PASS INFORMATION

Title	A Non interventional post authorisation study to determine the safety and effectiveness of flutiform® (A*ffi*rm Study).
Version identifier of the final study report	1.0
Date of last version of the final study report	19 July 2017
EU PAS register number	EUPAS4072
Active substance	Fluticasone propionate; formoterol fumarate,
Medicinal product	Flutiform®
Product reference	16950/0167 - 0169
Procedure number	UK/H/2872/001-003
Marketing authorisation holder(s)	See Page 3 of this report for list of MAs
Joint PASS	No
Research question and objectives	**Primary objectives:** Evaluation of the safety of flutiform® in routine clinical practice by: -Collection of data on the exposure to flutiform® and the frequency of adverse events associated with flutiform®, or which are known to be side effects of treatment with ICS/LABA combination drugs. -Recording all adverse events reported spontaneously or after physicians' open question by the patients as well as adverse events detected by diagnostic procedures during routine clinical practice at the physicians' discretion. **Secondary objectives:** To evaluate the effectiveness of flutiform treatment under real life conditions on asthma control
Country(-ies) of study	Czech Republic

	Denmark France Ireland Norway Slovak Republic Sweden United Kingdom
Author	Tim Overend, Clinical Leader; Mundipharma Research Ltd, Cambridge Science Park, Cambridge, CB4 0AB, UK

Marketing authorisation holder(s)	

Country	**MA Holder**
Czech Republic	Mundipharma Gesellschaft.m.b.H. Apollogasse 16-18, 1070 Wien Austria
Denmark	Mundipharma A/S Frydenlundsvej 30 2950 Vedbæk, Denmark
Norway	Mundipharma AS Vollsveien 13 C 1366 Lysaker, Norway
Sweden	Mundipharma AB Mölndalsvägen 30B 41263 Göteborg, Sweden
France	Mundipharma SAS 100 Avenue de Suffren, 75015 Paris France
Ireland	Mundipharma Pharmaceuticals Ltd Millbank House – Arkle Road Sandyford-Dublin 18 Republic of Ireland
Slovakia	Mundipharma Gesellschaft.m.b.H. Apollogasse 16-18, 1070 Wien Austria
United Kingdom	Napp Pharmaceuticals Limited Cambridge Science Park Milton Road Cambridge CB4 0GW

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1. ABSTRACT

Title

A non-interventional post-authorisation study to determine the safety and effectiveness of flutiform (Affirm Study).

Keywords:

Asthma, fluticasone propionate, formoterol fumarate, non-interventional study, safety.

Rationale and background

This study was conducted as part of an agreed European Risk Management Plan (EU RMP). The EU RMP was agreed with the Reference Member State during the decentralised procedure for flutiform.

Research question and objectives:

Primary objectives:

To evaluate the safety of flutiform in real life by collecting data on flutiform exposure and the frequency of its associated adverse events (AEs).

Secondary objectives:

To evaluate the effectiveness of flutiform treatment on asthma control under real-life conditions.

Study design: The objective of this post authorisation safety study (PASS) was to collect and analyse data on the safety and effectiveness of flutiform prescribed for outpatients with asthma aged ≥12 years. Safety observations were focused on AEs rate and severity while effectiveness was assessed in terms of achievement of asthma control.

This study was designed to be fluid and to fit with standard clinical practice. AEs were to be captured along with other parameters defined in the protocol, providing they were completed during normal clinical practice at participating investigator sites.

Data on the patient's asthma medical history was to be collected at the baseline visit (Visit 1) at the start (first dose of flutiform) of the 12-month observation period. Physicians' visits, diagnostic procedures, and assessments were to be performed as clinically indicated by the treating physician and according to asthma treatment guidelines. Patients were expected to return to the investigator at regular intervals over the course of their treatment with flutiform. There were estimated to be approximately 2-5 visits per patient (depending on local clinical practice).

Flutiform dose adjustments, if necessary, were to be performed at the physician's discretion and were to be documented, retrospectively, at the regular visits (along with changes in other medications required during the course of the observation). If treatment corrections were performed by the investigator, they were to be documented during the corresponding visit.

All reported AEs, including severe asthma exacerbations, were to be documented during the study.

Setting: The study was to be completed by general practitioners or respiratory physicians in primary or secondary care. The study started in participating countries after flutiform was launched.

The decision to prescribe flutiform necessarily preceded, and was independent of, the decision to enroll the patient into the study. Patients diagnosed with asthma were eligible for this study if they were not controlled on an inhaled corticosteroid (ICS) and 'as required' inhaled short-acting β_2-agonists (SABA), or if they were switched from another treatment with a fixed or a free inhaled corticosteroid/ long-acting β2 adrenergic receptor agonist (ICS/LABA) combination to flutiform. Only those patients who received a prescription for flutiform according to the Summary of Product Characteristics (SmPC) could be evaluated for their potential eligibility for the study.

Patients and study size: A total number of 2500 patients were intended to be enrolled within the EU. This sample size would allow AE rates to be estimated with a certain level of precision. For example, with 2500 patients, assuming an AE is reported by 5%, the two-sided 95% confidence interval (CI) would be between 4.1% and 5.9%.

2567 patients were enrolled and 1964 patients completed. All were aged ≥ 12 years, had a diagnosis of asthma and were receiving a prescription of flutiform according to the indication stated in the local approved SmPC.

Results: The most frequently reported reason for initiation of flutiform therapy was change from other ICS/LABA treatment due to lack of efficacy (45.3% overall). 1910 patients (75.2%) received flutiform for ≥12 months and 258 patients (10.2%) experienced a total of 375 treatment-related AEs.

The ACT™ mean total score increased from 16.3 (baseline) to 20.4 at the end of study (Last Observation Carried Forward - LOCF). The proportion of patients with controlled asthma (ACT score ≥ 20) also increased from 29.4% to 67.4% of patients at the end of study (LOCF). The number of severe exacerbations experienced by patients decreased while they were in the study. Over 90% of patients (2291 patients; 90.2%) did not experience any severe asthma exacerbations (mean (SD): 0.1 (0.52)). 83.3% of patients remained on a stable dose of flutiform during the study (i.e. no dose changes were reported).

At baseline, the percentage of physicians' who classed their satisfaction with the efficacy (of the prior treatment) as good or very good was 24.4% and 5.3% respectively. After changing to flutiform, by the end of study (LOCF) these ratings had improved to 46.9% and 41.4% respectively. Similarly, at baseline, the percentage of physicians' who classed their satisfaction with the tolerability as good or very good was 51.7% and 15.0% respectively. By the end of study (LOCF) these ratings were 42.9% and 51.5% respectively. Similar assessments of improvement in efficacy and tolerability were made by the patients.

Discussion: This study was designed as a non-interventional study and the results of statistical testing have to be interpreted with that in mind. However, the majority of patients remained in the study for a full year (and only 22.6% of patients discontinued the study overall) and by the end of the study improvements were seen in almost every parameter that was assessed. Treatment-related AEs were recorded in 10.2% of patients. In particular, many more patients were recorded as having controlled asthma and a greater percentage of patients and physicians rated their satisfaction with the efficacy and tolerability of flutiform as good or very good, compared to their previous treatment. There was a decrease in the number of severe exacerbations compared to the year prior to study entry. Notably, the number of patients experiencing 6 or more exacerbations was reduced

from 88 patients (3.5%) in the 12 months before the study, to just one patient during the study (<0.1%; overall annualised rate of severe asthma exacerbations during study: 0.15).

Marketing Authorisation Holder(s): This study was conducted by qualified Investigators under the Sponsorship of Mundipharma Research Limited. MAHs are listed in Section 4 of this report.

Names and affiliations of principal investigators: Prof Vibeke Backer, Bispebjerg Hospital, København NV, Denmark.

2. LIST OF ABBREVIATIONS

ACT	Asthma Control Test
AE	Adverse Event
AQLQ	Asthma Quality of Life Questionnaire
CI	Confidence Interval
CFC	Chlorofluorocarbon
CRA	Clinical Research Associate
CRO	Contract Research Organisation
DCF	Data Clarification Form
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
FEV_1	Forced Expiratory Volume in the first second
FVC	Forced Vital Capacity
HFA	Hydrofluoroalkane
ICS	Inhaled Corticosteroid
LABA	Long-acting β2 Agonist
LOCF	Last Observation Carried Forward
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
PASS	Post-Authorisation Safety Study
PEF	Peak Expiratory Flow
PT	Preferred Term
RMP	Risk Management Plan
SABA	Short-acting β2 Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
WHO	World Health Organisation
WHO-DD	World Health Organisation Drug Dictionary

3. INVESTIGATORS

The International Co-ordinating Investigator was: Prof Vibeke Backer, Bispebjerg Hospital, København NV, Denmark. Further details of all investigators are provided in Annex 1.

4. OTHER RESPONSIBLE PARTIES

This study was conducted by qualified Investigators under the Sponsorship of Mundipharma Research Limited (MRL), and was managed by Scope International AG. MRL centrally managed the conduct of the study for the local Marketing Authorisation Holders (MAH). A full list of MAHs is provided below.

Country	**MA Holder**
Czech Republic	Mundipharma Gesellschaft.m.b.H. Apollogasse 16-18, 1070 Wien Austria
Denmark	Mundipharma A/S Frydenlundsvej 30 2950 Vedbæk, Denmark
Norway	Mundipharma AS Vollsveien 13 C 1366 Lysaker, Norway
Sweden	Mundipharma AB Mölndalsvägen 30B 41263 Göteborg, Sweden
France	Mundipharma SAS 100 Avenue de Suffren, 75015 Paris France
Ireland	Mundipharma Pharmaceuticals Ltd Millbank House – Arkle Road Sandyford-Dublin 18 Republic of Ireland
Slovak Republic	Mundipharma Gesellschaft.m.b.H. Apollogasse 16-18, 1070 Wien Austria
United Kingdom	Napp Pharmaceuticals Limited Cambridge Science Park Milton Road Cambridge CB4 0GW

5. MILESTONES

Milestone	Planned date	Actual date	Comments
First patient, first visit	8 Nov 13	20 Nov 13	N/A
Last patient, last visit	31 Dec 15	9 Feb 16	N/A
Interim analysis	N/A	Apr 16	The interim analysis had no planned date. It was to be initiated when 50% of data had been accrued.
Final report of study results	N/A	18 Jul 17	N/A

6. RATIONALE AND BACKGROUND

In 2012, Napp Pharmaceuticals Limited submitted one Complex and two Standard Abridged Marketing Authorisation Applications (MAAs) through the Decentralised Procedure for Human Medicinal Products. The applications were for flutiform 50/5 micrograms pressurised inhalation, suspension; flutiform 125/5 micrograms pressurised inhalation, suspension and flutiform 250/10 micrograms pressurised inhalation, suspension, containing the active drug substances fluticasone propionate and formoterol fumarate in three strengths. All applications were for the treatment of asthma in adults and adolescents not adequately controlled with inhaled steroids alone or already controlled on a separate inhaled steroid and LABA. The MAAs were approved for use in adults and adolescents (≥12 years old) in 21 EC Member States.

The products are orally inhaled combination products containing the active substances fluticasone propionate, an inhaled glucocorticosteroid with anti-inflammatory activity in the lungs, and formoterol fumarate, a selective LABA. The combination of an inhaled glucocorticosteroid and a selective LABA is a well-established combination for use in the regular treatment of adults and children with asthma where the use of such a combination is deemed appropriate. However, the specific combination of these two well-known active substances, fluticasone propionate and formoterol fumarate, is new.

Fluticasone propionate has been shown to reduce symptoms and exacerbations of asthma and to decrease airway reactivity to histamine and methacholine in patients with hyper reactive airways. Fluticasone propionate is a well-established active substance and is recommended for use in the management of asthma in both adults and children.

Formoterol fumarate is a selective LABA and exerts a preferential effect on $ß_2$ adrenergic receptors on bronchial smooth muscle to produce relaxation and bronchodilatation. Formoterol fumarate is used via the orally inhaled route in the management of patients with reversible airways obstruction. Following oral inhalation of formoterol, the onset of bronchodilatation is rapid, within 1 - 3 minutes, and bronchodilatation following a single dose lasts for 12 hours. Formoterol fumarate is particularly useful in patients with

reversible airway obstruction who continue to experience symptoms despite treatment with an anti-inflammatory agent such as an inhaled corticosteroid. Guidelines for the management of reversible airway obstruction, and particularly asthma, recommend the addition of a LABA to the treatment regimen in these patients and studies have shown that the addition of a LABA provides better control of asthma than increasing the dose of inhaled corticosteroid.

Flutiform is a new fixed-dose combination product. It is formulated in three strengths as pressurised inhalation suspensions together with the hydrofluoroalkane (HFA) propellant, propellant HFA 227, a non-chlorofluorocarbon (CFC) alternative propellant.

During the decentralised procedure and discussions with the reference member state, a European Union Risk Management Plan (EU RMP) was agreed. Included in the EU RMP was a commitment to conduct a post authorisation safety study (PASS). The primary objective of the PASS was to collect safety information during routine clinical use of flutiform with a particular interest on the following important identified or suspected risks:

- Respiratory AEs including cough and paradoxical bronchospasm
- Asthma worsening/asthma exacerbation
- Serious asthma-related events (asthma hospitalisations, intubations, deaths)
- Local oral AEs
- Local immunosuppressive effects, infections
- Anaphylactic reactions
- Adrenal suppression/adrenal failure
- Growth retardation
- Decrease in bone mineral density
- Skin atrophy
- Skin contusion
- Cataract
- Glaucoma
- Hypokalaemia
- Hyperglycaemia / increased blood glucose
- Cardiac arrhythmias and QTc prolongation
- Cardiac ischaemia
- Psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression

To address the commitment, two similar non-interventional PASS, FLT9501 and FLT9503 were initiated, which together aimed to collect safety and efficacy data from approximately 4,000 patients treated with flutiform under normal conditions of use.

7. RESEARCH QUESTION AND OBJECTIVES

The aim of this non-interventional PASS was to collect safety and efficacy data during the real life clinical use of flutiform in the treatment of patients with moderate to severe asthma. This study is part of a European Risk Management Plan (EU RMP) commitment agreed during the decentralised marketing authorisation application for flutiform.

