In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

Information

Study Title	Encruse Ellipta Drug Use Investigation
Clinical Study Identifier	201450
Date of last version of the final study report	Report Final (6-Mar-2020)
Medicinal product	Encruse Ellipta
Marketing Authorisation Holder(s)	GlaxoSmithKline K.K.
Country of study	Japan

Marketing authorisation holder(s)

Marketing authorisation holder(s)	GlaxoSmithKline K.K. Akasaka Intercity AIR, 1-8-1 Akasaka, Minato-ku, Tokyo 107-0052 Japan
MAH contact person	PPD Post-marketing Surveillance (PMS) Department

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1. ABSTRACT

Objective : A drug use investigation (DUI) was conducted to examine the safety and effectiveness of umeclidinium bromide (UMEC) dry powder inhaler (DPI) (Encruse Ellipta, hereinafter Encruse) in patients with chronic obstructive pulmonary disease (COPD) in daily clinical practice.

Methods : Patients were included in the study when they were diagnosed with COPD and umeclidinium-naïve, and the observation period was one year from the start of administration. Safety was assessed based on the incidence of adverse drug reactions (ADRs), and effectiveness was globally assessed by investigators based on the courses of subjective and clinical symptoms, COPD exacerbations, values in respiratory function tests and changes in COPD assessment test (CAT) scores, etc.

Results : In the 1,017 patients of the safety analysis set, 29 (2.9%) experienced ADRs. The most common ADRs by type were “cough” in four patients (0.4%), followed by “dysgeusia”, “atrial fibrillation”, “laryngeal discomfort”, “nausea”, “dysuria” and “urinary retention” in two patients each (0.2%). The responder rate was 89.9% (789/878 patients) based on global assessment in the 878 patients of the effectiveness analysis set. Patients had a decreased proportion of experiencing COPD exacerbations and improved CAT scores and respiratory functions (forced expiratory volume in one second or FEV_1, forced vital capacity or FVC).

Conclusion : From the results of the present study, Encruse had no new issues for safety and showed effectiveness in daily clinical practice, which suggests that Encruse is one of the useful drugs for treatment of COPD.

Key Words : UMEC DPI, COPD, PMS

2. LIST OF ABBREVIATIOS

ADRs	adverse drug reactions
AEs	adverse events
CAT	COPD assessment test
COPD	chronic obstructive pulmonary disease
CRF	case report form
DPI	dry powder inhaler
DUI	drug use investigation
EDC	electronic data capture
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
GPSP	Good Post-marketing Surveillance Practice
GSK	GlaxoSmithKline K.K.
LABA	long-acting β_2 agonist
LAMA	long-acting muscarinic receptor antagonist
MHLW	Ministry of Health, Labour and Welfare
MR	medical representative
PMDA	Pharmaceuticals and Medical Devices Agency
PMS	post-marketing surveillance
PT	preferred terms
SABA	short-acting β2 agonists
SOC	system organ class
UMEC	umeclidinium bromide
VI	vilanterol trifenatate

3. ETHICS

This observational study was requested by Pharmaceuticals and Medical Devices Agency (PMDA) in the context of the licensure of Encruse in Japan on 26 March 2015. The study was sponsored by GSK Japan and was conducted according to Japan Pharmaceutical Affairs Law and Good Post-marketing Study Practice (GPSP) regulation (Ordinance No. 171 from the Ministry of Health, Labour and Welfare (MHLW) as of 20 December 2004).

4. OTHER RESPONSIBLE PARTIES

The following outsourcees were involved in the study:

1) Registration
   Outsourcee : CMIC Co., Ltd.
   Scope : patient registration and other related operations
2) Data management
   Outsourcee : CMIC Co., Ltd.
   Scope : data management and other related operations
3) Data tabulation
   Outsourcee : CACEXICARE Corporation
   Scope : data tabulation and other related operations
4) Electronic data capture (EDC) system
   Outsourcee : FUJITSU FIP CORPORATION
   Scope : development and operation of EDC system and other related operations

5. MILESTONES

Milestone	Actual date
Approval of protocol	28 April 2015
Start of data collection	6 April 2016
End of data collection	24 January 2019
Database freeze	1 August 2019
Study end	29 November 2019
Results reported to Japanese authority (PMDA)	6 March 2020

6. RATIONALE AND BACKGROUND

Encruse 62.5µg Ellipta is an inhalation powder for treatment of COPD containing UMEC, a long-acting muscarinic receptor antagonist (LAMA), and a once-daily inhalation drug using Ellipta, a DPI given as a single puff.

The Guidelines for the Diagnosis and Treatment of COPD, fourth Edition* recommends the regular use of long-acting bronchodilators in patients with moderate or more severe COPD. In COPD, it is thought that acetylcholine released from cholinergic nerves stimulates peripheral airways to contract. UMEC competitively blocks the binding of acetylcholine to the muscarinic receptors present on bronchial smooth muscles and inhibits bronchial smooth muscle contraction.

In Japan, Anoro Ellipta, a combination of UMEC and vilanterol trifenatate (VI), a long-acting β_2 agonist (LABA), was approved in July 2014, indicated for "relief of symptoms of obstructive airway disorder due to COPD (chronic bronchitis and emphysema) (when an inhaled LAMA/LABA combination is required), prior to Encruse 62.5μg Ellipta.

The manufacturing and marketing approval was applied based on the results of an international joint phase III clinical study and a Japanese long-term administration study, and Encruse 62.5μg Ellipta was approved in March 2015, indicated for "relief of symptoms of obstructive airway disorder due to COPD (chronic bronchitis and emphysema)".

In addition, it was approved in April 2014 in the United States, Europe and Canada, indicated for COPD.

*The Guidelines when Encruse was under development

7. RESEARCH QUESTION AND OBJECTIVES

The objective of the study was to collect and assess information regarding the safety and effectiveness of Encruse in daily clinical practice.

8. AMENDMENTS AND UPDATES

Protocol Version	Date	Section of study protocol	Amendment or update	Reason
1	28 April 2015	-	-	-
1.1	17 December 2015	Name, Address of the Outsourcees, and the Scope of Outsourced Operations	Amendment	Addition of an outsourcee

9. RESEARCH METHODS

9.1. Study design and procedures

In the study, the EDC system was used for patient registration and data collection.

1) Request for the study and contract

   (1) The medical representative (MR) explained the objectives, study population, study items, study methods, etc. to the potential investigators, etc. of the medical

institutions where Encruse had been adopted and delivered, and requested them to cooperate with the study.

(2) Once agreement on cooperation with the study was obtained, a written contract was concluded with the head (e.g., director) of the medical institution prior to initiation of the study.

2) Registration of study population

This study was conducted by a central registration method.

(1) The investigator entered the information of patients for whom administration of Encruse had been initiated after conclusion of the contract and who were listed in "9.2. Subjects" in the EDC system within 14 days after the start date of administration of Encruse (The start date of administration was regarded as Day 1) to complete the registration of the patients.

(2) When the number of registered patients reached the contracted sample size, registration of patients at the medical institution was completed.

3) Collection of data and entry in the EDC system.

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

(2) The investigator requested the registered patients to complete the "CAT" at the initiation of treatment with Encruse, and at one month and one year after the initiation of treatment (at withdrawal/completion, if a patient was withdrawn from/completed administration).

(3) The investigator collected the CAT of the registered patients, reviewed the content, and entered the information in the EDC system.

(4) During the observation period, the investigator monitored the information regarding safety and effectiveness, etc. If a patient did not visit the medical institution during the observation period, the investigator obtained the information regarding adverse events (AEs), etc. by telephone, etc. as far as possible.

(5) At the end of the observation period (or at withdrawal/completion, if a patient was withdrawn from/completed administration), the investigator entered the obtained information into the EDC system and sent it to the system.

9.2. Subjects

This study was conducted in patients who were first prescribed Encruse for the approved indication, "relief of symptoms of obstructive airway disorder due to COPD (chronic bronchitis and emphysema)".

9.3. Variables

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

1) Information regarding medical institutions
   Name of the institution, department, and investigator
2) Patient characteristics (at the start of administration of Encruse)
   Identification number, sex, year of birth, start date of administration of Encruse, hospitalization status, height, body weight, reason for use of Encruse, type of COPD, stage classification, duration of COPD, history of cigarette smoking, Brinkman index, and presence or absence of comorbidities (bronchial asthma, cardiovascular disorder, renal impairment, hepatic impairment other than the primary disease, etc.) and their names
   To protect the confidentiality regarding identification of an individual patient, the identification number was a unique number assigned to each patient by the investigator, etc. In this study, any other diseases or symptoms than COPD that had existed prior to the initiation of treatment with Encruse was handled as a "comorbidity".
3) Prior medications for COPD (four weeks before the initiation of treatment)
   Presence or absence of prior medications for COPD four weeks before the initiation of treatment, and the medication categories and product names
4) Status of treatment with Encruse
   Single dose and daily dose frequency of Encruse, start date of administration, end date of administration, and reason for revising Dosage and Administration during the observation period
5) Concomitant medications
   Presence or absence of concomitant medications, name of the medications, route of administration, reason for administration, during the observation period
6) Concomitant therapies for COPD (other than medications)
   Presence or absence of concomitant therapies for COPD, name of the therapies, during the observation period
7) COPD exacerbations
   Number of COPD exacerbations during the one-year period before and after the initiation of treatment with Encruse
8) Respiratory function tests (spirometry)
   Whether or not tests were performed, dates of tests, whether or not short-acting β_2 agonists (SABA) were used within four hours before measurement, FEV_1 and FVC at the initiation of treatment with Encruse, at one month and one year after the initiation of treatment, or at withdrawal/completion
9) CAT
   Whether or not the patient-completed "CAT" was available, the information at the initiation of treatment with Encruse, at one month and one year after the initiation of treatment, or at withdrawal/completion

10) Global assessment of effectiveness
One year after the initiation of treatment with Encruse or at the withdrawal/completion of treatment, effectiveness was assessed globally on a scale of "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. If effectiveness could not be determined for some reasons, it was assessed as "indeterminable", and the reason was entered into the EDC system.
11) Status of continuation of treatment with Encruse at the end of the observation period
Status of the continuation of treatment at the end of the treatment with Encruse and reason for the withdrawal/completion
12) Pregnancy
Whether or not Encruse was administered to a pregnant woman, whether or not a patient was pregnant during the observation period, and expected delivery date (if a patient is female)
The follow-up was performed on a mother and her fetus as far as possible regarding the course of delivery, miscarriage, abortion, etc. and AEs, etc.
13) AEs
Presence or absence of AEs after the initiation of treatment with Encruse, diagnosis or symptoms, dates of onset, outcomes of AEs, dates of outcome, seriousness, reasons for assessing as serious, relationship with Encruse, and other factors suspected of being related to AEs except Encruse
    (1) In the study, the priority investigation matters were defined as follows; cardiovascular events, urinary retention, eye-related events, gallbladder disorder, intestinal obstruction, anticholinergic effects, lower respiratory tract infection and pneumonia
    (2) To capture the priority investigation matters and ADRs, the investigator entered the information regarding all AEs (e.g., diseases, symptoms, abnormal laboratory values) occurring after the initiation of treatment with Encruse into the EDC system, regardless of the presence or absence of a relationship with Encruse. The relationship with Encruse was assessed on a scale of two categories, "related" or "not related", and it was entered into the EDC system.
    (3) The AEs assessed as "related" to Encruse were handled as "ADRs" suspected of being caused by Encruse.

9.4. Study size

1) Target number of patients: 1,000 (registration)
2) Rationale:
In the clinical study for Japanese COPD patients (131 patients), the incidence of ADRs related to "cardiovascular events", an important identified risk of Encruse,

was 4% [5/131 patients] (supraventricular tachycardia in two patients (2%), angina pectoris, palpitations, and sinus tachycardia in one patient each (0.76%)).
On assumption that the incidence used as a threshold for cardiovascular events is assumed to be 4%, 305 patients in the safety analysis set are required to check the incidence in the PMS with estimation accuracy which detects the 4% of threshold with a statistical power of ≥80% when the risk exists 2 times or more of the threshold. Accordingly, it is thought to be possible to examine the incidence of cardiovascular events in the DUI with 1,000 patients.

9.5. Statistical methods

1) Analysis matters
   (1) Matters 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 effectiveness 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 Effectiveness 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 Effectiveness 2 (global assessment of effectiveness and CAT scores), number of patients excluded from the analysis set and the reason for exclusion
   (2) Patient characteristics and baseline characteristics
      Distribution of patient characteristics and baseline characteristics
      - Stage classification, duration of COPD, type of prior medications and concomitant medications/therapies, history of cigarette smoking, age, body weight, comorbidities, whether or not a patient had comorbid bronchial asthma, etc.
      - CAT scores, number of COPD exacerbations
      - Spirometry
   (3) Matters related to safety
      [1] Incidence of ADRs by the Japanese version of MedDRA System Organ Class (SOC) and Preferred Terms (PT)
      [2] Priority investigation matters: MedDRA codes should be identified.
      - Cardiovascular events, urinary retention, eye-related events, gallbladder disorder, intestinal obstruction, anticholinergic effects, lower respiratory tract infection and pneumonia
      [3] Explorative assessment of factors that affect the presence or absence of ADRs and the presence or absence of ADRs set as the priority investigation matters (patient and baseline characteristics)

[4] Subgroup analysis of the presence or absence of ADRs and the presence or absence of ADRs set as the priority investigation matters (elderly, etc.)

(4) Matters related to effectiveness

[1] Effectiveness 1

- Distribution of FEV_1
- Explorative assessment of the effects of factors that affect FEV_1 (patient and baseline characteristics)
- Subgroup analysis of FEV_1 (elderly etc.)

[2] Effectiveness 2

- Distribution of global effectiveness assessment and CAT scores
- Explorative assessment of the effects of factors that affect the effectiveness and CAT scores (patient and baseline characteristics)

2) Analysis methods

For factors that may affect the matters related to the safety and effectiveness, etc., the odds ratios and their 95% confidence intervals were calculated. The results were 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 time of measurement and the changes from baseline were calculated and graphically presented using a boxplot, as appropriate.

10. RESULTS

See Attachment 1.

Study title	ENCRUSE ELLIPTA Drug Use Investigation
Protocol No.	201450
Date of preparation of final report	Final report (March 6, 2020)
Trade name	1. Encruse 62.5 μg Ellipta 7-dose inhaler 2. Encruse 62.5 μg Ellipta 30-dose inhaler
Active ingredient	Umeclidinium Bromide
Marketing Authorisation Holder (MAH)	GlaxoSmithKline K. K.

1. Protocol Outline

The protocol of this investigation is outlined below.

Protocol outline

Study title: ENCRUSE ELLIPTA Drug Use Investigation	
Objectives	This investigation is conducted to collect and assess information regarding the safety and effectiveness of ENCRUSE ELLIPTA (hereinafter referred to as “Encruse Ellipta”) in routine clinical practice.
Safety specification	Rationale: To collect information on a concern included in safety specification in routine clinical practice. ・Cardiovascular events
Priority investigation matters	Rationale: To collect information on the occurrence of priority investigation matters in routine clinical practice. ・Cardiovascular events ・Urinary retention ・Eye-related events ・Gallbladder disorder ・Intestinal obstruction ・Anticholinergic effects ・Lower respiratory tract infection and pneumonia
Concerns for effectiveness	Effectiveness in routine clinical practice
Study methods	Central registration method (data are entered and registered in the electronic data capture (EDC) system within 14 days after the start date of prescription of Encruse Ellipta (the start date of prescription is regarded as Day 1))
Target population	This investigation is conducted in patients who are first administered Encruse Ellipta for the approved indication of the product, “Relief of symptoms of obstructive airway disorder due to chronic obstructive pulmonary disease (COPD) (chronic bronchitis/emphysema)”.
Study period	November 1, 2015 to January 31, 2019
Target sample size	1,000 (as the number of subjects to be registered)
Observation period (treatment period)	The observation period (duration of treatment with Encruse Ellipta) in each patient is 1 year after the start date of administration of the product.
Study items	Information regarding the medical institutions Patient characteristics (at the initiation of administration of Encruse Ellipta) Prior medication for COPD (4 weeks before the initiation of treatment) Status of treatment with Encruse Ellipta Concomitant medications Concomitant therapies for COPD (other than medications) COPD exacerbations Respiratory function test (spirometry) COPD assessment test (CAT) Global assessment of effectiveness Status of continuation of treatment with Encruse Ellipta at the end of the observation period Pregnancy Adverse events (AEs)
Criteria for effectiveness evaluation	Effective, not effective, or indeterminable
Remarks	Protocol revision: April 20, 2015: First edition December 17, 2015: Minor revision of the protocol (changes in the name and address of the contractors)

2. Study Results

2.1. Number of Medical Institutions and Patient Disposition

The number of medical institutions and patient disposition are shown in Figure 1.

2.2. Patient Characteristics (Percentage Distribution of Patients)

The percentage distribution of 1,017 patients in the safety analysis set is shown in Table 1. The majority of the patients were “male” (77.9%), and the mean age was 69.8 ± 11.2 years. The most common disease type was “emphysema” (55.3%), and the most common baseline severity was “moderate (stage II)” (45.8%).

The percentage distribution in the effectiveness analysis set was similar to the above.

2.3. Status of Continuation of Treatment with Encruse Ellipta and Reasons for Discontinuation

The status of continuation of treatment with Encruse Ellipta at the end of the observation period in 1,017 patients in the safety analysis set is shown in Table 2. There were 595 patients (58.5%) who “continued the treatment”, and 422 patients (41.5%) who “discontinued the treatment”. The reasons for discontinuation included “premature stopping of visits” (160 patients, 15.7%) and “patient’s circumstances other than the above” (100 patients, 9.8%).

2.4. Safety

2.4.1. Occurrence of Adverse Drug Reactions (ADRs)

Among the 1,017 patients in the safety analysis set, 29 patients were reported to have experienced ADRs, and the proportion of patients with ADRs was 2.9% (29/1,017 patients) (Table 3-1).

The proportion of patients with ADRs in this investigation (2.9%, 29/1,017 patients) was lower than the overall proportion of patients with ADRs (9.3%, 17/183 patients) in the phase III open-label study in Japan (Study AC4115361), the phase III placebo-controlled, double-blind, comparative study (Study AC4115408), the phase III placebo-controlled, double-blind, comparative study (Study DB2113361) and the phase III placebo-controlled, double-blind, comparative study (Study DB2113373) conducted before the approval (Table 3-2).

The proportion of patients with ADRs by system organ class (SOC) was the highest for “Respiratory, thoracic and mediastinal disorders” and “Gastrointestinal disorders” (0.7% each, 7/1,017 patients), followed by “Renal and urinary disorders” (0.5%, 5/1,017 patients), and “Cardiac disorders” (0.4%, 4/1,017 patients).

The most common ADR by type was “Cough” (4 patients), followed by “Dysgeusia”, “Atrial fibrillation”, “Laryngeal discomfort”, “Nausea”, “Dysuria” and “Urinary retention” (2 patients each) (Table 3-1).

Serious ADRs were reported in 5 patients. The most common serious ADRs by type were “Urinary retention” and “Atrial fibrillation*” (2 patient each), followed by “Cardiac failure*” and “Arrhythmia” (1 patient each) (*same patient). The events reported and the outcome of each event are shown in Table 3-3.

Multiple episodes of an ADR of the same preferred term (PT) in the same patient was counted as 1 patient in the “number of patients (proportion of patients) with ADRs by type” based on the following order of priority.
Priority: [1] serious > non-serious, [2] death > recovered with sequelae > not recovered > recovering > recovered > unknown (for the time to the onset of ADRs, the priority was given to the initial onset)

No AEs were reported in the 56 patients excluded from the safety analysis set.

2.4.2. Factors that may Affect the Onset of ADRs

In order to investigate factors that may affect safety, the proportion of patients with ADRs was analyzed by patient characteristics. Analysis was performed using χ^2 test for n × 2 and Fisher's exact test for 2 × 2. A significance level of 5% (two-sided test in all analyses) was considered significant.

As a result of the investigation of factors that may affect safety, there was a significant difference in the proportion of patients with ADRs depending on “comorbidity (cardiovascular disorders)” as shown in Table 4. Therefore, the occurrence of ADRs was examined as follows.

2.4.2.1. “Comorbidity (Cardiovascular Disorders)”

The proportion of patients with ADRs was higher in patients with comorbidities (cardiovascular disorders). Therefore, the occurrence and seriousness of ADRs were examined by the presence or absence of comorbidities (cardiovascular disorders). Among patients with comorbidities (cardiovascular disorders), 9 patients were reported to have experienced ADRs. The most common SOCs were “Renal and urinary disorders” and “Cardiac disorders” in 3 patients each, followed by “Respiratory, thoracic and mediastinal disorders” in 2 patients. Common ADRs by type included “Atrial fibrillation” in 2 patients and others in 1 patient each (Table 4-1). There were 3 serious ADRs (“Atrial fibrillation*” in 2 patients, as well as “Urinary retention” and “Cardiac failure*” in 1 patient each (*same patient)). The outcome was recovered in all cases (Table 3-3). In 3 patients with ADRs corresponding to “Cardiac disorders” (“Atrial fibrillation*” in 2 patients, as well as “Cardiac failure*” and “Palpitations” in 1 patient each (*same patient)), comorbidities related to cardiovascular disorders were “Atrioventricular block complete”, “Angina pectoris” and “Atrial fibrillation” (Table 6-1).

As a result of the investigation of the occurrence and seriousness of ADRs in patients with comorbidities (cardiovascular disorders), no noteworthy trends were found.

2.4.3. Time to Onset of ADRs

For 29 patients with ADRs reported among 1,017 patients in the safety analysis set, the time from the initiation of treatment with Encruse Ellipta to the onset of ADRs was examined by type of ADRs. As a result, 51.7% (15/29 patients) of ADRs were reported before Day 28 after the start of treatment, and 72.4% (21/29 patients) of ADRs were reported before Day 84 after the start of treatment as shown in Table 5. Therefore, many ADRs occurred in an early stage of treatment. No other noteworthy trends were found.

2.4.4. Safety Specification (Cardiovascular Events)

The occurrence of ADRs related to the safety specification in the safety analysis set is shown in Table 6. Of these, “Atrial fibrillation” in 2 patients, as well as “Cardiac failure” and “Arrhythmia” in 1 patient each were reported as serious ADRs. The outcome was recovered in all cases (Table 6-1).

As a result of the investigation of the safety specification, no noteworthy matters were found.

2.4.5. Priority Investigation Matters

The occurrence of ADRs related to the priority investigation matters in the safety analysis set is shown in Table 7. There were no ADRs corresponding to “Gallbladder disorder”, “Intestinal obstruction” or “Lower respiratory tract infection and

pneumonia". Serious ADRs included "Atrial fibrillation" in 2 patients, as well as "Cardiac failure" and "Arrhythmia" in 1 patient each that were related to cardiovascular events (Table 6-1), and "Urinary retention" in 2 patients that were related to urinary retention and anticholinergic effects. The outcome was recovered in all cases (Table 7-1, Table 7-2).

As a result of the investigation of the priority investigation matters, no noteworthy matters were found.

2.5. Effectiveness

2.5.1. Evaluation of Effectiveness

One year after the initiation of treatment with Encruse Ellipta or at the discontinuation/completion of treatment, the effectiveness of the product was assessed by the investigator on a scale of two categories, “effective” or “not effective”, and three groups including “indeterminable”, 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 the 878 patients in the effectiveness analysis set, the proportion of responders was 89.9% (789/878 patients) (Table 8).

2.5.2. Factors that may Affect Effectiveness

In order to investigate factors that may affect effectiveness, stratified analysis was performed on the proportion of responders by patient characteristics. Analysis was performed using χ^2 test for n × 2 and Fisher's exact test for 2 × 2. A significance level of 5% (two-sided test in all analyses) was considered significant.

As a result of the investigation of factors that may affect effectiveness, there was a significant difference in the proportion of responders depending on “prior medications (COPD medications: others)” as shown in Table 8. Therefore, the following investigation was performed.

2.5.2.1. “Prior Medications (COPD Medications: Others)”

The proportion of responders was lower in patients with prior medications (COPD medications: others).

When the proportion of responders was examined by type of prior medications (COPD medications: others), the proportion of responders was lower in patients who had received “oral steroids” (75.0%, 9/12 patients), “expectorants” (81.5%, 53/65 patients) and “methylxanthine” (82.8%, 24/29 patients) (Table 8).

It was not possible to identify a clear cause as the number of non-responders among patients who had received prior medications (COPD medications: others) was as low as 17. However, the proportion of responders was 84.1% (90/107 patients) and thus it was not considered to be a clinically relevant factor.

2.5.3. COPD Exacerbations

Table 9 shows changes in the number of exacerbations in 495 patients who continued the treatment with the product for whom the number of COPD exacerbations during the 1-year period before and after the initiation of treatment with the product could be compared, out of the 878 patients in the effectiveness analysis set.

The proportion of patients without COPD exacerbation was 72.5% (359/495 patients) in 1 year before the initiation of treatment with the product, but it was increased to 91.7% (454/495 patients) in 1 year after the initiation of treatment. In patients who experienced 1, 2 and ≥3 exacerbations in 1 year before the initiation of treatment with the product, the proportion of patients who experienced fewer exacerbations in 1 year after the initiation of treatment was 82.6% (57/69 patients), 100.0% (38/38 patients) and 82.8% (24/29 patients), respectively.

2.5.4. COPD Assessment Test (CAT)

2.5.4.1. Evaluation Method

Summary statistics were calculated for CAT scores and changes before and after the initiation of treatment with Encruse Ellipta. For the changes, 1-sample paired t-test was performed to calculate 95% confidence interval (CI).

2.5.4.2. Patients Included in CAT Analysis Set

Of the 878 patients in the effectiveness analysis set, 448 patients whose CAT scores were obtained at the initiation of treatment with Encruse Ellipta, and at 1 month or 1 year after the initiation of treatment (or at the discontinuation/completion of treatment if treatment with the product had been discontinued/completed) were included in the CAT analysis.

2.5.4.3. Changes in CAT Score Before and After the Initiation of Treatment with Encruse Ellipta

As shown in Table 10, the mean change in CAT score from baseline to 1 month and 1 year after the initiation of treatment and discontinuation/completion of treatment if treatment had been discontinued/completed (95% CI) was -3.5 (-4.1, -2.8), -4.3 (-5.1, -3.4) and -2.6 (-5.0, -0.3), respectively. Therefore, significant reductions were observed ($p < 0.001$, $p < 0.001$ and $p = 0.028$).

2.5.4.4. Factors that may Affect CAT Scores

In order to investigate factors that may affect CAT scores, stratified analysis was performed on the summary statistics of changes in CAT score at 1 month after the initiation of treatment with Encruse Ellipta by patient characteristics. The analysis was performed using a 2-sample t-test for 2 category variables, and analysis of variance for variables with 3 or more categories. A significance level of 5% (two-sided test in all analyses) was considered significant.

As a result of the investigation of factors that may affect CAT scores, significant differences in changes were found for “sex”, “number of COPD exacerbations in 1 year before the initiation of treatment with Encruse Ellipta”, “number of COPD exacerbations in 1 year before the initiation of treatment with Encruse Ellipta (patients

who continued the treatment)", "prior medications (COPD medications): long-acting β_2 agonists (Hokunalin Tape)", "prior medications (COPD medications): long-acting β_2 agonists (other than the above)", and "concomitant medications (including non-COPD medications)" as shown in Table 10-1. Although there were differences in changes in each stratification, no noteworthy trends were found.

2.5.5. Respiratory Function Tests

2.5.5.1. Forced Expiratory Volume in 1 second (FEV_1)

2.5.5.1.1. Evaluation Method

Summary statistics were calculated for respiratory function test values (forced expiratory volume in 1 second, FEV_1) and changes before and after the initiation of treatment with Encruse Ellipta. For the changes, 1-sample paired t-test was performed to calculate 95% CI.

