

1 TITLE PAGE

Protocol Number: FLT9503

Title: A Non interventional post authorisation study to determine the safety and effectiveness of flutiform[®] (*Affirm* Study).

Short title Assessment of fluticasone /formoterol In Real life Maintenance treatment (Affirm).

Sponsor: Mundipharma Research Limited,
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Milton Road
Cambridge
CB4 0AB
UK

Market Authorisation Holders See Section 5 of the Protocol

Test Drug: Flutiform[®]

Indication: Chronic Moderate to severe Asthma

Phase: Post Authorisation Safety Study (PASS)

Release Date: 03 May 2013

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2 PASS STUDY ABSTRACT

Name of Company: Mundipharma Research Ltd	
Name of Finished Product: flutiform [®]	Name of Active Ingredient: Fluticasone propionate /Formoterol fumarate dihydrate
Protocol No.: FLT9503	
Short Title of the Study: Assessment of fluticasone /formoterol In Real life Maintenance treatment (Affirm).	
Full Title of the Study: A Non Interventional Post Authorisation Study To Determine The Safety and Effectiveness of Flutiform [®] .	
Rationale and Background This study is being 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 This study is a Post Authorisation Safety Study as defined in EMA/330405/2012. The study was included in the European Risk Management Plan for flutiform [®] defined during the decentralised approval procedure. Primary objectives: Evaluation of the safety of flutiform [®] in routine clinical practice by <ul style="list-style-type: none"> • 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 subjects as well as adverse events detected by diagnostic procedures during routine clinical practice at the physicians' discretion. Secondary objectives: Secondary objectives are 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 and further parameters (e.g. 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) and by lung function parameters. In addition, the study shall provide deeper insights in the course of the therapy with flutiform [®] over one year with regard to dose adjustments, changes in asthma-related co-medication and discontinuation due to lack of efficacy as well as the subjects' and the physicians' satisfaction with the flutiform [®] therapy.	
Sample size and Investigator(s)/Site(s): Approximately 300 centres in approx 7 countries in the EU will be included with the intention to recruit 2500 patients.	

Summary of Study Design:

This study is designed to be fluid and to fit with standard clinical practice. As a minimum, adverse events will be captured. Other parameters as defined in the protocol will be captured if they are completed during normal clinical practice at participating investigator sites.

The objective of this post approval safety surveillance study (PASS) is to collect and analyse data on the safety and effectiveness of flutiform[®] prescribed for outpatients aged ≥ 12 years with asthma. The subjects will be observed during routine clinical practice. It is planned to observe each subject for one year from the first dose of flutiform. If a subject stops flutiform[®] intake due to lack of efficacy or due to other reasons, the observation should be continued further until the next regular visit to investigate whether the subject's asthma will be controlled better by using another treatment and to follow up the subject's health status.

Primarily, safety and efficacy observations are focused on adverse events rate and severity as well as on achievement of asthma control.

In accordance with the Summary of Product Characteristics (SmPC) and treatment guidelines, subjects diagnosed with asthma will be eligible for this observation, if they are not controlled on ICS and 'as required' inhaled short-acting β_2 -agonists or if they are switched from another treatment with a fixed or a free ICS/LABA combination.

Data on the subject's asthma medical history will be collected at the baseline visit (Visit 1) at the start of the observation. Physicians' visits, diagnostic procedures, and assessments will be performed as clinically indicated in the opinion of the treating physician and according to asthma treatment guidelines. Once subjects have started treatment with flutiform[®]. It is expected that the subject will return to see the investigator at regular intervals over the course of their treatment. The frequency of these visits will be according to local clinical practice but the number of visits over 12 months is expected to be approximately 4-7 visits. The observation is scheduled to cover a period of 12 months. For details please refer to Table 1 (Schedule of visits and assessments).

Flutiform[®] dose adjustments (stepping down or stepping up) depending on asthma control level will be 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 have to be documented at the regular visits retrospectively. If treatment corrections are performed by the investigator they will be documented during the respective visit.

All reported adverse events including severe asthma exacerbations will be documented during the PASS.

Severe asthma exacerbation is defined as worsening of asthma that requires 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 should be treated as separate severe exacerbations.

Study Population

The decision to prescribe flutiform[®] will necessarily precede and will be independent of the decision to enrol the subject into the study. Subjects diagnosed with asthma may be eligible for this observation, if they are not controlled on ICS and 'as required' inhaled short-acting β_2 -agonists or if they are switched from another treatment with a fixed or a free ICS/LABA combination to flutiform[®]. Only those subjects who will have received a prescription for flutiform[®] according to the SmPC will be evaluated for their potential eligibility for the study.