7.1. Primary Objectives

Evaluation of the safety of flutiform in routine clinical practice by:

- Collection of data on the exposure to flutiform and the frequency of AEs associated with flutiform, or which are known to be side effects of treatment with ICS/LABA combination drugs.
- Recording all AEs reported spontaneously or after physicians' open questioning of the patients as well as AEs detected by diagnostic procedures, conducted at the physicians' discretion, during routine clinical practice in a real life setting.

7.2. Secondary Objectives

Secondary objectives were to evaluate the effectiveness of flutiform treatment under real life conditions on asthma control by:

- Comparing the Asthma Control Test (ACT) total score between baseline and end of study
- Severe exacerbation rate
- Use of asthma related rescue medication
- Asthma symptoms and sleep disturbance from the ACT sub scores
- Consultations and hospitalisations due to asthma
- Days of absence from work/school/college or inability to perform everyday activities due to asthma
- Lung function parameters.

In addition, the study was to provide deeper insights in the course of the therapy with flutiform over a 10-14-month window with regard to dose adjustments, changes in asthma-related co-medication and discontinuation due to lack of efficacy as well as the patients' and the physicians' satisfaction with the flutiform therapy.

8. AMENDMENTS AND UPDATES

Number	Date	Amendment or update
1	17 September 2014	i) Amendments made throughout the protocol to update the details on the countries involved in the study. A corrected list of Marketing Authorisation Holders was incorporated into Section 5.1 of the Protocol and the number of countries involved changed from 7 to 9. Since the finalisation of the protocol in May 2013 Finland was no longer involved in the study and Bulgaria, the Czech Republic and the UK were included. (Post amendment note: Bulgaria was included but did not open for patient recruitment). ii) Amendment made to the collection of demographic data on race in France to comply with a condition stipulated in the approval from the Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé (CCTIRS). All countries excluding France continued to collect details on the race of study participants. iii) Administrative corrections and additions.

9. RESEARCH METHODS

9.1. Study Design

This study was designed to be fluid and to fit with standard clinical practice. As a minimum, AEs were captured. Other parameters as defined in Table 1 were captured if they were completed during normal clinical practice at participating investigator sites.

The objective of this PASS was to collect and analyse data on the safety and effectiveness of flutiform prescribed for outpatients aged ≥12 years with asthma. The patients were observed during routine clinical practice. It was planned to observe each patient for one year from the first dose of flutiform. If a patient stopped flutiform intake due to lack of efficacy or due to other reasons, the observation was continued further until the next regular visit to investigate whether the patient's asthma could be controlled better by using another treatment and to follow up the patient's health status.

Primarily, safety and efficacy observations were focused on AEs rate and severity as well as on achievement of asthma control.

In accordance with the SmPC and treatment guidelines, patients diagnosed with asthma were eligible for this observation, if they were not controlled on ICS and 'as required' inhaled SABAs or if they had been switched from another treatment with a fixed or a free ICS/LABA combination.

Data on the patient's asthma medical history was collected at the baseline visit (Visit 1) at the start of the observation. Physicians' visits, diagnostic procedures, and assessments were performed as clinically indicated in the opinion of the treating physician and according to asthma treatment guidelines. Once patients had started treatment with flutiform, it was expected that the patient would return to see the investigator/site staff at regular intervals over the course of their treatment. The frequency of these visits was dependant upon local clinical practice but the number of visits over 12 months was expected to be approximately 4-7 visits. The observation was scheduled to cover a period of 12 months. For details please refer to Table 1 (Data collection and visit structure).

Flutiform dose adjustments (stepping down or stepping up) depending on asthma control level were performed at the discretion of the physician. If necessary, adjustments of flutiform doses as well as changes in other medications required during the course of the observation had to be documented at the regular visits retrospectively. If treatment corrections were performed by the investigator, they were documented during the respective visit.

All reported AEs including severe asthma exacerbations were documented during the PASS.

Severe asthma exacerbation was defined as a worsening of asthma that required either of the following actions:

- the use of systemic corticosteroids (oral, parenteral) related to the asthma exacerbation or
- hospitalisation or an unscheduled physicians' visit or an emergency department visit during which systemic corticosteroids were administered due to asthma symptoms.

For consistency, courses of corticosteroids separated by one week or more were treated as separate severe exacerbations.

Asthma exacerbations were also considered an efficacy outcome measure and collected as such within this study. Therefore, reporting of non-severe asthma exacerbations as AEs was not required by the protocol, as such exacerbations are to be expected to occur with some frequency in more difficult to control asthma patients. However, if participating physicians entered them into the electronic data capture (EDC) system, they were retained and thus those reported are presented.

Table 1 Data collection and visit structure

Study Visit[1]	Visit 1 (start of treatment)	Interim visits (estimated 2 to 5 over 12 months)	end of study visit (12 months after start of treatment)[7]
Clinic Visit	X	X[1]	X
Informed consent	X		
Assess eligibility criteria	X		
Demography[8]	X		
Asthma History	X		
Smoking history and current smoking situation	X	X	X
Assess prior and current asthma related medication use (inc rescue use, antibiotics, systemic Corticosteroids etc)[3].	X (last 30 days)	X	X
Other Concomitant medications	X	X	X
Days of absence from work/school/college/university due to asthma or inability to perform everyday activities	X (last 30 days)	X	X
Lung Function tests[2]	X	X (number of completions according to local practice)	X
Severe Asthma exacerbations	X (last 12 months)	X	X
Flutiform dose information including dose change and reason for discontinuation (if applicable)	X	X	X
Patients /Physicians assessment of asthma treatment	Previous treatment	X (flutiform treatment)	X
Asthma control evaluation (ACT)[4]	X (for last 4 weeks)	X (number of completions according to local practice)	X
Asthma Quality of Life Questionnaire (AQLQ)[5]	X		X
Consultations and hospitalisation due to asthma[6] (unscheduled consultations, emergency visits, hospital admissions, days spent in hospital)		X	X
Adverse events (non-elicited reporting)		X	X

[1] clinic visits were to be scheduled to fit with asthma treatment guidelines and local clinical practice. At each visit, assessments as indicated in the table were to be captured in the database if they were conducted.
[2] lung function tests included FEV1 (forced expiratory volume in the first second), FVC (forced vital capacity), PEF (peak expiratory flow). Lung function tests were to be completed at start and end of treatment as well as at regular intervals during treatment according to local practice and asthma treatment guidelines.
[3] Rescue use (i.e. salbutamol etc) was to be recorded for the 30 days before treatment start and then at each visit during treatment.
[4] ACT was collected at the start and end of treatment as well as at regular intervals during treatment, according to local practice.
[5] AQLQ was collected at the start and end of treatment.
[6] Any unscheduled visits to the physician or emergency treatment visits due to asthma were to be recorded.
[7] If a patient stopped flutiform treatment earlier than 12 months, the end of study visit was to be completed.
[8]Details of Race were not collected in France.

9.2. Setting

The study was completed by physicians and their associated site staff in primary or secondary care. These may have been general practitioners or respiratory physicians. The conduct of the study started in the participating countries after flutiform was launched.

The decision to prescribe flutiform necessarily preceded and was independent of the decision to enroll the patient into the study. Patients diagnosed with asthma were eligible for this observation, if they were not controlled on ICS and 'as required' inhaled SABAs or if they had been switched from another treatment with a fixed or a free ICS/LABA combination to flutiform. Only those patients who had received a prescription for flutiform according to the SmPC were evaluated for their potential eligibility for the study.

9.3. Patients

1. Male and female patients aged ≥ 12 years.
2. Patients with a diagnosis of asthma.
3. Patients who received a prescription of flutiform according to the indication stated in the local approved SmPC (patients not controlled on ICS and 'as required' inhaled SABA or patients who switched from treatment with a fixed or a free ICS/LABA combination).
4. Written informed consent signed by the patient or for patients younger than 18 years (adolescents) signed according to local requirements by one or both of the patient's parent(s) or legal representative(s) **and** by the patient
5. Planned treatment in line with the Summary of Product Characteristics, i.e. exclusion of all patients with contraindications.

9.4. Variables

See Table 1 for a full list of procedures recorded.

Assessments were completed at visits undertaken by the patient. The frequency of visits and the actual assessments undertaken at each visit were determined by clinical practice and asthma treatment guidelines. Where assessments were undertaken by investigator site staff, the following was captured in the database during the study:

- Demographic information (age, gender, race (not to be collected in France), height and weight, smoking history and current smoking situation including amount of cigarettes per day).
- Asthma history (duration, type, severity, prior and current asthma treatment including the last 30 days prior to enrolment).
- Reason for initiation of flutiform therapy (new ICS/LABA treatment or change from other ICS/LABA due to lack of efficacy, side effects, lack of compliance/satisfaction).

- Asthma control evaluation using the ACT™ (total score as well as the scores of the single items).
  The ACT™ consisted of 5 questions answered by the patient for the last 4 weeks. Each of the five items could be rated using a 5-point scale from 1 (the worst rating) to 5 (best rating). The following items were assessed:
  - Ability to perform daily activities
  - Shortness of breath
  - Sleep disturbance due to asthma
  - Necessity to use a rescue medication
  - Patient assessment of asthma control

  Total ACT score was calculated as the sum of the five single items scores. The total score ranged from 5 to 25. In case of missing single item score, the total score was set to missing.

  All patients were classified based on total ACT score as:
  - "controlled" asthma if total score ≥20
  - "somewhat controlled" asthma if a total score between 16 and 19
  - "poorly controlled" asthma if a total score of ≤15
  - "missing" asthma if assessment of ACT™ was missing

- Patients' and physicians' satisfaction with flutiform treatment as well as physicians' estimation of patient's adherence.
  Assessment of treatment (efficacy, tolerability, adherence) were rated on a 5-item scale (1=very good, 2=good, 3= moderate , 4=poor, 5=very poor).
- Quality of life assessment using AQLQ(S) 12+.

  The AQLQ(S) +12 contained 32 questions. Patients responded to each question on a seven-point scale in which 7 represents no impairment and 1 represents maximum impairment recalling their experiences during the previous 2 weeks. Each item within the AQLQ was equally weighted.

  Results are expressed as four domain scores. (For details on the scoring for each domain, please see section 13.2 of Statistical Analysis Plan [SAP]) The Total AQLQ score is the mean of 32 single questions scores.
- Lung function:
  - Forced Expiratory Volume in 1 second (FEV_1), absolute value and % predicted
  - Forced Vital Capacity (FVC), absolute value and % predicted
  - FEV_1 to FVC ratio (FEV_1/FVC) absolute value and % predicted
  - Peak expiratory flow (PEF), absolute value and % predicted
- Severe asthma exacerbations (for the period of 12 months prior to enrolment into the NIS as well as during the NIS).
- Flutiform administration, daily dose and dosage adjustments (step up, step down).
- Flutiform discontinuation and reason for discontinuation (e.g. lack of efficacy, AE).
- Prior / concomitant asthma related medication within the last 30 days before Visit 1 (e.g. systemic corticosteroids, antibiotics).

- Concomitant diseases, and concomitant medication.
- Unscheduled physician‘s consultations, emergency visits or hospital admission due to asthma.
- Unscheduled consultation to the doctor, emergency visits or hospital admissions that had occurred since the last visit as well as the number of days spent at hospital due to asthma since the last visit were to be documented based on the investigators knowledge and information provided by the patient.
- Days of absence at work/school/college/university due to asthma or inability to perform everyday activities.
- Depending on the patients’ personal situation either the number of days of absence at work/school/college/university or the number of days with inability to perform everyday activities between visits due to asthma were be documented. At Visit 1 this was limited to the last 30 days prior to the visit.
- Amount of oral or parenteral corticosteroid use as an effectiveness parameter and antibiotics due to lung/ lower respiratory tract infection was assessed.
- AEs and Serious Adverse Events (SAEs).

9.5. Data Sources

Data was entered into the electronic case report form (eCRF) by the investigator site staff. Patients attended the investigator site for regular visits during their treatment with flutiform® according to local clinical practice. Assessments conducted during these visits were according to clinical practice. Table 1 defines assessments that the investigator entered in the eCRF if the assessments were undertaken during patient visits. Demographic information, asthma history, prior and current medication were captured from the patients’ medical records or from patient interview.

Patients completed the AQLQ and ACT questionnaires and the information was transcribed into the eCRF by the investigator site staff.

9.6. Bias

This was an uncontrolled study. The assessments of exposure and outcome as well as data processing and analysis were performed in an unblinded manner.

9.7. Study Size

A total number of 2500 patients were intended to be enrolled within the European Union.

This sample size allowed AE rates to be estimated with a certain level of precision. For example, with 2500 patients, assuming an AE is reported by 5%, the two-sided 95% confidence interval (CI) will be between 4.1% and 5.9%.

The sample size was calculated using NQuery based on a CI for a proportion using normal approximation (large n).

9.8. Data Management

Data management and statistical analyses were the responsibility of the Data Management and Statistics department at the Sponsor's and Contract Research Organisation's (CRO's) site. Data as defined in Table 1, which was collected during routine clinical practice, was entered into the EDC system as specified in the Sponsor or CRO's data management plan. Quality control and data validation procedures were applied to ensure the validity and accuracy of the database. The Operations Manual and Data Management Plan detailed the data entry, cleaning, clarification, and validation procedures to be followed by all relevant study staff.

9.9. Statistical Methods

9.9.1. Main Summary Measures

All continuous variables were summarised using the following descriptive statistics: n, mean, standard deviation (SD), median, minimum (min) and maximum (max).

For categorical variables, the number (n) and percentage (%) of patients with non-missing data per category were the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. If not stated otherwise, percentages were based on either the analysis population or the number of patients with data available at the respective time point, as appropriate (the denominator used is specified in a footnote to the tables).

In general, data was slotted using assessment windows. However, baseline data was not slotted using assessment windows and neither were values before the first flutiform intake. Slotting was performed based on assessment date. For the treatment period (except Day 1) the visit slotting was performed according to the time intervals shown in the table below, with days relative to Day 1 which was defined as date of first flutiform intake on or after Visit 1.

