TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol

Title:	The effectiveness of Asthma Control Test guided treatment compared with usual care in China adult asthma patients

Compound Number: None

Development Phase IV

Effective Date: 27-JUN-2016

Author(s): PPD

SPONSOR SIGNATORY

PPD

27/06/2016

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Country Medica China and Hong Kong

Date

PPD

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial submission.

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 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 Address:		
Investigator Phone Number:		
Investigator Signature		Date

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Rationale

Current levels of asthma control in China fall short of the goals specified in international guidelines for asthma management (GINA). A nationwide multi-centre epidemiologic survey performed by China Asthma Alliance also showed that only 28.7% of the patients with asthma in China achieved complete asthma control. There is a large gap between what can be achieved with modern asthma management and what is currently being achieved. One of the main reasons for this is a lack of recognition of asthma control and the requirement for more effective treatment. Physicians can select appropriate treatment regimen only after they identify those patients with uncontrolled asthma. Simple methods aiming to improve the assessment of asthma control have been developed. The Asthma Control Test (ACT) is a validated, short, easy to use, and self-administered instrument used to assess asthma control. However, physicians do not use it, even though it was designed to assess the level of asthma control in patients and so guide physicians treatment decisions. This study is aimed at evaluating the effectiveness of ACT guided treatment compared with usual care in asthma patients in China. It is designed to assist Chinese patients and physicians improving adherence to the guidelines through the inclusion of the ACT in the patient's asthma management plan.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• **To compare the effectiveness of ACT guided treatment versus usual care in achieving asthma control**	• the percentage of subjects who have an ACT score ≥20 or an improvement of more than 3 points in ACT during the 24-week treatment period
Secondary	

• **To compare the effectiveness of ACT guided treatment versus usual care in asthma subjects with respect to the following parameters:**
  • **Symptoms**
  • **Forced Expiratory Volume in one second (FEV1)**
  • **Peak Expiratory Flow(PEF)**
  • **The quality of life**
  • **Time to asthma control**
	• Mean daytime symptom score over the 24-week treatment period
	• Mean night-time symptom score over the 24-week treatment period
	• Mean change from baseline to the end of study in FEV1
	• Mean morning(AM) PEF over the 24-week treatment period
	• Mean evening(PM) PEF over the 24-week treatment period
	• Mean change from baseline to the end of study in Standardised Asthma Quality of Life Questionnaire (AQLQ[S]) score
	• Time to first ACT score ≥20 or improvement of more than 3 points in ACT over the 24-week treatment period

Others	
• **To compare the effectiveness of ACT guided treatment versus usual care in asthma exacerbation**	• Rate of moderate/severe asthma exacerbation over the 24-week treatment period

Overall Design

This is a prospective, multicentre, cluster-randomised, open-label study.

Treatment Arms and Duration

The study is planned to be a 24-week study.

Baseline (week 0, visit 0): ACT, AQLQ(S) and lung function test will be completed as the baseline measurement in sequence.

Treatment period (week 0-week 24): a 24 week treatment period. Subsequent scheduled visits occur as follows: Week 4 (Visit 1), Week 8 (Visit 2), Week 12 (Visit 3), Week 16 (Visit 4), Week 20 (Visit 5) and Week 24 (Visit 6).

In this cluster-randomization design, each study centre, considered as a cluster, will be randomized to either ACT guided treatment group or control group (usual care group). The randomization will be stratified according to the hospital level (Tier 3 vs. Tier 2). The hospital level is determined in accordance with the uniform requirements of the government. A Tier 3 hospital is on a larger scale and provides superior medical care than a Tier 2 hospital.

For the subjects who are recruited in the ACT centres, they will be treated based on the ACT score. For subjects who are recruited in the control centres, they will be treated based on doctor's subjective judgment.

ACT score	**Treatment adjustment**
ACT=25, ≥3 months	Step-down treatment
ACT≥20, <25 or ACT=25, <3 months	No change
ACT≤19	Step-up treatment

Type and Number of Subjects

A total of 528 subjects are required in a total of 12 centres (6 centres per group) and around 44 asthma subjects per centre.

Analysis

The null hypothesis for this study is that there is no difference between ACT guided treatment and usual care in the percentage of subjects who have an ACT score ≥20 or an improvement of more than 3 points in ACT during the 24-week treatment period for the intention-to-treat (ITT) population.

The alternative hypothesis for this study is that there is a difference between ACT guided treatment and usual care in the percentage of subjects who have an ACT score ≥20 or an improvement of more than 3 points in ACT during the 24-week treatment period for the ITT population.

The primary endpoints will be analyzed using logistic regression. The statistical model on which the inference will be based will include terms for treatment, centre, type of baseline controller (inhaled corticosteroids [ICS] alone vs. ICS/long-acting β2 agonist [LABA]), gender and age. Centre, as the unit of randomization, will be treated as a random effect. The results of the primary analyses will be presented as point estimates, 95% confidence intervals and associated p-values for the adjusted mean differences between ACT guided treatment and usual care.