2.5.5.1.2. Patients Included in FEV_1 Analysis Set

Of the 878 patients in the effectiveness analysis set, 441 patients whose respiratory function test values (FEV_1) were obtained at the initiation of treatment with Encruse Ellipta, and at 1 month or 1 year after the initiation of treatment (or at the discontinuation/completion of treatment if treatment with the product had been discontinued/completed), who received or did not receive "short-acting β_2 agonists within 4 hours before measurement" at both time points (at and after the initiation of treatment with the product) were included in the analysis of respiratory function test (FEV_1).

2.5.5.1.3. Changes in FEV_1 Before and After the Initiation of Treatment with Encruse Ellipta

As shown in Table 11, the mean change in FEV_1 from baseline to 1 month and 1 year after the initiation of treatment and discontinuation/completion of treatment if treatment had been discontinued/completed (95% CI) was 119.6 mL (93.8, 145.5), 146.6 mL (115.5, 177.6) and 84.5 mL (15.4, 153.6), respectively. Therefore, significant improvements were observed ($p < 0.001$, $p < 0.001$ and $p = 0.018$).

2.5.5.1.4. Factors that may Affect FEV_1

In order to investigate factors that may affect FEV_1, stratified analysis was performed on the summary statistics of FEV_1 at 1 month after the initiation of treatment with Encruse Ellipta by patient characteristics. The analysis was performed using a 2-sample t-test for 2 category variables, and analysis of variance for variables with 3 or more categories. A significance level of 5% (two-sided test in all analyses) was considered significant.

As a result of the investigation of factors that may affect FEV_1, significant differences in changes were found for “age 1”, “age 2”, “reason for use (disease type)”, “history of cigarette smoking”, “comorbidity”, “comorbidity (bronchial asthma)”, “prior medications (COPD medications)”, “prior medications (COPD medications): long-acting anticholinergics” and “prior medications (COPD medications): long-acting anticholinergics (Spiriva)” as shown in Table 11-1. Although there were differences in changes in each stratification, no noteworthy trends were found.

2.5.5.2. Forced Vital Capacity (FVC)

2.5.5.2.1. Evaluation Method

Summary statistics were calculated for respiratory function test values (forced vital capacity, FVC) and changes before and after the initiation of treatment with Encruse Ellipta. For the changes, 1-sample paired t-test was performed to calculate 95% CI.

2.5.5.2.2. Patients included in FVC Analysis Set

Of the 878 patients in the effectiveness analysis set, 441 patients whose respiratory function test values (FVC) were obtained at the initiation of treatment with Encruse Ellipta and 1 month or 1 year after the initiation (or at discontinuation/completion of treatment if treatment had been discontinued/completed), who received or did not receive “short-acting β_2 agonists within 4 hours before measurement” at both time points (at and after the initiation of treatment with the product) were included in the analysis of respiratory function test (FVC).

2.5.5.2.3. Changes in FVC Before and After the Initiation of Treatment with Encruse Ellipta

As shown in Table 12, the mean change in FVC from baseline to 1 month and 1 year after the initiation of treatment and discontinuation/completion of treatment if treatment had been discontinued/completed (95% CI) was 112.4 mL (77.0, 147.7), 82.8 mL (44.7, 120.9) and 52.5 mL(-62.8, 167.8), respectively. Therefore, significant improvements were observed at 1 month and 1 year after the initiation of treatment ($p < 0.001$ each).

2.6. Patients with Special Background

2.6.1. Safety

2.6.1.1. Children (<15 Years)

Not applicable.

2.6.1.2. Elderly Patients (≥65 Years)

Among patients in the safety analysis set, there were 747 patients who used Encruse Ellipta (aged 65 to 96 years). The proportion of patients with ADRs was 3.1% (23/747 patients). The reported events are shown in Table 13.

2.6.1.3. Women in Pregnancy and Post-Delivery

Not applicable.

2.6.1.4. Patients with Renal Impairment

Among patients in the safety analysis set, there were 18 patients with renal impairment who used Encruse Ellipta. No ADRs were reported in these patients.

2.6.1.5. Patients with Hepatic Impairment

Among patients in the safety analysis set, there were 22 patients with hepatic impairment who used Encruse Ellipta. No ADRs were reported in these patients.

2.6.2. Effectiveness

2.6.2.1. Children (<15 Years)

Not applicable.

2.6.2.2. Elderly Patients (≥65 Years)

Among patients in the effectiveness analysis set, there were 652 patients who used Encruse Ellipta (aged 65 to 96 years). The proportion of responders was 89.7% (585/652 patients).

2.6.2.3. Women in Pregnancy and Post-Delivery

Not applicable.

2.6.2.4. Patients with Renal Impairment

Among patients in the effectiveness analysis set, there were 15 patients with renal impairment who used Encruse Ellipta. The proportion of responders was 93.3% (14/15 patients).

2.6.2.5. Patients with Hepatic Impairment

Among patients in the effectiveness analysis set, there were 19 patients with hepatic impairment who used Encruse Ellipta. The proportion of responders was 78.9% (15/19 patients).

3. Summary of Drug Use Investigation

3.1. Summary of Safety

In the 1,017 patients in the safety analysis set, the proportion of patients with ADRs was 2.9% (29/1,017 patients).

The most common ADR by type was “Cough” (4 patients), followed by “Dysgeusia”, “Atrial fibrillation”, “Laryngeal discomfort”, “Nausea”, “Dysuria” and “Urinary retention” (2 patients each).

As a result of the investigation of safety by patient characteristics, there was a factor that resulted in a significant difference in the proportion of patients with ADRs (comorbidity (cardiovascular disorders)). However, since an alert has already been provided in the current package insert, it was not considered necessary to take new measures to ensure proper use in relation to this factor.

There were no noteworthy matters in relation to the safety specification and priority investigation matters specified in this investigation.

It was not considered necessary to take new measures to ensure proper use for safety in the elderly, patients with renal impairment, and patients with hepatic impairment. Encruse Ellipta had not been used in children or women in pregnancy and post-delivery.

Based on the above, there were no new issues or problems in the safety of Encruse Ellipta in this investigation.

3.2. Summary of Effectiveness

In the 878 patients in the effectiveness analysis set, the proportion of responders was 89.9% (789/878 patients).

As a result of the investigation of effectiveness by patient characteristics, there was a factor that resulted in a significant difference in the proportion of responders (prior medications (COPD medications: others)). However, the proportion of responders was 84.1% (90/107 patients) and this factor was not clinically relevant. It was not considered necessary to take new measures to ensure proper use in relation to this factor.

It was not considered necessary to take new measures to ensure proper use for effectiveness in the elderly, patients with renal impairment, and patients with hepatic impairment. Encruse Ellipta had not been used in children or women in pregnancy and post-delivery.

Based on the above, there were no new issues or problems in the effectiveness of Encruse Ellipta in this investigation.

As of July 29, 2019

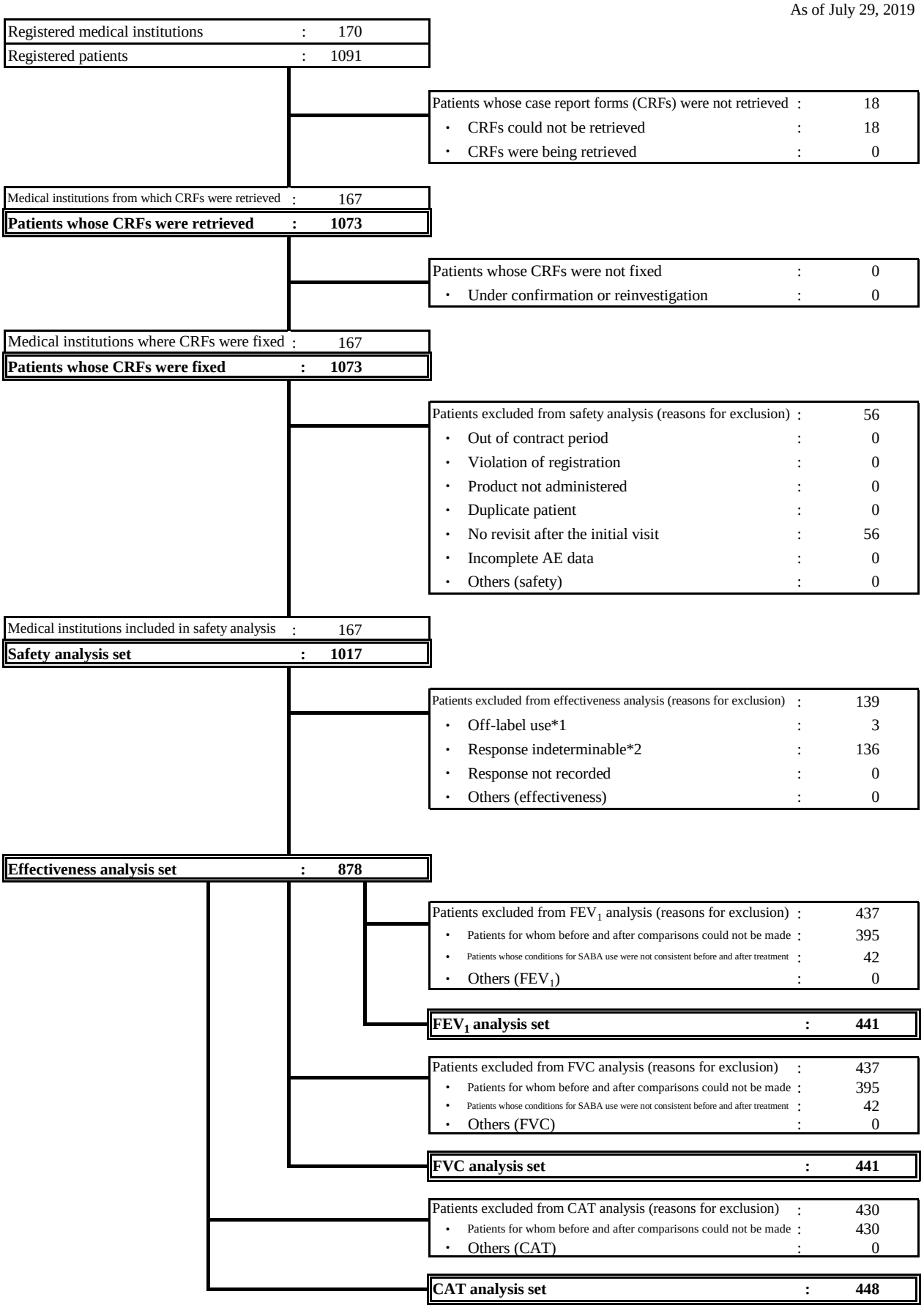

Figure 1 Number of Medical Institutions and Patient Disposition

*1: Bronchiectasis, post-lung cancer surgery and chronic bronchitis (1 patient each)
*2: Patients who were judged by the investigator to be unevaluable for response due to reasons such as “premature stopping of visits” and “short observation period”.

Table 1 Percentage Distribution of Patients

Safety analysis set, Effectiveness analysis set

As of July 29, 2019

Patient characteristics		Safety analysis set		Effectiveness analysis set	
		Number of patients surveyed	Percentage distribution (%)	Number of patients surveyed	Percentage distribution (%)
Total		1017	100.0	878	100.0
Sex	Male	792	77.9	689	78.5
	Female	225	22.1	189	21.5
Pregnancy (female only)	No	221	98.2	186	98.4
	Yes	0	0.0	0	0.0
	Unknown	4	1.8	3	1.6
Age 1 [years]*1 Mean ± SD: 69.8 ± 11.2 / 70.0 ± 11.1 Maximum: 96 / 96 Median: 71.0 / 72.0 Minimum: 22 / 22	<15	0	0.0	0	0.0
	≥15 - <65	270	26.5	226	25.7
	≥65 - <75	366	36.0	320	36.4
	≥75	381	37.5	332	37.8
	Unknown	0	0.0	0	0.0
Age 2 [years]	<65	270	26.5	226	25.7
	≥65	747	73.5	652	74.3
Hospitalization status	Inpatient	39	3.8	29	3.3
	Outpatient	978	96.2	849	96.7
	Unknown	0	0.0	0	0.0
BMI	<18.5	116	11.4	100	11.4
	≥18.5 - <25.0	569	55.9	493	56.2
	≥25.0	193	19.0	174	19.8
	Unknown	139	13.7	111	12.6
Number of COPD exacerbations in 1 year before the initiation of treatment with Encruse Ellipta	0	617	60.7	545	62.1
	1	135	13.3	113	12.9
	2	56	5.5	50	5.7
	≥3	39	3.8	34	3.9
	Unknown	170	16.7	136	15.5
Number of COPD exacerbations in 1 year after the initiation of treatment with Encruse Ellipta	0	825	81.1	749	85.3
	1	50	4.9	46	5.2
	2	14	1.4	12	1.4
	≥3	7	0.7	7	0.8
	Unknown	121	11.9	64	7.3
Number of COPD exacerbations in 1 year before the initiation of treatment with Encruse Ellipta (patients who continued the treatment: 595 patients / 577 patients*2)	0	373	36.7	360	41.0
	1	73	7.2	70	8.0
	2	39	3.8	38	4.3
	≥3	29	2.9	29	3.3
	Unknown	81	8.0	80	9.1
Number of COPD exacerbations in 1 year after the initiation of treatment with Encruse Ellipta (patients who continued the treatment: 595 patients / 577 patients*2)	0	531	52.2	517	58.9
	1	38	3.7	36	4.1
	2	9	0.9	8	0.9
	≥3	5	0.5	5	0.6
	Unknown	12	1.2	11	1.3
Reason for use (disease type)	Bronchitis chronic	233	22.9	199	22.7
	Emphysema	562	55.3	484	55.1
	Mixed	219	21.5	195	22.2
	Others	3	0.3	0	0.0
Baseline severity (disease stage)	Mild (stage I)	276	27.1	231	26.3
	Moderate (stage II)	466	45.8	417	47.5
	Severe (stage III)	156	15.3	138	15.7
	Very severe (stage IV)	41	4.0	34	3.9
	Unknown	78	7.7	58	6.6
Duration of COPD [years]	≤2	268	26.4	233	26.5
	>2 - ≤5	191	18.8	171	19.5
	>5 - ≤10	157	15.4	133	15.1
	10<	146	14.4	129	14.7
	Unknown	255	25.1	212	24.1
History of cigarette smoking	Never smoker	129	12.7	110	12.5
	Former smoker	582	57.2	511	58.2
	Current smoker	235	23.1	195	22.2
	Unknown	71	7.0	62	7.1
Brinkman Index (BI)	<400	65	6.4	56	6.4
	≥400 - <600	92	9.0	82	9.3
	≥600 - <1200	370	36.4	321	36.6
	≥1200	180	17.7	155	17.7
	Unknown	310	30.5	264	30.1
Comorbidity	No	309	30.4	275	31.3
	Yes	708	69.6	603	68.7
Comorbidity (bronchial asthma)	No	706	69.4	617	70.3
	Yes	311	30.6	261	29.7
Comorbidity (cardiovascular disorders)	No	888	87.3	770	87.7
	Yes	129	12.7	108	12.3
Comorbidity (renal impairment)	No	999	98.2	863	98.3
	Yes	18	1.8	15	1.7
Comorbidity (hepatic impairment)	No	995	97.8	859	97.8
	Yes	22	2.2	19	2.2
Comorbidity (others)	No	455	44.7	397	45.2
	Yes	562	55.3	481	54.8

Patient characteristics			Safety analysis set		Effectiveness analysis set	
			Number of patients surveyed	Percentage distribution (%)	Number of patients surveyed	Percentage distribution (%)
Total			1017	100.0	878	100.0
Prior medications (COPD medications)		No	554	54.5	472	53.8
		Yes	463	45.5	406	46.2
		Unknown	0	0.0	0	0.0
Long-acting anticholinergics		No	791	77.8	677	77.1
		Yes	226	22.2	201	22.9
	Spiriva	No	841	82.7	722	82.2
		Yes	176	17.3	156	17.8
	Seebri	No	981	96.5	845	96.2
		Yes	36	3.5	33	3.8
	Eklira	No	1007	99.0	870	99.1
		Yes	10	1.0	8	0.9
	Other than the above	No	1013	99.6	874	99.5
		Yes	4	0.4	4	0.5
Long-acting β_2 agonists		No	962	94.6	832	94.8
		Yes	55	5.4	46	5.2
	Serevent	No	1012	99.5	873	99.4
		Yes	5	0.5	5	0.6
	Onbrez	No	1003	98.6	866	98.6
		Yes	14	1.4	12	1.4
	Oxis	No	1014	99.7	877	99.9
		Yes	3	0.3	1	0.1
	Hokunalin Tape	No	988	97.1	853	97.2
		Yes	29	2.9	25	2.8
	Other than the above	No	1013	99.6	875	99.7
		Yes	4	0.4	3	0.3
Combination products of long-acting anticholinergics /long-acting β2 agonists		No	971	95.5	837	95.3
		Yes	46	4.5	41	4.7
	Ultibro	No	1004	98.7	866	98.6
		Yes	13	1.3	12	1.4
	Anoro	No	991	97.4	855	97.4
		Yes	26	2.6	23	2.6
	Other than the above	No	1010	99.3	872	99.3
		Yes	7	0.7	6	0.7
Combination products of long-acting β_2 agonists /inhaled steroids		No	762	74.9	651	74.1
		Yes	255	25.1	227	25.9
	Adoair	No	950	93.4	819	93.3
		Yes	67	6.6	59	6.7
	Symbicort	No	966	95.0	831	94.6
		Yes	51	5.0	47	5.4
	Relvar	No	902	88.7	774	88.2
		Yes	115	11.3	104	11.8
	Flutiform	No	996	97.9	862	98.2
		Yes	21	2.1	16	1.8
	Other than the above	No	1016	99.9	877	99.9
		Yes	1	0.1	1	0.1
Others		No	888	87.3	771	87.8
		Yes	129	12.7	107	12.2
	Short-acting anticholinergics	No	1016	99.9	877	99.9
		Yes	1	0.1	1	0.1
	Short-acting β_2 agonists	No	989	97.2	859	97.8
		Yes	28	2.8	19	2.2
	Methylxanthine	No	984	96.8	849	96.7
		Yes	33	3.2	29	3.3
	Inhaled steroids	No	1006	98.9	867	98.7
		Yes	11	1.1	11	1.3
	Oral steroids	No	1004	98.7	866	98.6
		Yes	13	1.3	12	1.4
	Expectorants	No	940	92.4	813	92.6
		Yes	77	7.6	65	7.4
Concomitant medications (including non-COPD medications)		No	324	31.9	280	31.9
		Yes	693	68.1	598	68.1
Concomitant therapies		No	949	93.3	819	93.3
		Yes	68	6.7	59	6.7
Type of concomitant therapy (duplicates included)		Respiratory rehabilitation	32	3.1	28	3.2
		Oxygen therapy	42	4.1	36	4.1
		Ventilatory support therapy	4	0.4	3	0.3
		Lung volume reduction surgery	0	0.0	0	0.0
		Lung transplant	0	0.0	0	0.0
		Other than the above	1	0.1	1	0.1
Forced expiratory volume in 1 second (FEV_1) (at the initiation of treatment with Encruse Ellipta) [mL]*1 Mean ± SD: 1760.65 ± 687.01 / 1751.40 ± 667.04 Maximum: 4400.0 / 4340.0 Median: 1725.00 / 1730.00 Minimum: 420.0 / 420.0		<500	4	0.4	3	0.3
		≥500 - <1000	91	8.9	82	9.3
		≥1000 - <1500	186	18.3	155	17.7
		≥1500 - <2000	201	19.8	182	20.7
		≥2000 - <2500	152	14.9	136	15.5
		≥2500	106	10.4	87	9.9
		Unknown	277	27.2	233	26.5
Forced vital capacity (FVC) (at the initiation of treatment with Encruse Ellipta) [mL] *1 Mean ± SD: 2887.49 ± 866.99 / 2889.84 ± 862.34 Maximum: 6010.0 / 6010.0 Median: 2850.00 / 2860.00 Minimum: 470.0 / 470.0		<2000	108	10.6	94	10.7
		≥2000 - <2400	127	12.5	106	12.1
		≥2400 - <2800	117	11.5	103	11.7
		≥2800 - <3200	132	13.0	118	13.4
		≥3200 - <3600	95	9.3	84	9.6
		≥3600	161	15.8	140	15.9
		Unknown	277	27.2	233	26.5
Percent forced expiratory volume in 1 second ($\%FEV_1$) [%] *1 Mean ± SD: 68.60 ± 23.74 / 68.23 ± 23.47 Maximum: 154.5 / 154.5 Median: 68.45 / 68.42 Minimum: 13.3 / 13.3		<30	31	3.0	30	3.4
		≥30 - <50	136	13.4	118	13.4
		≥50 - <80	321	31.6	279	31.8
		≥80	214	21.0	187	21.3
		Unknown	315	31.0	264	30.1

Patient characteristics		Safety analysis set		Effectiveness analysis set	
		Number of patients surveyed	Percentage distribution (%)	Number of patients surveyed	Percentage distribution (%)
Total		1017	100.0	878	100.0
Mean number of daily doses [times/day]*1	<1.0	0	0.0	0	0.0
Mean ± SD: 1.00 ± 0.00 / 1.00 ± 0.00	1.0	1017	100.0	878	100.0
Maximum: 1.0 / 1.0	1.0<-<2.0	0	0.0	0	0.0
Median: 1.00 / 1.00	≥2.0	0	0.0	0	0.0
Minimum: 1.0 / 1.0	Unknown	0	0.0	0	0.0
Mean daily dose [μg/day]*1	<62.5	0	0.0	0	0.0
Mean ± SD: 62.50 ± 0.00 / 62.50 ± 0.00	62.5	1017	100.0	878	100.0
Maximum: 62.5 / 62.5	62.5<-<125.0	0	0.0	0	0.0
Median: 62.50 / 62.50	≥125.0	0	0.0	0	0.0
Minimum: 62.5 / 62.5	Unknown	0	0.0	0	0.0
Total number of days of treatment [days]*1	<28	54	5.3	23	2.6
Mean ± SD: 263.4 ± 137.8 / 287.7 ± 123.5	≥28 - <84	151	14.8	94	10.7
Maximum: 435 / 435	≥84 - <168	92	9.0	74	8.4
Median: 365.0 / 365.0	≥168 - <252	57	5.6	49	5.6
Minimum: 1 / 1	≥252 - <365	67	6.6	60	6.8
	≥365	596	58.6	578	65.8
	Unknown	0	0.0	0	0.0
Total dose [μg]*1	<1750.0	54	5.3	23	2.6
Mean ± SD: 16459.93 ± 8609.88 / 17979.93 ± 7719.35	≥1750.0 - <5250.0	151	14.8	94	10.7
Maximum: 27187.5 / 27187.5	≥5250.0 - <10500.0	92	9.0	74	8.4
Median: 22812.50 / 22812.50	≥10500.0 - <15750.0	57	5.6	49	5.6
Minimum: 62.5 / 62.5	≥15750.0 - <22812.5	67	6.6	60	6.8
	≥22812.5	596	58.6	578	65.8
	Unknown	0	0.0	0	0.0

*1: The “mean ± SD”, “maximum”, “median” and “minimum” of each patient factor are presented in the order of “safety analysis set” and “analysis set for effectiveness”.

*2: The number of patients who continued the treatment is presented in the order of “safety analysis set” and “effectiveness analysis set”.

Table 2 Status of Continuation of Treatment with Encruse Ellipta and Reasons for Discontinuation

Number of patients in safety analysis set

As of July 29, 2019

Status of continuation of treatment with Encruse Ellipta and reasons for discontinuation		Number of patients (percentage distribution, %)	
Safety analysis set		1017	
Treatment continued		595	(58.5)
Treatment discontinued		422	(41.5)
Reasons for treatment discontinuation*	Occurrence of AEs	38	(3.7)
	Pregnancy	0	(0.0)
	Factors related to effectiveness	82	(8.1)
	No visit after the date of first prescription	0	(0.0)
	Premature stopping of visits	160	(15.7)
	Patient’s circumstances other than the above	100	(9.8)
	Physician's discretion other than the above	51	(5.0)

*: Duplicates included

Table 3-1 Occurrence of ADRs and Infections in Post-marketing Surveillance, etc.

