with COPD due to the nature of the disease, the safety and efficacy of the drug in long-term use under actual drug use should be confirmed.

The appropriate number needed for safety evaluation for long-term use of the study drug should be 300-600 commonly according to the regulatory notification by Director of MHLW Evaluation and Licensing Division, Yakushin 592 (as of 24-May-1995). Therefore, taking into account the number of withdrawn under actual drug use, the target number of patients in this investigation was decided as 1000.

3. Subject of the investigation

Among patients treated with the drug due to ‘relief of various symptoms associated with airway obstructive disorders of chronic obstructive pulmonary disease (chronic bronchitis, pulmonary emphysema), which is the indication of the drug, those who received the drug for the first time.

4. Observation period

1 year

5. Number of investigation centres (by department)

About 400 institutions mainly internal medicine and respiratory division.

6. Investigation method

1) Target investigation medical institutions are hospitals where this drug has been delivered and started to use. Medical Representatives (hereinafter referred as MRs) will explain objectives, target and method of the investigation to physicians of the hospitals who will conduct the investigation, and will request the investigation to the head of the hospital. Written contract must be obtained before the investigation is started.
2) The investigation is carried out with central registration method. After the contract is obtained, MRs deliver Case Registration Form and CRF of the investigation to the physicians who will conduct the investigation.
3) After the drug is started, the physician fills the Case Registration Form, signs on it and sends it by fax to the central registration centre to be received within 14 days after the drug start date (the start date is considered as Day 1).
4) After a patient is registered, MR communicates completion of registration to the physician.
5) The physician monitors the patient for 1 years, fills the CRF within around 4 weeks, and hands it to the MR in charge.

7. Investigation period

Registration period: November 1st 2012 to January 31th 2014

Investigation period: November 1st 2012 to January 31th 2015

8. Data Items

(1) Patient identification

Identification number

(2) Background factors

Age, gender, indication, COPD staging classification at the baseline, duration of illness, height, weight, smoking habit, inpatient/outpatient, with/without hospitalization with COPD for one year prior to the start of the drug, with/without steroid administration for treatment of COPD for one year prior to the start of the drug, with/without past medical history/concomitant disease (if with, the disease), with/without previous medication for COPD for four weeks prior to start of the drug (if with, the drug name and administration route).

(3) With/without pregnancy during the observation period (if with, the expected delivery date).

(4) Dosage and administration of this drug

Start date, date of change of dosage and administration, dose, daily frequency of administration, the reason for change in case the dosage and administration were changed, treatment continued/discontinued, stop date and the reason for withdrawal in case the drug was stopped.

(5) Clinical course

The items below at the start of the drug, Week 12, Week 26, 1 year, and the time when the drug was discontinued.

1) Respiratory function test (forced vital capacity [FVC] ,forced expiratory volume [FEV_1]).
2) CCQ(clinical questionnaire about chronic obstructive pulmonary disease [COPD])

(6) Dosage and administration of concomitant drug(s)

With/without concomitant drug(s) during Symbicort treatment (if with, the drug name, administration route, and indication)

In case with AE, daily dose and treatment duration.

(7) Concomitant therapy (other than medication)

With/without concomitant therapy during Symbicort treatment (if with, the name of therapy and treatment purpose)

In case with AE, treatment duration.

(8) Blood pressure, pulse, laboratory test

If blood pressure and pulse were measured or any laboratory test described below was performed during the observation period, the date of measurement or test and the value should be described in the CRF. If any adverse event was recognised after the start of the drug, the details should be described in the section of Adverse Event.

[Laboratory test item]

Thyroid function, adrenal cortex function, bone metabolism, blood sugar (fasting or as needed, HbA1c), CPK (CK), serum potassium

(9) Adverse event

Regarding all adverse events developed during the observation period, AE term, onset date, outcome, outcome date, seriousness*, causality with the drug, alternative contributing factor, and the clinical laboratory test associated with the adverse event (the data item, reference value at the institution, examination date, value, etc).

