# TITLE PAGE

**Division:** China Medicines Development
**Information Type:** Post Marketing Safety Study Protocol

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|---|---|
| **Title:** | Post-Marketing Observational Study to Evaluate Safety Profile of Flixotide 50 µg pMDI Treatment in Chinese Subjects with Asthma aged 1-<4 years |

| | |
|---|---|
| **Compound Number:** | CCI18781 |
| **Effective Date:** | 20-JUN-2017 |
| **Subject:** | Drug safety |
| **Author(s):** | PPD |

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# 1. LIST OF ABBREVIATIONS

| | |
|---|---|
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| ATC | Anatomical Therapeutic Chemical |
| bd | Two times a day |
| CFDA | China Food and Drug Administration |
| eCRF | Electronic Case Record Form |
| FP | Futicasone propionate |
| GCP | Good Clinical Practice |
| GCSP | Global Clinical Safety and Pharmacovigilance |
| GSK | GlaxoSmithKline |
| HFA | Hydrofluoroalkane |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| MedDRA | Medical Dictionary for Regulatory Activities |
| pMDI | Pressurized Metered-Dose Inhaler |
| qds | Four times a day |
| SAE | Serious Adverse Event |
| SADR | Serious Adverse Drug Reaction |
| SCG | Sodium Cromoglycate |
| WHO | World Health Organisation |
| µg | Microgram |

## Trademark Information

| Trademarks of the GlaxoSmithKline group of companies | Trademarks not owned by the GlaxoSmithKline group of companies |
|---|---|
| FLIXOTIDE | None |

# 2. RESPONSIBLE PARTIES

**Clinical Study Identifier: 207734**

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| Secondary Medical Monitor | | | | | 9F, Tower A, Ocean International Center No. 56, Mid 4th East Ring Rd. Beijing.100025 |
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Regulatory Agency Identifying Number(s): 2016B02085

# INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

| | |
|---|---|
| Investigator Signature | Date |

# 3. ABSTRACT

**Rationale**

Flixotide administered via a pressurized metered-dose inhaler (pMDI) formulated with the propellant hydrofluoroalkane (HFA) was approved in China in 2002 with the strength of 50, 125 and 250 μg of fluticasone propionate per actuation. It was indicated for prophylactic treatment of asthma, including adults, adolescents older than 16 years of age and children aged 4 to 16 years and has demonstrated a positive benefit/risk profile in Chinese patients.

In Nov 2016, China Food and Drug Administration (CFDA) approved the therapeutic use of Flixotide 50 μg (recommended dosing 50 to100 μg twice daily inhaled via a paediatric spacer device with a face mask) in children aged 1 to<4 years, with a requirement for GlaxoSmithKline (GSK) to conduct proactive safety monitoring in this population. To meet CFDA requirement, GSK will initiate this post-marketing safety monitoring program to evaluate the safety of Chinese patients aged 1 to <4 years when using Flixotide 50 μg via a paediatric spacer device with a face mask in clinical practice. It is anticipated that the obtained data from this post-marketing program will further enhance and supplement the currently available safety data from clinical trials as well as provide more detailed information than that obtained typically available through routine spontaneous adverse event reporting.

**Objective**

The objective of this program is to evaluate the post-marketing safety profile of Flixotide 50 μg inhaled via a paediatric spacer device with a face mask in patients aged 1 to <4 years. The adverse drug reactions and predictors of these adverse reactions among patients will be observed.

**Study Design**

This is an observational study with no medical interventions. Subjects (children aged 1 to<4 years) information that is pre-defined in the protocol will be collected in the electronic case record form (eCRF). The decision to prescribe Flixotide 50 μg will not be influenced by whether or not to participate in this observational program.

The observational program will include subjects who have been prescribed Flixotide 50 μg (recommended dosing 50 to100 μg twice daily inhaled via a paediatric spacer device with a face mask) for appropriate medical use for the first time. The subjects who have been exposed to Flixotide 50 μg, 125 μg and 250 μg previously will not be included.

The maximum program duration will be 12 weeks with 3 visits. Visit1 (Day 1) is the start of the observational program. The follow-up visits will be scheduled at 4 weeks (Visit 2), and 12 weeks (Visit 3). Unless subjects discontinue Flixotide 50 μg treatment or withdraw their consent for continued data collection, subjects will remain in the program until Visit 3.

This post-marketing program is planned to recruit paediatric subjects from 3 to5 hospitals (may be adjusted as per recruitment progress) in China. It is planned to include 150 asthmatic subjects, aged 1 to<4 years who have been prescribed Flixotide 50 μg treatment for appropriate medical use for the first time in China.

# 4. AMENDMENTS AND UPDATES

None.

# 5. MILESTONES

| Milestone | Planned date |
|---|---|
| Start of data collection | 31-Aug-2017 |
| Study progress report | 30-Sep-2017 |
| End of data collection | 30-Aug-2018 |
| Final report of study results | 31-Oct-2018 |

# 6. RATIONALE AND BACKGROUND

## 6.1. Background

Fluticasone Propionate Inhaled Aerosol (Flixotide™) is the brand-name product of GlaxoSmithKline (GSK) Group. Flixotide is an established inhaled corticosteroid which has been approved worldwide for use in the prophylactic treatment of mild, moderate and severe asthma in adults (maximum daily dose of 2000 µg/day) and children aged 4 to16 years (maximum daily dose of 400 µg/day). For children aged 1 to<4 years, Flixotide is currently registered for the treatment of asthma (100 to 200 µg/day) in East Asian markets including Hong Kong, Taiwan and Korea, as well as some countries in South East Asia and the West. Similar clinical pharmacology data was obtained for subjects aged 1 to<4 years compared to subjects aged 4 to11 years and adults for fluticasone propionate (FP) pMDI 100 µg bd [GlaxoSmithKline Document Number YM2002/00005/00, 2002].