Name of investigation/study: ENCRUSE ELLIPTA Drug Use Investigation As of July 29, 2019

		Status of post-marketing surveillance, etc.	
Safety analysis set		1017	
Number of patients with ADRs		29	
Proportion of patients with ADRs		2.9%	
Types of ADRs		Number of patients with ADRs by type (proportion of patients)	
Metabolism and nutrition disorders		1	(0.1%)
	Hyperuricaemia	1	(0.1%)
Nervous system disorders		3	(0.3%)
	Dysgeusia	2	(0.2%)
	Taste disorder	1	(0.1%)
Eye disorders		1	(0.1%)
	Visual acuity reduced	1	(0.1%)
Cardiac disorders		4	(0.4%)
	Arrhythmia	1	(0.1%)
	Atrial fibrillation	2	(0.2%)
	Cardiac failure	1	(0.1%)
	Palpitations	1	(0.1%)
Respiratory, thoracic and mediastinal disorders		7	(0.7%)
	Cough	4	(0.4%)
	Dyspnoea	1	(0.1%)
	Laryngeal discomfort	2	(0.2%)
Gastrointestinal disorders		7	(0.7%)
	Constipation	1	(0.1%)
	Dry mouth	1	(0.1%)
	Dyspepsia	1	(0.1%)
	Nausea	2	(0.2%)
	Oral discomfort	1	(0.1%)
	Chapped lips	1	(0.1%)
Renal and urinary disorders		5	(0.5%)
	Dysuria	2	(0.2%)
	Pollakiuria	1	(0.1%)
	Urinary retention	2	(0.2%)
Reproductive system and breast disorders		1	(0.1%)
	Benign prostatic hyperplasia	1	(0.1%)
General disorders and administration site conditions		1	(0.1%)
	Chest discomfort	1	(0.1%)
Investigations		1	(0.1%)
	Intraocular pressure increased	1	(0.1%)

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Table 3-2 Occurrence of ADRs and Infections at the Time of Approval

Name of investigation/study: Phase III open-label study in Japan (Study AC4115361)
Phase III placebo-controlled, double-blind, comparative study (Study AC4115408)
Phase III placebo-controlled, double-blind, comparative study (Study DB2113361)
Phase III placebo-controlled, double-blind, comparative study (Study DB2113373)

		Status at the time of approval	
Safety analysis set		183	
Number of patients with ADRs		17	
Proportion of patients with ADRs		9.3%	
Types of ADRs		Number of patients with ADRs by type (proportion of patients)	
Infections and infestations		1	(0.5%)
	Herpes zoster	1	(0.5%)
Nervous system disorders		1	(0.5%)
	Headache	1	(0.5%)
Eye disorders		2	(1.1%)
	Vision blurred	2	(1.1%)
Cardiac disorders		4	(2.2%)
	Angina pectoris	1	(0.5%)
	Palpitations	1	(0.5%)
	Sinus tachycardia	1	(0.5%)
	Supraventricular tachycardia	1	(0.5%)
Respiratory, thoracic and mediastinal disorders		5	(2.7%)
	Cough	1	(0.5%)
	Dysphonia	3	(1.6%)
	Nasal congestion	1	(0.5%)
	Throat irritation	1	(0.5%)
Gastrointestinal disorders		3	(1.6%)
	Constipation	2	(1.1%)
	Dry mouth	1	(0.5%)
Reproductive system and breast disorders		1	(0.5%)
	Benign prostatic hyperplasia	1	(0.5%)
General disorders and administration site conditions		2	(1.1%)
	Chest discomfort	1	(0.5%)
	Thirst	1	(0.5%)
Investigations		1	(0.5%)
	Blood bilirubin increased	1	(0.5%)
Product issues		1	(0.5%)
	Device colour issue	1	(0.5%)

For the “Status at the time of approval”, cases were coded with LLT of MedDRA/16.0 and tabulated with MedDRA/J/22.0. MedDRA/J Version (22.0)

Table 3-3 List of Serious ADRs

Patients in safety analysis set

As of July 29, 2019

Subject registration number	Name of the event (MedDRA_PT)	Seriousness	Time to onset (days)	Outcome	Sex	Age (years)	Reason for use	Comorbidities (MedDRA_PT)
PPD	Urinary retention	Serious	3	Recovered	Male	75	Emphysema	Hypertension, mitral valve incompetence, spinal osteoarthritis, tuberculosis, ventricular extrasystoles
	Urinary retention	Serious	15	Recovered	Male	75	Emphysema	None
	Atrial fibrillation	Serious	127	Recovered	Male	84	Mixed	Angina pectoris, asthma, cerebral infarction, constipation, hypercholesterolaemia, hypertension, lumbar spinal stenosis, myalgia, spinal osteoarthritis
	Cardiac failure	Serious	127	Recovered	Male	84	Mixed	Angina pectoris, asthma, cerebral infarction, constipation, hypercholesterolaemia, hypertension, lumbar spinal stenosis, myalgia, spinal osteoarthritis
	Arrhythmia	Serious	14	Recovered	Male	79	Emphysema	None
	Atrial fibrillation	Serious	70	Recovered	Male	63	Mixed	Atrial fibrillation, benign prostatic hyperplasia, hypertension, hypertonic bladder

MedDRA/J version (22.0)

Table 4 List of ADRs by Patient Characteristics

Patients in safety analysis set

As of July 29, 2019

Patient characteristics		Number of patients surveyed	Number of patients with ADRs	Proportion of patients with ADRs (%)	χ^2 test or Fisher's exact test	Odds ratio			
						Standard	Point estimate	Lower limit of 95% CI	Upper limit of 95% CI
Total		1017	29	2.9	-	-	-	-	-
Sex	Male	792	23	2.9	F) p=1.000	*	-	-	-
	Female	225	6	2.7			0.916	0.368	2.278
Pregnancy (female only)	No	221	6	2.7	-	*	-	-	-
	Yes	0	0	-			-	-	-
	Unknown	4	0	0.0			-	-	-
Age 1 [years]	<15	0	0	-	X) p=0.467		-	-	-
Mean ± SD: 69.8 ± 11.2	≥15 - <65	270	6	2.2		*	-	-	-
Maximum: 96	≥65 - <75	366	9	2.5			1.109	0.390	3.155
Median: 71.0	≥75	381	14	3.7			1.678	0.637	4.425
Minimum: 22	Unknown	0	0	-			-	-	-
Age 2 [years]	<65	270	6	2.2	F) p=0.531	*	-	-	-
	≥65	747	23	3.1			1.397	0.563	3.469
Hospitalization status	Inpatient	39	2	5.1	F) p=0.307	*	-	-	-
	Outpatient	978	27	2.8			0.525	0.120	2.292
	Unknown	0	0	-			-	-	-
BMI	<18.5	116	0	0.0	X) p=0.171	*	-	-	-
	≥18.5 - <25.0	569	17	3.0			-	-	-
	≥25.0	193	5	2.6			-	-	-
	Unknown	139	7	5.0			-	-	-
Number of COPD exacerbations in 1 year before the initiation of treatment with Encruse Ellipta	0	617	21	3.4	X) p=0.543	*	-	-	-
	1	135	3	2.2			0.645	0.190	2.194
	2	56	1	1.8			0.516	0.068	3.909
	≥3	39	0	0.0			-	-	-
	Unknown	170	4	2.4			-	-	-
Number of COPD exacerbations in 1 year after the initiation of treatment with Encruse Ellipta	0	825	24	2.9	Not tested	*	-	-	-
	1	50	0	0.0			-	-	-
	2	14	0	0.0			-	-	-
	≥3	7	0	0.0			-	-	-
	Unknown	121	5	4.1			-	-	-
Number of COPD exacerbations in 1 year before the initiation of treatment with Encruse Ellipta (patients who continued the treatment)	0	373	2	0.5	X) p=0.755	*	-	-	-
	1	73	1	1.4			2.576	0.231	28.791
	2	39	0	0.0			-	-	-
	≥3	29	0	0.0			-	-	-
	Unknown	81	0	0.0			-	-	-
Number of COPD exacerbations in 1 year after the initiation of treatment with Encruse Ellipta (patients who continued the treatment)	0	531	3	0.6	Not tested	*	-	-	-
	1	38	0	0.0			-	-	-
	2	9	0	0.0			-	-	-
	≥3	5	0	0.0			-	-	-
	Unknown	12	0	0.0			-	-	-
Reason for use (disease type)	Bronchitis chronic	233	9	3.9	X) p=0.748	*	-	-	-
	Emphysema	562	14	2.5			0.636	0.271	1.490
	Mixed	219	6	2.7			0.701	0.245	2.003
	Others	3	0	0.0			-	-	-
Baseline severity (disease stage)	Mild (stage I)	276	13	4.7	X) p=0.139	*	-	-	-
	Moderate (stage II)	466	11	2.4			0.489	0.216	1.107
	Severe (stage III)	156	3	1.9			0.397	0.111	1.414
	Very severe (stage IV)	41	0	0.0			-	-	-
	Unknown	78	2	2.6			-	-	-
Duration of COPD [years]	≤2	268	8	3.0	X) p=0.566	*	-	-	-
	>2 - ≤5	191	3	1.6			0.519	0.136	1.981
	>5 - ≤10	157	6	3.8			1.291	0.440	3.793
	10<	146	3	2.1			0.682	0.178	2.610
	Unknown	255	9	3.5			-	-	-
History of cigarette smoking	Never smoker	129	4	3.1	X) p=0.743	*	-	-	-
	Former smoker	582	18	3.1			0.997	0.332	2.998
	Current smoker	235	5	2.1			0.679	0.179	2.576
	Unknown	71	2	2.8			-	-	-
Brinkman Index (BI)	<400	65	1	1.5	X) p=0.411	*	-	-	-
	≥400 - <600	92	5	5.4			3.679	0.420	32.258
	≥600 - <1200	370	9	2.4			1.595	0.199	12.809
	≥1200	180	5	2.8			1.828	0.210	15.950
	Unknown	310	9	2.9			-	-	-
Comorbidity	No	309	6	1.9	F) p=0.309	*	-	-	-
	Yes	708	23	3.2			1.696	0.683	4.207
Comorbidity (bronchial asthma)	No	706	19	2.7	F) p=0.684	*	-	-	-
	Yes	311	10	3.2			1.201	0.552	2.614
Comorbidity (cardiovascular disorders)	No	888	20	2.3	F) p=0.007 **	*	-	-	-
	Yes	129	9	7.0			3.255	1.449	7.314
Comorbidity (renal impairment)	No	999	29	2.9	F) p=1.000	*	-	-	-
	Yes	18	0	0.0			-	-	-
Comorbidity (hepatic impairment)	No	995	29	2.9	F) p=1.000	*	-	-	-
	Yes	22	0	0.0			-	-	-
Comorbidity (others)	No	455	11	2.4	F) p=0.571	*	-	-	-
	Yes	562	18	3.2			1.335	0.624	2.857

Patient characteristics			Number of patients surveyed	Number of patients with ADRs	Proportion of patients with ADRs (%)	χ^2 test or Fisher's exact test	Odds ratio			
							Standard	Point estimate	Lower limit of 95% CI	Upper limit of 95% CI
Total			1017	29	2.9	-	-	-	-	-
Prior medications (COPD medications)		No	554	12	2.2	F) p=0.186	*	-	-	-
		Yes	463	17	3.7			1.722	0.814	3.643
		Unknown	0	0	-			-	-	-
	Long-acting anticholinergics	No	791	25	3.2	F) p=0.366	*	-	-	-
		Yes	226	4	1.8			0.552	0.190	1.603
		Spiriva No	841	26	3.1	Not tested	*	-	-	-
		Spiriva Yes	176	3	1.7			0.544	0.163	1.816
		Seebri No	981	28	2.9	Not tested	*	-	-	-
		Seebri Yes	36	1	2.8			0.973	0.129	7.353
		Eklira No	1007	29	2.9	Not tested	*	-	-	-
		Eklira Yes	10	0	0.0			-	-	-
		Other than the above No	1013	29	2.9	Not tested	*	-	-	-
		Other than the above Yes	4	0	0.0			-	-	-
	Long-acting β_2 agonists	No	962	28	2.9	F) p=1.000	*	-	-	-
		Yes	55	1	1.8			0.618	0.082	4.626
		Serevent No	1012	29	2.9	Not tested	*	-	-	-
		Serevent Yes	5	0	0.0			-	-	-
		Onbrez No	1003	28	2.8	Not tested	*	-	-	-
		Onbrez Yes	14	1	7.1			2.679	0.339	21.192
		Oxis No	1014	29	2.9	Not tested	*	-	-	-
		Oxis Yes	3	0	0.0			-	-	-
		Hokunalin Tape No	988	29	2.9	Not tested	*	-	-	-
		Hokunalin Tape Yes	29	0	0.0			-	-	-
		Other than the above No	1013	29	2.9	Not tested	*	-	-	-
		Other than the above Yes	4	0	0.0			-	-	-
	Combination products of long-acting anticholinergics /long-acting β2 agonists	No	971	27	2.8	F) p=0.381	*	-	-	-
		Yes	46	2	4.3			1.589	0.366	6.897
		Ultibro No	1004	29	2.9	Not tested	*	-	-	-
		Ultibro Yes	13	0	0.0			-	-	-
		Anoro No	991	29	2.9	Not tested	*	-	-	-
		Anoro Yes	26	0	0.0			-	-	-
		Other than the above No	1010	27	2.7	Not tested	*	-	-	-
		Other than the above Yes	7	2	28.6			14.569	2.705	78.459
	Combination products of long-acting β_2 agonists /inhaled steroids	No	762	19	2.5	F) p=0.276	*	-	-	-
		Yes	255	10	3.9			1.596	0.732	3.479
		Adoair No	950	28	2.9	Not tested	*	-	-	-
		Adoair Yes	67	1	1.5			0.499	0.067	3.724
		Symbicort No	966	25	2.6	Not tested	*	-	-	-
		Symbicort Yes	51	4	7.8			3.204	1.071	9.579
		Relvar No	902	25	2.8	Not tested	*	-	-	-
		Relvar Yes	115	4	3.5			1.264	0.432	3.700
		Flutiform No	996	28	2.8	Not tested	*	-	-	-
		Flutiform Yes	21	1	4.8			1.729	0.224	13.337
		Other than the above No	1016	29	2.9	Not tested	*	-	-	-
		Other than the above Yes	1	0	0.0			-	-	-
	Others	No	888	25	2.8	F) p=0.779	*	-	-	-
		Yes	129	4	3.1			1.105	0.378	3.227
		Short-acting anticholinergics No	1016	29	2.9	Not tested	*	-	-	-
		Short-acting anticholinergics Yes	1	0	0.0			-	-	-
		Short-acting β_2 agonists No	989	29	2.9	Not tested	*	-	-	-
		Short-acting β_2 agonists Yes	28	0	0.0			-	-	-
		Methylxanthine No	984	29	2.9	Not tested	*	-	-	-
		Methylxanthine Yes	33	0	0.0			-	-	-
		Inhaled steroids No	1006	29	2.9	Not tested	*	-	-	-
		Inhaled steroids Yes	11	0	0.0			-	-	-
		Oral steroids No	1004	29	2.9	Not tested	*	-	-	-
		Oral steroids Yes	13	0	0.0			-	-	-
		Expectorants No	940	25	2.7	Not tested	*	-	-	-
		Expectorants Yes	77	4	5.2			2.006	0.680	5.918
Concomitant medications (including non-COPD medications)		No	324	7	2.2	F) p=0.424	*	-	-	-
		Yes	693	22	3.2			1.485	0.628	3.512
Concomitant therapies		No	949	27	2.8	F) p=1.000	*	-	-	-
		Yes	68	2	2.9			1.035	0.241	4.447
Type of concomitant therapy (duplicates included)		Respiratory rehabilitation	32	2	6.3	Not tested	-	-	-	-
		Oxygen therapy	42	0	0.0			-	-	-
		Ventilatory support therapy	4	0	0.0			-	-	-
		Lung volume reduction surgery	0	0	-			-	-	-
		Lung transplant	0	0	-			-	-	-
		Other than the above	1	0	0.0			-	-	-
Forced expiratory volume in 1 second (FEV_1) (at the initiation of treatment with Encruse Ellipta) [mL] Mean ± SD: 1760.65 ± 687.01 Maximum: 4400.0 Median: 1725.00 Minimum: 420.0		<500	4	0	0.0	Not tested		-	-	-
		≥500 - <1000	91	0	0.0		*	-	-	-
		≥1000 - <1500	186	5	2.7			-	-	-
		≥1500 - <2000	201	6	3.0			-	-	-
		≥2000 - <2500	152	7	4.6			-	-	-
		≥2500	106	6	5.7			-	-	-
		Unknown	277	5	1.8			-	-	-
Forced vital capacity (FVC) (at the initiation of treatment with Encruse Ellipta) [mL] Mean ± SD: 2887.49 ± 866.99 Maximum: 6010.0 Median: 2850.00 Minimum: 470.0		<2000	108	2	1.9	Not tested		2.377	0.213	26.579
		≥2000 - <2400	127	1	0.8		*	-	-	-
		≥2400 - <2800	117	3	2.6			3.315	0.340	32.325
		≥2800 - <3200	132	7	5.3			7.055	0.856	58.180
		≥3200 - <3600	95	6	6.3			8.494	1.005	71.776
		≥3600	161	5	3.1			4.038	0.466	35.006
		Unknown	277	5	1.8			-	-	-
Percent forced expiratory volume in 1 second (%FEV_1) [%] Mean ± SD: 68.60 ± 23.74 Maximum: 154.5 Median: 68.45 Minimum: 13.3		<30	31	0	0.0	Not tested		-	-	-
		≥30 - <50	136	1	0.7		*	-	-	-
		≥50 - <80	321	10	3.1			4.340	0.550	34.241
		≥80	214	9	4.2			5.926	0.742	47.309
		Unknown	315	9	2.9			-	-	-
Mean number of daily doses [times/day] Mean ± SD: 1.00 ± 0.00 Maximum: 1.0 Median: 1.00 Minimum: 1.0		<1.0	0	0	-	-		-	-	-
		1.0	1017	29	2.9		*	-	-	-
		1.0<-<2.0	0	0	-			-	-	-
		≥2.0	0	0	-			-	-	-
		Unknown	0	0	-			-	-	-
Mean daily dose [μg/day] Mean ± SD: 62.50 ± 0.00 Maximum: 62.5 Median: 62.50 Minimum: 62.5		<62.5	0	0	-	-		-	-	-
		62.5	1017	29	2.9		*	-	-	-
		62.5<-<125.0	0	0	-			-	-	-
		≥125.0	0	0	-			-	-	-
		Unknown	0	0	-			-	-	-

Patient characteristics		Number of patients surveyed	Number of patients with ADRs	Proportion of patients with ADRs (%)	χ^2 test or Fisher's exact test	Odds ratio			
						Standard	Point estimate	Lower limit of 95% CI	Upper limit of 95% CI
Total		1017	29	2.9	-	-	-	-	-
Total number of days of treatment [days]	<28	54	14	25.9	Not tested	*	-	-	-
Mean ± SD: 263.4 ± 137.8	≥28 - <84	151	5	3.3			0.098	0.033	0.288
Maximum: 435	≥84 - <168	92	4	4.3			0.130	0.040	0.419
Median: 365.0	≥168 - <252	57	2	3.5			0.104	0.022	0.483
Minimum: 1	≥252 - <365	67	1	1.5			0.043	0.005	0.342
	≥365	596	3	0.5			0.014	0.004	0.052
	Unknown	0	0	-			-	-	-
Total dose [µg]	<1750.0	54	14	25.9	Not tested	*	-	-	-
Mean ± SD: 16459.93 ± 8609.88	≥1750.0 - <5250.0	151	5	3.3			0.098	0.033	0.288
Maximum: 27187.5	≥5250.0 - <10500.0	92	4	4.3			0.130	0.040	0.419
Median: 22812.50	≥10500.0 - <15750.0	57	2	3.5			0.104	0.022	0.483
Minimum: 62.5	≥15750.0 - <22812.5	67	1	1.5			0.043	0.005	0.342
	≥22812.5	596	3	0.5			0.014	0.004	0.052
	Unknown	0	0	-			-	-	-

No mark, $p \geq 0.05$; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$

Table 4-1 List of ADRs in Patients with Comorbidities (Cardiovascular Disorders)

Patients in safety analysis set

As of July 29, 2019

	Comorbidities (cardiovascular disorders)											
	Yes				No				Total			
	All ADRs		Serious ADRs		All ADRs		Serious ADRs		All ADRs		Serious ADRs	
Number of patients surveyed	129				888				1017			
Number of patients with ADRs	9		3		20		2		29		5	
Proportion of patients with ADRs	7.0		2.3		2.3		0.2		2.9		0.5	
Types of ADRs	Number of patients with ADRs (%)				Number of patients with ADRs (%)				Number of patients with ADRs (%)			
Respiratory, thoracic and mediastinal disorders	2	(1.6%)	0	(0.0%)	5	(0.6%)	0	(0.0%)	7	(0.7%)	0	(0.0%)
Cough	1	(0.8%)	0	(0.0%)	3	(0.3%)	0	(0.0%)	4	(0.4%)	0	(0.0%)
Laryngeal discomfort	0	(0.0%)	0	(0.0%)	2	(0.2%)	0	(0.0%)	2	(0.2%)	0	(0.0%)
Dyspnoea	1	(0.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Gastrointestinal disorders	0	(0.0%)	0	(0.0%)	7	(0.8%)	0	(0.0%)	7	(0.7%)	0	(0.0%)
Nausea	0	(0.0%)	0	(0.0%)	2	(0.2%)	0	(0.0%)	2	(0.2%)	0	(0.0%)
Constipation	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Dry mouth	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Dyspepsia	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Oral discomfort	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Chapped lips	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Renal and urinary disorders	3	(2.3%)	1	(0.8%)	2	(0.2%)	1	(0.1%)	5	(0.5%)	2	(0.2%)
Dysuria	1	(0.8%)	0	(0.0%)	1	(0.1%)	0	(0.0%)	2	(0.2%)	0	(0.0%)
Urinary retention	1	(0.8%)	1	(0.8%)	1	(0.1%)	1	(0.1%)	2	(0.2%)	2	(0.2%)
Pollakiuria	1	(0.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Cardiac disorders	3	(2.3%)	2	(1.6%)	1	(0.1%)	1	(0.1%)	4	(0.4%)	3	(0.3%)
Atrial fibrillation	2	(1.6%)	2	(1.6%)	0	(0.0%)	0	(0.0%)	2	(0.2%)	2	(0.2%)
Arrhythmia	0	(0.0%)	0	(0.0%)	1	(0.1%)	1	(0.1%)	1	(0.1%)	1	(0.1%)
Cardiac failure	1	(0.8%)	1	(0.8%)	0	(0.0%)	0	(0.0%)	1	(0.1%)	1	(0.1%)
Palpitations	1	(0.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Nervous system disorders	1	(0.8%)	0	(0.0%)	2	(0.2%)	0	(0.0%)	3	(0.3%)	0	(0.0%)
Dysgeusia	1	(0.8%)	0	(0.0%)	1	(0.1%)	0	(0.0%)	2	(0.2%)	0	(0.0%)
Taste disorder	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Metabolism and nutrition disorders	1	(0.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Hyperuricaemia	1	(0.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Eye disorders	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Visual acuity reduced	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Reproductive system and breast disorders	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Benign prostatic hyperplasia	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
General disorders and administration site conditions	1	(0.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Chest discomfort	1	(0.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Investigations	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Intraocular pressure increased	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)

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Table 5 Time to Onset of ADRs

Patients in safety analysis set

As of July 29, 2019

	Time to onset of ADRs (days)*1								
	<28	≥28 - <84	≥84 - <168	≥168 - <252	≥252 - <365	≥365	Unknown*2	Total Number of patients (%)*3	
Safety analysis set	1017	963	812	721	664	596	0	1017	
Types of ADRs	Number of patients with ADRs by type								
Metabolism and nutrition disorders	0	0	0	0	0	1	1	1	(0.1)
Hyperuricaemia	0	0	0	0	0	0	1	1	(0.1)
Nervous system disorders	3	0	0	0	0	0	0	3	(0.3)
Dysgeusia	2	0	0	0	0	0	0	2	(0.2)
Taste disorder	1	0	0	0	0	0	0	1	(0.1)
Eye disorders	1	0	0	0	0	0	0	1	(0.1)
Visual acuity reduced	1	0	0	0	0	0	0	1	(0.1)
Cardiac disorders	2	1	1	0	0	0	0	4	(0.4)
Arrhythmia	1	0	0	0	0	0	0	1	(0.1)
Atrial fibrillation	0	1	1	0	0	0	0	2	(0.2)
Cardiac failure	0	0	1	0	0	0	0	1	(0.1)
Palpitations	1	0	0	0	0	0	0	1	(0.1)
Respiratory, thoracic and mediastinal disorders	2	3	1	1	0	0	0	7	(0.7)
Cough	1	2	0	1	0	0	0	4	(0.4)
Dyspnoea	0	1	0	0	0	0	0	1	(0.1)
Laryngeal discomfort	1	0	1	0	0	0	0	2	(0.2)
Gastrointestinal disorders	4	2	0	0	1	0	0	7	(0.7)
Constipation	0	1	0	0	0	0	0	1	(0.1)
Dry mouth	0	0	0	0	1	0	0	1	(0.1)
Dyspepsia	1	0	0	0	0	0	0	1	(0.1)
Nausea	2	0	0	0	0	0	0	2	(0.2)
Oral discomfort	1	0	0	0	0	0	0	1	(0.1)
Chapped lips	0	1	0	0	0	0	0	1	(0.1)
Renal and urinary disorders	3	0	0	1	0	0	1	5	(0.5)
Dysuria	0	0	0	1	0	0	1	2	(0.2)
Pollakiuria	1	0	0	0	0	0	0	1	(0.1)
Urinary retention	2	0	0	0	0	0	0	2	(0.2)
Reproductive system and breast disorders	0	0	1	0	0	0	0	1	(0.1)
Benign prostatic hyperplasia	0	0	1	0	0	0	0	1	(0.1)
General disorders and administration site conditions	0	0	0	0	0	0	1	1	(0.1)
Chest discomfort	0	0	0	0	0	0	1	1	(0.1)
Investigations	0	0	1	0	0	0	0	1	(0.1)
Intraocular pressure increased	0	0	1	0	0	0	0	1	(0.1)
Number of patients with ADRs (%)*4	15 (51.7)	6 (20.7)	3 (10.3)	2 (6.9)	1 (3.4)	0 (0.0)	2 (6.9)	29 -	(2.9) -
Cumulative number of patients with ADRs (%)*5	15 (51.7)	21 (72.4)	24 (82.8)	26 (89.7)	27 (93.1)	27 (93.1)	2 (6.9)	- -	- -

MedDRA/J version (22.0)

*1: Multiple episodes of an ADR of the same SOC and PT in the same patient were tabulated using the number of days of treatment before the first onset of the ADR.

*2: If the date of onset of ADR was unknown, the time to the onset of ADR was regarded as unknown in tabulation.

*3: Data were tabulated excluding duplicate cases among treatment categories and types of ADRs.

*4: (Number of patients with ADRs / Total number of patients) * 100

*5: (Cumulative number of patients with ADRs / Total number of patients) * 100

Table 6 Occurrence of ADRs and Infections in Additional Pharmacovigilance Plan

Name of investigation/study: ENCRUSE ELLIPTA Drug Use Investigation As of July 29, 2019

Number of patients in safety analysis set	1017			
Concerns included in safety specification	Serious		Non-serious	
	Number of patients	(proportion of patients)	Number of patients	(proportion of patients)
Important identified risks	-		-	
Cardiovascular events*1	3	(0.3%)	1	(0.1%)
Important potential risks	-		-	
Not applicable	-	-	-	-

MedDRA/J version (22.0)

Multiple episodes of an ADR of the same SOC and PT in the same patient were included and tabulated based on the order of priority, serious > non-serious.

*1: Events corresponding to “cardiovascular events” in the attached list of MedDRA codes

List of MedDRA codes

Survey items	Special Interest AE Group	MedDRA Version	SMQ, HLGT, HLT, SOC, PT or LLT	Code	Term
Safety specifications/priority investigation matters	Cardiovascular events	22.0	SMQ		Arrhythmia
Safety specifications/priority investigation matters	Cardiovascular events	22.0	SMQ		Cardiac failure
Safety specifications/priority investigation matters	Cardiovascular events	22.0	SMQ		Myocardial infarction
Safety specifications/priority investigation matters	Cardiovascular events	22.0	SMQ		Other ischaemic heart disease
Safety specifications/priority investigation matters	Cardiovascular events	22.0	SMQ		Central nervous system haemorrhage
Safety specifications/priority investigation matters	Cardiovascular events	22.0	SMQ		Cerebrovascular disease

Table 6-1 List of ADRs Related to Cardiovascular Events

Patients in safety analysis set

Priority investigation matter : Cardiovascular events

As of July 29, 2019

Subject registration number	Name of the event (MedDRA_PT)	Seriousness	Time to onset (days)	Outcome	Sex	Age (years)	Reason for use	Comorbidities (MedDRA_PT)
PPD	Palpitations	Non-serious	15	Recovered	Male	67	Emphysema	Atrioventricular block complete, cerebral infarction, hypertension
	Atrial fibrillation	Serious	127	Recovered	Male	84	Mixed	Angina pectoris, asthma, cerebral infarction, constipation, hypercholesterolaemia, hypertension, lumbar spinal stenosis, myalgia, spinal osteoarthritis
	Cardiac failure	Serious	127	Recovered	Male	84	Mixed	Angina pectoris, asthma, cerebral infarction, constipation, hypercholesterolaemia, hypertension, lumbar spinal stenosis, myalgia, spinal osteoarthritis
	Arrhythmia	Serious	14	Recovered	Male	79	Emphysema	None
	Atrial fibrillation	Serious	70	Recovered	Male	63	Mixed	Atrial fibrillation, benign prostatic hyperplasia, hypertension, hypertonic bladder

MedDRA/J version (22.0)

Table 7 Occurrence of ADRs and Infections Related to Priority Investigation Matters

Name of investigation/study: ENCRUSE ELLIPTA Drug Use Investigation As of July 29, 2019

Number of patients in safety analysis set	1017			
Priority investigation matters	Serious		Non-serious	
	Number of patients	(proportion of patients)	Number of patients	(proportion of patients)
Cardiovascular events*1	3	(0.3%)	1	(0.1%)
Urinary retention*1	2	(0.2%)	0	(0.0%)
Eye-related events*1	0	(0.0%)	1	(0.1%)
Gallbladder disorder*1	0	(0.0%)	0	(0.0%)
Intestinal obstruction*1	0	(0.0%)	0	(0.0%)
Anticholinergic effects*1	2	(0.2%)	2	(0.2%)
Lower respiratory tract infection and pneumonia*1	0	(0.0%)	0	(0.0%)

MedDRA/J version (22.0)

Multiple episodes of an ADR of the same SOC and PT in the same patient were included and tabulated based on the order of priority, serious > non-serious.