Days relative to Day 1	Reference Days	Visit Slot
2-56 (up to 8 weeks after Start)	35 (4-6 weeks after Start)	1 month
57-120 (8 weeks to 4 months after Start)	90 (3 months after start)	3 months
121-210 (4 months to 7 months after Start)	180 (6 months after start)	6 months
211-300 (7 months to 10 months after Start)	270 (9 months after start)	9 months
301-420 (10 months to 14 months after Start)	360 (12 months after start)	12 months
> 420 days (>14 months)	NA	> 14 months

Slotting was done for efficacy and current smoking data. Where two or more non-missing assessments were slotted into the same visit interval, the data recorded closest to the reference day was used for the summary tables and analyses. If two non-missing assessments were equally close to the reference day, the later of the two assessments was used in tabulations and analyses; data from the earlier assessment(s) was only listed. However, all data on days of absence was used for summary tables and analyses.

In general, data was presented overall for all patients in the respective analysis population. Selected analyses were repeated by subgroup (Section 9.9.2.2).

In general, all data was listed, sorted by site, patient and, when appropriate, by study day within patient. Any deviations from the these analytical and summary approaches are noted in the following subsections.

9.9.2. Main Statistical Methods

This study is a post authorisation safety study. The primary objective of the study was to examine safety data. No primary efficacy endpoints were specified. All tests performed were purely exploratory. Due to the non-interventional study design, the results of statistical testing have to be interpreted with due caution.

All detail of the statistical methods are presented in the SAP and the SAP amendment. Selected details are presented below.

9.9.2.1. Analysis Populations

The following analysis populations were used:

Enrolled Population: All patients who signed informed consent.

Safety Population (SP): All patients who received at least one dose of study medication (flutiform).

The definition of the full analysis population was removed from the SAP. It was agreed to perform all analyses on the safety population to ensure that all available efficacy data would be considered for analysis.

As described in the Note to File on handling of patient data from sites which had withdrawn from the study during study conduct, dated 08JUL2015, data from sites 2017 and 4010 were not included in any statistical summary or analysis tables. Data from these sites are only included in the Appendix 16 listings.

9.9.3. Examination of Subgroups

Subgroups were defined as follows:

- Subgroups according to the ACT™ at Visit 1
- Subgroups according to prior treatment.
- Subgroups according to lung function assessments at Visit 1.
- Subgroups according to smoking habit.

Further details are provided in the SAP in Appendix 16.1.9

9.9.4. Handling of Missing Values

In general, the efficacy analyses used LOCF imputation approach for missing data, i.e. the last non-missing post-baseline value observed during the treatment period (but no longer than 14 months after first intake on or after Visit 1) was used for imputation. The approach for handling missing values and (partially) missing dates is described separately in the appropriate sections of the SAP for each variable that was analysed.

9.9.5. Sensitivity Analyses

Not applicable.

9.9.6. Amendments to the Statistical Analysis Plan (SAP)

The SAP, Final Version 2.0, dated 15JUL2016 defined that in frequency tables for categorical variables showing percentages of patients with non-missing data, those

percentages shall, in general, be based on the number of patients in the respective analysis population, i.e., be based on the Enrolled or on the Safety Population. Since the study is a non-interventional observation study, for several assessments and/or time points data is not available (missing) for many patients what leads to very low percentages in the categories, so that their interpretation may be misleading. Therefore, it was decided and documented in the SAP Amendment 1, Final Version, dated 30NOV2016, that rather the number of patients with data (for an assessment/variable at the relevant time) shall be used as the basis for the percentage calculation.

9.10. Quality Control

Quality control and data validation of the database are described in Section 9.7

9.10.1 Record Maintenance and Retention

Neither a patient's name nor initials were permitted to appear on documents transmitted to the Sponsor in order to maintain confidentiality. Additional anonymisation/pseudonymisation laws as applicable by country were also adhered to.

In order to provide the Sponsor/CRO with accurate, complete, and legible data, the following criteria were maintained:

- Source documents were completed to support the data that was entered into the EDC system.
- EDC entries were made as close to the visit of the patient as possible.

The circumstances of completion or termination of the study notwithstanding, the Investigator had the responsibility to retain all study documents, including but not limited to the protocol, copies of EDC data, informed consent forms, and Ethics Comittee correspondence.

The site was required to retain study documents for approximately 15 years after completion of the study. This included copies of the EDC.

It was requested that, at the completion of the required retention period, or should the Investigator retire or relocate, the Investigator contacted the Sponsor, allowing the Sponsor the option of permanently retaining the study records. Records retained were stored independently of the Sponsor, and the Sponsor would not be permitted direct access to this data.

9.10.2 Data Monitoring

To ensure the quality of data collected during the study, each site was monitored centrally by review of data collected in the eCRF. In addition, it was planned that sites would be attended by a clinical research associate (CRA) on at least one occasion. During the onsite visit by the CRA, the focus of activities was to review informed consent documents and selected source data seen as key to the recording of safety and efficacy endpoints.

This study was organised, performed, and reported in compliance with the protocol, Standard Operating Procedures of the Sponsor and CRO. Sponsor QA activity was undertaken as outlined in the study audit plan.

9.11 Limitations of the Research Method.

This study was designed to recruit patients who were prescribed flutiform during routine clinical practice. It was therefore critical to the recruitment of patients that flutiform was first launched in the country participating in the study and then that flutiform was prescribed by physicians. Recruitment rate of patients and the duration of the study was estimated based on likely prescription rates.

Owing to differing clinical practices between countries who recruited patients into the study, the study protocol had to be flexible to allow for different frequencies of patient visits and differing assessments conducted at each visit. It was accepted that for some patients there would be fewer data points than others.

10. RESULTS

An interim analysis was performed which included the first 1291 patients for whom data was available. (See the Interim analysis study report for details of the results obtained at this stage).

10.1. Participants

2567 patients were enrolled onto the study. The Safety Population (SP) comprised of 2539 (98.9%) patients. 1964 (77.4% of SP) patients completed the study.

Of the 1964 patients who completed the study, 1893 (74.6% of SP) continued with flutiform after the study; and 66 patients (2.6% of SP) were not prescribed flutiform after the study (the prescription for 5 patients (0.2% of SP) was not known). Of the 66 patients who completed but were not prescribed flutiform after the study, the top two reasons for not prescribing flutiform further were lack of efficacy (28 patients [1.1% of SP]) and patient's choice (23 patients [0.9% of SP]) (Table 14.1.4.1).

575 (22.6% of SP) of 1964 patients discontinued the study prematurely. 154 (6.1% of SP) of themthem went on to be prescribed flutiform. For these 154 patients, the top two reasons for discontinuation from the study were 'lost to follow up' (116 patients; 4.6% of SP) and patient's choice (24 patients; 0.9%).

303 patients (11.9%) who discontinued were not prescribed flutiform after leaving the study (the next prescription for 118 patients was not known) and the top two reasons for discontinuation of the study or why flutiform was not prescribed further among these patients (303 + 118) were AEs (134 patients; 5.3%) and being lost to follow up (108 patients; 4.3%) (Table 14.1.4.1).

10.2. Descriptive Data

10.2.1. Demography and Baseline Characteristics

The mean age of the 2539 patients in this analysis was 47.7 (17.47) [mean (SD)] years. The minimum age was 11 years, and the maximum age was 94 years.145 patients were under 18 years old (5.7%) and 2394 patients were 18 years or older (94.3%). The patient who is listed as being 11 (Patient 5061021) was actually only one day away from his 12th birthday.

There were more females (1609; 63.4%) than males (930; 36.6%) and the majority were Caucasian (Caucasian: 2470, 97.8%; Black: 22, 0.9%; Asian: 29, 1.1%) (Table 14.1.6.1.1).

1785 patients (70.3%)had taken at least one prior asthma controller medication. Of these, a total of 235 patients (9.3%) were already treated with ICS plus LABA in an open combination before study participation. 736 patients (29.1%) did not receive an ICS/LABA combination before, i.e. they were previously either treated with ICS without LABA (482 patients), with LABA without ICS (14 patients) or with other treatment (240 patients).

Flutiform had previously been prescribed to 624 (24.6%) of the patients. Among the patients who had been treated previously with ICS/LABA combinations other than flutiform (1915 patients), Fluticasone Propionate W/Salmeterol Xinafoate was the most commonly reported previous ICS/LABA treatment (400 patients, 15.8%). The next most common were Budesonide W/Formoterol Fumerate (343 patients, 13.5%) and Beclometasone Dipropionate W/Formoterol Fumarate (201 patients, 7.9%).

Most of the patients (1076 patients, 43.8%) had an asthma cscontrol status that was classified as poorly controlled at Visit 1 according to ACT™ total score, while the majority of patients (1350 patients, 60.7%) achieved more than 80% of the FEV_1 predicted at baseline.

At Visit 1 most patients were non-smokers (1856 patients [73.1%]) or ex-smokers (361 patients [14.2%]) (Table 14.1.1.2).

10.2.2. Asthma History

Duration of asthma and asthma type for the SP are presented in Table 1.

The mean asthma duration of this population at study start was 11.86 (11.693) (mean (SD)) years, ranging from 0 to 74.9 years. The majority had allergic asthma (1637 patients; 64.5%) and most patients' asthma severity was rated as 'persistent moderate' (1722 patients; 67.8%) (Table 14.1.10).

Table 2 Asthma History (Safety Population)

		Total (N=2539)
Asthma duration (years)	n	2538
	Mean (SD)	11.86 (11.693)
	Median	8.80
	Min, Max	0.0, 74.9
Type of asthma [n (%)]	Allergic	1637 (64.5)
	Intrinsic	897 (35.3)
	Exercise induced	335 (13.2)
	Analgesic induced	13 (0.5)
	Other	62 (2.4)
Severity of asthma [n (%)]	Intermittent	163 (6.4)
	Persistent mild	480 (18.9)
	Persistent moderate	1722 (67.8)
	Persistent severe	173 (6.8)
	Missing	1

Cross-reference: Table 14.1.10; Listing 16.2.1.5.
N: Number of patients in population. n: Number of patients with data available. %: Percentage based on N.
SD: Standard Deviation.
Notes: A patient may be counted in more than one type of asthma category.
Data from sites 2017 and 4010 is not included.

10.2.3. Prior and Concomitant Asthma Medication

An overview of prior and concomitant asthma medication for the SP is presented in Tables 14.1.8.3 and 14.1.8.5 (controller medications) and Tables 14.1.8.4 and 14.1.8.6 (rescue medications). A summary is provided in Table 3. Details on prior and concomitant medication of each individual patient are presented in Listing 16.2.1.6.

The majority of patients in the SP received at least one prior controller medication (1785 patients (70.3%)) within 30 days prior to Visit 1. 65 patients (2.6%) were taking rescue medication prior to the study.

Inhalative ICS/LABA fixed combinations were the most frequently reported previous asthma medication: 985 patients, (38.8%) as controller medication and 10 patients (0.4%) as rescue medication), followed by ICS: 769 patients (30.3%) as controller medication and 1 patient (<0.1%) as rescue medication, and inhalative LABA medications: 246 patients (9.7%) as controller medication and 8 (0.3%) patients as rescue medication.

During the study 1152 patients (45.4%) took a concomitant asthma controller medication and 1845 (72.7%) took concomitant asthma rescue medication. The most commonly taken rescue medications were inhalative SABAs: 1559 patients (61.4%) took SABAs as rescue medication) (Table 14.1.8.6) and 197 patients (7.8%) took SABAs as controller medication

(PRN/on demand, Table 14.1.8.5). The most commonly taken group of concomitant asthma controller medications was leucotriene antagonists: 675 patients (26.6%) took these as controller medication; no one took them as concomitant rescue medication.

Table 3 Prior and concomitant asthma medication (Safety Population)

	Total N = 2539		Total N=2539	
	Prior medication [n (%)]		Concomitant medication [n (%)]	
	Controller	Rescue	Controller	Rescue
Patients with at least one prior* or concomitant asthma medication	1785 (70.3)	65 (2.6)	1152 (45.4)	1845 (72.7)
Inhalative short-acting β_2-sympathomimetics /adrenergics/ agonists (short-acting β_2-agonists = SABA)	40 (1.6)	38 (1.5)	197 (7.8)	1559 (61.4)
Inhalative long-acting β_2-sympathomimetics /adrenergics/ agonists (long-acting β_2-antagonists = LABA)	246 (9.7)	8 (0.3)	9 (0.4)	11 (0.4)
Inhalative corticosteroids (ICS)	769 (30.3)	1 (<0.1)	63 (2.5)	2 (0.1)
Corticosteroids systemic (oral, i.v.)	50 (2.0)	-	300 (11.8)	34 (1.3)
Monoclonal antibodies: omalizumab (subcutaneous)	-	-	23 (0.9)	-
Inhalative ICS/LABA combination (fixed combination)	985 (38.8)	10 (0.4)	32 (1.3)	3 (0.1)
Inhalative long-acting anticholinergics (long-acting muscarinic antagonists = LAMA)	1 (<0.1)	-	44 (1.7)	-
Theophyllin (oral, emergency also i.v.)	18 (0.7)	-	254 (10.0)	16 (0.6)
Leucotriene antagonists	28 (1.1)	-	675 (26.6)	-
Cromoglicic acid (DNCG) inhalative	1 (<0.1)	-	-	-
Inhalative anticholinergics/SABA	1 (<0.1)	2 (0.1)	23 (0.9)	147 (5.8)
Oral β_2-sympathomimetics	1 (<0.1)	2 (0.1)	2 (0.1)	4 (0.2)
Inhalative short-acting anticholinergics	9 (0.4)	4 (0.2)	128 (5.0)	197 (7.8)

Cross reference: Tables 14.1.8.3; 14.1.8.4; 14.1.8.5; 14.1.8.6 and Listing 16.2.1.6
N: Number of patients in population. n: Number of patients with data available. %: Percentage based on N.
Medications coded using WHO and Anatomical Therapeutic Chemical (ATC) classification system (WHO-DD Version March 2013).
*Within the 30 days prior to Visit 1.
Notes: A patient may have taken more than one medication in any category.
Data from sites 2017 and 4010 is not included.