Data presented in the [Module 2.5, Fluticasone propionate. 2013], from both clinical trials and the published literature have shown that the Flixotide 50 µg can provide similar benefits in terms of enhanced lung function, decreased symptoms and an acceptable safety profile [Module 2.5, Fluticasone propionate. 2013]. In the global development program, a total of 703 subjects aged 1 to<4 years from the four key studies FAS30007 [GlaxoSmithKline Document Number GM2001/00151/00], FAS30009 [GlaxoSmithKline Report Number GM2001/00103/00], FLTB3016 [GlaxoSmithKline Report Number GM1996/00034/00] and FLTB3017 [GlaxoSmithKline Report Number GM1996/00033/00] received FP pMDI 100 µg bd for up to 12 or 52 weeks; this is calculated to be equivalent to 469 subject-years [GlaxoSmithKline Document Number YM2002/00005/00, 2002]. The safety profile has been summarized as below:

- The majority of adverse events (AEs) reported during the clinical programme were primarily from the ear, nose and throat and lower respiratory body systems; typical for this subject population. No new or unexpected events were identified.
- A higher percentage of subjects aged <2 years experienced AEs during treatment than did those aged ≥2 years.

- In the 52-Week study (FAS30009), there was no apparent evidence of any important clinical differences in the AEs occurring before and after Day 175, nor any evidence to suggest increasing rates of AEs in either the FP 100 µg bd or sodium cromoglycate (SCG) 5 mg qds treatment group after Day 175.
- Drug-related AEs were uncommon and not of clinical concern. The incidence of subjects withdrawing due to an AE was low. The incidence of serious adverse events (SAEs) was low, none were attributable to FP treatment and there were no deaths.
- A single incident of cataract was reported in subjects treated with FP 100 µg bd out of a total subject population of 703 and one further case was identified in a steroid naïve subject at Screening.
- FP 100 µg bd treatment for 52 weeks in children aged 1 to<4 years had no negative effect on growth compared to SCG.
- Serum/urinary cortisol levels generally reduced in subjects receiving FP 100 µg bd. Two subjects that received FP 100 µg bd in FAS30009 shifted from normal to low serum cortisol levels. No cortisol changes were associated with symptoms of adrenal insufficiency.
- No changes in clinical chemistry or haematology measurements examined were of clinical concern. There was no apparent evidence that treatment with FP 100 µg bd had any effects on vital signs and physical examinations. Incidence of oral candidiasis was uncommon.
- The SAEs reported from the studies were consistent with the known safety profile of FP, as established in the original Marketing Authorisation Application and variations. No new safety concerns, specific to the use of FP in a 1 to<4 year-old subject population were identified.

Overall, FP 100 µg bd was at least as well tolerated as placebo and the active comparator (SCG) in children 1 to<4 years old [for details please refer to Module 2.5, Fluticasone propionate. 2013]. The risk: benefit profile of FP 100 µg bd in the treatment of asthma in paediatrics aged 1 to<4 years old has been preferable.

In addition, GSK Global Clinical Safety and Pharmacovigilance (GCSP) regularly reviews the literature relating to matters of safety, and maintains a database of spontaneously reported AEs and literature references. In the recent [Periodic Benefit Risk Evaluation Report, 2016], it is concluded that benefit profile of FP in authorized indications continues to be positive; also there is no significant change to the risk profile.

## 6.2. Rationale

Flixotide administered via a pressurized metered-dose inhaler (pMDI) formulated with the propellant hydrofluoroalkane (HFA) was approved in China in 2002 with the strength of 50, 125 and 250 µg of FP per actuation. It was indicated for prophylactic treatment of asthma, including adults, adolescents older than 16 years of age and children aged 4 to 16 years and has demonstrated a positive benefit/risk profile in Chinese patients.

In Nov 2016, China Food and Drug Administration (CFDA) approved the therapeutic use of Flixotide 50 µg (recommended dosing 50 to100 µg twice daily inhaled via a paediatric spacer device with a face mask) in children aged 1 to <4 years, with a requirement for

GSK to conduct proactive safety monitoring in this population. To meet CFDA requirement, GSK initiates this post-marketing safety monitoring program to evaluate the safety of Chinese patients aged 1 to <4 years when using Flixotide 50 μg via a paediatric spacer device with a face mask in clinical practice.

# 7. RESEARCH QUESTION AND OBJECTIVE(S)

The data obtained from this post-marketing program will further enhance and supplement the currently available safety data from clinical trials as well as provide more detailed information than that obtained typically available through routine spontaneous adverse event reporting, thus justify the safety use of Flixotide 50 μg inhaled via a paediatric spacer device with a face mask in Chinese children aged 1 to <4 years old.

The objective of this program is to evaluate the post-marketing safety profile of Flixotide 50 μg in patients aged 1 to <4 years. The adverse drug reactions and predictors of these adverse reactions among patients will be observed. The primary goals of this program are listed below:

1. To observe the incidence of known adverse reactions in children aged 1 to <4 years.

2. To observe the occurrence of unexpected adverse reactions in children aged 1 to <4 years.

# 8. RESEARCH METHODS

## 8.1. Study Design

This is a single arm observational study with no medical interventions. Subjects (children aged 1 to <4 years) information that is pre-defined in the protocol will be collected in the electronic case record form (eCRF). The decision to prescribe Flixotide 50 μg (recommended dosing 50 to 100 μg twice daily inhaled via a paediatric spacer device with a face mask) will not be influenced by whether or not to participate in this observational program.

The observational program will include subjects who have been prescribed Flixotide 50 μg (recommended dosing 50 to 100 μg twice daily inhaled via a paediatric spacer device with a face mask) for appropriate medical use for the first time. The subjects who have been exposed to Flixotide 50 μg, 125 μg and 250 μg previously will not be included.

The maximum program duration will be 12 weeks with 3 visits. Visit1 (Day 1) is the start of the observational program. The follow-up visits will be scheduled at 4 weeks (Visit 2), and 12 weeks (Visit 3). Unless subjects discontinue Flixotide 50 μg treatment or withdraw their consent for continued data collection, subjects will remain in the program until Visit 3.