*1: Events corresponding to each priority investigation matter in the attached list of MedDRA codes

List of MedDRA codes

Survey items	Special Interest AE Group	MedDRA Version	SMQ, HLGT, HLT, SOC, PT or LLT	Code	Term
Safety specifications/priority investigation matters	Cardiovascular events	22.0	SMQ		Arrhythmia
Safety specifications/priority investigation matters	Cardiovascular events	22.0	SMQ		Cardiac failure
Safety specifications/priority investigation matters	Cardiovascular events	22.0	SMQ		Myocardial infarction
Safety specifications/priority investigation matters	Cardiovascular events	22.0	SMQ		Other ischaemic heart disease
Safety specifications/priority investigation matters	Cardiovascular events	22.0	SMQ		Central nervous system haemorrhage
Safety specifications/priority investigation matters	Cardiovascular events	22.0	SMQ		Cerebrovascular disease
Priority investigation matters	Urinary retention	22.0	PT	10046555	Urinary retention
Priority investigation matters	Urinary hesitation	22.0	PT	10046542	Urinary hesitation
Priority investigation matters	Micturition frequency decreased	22.0	PT	10059042	Micturition frequency decreased
Priority investigation matters	Urine flow decreased	22.0	PT	10046640	Urine flow decreased
Priority investigation matters	Fowler's syndrome	22.0	PT	10071718	Fowler's syndrome
Priority investigation matters	Eye-related events	22.0	SMQ	10001902	Amaurosis
Priority investigation matters	Eye-related events	22.0	SMQ	10001903	Amaurosis fugax
Priority investigation matters	Eye-related events	22.0	SMQ	10071364	Anterior chamber angle neovascularisation
Priority investigation matters	Eye-related events	22.0	SMQ	10069166	Blebitis
Priority investigation matters	Eye-related events	22.0	SMQ	10005169	Blindness
Priority investigation matters	Eye-related events	22.0	SMQ	10005178	Blindness day
Priority investigation matters	Eye-related events	22.0	SMQ	10005184	Blindness transient
Priority investigation matters	Eye-related events	22.0	SMQ	10005186	Blindness unilateral
Priority investigation matters	Eye-related events	22.0	SMQ	10007739	Cataract
Priority investigation matters	Eye-related events	22.0	SMQ	10069165	Conjunctival filtering bleb leak
Priority investigation matters	Eye-related events	22.0	SMQ	10079171	Deep anterior chamber of the eye
Priority investigation matters	Eye-related events	22.0	SMQ	10072729	Delayed dark adaptation
Priority investigation matters	Eye-related events	22.0	SMQ	10014456	Electrooculogram abnormal
Priority investigation matters	Eye-related events	22.0	SMQ	10074027	Exfoliation syndrome
Priority investigation matters	Eye-related events	22.0	SMQ	10072289	Eye colour change
Priority investigation matters	Eye-related events	22.0	SMQ	10057105	Eye laser surgery
Priority investigation matters	Eye-related events	22.0	SMQ	10015958	Eye pain
Priority investigation matters	Eye-related events	22.0	SMQ	10016059	Facial pain
Priority investigation matters	Eye-related events	22.0	SMQ	10052128	Glare
Priority investigation matters	Eye-related events	22.0	SMQ	10077986	Goniotomy
Priority investigation matters	Eye-related events	22.0	SMQ	10022943	Iridoschisis
Priority investigation matters	Eye-related events	22.0	SMQ	10022948	Iris atrophy
Priority investigation matters	Eye-related events	22.0	SMQ	10057420	Iris operation
Priority investigation matters	Eye-related events	22.0	SMQ	10068960	Narrow anterior chamber angle
Priority investigation matters	Eye-related events	22.0	SMQ	10029404	Night blindness
Priority investigation matters	Eye-related events	22.0	SMQ	10030041	Ocular hyperaemia
Priority investigation matters	Eye-related events	22.0	SMQ	10074349	Ophthalmic vein thrombosis
Priority investigation matters	Eye-related events	22.0	SMQ	10048544	Ophthalmodynamometry abnormal
Priority investigation matters	Eye-related events	22.0	SMQ	10061321	Optic disc disorder
Priority investigation matters	Eye-related events	22.0	SMQ	10034960	Photophobia
Priority investigation matters	Eye-related events	22.0	SMQ	10037520	Pupillary block
Priority investigation matters	Eye-related events	22.0	SMQ	10059663	Retinogram abnormal
Priority investigation matters	Eye-related events	22.0	SMQ	10067126	Seidel test positive
Priority investigation matters	Eye-related events	22.0	SMQ	10066418	Tenon's cyst
Priority investigation matters	Eye-related events	22.0	SMQ	10047513	Vision blurred
Priority investigation matters	Eye-related events	22.0	SMQ	10047531	Visual acuity reduced
Priority investigation matters	Eye-related events	22.0	SMQ	10047532	Visual acuity reduced transiently
Priority investigation matters	Eye-related events	22.0	SMQ	10047549	Visual evoked potentials abnormal
Priority investigation matters	Eye-related events	22.0	SMQ	10047571	Visual impairment
Priority investigation matters	Gallbladder disorder	22.0	PT	10056529	Biliary dyskinesia
Priority investigation matters	Gallbladder disorder	22.0	PT	10008611	Cholecystectomy
Priority investigation matters	Gallbladder disorder	22.0	PT	10008612	Cholecystitis
Priority investigation matters	Gallbladder disorder	22.0	PT	10008614	Cholecystitis acute
Priority investigation matters	Gallbladder disorder	22.0	PT	10008617	Cholecystitis chronic
Priority investigation matters	Gallbladder disorder	22.0	PT	10067426	Cholecystoenterostomy
Priority investigation matters	Gallbladder disorder	22.0	PT	10008624	Cholecystostomy
Priority investigation matters	Gallbladder disorder	22.0	PT	10008629	Cholelithiasis
Priority investigation matters	Gallbladder disorder	22.0	PT	10008630	Cholelithiasis obstructive
Priority investigation matters	Gallbladder disorder	22.0	PT	10052925	Cholelithotomy
Priority investigation matters	Gallbladder disorder	22.0	PT	10017624	Gallbladder cholesterolosis
Priority investigation matters	Gallbladder disorder	22.0	PT	10017626	Gallbladder disorder
Priority investigation matters	Gallbladder disorder	22.0	PT	10062693	Gallbladder enlargement

Survey items	Special Interest AE Group	MedDRA Version	SMQ, HLGT, HLT, SOC, PT or LLT	Code	Term
Priority investigation matters	Gallbladder disorder	22.0	PT	10017631	Gallbladder fistula
Priority investigation matters	Gallbladder disorder	22.0	PT	10058383	Gallbladder fistula repair
Priority investigation matters	Gallbladder disorder	22.0	PT	10017642	Gallbladder injury
Priority investigation matters	Gallbladder disorder	22.0	PT	10057987	Gallbladder mucocoele
Priority investigation matters	Gallbladder disorder	22.0	PT	10059446	Gallbladder necrosis
Priority investigation matters	Gallbladder disorder	22.0	PT	10080936	Gallbladder hypofunction
Priority investigation matters	Gallbladder disorder	22.0	PT	10017636	Gallbladder obstruction
Priority investigation matters	Gallbladder disorder	22.0	PT	10017637	Gallbladder oedema
Priority investigation matters	Gallbladder disorder	22.0	PT	10061962	Gallbladder operation
Priority investigation matters	Gallbladder disorder	22.0	PT	10004663	Biliary colic
Priority investigation matters	Gallbladder disorder	22.0	PT	10081151	Gallbladder rupture
Priority investigation matters	Gallbladder disorder	22.0	PT	10072319	Gallbladder varices
Priority investigation matters	Gallbladder disorder	22.0	PT	10056972	Hydrocholecystis
Priority investigation matters	Gallbladder disorder	22.0	PT	10020732	Hyperplastic cholecystopathy
Priority investigation matters	Gallbladder disorder	22.0	PT	10050899	Porcelain gallbladder
Priority investigation matters	Intestinal obstruction	22.0	PT	10051268	Anastomotic stenosis
Priority investigation matters	Intestinal obstruction	22.0	PT	10002250	Anastomotic ulcer, obstructive
Priority investigation matters	Intestinal obstruction	22.0	PT	10002581	Anorectal stenosis
Priority investigation matters	Intestinal obstruction	22.0	PT	10069083	Barium impaction
Priority investigation matters	Intestinal obstruction	22.0	PT	10062062	Large intestinal obstruction
Priority investigation matters	Intestinal obstruction	22.0	PT	10074061	Large intestinal stenosis
Priority investigation matters	Intestinal obstruction	22.0	PT	10056361	Distal intestinal obstruction syndrome
Priority investigation matters	Intestinal obstruction	22.0	PT	10056361	Distal intestinal obstruction syndrome
Priority investigation matters	Intestinal obstruction	22.0	PT	10013830	Duodenal obstruction
Priority investigation matters	Intestinal obstruction	22.0	PT	10081656	Gastrointestinal scarring
Priority investigation matters	Intestinal obstruction	22.0	PT	10050094	Duodenal stenosis
Priority investigation matters	Intestinal obstruction	22.0	PT	10013850	Duodenal ulcer perforation, obstructive
Priority investigation matters	Intestinal obstruction	22.0	PT	10013855	Duodenal ulcer, obstructive
Priority investigation matters	Intestinal obstruction	22.0	PT	10052072	Fibrosing colonopathy
Priority investigation matters	Intestinal obstruction	22.0	PT	10061970	Gastric stenosis
Priority investigation matters	Intestinal obstruction	22.0	PT	10017829	Gastric ulcer haemorrhage, obstructive
Priority investigation matters	Intestinal obstruction	22.0	PT	10017836	Gastric ulcer perforation, obstructive
Priority investigation matters	Intestinal obstruction	22.0	PT	10017840	Gastric ulcer, obstructive
Priority investigation matters	Intestinal obstruction	22.0	PT	10065879	Gastrointestinal anastomotic leak
Priority investigation matters	Intestinal obstruction	22.0	PT	10052105	Gastrointestinal hypomotility
Priority investigation matters	Intestinal obstruction	22.0	PT	10061173	Gastrointestinal motility disorder
Priority investigation matters	Intestinal obstruction	22.0	PT	10061974	Gastrointestinal obstruction
Priority investigation matters	Intestinal obstruction	22.0	PT	10018007	Gastrointestinal stenosis
Priority investigation matters	Intestinal obstruction	22.0	PT	10021307	Ileal stenosis
Priority investigation matters	Intestinal obstruction	22.0	PT	10021518	Impaired gastric emptying
Priority investigation matters	Intestinal obstruction	22.0	PT	10022687	Intestinal obstruction
Priority investigation matters	Intestinal obstruction	22.0	PT	10022699	Intestinal stenosis
Priority investigation matters	Intestinal obstruction	22.0	PT	10023176	Jejunal stenosis
Priority investigation matters	Intestinal obstruction	22.0	PT	10062062	Large intestinal obstruction
Priority investigation matters	Intestinal obstruction	22.0	PT	10023794	Large intestinal obstruction reduction
Priority investigation matters	Intestinal obstruction	22.0	PT	10074061	Large intestinal stenosis
Priority investigation matters	Intestinal obstruction	22.0	PT	10051606	Necrotising colitis
Priority investigation matters	Intestinal obstruction	22.0	PT	10049150	Necrotising gastritis
Priority investigation matters	Intestinal obstruction	22.0	PT	10055668	Necrotising oesophagitis
Priority investigation matters	Intestinal obstruction	22.0	PT	10028951	Neonatal intestinal obstruction
Priority investigation matters	Intestinal obstruction	22.0	PT	10029957	Obstruction gastric
Priority investigation matters	Intestinal obstruction	22.0	PT	10030178	Oesophageal obstruction
Priority investigation matters	Intestinal obstruction	22.0	PT	10030194	Oesophageal stenosis
Priority investigation matters	Intestinal obstruction	22.0	PT	10034358	Peptic ulcer perforation, obstructive
Priority investigation matters	Intestinal obstruction	22.0	PT	10034365	Peptic ulcer, obstructive
Priority investigation matters	Intestinal obstruction	22.0	PT	10050173	Prepyloric stenosis
Priority investigation matters	Intestinal obstruction	22.0	PT	10065707	Rectal obstruction
Priority investigation matters	Intestinal obstruction	22.0	PT	10038079	Rectal stenosis
Priority investigation matters	Intestinal obstruction	22.0	PT	10078158	Gastrointestinal bacterial overgrowth
Priority investigation matters	Intestinal obstruction	22.0	PT	10041101	Small intestinal obstruction
Priority investigation matters	Intestinal obstruction	22.0	PT	10062263	Small intestinal stenosis
Priority investigation matters	Intestinal obstruction	22.0	PT	10017649	Gallstone ileus
Priority investigation matters	Intestinal obstruction	22.0	PT	10058035	Gastric ileus
Priority investigation matters	Intestinal obstruction	22.0	PT	10021328	Ileus
Priority investigation matters	Intestinal obstruction	22.0	PT	10021333	Ileus paralytic
Priority investigation matters	Intestinal obstruction	22.0	PT	10021335	Ileus spastic
Priority investigation matters	Intestinal obstruction	22.0	PT	10051399	Mechanical ileus
Priority investigation matters	Intestinal obstruction	22.0	PT	10054048	Postoperative ileus
Priority investigation matters	Intestinal obstruction	22.0	PT	10050396	Subileus
Priority investigation matters	Anticholinergic effects	22.0	PT	10002757	Anticholinergic syndrome

Survey items	Special Interest AE Group	MedDRA Version	SMQ, HLGT, HLT, SOC, PT or LLT	Code	Term
Priority investigation matters	Anticholinergic effects	22.0	PT	10003591	Ataxia
Priority investigation matters	Anticholinergic effects	22.0	PT	10003840	Autonomic nervous system imbalance
Priority investigation matters	Anticholinergic effects	22.0	PT	10049848	Balance disorder
Priority investigation matters	Anticholinergic effects	22.0	PT	10010947	Coordination abnormal
Priority investigation matters	Anticholinergic effects	22.0	PT	10012373	Depressed level of consciousness
Priority investigation matters	Anticholinergic effects	22.0	PT	10013573	Dizziness
Priority investigation matters	Anticholinergic effects	22.0	PT	10071552	Hyporesponsive to stimuli
Priority investigation matters	Anticholinergic effects	22.0	PT	10024855	Loss of consciousness
Priority investigation matters	Anticholinergic effects	22.0	PT	10036653	Presyncope
Priority investigation matters	Anticholinergic effects	22.0	PT	10039897	Sedation
Priority investigation matters	Anticholinergic effects	22.0	PT	10041045	Slow response to stimuli
Priority investigation matters	Anticholinergic effects	22.0	PT	10041349	Somnolence
Priority investigation matters	Anticholinergic effects	22.0	PT	10042264	Stupor
Priority investigation matters	Anticholinergic effects	22.0	PT	10001497	Agitation
Priority investigation matters	Anticholinergic effects	22.0	PT	10010305	Confusional state
Priority investigation matters	Anticholinergic effects	22.0	PT	10012218	Delirium
Priority investigation matters	Anticholinergic effects	22.0	PT	10013395	Disorientation
Priority investigation matters	Anticholinergic effects	22.0	PT	10019063	Hallucination
Priority investigation matters	Anticholinergic effects	22.0	PT	10019070	Hallucination, auditory
Priority investigation matters	Anticholinergic effects	22.0	PT	10019071	Hallucination, gustatory
Priority investigation matters	Anticholinergic effects	22.0	PT	10019072	Hallucination, olfactory
Priority investigation matters	Anticholinergic effects	22.0	PT	10062824	Hallucination, synaesthetic
Priority investigation matters	Anticholinergic effects	22.0	PT	10019074	Hallucination, tactile
Priority investigation matters	Anticholinergic effects	22.0	PT	10019075	Hallucination, visual
Priority investigation matters	Anticholinergic effects	22.0	PT	10019079	Hallucinations, mixed
Priority investigation matters	Anticholinergic effects	22.0	PT	10038743	Restlessness
Priority investigation matters	Anticholinergic effects	22.0	PT	10043431	Thinking abnormal
Priority investigation matters	Anticholinergic effects	22.0	PT	10017581	Gait inability
Priority investigation matters	Anticholinergic effects	22.0	PT	10000389	Accommodation disorder
Priority investigation matters	Anticholinergic effects	22.0	PT	10002512	Anhidrosis
Priority investigation matters	Anticholinergic effects	22.0	PT	10005184	Blindness transient
Priority investigation matters	Anticholinergic effects	22.0	PT	10011719	Cycloplegia
Priority investigation matters	Anticholinergic effects	22.0	PT	10013774	Dry eye
Priority investigation matters	Anticholinergic effects	22.0	PT	10013781	Dry mouth
Priority investigation matters	Anticholinergic effects	22.0	PT	10013950	Dysphagia
Priority investigation matters	Anticholinergic effects	22.0	PT	10017577	Gait disturbance
Priority investigation matters	Anticholinergic effects	22.0	PT	10020565	Hyperaemia
Priority investigation matters	Anticholinergic effects	22.0	PT	10020741	Hyperpyrexia
Priority investigation matters	Anticholinergic effects	22.0	PT	10021013	Hypohidrosis
Priority investigation matters	Anticholinergic effects	22.0	PT	10028521	Mydriasis
Priority investigation matters	Anticholinergic effects	22.0	PT	10037660	Pyrexia
Priority investigation matters	Anticholinergic effects	22.0	PT	10043071	Tachycardia
Priority investigation matters	Anticholinergic effects	22.0	PT	10043458	Thirst
Priority investigation matters	Anticholinergic effects	22.0	PT	10070863	Toxicity to various agents
Priority investigation matters	Anticholinergic effects	22.0	PT	10046555	Urinary retention
Priority investigation matters	Anticholinergic effects	22.0	PT	10047513	Vision blurred
Priority investigation matters	Anticholinergic effects	22.0	PT	10047531	Visual acuity reduced
Priority investigation matters	Anticholinergic effects	22.0	PT	10047532	Visual acuity reduced transiently
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10003487	Aspergilloma
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10074171	Aspergillus infection
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10066798	Bacterial tracheitis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10006448	Bronchiolitis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10006451	Bronchitis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10061736	Bronchitis bacterial
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10061737	Bronchitis fungal
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10006460	Bronchitis haemophilus
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10062486	Bronchitis moraxella
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10062487	Bronchitis pneumococcal
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10053160	Bronchitis viral
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10006473	Bronchopulmonary aspergillosis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10009115	Chronic pulmonary histoplasmosis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10054220	Enterobacter tracheobronchitis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10051011	Fibrinous bronchitis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10069508	Fungal tracheitis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10019143	Hantavirus pulmonary infection
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10056971	Infective exacerbation of chronic obstructive airways disease
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10061266	Legionella infection
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10024968	Lower respiratory tract infection
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10063890	Lower respiratory tract infection bacterial
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10065187	Lower respiratory tract infection fungal

Survey items	Special Interest AE Group	MedDRA Version	SMQ, HLGT, HLT, SOC, PT or LLT	Code	Term
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10065188	Lower respiratory tract infection viral
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10025028	Lung abscess
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10070831	Necrotising bronchiolitis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10061351	Pleural infection
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10067334	Pleural infection bacterial
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10067024	Pseudomonas bronchitis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10037374	Pulmonary echinococciasis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10037422	Pulmonary mycosis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10075078	Organic dust toxic syndrome
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10051739	Pulmonary sepsis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10068184	Pulmonary trichosporonosis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10038705	Respiratory moniliasis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10038718	Respiratory syncytial virus bronchiolitis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10069811	Respiratory syncytial virus bronchitis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10060693	Respiratory tract infection bacterial
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10048979	Sinobronchitis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10044302	Tracheitis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10044304	Tracheitis obstructive
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10044314	Tracheobronchitis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10044315	Tracheobronchitis mycoplasmal
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10061556	Tracheobronchitis viral
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10047481	Viral tracheitis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10001027	Acute pulmonary histoplasmosis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10071075	Atypical mycobacterial pneumonia
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10003757	Atypical pneumonia
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10005098	Blastomycosis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10053582	Bronchopneumopathy
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10053158	Candida pneumonia
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10009825	Coccidioidomycosis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10011490	Cryptococcosis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10014568	Empyema
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10054218	Enterobacter pneumonia
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10020141	Histoplasmosis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10071699	Infectious pleural effusion
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10070092	Legionella test positive
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035664	Pneumonia
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10025080	Lung consolidation
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10061229	Lung infection
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10055088	Miliary pneumonia
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10070323	Mycobacterium test positive
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10029444	Nocardiosis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10067472	Organising pneumonia
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10073755	Pneumocystis jirovecii pneumonia
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035664	Pneumonia
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035665	Pneumonia adenoviral
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035667	Pneumonia anthrax
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035669	Pneumonia aspiration
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10060946	Pneumonia bacterial
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035671	Pneumonia blastomyces
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035672	Pneumonia bordetella
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035673	Pneumonia chlamydial
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10067565	Pneumonia cryptococcal
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035676	Pneumonia cytomegaloviral
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035699	Pneumonia escherichia
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10061354	Pneumonia fungal
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035702	Pneumonia haemophilus
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10065246	Pneumonia helminthic
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035703	Pneumonia herpes viral
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035714	Pneumonia influenzal
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035717	Pneumonia klebsiella
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035718	Pneumonia legionella
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035722	Pneumonia measles
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035723	Pneumonia moraxella
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035724	Pneumonia mycoplasmal
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10055672	Pneumonia necrotising
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035727	Pneumonia parainfluenzae viral
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035728	Pneumonia pneumococcal
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10057582	Lung infection pseudomonal
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035732	Pneumonia respiratory syncytial viral
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035733	Pneumonia salmonella

Survey items	Special Interest AE Group	MedDRA Version	SMQ, HLGT, HLT, SOC, PT or LLT	Code	Term
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035734	Pneumonia staphylococcal
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035735	Pneumonia streptococcal
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10067566	Pneumonia toxoplasmal
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035736	Pneumonia tularaemia
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035737	Pneumonia viral
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10053026	Pneumonic plague
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10035742	Pneumonitis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10037440	Pulmonary tuberculosis
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10057102	Pyopneumothorax
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10037688	Q fever
Priority investigation matters	Lower respiratory tract infection and pneumonia	22.0	PT	10044755	Tuberculosis

Table 7-1 List of ADRs Related to Urinary Retention

Patients in safety analysis set

Priority investigation matter : Urinary retention

As of July 29, 2019

Subject registration number	Name of the event (MedDRA_PT)	Seriousness	Time to onset (days)	Outcome	Sex	Age (years)	Reason for use	Comorbidities (MedDRA_PT)
PPD	Urinary retention	Serious	3	Recovered	Male	75	Emphysema	Hypertension, mitral valve incompetence, spinal osteoarthritis, tuberculosis, ventricular extrasystoles
	Urinary retention	Serious	15	Recovered	Male	75	Emphysema	None

MedDRA/J version (22.0)

Table 7-2 List of ADRs Related to Anticholinergic Effects

Patients in safety analysis set

Priority investigation matter : Anticholinergic effects

As of July 29, 2019

Subject registration number	Name of the event (MedDRA_PT)	Seriousness	Time to onset (days)	Outcome	Sex	Age (years)	Reason for use	Comorbidities (MedDRA_PT)
PPD	Urinary retention	Serious	3	Recovered	Male	75	Emphysema	Hypertension, mitral valve incompetence, spinal osteoarthritis, tuberculosis, ventricular extrasystoles
	Dry mouth	Non-serious	281	Recovering	Male	73	Bronchitis chronic	None
	Urinary retention	Serious	15	Recovered	Male	75	Emphysema	None
	Visual acuity reduced	Non-serious	5	Recovered	Male	80	Bronchitis chronic	Waldenstrom's macroglobulinaemia

MedDRA/J version (22.0)

Table 8 Proportion of Responders by Patient Characteristics

Patients in effectiveness analysis set

As of July 29, 20

Patient characteristics		Number of patients surveyed	Number of responders	Number of non-responders	Proportion of responders (%)	χ^2 test or Fisher's exact test	Odds ratio			
							Standard	Point estimate	95%CI Lower limit	95%CI Upper limit
Total		878	789	89	89.9	-	-	-	-	-
Sex	Male	689	619	70	89.8	F) p=1.000	*	-	-	-
	Female	189	170	19	89.9			1.012	0.593	1.727
Pregnancy (female only)	No	186	167	19	89.8	-	*	-	-	-
	Yes	0	0	0	-			-	-	-
	Unknown	3	3	0	100.0			-	-	-
Age 1 [years]	<15	0	0	0	-	X) p=0.736		-	-	-
Mean ± SD: 70.0 ± 11.1	≥15 - <65	226	204	22	90.3		*	-	-	-
Maximum: 96	≥65 - <75	320	290	30	90.6			1.042	0.585	1.859
Median: 72.0	≥75	332	295	37	88.9			0.860	0.493	1.501
Minimum: 22	Unknown	0	0	0	-			-	-	-
Age 2 [years]	<65	226	204	22	90.3	F) p=0.899	*	-	-	-
	≥65	652	585	67	89.7			0.942	0.567	1.564
Hospitalization status	Inpatient	29	29	0	100.0	F) p=0.064	*	-	-	-
	Outpatient	849	760	89	89.5			-	-	-
	Unknown	0	0	0	-			-	-	-
BMI	<18.5	100	87	13	87.0	X) p=0.533	*	-	-	-
	≥18.5 - <25.0	493	447	46	90.7			1.452	0.753	2.801
	≥25.0	174	157	17	90.2			1.380	0.640	2.975
	Unknown	111	98	13	88.3			-	-	-
Number of COPD exacerbations in 1 year before the initiation of treatment with Encruse Ellipta	0	545	488	57	89.5	X) p=0.987	*	-	-	-
	1	113	102	11	90.3			1.083	0.549	2.137
	2	50	45	5	90.0			1.051	0.401	2.756
	≥3	34	31	3	91.2			1.207	0.358	4.073
	Unknown	136	123	13	90.4			-	-	-
Number of COPD exacerbations in 1 year after the initiation of treatment with Encruse Ellipta	0	749	688	61	91.9	Not tested	*	-	-	-
	1	46	39	7	84.8			0.494	0.212	1.151
	2	12	7	5	58.3			0.124	0.038	0.403
	≥3	7	4	3	57.1			0.118	0.026	0.540
	Unknown	64	51	13	79.7			-	-	-
Number of COPD exacerbations in 1 year before the initiation of treatment with Encruse Ellipta (patients who continued the treatment)	0	360	346	14	96.1	X) p=0.512	*	-	-	-
	1	70	67	3	95.7			0.904	0.253	3.231
	2	38	38	0	100.0			-	-	-
	≥3	29	27	2	93.1			0.546	0.118	2.529
	Unknown	80	79	1	98.8			-	-	-
Number of COPD exacerbations in 1 year after the initiation of treatment with Encruse Ellipta (patients who continued the treatment)	0	517	503	14	97.3	Not tested	*	-	-	-
	1	36	33	3	91.7			0.306	0.084	1.119
	2	8	7	1	87.5			0.195	0.022	1.692
	≥3	5	3	2	60.0			0.042	0.006	0.270
	Unknown	11	11	0	100.0			-	-	-
Reason for use (disease type)	Bronchitis chronic	199	175	24	87.9	X) p=0.583	*	-	-	-
	Emphysema	484	437	47	90.3			1.275	0.757	2.149
	Mixed	195	177	18	90.8			1.349	0.707	2.573
	Others	0	0	0	-			-	-	-
Baseline severity (disease stage)	Mild (stage I)	231	203	28	87.9	X) p=0.610	*	-	-	-
	Moderate (stage II)	417	376	41	90.2			1.265	0.760	2.106
	Severe (stage III)	138	127	11	92.0			1.592	0.766	3.309
	Very severe (stage IV)	34	30	4	88.2			1.035	0.339	3.157
	Unknown	58	53	5	91.4			-	-	-
Duration of COPD [years]	≤2	233	204	29	87.6	X) p=0.450	*	-	-	-
	>2 - ≤5	171	153	18	89.5			1.208	0.647	2.256
	>5 - ≤10	133	119	14	89.5			1.208	0.614	2.377
	10<	129	120	9	93.0			1.895	0.868	4.139
	Unknown	212	193	19	91.0			-	-	-
History of cigarette smoking	Never smoker	110	98	12	89.1	X) p=0.124	*	-	-	-
	Former smoker	511	450	61	88.1			0.903	0.469	1.741
	Current smoker	195	182	13	93.3			1.714	0.753	3.901
	Unknown	62	59	3	95.2			-	-	-
Brinkman Index (BI)	<400	56	51	5	91.1	X) p=0.915	*	-	-	-
	≥400 - <600	82	75	7	91.5			1.050	0.316	3.492
	≥600 - <1200	321	286	35	89.1			0.801	0.300	2.142
	≥1200	155	139	16	89.7			0.852	0.297	2.444
	Unknown	264	238	26	90.2			-	-	-
Comorbidity	No	275	248	27	90.2	F) p=0.904	*	-	-	-
	Yes	603	541	62	89.7			0.950	0.590	1.530
Comorbidity (bronchial asthma)	No	617	548	69	88.8	F) p=0.142	*	-	-	-
	Yes	261	241	20	92.3			1.517	0.902	2.553
Comorbidity (cardiovascular disorders)	No	770	697	73	90.5	F) p=0.090	*	-	-	-
	Yes	108	92	16	85.2			0.602	0.336	1.079
Comorbidity (renal impairment)	No	863	775	88	89.8	F) p=1.000	*	-	-	-
	Yes	15	14	1	93.3			1.590	0.207	12.234
Comorbidity (hepatic impairment)	No	859	774	85	90.1	F) p=0.117	*	-	-	-
	Yes	19	15	4	78.9			0.412	0.134	1.269
Comorbidity (others)	No	397	357	40	89.9	F) p=1.000	*	-	-	-
	Yes	481	432	49	89.8			0.988	0.636	1.535