10.2.4. Reasons for Flutiform Therapy Initiation

Just over one third of patients had not previously received ICS/LABA combination therapy (39.4%, 1001 patients). Of the 1538 patients (60.6%) who had previously received

ICS/LABA treatment, the most common reason for the initiation of flutiform therapy was lack of efficacy of previous ICS/LABA treatment (1150 patients [45.3%]) and the second most common reason was lack of compliance / satisfaction with current ICS / LABA treatment (319 patients [12.6%]).

A summary of reasons for flutiform therapy initiation is presented in Table 4.

Table 4 Reasons for Flutiform Therapy Initiation (Safety Population)

		Total (N=2539) n (%)
Reasons for flutiform therapy initiation	New ICS/LABA treatment	1001 (39.4)
	Change from other ICS/LABA treatment due to:	
	Lack of efficacy	1150 (45.3)
	Side effects	137 (5.4)
	Lack of compliance/satisfaction	319 (12.6)
	Other reasons	138 (5.4)
	Total	1538 (60.6)

Cross-reference: Table 14.1.11; Listing 16.2.1.10.
N: Number of patients in population. n: Number of patients with data available. %: Percentage based on N.
Notes: A patient may be in more than one category.
Data from sites 2017 and 4010 is not included.

10.2.5. Smoking History

Smoking history was assessed at Visit 1 for all patients and a summary (overall, smokers and ex-smokers) is presented in Table 5. Details of patients' smoking situation during the study are discussed in Section 10.2.6 and individual patient data are presented in Listing 16.2.1.7. Almost two thirds of patients in the safety population were non-smokers (1856 [73.1%], Table 5).

Table 5 Smoking History (Safety Population)

			Total (N=2539)
Overall	Smoking situation [n (%)]	Non-smokers	1856 (73.1)
		Smokers	274 (10.8)
		Ex-smokers	409 (16.1)
	Smoking duration (years)	n	2493
		Mean (SD)	4.9 (10.55)
		Median	0.0
		Min, Max	0, 60
	Pack Years	n	2466
		Mean (SD)	3.3 (9.12)
		Median	0.0
		Min, Max	0, 120
Smokers and ex-smokers	Smoking duration (years)	n	637
		Mean (SD)	19.1 (12.74)
		Median	18.0
		Min, Max	0, 60
	Pack Years	n	610
		Mean (SD)	13.3 (14.28)
		Median	9.0
		Min, Max	0, 120

Cross-reference: Table 14.1.12.1; Listing 16.2.1.7.
N: Number of patients in population. n: Number of patients with data available. %: Percentage based on N.
SD: Standard Deviation.
Notes: Smoking status at Visit 1 is summarised in this table.
Data from sites 2017 and 4010 is not included.

10.2.6. Current Smoking Situation

Table 14.1.12.2 shows changes with respect to the current smoking situation (non-smoker, smoker, ex-smoker and missing) between baseline (Visit 1) and at each time-point and at the End of Study (LOCF). The shift from Baseline to End of Study (LOCF) by smoking situation is presented in Table 6.

Table 6 Shift Table of Smoking Situation from Baseline to End of Study (LOCF) (Safety Population)

Time-point		Baseline (N=2539)			
		Non-smokers n (%)	Smokers n (%)	Ex-smokers n (%)	Total n (%)
End of study (LOCF)	Non-smokers	1737 (73.5)	-	-	1737 (73.5)
	Smokers	14 (0.6)	215 (9.1)	5 (0.2)	234 (9.9)
	Ex-smokers	-	31 (1.3)	362 (15.3)	393 (16.6)
	Total	1751 (74.1)	246 (10.4)	367 (15.5)	2364 (100.0)

Cross-reference: Table 14.1.12.2; Listing 16.2.1.8.
n: Number of patients with data available. %: Percentage based on number of patients with data available at respective time-point.
Note: Data from sites 2017 and 4010 is not included.

At the start of the study, the majority of patients (mean; %) were non-smokers (1856; 73.1%) or ex-smokers (361; 14.2%). (See section 10.2.5 for details on the smoking history of patients; Table 14.1.1.2). 14 patients (0.6%) who had been non-smokers at baseline and 5 patients who had been ex-smokers at baseline (0.2%) were smokers at the end of the study. The number of smokers that gave up smoking (i.e. became ex-smokers) increased throughout the study, and reached 31 (1.2%) at the End of Study (LOCF).

10.2.7. Concomitant Illnesses and Medical Conditions

An overview of medical history and current medical conditions by system organ class (SOC) and preferred term (PT) is presented in Tables 14.1.7.1 and 14.1.7.2, respectively. Conditions of each individual patient are listed in Listing 16.2.1.4.

314 Patients (12.4%) reported a history of at least one medical condition (other than the asthma because of which they were enrolled into the study). The two most common prior medical conditions were within the SOC ‘Surgical and Medical Procedures’. These were: Hysterectomy (29 patients [1.1%] and Cholecystectomy (27 patients [1.1%]). The third most common prior medical condition was within the SOC ‘Infections and Infestations’ with the PT Pneumonia (19 patients [0.7%])

More than three quarters of patients reported at least one current (ongoing at Visit 1) medical condition (2199 patients [86.6%]). Of the medical conditions that were reported, the most common condition was Rhinitis allergic (803 patients [31.6%]) followed by Hypertension (670 patients [26.4%]) and Obesity (324 patients [12.8%]).

10.2.8. Prior and Concomitant Non-Asthma Medication

All prior and concomitant therapies by patient are listed in Listing 16.2.1.6. An overview of prior and concomitant non-asthma medication (SP) is presented in Tables 14.1.8.1 and 14.1.8.2.

A total of 170 patients (6.7%) had previously taken at least one non-asthma medication. The most common types of non-asthma medication previously taken by patients were within the Anatomical Classes: ‘Anti-infectives for Systemic Use’ (61 patients [2.4%]) and ‘Respiratory System’ (92 patients [3.6%]) The vast majority of medications in the ‘Anti-infectives for systemic use’ anatomical class comprised of those in the pharmacological class: ‘Antibacterials for systemic use’ (58 patients [2.3%]) Of the medications in this

pharmacological class, the three most common sub-classes were: Macrolides lincosamides and streptogramins (23 patients [0.9%]), Beta-lactam antibacterials, penicillins (18 patients [0.7%]) and Tetracyclines (11 patients [0.4%]).

More than three quarters of patients were taking at least one non-asthma medication concomitantly (2254 patients [88.8%]). The Anatomical Class with the most reported concomitant non-asthma medication was the 'Respiratory System' class (1655 patients [65.2%]) followed by 'Cardiovascular System' (820 patients [32.3%]) and 'Anti-infectives for systemic use' (760 patients [29.9%]). Of those medications reported within the Respiratory System Class, the most common were 'Antihistamines for systemic use' (1342 patients [52.9%]) followed by 'Decongestants and other nasal preparations for topical use' (954 patients [37.6%]).

10.2.9. Extent of Exposure and Total Daily Dose

A summary of on-study exposure to flutiform and number of patients by most frequently reported total daily doses is presented in Table 7. Full details on exposure (on-study and overall) to flutiform are provided in Table14.1.9. Details on exposure of each individual patient can be found in Listing 16.2.1.9.

Mean (SD) time of on-study exposure (defined as the time between first intake of flutiform intake but not earlier than Visit 1 until last flutiform intake in this study) was 344.3 (103.34) days with a maximum exposure of 674 days. A total of 1910 patients (75.2%) had a cumulative on-study exposure to flutiform of at least 12 months.

Mean (SD) time of overall exposure (defined as the time between earliest start date of flutiform intake, which may have been before the study start, until last flutiform intake in this study) was 382.2 (143.93) days in the SP with a maximum exposure of 1419 days.

For the majority of patients (2116 patients [83.3%]), no dose changes were reported, i.e. they had a stable flutiform dose during the study (see Table 7). There were 165 patients who had a dose increase, 145 patients with multiple dosage adjustments and 113 patients who had a dose decrease.

Table 7 Exposure to Flutiform (Safety Population)

			Total (N=2539)
Overall	Exposure[a] (days)	n	2539
		Mean (SD)	382.2 (143.93)
		Median	380.0
		Min, Max	1, 1419
On-study	Exposure (days)	n	2539
		Mean (SD)	344.3 (103.34)
		Median	372.0
		Min, Max	1, 674
	Cumulative exposure [n (%)]	Any	2539 (100.0)
		≥ 1 month	2499 (98.4)
		≥ 2 months	2436 (95.9)
		≥ 4 months	2347 (92.4)
		≥ 8 months	2226 (87.7)
		≥ 12 months	1910 (75.2)
	Number of patients with stable dosage	n (%)	2116 (83.3)
	Number of patients with increased dosage	n (%)	165 (6.5)
	Number of patients with decreased dosage	n (%)	113 (4.5)
	Number of patients with multiple* dosage adjustments	n (%)	145 (5.7)
	Number of patients with interrupted dosage	n (%)	41 (1.6)
	Number of patients who only used low dosage	n (%)	121 (4.8)
	Number of patients who only used medium dosage	n (%)	1218 (48.0)
	Number of patients who only used high dosage	n (%)	777 (30.6)
	Number of patients with dose adjustments in the same dose level	n (%)	139 (5.5)
	Number of patients who started on low dose and increased dosage	n (%)	24 (0.9)
	Number of patients who started on medium dose and increased dosage	n (%)	143 (5.6)
	Number of patients who started on medium dose and decreased dosage	n (%)	14 (0.6)
	Number of patients who started on high dose and decreased dosage	n (%)	94 (3.7)
	Number of patients with multiple dose ranges**	n (%)	9 (0.4)
	Dose adjustments:		
	Number of dose interruptions		44
	Number of dose increases		338
	Number of dose decreases		300

Cross-reference: Table 14.1.9; Listing 16.2.1.9.
N: Number of patients in population. n: Number of patients with data available. %: Percentage based on N.
*Increased and decreased dose adjustments or dose range. [a] May have included exposure from before the study.
Notes: Data from sites 2017 and 4010 is not included. Overall exposure includes days from the earliest date of flutiform start. On-study exposure includes days from the first intake of flutiform® but not earlier than Visit 1.

10.3. Outcome Data

The Safety Population (SP), defined as all patients who received at least one dose of observed medication, comprised 2539 patients. The safety results presented in Section 10.6 are based on the SP.

10.4. Main Results

10.4.1. Asthma Control

Summary statistics of ACT™ total scores and for the five individual items by visit, as well as absolute and relative changes from baseline including statistical testing of absolute changes are provided in Tables 14.2.1.1 – 14.2.1.6.The results for ACT™ total scores are summarised in Table 8. Details of each individual patient are presented in Listing 16.2.2.1.

Table 8 Asthma Control Test: Total Score (Safety Population)

Time-point	Statistic	Total (N=2539)	
		Value	Change from baseline
Baseline	n	2456	
	Mean (SD)	16.3 (4.75)	
	Median	16.0	
	Min, Max	5, 25	
1 Month	n	800	796
	Mean (SD)	19.2 (4.15)	3.5 (4.67)
	Median	20.0	3.0
	Min, Max	5, 25	-18, 19
	95% CI		(3.20, 3.85)
	P-value		<.001
3 Months	n	1362	1356
	Mean (SD)	19.4 (4.27)	3.1 (4.72)
	Median	20.0	3.0
	Min, Max	5, 25	-17, 18
	95% CI		(2.85, 3.36)
	P-value		<.001
6 Months	n	1535	1527
	Mean (SD)	20.2 (4.08)	4.0 (5.05)
	Median	21.0	4.0
	Min, Max	5, 25	-17, 20
	95% CI		(3.79, 4.29)
	P-value		<.001
9 Months	n	1358	1349
	Mean (SD)	20.6 (3.88)	4.5 (4.98)
	Median	21.0	4.0
	Min, Max	5, 25	-12, 20
	95% CI		(4.26, 4.79)
	P-value		<.001
12 Months	n	1783	1771
	Mean (SD)	20.8 (3.95)	4.6 (5.05)
	Median	22.0	4.0
	Min, Max	5, 25	-16, 20
	95% CI		(4.35, 4.82)
	P-value		<.001
End of Study (LOCF)	n	2220	2197
	Mean (SD)	20.4 (4.28)	4.2 (5.23)
	Median	21.0	4.0
	Min, Max	5, 25	-17, 20
	95% CI		(3.93,4.37)
	P-value		<.001

Cross-reference: Table 14.2.1.1; Listing 16.2.2.1.
N: Number of patients in population. n: Number of patients with data available.
CI: Confidence Interval. LOCF: Last Observation Carried Forward. SD: Standard Deviation.
Notes: p-value is from t-test for baseline / post baseline time-point comparison with corresponding 95% CI.
Data from sites 2017 and 4010 is not included.

At baseline, a mean (SD) total score of 16.3 (4.75) was reported, which increased to 20.6 (3.88) at 9 months and remained at that level to 12 months (20.8 [3.95]). At the end of the study (LOCF), defined as the last visit with data available of each patient during the treatment period, a mean (SD) total score of 20.4 (4.28) was observed (Table 14.2.1.1). Statistical testing of absolute changes revealed significant changes as compared to baseline at each time-point (*p*-values <0.001).

Mean (SD) scores of the five individual items each increased during treatment in a similar fashion to the total scores (see Tables 14.2.1.1 – 14.2.1.6). The five item scores that made up the overall ACT score were: ability to perform daily activities, shortness of breath, sleep disturbances due to asthma, necessity to use and rescue medication; subject assessment of asthma control score.

The ACT Total Score Classification is presented in Table 9. The proportion of patients with controlled asthma increased from a baseline of 29.4% to 53.6% after one month and increased steadily. After 12 months 70.7% of patients had controlled asthma (1261 patients). At end of study (LOCF) 67.4% of patients had controlled asthma (the LOCF value includes patients who stopped before month 12).

Accordingly, the proportion of patients with somewhat or poorly controlled asthma decreased throughout the duration of the study. At baseline, 26.8% of patients were classified as having somewhat controlled asthma and 43.8% were classified as having poorly controlled asthma. By the end of the study (LOCF) these proportions decreased to 18.7% and 13.8% respectively.