Eligibility criteria:

1. Male and female subjects aged ≥ 12 years
2. Subjects with a diagnosis of asthma
3. Subjects who receive a prescription of flutiform[®] according to the indication stated in the local approved SmPC (subjects not controlled on ICS and 'as required' inhaled short-acting β_2 -agonist or subjects who are switched from treatment with a fixed or a free ICS/LABA combination)
4. Written informed consent signed by the subject or for subjects younger than 18 years (adolescents) signed according to local requirements by one or both of the subject's parent(s) or legal representative(s) **and** by the subject
5. Planned treatment in line with the Summary of Product Characteristics, i.e. exclusion of all subjects with contraindications.

Variables**Safety Assessments:**

Adverse events (AEs) including serious adverse events (SAEs) reported spontaneously or after physicians' open question by the patient as well as AEs detected by diagnostic procedures during routine clinical practice will be documented at each visit starting from Visit 1 on.

Adverse events of special interest are:

- Respiratory adverse events including cough and paradoxical bronchospasm
- Asthma worsening/asthma exacerbation
- Serious asthma-related events (asthma hospitalisations, intubations, deaths)
- Local oral adverse events
- 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

Efficacy Assessment(s):

Assessments will be completed at visits undertaken by the subject. The frequency of visits and the actual assessments undertaken at each visit will be determined by clinical practice and asthma treatment guidelines. Where assessments are undertaken by clinicians or their staff the following will be captured in the database during the study :

- Demographic information (age, gender, race, 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
- Asthma control evaluation using the ACT™ (total score as well as the scores of the single items)
- Subjects' and physicians' satisfaction with flutiform® treatment as well as physicians' estimation of subject's adherence
- Quality of life assessment using AQLQ(S) 12+
- Lung function:
 - Forced Expiratory Volume in 1 second (FEV₁), absolute value and % predicted
 - Forced Vital Capacity (FVC), absolute value and % predicted
 - FEV₁ to FVC ratio (FEV₁/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, adverse event)
- 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
- Days of absence at work/school/college/university due to asthma or inability to perform everyday activities
- Amount of oral or parenteral corticosteroid use as an effectiveness parameter and antibiotics due to lung/ lower respiratory tract infection will be assessed.

Data Sources

Data will be obtained from patients at routine patient visits to investigators. Data will be recorded in source data and an electronic case report form (eCRF) designed for the study.

Data Analyses

The primary objective of the study is to examine safety data. All safety analyses will be based on the safety population (SP)

A secondary objective of the study is to evaluate efficacy. All efficacy analyses will be based on the full analysis population (FAP) unless otherwise stated.

Planned Milestones

Study start: planned for July 2013 (Recruitment dependent on launch of flutiform[®] in each territory conducting the study)

Recruitment completed: planned end 2014

Interim analysis: to be conducted when approximately 50% patients have completed treatment with flutiform.

Last data collection: early 2016

Report of study: end 2016

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4 LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CA	Competent Authorities
CI	Confidence interval
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
DCF	Data Clarification Form
EC	Ethics Committee
EDC	Electronic Data Capture
EU	European Union
FAP	Full Analysis Population
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
µg	Micrograms
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SP	Safety population
SD	Standard Deviation
SEM	Standard error of the mean
SOC	System Organ Class
SOPs	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
WHO	World Health Organisation
WHO-DD	WHO Drug Dictionary

5 Responsible Parties

5.1 Sponsor

This study will be conducted by qualified Investigators under the Sponsorship of Mundipharma Research Limited (MRL). MRL will centrally manage the conduct of the study for the local Marketing Authorisation Holders (MAH). A full list of MAHs is provided below.

Country	MA Holder
Denmark	Norpharma A/S Slotsmarken 15 2970 Hørsholm, Denmark
Finland	Mundipharma Oy Rajatorpantie 41B 01640 Vantaa; Finland
Norway	Mundipharma AS Vollsveien 13 C 1366 Lysaker, Norway
Sweden	Mundipharma AB Mölnadalsvägen 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

5.2 Declaration of Ethical Conduct

This study will be conducted in accordance with the standard operating practices of the Sponsor and Contract Research Organisation (CRO).

5.3 Investigators and Study Personnel

The study will be conducted at approximately 300 sites in 7 countries.

5.4 Data Management

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

Data collection will be by EDC. Data will be available electronically to the Sponsor/CRO and an electronic copy supplied to the site. Subjects will complete questionnaires which will be returned to the Investigator as detailed in Section 9.

5.5 Monitoring

The study will be monitored by qualified personnel from the Sponsor's local representatives /CRO. The Operations Manual for the study will detail this process. The Investigator will allow monitoring, audit and inspection of the clinical facilities as requested. The EDC system and subject's corresponding original medical records (source documents) are to be fully available for review by the CRO/Sponsor's representatives if requested. These reviews verify data accuracy. All records at the site are subject to inspection by the local competent and European authorities.