Patient characteristics			Number of patients surveyed	Number of responders	Number of non-responders	Proportion of responders (%)	χ^2 test or Fisher's exact test	Odds ratio			
								Standard	Point estimate	95%CI Lower limit	95%CI Upper limit
Total			878	789	89	89.9	-	-	-	-	-
Prior medications (COPD medications)		No	472	421	51	89.2	F) p=0.503	*	-	-	-
		Yes	406	368	38	90.6			1.173	0.754	1.826
		Unknown	0	0	0	-			-	-	-
Long-acting anticholinergics		No	677	610	67	90.1	F) p=0.690	*	-	-	-
		Yes	201	179	22	89.1			0.894	0.537	1.488
	Spiriva	No	722	650	72	90.0	Not tested	*	-	-	-
		Yes	156	139	17	89.1			0.906	0.518	1.585
	Seebri	No	845	761	84	90.1	Not tested	*	-	-	-
		Yes	33	28	5	84.8			0.618	0.232	1.644
	Eklira	No	870	781	89	89.8	Not tested	*	-	-	-
		Yes	8	8	0	100.0			-	-	-
	Other than the above	No	874	785	89	89.8	Not tested	*	-	-	-
		Yes	4	4	0	100.0			-	-	-
Long-acting β_2 agonists		No	832	748	84	89.9	F) p=0.802	*	-	-	-
		Yes	46	41	5	89.1			0.921	0.354	2.394
	Serevent	No	873	784	89	89.8	Not tested	*	-	-	-
		Yes	5	5	0	100.0			-	-	-
	Onbrez	No	866	778	88	89.8	Not tested	*	-	-	-
		Yes	12	11	1	91.7			1.244	0.159	9.749
	Oxis	No	877	788	89	89.9	Not tested	*	-	-	-
		Yes	1	1	0	100.0			-	-	-
	Hokunalin Tape	No	853	767	86	89.9	Not tested	*	-	-	-
		Yes	25	22	3	88.0			0.822	0.241	2.803
	Other than the above	No	875	787	88	89.9	Not tested	*	-	-	-
		Yes	3	2	1	66.7			0.224	0.020	2.491
Combination products of long-acting anticholinergics		No	837	753	84	90.0	F) p=0.597	*	-	-	-
		Yes	41	36	5	87.8			0.803	0.307	2.102
	Ultibro	No	866	781	85	90.2	Not tested	*	-	-	-
		Yes	12	8	4	66.7			0.218	0.064	0.738
	Anoro	No	855	767	88	89.7	Not tested	*	-	-	-
		Yes	23	22	1	95.7			2.523	0.336	18.938
	Other than the above	No	872	783	89	89.8	Not tested	*	-	-	-
		Yes	6	6	0	100.0			-	-	-
Combination products of long-acting β_2 agonists /inhaled steroids		No	651	588	63	90.3	F) p=0.445	*	-	-	-
		Yes	227	201	26	88.5			0.828	0.510	1.344
	Adoair	No	819	736	83	89.9	Not tested	*	-	-	-
		Yes	59	53	6	89.8			0.996	0.416	2.388
	Symbicort	No	831	751	80	90.4	Not tested	*	-	-	-
		Yes	47	38	9	80.9			0.450	0.210	0.964
	Relvar	No	774	694	80	89.7	Not tested	*	-	-	-
		Yes	104	95	9	91.3			1.217	0.591	2.504
	Flutiform	No	862	775	87	89.9	Not tested	*	-	-	-
		Yes	16	14	2	87.5			0.786	0.176	3.514
	Other than the above	No	877	788	89	89.9	Not tested	*	-	-	-
		Yes	1	1	0	100.0			-	-	-
Others		No	771	699	72	90.7	F) p=0.041 *	*	-	-	-
		Yes	107	90	17	84.1			0.545	0.308	0.966
	Short-acting anticholinergics	No	877	788	89	89.9	Not tested	*	-	-	-
		Yes	1	1	0	100.0			-	-	-
	Short-acting β_2 agonists	No	859	771	88	89.8	Not tested	*	-	-	-
		Yes	19	18	1	94.7			2.054	0.271	15.574
	Methylxanthine	No	849	765	84	90.1	Not tested	*	-	-	-
		Yes	29	24	5	82.8			0.527	0.196	1.418
	Inhaled steroids	No	867	779	88	89.9	Not tested	*	-	-	-
		Yes	11	10	1	90.9			1.130	0.143	8.929
	Oral steroids	No	866	780	86	90.1	Not tested	*	-	-	-
		Yes	12	9	3	75.0			0.331	0.088	1.244
	Expectorants	No	813	736	77	90.5	Not tested	*	-	-	-
		Yes	65	53	12	81.5			0.462	0.237	0.902
Concomitant medications (including non-COPD medications)		No	280	244	36	87.1	F) p=0.073	*	-	-	-
		Yes	598	545	53	91.1			1.517	0.968	2.378
Concomitant therapies		No	819	739	80	90.2	F) p=0.180	*	-	-	-
		Yes	59	50	9	84.7			0.601	0.285	1.268
Type of concomitant therapy (duplicates included)		Respiratory rehabilitation	28	26	2	92.9	Not tested	-	-	-	-
		Oxygen therapy	36	29	7	80.6			-	-	-
		Ventilatory support therapy	3	1	2	33.3			-	-	-
		Lung volume reduction surgery	0	0	0	-			-	-	-
		Lung transplant	0	0	0	-			-	-	-
		Other than the above	1	1	0	100.0			-	-	-
Forced expiratory volume in 1 second (FEV_1) (at the initiation of treatment with Encruse Ellipta) [mL] Mean ± SD: 1751.40 ± 667.04 Maximum: 4340.0 Median: 1730.00 Minimum: 420.0		<500	3	3	0	100.0	Not tested		-	-	-
		≥500 - <1000	82	77	5	93.9		*	-	-	-
		≥1000 - <1500	155	143	12	92.3			0.774	0.263	2.277
		≥1500 - <2000	182	164	18	90.1			0.592	0.212	1.652
		≥2000 - <2500	136	121	15	89.0			0.524	0.183	1.499
		≥2500	87	82	5	94.3			1.065	0.297	3.823
		Unknown	233	199	34	85.4			-	-	-
Forced vital capacity (FVC) (at the initiation of treatment with Encruse Ellipta) [mL] Mean ± SD: 2889.84 ± 862.34 Maximum: 6010.0 Median: 2860.00 Minimum: 470.0		<2000	94	88	6	93.6	Not tested		0.880	0.274	2.828
			106	100	6	94.3		*	-	-	-
		≥2400 - <2800	103	90	13	87.4			0.415	0.152	1.139
		≥2800 - <3200	118	105	13	89.0			0.485	0.177	1.324
		≥3200 - <3600	84	80	4	95.2			1.200	0.327	4.398
		≥3600	140	127	13	90.7			0.586	0.215	1.597
		Unknown	233	199	34	85.4			-	-	-
Percent forced expiratory volume in 1 second (%FEV_1) [%] Mean ± SD: 68.23 ± 23.47 Maximum: 154.5 Median: 68.42 Minimum: 13.3		<30	30	29	1	96.7	Not tested		2.682	0.330	21.801
		≥30 - <50	118	108	10	91.5		*	-	-	-
		≥50 - <80	279	252	27	90.3			0.864	0.404	1.847
		≥80	187	172	15	92.0			1.062	0.460	2.448
		Unknown	264	228	36	86.4			-	-	-
Mean number of daily doses [times/day] Mean ± SD: 1.00 ± 0.00 Maximum: 1.0 Median: 1.00 Minimum: 1.0		<1.0	0	0	0	-	-		-	-	-
		1.0	878	789	89	89.9		*	-	-	-
		1.0<-<2.0	0	0	0	-			-	-	-
		≥2.0	0	0	0	-			-	-	-
		Unknown	0	0	0	-			-	-	-

Patient characteristics		Number of patients surveyed	Number of responders	Number of non-responders	Proportion of responders (%)	χ^2 test or Fisher's exact test	Odds ratio			
							Standard	Point estimate	95%CI Lower limit	95%CI Upper limit
Total		878	789	89	89.9	-	-	-	-	-
Mean daily dose [µg/day]	<62.5	0	0	0	-	-		-	-	-
Mean ± SD: 62.50 ± 0.00	62.5	878	789	89	89.9		*	-	-	-
Maximum: 62.5	62.5<-<125	0	0	0	-			-	-	-
Median: 62.50	≥125	0	0	0	-			-	-	-
Minimum: 62.5	Unknown	0	0	0	-			-	-	-
Total number of days of treatment [days]	<28	23	13	10	56.5	Not tested	*	-	-	-
Mean ± SD: 287.7 ± 123.5	≥28 - <84	94	61	33	64.9			1.423	0.563	3.595
Maximum: 435	≥84 - <168	74	63	11	85.1			4.408	1.552	12.521
Median: 365.0	≥168 - <252	49	44	5	89.8			6.774	1.962	23.384
Minimum: 1	≥252 - <365	60	50	10	83.3			3.849	1.323	11.197
	≥365	578	558	20	96.5			21.475	8.411	54.828
	Unknown	0	0	0	-			-	-	-
Total dose [µg]	<1750.0	23	13	10	56.5	Not tested	*	-	-	-
Mean ± SD: 17979.93 ± 7719.35	≥1750.0 - <5250.0	94	61	33	64.9			1.423	0.563	3.595
Maximum: 27187.5	≥5250.0 - <10500.0	74	63	11	85.1			4.408	1.552	12.521
Median: 22812.50	≥10500.0 - <15750.0	49	44	5	89.8			6.774	1.962	23.384
Minimum: 62.5	≥15750.0 - <22812.5	60	50	10	83.3			3.849	1.323	11.197
	≥22812.5	578	558	20	96.5			21.475	8.411	54.828
	Unknown	0	0	0	-			-	-	-

No mark, $p \geq 0.05$; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$

Table 9 COPD Exacerbations

Patients in the effectiveness analysis set in whom the number of exacerbations could be compared before and after the treatment, who completed the 1-year follow-up (ongoing patients)

All patients As of July 29, 2019

Timing	Number of exacerbations	1 year after the initiation of treatment with Encruse Ellipta				
		0	1	2	≥3	Total
1 year before the initiation of treatment with Encruse Ellipta	0	350	9	0	0	359
	1	57	11	1	0	69
	2	30	8	0	0	38
	≥3	17	4	3	5	29
	Total	454	32	4	5	495

Table 10 CAT

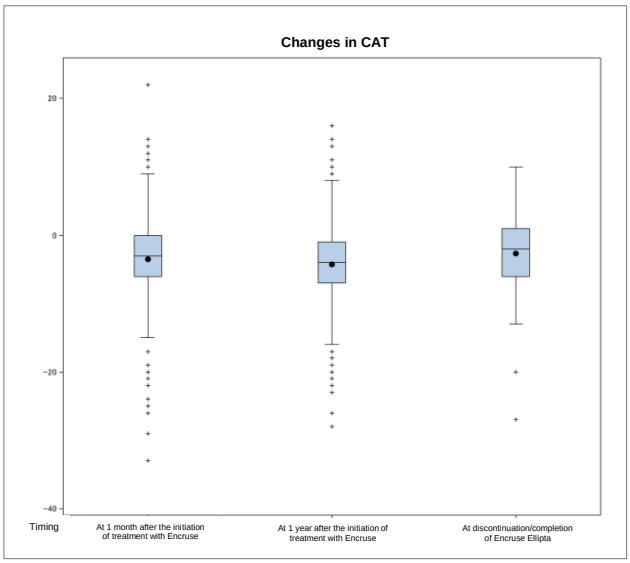
Patients included in CAT analysis set

All patients

As of July 29, 2019

Parameters	Timing	Number of patients	Mean	Standard deviation	Minimum	25 percentile	Median	75 percentile	Maximum	1-sample t-test	95% CI of the mean
CAT scores	At the initiation of treatment with Encruse Ellipta	448	13.9	8.2	0	7.0	12.0	20.0	40	-	-
	At 1 month after the initiation of treatment with Encruse Ellipta	382	10.4	7.3	0	5.0	8.0	15.0	34	-	-
	At 1 year after the initiation of treatment with Encruse Ellipta	254	9.5	7.5	0	4.0	7.0	14.0	34	-	-
	At discontinuation/completion of Encruse Ellipta	38	12.7	7.2	0	5.0	13.0	18.0	25	-	-
Changes in CAT score	At 1 month after the initiation of treatment with Encruse Ellipta	382	-3.5	6.7	-33	-6.0	-3.0	0.0	22	p<0.001 ***	-4.1--2.8
	At 1 year after the initiation of treatment with Encruse Ellipta	254	-4.3	7.0	-28	-7.0	-4.0	-1.0	16	p<0.001 ***	-5.1--3.4
	At discontinuation/completion of Encruse Ellipta	38	-2.6	7.1	-27	-6.0	-2.0	1.0	10	p=0.028 *	-5.0--0.3

No mark, p ≥ 0.05; *, p < 0.05; **, p < 0.01; ***, p < 0.001



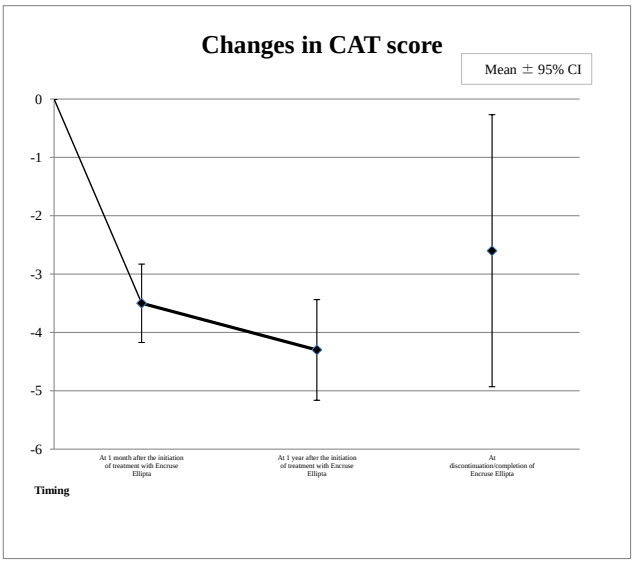


Table 10-1 CAT by Patient Characteristics

Patients included in CAT analysis set

Changes at 1 month after the initiation of treatment with Encruse Ellipta

As of July 29, 2019

Patient characteristics		Number of patients	Mean	Standard deviation	Minimum	25 percentile	Median	75 percentile	Maximum	Test T): 2-sample t-test A): Analysis of variance
Total		382	-3.5	6.7	-33	-6.0	-3.0	0.0	22	-
Sex	Male	311	-2.9	6.0	-33	-5.0	-3.0	0.0	22	T) p<0.001 ***
	Female	71	-6.1	8.5	-33	-10.0	-5.0	-2.0	14	
Pregnancy (female only)	No	70	-6.0	8.6	-33	-9.0	-5.0	-2.0	14	-
	Yes	0	-	-	-	-	-	-	-	
	Unknown	1	-12.0	-	-12	-12.0	-12.0	-12.0	-12	
Age 1 [years]	<15	0	-	-	-	-	-	-	-	A) p=0.955
	≥15 - <65	90	-3.4	6.9	-29	-6.0	-3.0	0.0	12	
	≥65 - <75	153	-3.6	7.4	-33	-7.0	-3.0	0.0	22	
	≥75	139	-3.4	5.7	-24	-6.0	-3.0	0.0	14	
	Unknown	0	-	-	-	-	-	-	-	
Age 2 [years]	<65	90	-3.4	6.9	-29	-6.0	-3.0	0.0	12	T) p=0.909
	≥65	292	-3.5	6.6	-33	-7.0	-3.0	0.0	22	
Hospitalization status	Inpatient	8	-6.3	8.9	-24	-10.0	-5.5	0.0	5	T) p=0.237
	Outpatient	374	-3.4	6.6	-33	-6.0	-3.0	0.0	22	
	Unknown	0	-	-	-	-	-	-	-	
BMI	<18.5	51	-3.9	5.7	-24	-7.0	-3.0	0.0	10	A) p=0.276
	≥18.5 - <25.0	229	-3.4	6.0	-29	-6.0	-3.0	0.0	13	
	≥25.0	84	-2.3	7.6	-33	-6.0	-2.0	1.5	22	
	Unknown	18	-8.1	10.6	-33	-9.0	-5.0	-3.0	8	
Number of COPD exacerbations in 1 year before the initiation of treatment with Encruse Ellipta	0	237	-2.4	5.9	-33	-5.0	-2.0	1.0	13	A) p=0.004 **
	1	50	-4.2	7.5	-19	-8.0	-5.0	-1.0	22	
	2	23	-4.2	6.5	-14	-10.0	-4.0	-1.0	11	
	≥3	20	-7.0	5.9	-20	-11.0	-7.5	-3.0	4	
	Unknown	52	-6.2	8.5	-33	-7.5	-4.0	-1.0	8	
Number of COPD exacerbations in 1 year after the initiation of treatment with Encruse Ellipta	0	325	-3.2	6.4	-33	-6.0	-3.0	0.0	22	Not tested
	1	25	-3.6	6.2	-12	-8.0	-5.0	-1.0	14	
	2	7	-12.1	10.9	-33	-20.0	-7.0	-4.0	-3	
	≥3	4	-0.8	9.6	-15	-6.5	3.0	5.0	6	
	Unknown	21	-4.6	8.1	-26	-6.0	-3.0	-1.0	11	
Number of COPD exacerbations in 1 year before the initiation of treatment with Encruse Ellipta (patients who continued the treatment)	0	171	-2.3	5.8	-33	-5.0	-2.0	1.0	13	A) p=0.004 **
	1	33	-2.6	7.9	-15	-7.0	-4.0	0.0	22	
	2	17	-5.6	5.5	-14	-11.0	-5.0	-3.0	5	
	≥3	17	-7.2	6.2	-20	-11.0	-8.0	-3.0	4	
	Unknown	33	-6.3	8.9	-33	-7.0	-4.0	-1.0	8	
Number of COPD exacerbations in 1 year after the initiation of treatment with Encruse Ellipta (patients who continued the treatment)	0	231	-2.9	6.2	-33	-6.0	-2.0	0.0	22	Not tested
	1	22	-3.1	6.3	-11	-8.0	-4.5	0.0	14	
	2	7	-12.1	10.9	-33	-20.0	-7.0	-4.0	-3	
	≥3	3	-3.0	10.4	-15	-15.0	2.0	4.0	4	
	Unknown	8	-7.1	11.2	-26	-13.5	-2.0	-1.0	2	
Reason for use (disease type)	Bronchitis chronic	66	-3.4	8.2	-33	-6.0	-3.0	0.0	22	A) p=0.549
	Emphysema	213	-3.2	6.8	-33	-5.0	-3.0	0.0	13	
	Mixed	103	-4.1	5.3	-21	-8.0	-3.0	0.0	8	
	Others	0	-	-	-	-	-	-	-	
Baseline severity (disease stage)	Mild (stage I)	97	-3.9	6.3	-26	-7.0	-3.0	0.0	12	A) p=0.310
	Moderate (stage II)	194	-2.8	6.5	-33	-5.0	-2.0	0.0	22	
	Severe (stage III)	63	-4.4	7.8	-33	-9.0	-3.0	0.0	10	
	Very severe (stage IV)	16	-4.2	6.4	-20	-7.0	-4.0	-1.5	8	
	Unknown	12	-5.3	7.1	-24	-7.5	-4.5	-2.0	4	
Duration of COPD [years]	≤2	90	-3.1	6.9	-33	-5.0	-2.0	0.0	22	A) p=0.821
	>2 - ≤5	79	-3.4	7.7	-33	-7.0	-2.0	0.0	13	
	>5 - ≤10	66	-3.7	5.3	-21	-6.0	-3.5	-1.0	7	
	10<	71	-4.1	5.8	-24	-7.0	-3.0	-1.0	9	
	Unknown	76	-3.2	7.3	-29	-6.5	-3.0	0.0	14	
History of cigarette smoking	Never smoker	40	-3.3	6.8	-26	-7.0	-2.0	0.0	14	A) p=0.850
	Former smoker	227	-3.4	7.0	-33	-6.0	-3.0	0.0	22	
	Current smoker	94	-3.8	6.1	-33	-7.0	-4.0	-1.0	13	
	Unknown	21	-3.2	6.3	-25	-5.0	-3.0	1.0	8	
Brinkman Index (BI)	<400	21	-2.0	3.9	-10	-5.0	-2.0	0.0	5	A) p=0.055
	≥400 - <600	39	-1.4	5.7	-15	-4.0	-2.0	2.0	12	
	≥600 - <1200	155	-4.2	6.5	-33	-7.0	-3.0	-1.0	12	
	≥1200	71	-4.3	7.7	-33	-7.0	-4.0	-1.0	22	
	Unknown	96	-2.8	6.8	-26	-5.5	-2.0	1.0	14	
Comorbidity	No	104	-3.4	6.3	-33	-5.0	-2.5	0.0	11	T) p=0.890
	Yes	278	-3.5	6.8	-33	-7.0	-3.0	0.0	22	
Comorbidity (bronchial asthma)	No	258	-3.3	6.3	-33	-6.0	-3.0	0.0	13	T) p=0.490
	Yes	124	-3.8	7.4	-33	-7.0	-3.0	0.0	22	
Comorbidity (cardiovascular disorders)	No	320	-3.4	6.8	-33	-6.0	-3.0	0.0	22	T) p=0.546
	Yes	62	-4.0	6.3	-24	-7.0	-4.0	-1.0	12	
Comorbidity (renal impairment)	No	375	-3.4	6.7	-33	-6.0	-3.0	0.0	22	T) p=0.404
	Yes	7	-5.6	7.9	-21	-9.0	-3.0	1.0	2	
Comorbidity (hepatic impairment)	No	370	-3.5	6.7	-33	-6.0	-3.0	0.0	22	T) p=0.462
	Yes	12	-2.1	6.4	-12	-7.0	-2.5	2.0	9	
Comorbidity (others)	No	161	-3.3	6.0	-33	-5.0	-3.0	0.0	12	T) p=0.659
	Yes	221	-3.6	7.1	-33	-7.0	-3.0	0.0	22	

Patient characteristics			Number of patients	Mean	Standard deviation	Minimum	25 percentile	Median	75 percentile	Maximum	Test T): 2-sample t-test A): Analysis of variance
Total			382	-3.5	6.7	-33	-6.0	-3.0	0.0	22	-
Prior medications (COPD medications)		No	175	-3.8	6.2	-33	-7.0	-3.0	-1.0	12	T) p=0.455
		Yes	207	-3.2	7.1	-33	-6.0	-3.0	0.0	22	
		Unknown	0	-	-	-	-	-	-	-	
Long-acting anticholinergics		No	286	-3.7	7.2	-33	-7.0	-3.0	0.0	22	T) p=0.296
		Yes	96	-2.9	5.0	-20	-5.0	-3.0	0.0	8	
	Spiriva	No	307	-3.7	7.0	-33	-7.0	-3.0	0.0	22	T) p=0.224
		Yes	75	-2.6	5.1	-15	-5.0	-2.0	0.0	8	
	Seebri	No	367	-3.5	6.7	-33	-7.0	-3.0	0.0	22	T) p=0.790
		Yes	15	-3.9	5.1	-20	-5.0	-3.0	0.0	1	
	Eklira	No	377	-3.5	6.7	-33	-6.0	-3.0	0.0	22	T) p=0.618
		Yes	5	-2.0	4.6	-8	-5.0	-1.0	0.0	4	
	Other than the above	No	381	-3.5	6.7	-33	-6.0	-3.0	0.0	22	T) p=0.499
		Yes	1	-8.0	-	-8	-8.0	-8.0	-8.0	-8	
Long-acting β_2 agonists		No	353	-3.3	6.1	-33	-6.0	-3.0	0.0	14	T) p=0.073
		Yes	29	-5.6	11.9	-33	-9.0	-4.0	2.0	22	
	Serevent	No	382	-3.5	6.7	-33	-6.0	-3.0	0.0	22	-
		Yes	0	-	-	-	-	-	-	-	
	Onbrez	No	376	-3.5	6.7	-33	-7.0	-3.0	0.0	22	T) p=0.142
		Yes	6	0.5	3.5	-5	-1.0	0.5	4.0	4	
	Oxis	No	381	-3.5	6.7	-33	-6.0	-3.0	0.0	22	T) p=0.412
		Yes	1	2.0	-	2	2.0	2.0	2.0	2	
	Hokunalin Tape	No	362	-3.3	6.2	-33	-6.0	-3.0	0.0	14	T) p=0.049 *
		Yes	20	-6.4	12.3	-33	-11.0	-4.5	0.0	22	
	Other than the above	No	380	-3.4	6.5	-33	-6.0	-3.0	0.0	22	T) p<0.001 ***
		Yes	2	-20.5	17.7	-33	-33.0	-20.5	-8.0	-8	
Combination products of long-acting anticholinergics/long-acting β2 agonists		No	362	-3.6	6.7	-33	-7.0	-3.0	0.0	22	T) p=0.117
		Yes	20	-1.2	5.8	-12	-4.0	-1.5	1.0	13	
	Ultibro	No	376	-3.5	6.7	-33	-7.0	-3.0	0.0	22	T) p=0.245
		Yes	6	-0.3	3.1	-3	-3.0	-1.0	1.0	5	
	Anoro	No	371	-3.6	6.7	-33	-6.0	-3.0	0.0	22	T) p=0.212
		Yes	11	-1.0	7.3	-12	-8.0	-1.0	4.0	13	
	Other than the above	No	379	-3.5	6.7	-33	-6.0	-3.0	0.0	22	T) p=0.962
		Yes	3	-3.7	4.5	-8	-8.0	-4.0	1.0	1	
Combination products of long-acting β_2 agonists/inhaled steroids		No	264	-3.6	6.4	-33	-6.0	-3.0	0.0	13	T) p=0.531
		Yes	118	-3.2	7.3	-26	-7.0	-3.0	1.0	22	
	Adoair	No	346	-3.5	6.8	-33	-6.0	-3.0	0.0	22	T) p=0.559
		Yes	36	-2.9	5.8	-14	-7.0	-3.0	0.5	11	
	Symbicort	No	366	-3.5	6.7	-33	-6.0	-3.0	0.0	22	T) p=0.752
		Yes	16	-4.0	6.2	-15	-9.0	-3.5	1.5	4	
	Relvar	No	328	-3.5	6.3	-33	-6.0	-3.0	0.0	13	T) p=0.947
		Yes	54	-3.4	8.7	-26	-8.0	-2.0	1.0	22	
	Flutiform	No	370	-3.5	6.7	-33	-6.0	-3.0	0.0	22	T) p=0.362
		Yes	12	-1.8	6.0	-10	-7.0	-3.0	2.5	9	
	Other than the above	No	382	-3.5	6.7	-33	-6.0	-3.0	0.0	22	-
		Yes	0	-	-	-	-	-	-	-	
Others		No	322	-3.5	6.6	-33	-7.0	-3.0	0.0	22	T) p=0.935
		Yes	60	-3.4	7.4	-33	-5.5	-3.0	0.0	14	
	Short-acting anticholinergics	No	381	-3.5	6.7	-33	-6.0	-3.0	0.0	22	T) p=0.261
		Yes	1	-11.0	-	-11	-11.0	-11.0	-11.0	-11	
	Short-acting β_2 agonists	No	369	-3.5	6.7	-33	-6.0	-3.0	0.0	22	T) p=0.696
		Yes	13	-2.8	5.7	-10	-6.0	-4.0	0.0	8	
	Methylxanthine	No	364	-3.5	6.6	-33	-7.0	-3.0	0.0	22	T) p=0.755
		Yes	18	-3.0	9.0	-24	-5.0	-2.5	0.0	14	
	Inhaled steroids	No	376	-3.5	6.7	-33	-6.5	-3.0	0.0	22	T) p=0.662
		Yes	6	-4.7	3.8	-12	-5.0	-3.5	-3.0	-1	
	Oral steroids	No	375	-3.5	6.7	-33	-7.0	-3.0	0.0	22	T) p=0.446
		Yes	7	-1.6	3.5	-4	-4.0	-3.0	-1.0	6	
	Expectorants	No	345	-3.5	6.5	-33	-6.0	-3.0	0.0	22	T) p=0.996
		Yes	37	-3.5	8.0	-33	-6.0	-2.0	0.0	14	
Concomitant medications (including non-COPD medications)		No	127	-2.2	5.4	-25	-4.0	-2.0	0.0	12	T) p=0.010 **
		Yes	255	-4.1	7.2	-33	-8.0	-4.0	0.0	22	
Concomitant therapies		No	357	-3.4	6.6	-33	-6.0	-3.0	0.0	22	T) p=0.253
		Yes	25	-5.0	8.0	-25	-9.0	-5.0	1.0	9	
Type of concomitant therapy (duplicates included)		Respiratory rehabilitation	12	-8.5	7.3	-25	-11.5	-8.5	-5.5	4	Not tested
		Oxygen therapy	15	-2.8	7.6	-20	-8.0	-4.0	5.0	9	
		Ventilatory support therapy	1	-4.0	-	-4	-4.0	-4.0	-4.0	-4	
		Lung volume reduction surgery	0	-	-	-	-	-	-	-	
		Lung transplant	0	-	-	-	-	-	-	-	
		Other than the above	0	-	-	-	-	-	-	-	
Forced expiratory volume in 1 second (FEV_1) (at the initiation of treatment with Encruse Ellipta)		<500	2	-3.0	1.4	-4	-4.0	-3.0	-2.0	-2	Not tested
		≥500 - <1000	47	-5.7	8.1	-33	-9.0	-5.0	-1.0	10	
		≥1000 - <1500	84	-4.0	7.0	-33	-6.5	-3.0	-1.0	14	
		≥1500 - <2000	96	-3.3	6.0	-25	-6.5	-3.0	0.0	13	
		≥2000 - <2500	61	-1.9	6.5	-22	-5.0	-2.0	1.0	22	
		≥2500	46	-2.7	4.9	-21	-4.0	-3.0	0.0	7	
		Unknown	46	-3.7	7.4	-26	-6.0	-2.5	0.0	11	
Forced vital capacity (FVC) (at the initiation of treatment with Encruse Ellipta) [mL]		<2000	57	-5.0	8.5	-33	-9.0	-4.0	-1.0	14	Not tested
		≥2000 - <2400	48	-4.3	5.3	-21	-7.0	-4.0	-2.0	9	
		≥2400 - <2800	53	-5.0	8.3	-33	-8.0	-3.0	-1.0	12	
		≥2800 - <3200	58	-2.7	6.4	-21	-6.0	-3.0	0.0	22	
		≥3200 - <3600	45	-2.3	4.8	-14	-5.0	-2.0	0.0	8	
		≥3600	75	-1.9	4.7	-13	-4.0	-2.0	1.0	13	
		Unknown	46	-3.7	7.4	-26	-6.0	-2.5	0.0	11	
Percent forced expiratory volume in 1 second ($\%FEV_1$) [%]		<30	18	-4.2	5.1	-12	-7.0	-4.5	-2.0	8	Not tested
		≥30 - <50	68	-4.4	7.5	-33	-8.0	-3.0	-1.0	10	
		≥50 - <80	153	-3.0	6.8	-33	-5.0	-3.0	1.0	22	
		≥80	89	-3.4	5.8	-25	-6.0	-3.0	0.0	12	
		Unknown	54	-3.6	7.1	-26	-6.0	-3.0	0.0	11	