Regarding serious event*, comment on the progress of the AE and the causality should be described.

If the outcome of the adverse event was 'death', the date of death, the cause of death, existence of the causality between the death and this drug, and with/without autopsy should be described. (If autopsy was conducted, the findings should be described.)

If the patient experienced worsening of existing COPD symptoms or sign (bronchitis, cough, sputum, sputum increased, dyspnoea, wheeze, etc.) which applies to any of the followings, it should be recorded as adverse events. For the worsening of COPD, whether or not treatment with systemic steroids was required and whether or not hospital admission was required should be recorded.

- The symptom(s) met the definition of serious adverse event*
- The symptom(s) led to treatment discontinuation.
- The symptom(s) was (were) judged by the investigator to be a new onset or different from the past COPD history (within one year before the start of the observation period).

*The definition of serious is based on 'serious' criteria by ICH (Yakushokuan No 0328007, 28 Mar 2005) as follows:

Patient died, life threatening, involved or prolonged inpatient hospitalization, involved persistence or significant disability or incapacity, congenital anomaly, other medically important condition

(10) Key investigation items, the rationale and the practical investigation method for them

- Development of ADRs possibly related to pharmacological effect of beta2 stimulant (palpitations, tachycardia, tremor, muscle cramp, etc), aggravation of the underlying disease in patients with hyperthyroidism.
- Development of ADRs possibly related to pharmacological effect of steroid (local effect and systemic effect)
- Development of serious cardiovascular adverse events (arrhythmia, atrial fibrillation, supraventricular tachycardia, extrasystoles, angina pectoris, etc)

- Development of adverse events related to pneumonia (pneumonia, bacterial pneumonia, bronchial pneumonia, etc.)

Ground: The adverse events reported in the domestic clinical studies and the international joint clinical studies were considered as common health problems in COPD patients or class effect recognized with beta2 stimulants and inhalation steroids. However, considering that the drug is used more broadly in the post-marketing phase, it was decided to focus on investigation of development of these AEs.

Cardiovascular AEs such as arrhythmia (atrial fibrillation, supraventricular tachycardia, extrasystole, etc) and angina pectoris, and AEs related to pneumonia have been reported with using the drug although they were rare. It was decided to focus on investigation of these evens as the symptoms may become serious.

Investigation method: The AEs possibly related to the pharmacological effect of beta2 stimulant and steroid should be described clearly with case examples as key investigation item in the section of adverse event of CRF and the implementation guideline. It is instructed to fill the Adverse Event section without fail if any of these events occurred.

(11) Others

If it is confirmed that the drug was used for a pregnant woman during the observation period of this investigation, follow-up investigation should be performed for the delivery and the neonate.

<Observation schedule>

	Start of treatment	Week12 Observation day***	Week26 Observation day***	Observation day after 1 year or at discontinuation ***
Patient's background factors	○			
Dosage and administration of this drug	←	—	—	→
Concomitant medications	←	—	—	→
Concomitant therapy	←	—	—	→
Clinical course*				
① Respiratory function test (FVC, FEV_1)	○**	○	○	○
② CCQ(clinical questionnaire about chronic obstructive pulmonary disease[COPD])	○**	○	○	○
Blood pressure, pulse, laboratory test	←	—	—	→
Adverse event	←	—	—	→

* Only the patients treated under daily practice should be the subject.

** The data within 4 weeks prior to initiation of Symbicort Turbuhaler should be entered.

*** Week 12 observation day should be the nearest date to the last dose during 12 weeks +- 4 weeks.
Week 26 observation day should be the nearest date to the last dose during 26 weeks +- 4 weeks.
Observation day after 1 year should be the nearest date to the last dose during 1 year +- 4 weeks.
'At discontinuation' should be the day of the last visit under the treatment or the last dose.

9. Items and method for analysis

Further details about conditions of target populations and analysis method are included in the statistical analysis plan.