6 Milestones

- Study start: planned for July 2013 (Recruitment dependent on launch of flutiform[®] in each territory conducting the study)
- Recruitment completed: planned end 2014
- Interim analysis: to be conducted when approximately 50% patients completed treatment
- Last data collection: early 2016
- Report of study: end 2016

7 Rationale and Background

In 2012, Napp Pharmaceuticals Limited submitted one Complex and two Standard Abridged Marketing Authorisation Applications 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, through the Decentralised Procedure for Human Medicinal Products. The MAAs were approved 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 long-acting inhaled β_2 adrenoceptor agonist. The combination of an inhaled glucocorticosteroid and a selective long-acting β_2 adrenergic agonist 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 long-acting β_2 adrenergic agonist and exerts a preferential effect on β_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 airways obstruction who continue to experience symptoms despite treatment with an anti-inflammatory agent such as an inhaled corticosteroid. Guidelines for the management of reversible airways obstruction and particularly asthma recommend the addition of a long-acting β_2 agonist to the treatment regimen in these patients and studies have shown that the addition of a long-acting β_2 agonist 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 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 is to collect safety information during routine clinical use of flutiform[®] with a particular interest on the prevalence of the following adverse events:

- Respiratory adverse events including cough and paradoxical bronchospasm
- Asthma worsening/asthma exacerbation
- Serious asthma-related events (asthma hospitalisations, intubations, deaths)
- Local oral adverse events
- 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.

8 RESEARCH QUESTION AND OBJECTIVES

8.1 Aim of the study

The aim of this study is 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) agreed during the decentralised marketing authorisation application for flutiform[®]

8.2 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 subjects as well as adverse events detected by diagnostic procedures during routine clinical practice at the physicians' discretion.

8.3 Secondary Objectives

Secondary objectives are to evaluate the effectiveness of flutiform[®] treatment under real life conditions on asthma control by:

- comparing the 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 shall provide deeper insights in the course of the therapy with flutiform[®] over one year with regard to dose adjustments, changes in asthma-related co-medication and discontinuation due to lack of efficacy as well as the subjects' and the physicians' satisfaction with the flutiform[®] therapy.

9 RESEARCH METHODS

9.1 Study Design

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

The objective of this post approval safety surveillance study (PASS) is to collect and analyse data on the safety and effectiveness of flutiform[®] prescribed for outpatients aged ≥ 12 years with asthma. The subjects will be observed during routine clinical practice. It is planned to observe each subject for one year from the first dose of flutiform. If a subject stops flutiform[®] intake due to lack of efficacy or due to other reasons, the observation should be continued further until the next regular visit to investigate whether the subject's asthma will be controlled better by using another treatment and to follow up the subject's health status.

Primarily, safety and efficacy observations are focused on adverse events rate and severity as well as on achievement of asthma control.

In accordance with the Summary of Product Characteristics (SmPC) and treatment guidelines, subjects diagnosed with asthma will be eligible for this observation, if they are not controlled on ICS and 'as required' inhaled short-acting β_2 -agonists or if they are switched from another treatment with a fixed or a free ICS/LABA combination.

Data on the subject's asthma medical history will be collected at the baseline visit (Visit 1) at the start of the observation. Physicians' visits, diagnostic procedures, and assessments will be performed as clinically indicated in the opinion of the treating physician and according to asthma treatment guidelines. Once subjects have started treatment with flutiform It is expected that the subject will return to see the investigator/site staff at regular intervals over the course of their treatment. The frequency of these visits will be according to local clinical practice but the number of visits over 12 months is expected to be approximately 4-7 visits. The observation is 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 will be 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 have to be documented at the regular visits retrospectively. If treatment corrections are performed by the investigator they will be documented during the respective visit.

All reported adverse events including severe asthma exacerbations will be documented during the PASS.

Severe asthma exacerbation is defined as worsening of asthma that requires 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 should be treated as separate severe exacerbations.

Table 1 Data collection and visit structure

Study Visit ¹	Visit 1 (start of treatment)	Interim visits (approx 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	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 ⁵	X		X
Consultations and hospitalisation due to asthma (unscheduled consultations, emergency visits, hospital admissions, days spent in hospital)		X	X
Adverse events (non-elicited reporting)		X	X

Footnotes

¹ clinic visits to be scheduled to fit with asthma treatment guidelines and local clinical practice. At each visit assessments as indicated in table should be captured in the database if they are conducted.

² lung function tests include FEV1, FVC, PEF. Lung function tests should 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) to be recorded for the 30 days before treatment start and then at each visit during treatment.

⁴ ACT should be completed at the start and end of treatment as well as at regular intervals during treatment according to local practice.

⁵ AQLQ should be completed at the start and end of treatment.

⁶ Any unscheduled visits to the physician or emergency treatment visits due to asthma are to be recorded.