Patient characteristics		Number of patients	Mean	Standard deviation	Minimum	25 percentile	Median	75 percentile	Maximum	Test T): 2-sample t-test A): Analysis of variance
Total		382	-3.5	6.7	-33	-6.0	-3.0	0.0	22	-
Mean number of daily doses [times/day]	<1.0	0	-	-	-	-	-	-	-	-
	1.0	382	-3.5	6.7	-33	-6.0	-3.0	0.0	22	
	1.0<-<2.0	0	-	-	-	-	-	-	-	
	≥2.0	0	-	-	-	-	-	-	-	
	Unknown	0	-	-	-	-	-	-	-	
Mean daily dose [µg/day]	<62.5	0	-	-	-	-	-	-	-	-
	62.5	382	-3.5	6.7	-33	-6.0	-3.0	0.0	22	
	62.5<-<125.0	0	-	-	-	-	-	-	-	
	≥125.0	0	-	-	-	-	-	-	-	
	Unknown	0	-	-	-	-	-	-	-	
Total number of days of treatment [days]	<28	5	-12.2	8.9	-25	-17.0	-10.0	-6.0	-3	Not tested
	≥28 - <84	32	-2.0	5.0	-13	-4.0	-3.0	1.0	11	
	≥84 - <168	27	-3.8	7.8	-29	-6.0	-3.0	0.0	12	
	≥168 - <252	20	-6.4	6.0	-21	-8.5	-4.0	-3.0	1	
	≥252 - <365	27	-2.7	5.6	-15	-6.0	-3.0	0.0	10	
	≥365	271	-3.3	6.7	-33	-7.0	-3.0	0.0	22	
	Unknown	0	-	-	-	-	-	-	-	
Total dose [µg]	<1750.0	5	-12.2	8.9	-25	-17.0	-10.0	-6.0	-3	Not tested
	≥1750.0 - <5250.0	32	-2.0	5.0	-13	-4.0	-3.0	1.0	11	
	≥5250.0 - <10500.0	27	-3.8	7.8	-29	-6.0	-3.0	0.0	12	
	≥10500.0 - <15750.0	20	-6.4	6.0	-21	-8.5	-4.0	-3.0	1	
	≥15750.0 - <22812.5	27	-2.7	5.6	-15	-6.0	-3.0	0.0	10	
	≥22812.5	271	-3.3	6.7	-33	-7.0	-3.0	0.0	22	
	Unknown	0	-	-	-	-	-	-	-	

No mark, $p \geq 0.05$; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$

Table 11 Respiratory Function Test (Spirometry): FEV_1

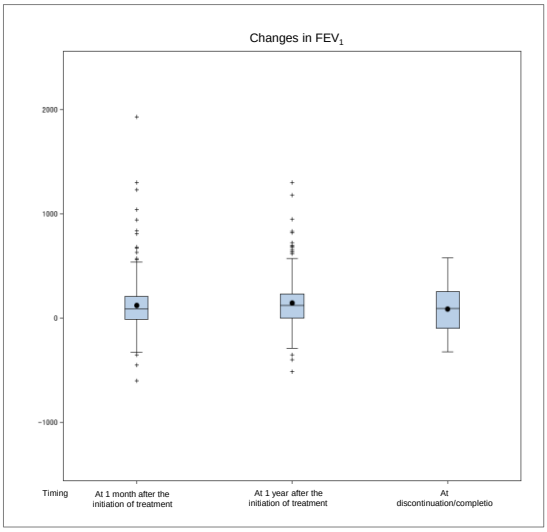
Patients included in FEV_1 analysis set

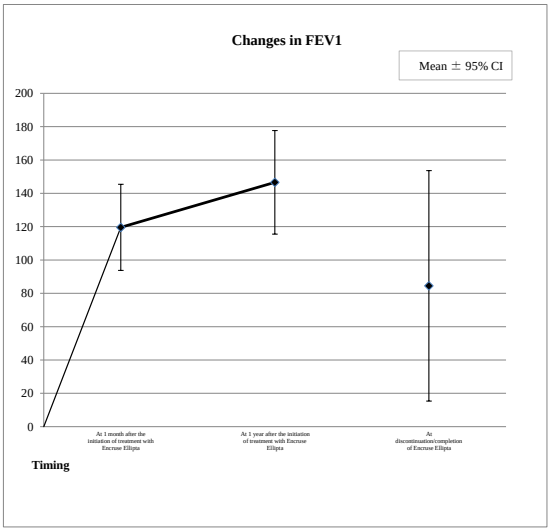
All patients

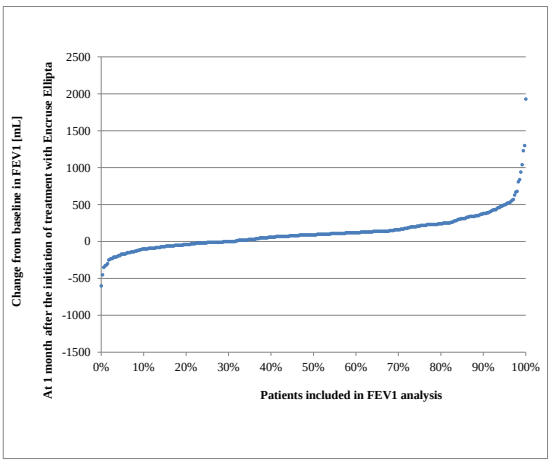
As of July 29, 2019

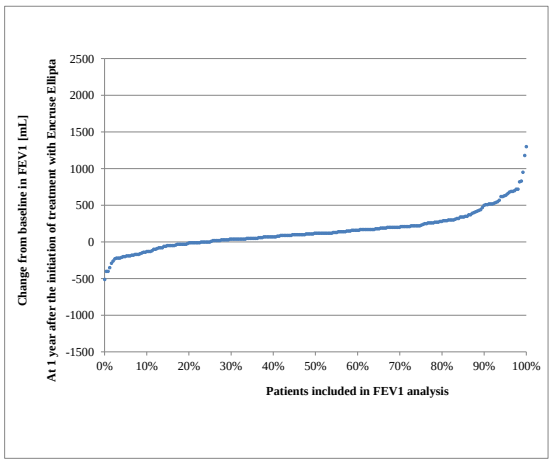
Parameters	Timing	Number of patients	Mean	Standard deviation	Minimum	25 percentile	Median	75 percentile	Maximum	1-sample t-test	95% CI of the mean
FEV1[mL]	At the initiation of treatment with Encruse Ellipta	441	1762.4	679.3	420	1260.0	1720.0	2200.0	4340	-	-
	At 1 month after the initiation of treatment with Encruse Ellipta	341	1873.8	719.1	460	1320.0	1830.0	2330.0	4710	-	-
	At 1 year after the initiation of treatment with Encruse Ellipta	250	1910.2	714.3	500	1400.0	1845.0	2360.0	3820	-	-
	At discontinuation/completion of Encruse Ellipta	40	1768.5	613.4	580	1370.0	1750.0	2055.0	3100	-	-
Changes in FEV_1 [mL]	At 1 month after the initiation of treatment with Encruse Ellipta	341	119.6	242.6	-600	-10.0	90.0	210.0	1930	p<0.001 ***	93.8-145.5
	At 1 year after the initiation of treatment with Encruse Ellipta	250	146.6	249.2	-510	0.0	120.0	230.0	1300	p<0.001 ***	115.5-177.6
	At discontinuation/completion of Encruse Ellipta	40	84.5	216.1	-320	-95.0	95.0	255.0	580	p=0.018 *	15.4-153.6

No mark, $p \geq 0.05$; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$









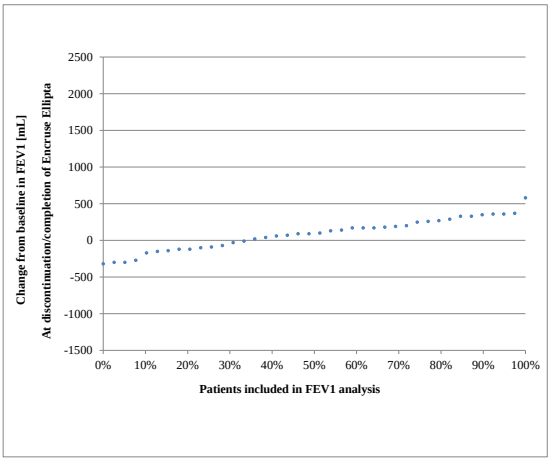


Table 11-1 Respiratory Function Test by Patient Characteristics (Spirometry): FEV_1

Patients included in FEV_1 analysis set

Changes at 1 month after the initiation of treatment with Encruse Ellipta

As of July 29, 2019

Patient characteristics		Number of patients	Mean	Standard deviation	Minimum	25 percentile	Median	75 percentile	Maximum	Test T): 2-sample t-test A): Analysis of variance
Total		341	119.6	242.6	-600	-10.0	90.0	210.0	1930	-
Sex	Male	283	116.9	248.4	-600	-20.0	90.0	220.0	1930	T) p=0.647
	Female	58	132.9	213.4	-100	0.0	100.0	190.0	1300	
Pregnancy (female only)	No	58	132.9	213.4	-100	0.0	100.0	190.0	1300	-
	Yes	0	-	-	-	-	-	-	-	
	Unknown	0	-	-	-	-	-	-	-	
Age 1 [years]	<15	0	-	-	-	-	-	-	-	A) p=0.004 **
	≥15 - <65	84	191.4	351.8	-320	-10.0	100.0	345.0	1930	
	≥65 - <75	129	112.4	212.9	-600	-10.0	110.0	220.0	1230	
	≥75	128	79.8	161.0	-450	-20.0	70.0	145.0	530	
	Unknown	0	-	-	-	-	-	-	-	
Age 2 [years]	<65	84	191.4	351.8	-320	-10.0	100.0	345.0	1930	T) p=0.002 **
	≥65	257	96.1	189.2	-600	-20.0	90.0	180.0	1230	
Hospitalization status	Inpatient	12	160.8	141.5	-40	55.0	140.0	260.0	450	T) p=0.550
	Outpatient	329	118.1	245.5	-600	-20.0	90.0	210.0	1930	
	Unknown	0	-	-	-	-	-	-	-	
BMI	<18.5	46	138.9	220.9	-230	20.0	115.0	240.0	1040	A) p=0.646
	≥18.5 - <25.0	207	106.6	248.9	-600	-20.0	80.0	190.0	1930	
	≥25.0	69	126.1	211.4	-350	-20.0	100.0	200.0	940	
	Unknown	19	191.1	321.9	-190	10.0	150.0	250.0	1300	
Number of COPD exacerbations in 1 year before the initiation of treatment with Encruse Ellipta	0	233	100.4	239.0	-450	-20.0	80.0	160.0	1930	A) p=0.491
	1	45	159.6	263.2	-150	0.0	90.0	230.0	1230	
	2	16	108.1	145.1	-190	15.0	120.0	220.0	340	
	≥3	13	137.7	303.8	-600	30.0	120.0	230.0	630	
	Unknown	34	197.1	240.7	-230	50.0	210.0	310.0	940	
Number of COPD exacerbations in 1 year after the initiation of treatment with Encruse Ellipta	0	298	125.3	239.4	-450	-10.0	100.0	220.0	1930	Not tested
	1	21	80.0	134.6	-90	-60.0	90.0	160.0	340	
	2	4	95.0	119.6	-60	15.0	105.0	175.0	230	
	≥3	3	-266.7	316.6	-600	-600.0	-230.0	30.0	30	
	Unknown	15	146.0	366.0	-300	-80.0	70.0	250.0	1300	
Number of COPD exacerbations in 1 year before the initiation of treatment with Encruse Ellipta (patients who continued the treatment)	0	170	93.9	237.1	-450	-30.0	75.0	150.0	1930	A) p=0.410
	1	33	164.5	221.1	-150	30.0	120.0	230.0	1040	
	2	14	87.1	139.3	-190	10.0	110.0	200.0	280	
	≥3	10	65.0	289.4	-600	20.0	105.0	130.0	570	
	Unknown	18	211.1	263.9	-200	50.0	215.0	280.0	940	
Number of COPD exacerbations in 1 year after the initiation of treatment with Encruse Ellipta (patients who continued the treatment)	0	221	117.1	239.9	-450	-10.0	90.0	200.0	1930	Not tested
	1	19	77.4	141.4	-90	-60.0	90.0	200.0	340	
	2	3	96.7	146.4	-60	-60.0	120.0	230.0	230	
	≥3	2	-285.0	445.5	-600	-600.0	-285.0	30.0	30	
	Unknown	0	-	-	-	-	-	-	-	
Reason for use (disease type)	Bronchitis chronic	54	197.6	278.0	-140	0.0	125.0	280.0	1300	A) p=0.019 *
	Emphysema	202	94.4	212.1	-600	-20.0	90.0	170.0	1230	
	Mixed	85	130.1	276.1	-350	-20.0	90.0	230.0	1930	
	Others	0	-	-	-	-	-	-	-	
Baseline severity (disease stage)	Mild (stage I)	99	111.5	206.3	-600	-10.0	100.0	220.0	810	A) p=0.861
	Moderate (stage II)	167	114.8	244.6	-350	-20.0	100.0	200.0	1930	
	Severe (stage III)	56	134.3	267.9	-230	-25.0	90.0	230.0	1230	
	Very severe (stage IV)	17	155.9	339.4	-100	-20.0	70.0	120.0	1300	
	Unknown	2	205.0	233.3	40	40.0	205.0	370.0	370	
Duration of COPD [years]	≤2	93	107.3	220.8	-600	-20.0	90.0	210.0	1040	A) p=0.695
	>2 - ≤5	72	121.4	266.0	-330	-50.0	70.0	215.0	1230	
	>5 - ≤10	58	82.6	163.9	-300	-50.0	85.0	150.0	520	
	10<	55	86.2	156.4	-350	-10.0	100.0	170.0	500	
	Unknown	63	199.0	338.3	-450	20.0	120.0	310.0	1930	
History of cigarette smoking	Never smoker	36	130.0	185.4	-100	0.0	115.0	200.0	810	A) p=0.029 *
	Former smoker	211	96.4	212.6	-600	-30.0	80.0	170.0	1230	
	Current smoker	79	182.3	332.9	-450	0.0	120.0	310.0	1930	
	Unknown	15	90.7	127.4	-210	10.0	70.0	210.0	250	
Brinkman Index (BI)	<400	18	159.4	216.0	-200	40.0	120.0	180.0	680	A) p=0.146
	≥400 - <600	32	101.3	141.6	-190	0.0	115.0	160.0	420	
	≥600 - <1200	135	154.0	290.5	-600	-10.0	100.0	240.0	1930	
	≥1200	77	75.8	211.0	-450	-50.0	80.0	160.0	840	
	Unknown	79	101.9	212.7	-330	-20.0	70.0	200.0	1040	
Comorbidity	No	116	83.4	232.0	-600	-40.0	75.0	155.0	1300	T) p=0.048 *
	Yes	225	138.3	246.3	-350	-10.0	100.0	230.0	1930	
Comorbidity (bronchial asthma)	No	243	101.1	217.5	-600	-20.0	90.0	200.0	1300	T) p=0.026 *
	Yes	98	165.6	292.0	-350	0.0	105.0	230.0	1930	
Comorbidity (cardiovascular disorders)	No	300	125.1	252.5	-600	-20.0	100.0	220.0	1930	T) p=0.263
	Yes	41	79.8	147.3	-350	-10.0	90.0	130.0	430	
Comorbidity (renal impairment)	No	336	120.1	244.0	-600	-15.0	90.0	215.0	1930	T) p=0.755
	Yes	5	86.0	125.0	-110	50.0	130.0	140.0	220	
Comorbidity (hepatic impairment)	No	338	120.5	243.4	-600	-10.0	90.0	220.0	1930	T) p=0.491
	Yes	3	23.3	89.6	-80	-80.0	70.0	80.0	80	
Comorbidity (others)	No	156	107.5	270.5	-600	-35.0	80.0	180.0	1930	T) p=0.398
	Yes	185	129.8	216.5	-350	-10.0	100.0	230.0	1230	

Patient characteristics			Number of patients	Mean	Standard deviation	Minimum	25 percentile	Median	75 percentile	Maximum	Test T): 2-sample t-test A): Analysis of variance
Total			341	119.6	242.6	-600	-10.0	90.0	210.0	1930	-
Prior medications (COPD medications)		No	172	155.1	270.4	-450	0.0	110.0	240.0	1930	T) p=0.006 **
		Yes	169	83.5	205.2	-600	-50.0	70.0	150.0	1230	
		Unknown	0	-	-	-	-	-	-	-	
	Long-acting anticholinergics	No	255	150.0	258.7	-450	0.0	110.0	240.0	1930	T) p<0.001 ***
		Yes	86	29.5	156.4	-600	-60.0	25.0	110.0	520	
	Spiriva	No	274	141.4	255.4	-450	-10.0	110.0	230.0	1930	T) p<0.001 ***
		Yes	67	30.7	152.8	-600	-50.0	40.0	110.0	520	
	Seebri	No	326	124.1	244.6	-600	-10.0	100.0	220.0	1930	T) p=0.111
		Yes	15	22.0	173.5	-250	-90.0	-20.0	80.0	370	
	Eklira	No	339	120.7	242.6	-600	-10.0	90.0	220.0	1930	T) p=0.268
		Yes	2	-70.0	226.3	-230	-230.0	-70.0	90.0	90	
	Other than the above	No	339	119.5	243.2	-600	-20.0	90.0	210.0	1930	T) p=0.882
		Yes	2	145.0	134.4	50	50.0	145.0	240.0	240	
	Long-acting β_2 agonists	No	320	118.7	246.9	-600	-20.0	90.0	205.0	1930	T) p=0.790
		Yes	21	133.3	166.4	-150	0.0	100.0	240.0	460	
	Serevent	No	340	119.2	242.8	-600	-15.0	90.0	210.0	1930	T) p=0.591
		Yes	1	250.0	-	250	250.0	250.0	250.0	250	
	Onbrez	No	336	121.1	243.0	-600	-10.0	90.0	215.0	1930	T) p=0.365
		Yes	5	22.0	208.3	-150	-90.0	-30.0	0.0	380	
	Oxis	No	341	119.6	242.6	-600	-10.0	90.0	210.0	1930	-
		Yes	0	-	-	-	-	-	-	-	
	Hokunalin Tape	No	329	118.0	245.3	-600	-20.0	90.0	210.0	1930	T) p=0.510
		Yes	12	165.0	151.1	0	70.0	100.0	250.0	460	
	Other than the above	No	338	119.3	243.4	-600	-20.0	90.0	210.0	1930	T) p=0.809
		Yes	3	153.3	141.5	-10	-10.0	230.0	240.0	240	
	Combination products of long-acting anticholinergics/long-acting β2 agonists	No	328	123.9	243.9	-600	-10.0	90.0	220.0	1930	T) p=0.099
		Yes	13	10.8	180.1	-330	-80.0	90.0	120.0	240	
	Ultibro	No	336	121.1	243.2	-600	-15.0	90.0	220.0	1930	T) p=0.356
		Yes	5	20.0	190.8	-320	90.0	90.0	110.0	130	
	Anoro	No	335	121.7	242.9	-600	-10.0	90.0	220.0	1930	T) p=0.244
		Yes	6	5.0	208.1	-330	-80.0	15.0	170.0	240	
	Other than the above	No	339	120.3	243.0	-600	-10.0	90.0	220.0	1930	T) p=0.504
		Yes	2	5.0	162.6	-110	-110.0	5.0	120.0	120	
	Combination products of long-acting β_2 agonists/inhaled steroids	No	248	130.2	248.8	-450	-10.0	100.0	225.0	1930	T) p=0.187
		Yes	93	91.3	224.0	-600	-40.0	70.0	160.0	1230	
	Adoair	No	320	125.8	247.7	-600	-10.0	95.0	225.0	1930	T) p=0.067
		Yes	21	25.7	110.7	-170	-60.0	10.0	120.0	210	
	Symbicort	No	325	124.4	243.2	-450	-10.0	90.0	220.0	1930	T) p=0.103
		Yes	16	23.1	215.3	-600	-65.0	60.0	170.0	250	
	Relvar	No	296	117.3	240.9	-600	-10.0	100.0	210.0	1930	T) p=0.651
		Yes	45	134.9	255.9	-170	-20.0	60.0	230.0	1230	
	Flutiform	No	331	118.8	243.0	-600	-20.0	90.0	220.0	1930	T) p=0.728
		Yes	10	146.0	238.8	-250	70.0	100.0	170.0	630	
	Other than the above	No	340	119.8	242.9	-600	-15.0	90.0	215.0	1930	T) p=0.774
		Yes	1	50.0	-	50	50.0	50.0	50.0	50	
	Others	No	298	128.0	247.4	-450	-10.0	100.0	220.0	1930	T) p=0.095
		Yes	43	61.9	199.2	-600	-60.0	20.0	140.0	630	
	Short-acting anticholinergics	No	341	119.6	242.6	-600	-10.0	90.0	210.0	1930	-
		Yes	0	-	-	-	-	-	-	-	
	Short-acting β_2 agonists	No	333	119.9	243.3	-600	-10.0	90.0	220.0	1930	T) p=0.875
		Yes	8	106.3	223.7	-60	-40.0	65.0	115.0	630	
	Methylxanthine	No	329	121.2	244.5	-600	-10.0	90.0	210.0	1930	T) p=0.533
		Yes	12	76.7	183.9	-120	-40.0	0.0	175.0	500	
	Inhaled steroids	No	337	118.5	243.2	-600	-20.0	90.0	210.0	1930	T) p=0.430
		Yes	4	215.0	183.4	70	95.0	155.0	335.0	480	
	Oral steroids	No	337	121.5	243.1	-600	-10.0	90.0	220.0	1930	T) p=0.179
		Yes	4	-42.5	115.3	-170	-115.0	-55.0	30.0	110	
	Expectorants	No	315	125.0	245.5	-450	-10.0	100.0	220.0	1930	T) p=0.158
		Yes	26	55.0	197.4	-600	-20.0	45.0	170.0	500	
Concomitant medications (including non-COPD medications)		No	106	101.6	208.5	-450	-10.0	90.0	170.0	1300	T) p=0.358
		Yes	235	127.7	256.5	-600	-20.0	90.0	230.0	1930	
Concomitant therapies		No	322	118.4	238.0	-600	-10.0	90.0	210.0	1930	T) p=0.707
		Yes	19	140.0	318.5	-170	-20.0	90.0	220.0	1300	
Type of concomitant therapy (duplicates included)		Respiratory rehabilitation	6	226.7	129.3	90	120.0	210.0	280.0	450	Not tested
		Oxygen therapy	13	34.6	159.0	-170	-40.0	-20.0	90.0	450	
		Ventilatory support therapy	1	-10.0	-	-10	-10.0	-10.0	-10.0	-10	
		Lung volume reduction surgery	0	-	-	-	-	-	-	-	
		Lung transplant	0	-	-	-	-	-	-	-	
		Other than the above	1	1300.0	-	1300	1300.0	1300.0	1300.0	1300	
Forced expiratory volume in 1 second (FEV_1) (at the initiation of treatment with Encruse Ellipta)		<500	2	235.0	148.5	130	130.0	235.0	340.0	340	Not tested
		≥500 - <1000	46	151.1	239.4	-170	0.0	90.0	230.0	1300	
		≥1000 - <1500	76	134.7	315.9	-250	-45.0	100.0	215.0	1930	
		≥1500 - <2000	100	123.9	190.7	-350	20.0	110.0	205.0	940	
		≥2000 - <2500	66	74.1	220.9	-320	-50.0	70.0	120.0	1040	
		≥2500	51	114.7	241.7	-600	-40.0	110.0	240.0	810	
		Unknown	0	-	-	-	-	-	-	-	
Forced vital capacity (FVC) (at the initiation of treatment with Encruse Ellipta) [mL]		<2000	47	122.3	221.5	-350	0.0	100.0	210.0	1230	Not tested
		≥2000 - <2400	49	114.1	222.0	-210	0.0	90.0	170.0	1300	
		≥2400 - <2800	52	104.8	205.1	-230	-20.0	65.0	180.0	840	
		≥2800 - <3200	65	159.7	308.5	-250	0.0	90.0	280.0	1930	
		≥3200 - <3600	50	64.4	186.6	-450	-50.0	100.0	210.0	520	
		≥3600	78	133.3	258.9	-600	-40.0	100.0	220.0	1040	
		Unknown	0	-	-	-	-	-	-	-	
Percent forced expiratory volume in 1 second ($\%FEV_1$) [%]		<30	20	156.0	192.1	-90	45.0	100.0	290.0	560	Not tested
		≥30 - <50	60	167.3	346.7	-250	-15.0	90.0	235.0	1930	
		≥50 - <80	148	99.9	209.3	-350	-30.0	90.0	190.0	1040	
		≥80	101	100.4	192.8	-600	-10.0	90.0	190.0	810	
		Unknown	12	225.8	388.7	-160	10.0	130.0	365.0	1300	