Visit1 is an on-site visit where subjects have been prescribed Flixotide 50 μg for appropriate medical use. The following procedures/assessments will be performed and recorded during Visit1:

- Obtain written informed consent
- Verification of inclusion criteria
- Obtain the demographic information
- Obtain the medical history
    - Disease history: asthma disease history and other systemic severe disease assessed by investigator.
- Collect concomitant medication use
    - Asthma treatment medication within 30 days prior to Visit 1.
    - Other important medications for severe disease treatment in the past 1 month.
- AEs and SAEs

Visit 2 and Visit 3 are follow-up visit. The follow-up can be conducted on site or by telephone based on the decision made by qualified medical staff. The following assessments will be performed at Visit 2 and Visit3:

- AEs and SAEs
- Collect Flixotide 50 μg treatment information
- Review concomitant medication use

Time and Events Table (Table 1) provides an outline of the information that will be collected on subjects who have provided consent for data collection according to local ethical guidelines for observational program. Visit 1 is an on-site visit; Visit 2 and Visit 3 are follow-up visits which can be conducted on site or by telephone.

**Table 1 Time and Events Table**

| Procedure | Visit Number | | | |
|---|---|---|---|---|
| Visit<br><br>(Visit Window) | 1[1]<br><br>Day1 | 2<br><br>4Ws ±3d | 3<br><br>12Ws±3d | Early Withdrawal |
| Informed consent | × | | | |
| Demographic data | × | | | |
| Medical history | × | | | |
| Flixotide 50 μg therapy[2] | × | × | × | × |

| Procedure | Visit Number | | | |
|---|---|---|---|---|
| Visit<br><br>(Visit Window) | 1[1]<br><br>Day1 | 2<br><br>4Ws ±3d | 3<br><br>12Ws±3d | Early Withdrawal |
| Concomitant medication | × | × | × | × |
| Adverse Event[3] | × | × | × | × |
| Serious Adverse event[3] | × | × | × | × |
| Diary card dispense[4] | × | | | |

1. Visit 1 marks the start of the observational period.
2. Change in drug dosage, discontinuation or resumption and reasons for these changes, and compliance of Flixotide 50 µg therapy.
3. SAEs will be recorded from the time the consent form is signed through Visit 3; AEs will be recorded from the start of Flixotide 50 µg treatment through Visit 3.
4. Paper diary cards will be dispensed at Visit 1 for the parent/guardian of the subject to record Flixotide 50 µg therapy, concomitant medication, AEs and SAEs. The investigator will record the source information in the medical records by asking the parent/guardian of the subject during the follow-up on site or telephone visits.

## 8.2. Monitoring Populations and Collaborative Hospitals

### 8.2.1. Subject selection

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

I. Informed consent

An appropriately signed and dated assent must be obtained from the parent/guardian of the subject.

II. Age

1 to<4 years of age at Visit 1.

III. Flixotide 50 µg treatment

Subjects who have been prescribed Flixotide 50 µg for a medically appropriate use for the first time will be included in this observational program. Flixotide 50 µg therapy should be in line with the approved dosing: 50 to100 µg twice daily. Subjects should have the ability to inhale the doses via a paediatric spacer with a face mask appropriately. Subjects who have been exposed to Flixotide 50 µg, 125 µg and 250 µg treatment previously will not be included.

IV. The parent/guardian of the subject must provide reliable contact information which includes home phone or cell phone for the follow up visits.

V. The parent/guardian of the subject must have the ability to comply study procedures.

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on Flixotide 50 μg that may impact subject eligibility is provided in the approved product label.

### 8.2.2. Subject Withdrawal

A subject and their parent/guardian may withdraw consent to have their data collected in the program at any time. If this occurs, they must be withdrawn from this study. Data collected until the point of consent withdrawal will be used.

### 8.2.3. Collaborative Hospitals

This post-marketing program is planned to recruit paediatric subjects from 3 to5 hospitals (may be adjusted as per recruitment progress) in China.

## 8.3. Study size

It is planned to include 150 asthmatic subjects, aged 1 to 4 years who have been prescribed Flixotide 50 μg treatment for appropriate medical use for the first time in China.

## 8.4. Data collection

The information of the subjects' demographic factors, medical history, Flixotide 50 μg therapy, concomitant medications, AEs and SAEs, will be collected. Paper diary cards will be dispensed at Visit 1 for the parent/guardian of the subject to record Flixotide 50 μg therapy, concomitant medication, AEs and SAEs. The investigator will record the source information in the medical records by asking the parent/guardian of the subject during the follow-up on site or telephone visits.

Subjects' data will be entered into GSK defined eCRFs.

No data will be collected on subjects until consent for data collection has been obtained in line with local ethical standards for observational program.

## 8.5. Data management

### 8.5.1. Data handling conventions

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data. Adverse events and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and, World Health Organisation (WHO)Drug. CRFs including queries and audit trails will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

### 8.5.2. Timings of Assessment during follow-up

Visit 1 will be defined as baseline. Follow-up visits will be performed at 4 weeks and 12 weeks since baseline visit. There is ±3 day window period for every follow up visit.

## 8.6. Statistical analysis

### 8.6.1. Hypotheses

This is a post-marketing observational study. A descriptive approach will be used and no formal inference is planned in this study. Some justification is provided as follows.

### 8.6.2. Sample Size Consideration

Considering that Flixotide is an established brand, which has been in the China market for more than 10 years, it is more sensible to consider drug related AE (adverse drug reaction, ADR) instead of any specific rare case.

Based on global phase III studies FAS30007 [GlaxoSmithKline Document Number GM2001/00151/00], FAS30030 [GlaxoSmithKline Document Number RM2004/0187/00] and FAS30009 [GlaxoSmithKline Report Number GM2001/00103/00] on 1 to<4 years old, the smallest incidence rate of ADR in a given study was 3%. The Japanese post market safety survey reported the ADR rate as 1.68%. Taken the lowest estimate between two approaches, assuming the ADR rate in Chinese 1 to<4 year old children patients is not lower than 1.5%, it is calculated that a study with 150 subjects will have approximately 90% probability to observe at least one ADR.

### 8.6.3. Data Analysis Consideration

The safety population is defined as all included subjects who received at least one dose of Flixotide 50 µg and complete one follow up visit, including scheduled or unscheduled visit. Subjects who retrospectively received will also be included in.

### 8.6.4. Key Elements of Analysis Plan

#### Safety Analysis

Safety data will be summarized and/or listed for the safety population.