Table 9 Asthma Control Test Total Score Classification (Safety Population)

Time-point		Total (N=2539) n (%)
Baseline	Controlled asthma	722 (29.4)
	Somewhat controlled asthma	659 (26.8)
	Poorly controlled asthma	1075 (43.8)
	Missing / No data available	81
1 Month	Controlled asthma	429 (53.6)
	Somewhat controlled asthma	226 (28.3)
	Poorly controlled asthma	145 (18.1)
	Missing / No data available	105
3 Months	Controlled asthma	764 (56.1)
	Somewhat controlled asthma	351 (25.8)
	Poorly controlled asthma	247 (18.1)
	Missing / No data available	160
6 Months	Controlled asthma	1019 (66.4)
	Somewhat controlled asthma	311 (20.3)
	Poorly controlled asthma	205 (13.4)
	Missing / No data available	136
9 Months	Controlled asthma	925 (68.1)
	Somewhat controlled asthma	293 (21.6)
	Poorly controlled asthma	140 (10.3)
	Missing / No data available	108
12 Months	Controlled asthma	1261 (70.7)
	Somewhat controlled asthma	326 (18.3)
	Poorly controlled asthma	196 (11.0)
	Missing / No data available	103
End of study (LOCF)	Controlled asthma	1497 (67.4)
	Somewhat controlled asthma	416 (18.7)
	Poorly controlled asthma	307 (13.8)
	Missing / No data available	319

Cross-reference: Table 14.2.1.8; Listing 16.2.2.1.
N: Number of patients in population. n: Number of patients with data available. %: Percentage based on N.
LOCF: Last Observation Carried Forward.
Note: Data from sites 2017 and 4010 is not included.

10.4.2. Severe Asthma Exacerbations

Table 10 presents a summary of severe asthma exacerbations experienced by patients in the SP. Severe asthma exacerbations by individuals are presented in Listing 16.2.2.5.

Table 10 Severe Asthma Exacerbations (Safety Population)

Period			Total N=2539
Within 12 months prior to enrolment	Number of severe asthma exacerbations per subject		
	0	n (%)	1629 (64.2)
	1	n (%)	461 (18.2)
	2	n (%)	188 (7.4)
	3	n (%)	107 (4.2)
	4	n (%)	37 (1.5)
	5	n (%)	28 (1.1)
	≥6	n (%)	88 (3.5)
	Missing / No data available	n	1
	Number of severe asthma exacerbations	n	2538
		Mean (SD)	0.9 (1.75)
		Median	0.0
		Min, Max	0, 12
Treatment period	Number of severe asthma exacerbations		
	0	n (%)	2291 (90.2)
	1	n (%)	166 (6.5)
	2	n (%)	53 (2.1)
	3	n (%)	22 (0.9)
	4	n (%)	5 (0.2)
	5	n (%)	1 (<0.1)
	≥6	n (%)	1 (<0.1)
	Number of severe asthma exacerbations	n	2539
		Mean (SD)	0.1 (0.52)
		Median	0.0
		Min, Max	0, 7
	Severe asthma exacerbations rate per 100 years of exposure	n	2539
		Mean (SD)	18.18 (79.978)
		Median	0.00
		Min, Max	0.0, 1197.5
	Total number of severe asthma exacerbations		370
	Total time on treatment (days)		891961
	Total time on treatment (years)		2442.1
	Overall annualised rate of severe asthma exacerbations		0.15

Cross-reference: Table 14.2.5.1.1; Listing 16.2.2.5.
N: Number of patients in population. n: Number of patients with data available. %: Percentage based on N.
SD: Standard Deviation.
Note: Data from sites 2017 and 4010 is not included.

In the 12 months *prior* to enrolment in this study, most patients had experienced no severe asthma exacerbations (1629 patients; 64.2%); 461 patients (18.2%) had experienced one severe asthma exacerbation and 188 (7.4%) experienced two severe exacerbations.

However, there were 88 patients (3.5%) who had experienced severe asthma exacerbations 6 times or more (maximum number was 12). The median number of severe exacerbations experienced was 0.

During the treatment period of this study, most patients (2291; 90.2%) did not experience any severe asthma exacerbations, 166 (6.5%) experienced only one severe asthma exacerbation; 53 patients (2.1%) experienced two severe exacerbations. The number of patients who experienced 6 or more severe exacerbations reduced to 1 (<0.1%, maximum number was 7). During the treatment period, the median number of severe exacerbations experienced was 0 and the overall annualised rate of severe asthma exacerbations on flutiform treatment was 0.15 (Table 14.2.5.1.1).

10.4.3. Asthma Quality of Life

Table 11 presents a summary of the Total Scores obtained from the AQLQ at Baseline and at End of Study. Patient-level data for the AQLQ(S) +12 is provided in the listing (Listing 16.2.2.2).

Table 11 Asthma Quality of Life Questionnaire: Total Score (Safety Population)

Time-point	Statistic	Total (N=2539)	
		Value	Change from Baseline
Baseline	n	2381	
	Mean (SD)	4.691 (1.2285)	
	Median	4.719	
	Min, Max	1.19, 7.00	
End of study	n	1781	1772
	Mean (SD)	5.635 (1.1007)	1.013 (1.1152)
	Median	5.969	0.906
	Min, Max	1.63, 7.00	-4.50, 4.81
	95% CI		(0.96, 1.06)
	P-value		<.001

Cross-reference: Table 14.2.2.1; Listing 16.2.2.2.
N: Number of patients in population. n: Number of patients with data available.
CI: Confidence Interval. SD: Standard Deviation.
Notes: p-value is from t-test for baseline / end of study comparison with corresponding 95% CI. Data from sites 2017 and 4010 is not included.

At Baseline (Visit 1/Start of Treatment), a total of 2381 patients were assessed and the mean (SD) total AQLQ score was 4.691 (1.2285). At the end of the study, the mean total score had increased to 5.635 (1.1007). (A total of 1781 patients were assessed at this stage.) Therefore, the change in mean total score from baseline was 1.013 (1.1152).

AQLQ subscores showed a mean change between 0.919 and 1.136 (Tables 14.2.2.2 – 14.2.2.5). The scores at baseline, scores at end of study and changes from baseline were similar across all domains. Tables 14.2.2.2 – 14.2.2.5 summarise the total scores obtained from the AQLQ at Baseline and end of study, for each of these 4 domains (which were: activities limitation, emotional function, environmental stimuli; symptoms score).

10.4.4. Lung Function Parameters

Lung function parameters were completed at the start and the end of treatment as well as at visits during the treatment period according to local practice and asthma treatment guidelines. Recalculated predicted FEV_1, FVC and PEF values were used for summary. An overview on mean values as well as absolute and relative changes from baseline for each parameter and statistical analysis of absolute changes is presented in Tables 14.2.3.1 – 14.2.3.8. By-patient lung function parameters are listed in Listing 16.2.4.

A summary of lung function parameters at baseline and at the end of study (LOCF) including change from baseline is presented in Table 12.

Table 12 Lung Function Parameters at Baseline and After End of Study, Including Changes from Baseline (Safety Population)

Lung function parameter per visit	Statistic	Total (N=2539)	
		Value	Change from Baseline
FEV_1 (L)			
Baseline	n	2205	
	Mean (SD)	2.578 (0.864)	
	Median	2.500	
	Min, Max	0.58, 6.19	
End of study (LOCF)	n	2059	1979
	Mean (SD)	2.720 (0.931)	0.132 (0.494)
	Median	2.630	0.070
	Min, Max	0.60, 6.34	-2.60, 3.76
	95% CI		(0.110, 0.154)
	P-value		<0.001
FEV_1 Predicted (%)			
Baseline	n	2243	
	Mean (SD)	84.9 (18.49)	
	Median	85.0	
	Min, Max	18, 170	
End of study (LOCF)	n	2080	2016
	Mean (SD)	88.8 (19.76)	4.1 (16.23)
	Median	89.0	2.0
	Min, Max	19, 229	-104, 140
	95% CI		(3.39, 4.81)
	P-value		<0.001
FVC (L)			
Baseline	n	2178	
	Mean (SD)	3.320 (1.091)	
	Median	3.190	
	Min, Max	0.58, 8.72	
End of study (LOCF)	n	2051	1966
	Mean (SD)	3.430 (1.122)	0.101 (0.574)
	Median	3.270	0.070
	Min, Max	0.70, 7.41	-6.24, 3.71
	95% CI		(0.076, 0.127)
	P-value		<0.001

Lung function parameter per visit	Statistic	Total (N=2539)	
		Value	Change from Baseline
FVC Predicted (%)			
Baseline	n	2212	
	Mean (SD)	91.7 (21.42)	
	Median	92.0	
	Min, Max	16, 550	
End of study (LOCF)	n	2070	2001
	Mean (SD)	93.9 (19.10)	2.7 (16.12)
	Median	94.0	2.0
	Min. Max	15, 211	-188, 115
	95% CI		(1.99, 3.40)
	P-value		<0.001
FEV_1/FVC			
Baseline	n	2180	
	Mean (SD)	0.784 (0.118)	
	Median	0.790	
	Min. Max	0.25, 2.35	
End of study (LOCF)	n	2051	1967
	Mean (SD)	0.797 (0.121)	0.012 (0.087)
	Median	0.801	0.005
	Min. Max	0.33, 3.59	-0.62, 0.70
	95% CI		(0.009, 0.016)
	P-value		<0.001
FEV1/FVC Predicted (%)			
Baseline	n	2206	
	Mean (SD)	98.2 (14.91)	
	Median	99.0	
	Min. Max	31, 312	
End of study (LOCF)	n	2067	1980
	Mean (SD)	99.8 (15.34)	1.7 (14.09)
	Median	101.0	1.0
	Min. Max	41, 481	-77, 393
	95% CI		(1.03, 2.27)
	P-value		<0.001
PEF (L/min)			
Baseline	n	2257	
	Mean (SD)	356.14 (124.659)	
	Median	348.0	
	Min. Max	55.2, 842.0	
End of study (LOCF)	n	2108	2017
	Mean (SD)	376.96 (127.876)	20.87 (77.441)
	Median	365.40	14.40
	Min. Max	55.8, 1015.0	-628.2, 369.0
	95% CI		(17.49, 24.25)
	P-value		<0.001
PEF Predicted (%)			
Baseline	n	2284	
	Mean (SD)	82.9 (32.23)	
	Median	83.0	

Lung function parameter per visit	Statistic	Total (N=2539)	
		Value	Change from Baseline
	Min. Max	13, 540	
End of study (LOCF)	n	2125	2043
	Mean (SD)	88.2 (35.84)	4.8 (35.66)
	Median	87.0	3.0
	Min. Max	15, 540	-440, 435
	95% CI		(3.24, 6.33)
	P-value		<0.001

Cross-reference Tables 14.2.3.1; 14.2.3.2; 14.2.3.3;14.2.3.4; 14.2.3.5; 14.2.3.6; 14.2.3.7; 14.2.3.8; Listing 16.2.2.3.
N: Number of patients in population. n: Number of patients with data available.
CI: Confidence Interval. LOCF: Last Observation Carried Forward. SD: Standard Deviation.
Notes: p-value is from t-test for baseline / post baseline time-point comparison with corresponding 95% CI. Quanjer prediction equations were used. Data from sites 2017 and 4010 is not included

The mean values of each lung function parameter at least slightly increased during the course of the study, with the exception of FEV_1/FVC which remained constant throughout the study. The highest mean (SD) increase was observed for PEF: 20.87L/min (77.441).

FEV_1 increased from a mean (SD) value of 2.578L (0.864) at baseline (84.9% [18.49%] predicted) to a mean of 2.736 L (1.001) at the 2nd observation (after approximately one month of treatment; number (n) of patients reporting at this timepoint was 740) and 2.678 L (0.927) at 3 months (n = 1288) and remained at around 2.7 L for each subsequent visit (Table 14.2.3.1). This resulted in a mean (SD) change from baseline of 0.132 L (0.494) at the end of study (LOCF; 4.1% (16.23) predicted (Table 14.2.3.2)). Statistical testing revealed significant mean absolute changes of FEV_1 and FEV_1 predicted (*p*-value <0.001) at each visit during treatment; however, this result has to be viewed cautiously because of a high variability among patients, presented by high SD values for absolute and changes from baseline. The large number of patients also means that small differences can result in a low p-value (see Tables 14.2.3.1 and 14.2.3.20.

Mean (SD) PEF increased from 356.14 L/min(124.659) at baseline (82.9% [32.23] predicted) to a maximum of 376.96 L/min (127.76) at end of study (LOCF). A mean (SD) change from baseline of 20.87 (77.441) was observed at the end of study (LOCF; 4.8% (35.66) predicted). Statistical testing revealed significant mean absolute changes of PEF and PEF predicted (*p*-value < 0.001) at each visit during treatment, however, again this value has to be viewed cautiously because of a high variability among patients, as shown by high SD values for changes from baseline (see Tables 14.2.3.7 and 14.2.3.8).

FVC (absolute and predicted) saw a slight increase during the course of the study (*p*-value < 0.001 at each observation). As the changes observed for both FEV_1 and FVC (as described above) were both very slight, FEV_1/FVC (absolute and predicted) remained unchanged during the course of the study. For details, please refer to Tables 14.2.3.3-14.2.3.6.

10.4.5. Satisfaction with Asthma Treatment by the Physician and the Patient

Assessment of previous asthma treatment was completed at the start of treatment and the assessment of current (flutiform) treatment was completed at the end of treatment and at visits during the treatment period.

Patients' and physicians' satisfaction with previous/current asthma treatment as well as physicians' estimation of patient's adherence was provided. Assessment of treatment (efficacy, tolerability, adherence) was rated on a 5-item scale (1=very good, 2=good, 3= moderate, 4=poor, 5=very poor).

Physicians' and patients' satisfaction for adherence, tolerability and efficacy are summarised in Tables 14.2.4.3 – 14.2.4.5. Patient-level data about satisfaction with asthma treatment by the physician and the patient are provided in Listing 16.2.2.4.