Patient characteristics		Number of patients	Mean	Standard deviation	Minimum	25 percentile	Median	75 percentile	Maximum	Test T): 2-sample t-test A): Analysis of variance
Total		341	119.6	242.6	-600	-10.0	90.0	210.0	1930	-
Mean number of daily doses [times/day]	<1.0	0	-	-	-	-	-	-	-	-
	1.0	341	119.6	242.6	-600	-10.0	90.0	210.0	1930	
	1.0<-<2.0	0	-	-	-	-	-	-	-	
	≥2.0	0	-	-	-	-	-	-	-	
	Unknown	0	-	-	-	-	-	-	-	
Mean daily dose [µg/day]	<62.5	0	-	-	-	-	-	-	-	-
	62.5	341	119.6	242.6	-600	-10.0	90.0	210.0	1930	
	62.5<-<125.0	0	-	-	-	-	-	-	-	
	≥125.0	0	-	-	-	-	-	-	-	
	Unknown	0	-	-	-	-	-	-	-	
Total number of days of treatment [days]	<28	4	105.0	213.8	-160	-40.0	110.0	250.0	360	Not tested
	≥28 - <84	24	94.2	177.8	-210	-50.0	75.0	205.0	520	
	≥84 - <168	28	195.0	292.4	-300	20.0	150.0	255.0	1230	
	≥168 - <252	17	141.2	216.2	-230	-10.0	90.0	340.0	530	
	≥252 - <365	21	157.6	326.9	-350	0.0	100.0	170.0	1300	
	≥365	247	109.1	236.1	-600	-20.0	90.0	200.0	1930	
	Unknown	0	-	-	-	-	-	-	-	
Total dose [µg]	<1750.0	4	105.0	213.8	-160	-40.0	110.0	250.0	360	Not tested
	≥1750.0 - <5250.0	24	94.2	177.8	-210	-50.0	75.0	205.0	520	
	≥5250.0 - <10500.0	28	195.0	292.4	-300	20.0	150.0	255.0	1230	
	≥10500.0 - <15750.0	17	141.2	216.2	-230	-10.0	90.0	340.0	530	
	≥15750.0 - <22812.5	21	157.6	326.9	-350	0.0	100.0	170.0	1300	
	≥22812.5	247	109.1	236.1	-600	-20.0	90.0	200.0	1930	
	Unknown	0	-	-	-	-	-	-	-	

No mark, $p \geq 0.05$; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$

Table 12 Respiratory function tests: FVC

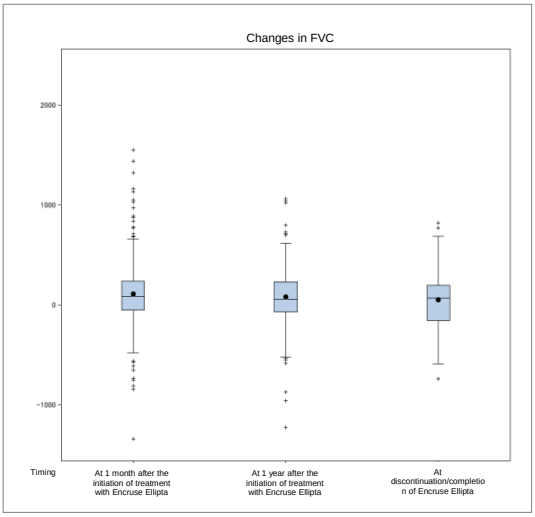
Patients included in FVC analysis set

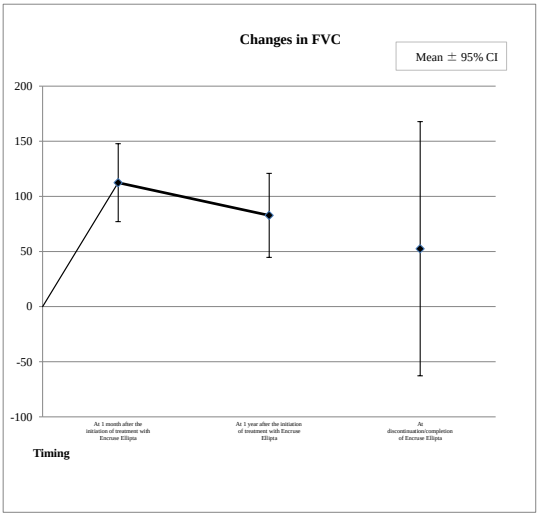
All patients

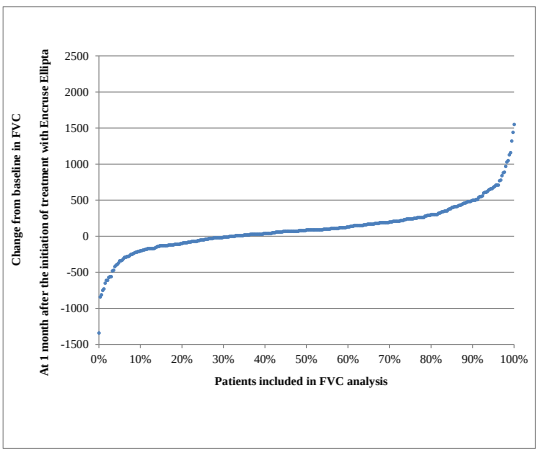
As of July 29, 2019

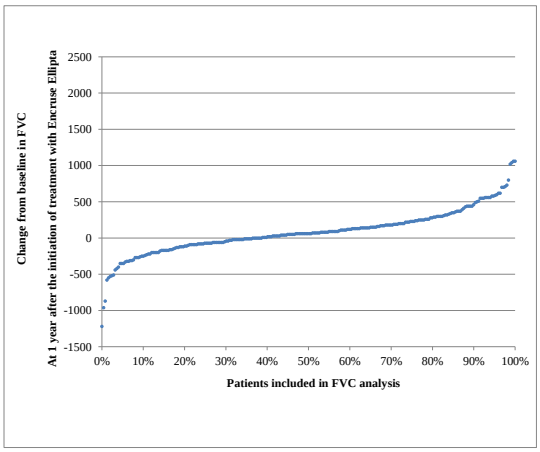
Parameters	Timing	Number of patients	Mean	Standard deviation	Minimum	25 percentile	Median	75 percentile	Maximum	1-sample t-test	95% CI of the mean
FVC [mL]	At the initiation of treatment with Encruse Ellipta	441	2935.6	876.4	470	2290.0	2910.0	3580.0	6010	-	-
	At 1 month after the initiation of treatment with Encruse Ellipta	341	3046.5	878.8	690	2430.0	3040.0	3600.0	6310	-	-
	At 1 year after the initiation of treatment with Encruse Ellipta	250	3058.9	912.6	880	2360.0	3070.0	3770.0	5210	-	-
	At discontinuation/completion of Encruse Ellipta	40	3028.3	713.1	1630	2535.0	2970.0	3505.0	4400	-	-
Changes in FVC [mL]	At 1 month after the initiation of treatment with Encruse Ellipta	341	112.4	331.9	-1340	-50.0	90.0	240.0	1550	p<0.001 ***	77.0-147.7
	At 1 year after the initiation of treatment with Encruse Ellipta	250	82.8	305.9	-1220	-70.0	60.0	230.0	1060	p<0.001 ***	44.7-120.9
	At discontinuation/completion of Encruse Ellipta	40	52.5	360.5	-740	-155.0	70.0	195.0	820	p=0.363	-62.8-167.8

No mark, p ≥ 0.05; *, p < 0.05; **, p < 0.01; ***, p < 0.001









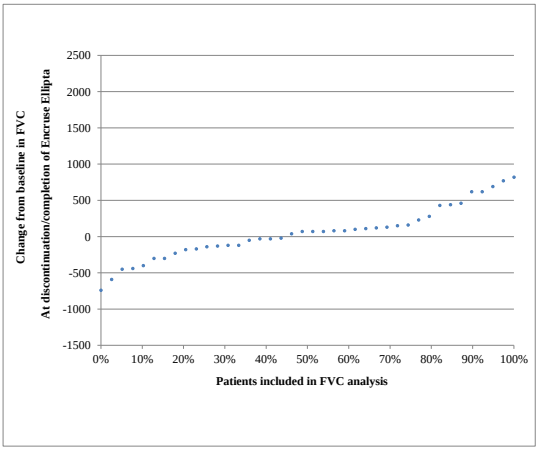


Table 13 List of Occurrence of ADRs in Elderly Patients (≥65 years)

Patients in safety analysis set

As of July 29, 2019

	Age [years]							
	≥65				Total			
	All ADRs		Serious ADRs		All ADRs		Serious ADRs	
Number of patients surveyed	747				1017			
Number of patients with ADRs	23		4		29		5	
Proportion of patients with ADRs	3.1		0.5		2.9		0.5	
Types of ADRs	Number of patients with ADRs (%)				Number of patients with ADRs (%)			
Respiratory, thoracic and mediastinal disorders	7	(0.9%)	0	(0.0%)	7	(0.7%)	0	(0.0%)
Cough	4	(0.5%)	0	(0.0%)	4	(0.4%)	0	(0.0%)
Laryngeal discomfort	2	(0.3%)	0	(0.0%)	2	(0.2%)	0	(0.0%)
Dyspnoea	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Gastrointestinal disorders	5	(0.7%)	0	(0.0%)	7	(0.7%)	0	(0.0%)
Nausea	1	(0.1%)	0	(0.0%)	2	(0.2%)	0	(0.0%)
Constipation	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Dry mouth	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Dyspepsia	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Oral discomfort	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Chapped lips	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Renal and urinary disorders	5	(0.7%)	2	(0.3%)	5	(0.5%)	2	(0.2%)
Dysuria	2	(0.3%)	0	(0.0%)	2	(0.2%)	0	(0.0%)
Urinary retention	2	(0.3%)	2	(0.3%)	2	(0.2%)	2	(0.2%)
Pollakiuria	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Cardiac disorders	3	(0.4%)	2	(0.3%)	4	(0.4%)	3	(0.3%)
Atrial fibrillation	1	(0.1%)	1	(0.1%)	2	(0.2%)	2	(0.2%)
Arrhythmia	1	(0.1%)	1	(0.1%)	1	(0.1%)	1	(0.1%)
Cardiac failure	1	(0.1%)	1	(0.1%)	1	(0.1%)	1	(0.1%)
Palpitations	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Nervous system disorders	1	(0.1%)	0	(0.0%)	3	(0.3%)	0	(0.0%)
Dysgeusia	1	(0.1%)	0	(0.0%)	2	(0.2%)	0	(0.0%)
Taste disorder	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Metabolism and nutrition disorders	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Hyperuricaemia	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Eye disorders	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Visual acuity reduced	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Reproductive system and breast disorders	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Benign prostatic hyperplasia	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
General disorders and administration site conditions	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Chest discomfort	1	(0.1%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Investigations	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)
Intraocular pressure increased	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)

MedDRA/J version (22.0)

ENCRUSE®ELLIPTA®
Drug Use Investigation

Protocol

GlaxoSmithKline K.K.

Prepared on 17 Dec, 2015 (Ver. 1.1)

Table of Contents

1. Objectives

This investigation will be conducted to collect and assess information regarding the safety and effectiveness of ENCRUSE®ELLIPTA® (hereinafter referred to as "Encruse Ellipta") in routine clinical practice.

2. Safety Specifications

In the investigation, safety specifications are defined as follows;

・Cardiovascular events

Since Encruse Ellipta contains a long-acting muscarinic receptor antagonist , the priority investigation matters are defined to monitor occurance of them, etc. as follows;

・Cardiovascular events, urinary retention, eye related problems, gallbladder disorder, intestinal obstruction, anticholinergic effects, lower respiratory tract infection and pneumonia.

3. Study Population

This investigation will be conducted in patients who are first prescribed Encruse 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)".

4. Planned Sample Size and Its Rationale

1) Target number of patients: 1,000 (as number of subjects to be registered)
2) Rationale:

In the clinical study for Japanese COPD patients (131 pts), the incidence of adverse drug reactions (ADRs) related to "cardiovascular events", an important identified risk of Encruse Ellipta, was 4% (5/131 pts). Among 5 patients, supraventricular tachycardia in 2 patients (2%), angina pectoris, palpitations, and sinus tachycardia in 1 patient each (0.76%) were reported as ADRs.

On assumption that the incidence used as a threshold for cardiovascular events is assumed to be 4%, 305 patients in the safety analysis set are required to check the incidence in the post-marketing surveillance with estimation accuracy which detects the 4% of threshold with a statistical power of ≥80% when the risk exists 2 times or more of the threshold. Accordingly, it is thought to be possible to examine the incidence of cardiovascular events in the drug use investigation with 1,000 patients.

5. Planned Number of Medical Institutions by Department

Approximately 200 medical institutions, primarily the department of respiratory medicine

6. Study Period

Study period: November 2015 to January 2019

Observation period: The observation period (duration of treatment with Encruse Ellipta) in each patient will be 1 year after the start date of administration of the product.

Planned registration period: November 2015 to October 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 Methods

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 (hereinafter referred to as "MR") will explain the study objectives, study population, study items, study methods, etc. to the potential investigators, etc. of the medical institutions where Encruse 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., director) of the medical institution prior to initiation of the investigation.
2) Registration of study population
   This investigation will be conducted by the central registration system.
   (1) The investigator will enter the information of patients for whom administration of Encruse 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 start date of administration of Encruse Ellipta (the start date of administration 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 completed.
3) 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 Encruse Ellipta, and at 1 month and 1 year after the initiation of treatment (or at the discontinuation/completion of treatment if treatment with Encruse Ellipta is discontinued/completed).
   (3) The investigator will collect the CAT of the registered patients, review the content, and enter the information in the EDC system.

(4) During the observation period, the investigator will monitor the information regarding safety and effectiveness, 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) At the end of the observation period (or at the time of withdrawal/completion, if a patient has withdrawn from/completed administration of the drug), the investigator will record the obtained information in the EDC system and submit.

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 institutions
Name of the institution, department, and investigator
2) Patient characteristics (at the start of administration of Encruse Ellipta)
Identification number, sex, year of birth, start date of administration of Encruse Ellipta, hospitalization status, height, body weight, reason for use of Encruse 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 regarding identificaton of an individual patient, the identification number should 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 Encruse 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 Encruse Ellipta
Single dose and daily dose frequency of Encruse Ellipta, start date of administration, end date of administration, and reason for revising Dosage and Administration during the observation period
5) Concomitant medications
Presence or absence of concomitant medications, name of the medications, route of administration, reason for administration, during the observation period.
6) Concomitant therapies for COPD (other than medications)
Presence or absence of concomitant therapies for COPD, name of the therapies, during the observation period.
7) COPD exacerbations

Number of COPD exacerbations during the 1-year period before and after the initiation of treatment with Encruse Ellipta

8) 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 Encruse 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.

9) COPD assessment test (CAT)
Information of the "COPD Assessment Test (CAT)" filled out by patients at the initiation of treatment with Encruse Ellipta, at 1 month and 1 year after the initiation of treatment, and at the time of discontinuation/completion.

10) Global assessment of effectiveness
One year after the initiation of treatment with Encruse Ellipta or at the discontinuation/completion of treatment, the effectiveness 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. If effectiveness cannot be determined for some reasons, it should be assessed as "indeterminable", and the reason should be entered in the EDC system.

11) Status of continuation of treatment with Encruse Ellipta at the end of the observation period
Status of the continuation of treatment at the end of the treatment with Encruse Ellipta and reason for the discontinuation/completion

12) Pregnancy
Whether Encruse 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 Encruse 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 a mother and her fetus as far as possible regarding the course of delivery, miscarriage, abortion, etc. and AEs, etc.

13) AEs
Presence or absence of AEs after the initiation of treatment with Encruse Ellipta, name of diagnosis or symptoms, date of onset, outcome of AEs, date of outcome, seriousness, reason for assessing as serious, relationship with Encruse Ellipta, and other factors suspected of being related to AEs except Encruse Ellipta
(1) In the investigation, priority investigation matters are defined as follows;

・Cardiovascular events, urinary retention, eye related problems, gallbladder disorder, intestinal obstruction, anticholinergic effects, 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 Encruse Ellipta in the EDC system, regardless of the presence or absence of a relationship with the product. The relationship with Encruse 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 Encruse 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 effectiveness 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 Effectiveness 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 Effectiveness 2 (global effectiveness 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 by MedDRA SOC and PT

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

- Cardiovascular events, urinary retention, eye related problems, gallbladder disorder, intestinal obstruction, anticholinergic effects, 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 effectiveness

[1] Effectiveness 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] Effectiveness 2

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

2) Analysis methods

For factors that may affect the items related to the safety and effectiveness, etc., the odds ratios and their 95% confidence intervals will be calculated. 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 time of measurement and the changes from baseline will be calculated and graphically presented using a boxplot, as appropriate.

10. Organization

Same as the Risk Management Plan

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

1) Registration operations
Outsourcee: CMIC Co., Ltd.
Scope: patient registration and other related operations

2) Data management operations
Outsourcee: CMIC Co., Ltd.
Scope: data management and other related operations

3) Data tabulation operations
Outsourcee: CACEXICARE Corporation
Scope: data tabulation and other related operations

4) EDC system operarions
Outsourcee: FUJITSU FIP CORPORATION
Scope: development and operation of EDC system and other related operations

12. Progress of the Investigation and Evaluation of the Results Obtained or the Timing of Milestones for Reporting to the Pharmaceuticals and Medical DevicesAgency (PMDA) and Their Rationales

- At the time of a periodic safety reports: To conduct a comprehensive review of the safety information

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

13. 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.

- If the investigation discloses the incidence, date of onset of the primary study items such as cardiovascular events, urinary retention, eye related problems, gallbladder disorder, intestinal obstruction, anticholinergic effects, lower respiratory tract infection and pneumonia , reported as ADR's to Encruse Ellipta, necessity of revision of the prescribing information and other materials will be considered.
- 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.
- Necessity of adopting risk minimization measures to new safety considerations will be considered

14. Publication of Study Results

The information regarding the results of this investigation will be provided to clinical sites as interim and final reports as appropriate for the purpose of "proper use" and "safety securing", considering a proper timing and number of patients whose CRF is collected, etc., by means of presentation at an academic conference and papers.

In addition, the summary of plan and results in this investigation will be disclosed in GSK Clinical Study Register.

15. Other Requirements

1) Protocol Revision

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, validity of study items, etc. should be monitored accordingly, 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) Any change in the planned number of medical institutions (by department)

(2) EDC system
  [1] Any change in layout of the study items (movement in the position of described items, enlargement/reduction of field size)
  [2] Any change in the explanation of study items
  [3] Any addition of examples of ADRs resulting from revision to the precautions and addition of appreciable ADRs
(3) Any addition, change and deletion of the items NOT affecting analysis of the whole investigation, specially effectiveness and safety
(4) Study period
  [1] Any change in the start date of the investigation resulting from delay of sales 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) Measures taken in detecting an issue or concern
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 ENCRUSE®ELLIPTA®
Attachment 1
2) Implementation Guidance for the Drug Use Investigation of ENCRUSE ®ELLIPTA®
Attachment 2
3) Registration Form for the Drug Use Investigation of ENCRUSE ®ELLIPTA®
Attachment 3
4) Case Report Form for the Drug Use Investigation of ENCRUSE ®ELLIPTA®
Attachment 4
5) CAT for the Drug Use Investigation of ENCRUSE ®ELLIPTA®
Attachment 5

Encruse ® Elliptor ® Drug Use Investigation (Study:201450)

Statistical Analysis Plan

Version 4.0

July 3, 2019

The Author(s) Biomedical Data Sciences Department
PPD PMS Statistical Group

Approver Biomedical Data Sciences Department
PMS Statistical Group PPD
Day Month Year

History of preparation and revision

Version	Date of preparation and revision	Prepared and revised by	Remarks
1.0	November 22, 2016	PPD	New preparation
2.0	October 13, 2017		・ 4.1.1、8.2、9.1、12: Changing the term from 'complete' to 'fixation'. ・ 4.1.2.3: Modified conditions for "same patient" ・ Change code (priority) ・ Adding "No visit after the first visit" ・ Modified conditions for "Adverse event data not completed" ・ 4.1.2.4: "drug dose unknown" was deleted, and "efficacy assessment not described" was added. ・ 4.3.3: Change acceptable ranges ・ 5.2: Elderly and high-dose definitions were removed ・ 11.7: Addition of forms (Appendix 18) ・ 12: Adding list (Appendix 19) ・ Other, error correction
3.0	December 06, 2018		・ 4.1.1: Added "being checked after approval" and "being reexamined after approval" to the collection sites and case report form collection subjects. Added subjects included in FEV1 analysis, subjects included in the FVC analysis, and subjects included in the CAT analysis. ・ 4.1.2.1: Revised to not recalled case report form. ・ 4.1.2.5～4.1.2.7: Add condition. ・ 4.7: Definition modification. ・ 4.12: Added definition. ・ 5.1.1: Deletion of entries on the number of Subjects. ・ 5.2: Safety Specification Added. ・ Appendix 3: Add description of summary statistics. ・ Appendix 4, 5: Number of items removed. Rates were changed to proportions. Added description of summary statistics. ・ Appendix 6-8: Rates changed to proportions.

			・ Appendix 10: Number of items removed. Added Criteria Modification of Incomplete Dating. ・ Appendix 11, 14-1, 14-3, 18-x, 17: deleted. ・ Appendix 13: Rate was changed to a ratio. ・ Added Appendix 20-21, 15-3, 12-2, Appendix 12, Appendix 12-2, Appendix 16, Appendix 22, Appendix 23: Newly. Appendixes 14-2, 15-1, and 15-2: Prepare entries.
4.0	July 3, 2019	PPD	・ 4.1.1 Analysis set and sites: Removed research contract sites and research contract subjects ・ 4.1.2.5 Subjects included in FEV1 analysis set, 4.1.2. subjects included in 6 FVC analysis: Discordant subjects were added before and after SABA use condition ・ 4.6 Switching from single-agent LAMA: deleted ・ 4.7 Switch from LAMA+LABA: Deleted ・ 6.1 Parameter (validity): Modify the units of FEV1 and FVC. ・ 8.3 Treatment continuation status and reason for discontinuation of drug: Addition ・ 8.2 Survey implementation status and sample composition (Appendix 2): The number of study contract sites and sample size were deleted, and the number of FEV1 FVC, and CAT Subjects/excluded Subjects and reasons were added. ・ 10.1 Adverse drug reactions/infections by patient characteristics: Added tabulations by priority survey items ・ 10.6 Occurrence of key safety survey items: deleted because of the use of Form 12 ・ 11.2 Concomitant medication use by subjects with or without complications (bronchial asthma) (Appendix 5-2): Added because the differences were significant ・ 11. 3 (Old 11.2) Respiratory Function Test (Spylometry):FEV1 (Appendix 14-2-x): Corrected the study of analysis. Additional subgroup analysis of the elderly. Changed to MEAN ± 95% CIs, added Waterfall

			plot ・ 11.4 Respiratory Function Tests (Spirometry) by Patient Background: FEV1 (Appendix 14-3): Additional ・ 11.5 (formerly 11.3) COPD Assessment Tests (CATs) (Appendix 15-1): MEAN ± 95% CIs changed ・ 11.6 COPD Assessment Tests (CATs) (Appendix 15-4) by Patient Demographics: Added ・ 11.8 (Former 11.5) Respiratory Function Tests (Spirometry): FVC (Appendix 15-3): Modified analysis set. Changed to MEAN ± 95% CIs, added Waterfall plot ・ Added descriptions such as explanations were improved (4.1.2.1, 4.1.2.5, 4.1.2.6, 4.1.2.7, 8.1).

Contents

1. Introduction

1.1 Positioning of the statistical analysis plan

This statistical analysis plan (hereinafter called this plan) represents the plan for statistical analysis in the Enclasse Elipta Drug Use Investigation (hereinafter called this DUI).

2. Software and dictionary to be used

2.1 Statistical analysis and tabulation software

	Software and Version
OS	After Microsoft Windows 7
Statistical analysis software	SAS Ver.9. From 3 onwards
Tabulation software	After Microsoft Excel 2007

2.2 Dictionary to use

Item	Dictionary name
Name of disease (complication), name of adverse event, name of adverse drug reaction	MedDRA/J (tabulate in versions used for coding in DM. ∗ As a general rule, use the most recent version)
Name of the medicine and name of the drug	Prescription drug name data file (tabulate using the version used for coding in DM. ∗ As a rule, use the most recent one)

3. Definition of Terms

Term	Definitions
COPD	Chronic Obstructive Pulmonary Disease
CAT	COPD Assessment Test
IDSL	Integrated Data Standard Library (standardized rules at GSK)

4. Handling of Subjects and Data

4.1 Handling of Subjects

4.1.1 Analysis Population/Site

Analysis Population/Site	Definitions
Registration Sites	Site for all Subjects enrolled in this survey. ・ In the PMS Progress Management System case report form information, "case report form Status" is a value other than "Exclusion from Registration" and "Patient Approval Date" is a value and is a date prior to the data lock date.
Registered subjects	Subjects for all Subjects enrolled in this DUI ・ Subjects in which the "case report form Status" is other than "Exclusion from Registration" in the PMS Progress Management System case report form information And a patient with a value on the "Patient Approval Date" and a date prior to the Data Lock Date
Collection sites for Case Report Form	Institution for all Subjects in which the survey form was collected in this survey among the enrolled institutions ・ Sites for subjects in which the "case report form Status" in the PMS Progress Management System case report form information is either "this approval", "Survey Form Re-survey", "Content Confirmation", "Content Confirmation", "Post-approval Confirmation" or "Post-approval Re-investigation". -Site for Subjects with values in the "Receipt date of the Survey Form Headquarters" and dates before the date of data locking
Subjects collected from the Case Report Form	All Subjects for which case report forms were collected in this DUI among the subjects registered in the survey ・ Subjects in which the "case report form Status" is either "this approval", "Survey case report form Re-survey", "Content Confirmation", "Content Confirmation", "Confirmation after approval" or "Review after approval" in the PMS Progress Management System case report form information -subjects who have a value on the date of receipt of the case report form from the head office and are dated before the date of data locking
Fixed sites in the Case Report Form	Institution for subjects in whom the case report form was approved out of the Subjects collected from the case report form ・ Institution for Subjects in which "case report form Status" is "this approval" in the PMS Progress Management System case report form information •Site for subjects who have a value on the Survey Form Approval Dates and are dated before the date of data locking.
Subjects with fixed Case Report Form	Subjects for which the case report form was approved among the Subjects collected from the case report form. ・ subjects in which "case report form Status" is "this approval" in the case report form information of the PMS Progress Management System -and subjects who have values on the Survey Sheet Approval Dates and are dated before the date of data locking
Subject included in the safety analysis	Subjects for which the safety assessment was considered inadequate (see Section 4.1.2.3) were excluded from the subjects with fixed case report forms.
Subjects included in the efficacy analysis	Studys excluded from the safety analysis set who were considered inappropriate for efficacy evaluation (see Section 4.1.2.4)
Subjects included in the FEV1 analysis	Subjects in which the efficacy analysis set excluded subjects who were considered inappropriate for evaluating FEV1 (see Section 4.1.2.5)

Analysis Population/Site	Definitions
subjects included in the FVC analysis	Subjects in which FVC was considered inappropriate for evaluation (see Section 4.1.2.6) were excluded from the efficacy analysis study.
subjects included in the CAT analysis	Subjects for which CAT was considered inappropriate for evaluation (see Section 4.1.2.7) were excluded from the efficacy analysis set.