The duration of exposure to Flixotide 50 µg will be summarized and patient medical history will be listed.

Concomitant medication will be coded using WHO drug and will be summarized by Anatomical Therapeutic Chemical (ATC) classification.

AEs will be coded using MedDRA, and grouped by body system. AEs occurring during administration of Flixotide 50 µg will be summarized. The number and percentage of subjects experiencing at least one AE of any type, AEs within each body system and AEs within each preferred term will be presented. Separate summaries will be provided for all AEs, drug related AEs, SAEs, and for AEs leading treatment discontinuation.

### Analysis methods

No formal hypothesis will be tested in this study. AEs will be listed and summarized descriptively to provide frequency estimate of ADR (=incidence rate of any drug related AEs in safety population) and frequency estimates for any other adverse events reported.

## 8.7. Quality control and Quality Assurance

In accordance with applicable regulations, applicable standards for the conduct of observational studies, and GSK procedures, monitors will contact the site prior to the inclusion of the first subject to review with the site staff the protocol, program requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

The sites will be monitored to ensure that the:

- Subjects included in the program are authentic.
- Safety and rights of subjects are being protected.
- The program is conducted in accordance with the currently approved protocol and any other program agreements, applicable standards for the conduct of observational studies, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor access to all relevant documents in accordance with applicable standards for the conduct of observational studies.

To ensure compliance with applicable standards for the conduct of observational studies and all applicable regulatory requirements, GSK may conduct a quality assurance audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the program.

In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

## 8.8. Limitations of the research methods

### 8.8.1. Study closure/uninterpretability of results

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.

- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) promptly and provide the reason for the suspension or premature discontinuation.

### 8.9. Other aspects

None.

## 9. PROTECTION OF HUMAN SUBJECTS

### 9.1. Ethical approval and subject consent

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Signed informed consent must be obtained for each subject (from their parent/guardian) before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.

## 9.2. Subject confidentiality

Documented evidence that a potential investigator is aware of and agrees to the confidential nature of the information related to the study must be obtained by means of a confidentiality agreement.

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (i) information which becomes publicly available through no fault of the investigator or site staff; (ii) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (iii) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (iv) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

# 10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

## 10.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

- Results in death,
- Is life-threatening,
- Requires hospitalization or prolongation of existing hospitalization,
- Results in disability/incapacity,
- Is a congenital anomaly/birth defect,
- Other: medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- possible drug-induced liver injury

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

### 10.1.1. Time Period and Frequency for Collecting AE and SAE information

- The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.
- SAEs will be recorded from the time the consent form is signed through Visit 3; AEs will be recorded from the start of Flixotide 50 μg treatment through Visit 3.
- Investigators will assess causality within 24 hours. Once the investigator determines that an AE/SAE is identified as explicitly attributed to any GSK product (including products not covered in the specific study objective), the investigator must report the ADR to Vendor and GSK China within 5 calendar days upon awareness. All SAEs will be recorded and reported to GSK within 24 hours of awareness. GSK standard AE and SAE Collection Forms (Appendix 1, Appendix 2) will be used to collect safety information. GSK China will forward the information to GCSP following internal process.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

#### 10.1.1.1. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?" **or** "How does your child seem to feel?"
- "Have you had any (other) medical problems since your last visit/contact?" **or** "Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?" **or** "Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?"

#### 10.1.1.2. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All ADRs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Any follow-up information on a previously reported ADR and SAE must also be reported to vendor and GSK China within the same timeline as initial reports.

# 11. REFERENCES

GlaxoSmithKline Document Number RM2004/0187/00. Study ID FAS30030. A Randomized (2:1), Stratified, Double-Blind, Parallel-Group, Placebo-Controlled, 12-week, Multi-Center Trial of Fluticasone Propionate HFA Inhalation Aerosol 88mcg BID versus Placebo HFA Delivered via an MDI and a Valved Holding Chamber with Facemask in Pediatric Subjects 1 to <4 Years of Age with Asthma (2004).

GlaxoSmithKline Document Number YM2002/00005/00. Expert Report on The Clinical Documentation of Inhaled Fluticasone Propionate 100µg Twice Daily in Children Aged 1-4 Years with Asthma. 2002.

GlaxoSmithKline Report Number GM1996/00033/00. Study ID FLTB3017. A multi-centre, randomised, double-blind, placebo-controlled parallel group study to determine the efficacy and safety of inhaled fluticasone proprionate 100mcg bd and 250mcg bd delivered via the Babyhaler and spacer device in the mangement of asthma symptoms in children aged 12 47 months inclusive. 1997.

GlaxoSmithKline Report Number GM1996/00034/00. Study ID FLTB3016. A multi-centre, randomised, double-blind, placebo-controlled parallel group study to determine the efficacy and safety of inhaled fluticasone proprionate 50mcg bd and 100mcg bd delivered via the Babyhaler and spacer device in the mangement of asthma symptoms in children aged 12 47 months inclusive. 1997.

GlaxoSmithKline Report Number GM2001/00103/00. Study ID FAS30009. A Multicentre, Randomised, Parallel Group, Open Label Study to Assess the Long Term Safety (Including Growth) of Fluticasone Propionate 100mcg bd via the Metered Dose Inhaler and Babyhaler Spacer Device Compared with Sodium Cromoglycate 5mg qds delivered via Metered Dose Inhaler and Nebuhaler Spacer Device in Children aged 12 47 Months With Documented Evidence of Recurrent/Persistent Asthma like Symptoms over a 52 Week Treatment Period. 2001.

GlaxoSmithKline Report Number GM2001/00151/00. Study ID FAS30007. A multicentre, randomised, double-blind, parallel group, placebo-controlled study to determine the efficacy and safety of fluticasone propionate 200 mcg/day delivered for 12 weeks via the Babyhaler in paediatric subjects aged 12 to 47 months with recurrent/persistent asthma like symptoms. 2002.

Module 2.5 Clinical Overview for Fluticasone propionate. 2013.

Periodic Benefit Risk Evaluation Report(PBRER). 01Mar2015-29Feb2016.