A summary of physicians' satisfaction with treatment across all parameters is presented in Table 13.

Table 13 Satisfaction with Asthma Treatment by the Physician at Baseline, After 3 Months and at the End of Study (LOCF) (Safety Population)

		Assessments N = 2539 n (%)		
		Baseline	**3 Months**	**End of study (LOCF)**
Efficacy	Very good	135 (5.3)	527 (35.2)	970 (41.4)
	Good	616 (24.3)	768 (51.2)	1098 (46.9)
	Moderate	1031 (40.8)	172 (11.5)	198 (8.5)
	Poor	684 (27.1)	30 (2.0)	72 (3.1)
	Very poor	58 (2.3)	2 (0.1)	5 (0.2)
	Missing/no data available	15	23	196
Tolerability	Very good	376 (15.0)	639 (42.6)	1204 (51.5)
	Good	1294 (51.7)	749 (50.0)	1004 (42.9)
	Moderate	582 (23.3)	92 (6.1)	85 (3.6)
	Poor	226 (9.0)	15 (1.0)	39 (1.7)
	Very poor	24 (1.0)	4 (0.3)	8 (0.3)
	Missing/no data available	37	23	199
Adherence	Very good	473 (18.9)	619 (41.5)	1103 (47.2)
	Good	1143 (45.7)	708 (47.5)	973 (41.6)
	Moderate	543 (21.7)	132 (8.9)	176 (7.5)
	Poor	297 (11.9)	24 (1.6)	67 (2.9)
	Very poor	45 (1.8)	7 (0.5)	19 (0.8)
	Missing/no data available	38	32	201

Cross-reference: Table 14.2.4.1; 14.2.4.2; 14.2.4.3; Listing 16.2.2.4.
N: Number of patients in population. n: Number of patients with data available. %: Percentage based on N.
LOCF: Last Observation Carried Forward.
Notes: Baseline represents assessment of previous asthma treatment, while the other time-points correspond to flutiform treatment. Data from sites 2017 and 4010 is not included.

In the opinion of physicians, the efficacy of patients' previous asthma treatment (baseline) in the majority of patients was moderate (40.8%) or poor (27.1%) while only 5.3% were assessed as receiving treatment with a 'very good' efficacy and 24.4% were assessed as receiving treatment with 'good' efficacy. Upon starting flutiform treatment, the proportions of patients with 'very good' or 'good' efficacy at 3 months increased significantly to 35.2% and 51.2%, respectively.

This improvement in opinion of efficacy was also visible earlier than 3 months, at the one-month time point, but the number of patients who had an assessment at one month was lower than at any other timepoint in the study, therefore the 3-month values are discussed here and subsequently. Results for all timepoints are available in Tables 14.2.4.1; 14.2.4.2 and 14.2.4.3.

Efficacy assessment values remained high throughout the study. By the end of the study (LOCF), 41.4 % were assessed as receiving treatment with a ‘very good’ efficacy and 46.9% were assessed as receiving treatment with ‘good’ efficacy.

The tolerability of previous treatment (baseline) was rated as ‘good’ in the majority of the patients (51.7%) and moderate in 23.3%. Upon starting flutiform treatment, the proportion of patients with ‘good’ tolerability dropped very slightly but remained at a similar level until the end of study (LOCF) (42.9%). Furthermore, the proportion of patients with ‘very good’ tolerability increased significantly throughout the duration of the study. Only 15% of patients were assessed as having ‘very good’ tolerability to their previous treatment. By the 3-month treatment time point this percentage had increased significantly to 42.6% after treatment (similar results were seen as early as 1 month) and remained high until the end of study (LOCF) (51.5%).

The physicians assessed the adherence with the previous asthma treatment (baseline) as ‘good’ in 45.7% of the patients, as ‘very good’ in 18.9% of the patients and as moderate in 21.7% of the patients. Patients assessed as having ‘very good’ and ‘good’ adherence with flutiform treatment were 47.2% and 41.6% respectively at the end of the study (LOCF).

A summary of patient’s satisfaction with their own treatment in terms of efficacy and tolerability is presented in Table 14.

Table 14 Satisfaction with Previous and Current Asthma Treatment by the Patient (Safety Population)

		Assessments N = 2539 n (%)		
		Baseline	3 Months	End of study (LOCF)
Efficacy	Very good	179 (7.1)	549 (36.5)	1008 (43.1)
	Good	754 (29.7)	728 (48.4)	1045 (44.7)
	Moderate	893 (35.4)	191 (12.7)	198 (8.5)
	Poor	634 (25.1)	35 (2.3)	74 (3.2)
	Very poor	62 (2.5)	2 (0.1)	14 (0.6)
	Missing/No data available	17	17	200
Tolerability	Very good	399 (15.9)	663 (44.1)	1216 (52.1)
	Good	1242 (49.6)	708 (47.1)	945 (40.5)
	Moderate	569 (22.7)	106 (7.0)	110 (4.7)
	Poor	262 (10.5)	19 (1.3)	46 (2.0)
	Very poor	30 (1.2)	8 (0.5)	19 (0.8)
	Missing/No data available	37	18	203

Cross-reference: Table 14.2.4.4; 14.2.4.5; Listing 16.2.2.4.
N: Number of patients in population. n: Number of patients with data available. %: Percentage based on N.
LOCF: Last Observation Carried Forward.
Notes: Baseline represents assessment of previous asthma treatment, while the other time-points correspond to flutiform treatment. Data from sites 2017 and 4010 is not included.

The ratings of the patients in terms of efficacy and tolerability were similar as compared to the corresponding assessments of the physicians. Most of the patients assessed the efficacy of their previous asthma treatment as moderate (35.4%) or good (29.7%). The tolerability was assessed as good (49.6%) or moderate (22.7%) by the patients. As observed for the physician's assessments, proportions of patients assessing the efficacy and tolerability of treatment as very good each increased under flutiform treatment.

10.4.6. Healthcare Resource Use

10.4.6.1. Days of absence due to asthma

Depending on the patients' personal situation, either the number of days of absence at work/school/college/university or the number of days with inability to perform everyday activities between visits due to asthma were documented at the end of treatment as well as at visits during treatment. This was limited to the last 30 days prior to each visit.

Unscheduled consultation to the doctor, emergency visits or hospital admissions that occurred since the last visit as well as the number of days spent at hospital due to asthma since the last visit were documented at the end of treatment as well as at visits during treatment period.

Results normalised per month for each visit are presented in Table 14.2.6.1 and an overview on the results at baseline, at the 2nd observation and at the end of the study

(LOCF) is provided in Table 15 below. For each individual patient, absolute and normalised number of days at each observation are listed in Listing 16.2.2.6.

Table 15 Days of Absence or Inability to Perform Everyday Activities

Time-point	Statistics	Total N = 1410
Baseline	n	2538
	Mean (SD)	1.4 (3.89)
	Median	0.0
	Min, Max	0, 30
3 Months	n	1514
	Mean (SD)	0.6 (2.60)
	Median	0.0
	Min, Max	0, 30
End of study (LOCF)	n	2353
	Mean (SD)	0.3 (2.04)
	Median	0.0
	Min, Max	0, 30

Cross-reference: Table 14.2.6.1; Listing 16.2.2.6.
N: Number of patients in population. n: Number of patients with data available. %: Percentage based on N.
LOCF: Last Observation Carried Forward.
*Notes:*Baseline represents assessment of previous asthma treatment, while the other time-points correspond to flutiform treatment. Data from sites 2017 and 4010 is not included.

The mean (SD) number of days of absence or inability to perform everyday activities 30 days prior to start of study was 1.4 (3.89) days, ranging between zero days up to 30 days for a patient. However, the median of 0.0 days demonstrates that at least half of the patients did not report any days of absence or inability to perform everyday activities. Within 3 months (and, actually as early as 1 month) after the start of the study, the mean number of days of absence or inability to perform everyday activities deceased to 0.6 days. The maximum number of days reported by an individual patient was 14 days (at >14 months, Table 14.2.6.1) . At the end of study, the mean number of days of absence of inability to perform everyday activities was 0.3 (2.04) (see Table 15).

10.4.6.2. Unscheduled visits, emergency visits and hospital admissions due to asthma.

Unscheduled consultations to the doctor, emergency visits or hospital admissions that occurred since the last visit and number of days spent at hospital due to asthma since the last visit were documented at the end of treatment as well as at visits during treatment period.

Annualised rates for all parameters during on-study treatment were calculated and are presented in Table 16. An overview on the number of unscheduled visits, emergency visits and hospital admissions due to asthma for each individual patient is given in Listing 16.2.2.6.

Table 16 Consultation and Hospitalisation Due to Asthma (Safety Population)

	Statistic	Total (N=2539)
Annualised rate of unscheduled visits	n	2370
	Mean (SD)	0.36 (1.334)
	Median	0.00
	Min, Max	0.0, 22.8
Annualised rate of emergency visits	n	2369
	Mean (SD)	0.04 (0.434)
	Median	0.00
	Min, Max	0.0, 15.2
Annualised rate of hospital admissions	n	2369
	Mean (SD)	0.01 (0.281)
	Median	0.00
	Min, Max	0.0, 12.2
Annualised rate of days spent at hospital	n	2367
	Mean (SD)	0.10 (2.577)
	Median	0.00
	Min, Max	0.0, 121.8

Cross-reference: Table 14.2.6.2; Listing 16.2.2.6.
N: Number of patients in population. n: Number of patients with data available.
SD: Standard Deviation. *Note:* Data from sites 2017 and 4010 is not included.

Overall, the annualised rates of unscheduled visits, of emergency visits and of hospital admissions were low with mean (SD) values of 0.36 (1.334), 0.04 (0.434) and 0.01 (0.281), respectively, and median rates of 0.00 per year, each. However, for some individual patients, these visits / admissions were much higher. The maximum annualized rate of unscheduled visits, emergency visits and hospital admissions was 22.8, 15.2 and 12.2.

With regards to hospital admissions, the number of days spent in hospital in most cases remained low with a mean (SD) annualised rate of 0.10 (2.577) days spent in hospital, a median of 0.00 and a maximum rate of 121.8 days.

10.4.6.3. Use of oral/parenteral corticosteroid

Table 17 summarises the number of patients with at least one systemic corticosteroid due to asthma or at least one antibiotic due to lung/lower respiratory tract infection. This information is presented by individual in Listing 16.2.2.7.

Table 17 Number of Patients with Systemic Corticosteroids, Antibiotics

	Total (N=2539) n (%)
Patients with at least one systemic corticosteroid due to asthma	373 (14.7)
Patients with at least one antibiotic due to lung/lower respiratory tract infection	479 (18.9)

Cross-reference: Table 14.2.6.3; Listing 16.2.2.7.
N: Number of patients in population. n: Number of patients with data available.
%: Percentage based on N.
Notes: A patient may be in more than one category.
Data from sites 2017 and 4010 is not included.

10.4.7. Rescue Medication Use

All asthma medications were classified as rescue medications or controller (maintenance) medications. Concomitant asthma medications were summarised in the same manner as prior asthma medications as described in the Section 10.2.3: “Prior and Concurrent Therapies”.

10.5. Adverse events (AEs)

10.5.1. Summary of AEs

All AEs reported hereafter are treatment-emergent AEs. An overall summary of AEs is presented in Table 18.

Of the 2539 patients in the Safety Population, 1523 (60.0%) experienced a total of 4264 AEs. Of these, 375 AEs in 258 (10.2%) patients were considered possibly related (indicated as “related” in the tables and appendices) to treatment with flutiform. Of those patients who had AEs (related or not related), 1223 (48.2%) patients required additional therapy and 134 (5.3%) patients required an increase in dose of study medication. (Note: A patient could have been included in more than one category. E.g. they could have had an AE requiring additional therapy *and* had an AE leading to dose increase.)

There were 36 possibly related severe AEs in 29 (1.1%) patients and 139 SAEs in 107 (4.2%) patients. All SAEs were considered to be not related to treatment.

Four (0.2%) patients had AEs leading to death but none of these AEs was considered by the Investigator to be related to treatment (Table 14.3.1.1.1 and Table 14.3.1.1.2). For more details of the SAEs, see Section 10.6.4).

Table 18 Overall Summary of AEs (Safety Population)

	Total (N=2539)
Patients with at least one AE [n (%)]	1523 (60.0)
Number of AEs	4264
Patients with at least one related[a] AE [n (%)]	258 (10.2)
Number of related[a] AEs	375
Patients with at least one severe AE [n (%)]	319 (12.6)
Number of severe AEs	508
Patients with at least one related[a] severe AE [n (%)]	29 (1.1)
Number of related[a] severe AEs	36
Patients with at least one SAE [n (%)]	107 (4.2)
Number of SAEs	139
Patients who had AEs leading to death	4 (0.2)
Patients with at least one AE leading to discontinuation[b] from study	152 (6.0)
Patients with at least one related[a] AE leading to discontinuation[c]	112 (4.4)
Patients with at least one AE requiring additional therapy[d]	1223 (48.2)
Patients with at least one AE leading to dose reduction	39 (1.5)
Patients with at least one AE leading to dose interruption	28 (1.1)
Patients with at least one AE leading to dose increase	134 (5.3)
Patients with at least one related[a] AE of special interest	211 (8.3)

Cross-reference: Table 14.3.1.1.1; 14.3.1.1.2; Listing 16.2.3.1.2.
AE: Adverse Event. SAE: Serious Adverse Event. N: Number of patients in population.
n: Number of patients with data available. #: Number of events. %: Percentage based on N.
a: Investigator considered reasonable possibility of causal relationship to flutiform.
b: An AE was considered as leading to discontinuation from study if other action taken contains “discontinued from observation” or if action taken with flutiform is “withdrawn”.
c: Includes 6 study completers who stopped flutiform due to AE, 1 subject who discontinued study due to AE and flutiform was described further, 11 subjects who discontinued study due to lack of efficacy and stopped flutiform due to AE, 1 subject who discontinued study with reason “Other” due to lack of efficacy and stopped flutiform
d: An AE will be considered as requiring additional therapy if the investigator answered “medication given” or “other treatment” or “medication given and other treatment” to the other action taken question.
Notes: A patient may have findings in more than one category.
Data from sites 2017 and 4010 is not included.
AEs coded using MedDRA version 16.0.