⁷ If subject stops flutiform treatment earlier than 12 months then the end of study visit should be completed.

9.2 Setting and study population

The study will be completed by physicians and their associated site staff in primary or secondary care. These may be general practitioners or respiratory physicians. The conduct of the study will start in the participating countries after flutiform[®] has been launched.

The decision to prescribe flutiform[®] will necessarily precede and will be independent of the decision to enrol the patient into the study. Patients diagnosed with asthma may be eligible for this observation, if they are not controlled on ICS and 'as required' inhaled short-acting β_2 -agonists or if they are switched from another treatment with a fixed or a free ICS/LABA combination to flutiform[®]. Only those patients who will have received a prescription for flutiform[®] according to the SmPC will be evaluated for their potential eligibility for the study.

9.3 Eligibility Criteria

1. Male and female subjects aged \geq 12 years.

2. Patients with a diagnosis of asthma.
3. Patients who receive a prescription of flutiform[®] according to the indication stated in the local approved SmPC (patients not controlled on ICS and 'as required' inhaled short-acting β_2 -agonist or patients who are 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 to be recorded.

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

- Demographic information (age, gender, race, 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™ consists of 5 questions answered by the patient for the last 4 weeks. Each of the five items can be rated using a 5-point scale from 1 (the worst rating) to 5 (best rating). The following items will be 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
- Subjects' and physicians' satisfaction with flutiform® treatment as well as physicians' estimation of subject's adherence.
Assessment of treatment (efficacy, tolerability, adherence) will be 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+.
- Lung function:
 - Forced Expiratory Volume in 1 second (FEV₁), absolute value and % predicted
 - Forced Vital Capacity (FVC), absolute value and % predicted
 - FEV₁ to FVC ratio (FEV₁/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, adverse event).

- 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 occurred since the last visit as well as the number of days spent at hospital due to asthma since the last visit are 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 will be documented. At visit 1 this is 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 will be assessed.
- Adverse Events and Serious Adverse Events.

9.5 Data Sources

Data will be entered into the eCRF by the investigator site staff. Subjects will attend the investigator site for regular visits during their treatment with flutiform[®] according to local clinical practice. Assessments conducted during these visits will be according to clinical practice. Table 1 defines assessments that the investigator will enter in the eCRF if the assessments have been undertaken during subject visits. Demographic information, asthma history, prior and current medication will be captured from the subjects medical records or from patient interview.

Subjects will complete the AQLQ and ACT questionnaires and the information will be transcribed into the eCRF by the investigator site staff.

9.6 Study size

A total number of 2500 subjects is intended to be enrolled within the European Union.

This sample size will allow adverse event rates to be estimated with a certain level of precision. For example, with 2500 subjects, assuming an adverse event is reported by 5%, the two-sided 95% confidence interval will be between 4.1% and 5.9%.

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

9.7 Data Management

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

Data collection will be by EDC. Data will be available electronically to the Sponsor/CRO and an electronic copy supplied to the site. Subjects will complete questionnaires which will be returned to the Investigator as detailed in Section 9.

9.8 Data Analysis

All data analyses will be performed by the CRO after the study is completed and the database is locked. Statistical programming and analyses will be performed using SAS and/or other validated statistical software as required.

9.8.1 Statistical Methodology and Analytical Plans

The statistical analyses described in this section will be performed as further outlined in the Statistical Analysis Plan (SAP), which will be finalised prior to database lock and will be included in the clinical study report for this protocol. The final SAP will take into account any amendment to the protocol.

9.8.2 Statistical Considerations

All data will be listed by subject.

In general, continuous data will be summarised using the following descriptive statistics: n, mean, standard deviation, median, minimum and maximum. Two sided 95% confidence intervals will be presented around mean values where appropriate. Categorical data will be summarised as the number and percentage of subjects in each category.

Further details of statistical methods and analyses will be documented in the SAP. This will include assessment windows around time-points and methods for dealing with missing data.

9.8.3 Analysis Populations

Enrolled Population: All subjects who signed informed consent.

Full Analysis Population (FAP): All subjects who receive at least one dose of study medication (flutiform[®]) and have at least one post-baseline efficacy assessment.

Safety Population (SP): All subjects who receive at least one dose of study medication (flutiform®).

9.8.4 Safety Analyses/Adverse Outcomes

The primary objective of the study is to examine safety data.

All safety analyses will be based on the SP.

9.8.4.1. Analysis of Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system to give a System Organ Class (SOC) and preferred term for each event.

Only treatment emergent AEs will be summarised. A treatment emergent AE will be defined as any AE with an onset date on or after the first dose of flutiform if the AE was absent before the first dose of flutiform, or worsened after the first dose of flutiform. This will also include AEs with an onset date up to and including 7 days after the last dose of flutiform.