(1) Items about structure of patients to analyse

Number of registered patients, number of patients whose CRF was collected, number of safety evaluable patients, number of efficacy evaluable patients, number of patients to exclude and the reason for exclusion

(2) Items about patient's background factors

Age, gender, indication of the drug, COPD staging classification at baseline, duration of illness, height, weight, BMI, smoking habit, inpatient/outpatient, with/without hospitalisation due to COPD during one year prior to the start of the drug, with/without treatment of COPD with systemic steroid and history of using steroid during one year prior to the start of the drug, past medical history, concomitant disease (with/without and the type), with/without previous therapeutic drug for COPD (with/without and the type)

(3) Items about treatment

Dose, daily frequency of administration, daily dose, concomitant drug (with/without, the type), concomitant therapy (with/without, the type)

(4) Safety items

1) ADR/infection development by category
2) ADR/infection development by patient's background factor and by treatment
   ADR/infection development by patient's background factor and by treatment should be confirmed to review factors affecting the safety of this drug.
   In addition, influence of concomitant disease(s), especially concomitant asthma, to the safety should be confirmed.
3) ADR development by treatment period
   ADR development should be confirmed by treatment period to review the safety in long-term use.
4) Development of serious adverse event by category
5) Development of serious AEs by treatment period
6) Development of ADRs possibly related to pharmacological effect of beta2 stimulant (Palpitations, Tachycardia, Tremor, Muscle cramp, etc).
7) Underlying disease aggravated in patients with hyperthyroidism
8) Development of ADRs possibly related to pharmacological effect of inhalation steroid (local effect and systemic effect)
9) Development of serious cardiovascular adverse events (such as arrhythmia, atrial fibrillation, supraventricular tachycardia, extrasystole, and angina pectoris)
10) Development of pneumonia-related adverse events (such as pneumonia, bacterial pneumonia, and bronchopneumonia)

(5) Efficacy items

1) Variation of respiratory function test (FVC, FEV_1) from the baseline at Week 12, Week 26, 1 year, or the time this drug was discontinued.
2) Variation of total CCQ score from the baseline at Week 12, Week 26, 1 year, or at the time this drug was discontinued.
3) Variation of total CCQ score by patient's background factor and by treatment

factor.

(6) Other items

COPD exacerbation should be confirmed.

COPD exacerbation is defined as the case in which any of the following conditions was met: hospitalization (including prolongation of hospitalization) due to worsening of COPD, and systemic steroid for COPD treatment.

10. Organisation to conduct the investigation

The organisation to conduct the investigation is same as that in the attachment (2) of the PMS Basic Plan.

11. In case of entrusting investigational operation partially, name and address of the contractor and the entrusted operations

Contractor:

Address: [redacted]

Name: [redacted]

Entrusted operations: Operations provided in the 'Contract about entrusted business of PMS operations'

Request to and contract with medical institutions, promotion of case registration, collection of CRFs and follow-up investigation, progress management, etc.

Address: [redacted]

Name: [redacted]

Entrusted operations: Case registration process, data management (data input, check and fixation of CRF data, preparation of follow-up investigation form, data base fixation, preparation of data set)

12. Other necessary items

(1) Amendment of the protocol

During the investigational period, the number of withdrawal, development of unexpected serious ADRs, remarkable increase of incidence of specific ADRs, and validity of investigational items should be grasped continuously. If needed, the protocol should be reviewed and revised.

In case of s-NDA is approved for dosage and administration or indications during the investigation period of Symbicort (except the case when the re-examination period is established newly), the protocol should be reviewed and revised appropriately.

(2) Actions when issues/questions are recognized

Conduct of Specific Clinical Experience Investigation and Post-marketing Clinical Studies is to be examined to detect/confirm their factors and to verify discussion outcome in following conditions: when development of a significant ADR unexpected from Precautions for use is suggested, when frequency of an ADR is excessively increased, when an issue was recognized in safety and efficacy compared to their condition before launch, and when development of a different kind of ADR is suggested.

*Attachment

A. Contract (draft)

B. Implementation Guidance of the investigation (draft)

C. Case Registration Form of the investigation (draft)

D. Case Reporting Form of the investigation (draft)