4.1.2 Analysis exclusion criteria

4.1.2.1 Subjects not recalled from the case report form

Reasons for non-recall of the case report form will be assigned to Subjects excluded from the case report form-recalled Subjects.

Code	Survey form not recalled	Conditions of exclusion
1	Unretrievable	PMS progress management system case report form information [case report form status] is not available
2	During collection of case report forms	PMS progress management system case report form information [case report form status] other than "not available" above

4.1.2.2 Unfixed subjects on the case report form

Code	Unfixed case report form	Conditions of exclusion
3	During checks or re-examinations	PMS Progress Management System "Number of Subjects Recovered by Survey Sheet" and "Number of Subjects Fixed by Survey Sheet"

4.1.2.3 subjects excluded from safety analysis

If reasons for exclusion overlap and prioritize, the reason for exclusion from the safety analysis will be assigned according to the following ranking:

Code	Exclusion of safety analysis	Priority Rank order	Conditions of exclusion	Logic decision
4	Agreement violation	1	Starting date of the first dose of drug or completion date of treatment is outside the contract period	○
5	Registration violation	2	Not registered within 14 days of the starting date of drug prescribing	○
6	Drug naive	3	Subjects in which the dose and administration of drug is not described at all or the dose is described as 0	○
7	Same case	4	Subjects judged to be the same case, such as duplicate registration or transfer within the same institution.	×
8	No visit after the first visit	5	[Continuation of drug treatment at the end of the run-in period]. Subjects in which the reason for discontinuation/termination of administration is "No visit after the date of the	△

			first prescription".	
9	Adverse event data not completed	6	Subjects in which the presence or absence of adverse events is blank and adverse event data is not available	○
10	Other (Safety)	7	Subjects for which exclusion reasons were other than those mentioned above (4-9)	×

4.1.2.4 subjects excluded from efficacy analysis

If reasons for exclusion overlap and prioritize, then the reason for exclusion from the efficacy analysis will be assigned according to the following ranking:

Code	Efficacy analysis excluded	Priority Rank order	Conditions of exclusion	Logic decision
11	Off-label use	1	Reasons for use other than "chronic obstructive pulmonary disease"	×
12	Unable to determine the effect	2	[Overall Efficacy Evaluation]. Subjects in which "cannot be assessed"	○
13	Efficacy assessment not described	3	[Overall Efficacy Evaluation]. Subjects that are not listed	○
14	Other (Efficacy)	4	Subjects other than those listed above (11-13) for exclusion reasons	×

4.1.2.5 Subjects included in the FEV1 analysis

Code	Efficacy analysis excluded	Priority Rank order	Conditions of exclusion	Logic decision
15	Subjects in which anterior-posterior compares are not possible	1	Subjects who do not have either or both of these data at the start of drug treatment and after the start of drug treatment (1 month after the start of drug treatment or 1 year after the start of drug treatment or at the end of drug treatment).	○
16	Subjects of discordance between before and after conditions of SABA use	2	Subjects who do not agree with the use of short-acting β2-agonists within 4 hours prior to treatment and after the start of treatment (1 month after the start of treatment or 1 year after the start of treatment or at the end of treatment).	○
17	Others (FEV1)	3	Reasons for exclusions other than those listed above (15, 16)	×

4.1.2.6 subjects included in the FVC analysis

Code	Efficacy analysis excluded	Priority Rank order	Conditions of exclusion	Logic decision
18	Subjects in which anterior-posterior compares are not possible	1	Subjects who do not have either or both of these data at the start of drug treatment and after the start of drug treatment (1 month after the start of drug treatment or 1 year after the start of drug treatment or at the end of drug treatment).	○

Code	Efficacy analysis excluded	Priority Rank order	Conditions of exclusion	Logic decision
19	Subjects of discordance between before and after conditions of SABA use	2	Regarding the acceptable time ranges of "4.3.3 timing" in Subjects where there is no agreement between the use of short-acting β2-agonists within 4 hours prior to the measurement in the data obtained at the start of treatment and after the start of treatment (1 month after the start of treatment or 1 year after the start of treatment or at the end of treatment).	○
20	Other (FVC)	3	Subjects other than those mentioned above (18, 19) for reasons of exclusion	×

4.1.2.7 subjects included in the CAT analysis

Code	Efficacy analysis excluded	Priority Rank order	Conditions of exclusion	Logic decision
21	Subjects in which anterior-posterior compares are not possible	1	Subjects who do not have either or both of these data at the start of drug treatment and after the start of drug treatment (1 month after the start of drug treatment or 1 year after the start of drug treatment or at the end of drug treatment).	○
22	Other (CAT)	2	Subjects other than those listed above (21) for exclusion reasons	×

4.2 Handling of missing data

4.2.1 Complement to the data

Data are not imputed for missing data unless otherwise stated.

When calculating the sum of CAT scores, if missing data are 2 or fewer items, they are imputed with the mean of the other items. If there are more than three missing data items, this will not be calculated.

4.2.2 Missing successive quantities

If there is a missing result in the collection of continuous quantities, the data shall be excluded from the tabulation. When continuous quantities are classified into categorical categories, "4.2.3 Categorical Data" should be followed.

4.2.3 Categorical data

- Treat as "unknown" without distinguishing between missing, unknown, and undescribed.
- Included as a percentage denominator unless otherwise stated.
- Excluded from test and odds ratio.

4.2.4 For dating variables

If the completion day of treatment is not completed (checked for continuation of administration), the completion dayof the plan observation period is regarded as the completion dayof administration, and the number of days of administration is calculated.

The completion dayof the plan observation period is calculated by +1 and-1 the year and day of the starting day of treatment, respectively.

4.3 Handling of time course data

4.3.1 Days (days)

The dates based on the starting day of treatment are calculated as follows: before and after the start date of treatment n.

・ Target day < For the first day of treatment: n days after the start of treatment = Target date - Start date of treatment

・ Target day >= For the first day of treatment: n days after the start of treatment = Target day - Start date of treatment + 1

※ The labeling of the period (days) after the start of treatment is labeled as 1 for the starting day of treatment and-1 for the day before the start of treatment, and 0 is not used.

※ If all dates are missing or partial dates, they are not supplemented and are unknown.

Except for the completion dayof treatment in "4.2.4 Dating Variables".4.2.4

4.3.2 start date of treatment

The first day of administration listed in the "Treatment Status of drug" of the survey form is the starting day of treatment.

4.3.3 Acceptable time ranges

Acceptable time ranges for analysis should not be specified, and data as judged by the treating physician should be used.

4.3.4 Baseline Value

The value at the start of treatment is defined as the baseline value.

4.4 Age

Age [years] will be calculated using the date of the start of treatment, complemented with June 30 in the year of birth of the case report form.

<Reference IDSL Algorithm>

- GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  - Any subject with a missing day will have this imputed as day '15'.
  - Any subject with a missing date and month will have this imputed as '30th June'.

Birth date will be presented in listings as 'YYYY'.

4.5 Prior medications

All medications entered on the “Prior medications Drugs for Chronic Obstructive Pulmonary Disease” page of the case report form.

4.6 Concomitant medication

All medications entered on the “Concomitant Medications” page of the case report form.

Subjects in which the medication is listed on the relevant page are classified as "yes" with or without concomitant medications.

4.7 Combination Therapy

All therapies entered on the 'Combination Therapy for Chronic Obstructive Pulmonary Disease' page of the case report form.

Subjects in which therapy is listed on the relevant page are designated as "yes" with or without concomitant therapy.

4.8 Discontinuation/end Subjects, continuation Subjects

Among the subjects with fixed case report forms, subjects who were checked for discontinuation/completion of administration or who were checked for reasons for discontinuation/completion of administration on the "drug Treatment Continuation Status at the End of the Observation Period" page of the case report form will be selected as discontinued/terminated Subjects, and others will be considered as continued Subjects.

4.9 Complications

All events entered in the Complications section of the “Patient Characteristics” page of the case report form.

Subjects in which an event is listed in the relevant item are classified as "present" according to the presence or absence of a complication.

The system organ class uses SOC and PT unless otherwise specified for symptoms and diseases. In addition, if SOCs are displayed, they are displayed according to the order of international agreement, and if PTs are displayed, they are displayed according to the order of PT codes.

4.10 Handling of Respiratory Function Test Values

When FEV1 or FVC values are "0" or Null, respiratory function test values are considered unmeasured and are not used for analysis. Respiratory function test values shall not be used for analysis if the investigator confirms that physician has not measured.

5. Safety end point

5.1 Adverse Events and Adverse Drug Reactions

Term	Definitions
Adverse events (AEs)	Any unfavourable or unintended sign (including laboratory abnormalities), symptom, or disease occurring after the starting day of drug treatment (including the day of the day), whether or not related to drug. Argus data are used for analysis.
Adverse Drug Reactions (ADRs)	AEs other than "determined causality" and "reported causality" that are "unrelated" or "can be denied".
Serious Adverse Events (SAE)	Among adverse events (ADRs), events assessed as "serious" are defined as events assessed as "serious".

5.1.1 Summary of Adverse Events

The system organ class uses SOC and PT unless otherwise specified for symptoms and diseases. In addition, if SOCs are displayed, they are displayed according to the order of international agreement, and if PTs are displayed, they are displayed according to the order of PT codes.

5.2 Survey items

The definition of the survey items is shown below.

Survey items		Definitions
Safety specification	Cardiovascular AEs	Events corresponding to MedDRA codes designated by G in the ADR data (Argus data).
Major investigation items	Cardiovascular AEs	Events corresponding to each of MedDRA codes specified separately.
	Urinary retention	
	Eye-related events	
	Gallbladder disorder	
	Intestinal obstruction	
	Anticholinergic effect	
	Lower respiratory tract infection and pneumonia	
Complications	Bronchial asthma	Events corresponding to each of MedDRA codes

Survey items		Definitions
	Cardiovascular events	specified separately.
	Renal impairment	
	Hepatic dysfunction	
Smoker		Subjects who are current smokers, current smokers, or non-current smokers.

5.3 Test Items (Safety)

Item name	Unit	Display digit	Definitions
Height	[cm]	0.1	
Weight	[kg]	0.1	
BMI	-	0.1	Body weight [kg]/height [m]/height [m]
Average daily dose	[μg/day]	0.1	Total dose [μg]/total days of treatment [days]
Average number of daily doses	[times/day]	0.1	Total number of doses [times]/total days of treatment [days]
Total dose	[μg]	0.1	Total of one dose [inhalation/dose] × number of daily doses [times/day] × 62.5μg× number of days of administration*1 for each record Calculate to μg of UMEC. Inhalation/dose × 62.5μg
Total number of doses	[Times]	1	Total of one dose [inhalation/dose] × number of daily doses [times/day] × number of days of administration*1 for each record
Total number of days of administration	[Day]	1	Total number of days of administration*1 for each record

※1: The number of days of treatment is calculated from the "completion day of treatment - start day of treatment + 1".

※2: If missing even one item is present in the formula, it is considered missing. However, the total number of days of administration is in accordance with the rules described in 4.2.4.

6. Efficacy endpoint

6.1 Examination Items (Efficacy)

Item name	Unit	Display digit	Remarks
Forced expiratory volume in 1 second (FEV1)	[mL]	0.1	

Item name	Unit	Display digit	Remarks
Forced vital capacity (FVC).	[mL]	0.1	
Forced expiratory volume one second percent (FEV1%)	[%]	0.1	FEV1 / FVC×100
Percentage of forced expiratory volume in 1 second by predeictive FEV1 (%FEV1)	[%]	0.1	FEV1 / Predictive FEV1×100
Predictive FEV1	[mL]	0.1	[FEV1 - J formula] Males: FEV1 [mL] = 0.036 × height [cm]-0.028 × age-1.178 × 1000 Female: FEV1 [mL] = 0.022 × height [cm]-0.022 × age-0.005 × 1000 ※ Age is the age at the beginning of drug treatment.
CAT score	[Points]	1	

7. Items Related to Statistical Processing

7.1 Summary statistics

Number of subjects, mean, standard deviation, minimum, 25% point, median, 75% point, maximum.

7.2 Change, rate of change, and rate (percentage)

The change from baseline and the percentage change will be calculated using the following formula.

Change from baseline = Value at each visit – Baseline value

$$\text{Rate of change from baseline (\%)} = \frac{\text{Change from baseline}}{\text{Baseline value}} * 100$$

Percentage (%) = number of studies/number of subjects included in the analysis × 100

7.3 Display of the results

The number of orders of magnitude in displaying the aggregated results is indicated below. The label digits for each item should be described in the respective analysis content.

Classification	Display digit
Rate and percentage	The third decimal level is rounded and displayed up to the second level.
N	You display as an integer.
Mean, standard deviation; 25th percentile, median; 75th percentile, confidence interval of the mean	The two orders of magnitude below the indicated number are rounded and displayed up to one order of magnitude below the indicated number.
Min, max	Round down to the nearest digit of the number of digits to be displayed, and display up to the same digit as the number of digits to be displayed.
P value	The fourth decimal level is rounded and displayed to the third decimal level. However, if the pre-rounding p-value is less than 0.001, it is uniformly labeled p<0.001. [When adding *, etc.] When the pre-rounding p-value is the following value, * (asterisks) are displayed in conjunction with the p-value: P-value >= 0.05: none P value < 0.05 : * p value < 0.01 : ** P value < 0.001 : *** <Example> Original value: 0.0098 Display :p=0.010**
Odds ratio, confidence interval of odds ratio	The fourth decimal level is rounded and displayed to the third decimal level.

7.4 Patient characteristics

Handling of tabulated background items by patient characteristics by aggregate table is summarized below.

For details, see Appendix 3 of the output plan.

"Unknown" should be indicated when relevant Subjects exist.

However, the items for which there are others in the case report form are displayed even if there are no relevant Subjects.

Items not in the case report form will be tabulated as "unknown".

Baseline data will be tabulated for items measured by time period.

With respect to the presence or absence of adverse drug reactions and effectiveness / noteffectiveness, the odds ratio for the ○ category will be calculated based on [*] in the reference column for each item in Appendix 4 and Appendix 5.

7.5 SAS Sample Code

7.5.1 Age calculation

Age = intck ('year', date of birth, start date of treatment)-(month (start date of treatment) < month (date of birth) or (month (start date of treatment) = month (date of birth) < and day (start date of treatment) < day (date of birth))

7.5.2 Fisher test, χ2 test

```
Proc freq data=data ;
   Tables Gun * Tarvar / chisq ;
   Output out=out chisq exact ;
Run ;
```

7.5.3 Odds ratio

```
Proc logistic data=data ;
   Class key / param=ref ref=first ;
   Model res(event='1')=key ;
   Ods output CloddsWald = outdata ;
Run ;
```

7.5.4 Two-sample t-test

```
Proc mixed data=data ;
   Class Gun ;
   Model Tarvar = Gun ;
   Lsmeans Gun / cl pdiff tdiff alpha=0.05 ;
   Ods output Diffs=outdata ;
Run ;
```

7.5.5 Analysis of variance (ANOVA)

```
Proc glm data= data outstat=outdata ;
  Class Gun ;
    Model Tarvar = Gun / SS3 ;
Run ;
```

7.5.6 One-sample t-test

```
Proc univariate data=data noprint ;
   Var Tarvar ;
   Output out =outdata
   Probt =Pvar ; /* 1-sample t-test p-value */
Run ;
```

7.6 Test method

・Categorical data

The two-sided Fisher test is used for the 2x2 categories, and the two-sided $\chi 2$ test is used for the n×2 categories (where n is greater than or equal to 3). Also, the unknown category is not included in the test, and the odds ratio is not calculated.

・Continuous data

Two-sample t-test is used for two categories and analysis of variance for more than three categories.

8. Case Composition

8.1 Number of registered sites and subjects (Appendix 1)

Analysis set: Registrated Subjects

Content of analysis: The maximum, minimum, and mean number of subjects enrolled at a single institution will be calculated.
The number of sites is not considered for clinical departments and is summarized on an institutional basis.

8.2 Case Composition (Figure 1)

Analysis set: -

Content of analysis: The following sample size, number of excluded Subjects and reasons for exclusion are presented using a flow chart:
If the reason for exclusion was the same patient and multiple entries were found, the data should be aggregated into high-priority items.
The number of sites is not considered for clinical departments, and it is totaled on an institutional basis.

- Number of registrated sites
- Number of registrated subjects
- Number of subjects not recalled from the case report form and reasons for exclusion
- Number of collection sites for case report forms
- Number of subjects collected from the case report form
- Number of subjects with unfixed case report forms and reasons for exclusion
- Number of fixed sites in the case report form
- Number of subjects with fixed case rport forms
- Number of subjects excluded from safety analysis and reasons for exclusion
- Number of sites and number of subjects included in the safety analysis
- Number of subjects excluded from efficacy analysis and reasons for exclusion
- Number of subjects included in the efficacy analysis
- Number of subjects included in the FEV1 analysis
- Number of subjects excluded from FEV1 analysis and reasons for exclusions
- Number of subjects included in the FVC analysis
- Number of subjects excluded from FVC analysis and reasons for exclusion
- Number of subjects included in the CAT analysis
- Number of subjects excluded from CAT analysis and reasons for exclusion

8.1 Treatment continuation status and reason for discontinuation of drug (Appendix 24)

Analysis set: Subjects included in the safety analysis

Content of analysis: The reasons for continuation, discontinuation, and discontinuation of drug treatment will be tabulated.
Reasons for discontinuation will be summarized in duplicate if there are multiple reasons for discontinuation.

9. Patient characteristics

9.1 Case Composition Ratio in Fixed Subjects on the case report form (Appendix 3)

Analysis set:	Subjects with fixed Case Report Forms, Subjects included in the safety analysis, Subjects included in the efficacy analysis
Content of analysis:	The number of subjects and the component percentages (%) and/or summary statistics will be calculated for subjects with fixed case report forms, subjects for safety analysis, and subjects for efficacy analysis according to patient characteristics. Summary statistics will be tabulated for subjects included in the safety analysis. Unless otherwise stated, the denominator of the component percentage (%) is the sum of each analysis case. No calculations are made for the 25% and 75% points of the summary statistics.

10. Safety Evaluation

10.1 adverse drug reactions/infections by patient characteristics (Appendix 4, Appendix 4-x)

Analysis set:	Subjects included in the safety analysis
Content of analysis:	The number of subjects, the number of subjects with adverse drug reactions, and the incidence of adverse drug reactions (%) will be calculated for each patient characteristics, and and/or summary statistic will be calculated. Summary statistics will be tabulated for subjects included in the safety analysis. Analyses will also be conducted by key survey items. The denominator of the incidence (%) of adverse drug reactions is the number of subjects included in each background parameter. We will also test for uniformity and calculate odds ratios.

10.2 Number of subjects with complications (SOC, PT) by symptoms (Appendix 6)

Analysis set:	Subjects included in the safety analysis, Subjects included in the efficacy analysis
Content of analysis:	The number of subjects (number of complicated Subjects) and the complication rate (%) will be calculated for each SOC and PT according to the categories of complications (6-1: bronchial asthma, 6-2: cardiovascular disorders, 6-3: renal dysfunction, 6-4: hepatic dysfunction, 6-5: other). The denominator of the complication percentage (%) is the number of subjects included in each analysis. The number of subjects with adverse drug reactions and the incidence of adverse drug reactions (%) will be calculated for the safety analysis set, and the efficacy analysis set will include the efficacy subjects and the percentage of effectiveness (%). The denominator of the incidence (%) of adverse drug reactions and the the percentage of effectiveness (%) is the number of subjects included by SOC and PT.

10.3 Number of subjects by prior medication (Appendix 7)

Analysis set:	Subjects included in the safety analysis, Subjects included in the efficacy analysis
Content of analysis:	For each drug category, product name, and drug code, the denominator of the number of subjects included is the number of subjects included in each analysis. Percent use is calculated. The safety analysis set will also include the number of subjects with adverse drug reactions, the incidence of adverse drug reactions (%), and the efficacy analysis set

will also include the efficacy subjects and the percentage of effectiveness (%).
The denominator of proportion use is the number of subjects included in each analysis.
The denominator of the incidence rate (%) of adverse drug reactions and the percentage of effectiveness (%) is the number of subjects included in each analysis by drug as the denominator of the number of subjects included in the analysis.

10.4 Number of subjects by concomitant medication (Appendix 8)

Analysis set:	Subjects included in the safety analysis, Subjects included in the efficacy analysis
Content of analysis:	The use category, drug code (seven digits), number of subjects covered (number of concomitant drug use Subjects), and percentage of use (%) are calculated for each generic name. The safety analysis set will also include the number of subjects with adverse drug reactions, the incidence of adverse drug reactions (%), and the efficacy analysis set will also include the efficacy subjects and the percentage of effectiveness (%). The denominator of proportion use is the number of subjects included in each analysis. The denominator of the incidence (%) of adverse drug reactions and the effective rate (%) is the number of subjects covered by each drug (number of subjects who used concomitant drugs).

10.5 Time to onset by type of adverse reaction (Appendix 10)

Analysis set:	Subjects included in the safety analysis
Content of analysis:	The number (%) of subjects per SOC and PT will be summarized by the categories of days to the onset of adverse drug reactions for each PT. In addition, the number of subjects with adverse drug reactions (%) and the cumulative number of subjects with adverse drug reactions (%) will be tabulated. ※ SOC and PT are tabulated by index SOC and PT, respectively. ※ When adopting the index SOC and PT, an incomplete date should be adopted if the full and incomplete dates were expressed in the same case, the same PT. Calculation of the number of days of onset is as follows: Day of onset-starting day of administration + 1

10.6 Incidence of adverse drug reactions by background factors (Appendix 20)

Analysis set:	Subjects included in the safety analysis
Content of analysis:	Concerning adverse drug reactions, the proportion of each SOC and PT will be tabulated by seriousness (serious/total) according to the background factors. The output permutations are outputted in descending order of the number of examples of SOCs in the overall side effect column of the total column, the international consensus order of SOCs, the descending order of the number of examples of PTs, and the PT code order. The denominator is the number of subjects surveyed in each category of the item.

10.7 Outcomes by Seriousness of adverse drug reactions (by Event) (Appendix 21)

Analysis set:	Subjects included in the safety analysis

Content of analysis: Concerning adverse drug reactions, the proportion of each SOC/PT will be tabulated by seriousness (serious/total) and outcome. The output order is outputted in descending order of the number of Subjects of SOC for all ADRs in the total column, the international consensus order of SOC, the descending order of the number of Subjects of PT, and the PT code order.
The denominator is the number of subjects study for each item.

※ If the same case and the same SOC or PT are present in the summary by outcome, the following priorities will be adopted and summarized.
Death > sequelae > unresolved > remission > recovery > unknown

11. EFFICACY EVALUATION

11.1 Overall Efficacy Evaluation by Patient Demographics (Appendix 5)

Analysis set: Subjects included in the efficacy analysis
Content of analysis: The number of studies, active subjects, ineffective subjects, and effective rate (%) will be calculated for each patient characteristics, and and/or summary statistic will be calculated. Summary statistics will be tabulated for subjects included in the efficacy analysis.
The denominator of the effective rate (%) is the number of subjects included in each background parameter.
We will also test for uniformity and calculate odds ratios.

11.2 Use of concomitant medications in subjects with and without complications (bronchial asthma) (Appendix 5-2)

Analysis set: Subjects included in the efficacy analysis
Content of analysis: To calculate the proportion of subjects with and without concomitant drugs according to the presence or absence of complications (bronchial asthma).

11.3 Respiratory function tests (spirometry):FEV1 (Appendix 14-2-x)

Analysis set: Subgroups of subjects included in FEV1 analysis and elderly (≧ 65)
Content of analysis: Obtain summarized FEV1 and change statistics at specific time intervals.
A one-sample t-test will be performed for changes, and 95% CIs will be calculated.
Also, BOX-plots of changes, transition graphs (MEAN ± 95% CIs) and Waterfall Plot are generated.

11.4 Respiratory function tests (spirometry) by backgrounds of subjects: FEV1 (Appendix 14-3)

Analysis set: Subjects included in the FEV1 analysis
Content of analysis: Summary statistics of the change in FEV1 at 1 month after the start of drug treatment, 1 year after the start of drug treatment, and at the time of discontinuation/completion of drug treatment will be calculated by patient characteristics.

11.5 COPD Assessment Tests (CATs) (Appendix 15-1)

Analysis set:	Subjects included in the CAT analysis
Content of analysis:	Summary statistics of CAT scores and changes will be calculated for each time period. A one-sample t-test will be performed for changes, and 95% CIs will be calculated. We will also generate BOX-plots and transition graphs (MEAN ± 95% CIs) of changes.

11.6 COPD Assessment Tests (CATs) (Appendix 15-4-x) by Patient Demographics

Analysis set:	Subjects included in the CAT analysis
Content of analysis:	Summary statistics of the change in CAT-score at 1 month after initiation of drug treatment, 1 year after initiation of drug treatment, and at discontinuation/completion of drug treatment will be calculated for each patient characteristics.

11.7 Exacerbations of chronic obstructive pulmonary disease (Appendix 15-2)

Analysis set:	Subjects included in the efficacy analysis, comparable before and after the end of 1 year of observation (continued treatment)
Content of analysis:	A shift table will be created for the number of exacerbations of COPD for 1 year prior to the start of drug treatment versus 1 year after the start of drug treatment.

11.8 Respiratory function tests (spirometry): FVC (Appendix 15-3)

Analysis set:	Subjects included in the FVC analysis
Content of analysis:	Summary statistics of FVC values and changes will be calculated for each time period. A one-sample t-test will be performed for changes, and 95% CIs will be calculated. Also, BOX-plots of changes, transition graphs (MEAN±95%CI) and Waterfall Plot are generated.

12. List to create

- List for identification of exclusion Subjects (Prior output A)
- List of AEs (Subjects included in the safety analysis) (safety analysis set) (Appendix 9)
- List of Case Report Forms and subjects (Subjects with fixed Case Report Forms) (Appendix 12)
- List of suspected factors other than drug (Appendix 12_2)
- List of Exclusion from Analysis for 2 in Appendix Formats 2 and 2 (Subjects with exclusion from Safety Analysis among subjects with fixed case report forms) (Appendix 16)
- List of Priority Investigation Items (Appendix 19)
- Onset Status of ADR/Infections in the additional medicinal product safety monitoring plan (safety analysis set) (Form 12)
- Onset Status of ADR/Infections in the additional medicinal product safety monitoring plan (safety

analysis set) (Form 12_2)

- Subject summaries during Post-Marketing Surveillance (subjects with fixed case report form) (Form 16)
- List of Serious ADRs (Appendix 22)
- List of ADRs Exclusion from Safety Analysis (Appendix 23)

13. References

Guideline for Diagnosing and Treating Chronic Obstructive Pulmonary Disease (COPD) 4th Edition.

Comparison between predicted equations obtained by standard Japanese values and present predicted equations for vital capacity and forced expiratory volume in one second. Respiratory Journal 2010; 48