The number and percentage of subjects reporting any AE will be summarised by the 'preferred term' nested within the SOC. In addition, the number of reported AEs will be summarised.

AEs will be summarised by worst severity and relationship to flutiform. In addition, severe AEs, AEs leading to death, serious AEs, AEs leading to discontinuation from study, and AEs requiring additional therapy will be summarised.

In order to account for the different durations of exposure, the rates for the most frequent AEs will be normalised to subject exposure so as to evaluate the incidence according to time of exposure. The most frequent AEs per 100 subject years of exposure (defined as an incidence of ≥ 2 per 100 subject years of exposure to treatment) will be summarised by preferred term.

The number and percentage of subjects reporting AEs of special interest (defined in section 7) will also be summarised. The 95% confidence intervals will also be presented.

9.8.5 Efficacy Variables

A secondary objective of the study is to evaluate efficacy.

All efficacy analyses will be based on the FAP unless otherwise stated.

9.8.5.1. Asthma Control Test

The asthma control test (ACT) total score, and the scores of the single items recorded at each time-point, and the change from baseline to each post baseline time-point and end of study will be summarised as continuous data for the FAP.

The change from baseline in the ACT total score, and the scores of the single items between baseline and end of study will be analysed using a paired t-test. The primary analysis population is the FAP.

9.8.5.2. Asthma Exacerbations

The number and percentage of subjects reporting severe asthma exacerbations at baseline and during study treatment will be summarised. In addition, the annualised rate of severe asthma exacerbations will be summarised.

9.8.5.3. Rescue Medication Use

Asthma related medication (maintenance and reliever/rescue medication) including use of corticosteroids applied within the last 30 days before visit 1 as well as all concomitant asthma related medication during treatment with flutiform will be summarised according to the SAP.

9.8.5.4. Health Care Resource Use

Health care resource use, including the number of unscheduled visits, emergency visits and hospital admissions due to asthma will be summarised. In addition, the days of absence at work/school/college/university due to asthma or inability to perform everyday activities will be summarised.

The amount of oral or parenteral corticosteroid use as an effectiveness parameter and antibiotics due to lung/lower respiratory tract infection as assessments of healthcare resource consumption will also be summarised.

9.8.5.5. Quality of Life

The Asthma Quality of Life Questionnaire (AQLQ) total score, and the scores for each of the 4 domains (symptoms, activity limitation, emotional function and environmental stimuli) recorded at baseline and end of study, and the change from baseline to end of study will be summarised as continuous data.

The change from baseline in the AQLQ total score, and the scores for each of the 4 domains between baseline and end of study will be analysed using a paired t-test.

9.8.5.6. Lung Function Parameters

The lung function parameters (FEV₁, FVC, FEV₁/FVC and PEF) recorded at each time-point, and the change from baseline to each time-point and end of study will be summarised as continuous data.

The change from baseline in lung function parameters between baseline and end of study will be analysed using a paired t-test.

9.8.5.7. Satisfaction with Treatment

Subject's and physician's satisfaction with treatment and physician's estimation of subject adherence will also be summarised as categorical data.

9.8.6 Subject Disposition

The number and percentage of subjects in each population will be summarised for subjects in the enrolled population.

The number and percentage of subjects that complete the study and the primary reason for discontinuation will be summarised for subjects in the SP.

The number and percentage of subjects enrolled from each country and site will be summarised for subjects in the SP.

9.8.7 Demographic/Baseline Analyses

Demographic and baseline variables will be summarised for subjects in the SP.

Age, weight, height, and body mass index will be summarised as continuous data. Gender and race will be summarised as categorical data.

Smoking status and number of exacerbations in the previous 12 months (recorded at visit 1) will be summarised as categorical data. The number of smoking pack years will be summarised as continuous data.

Current asthma history will be summarised as detailed in the SAP.

9.8.8 Treatment exposure Analyses

Treatment exposure will be defined as the number of days on flutiform. This will be calculated as the number of days between the first and last dose of flutiform. Treatment exposure will be summarised as continuous data.

Treatment exposure will also be summarised as the number and percentage of subjects in each of the following categories: < 1 week, ≥ 1 week to < 4 weeks, ≥ 4 weeks to < 8 weeks, ≥ 8 weeks to < 12 weeks, ≥ 12 weeks, ≥ 26 weeks, ≥ 39 weeks and ≥ 52 weeks.

The average daily dose and the number of dose adjustments (increase, decrease) will be summarised.

9.8.9 Concomitant Medication Analyses

The number and percentage of subjects taking previous asthma medications, ICS alone (i.e. without LABA), LABA alone (i.e. without ICS) and ICS-LABA combinations at screening will be summarised.

Concomitant medications will be assigned an 11-digit code using the current version of the World Health Organisation Drug Dictionary (WHO-DD) drug codes. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification.