# 12. APPENDICES

## 12.1. Appendix 1 Non-Serious Adverse Events/Adverse Drug Reaction (AE/ADR) Pages

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***NON-SERIOUS ADVERSE EVENTS (AE) (Page 1 of 4)***

***DEFINITION OF A NON-SERIOUS ADVERSE EVENT (AE)***

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Examples of an AE **include:**

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition(s) detected or diagnosed after GSK product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either GSK product or a concomitant medication (overdose per se should not be reported as an AE/SAE).

Examples of an AE **do NOT include** a/an:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

For GSK clinical studies, AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of subject's previous therapeutic regimen). See protocol for clarification.

***IF THIS EVENT MEETS THE DEFINITION OF SERIOUS, COMPLETE THE SERIOUS ADVERSE EVENT SECTION***

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## *NON-SERIOUS ADVERSE EVENTS (AE) (Page 2 of 4)*

### *MONITOR DATA VALIDATION CHECKS*

- Check that either 'Yes' or 'No' box at the top of the page has been completed.
- Start dates must be provided for the reporting of adverse event data. If the exact date is not known, liaise with the investigator to ensure that a best estimate is provided.
- Ensure that **no** medical or investigational procedures are captured on Non-Serious Adverse Events pages.
- Non-serious adverse event terms should be reviewed for potential SAEs per protocol.
- Confirm that any adverse events marked as **Recovering/Resolving** or **Not recovered/Not resolved** have been followed up for details of resolution.
- If the subject was withdrawn from the study due to an adverse event, confirm that the following variables are consistent for the adverse event which resulted in withdrawal:
  - If GSK product was permanently withdrawn due to an adverse event...
    - 'Primary Reason for Withdrawal' on the Study Conclusion page is recorded as 'Adverse Event'
  - If the subject was withdrawn from the study for an adverse event...
    - 'Withdrawal' on the Non-Serious Adverse Events page is recorded as 'Yes'.
    - 'Action Taken with GSK Product(s) as a Result of the Non-Serious AE' on the Non-Serious Adverse Events page is recorded as 'GSK Product Withdrawn'.

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## *NON-SERIOUS ADVERSE EVENTS (AE) (Page 3 of 4)*
### *INVESTIGATOR INSTRUCTIONS*

| | |
|---|---|
| **Diagnosis** | Enter only the diagnosis (if known); otherwise enter sign or symptom. If a diagnosis subsequently becomes available, then this should be entered and the sign or symptom crossed out, initialled and dated by the investigator. If this non-serious event progresses to serious, put a line through the Non-Serious AE record and transcribe the details onto the SAE form. |
| **Start Date**<br>**Start Time** | Record the start date of the first occurrence of the AE.<br>Record the start time of the AE. |
| **Outcome** | All AEs must be followed until the events are resolved, the condition stabilises, the events are otherwise explained, or the subject is lost to follow-up. Indicate if the event was 'Recovered/Resolved' or 'Recovered/Resolved with sequelae'. If the AE is ongoing at the time the subject completes the study or becomes lost to follow-up, the outcome must be recorded as 'Not recovered/Not resolved' or 'Recovering/Resolving'. Also enter 'Not recovered/Not resolved' if the AE was ongoing at the time of death, but was not the cause of death. |
| **End Date**<br>**End Time** | Record the end date. This is the date the AE Recovered/Resolved. If the event Recovered/Resolved with sequelae, enter the date the subject's medical condition resolved or stabilised. Leave blank if the AE is 'Not recovered/Not resolved' or 'Recovering/Resolving'. Record the end time of the AE. |
| **Maximum Intensity** | Record the maximum intensity that occurred over the duration of the event. Amend the intensity if it increases.<br>Mild = An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.<br>Moderate = An event that is sufficiently discomforting to interfere with normal everyday activities.<br>Severe = An event that prevents normal everyday activities.<br>Not applicable = those event(s) where intensity is meaningless or impossible to determine (i.e., blindness and coma). |
| **ActionTaken with GSK Product(s) as a Result of the Non-Serious AE** | Indicate the response to the adverse event, whether it be from the investigator, local physician not in the study, or the subject.<br>GSK product(s) withdrawn = Administration of GSK product(s) was permanently discontinued.<br>Dose reduced = Dose is reduced for one or more GSK product(s).<br>Dose increased = Dose increased for one or more GSK product(s).<br>Dose not changed = GSK product(s) continues even though an adverse event has occurred.<br>Dose interrupted/Delayed = Administration of one or more GSK product(s) was stopped temporarily but then restarted.<br>Not applicable = Subject was not receiving GSK product(s) when the event occurred (e.g., pre-or post-dosing). |
| **Did the subject withdraw from the study as a result of this AE** | Indicate 'Yes' if the event(s) were directly responsible for the subject's withdrawal from the study, otherwise indicate 'No'. |

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## *NON-SERIOUS ADVERSE EVENTS (AE) (Page 4 of 4)*

### *INVESTIGATOR INSTRUCTIONS*

| | |
|---|---|
| **Relationship to GSK Product(s)** | It is a regulatory requirement for investigators to assess relationship to GSK product(s) based on information available. The assessment should be reviewed on receipt of any new information and amended if necessary. 'A reasonable possibility' is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence or arguments that may support 'a reasonable possibility' include, e.g., a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered.<br><br>***Note: If the event is related to the use of a GSK Product the ADR pages must be completed.*** |

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| Protocol Identifier | Subject Identifier | |
|---|---|---|
| | | |

## *NON-SERIOUS ADVERSE EVENTS (AE)*

*Note: If this is a Serious Adverse Event (SAE), do not complete this form, go to the SAE section and complete the SAE form.*
*Note: If this Adverse Event (AE) is related to the GSK Product(s), complete both this AE form AND the Adverse Drug Reaction (ADR) form.*