Most AEs were considered to be not related to flutiform. In fact, 1265 of the 1523 patients who experienced at least one AE during this study had AEs that were not related to flutiform (i.e. 49.8% of the total number patients in the study experienced AEs that were not related to flutiform (Table 14.3.1.4.1). Note: the ‘highest relationship’ to study medication was counted if an AE was reported more than once by the same patient. E.g. if an AE was reported once as not related and then occurred again in the same patient but was reported as related, then it was counted as being related for that patient).

Most AEs (related or not related to treatment) were moderate or mild in severity. 634 (25.0%) patients experienced moderate AEs (and no severe AEs) and 570 (22.4%) patients experienced only mild AEs. Only 319 (12.6%) patients experienced at least one severe AE (Table 14.3.1.3.1. Note: the highest severity was counted if an AE was reported more than once by the same patient. E.g., if an AE was reported once as moderate and

then occurred again in the same patient but was reported as mild, then it was counted as being moderate for that patient).

Asthma was the only AE for which the number of patients experiencing it at a severe level was above 1.0% of patients (severe asthma was experienced by 248 (9.8%) patients Table 14.3.1.3.1). The majority of events of reported asthma (i.e. in 385 patients; 15.2%) were not related to treatment (Table 14.3.1.4.1) (N.B. sites were not required to report mild or moderate asthma as it was the underlying disease but some sites reported it anyway). As pointed out in Section 10.4.2 the number of severe exacerbations was significantly decreased during the study, compared to patient's historic data for the year prior to entry into the study.

From the 2539 patients included in this analysis, only 29 patients experienced a total of 36 severe AEs that were considered possibly related to flutiform (Table 14.3.1.1.1).

10.5.2. Incidence of Adverse Events

An overview on the number of patients with AEs as well as the number of events by PT for all events with a frequency of at least 1.0% is provided in Table 19. An overview on the incidence of all AEs is provided in Tables 14.3.1.2.1 and 14.3.1.2.2.

A total of 1523 (60.0%) patients experienced at least one AE. The total number of AEs experienced by patients was 4264.

The most frequently reported AEs by PT were asthma (647 events in 435 patients; 17.1%), nasopharyngitis (199 events in 165 patients; 6.5%), bronchitis (189 events in 149 patients; 5.9%) and respiratory tract infection (121 events in 105 patients; 4.1%).

Table 19 Most Frequently Reported Treatment-Emergent Adverse Events (Preferred Term reported by ≥ 1.0%) by Preferred Term within System Organ Class (Safety Population)

System Organ Class (SOC)	**Total (N=2539)**	
Preferred Term (PT)	Number of Patients n (%)	Number of AEs
Patients with at least 1 AE	1523 (60.0)	4264
Eye Disorders		
Conjunctivitis allergic	52 (2.0)	53
Gastrointestinal Disorders		
Gastrooesophageal reflux disease	34 (1.3)	34
Immune System Disorders		
Seasonal allergy	28 (1.1)	29
Infections and Infestations		
Bronchitis	149 (5.9)	189
Influenza	35 (1.4)	35
Laryngitis	28 (1.1)	31
Lower respiratory tract infection	93 (3.7)	143
Nasopharyngitis	165 (6.5)	199
Pharyngitis	66 (2.6)	74
Pneumonia	35 (1.4)	36
Respiratory tract infection	105 (4.1)	121
Rhinitis	53 (2.1)	55
Sinusitis	69 (2.7)	76
Tonsillitis	26 (1.0)	33
Tracheitis	33 (1.3)	39
Tracheobronchitis	32 (1.3)	38
Upper respiratory tract infection	94 (3.7)	118
Urinary tract infection	26 (1.0)	35
Viral infection	63 (2.5)	71
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	39 (1.5)	41
Back pain	53 (2.1)	57
Nervous system disorders		
Headache	32 (1.3)	32
Respiratory, Thoracic and Mediastinal Disorders		
Asthma	435 (17.1)	647
Cough	94 (3.7)	105
Dysphonia	66 (2.6)	69
Oropharyngeal pain	32 (1.3)	36
Rhinitis allergic	102 (4.0)	112
Vascular Disorders		
Hypertension	37 (1.5)	37

Cross-reference: Table 14.3.1.2.1; Table 14.3.1.2.2; Listing 16.2.3.1.2.
AE: Adverse Event. N: Number of patients in population. #: Number of events.
Note: Data from sites 2017 and 4010 is not included.
AEs coded using MedDRA version 16.0.

A total of 319 (12.6%) patients experienced at least one severe treatment-emergent AE. The most frequently observed severe AEs were asthma (248 patients; 9.8%) (within the respiratory, thoracic and mediastinal disorders SOC), lower respiratory tract infection (10 patients; 0.4%) and bronchitis (8 patients; 0.3%) (within the infections and infestations SOC) (see Table 14.3.1.3.2). The number of patients with AEs by worst severity is provided in Table 14.3.1.3.1.

Treatment-emergent 'related' AEs observed in more than two patients by PT within corresponding SOC are presented in Table 20. An overview on the incidence of all possibly related AEs is provided in Table 14.3.1.4.3.

Table 20 Number of Patients with Adverse Events Related to Flutiform (observed in more than 2 patients) (Safety Population)

System Organ Class Preferred term	**Total (N=2539) n (%)** Number of Patients n (%)	Number of related AEs
Number of patients with at least one related AE	258 (10.2%)	-
Number of related AEs		375
Cardiac Disorders		
Palpitations	14 (0.6)	14
Tachycardia	7 (0.3)	7
Gastrointestinal Disorders		
Dry mouth	4 (0.2)	4
Dyspepsia	3 (0.1)	4
Nausea	6 (0.2)	6
General Disorders		
Chest discomfort	5 (0.2)	5
Infections and Infestations		
Bronchopneumonia	3 (0.1)	3
Lower respiratory tract infection	7 (0.3)	11
Nasopharyngitis	3 (0.1)	3
Oral candidiasis	17 (0.7)	21
Oral fungal infection	4 (0.2)	5
Oropharyngeal candidiasis	3 (0.1)	3
Respiratory tract infection	3 (0.1)	3
Upper respiratory tract infection	4 (0.2)	4
Musculoskeletal and connective tissue disorders		
Back pain	3 (0.1)	3
Muscle spasms	7 (0.3)	7
Nervous system disorders		
Dizziness	3 (0.1)	3
Headache	10 (0.4)	10
Tremor	16 (0.6)	16
Respiratory, thoracic and mediastinal disorders		
Asthma	50 (2.0)	59
Cough	28 (1.1)	28
Dysphonia	46 (1.8)	47
Dyspnoea	5 (0.2)	5
Oropharyngeal pain	13 (0.5)	14
Upper-airway cough syndrome	3 (0.1)	3
Vascular Disorders		
Hypertension	3 (0.1)	3

Cross-reference: Table 14.3.1.4.1; Table 14.3.1.4.2; Listing 16.2.3.1.2.
AE: Adverse Event. N: Number of patients in population. n: Number of patients with data available.
%: Percentage based on N.
a: Investigator considered reasonable possibility of causal relationship to investigational medicinal product.
Notes: A patient may have more than one AE in any category. Data from sites 2017 and 4010 is not included. Highest relationship to study medication is counted if an AE is reported more than once by the same patient. AEs coded using MedDRA version 16.0.

Asthma (exacerbation) was the most frequently reported treatment-emergent related AE (Table 14.3.1.4.1). Of the 435 patients who reported asthma as an AE during the study, 50 patients (59 AEs in total) had asthma that was reported as being related to flutiform. The second most common related AE was dysphonia (47 AEs in 46 patients; 1.8%) followed by cough (28 AEs in 28 patients; 1.1%). For a list of related AEs by individual patients, see Listing 16.2.3.1.2.

The exposure-adjusted event rate per 100 patient-years, by PT was calculated and an overview of AEs with a rate equal or above 2.0 events per 100 patient-years is given in Table 21 (and Table 14.3.1.5). Incidence rates for all AEs and for AEs classified as possibly related are provided overall and by subgroups according to smoking habit in Table 14.3.2.5.3.

Table 21 Exposure-Adjusted Event Rate (Number of Events per 100 Patient-Years) Event Rates ≥ 2.0 (Safety Population)

	Total (N=2539) Event rate
Asthma	27.0
Nasopharyngitis	8.3
Bronchitis	7.9
Lower respiratory tract infection	6.0
Respiratory tract infection	5.1
Upper respiratory tract infection	4.9
Rhinitis allergic	4.7
Cough	4.4
Sinusitis	3.2
Pharyngitis	3.1
Viral infection	3.0
Dysphonia	2.9
Back pain	2.4
Rhinitis	2.3
Conjunctivitis allergic	2.2

Cross-reference: Table 14.3.1.5 Listing 16.2.3.1.2.
AE: Adverse Event. N: Number of patients in population.
Notes: The event rate for AEs per 100 patient-years of exposure.
Data from sites 2017 and 4010 is not included.
AEs coded using MedDRA version 16.0.

The highest rate was observed for asthma (exacerbation) (27.0), followed by nasopharyngitis (8.3), bronchitis (7.9) and lower respiratory tract infection (6.0). (Table 14.3.1.5 presents this data with no cut off at ≥ 2.0).

10.5.3. Deaths, Other Serious Events and Other Significant Adverse Events

An overall summary of AEs leading to death, other SAEs and other significant AEs is presented in Table 22. A summary of AEs leading to death, other SAEs and other significant AEs by smoking habit is presented in Table 14.3.2.5.3

Table 22 Overall Summary of Deaths, Other Serious Adverse Events and Other Significant Events (Safety Population)

	Total (N=2539) n (%)
Patients with AEs leading to death	4 (0.2)
Patients with at least one SAE	107 (4.2)
Patients with at least one AE leading to discontinuation[b] from study	150 (5.9)
Patients with at least one related AE leading to discontinuation	112 (4.4)
Patients with at least one AE requiring additional therapy	1223 (48.2)
Patients with at least one AE leading to dose reduction	39 (1.5)
Patients with at least one AE leading to dose interruption	28 (1.1)
Patients with at least one AE leading to dose increase	134 (5.3)
Patients with at least one related AE of special interest	211 (8.3)

Cross-reference: Table 14.3.1.1.2; Listing 16.2.3.1.2. AE: Adverse Event. SAE: Serious Adverse Event.
N: Number of patients in population. n: Number of patients with data available. %: Percentage based on N.
a: Investigator considered reasonable possibility of causal relationship to investigational medicinal product.
b: An AE was considered as leading to discontinuation from study if other action taken contained "discontinued from observation" or if action taken with flutiform was "withdrawn".
Notes: A patient may have findings in more than one category.
An AE was considered as requiring additional therapy if the investigator answered "medication given" or "other treatment" or "medication given and other treatment" to the other action taken question.
Data from sites 2017 and 4010 is not included. AEs coded using MedDRA version 16.0.

10.5.3.1. Deaths

An overview of patients with AEs leading to death is provided in Table 23. A list of individual events is provided in Listing 16.2.3.1.2.

Table 23 Number of Patients with Adverse Events Leading to Death (Safety Population)

Preferred Term	Total (N=2539) n (%)
Number of patients who had AEs leading to death:	4 (0.2)
Bronchopneumonia	1 (<0.1)
Metastases to liver	1 (<0.1)
Cerebrovascular accident	1 (<0.1)
Pulmonary embolism	1 (<0.1)

Cross-reference: Table: 14.3.2.1.1; Listing 16.2.3.1.2.
N: Number of patients in population. n: Number of patients with data available. %: Percentage based on N.
Notes: A patient may have more than one AE in any category. Data from sites 2017 and 4010 is not included. AEs coded using MedDRA version 16.0.

10.5.3.2. Other Serious Adverse Events

A summary of SAEs by PT within SOC which occurred in at least two patients is presented in Table 24. An overview of the incidence of all SAEs is given in Table 14.3.2.2.1, and Table 14.3.2.2.2 presents a by-patient listing of all SAEs.

Table 24 Number of Patients with Serious Adverse Events which occurred in at least two patients (Safety Population)

System Organ Class Preferred Term	Total (N=2539) n (%)
Patients with at least one SAE	107 (4.2)
Cardiac Disorders	
Atrial fibrillation	2 (0.1)
Cardiac failure	3 (0.1)
Ear and labyrinth disorders	
Vertigo	2 (0.1)
General disorders and administration site conditions	
Chest pain	3 (0.1)
Infections and Infestations	
Appendicitis	2 (0.1)
Bronchopneumonia	5 (0.2)
Gastroenteritis	2 (0.1)
Pneumonia	6 (0.2)
Investigations	
Blood pressure increased	2 (0.1)
Musculoskeletal and connective tissue disorders	
Back pain	3 (0.1)
Intervertebral disc protrusion	2 (0.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Prostate cancer	2 (0.1)
Thyroid adenoma	2 (0.1)
Nervous system disorders	
Cerebrovascular accident	2 (0.1)
Respiratory, thoracic and mediastinal disorders	
Asthma	17 (0.7)
Dyspnoea	2 (0.1)

Cross-reference: Table 14.3.2.2.1; Listing 16.2.3.1.2.
SAE: Serious Adverse Event. N: Number of patients in population. n: Number of patients with data available. %: Percentage based on N. *Notes*: A patient may have more than one SAE in any category. Data from sites 2017 and 4010 is not included.
AEs coded using MedDRA version 16.0.

A total 107 (4.2%) patients reported 139 treatment-emergent SAEs. No treatment-emergent SAEs were assessed as being related to flutiform. The SOCs in which SAEs occurred most commonly were infections and infestations (22 patients; 0.9%) and respiratory, thoracic and mediastinal disorders (21 patients; 0.8%).

SAEs reported by the highest number of patients included asthma (17 patients; 0.7%) and pneumonia (6 patients; 0.2%) followed by bronchopneumonia (5 patients; 0.2%)

Out of the 1523 (60.0%) patients who had at least one treatment-emergent AE, 150 patients were discontinued from the study. For a list of AEs by individual patients (detailing any patients who were discontinued from the study) please see Listing 16.2.3.1.2.