The number and percentage of subjects taking concomitant medications will be summarised by ATC anatomical class, pharmacological class, and pharmacological sub-class for subjects in the SP.

9.8.10 Interim Analysis

An interim analysis will be conducted according to the SAP. This will occur when approximately 50% of planned subjects have completed treatment with flutiform. Descriptive summaries will be provided for demography, exposure and adverse events. As there will be no statistical tests performed, no alpha adjustment is required.

9.9 Quality Control

9.9.1 Record maintenance and retention

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

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

- Source documents will be completed to support the data that is entered into the EDC system.
- EDC entries should be made as close to the visit of the subject as possible.

The circumstances of completion or termination of the study notwithstanding, the Investigator has the responsibility to retain all study documents, including but not limited to the protocol, copies of EDC data, ICFs, and EC correspondence.

The site should plan on retaining study documents for approximately 15 years after completion of the study. This will include copies of the EDC.

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

9.9.2 Data Monitoring

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

This study will be organised, performed, and reported in compliance with the protocol, Standard Operating Procedures (SOPs) of the Sponsor and CRO. Sponsor QA activity will be undertaken as outlined in the study audit plan. Section 5.19.3(b) of ICH E6 states that the audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to competent authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects and any identified problem(s). QA activities may be outsourced to CROs or independent consultants. The investigator is required to support audit activities, to be available to the auditors upon request and to permit the auditor direct access to source data/documents.

A CA/authorised third party may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a CA, the Investigator must inform the Sponsor immediately that this request has been made.

9.10 Limitations of the Research Method.

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

Owing to differing clinical practice between countries who will recruit subjects into the study the study protocol has to be flexible to allow for different frequencies of subject visits and differing assessments conducted at each visit. It is accepted that for some subjects there will be fewer data points than others.

10 PROTECTION OF HUMAN SUBJECTS

10.1 Declaration of Ethical Conduct

This study will be conducted in accordance with the standard operating practices of the Sponsor and CRO. The study will be conducted according to the following guidelines:

1. Declaration of Helsinki, 1964 (“Recommendations Guiding Physicians in Biomedical Research Involving Human Patients”), and all its accepted amendments to date concerning medical research in humans.

2. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use
3. Guideline on good pharmacovigilance practices (GVP) Module VIII- Post-authorisation safety studies EMA/330405/2012

This study will be conducted in accordance with national and local laws of the countries where study sites are located.

The participating physician agrees, when signing the protocol signature page, to adhere to the instructions and procedures described in the protocol.

10.2 Ethical, Regulatory and Other Local Review

According to local country specific requirements the protocol and associated documentation will be submitted to all relevant local approving bodies. This may include Ethics committees, data protection bodies etc.

Signed letters of positive opinion regarding the study from the relevant local approving bodies must be sent to the Investigator who will provide the Sponsor/ CRO with a copy prior to the start of data collection for any subject in the EDC. Investigators or CRO/ Sponsor will submit, depending on local regulations, periodic reports to local approving bodies.

Adverse event safety reporting will be conducted in accordance with current European and local legislation

10.3 Adherence to the Protocol

The Investigator and associated site staff will collect information according to the protocol.

Subjects who have not signed an approved ICF cannot have their data entered into the eCRF.

The Investigator and associated site staff must comply with local regulatory laws and regulations concerning post approval safety studies.

10.4 Subject Information and Consent

Informed consent should be obtained by means of a patient information sheet (PIS) and Informed Consent Form (ICF), prepared in accordance with ICH E6 Section 4.8.10 and applicable local regulations, written in non-technical language. All subjects and/or their guardians/legally authorised representatives will be provided with oral and written information describing the nature and duration of the study and the procedures to be performed. The subject will be asked to sign and date an ICF prior to any study-specific information being collected in the eCRF. No subject can enter the study before his/her informed consent has been obtained. A sample subject ICF used in the study will be included in the clinical study report for this protocol.

As part of administering the informed consent document, the Investigator must explain to each subject and/or their guardian/legally authorised representative the nature of the study, its purpose, the data collection procedures involved, and the expected duration. Each subject must

be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. The subject should understand the patient information sheet (PIS) and ICF before signing and dating the ICF. The Investigator or person obtaining consent must also sign and date the form. Each subject will be given a copy of the signed informed consent and written information.

The original signed ICF for each subject will be verified by the Sponsor/CRO monitors and kept in the study centre investigational site files.

10.5 Data Protection and Human Tissue Sampling

Data protection will be carried out in accordance with the Principles of the Data Protection Act (1998) 95/46/EC. This will apply to all study data in whatever format it is collected and recorded.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS / ADVERSE REACTIONS

Safety assessments will be recorded from the point at which the Informed Consent is signed. These will consist of:

- monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), observed or volunteered, regardless of suspected causal relationship to flutiform. This includes reactions, interactions, accidents, illnesses, misuse and abuse.