Did the subject experience any non-serious adverse events during the study? [Y] ☐ Yes [N] ☐ No *If Yes, record details below.*

| Event | Start Date | Start Time | Outcome | End Date | End Time | Maximum Intensity | Action Taken with GSK Product(s) as a Result of the Non-Serious AE | With-drawal | Relation-ship to GSK Product(s) |
|---|---|---|---|---|---|---|---|---|---|
| Diagnosis Only (If known) Otherwise Sign/Symptom | Day Month Year | Hr : Min 00:00-23:59 | 1=Recovered/ Resolved 2=Recovering/ Resolving 3=Not recovered/ Not resolved 4=Recovered/ Resolved with sequelae | Day Month Year | Hr : Min 00:00-23:59 | 1=Mild 2=Moderate 3=Severe X=Not appli-cable | 1=GSK product(s) withdrawn 2=Dose reduced 3=Dose increased 4=Dose not changed 5=Dose interrupted/ Delayed X=Not applicable | Did the subject withdraw from study as a result of this AE? Y=Yes[1] N=No | Is there a reasonable possibility the AE may have been caused by the GSK product(s)? Y=Yes[2] N=No |
| *e.g., Headache* | *25 JAN 12* | *13:25* | *1* | *27 JAN 12* | *10:20* | *1* | *4* | *N* | *N* |
| 1. | | : | | | : | | | | |
| 2. | | : | | | : | | | | |
| 3. | | : | | | : | | | | |
| 4. | | : | | | : | | | | |

[1] *Complete Study Conclusion page and ✓Adverse event as reason for withdrawal.* [2]***The ADR pages should be completed only if this question is answered Yes.***

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## *ADVERSE DRUG REACTION (ADR)*
### *INVESTIGATOR INSTRUCTIONS*

| | |
|---|---|
| **SECTION 3**<br><br>**If GSK Product(s) was Stopped, Did the Reported Event(s) Recur After Further GSK Product(s) Were Administered?** | If deliberate or inadvertent administration of further dose(s) of GSK product(s) to the subject occurred, did the reported adverse event recur? |

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| Protocol Identifier | Subject Identifier | |
|---|---|---|
| | | |

## *ADVERSE DRUG REACTION (ADR)*

**SECTION 1 Event Details**

*Use this section to record adverse drug reactions which are clinically or temporally related. If adverse drug reactions are not clinically or temporally related, use a new ADR form for this subject.*

| Row Number | Event Details *(As reported on the AE Form)* | Start Date Day Month Year |
|---|---|---|
| | | |
| | | |
| | | |
| | | |

**SECTION 2 Demography Data**

***For GSK use only***
*Enter the subject's year of birth.*

Year of birth ____ Year

Imputed date of birth PPD Day Month Year

Sex ☐ Male ☐ Female Weight ____.__ kg Height ____ cm

**SECTION 3 If GSK Product(s) was Stopped, Did the Reported Event(s) Recur After Further GSK Product(s) were Administered?**

☐ Yes ☐ No ☐ Unknown at this time ☐ Not applicable

**SECTION 4 Possible Causes of ADR Other Than GSK Product(s),** ✓*all that apply:*

☐ Disease under study
☐ Lack of efficacy
☐ Withdrawal of GSK product(s)
☐ Transmission of an infectious agent via a medicinal product
☐ Concomitant medication(s) *specify* _____
☐ Medical condition(s) *specify* _____
☐ Other, *specify* _____

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## *ADVERSE DRUG REACTION (ADR)*
### *INVESTIGATOR INSTRUCTIONS*

| | |
|---|---|
| **SECTION 7**<br><br>**Details of GSK Product(s)** | Complete this section using the information in the GSK Product page. Details of all GSK product(s) which may have caused the AE should be included. Provide specific details in Section 9 Adverse Drug Reaction summary if the subject has taken an overdose of GSK product(s), including whether it was accidental or intentional. |

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| Protocol Identifier | Subject Identifier | |
|---|---|---|
| | | |

## *ADVERSE DRUG REACTION (ADR) (Continued)*

**SECTION 5 RELEVANT Medical Conditions**

| *Specify any RELEVANT past or current medical disorders, allergies, surgeries that can help explain the ADR. Ensure each medical condition recorded in this section is also recorded in the appropriate Medical Conditions form* | Date of Onset<br>Day Month Year | Condition Present at Time of the ADR?<br>Y= Yes N=No | *If No, Date of Last Occurrence*<br>Day Month Year |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |

**SECTION 6 Other RELEVANT Risk Factors** *Provide any family history or social history (e.g. smoking, alcohol, diet, drug abuse, occupational hazard) relevant to the ADR).*

**SECTION 7 Details of GSK Product(s)**

| Drug Name<br>*(Trade Name preferred)* | Dose | Unit | Frequency | Route | Start Date<br>Day Month Year | Stop Date<br>Day Month Year | Reason for Medication |
|---|---|---|---|---|---|---|---|
| *e.g., Zantac* | *150* | *mg* | *BID* | *PO* | *25 JAN 12* | *27 JAN 12* | *Gastric ulcer* |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |

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| Protocol Identifier | Subject Identifier | |
|---|---|---|
| | | |

## *ADVERSE DRUG REACTION (ADR) (Continued)*

**SECTION 8 RELEVANT Concomitant Medications** *Include details of any concomitant medication(s) that may help explain the ADR, may have caused the ADR or was used to treat the ADR.*

| Drug Name (Trade Name preferred) | Dose | Unit | Frequency | Route | Start Date Day Month Year | Stop Date Day Month Year | Reason for Medication |
|---|---|---|---|---|---|---|---|
| e.g., Zantac | 150 | mg | BID | PO | 25 JAN 12 | 27 JAN 12 | Gastric ulcer |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |

**SECTION 9 Adverse Drug Reaction Summary/Comments** *Provide a full description of the ADR including details of any tests or procedures carried out to diagnose or confirm the ADR (e.g., laboratory data with units and normal range and any details of the treatment given).*

Investigator's signature _____
*(confirming that the data on the ADR pages are accurate and complete)*

Date ☐☐ ☐☐☐ ☐☐ (Day Month Year)

Investigator's name (print) _____

## 12.2. Appendix 2 Serious Adverse Events Pages

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***SERIOUS ADVERSE EVENTS (SAE) (Page 1 of 6)***
***DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)***

A serious adverse event is any untoward medical occurrence that, at any dose:

a) **results in death.**

b) **is life-threatening.**

*Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.*

c) **requires hospitalisation or prolongation of existing hospitalisation.**

*Note: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is 'serious'.*

When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered 'serious'. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) **results in disability/incapacity, or**

*Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.*

e) **is a congenital anomaly/birth defect.**

f) **other.**

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

g) **possible drug-induced liver injury**

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## *SERIOUS ADVERSE EVENTS (SAE) (Page 2 of 6)*

### *MONITOR DATA VALIDATION CHECKS*

- Check that either 'Yes' or 'no' box at the top of the page has been completed.
- Start dates must be provided for the reporting of serious adverse event data. If the exact date is not known, liaise with the investigator to ensure that a best estimate is provided.
- Ensure that **no** medical or investigational procedures are captured on Serious Adverse Events pages.
- **Death** should not be recorded as an SAE but should be recorded as the outcome of an SAE. The condition that resulted in the death should be recorded as the SAE.
- Confirm that any SAEs marked as **Recovering/Resolving** or **Not recovered/Not resolved** have been followed up for details of resolution.
- If the subject was withdrawn from the study due to an SAE, confirm that the following variables are consistent for the SAE which resulted in withdrawal:
  - If study treatment was permanently withdrawn due to an adverse event ...
    - 'Primary Reason for Withdrawal' on the Study Conclusion page is recorded as 'Adverse Event'
  - If the subject was withdrawn from the study for an adverse event ...
    - 'Withdrawal' on the SAE page is recorded as 'Yes'.
    - 'Most Clinically Significant Action Taken with Study Treatment(s) as a Result of the SAE' on the SAE page is recorded as 'Study Treatment Withdrawn'.

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***THE INVESTIGATOR MUST INFORM GSK OF SERIOUS ADVERSE EVENTS BY FAX OR TELEPHONE (FAX PREFERRED) WITHIN 24 HOURS OF BECOMING AWARE OF THE EVENT. ALL OF THE HEADER INFORMATION MUST BE COMPLETED BEFORE SENDING BACK TO GSK.***
***(The original pages must remain in the Case Report Form/Study File).***

## *SERIOUS ADVERSE EVENTS (SAE) (Page 3 of 6)*
### *INVESTIGATOR INSTRUCTIONS*

| | |
|---|---|
| **Diagnosis** | Record one SAE diagnosis per line, or a sign/symptom if the diagnosis is not available. If a diagnosis subsequently becomes available, this then should be entered and the sign/symptom crossed out, initialled and dated by the investigator. A separate form should be used for each SAE. However, if multiple SAEs which are temporally or clinically related are apparent at the time of initial reporting then these may be reported on the same page. If this was recorded previously as a non-serious event but has progressed to serious, put a line through the Non-Serious AE record and transcribe the details onto the SAE form. |
| **Start Date Start Time** | Record the start date and time of the first occurrence of the event or signs/symptoms of the serious event, not the date and time the event became serious. |
| **Outcome** | All SAEs must be followed until the events are resolved, the condition stabilises, the events are otherwise explained, or the subject is lost to follow-up. Indicate if the event was 'Recovered/Resolved' or 'Recovered/Resolved with sequelae'. If the SAE is ongoing at the time the subject completes the study or becomes lost to follow-up, the outcome must be recorded as 'Not recovered/Not resolved' or 'Recovering/Resolving'. Also enter 'Not recovered/Not resolved' if the SAE was ongoing at the time of death, but was not the cause of death, enter fatal for the SAE which was the direct cause of death. |
| **End Date End Time** | Record the end date. This is the date the SAE Recovered/Resolved, or if the outcome was fatal, record the date the subject died. If the event Recovered/ Resolved with sequelae, enter the date the subject's medical condition resolved or stabilised. Leave blank if the SAE is 'Not recovered/Not resolved' or 'Recovering/Resolving'. Record the end time of the SAE. |
| **Maximum Intensity** | Record the maximum intensity that occurred over the duration of the event. Amend the intensity if it increases.<br>Mild = An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.<br>Moderate = An event that is sufficiently discomforting to interfere with everyday activities.<br>Severe = An event that prevents normal everyday activities.<br>Not applicable = Those event(s) where intensity is meaningless or impossible to determine (i.e., blindness and coma). |
| **Most Clinically Significant Action Taken with Study Treatment(s) as a Result of the SAE** | Indicate the response to the adverse event, whether it be from the investigator, local physician not in the study, or the subject.<br>Study treatment(s) withdrawn = Administration of study treatment(s) was permanently discontinued.<br>Dose reduced = Dose is reduced for one or more study treatment(s).<br>Dose increased = Dose increased for one or more study treatment(s).<br>Dose not changed = Study treatment(s) continues even though an adverse event has occurred.<br>Dose interrupted/Delayed = Administration of one or more study treatment(s) was stopped/interrupted temporarily but then restarted.<br>Not applicable = Subject was not receiving study treatment(s) when the event occurred (e.g., pre-or post-dosing) or the subject died and there was no prior decision to discontinue Study Treatment(s). |

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## *SERIOUS ADVERSE EVENTS (SAE) (Page 4 of 6)*

### *INVESTIGATOR INSTRUCTIONS*

| | |
|---|---|
| **Did the subject withdraw from the study as a result of this SAE** | Indicate 'Yes' if the event(s) were directly responsible for the subject's withdrawal from the study, otherwise indicate 'No'. |
| **Relationship to Study Treatment(s)** | It is a regulatory requirement for investigators to assess relationship to study treatment(s) based on information available. The assessment should be reviewed on receipt of any new information and amended if necessary. 'A reasonable possibility' is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence or arguments that may support 'a reasonable possibility' include, e.g., a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered. |

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| Protocol Identifier | Subject Identifier | Centre Number | Randomisation Number | |
|---|---|---|---|---|
| | | | | |

## *SERIOUS ADVERSE EVENT (SAE)*

Did the subject experience a serious adverse event during the study? [Y] ☐ Yes [N] ☐ No *If Yes, record details below.*