10.5.3.3. Adverse Events of Special Interest

Only details of patients with AEs of special interest are presented here. For an overview of AEs requiring therapy or leading to dose interruption, dose increase or dose reduction, please refer to Tables 14.3.2.4.1, 14.3.2.4.2, 14.3.2.4.3 and 14.3.2.4.4.

Number of patients with AEs of special interest are presented in in Table 25 (and Table 14.3.2.5.1) and number of patients with AEs of special interest related to flutiform are presented in Table 14.3.2.5.2. Table 14.3.2.5.3 presents the AEs of special interest split by smoking habit subgroup.

Table 25 Number of Patients with Adverse Events of Special Interest (Safety Population)

Adverse Events of Special Interest	Total (N=2539)	
	n (%)	(95% CI)
Patients with at least one AE of special interest	1247 (49.1)	(47.2, 51.1)
Respiratory AEs including cough and paradoxical bronchospasm*	222 (8.7)	(7.7, 9.9)
Asthma worsening/asthma exacerbation	430 (16.9)	(15.5, 18.5)
Serious asthma-related events (asthma hospitalisations, intubations, deaths)	18 (0.7)	(0.4, 1.1)
Local oral adverse events	64 (2.5)	(1.9, 3.2)
Local immunosuppressive effects, infections	899 (35.4)	(33.5, 37.3)
Anaphylactic reactions	2 (0.1)	(0.0, 0.3)
Adrenal suppression/adrenal failure	-	-
Growth retardation	-	-
Decrease in bone mineral density	22 (0.9)	(0.5, 1.3)
Skin atrophy	-	-
Skin contusion	7 (0.3)	(0.1, 0.6)
Cataract	3 (0.1)	(0.0, 0.3)
Glaucoma	5 (0.2)	(0.1, 0.5)
Hypokalaemia	2 (0.1)	(0.0, 0.3)
Hyperglycaemia/increased blood glucose	9 (0.4)	(0.2, 0.7)
Cardiac arrhythmias and QTc prolongation	42 (1.7)	(1.2, 2.2)
Cardiac ischaemia	9 (0.4)	(0.2, 0.7)
Psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression	74 (2.9)	(2.3, 3.6)

Cross-reference: Table 14.3.2.5.1; Listing 16.2.3.1.2
n: Number of subjects with data available. %: Percentage based on N. CI: confidence interval (for event rate).
AE: Adverse Event. N: Number of subjects in population. n: Number of subjects with data available.
Notes: A subject may have more than one AE in any category. Data from sites 2017 and 4010 is not included.
CIs obtained using Clopper–Pearson method.
AEs coded using MedDRA version 16.0.
*N.B. Despite the name of this grouping of adverse events of special interest, no events of paradoxical bronchospasm occurred.

The total number of patients with at least one AE of special interest was 1247 (49.1%) The 95% CIs for the percentage of patients were 47.2 and 51.1.

The most common AE of special interest amongst patients was 'Local immunosuppressive effects, infections' (899 patients; 35.4%; CI: 33.5, 37.3) followed by asthma worsening/ asthma exacerbation (430 patients; 16.9%; CI: 15.5, 18.5) and respiratory AEs including cough and paradoxical bronchospasm (222 patients; 8.7% CI; 7.7, 9.9) N.B. The AE of special interest "Respiratory adverse events including cough and paradoxical bronchospasm" was a composite term consisting of respiratory adverse events identified by the study Medical Monitor, excluding asthma worsening/ exacerbation and events associated with asthma worsening/ exacerbation. Although this AE of special interest refers to paradoxical bronchospasm, no such events were reported in the study. For details of AEs of special interest by individual patient, please see Listing 16.2.3.1.2.

10.5.4. Narrative of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

4 patients experienced AEs leading to death during the study. None of these AEs was considered to be related to flutiform. Patient 3002021 (case number GBR-2014-0018225) a 45-year-old Caucasian male, died of a pulmonary embolism. The patient was diagnosed with asthma one day prior to being entered into the study. The patient was found dead due to massive pulmonary embolism 10 days after having entered into the study. Concomitant medications were Ventolin (salbutamol) and Deltacortril (prednisolone). The event of pulmonary embolism was considered by the Investigator to be not related to flutiform. (Listing 16.2.3.1.2 and 16.2.1.6)

Patient 7015001 a 94-year-old Caucasian female, died of bronchopneumonia. The patient died 277 days after having entered into the study. The patient was taking Salbutamol concomitantly as a treatment for asthma. The patient was also treated with Amoxicillin for a respiratory tract infection. The patient suffered from a transient ischaemic attack and was subsequently treated with aspirin 25mg/ dipyrimidole. The event of bronchopneumonia was not considered to be related to flutiform (Listing 16.2.3.1.2 and 16.2.1.6)

Patient 3005008, a 45-year-old Caucasian female, died of metastases to liver. The patient was diagnosed with the condition 183 days into the study and died 310 days later. The patient was taking the medications Ventolin (Salbutermol) and Deltacortril (prednisolone) concomitantly. Additionally, the patient received Tranexamic acid as a treatment for their metastases to the liver concomitantly. The event of metastases to the liver was considered by the Investigator to be not related to flutiform. (Listing 16.2.3.1.2 and 16.2.1.6)

Patient 5024058, a 77-year-old Caucasian female, died of an acute cerebrovascular episode (stroke) 266 days into the study. The patient was taking Ventolin inhaler concomitantly due to uncontrolled asthma. Additionally, the patient was taking Egilok and Tezeo hct for Arterial Hypertension, and Monosan as well as Protevasc for ischaemic heart disease. The event of an acute cerebrovascular episode (stroke) was considered by the Investigator to be not related to flutiform (Listing 16.2.3.1.2 and 16.2.1.6)

11. KEY RESULTS

11.1. Descriptive Data

- Both the safety and efficacy data were analysed in the safety population (2539 patients).

- Mean time of on-study exposure to flutiform was 344.3 days. The majority of patients (75.2%) were under cumulative on-study exposure to flutiform for at least 12 months. Most patients (83.3%) had a stable flutiform dose during the study (i.e. no dose changes were reported during the study). For those patients that required a change to flutiform dose during the study, the most common change was dose increase (165 patients) followed by multiple dosage adjustments (145 patients) and dose decrease (113 patients).

- With regards to the demography of patients, the majority (2394 patients, 94.3%) were at least 18 years of age and over, and almost two thirds (1609 patients, 63.4%) were female.

- The most frequently reported reason for initiation of flutiform therapy was change from other ICS/LABA treatment due to lack of efficacy (45.3% overall).

- At the start of the study, the majority of patients were non-smokers (1856 patients; 73.1%) or ex-smokers (361 patients; 14.2%). In the course of the study the number of smokers that gave up smoking increased from 5 (0.6%) patients at 1 month to 31 (1.3%) patients by the End of Study (LOCF). The number of non-smokers who started smoking during the study rose from 1 (0.1%) at 1 month to 14 (0.6%) by the End of Study (LOCF).

- Less than a quarter of patients discontinued from the study (22.6% of patients). The most common reason for discontinuation among patients who would still go on to be prescribed flutiform, was loss to follow-up (4.6% of patients). For those patients who would not go on to be prescribed flutiform, the most common reason for discontinuation or why flutiform would not be prescribed any further was adverse events (5.3% of patients).

11.2. Main Results

- The ACT™ mean total score for patients increased during the course of the study, from 16.3 (baseline) to 20.4 at end of study (LOCF).

- Correspondingly, the proportion of patients with controlled asthma increased throughout the study from 29.4% patients with controlled asthma at baseline to 67.4% at the end of study (LOCF). Accordingly, the proportion of patients with somewhat or poorly controlled asthma decreased throughout the duration of the study.

- In the 12 months *prior* to enrolment in this study, most patients had experienced either no or one severe asthma exacerbation(s) (1629 patients; 64.2% and 461 patients; 18.2% respectively) and 17.7% of patients had experienced 2 or more severe exacerbations. The average number (SD) of severe exacerbations experienced by patients was 0.9 (1.75).
  Incidence of severe asthma exacerbations during the observational period was lower compared to the 12 months prior to the study: over 90% of patients (2291 patients; 90.2%) did not experience any severe asthma exacerbations and 3.2% of patients had experienced 2 or more severe exacerbations. The average number (SD) was 0.1 (0.52).

- The mean total Asthma Quality of Life (AQL) score increased from the start of treatment (4.691) to the end of the study (5.635), corresponding to a mean change from baseline of 1.013. This increase was similar across the four domains and was a clinically significant change.

- Mean values of each lung function parameter (with the exception of FEV_1/FVC) all increased during the course of the study. Examples are FEV_1 with a mean (SD) change from baseline of 0.132L (0.494) and FVC with a mean (SD) change of 0.101L (0.574). The highest mean (SD) increase from baseline was observed for PEF (20.87L/min [77.441]).

- In the opinion of physicians, flutiform had a higher efficacy than the treatment patients were receiving prior to the study. Previous treatment was assessed as moderate or poor for the majority of patients (40.8% and 27.1% respectively). By the end of the study (LOCF), the majority of patients were assessed as receiving treatment with 'Very good' or 'good' efficacy (41.4 % and 46.9% of patients respectively)

- With regard to treatment tolerability, physicians assessed patients' previous treatment as mainly 'good' or 'moderate' (51.7% and 23.3% of patients respectively). Only 15.0% of patients were assessed as having 'very good' tolerability to their previous treatment, whereas 51.5% of patients were assessed as having 'Very Good' tolerability to flutiform by the end of the study (LOCF).

- Adherence to previous asthma treatment was assessed as good in 45.7% of patients and as very good in 18.9% of the patients at baseline. Patients assessed as having very good and good adherence with flutiform reached proportions of 47.2% and 41.6% respectively at the end of the study (LOCF).

- The ratings by patients in terms of efficacy and tolerability were similar as compared to the corresponding assessments of the physicians. The proportion of patients assessing the efficacy and tolerability of treatment as 'very good' increased under flutiform treatment.

- The average number of days of absence or inability to perform everyday activities (30 days prior to visit) decreased from 1.4 days at the start of the study to 0.3 days at the end of the study (LOCF). Additionally, the annualised rates of unscheduled visits, of emergency visits and of hospital admissions were low with mean (SD) values of 0.36 (1.334), 0.04 (0.434) and 0.01 (0.281) respectively, and median rates of 0.00 per year, each. With regards to hospital admissions, the number of days spent in hospital in most cases remained low with a mean (SD) annualised rate of 0.10 (2.577) days spent in hospital and a median of 0.00.

- Most AEs were considered to be not related to flutiform. In fact, at least 1265 of the 1523 patients who experienced at least one AE during this study had AEs that were not related to flutiform.

- Most AEs (related or not related to treatment) were moderate or mild in severity. 634 patients (25.0%) experienced moderate AEs and 570 patients (22.4%) experienced mild AEs. Only 319 patients (12.6%) experienced severe AEs and only 29 patients experienced a total of 36 severe AEs that were considered possibly related to flutiform.

- Asthma was the most frequently reported AE (related or not related to treatment). Of the 435 patients who reported asthma as an AE during the study, 50 patients (59 AEs in total) experienced asthma that was reported as being related to flutiform. The next most common related AE was dysphonia (47 AEs in 46 patients; 1.8%) followed by cough (28 AEs in 28 patients; 1.1%).

- The most common AEs of special interest were 'local immunosuppressive effects, infections' (899 patients; 35.4% CI: 33.5, 37.3; Related AEs: 57 patients; 2.2% CI: 1.7, 2.9) and 'asthma worsening/asthma exacerbation' (430 patients; 16.9% CI: 15.5, 18.5; Related AEs: 50 patients; 2.0% CI: 1.5, 2.6).

11.3. Limitations

This PASS study was designed to observe real-world clinical practice and usage of flutiform, and as such, measurements and recordings of AEs may not have been recorded as they would in an interventional clinical trial. As a consequence of this, for some timepoints many patients do not have data (this is particularly relevant for the 1-month data timepoint, which has the lowest number of patient data points for any timepoint in this trial). Also, this was an open-label study and observations were made with full knowledge of the treatment received, which has the potential to introduce bias. Therefore, any analysis should be interpreted with 'real world practice' in mind. None the less, the results give a good indication of what can be expected when flutiform is used as part of standard clinical practice.

12. CONCLUSION

Of the patients who were enrolled in this study, the greatest percentage had received a prescription for flutiform because of a lack of efficacy with their previous asthma medication (45.3%). During the year of observation, most patients (75.2%) remained on flutiform for at least a year and 83.3% of patients were on a stable dose during the study. The low discontinuation rate (22.6% of patients) was particularly notable for a study of this length.

Almost all measurements of asthma control were observed as improving by the end of the study. For example, the proportion of patients with controlled asthma showed a general increase, from 29.4% of patients at baseline to 67.4% of patients with controlled asthma at the end of study; the ACT™ mean total score increased from 16.3 at baseline to 20.4 by the end of the study. In addition, during the study, patients recorded a reduced number or days of absence or inability to perform everyday activities.

Also, during the 12 months prior to the study, 18.2% of these patients had experienced 1 severe exacerbation (mean [SD] exacerbation rate: 0.9 [1.75]). Importantly, however, by the end of the study 90.2% of patients had not experienced any exacerbation (mean [SD] exacerbation rate 0.1 [0.52]).

The AEs experienced most commonly during the study and considered to be related to flutiform were asthma (exacerbation), dysphonia and cough. These are AEs that are to be expected in patients with asthma. However, most of the AEs experienced during the study were not related to flutiform and the number of severe AEs was very low.

The combination of most AEs being mild or moderate, low numbers of discontinuations from the study, and improvements in asthma control, are likely to be contributing to a

favourable opinion of flutiform treatment. When assessed at the end of the study, it could be seen that larger numbers of physicians and patients rated flutiform treatment as having better efficacy and tolerability than previous treatment.

The results of this study support the conclusion that flutiform is safe and well-tolerated in patients with asthma and no specific safety concerns were observed.

13. REFERENCES

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