The obligations and responsibilities with regards to collection, distribution and onward reporting of adverse events and reactions to the appropriate regulatory bodies and committees will be carried out in accordance with current European and local regulations and are documented in a separate Safety Management Plan.

11.1 Adverse Events (AEs) and Serious Adverse Events (SAEs)

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can be:

- Any unfavourable and unintended sign (including reactions from overdose, abuse, incorrect use of any treatment, or interaction)
- Any new disease or exacerbation of an existing disease (e.g. increase in frequency or worsening in nature)
- Any deterioration in measurements of laboratory values or other clinical tests (e.g. ECG, vital signs or X-ray) that results in symptoms, a change in treatment, or discontinuation of flutiform
- Recurrence of an intermittent medical condition (e.g. headache) not present at baseline
- Other medical events regardless of their relationship to flutiform, such as accidents, falls and any injuries resulting from them.

All Non-serious AEs must be reported within 7 calendar days, the format and mandatory data fields required will be specified in the Safety Management Plan.

A Serious Adverse Event (SAE) is any AE that:

- results in death
- is life-threatening (i.e. the subject was at immediate risk of death from the AE as it occurred)
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect (in the child of a subject who was exposed to flutiform)
- is a medically important event or reaction.

A SAE must be reported *immediately* (within 24 hours), independent of the circumstances or suspected cause, if it occurs or comes to the attention of the Investigator at any time during the study period. Any SAE with a suspected causal relationship to flutiform occurring at any other time after completion of the study must be promptly reported.

The following **mandatory information** must be provided to the Sponsor/CRO pharmacovigilance contact within 24 hours for each SAE:

- Protocol number
- Site number
- Subject number
- AE
- flutiform dose
- Investigator's name and contact details

Causality assessment should be completed as soon as possible.

Follow-up information should be actively sought until the SAE has resolved or sequelae have stabilised. Additional information e.g. hospital reports or death certificates, may be requested by the Sponsor or CRO and should be anonymised/pseudonymised before transmission and subsequently filed in the Investigator Site File.

The medical safety of the subject is of paramount importance when discussing study continuation.

11.2 Reporting of Adverse Events

See also Figure 1, Appendix Section 14.1.

Reporting period – Events will be recorded from the point at which the Informed Consent is signed until 7 days after the subject leaves the study. This includes new AEs that are reported

in the 7 days following the subject's completion/discontinuation visit. Any AE that is still ongoing 7days after the completion/discontinuation visit will have an outcome of 'ongoing' in the CRF, however the Investigator will continue to follow up ongoing AEs and record information in the source documents. SAEs will be followed until the event resolves or the event or sequelae stabilise and this information will be reported to the Sponsor using the SAE Data Form.

Medical conditions that are present at the screening visit will *only* be documented as adverse events if they are known to have started or are suspected to have started after the subject has signed the informed consent form. Medical judgement should be exercised to estimate if a condition is likely to have started between the signing of the informed consent and commencement of treatment with flutiform.

If the Investigator becomes aware of a AE after the completion of the study, which may have been caused by flutiform , they should report it to the Sponsor by phone, fax or e-mail.

For subjects who receive at least one dose of study medication - All AEs will be collected on the AE section of the EDC. In addition, a note should be made in the source documentation of the subject.

SAEs - All SAEs will be collected on the AE section of the EDC and flagged as serious. A separate paper SAE Data Form is supplied for immediate reporting in case the EDC is unavailable.

Reporting term - A cluster of signs and symptoms that results from a single cause or that could form a diagnosis should be reported as a single AE (e.g. fever, elevated WBC, cough, abnormal chest x-ray, etc. can all be reported as "pneumonia.").

Contact - The contact phone number at the CRO for SAE reporting in case the EDC is unavailable will be stored in the Investigator Site File. Questions relating to Drug Safety and Pharmacovigilance should be addressed to this number.

Scope International Pharmacovigilance

Fax: +370 52 327 903

Email: [safety @scope-international.com](mailto:safety@scope-international.com)

11.3 Causality Assessment

The question of the relationship of an AE to flutiform should be determined by the Investigator after thorough consideration of all facts that are available.

Assessment of causality is based on considering associative connections (time or place), pharmacological explanations, previous knowledge of the drug, presence of characteristic clinical or pathological phenomena, underlying conditions in the study population, exclusion of other causes, and/or absence of alternative explanations.

The physician will be asked if a **reasonable possibility of a causal relationship** to flutiform is suspected.

- “Yes” should be selected if there are facts (evidence) or arguments to suggest a causal relationship.
- “No” should be selected if there are no facts (evidence) or arguments to suggest a causal relationship.

Please note that causality assessment of adverse events in the CRF only relates to flutiform.