**SECTION 1**

| Event | Start Date | Start Time | Outcome | End date | End Time | Maximum Intensity | Most Clinically Significant Action Taken with Study Treatment(s) as a Result of the SAE | With-drawal | Relationship to Study Treatment(s) |
|---|---|---|---|---|---|---|---|---|---|
| Diagnosis Only (*if known*) Otherwise Sign/Symptom | Day Month Year | Hr : Min 00:00-23:59 | 1=Recovered/ Resolved<br>2=Recovering/ Resolving<br>3=Not recovered/ Not resolved<br>4=Recovered/ Resolved with sequelae<br>5=Fatal | *If fatal, record date of death.* Day Month Year | Hr : Min 00:00-23:59 | 1=Mild<br>2=Moderate<br>3=Severe<br>X=Not applicable | 1=Study Treatment(s) withdrawn<br>2=Dose reduced<br>3=Dose increased<br>4=Dose not changed<br>5=Dose interrupted/ Delayed<br>X=Not applicable | Did the subject withdraw from study as a result of this SAE? Y=Yes† N=No | Is there a reasonable possibility the SAE may have been caused by the study treatment? Y=Yes N=No |
| *e.g., Anaphylaxis* | *25 JAN 10* | *13:25* | *1* | *27 JAN 10* | *10:20* | *1* | *4* | *Y* | *Y* |
| | | : | | | : | | | | |
| | | : | | | : | | | | |

† *Complete Study Conclusion page and ✓Adverse event as reason for withdrawal.*

**SECTION 2 Seriousness** *(specify reason(s) for considering this a SAE, ✓all that apply:*

[A] ☐ Results in death

[B] ☐ Is life-threatening

[C] ☐ Requires hospitalisation or prolongation of existing hospitalisation

[D] ☐ Results in disability/incapacity

[E] ☐ Congenital anomaly/birth defect

[F] ☐ Other, *specify* _____ (*see definition of SAE*)

[G] ☐ Possible drug-induced liver injury (see definition in SAE section of the protocol)

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Page 1

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## *SERIOUS ADVERSE EVENTS (SAE) (Page 5 of 6)*

*INVESTIGATOR INSTRUCTIONS*

| | |
|---|---|
| **SECTION 4**<br><br>**If Study Treatment was Stopped, Did the Reported Event(s) Recur After Further Study Treatment(s) Were Administered?** | If deliberate or inadvertent administration of further dose(s) of study treatment(s) to the subject occurred, did the reported adverse event recur? |

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| Protocol Identifier | Subject Identifier | |
|---|---|---|
| | | |

## *SERIOUS ADVERSE EVENT (SAE) (Continued)*

**SECTION 3**
**Demography Data**

*For GSK use only*
*Enter the subject's year of birth.*

Year of birth ____ Year

Imputed date of birth PPD ____ Day ____ Month ____ Year

Sex ☐ Male ☐ Female Weight ____.__ kg Height ____ cm

**SECTION 4 If Study Treatment(s) was Stopped, Did the Reported Event(s) Recur After Further Study Treatment(s) were Administered?**

☐ Yes ☐ No ☐ Unknown at this time ☐ Not applicable

**SECTION 5 Possible Causes of SAE Other Than Study Treatment(s),** ✓*all that apply:*

☐ Disease under study
☐ Medical condition(s) *specify* _____
☐ Lack of efficacy
☐ Withdrawal of study treatment(s)
☐ Concomitant medication(s) *specify* _____
☐ Activity related to study participation *(e.g., procedures)*
☐ Other, *specify* _____

**SECTION 6 RELEVANT Medical Conditions**

| *Specify any RELEVANT past or current medical disorders, allergies, surgeries that can help explain the SAE. Ensure each medical condition recorded in this section is also recorded in the appropriate Medical Conditions form.* | Date of Onset<br>Day Month Year | Condition Present at Time of the SAE?<br>Y=Yes N=No | *If No, Date of Last Occurrence*<br>Day Month Year |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

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## *SERIOUS ADVERSE EVENTS (SAE) (Page 6 of 6)*

### *INVESTIGATOR INSTRUCTIONS*

| | |
|---|---|
| **SECTION 9**<br><br>**Details of Study Treatment(s)** | Complete this section using the information in the Study Treatment page. Details of all study treatment(s) taken until the time of the SAE should be included. Provide specific details in Section 11 Narrative Remarks if the subject has taken an overdose of study treatment(s), including whether it was accidental or intentional. |

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| Protocol Identifier | Subject Identifier | |
|---|---|---|
| | | |

## *SERIOUS ADVERSE EVENT (SAE) (Continued)*

**SECTION 7 Other RELEVANT Risk Factors** *Provide any family history or social history (e.g., smoking, alcohol, diet, drug abuse, occupational hazard) relevant to the SAE). Ensure each risk factor recorded in this section is also recorded in the appropriate Medical Conditions form.*

**SECTION 8 RELEVANT Concomitant Medications** *Include details of any concomitant medication(s) that may help explain the SAE, may have caused the SAE or was used to treat the SAE. Ensure each concomitant medication recorded in this section is also recorded in the Concomitant Medication form.*

| Drug Name (Trade Name preferred) | Dose | Unit | Frequency | Route | Taken Prior to Study? Y=Yes N=No | Start Date Day Month Year | Stop Date Day Month Year | Ongoing Medication? Y=Yes N=No | Reason for Medication |
|---|---|---|---|---|---|---|---|---|---|
| *e.g., Zantac* | *150* | *mg* | *BID* | *PO* | *N* | *25 JAN 10* | *27 JAN 10* | *N* | *Gastric ulcer* |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |

**SECTION 9 Details of Study Treatment(s)**

Was treatment blind broken at investigational site? ☐ Yes ☐ No ☐ Not applicable

GlaxoSmithKline CONFIDENTIAL

| Protocol Identifier | Subject Identifier | |
|---|---|---|
| | | |

## *SERIOUS ADVERSE EVENT (SAE) (Continued)*

**SECTION 10 Details of RELEVANT Assessments** *Provide details of any tests or procedures carried out to diagnose or confirm the SAE (e.g., laboratory data with units and normal range) if data for this SAE have not been previously entered, and the CRF includes a page for the test, ensure the data is also entered on the page.*

**SECTION 11 Narrative Remarks** *(provide a brief narrative description of the SAE and details of treatment given)*

Investigator's signature _____
*(confirming that the data on the SAE pages are accurate and complete)*

Date ☐☐ ☐☐☐ ☐☐ Day Month Year

Investigator's name (print) _____