If an AE is not related to flutiform e.g. concomitant therapy only, and not an interaction or effect of flutiform, the causality assessment will be “No” (no reasonable possibility of a causal relationship to flutiform).

11.4 Severity Assessment

The Investigator (or medically qualified designee) will evaluate the comments of the subject and the response to treatment to judge the severity of the AE. Severity refers to the accumulated intensity of discomfort/impairment of health and will be assessed according to the following criteria:

Mild: Awareness of sign, symptom, or event, but easily tolerated.

Moderate: Discomfort enough to cause interference with usual activity and may warrant intervention.

Severe: Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention.

Note: A severe adverse event will not necessarily be a serious adverse event.

Any medication necessary for the treatment of an adverse event must be recorded on the Concomitant Therapy Section of the EDC and, if applicable, on the SAE Data Form.

11.5 Pregnancy

Pregnancy occurring in a subject [or a male subject’s female partner] during a clinical study must be reported to the CRO using the Pregnancy Notification Form. The Sponsor will contact the investigator to confirm significant pregnancy information i.e. AEs during pregnancy, the pregnancy outcome, and any events to 3 months post-partum.

11.6 Laboratory Abnormalities

Abnormalities in laboratory test values should only be reported as AEs if any of the following apply:

- **They result in a change in flutiform schedule of administration** (change in dosage, delay in administration, flutiform discontinuation, **or other medical or treatment intervention** (e.g. anaemia requiring transfusions or hyperglycaemia requiring potassium supplement))
- They are considered as **clinically significant** by the Investigator.

Where possible, the AE description should be the diagnosis rather than the abnormal laboratory value. The same is true if abnormal values reflect a worsening of an underlying condition. Abnormal laboratory values that are present at Screening are not AEs (unless they are a consequence of a Screening procedure). Where an Investigator does not deem an abnormal (or markedly abnormal) laboratory value to be clinically significant, the reason must be clearly document in the source notes (e.g. normal fluctuation of the disease).

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical or administrative reasons at any time, however not without good cause. Reimbursement of professional fees will be made.

The Investigator reserves the right to discontinue the study should his/her judgement so dictate. In such an event, final settlement of the grant-in-aid will be adjusted pro rata, and the Investigator will refund the excess of payments made in advance. The Investigator will notify applicable local approval authorities in case of study discontinuation. Study records must be retained as noted in Section 9.

12.2 Registration and Publication of Study Summary and Results

If a study design is of the type required for registration in a public database as detailed in the guidance on www.clinicaltrial.gov or www.ClinicalTrialResults.org the study will be registered on a public database according to the Sponsor's SOPs. As a general guide phase 1, exploratory and post marketing studies will not require registration.

Following the end of the study the results should be published within a year of product approval for newly registered products, or within a year of completion of the clinical study report (CSR) if the product is already approved. If results are intended for publication in a peer review scientific journal, no detailed results will be published on a public database beforehand.

The site may publish or present the results of this protocol subject to the protection of any patentable rights of the Sponsor or its nominee(s) and subject to the protection of the Sponsor's confidential information. The Sponsor will be furnished with a copy of any proposed publication or presentation at least 60 days prior to submission for review of confidential or patentable information. Upon notice by the Sponsor, however, that the Sponsor reasonably believes that a patent application claiming an invention relating to flutiform made during the performance of the study will be filed prior to such publication, such publication may be delayed for an additional 30 days or until any patent application or applications have been filed, whichever will first occur.

For multi-site studies, it is mandatory that the first publication be based on data obtained from all analysed subjects; therefore Investigators participating in multi-site studies must agree not to present data gathered individually or by a subgroup of sites prior to the full, initial publication, unless this has been agreed to by all other Investigators and the Sponsor. Publication of clinical trial results may include the presentation of such work at national and international congresses,

symposia, professional meetings, peer-reviewed journals, and via other appropriate channels. Named authors and contributors to such publications shall be determined by the Sponsor in accordance with both the Company Publication Policy and the criteria as outlined by standard authorship guidelines. Selected Investigators, Consultants and Scientific Advisors may be invited to be named authors on such publications by the Sponsor. If the Investigator/Consultant/Scientific Advisor agrees to participate in the publication as an author, they will be asked to participate in the creation of all versions of the document(s) in question prior to submission or public dissemination. The Sponsor will ensure that any reasonable comments made by the invited author will be incorporated into the publication and that the named author will consent to the publication of the final version of the document. The copyright associated with any publication will be and shall remain the sole property of the Sponsor, unless or until the copyright of the document is transferred to the scientific peer-reviewed journal prior to and as part of the publication process.

13 REFERENCE LIST

Copies of all references will be held in the trial master file.

14 APPENDICES

14.1 Adverse Event Reporting Process

Figure 1: Flow diagram for AE reporting (to be considered alongside Section 11 of the protocol)