2. INTRODUCTION

2.1. Study Rationale

Current levels of asthma control in China fall short of the goals specified in international guidelines for asthma management (GINA). A nationwide multi-centre epidemiologic survey performed by China Asthma Alliance also showed that only 28.7% of the patients with asthma in China achieved complete asthma control [Nan, 2013]. There is a major gap between what can be achieved with modern asthma management and what is currently being achieved. One of the main reasons for this is a lack of recognition of asthma control and the requirement for more effective treatment. Physicians can select appropriate treatment regimen only after they identify those patients with uncontrolled asthma. Simple methods aiming to improve the assessment of asthma control have been developed. The asthma control test (ACT) is a validated, short, easy to use, and self-administered instrument used to assess asthma control [Nathan, 2004]. However, physicians do not use it, even though it was designed to assess the level of asthma control in patients and so guide physicians treatment decisions. This study is aimed to evaluate the effectiveness of ACT guided treatment compared with usual care in asthma patients in China. It is designed to assist Chinese patients and physicians improving adherence to the guidelines through the inclusion of the ACT in the patient's asthma management plan.

2.2. Brief Background

GINA has adopted a five-step approach to control asthma, where each step represents a different treatment option with increasing efficacy [GINA, 2013]. The five-step approach provides treatment options to achieve and maintain control, with the least amount of medication. Asthma control assessment is very important to assess what is the appropriate treatment for the patient. In a questionnaire survey in Canada, primary care physicians were given questionnaires to guide them through control assessments. They were also asked to indicate whether or not they considered the patient's asthma to be under control. It was found that physicians significantly overestimated control among their patients and were discordant with guideline classification of control as 31% of the patients were assessed as uncontrolled patients, 13% were well-controlled and 2% were totally controlled [Chapman, 2008]. In China, poor physician:patient dialogue has made the situation worse. During busy clinical practice, physicians often make management

decisions based on their subjective perceived level of asthma control. This potentially leads to under-treatment and consequently sub-optimal asthma control.

3. OBJECTIVE(S) AND ENDPOINT(S)

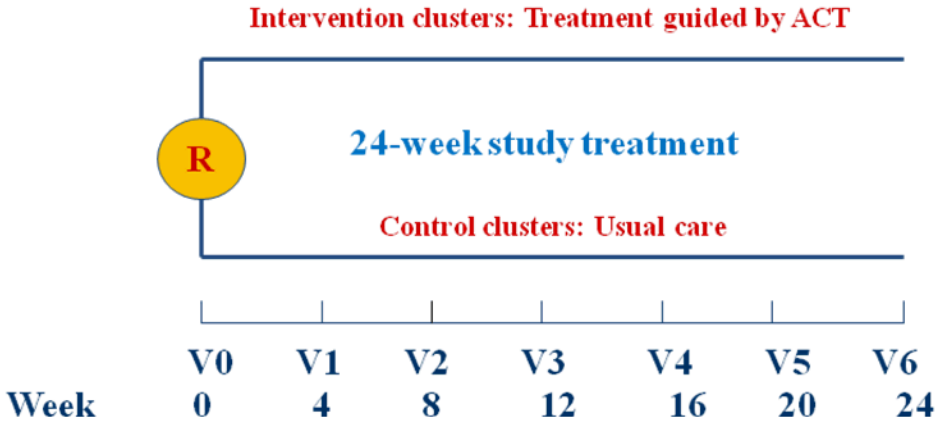
Objectives	Endpoints
Primary	
• **To compare the effectiveness of ACT guided treatment versus usual care in achieving asthma control**	• the percentage of subjects who have an ACT score ≥20 or an improvement of more than 3 points in ACT during the 24-week treatment period
Secondary	

• **To compare the effectiveness of ACT guided treatment versus usual care in asthma subjects with respect to the following parameters:**
  • **Symptoms**
  • **Forced Expiratory Volume in one second (FEV1)**
  • **Peak Expiratory Flow(PEF)**
  • **The quality of life**
  • **Time to asthma control**
	• Mean daytime symptom score over the 24-week treatment period
	• Mean night-time symptom score over the 24-week treatment period
	• Mean change from baseline to the end of study in FEV1
	• Mean morning (AM) PEF over the 24-week treatment period
	• Mean evening (PM) PEF over the 24-week treatment period
	• Mean change from baseline to the end of study in Standardised Asthma Quality of Life Questionnaire (AQLQ(S)) score
	• Time to first ACT score ≥20 or improvement of more than 3 points in ACT over the 24-week treatment period

Others	
• **To compare the effectiveness of ACT guided treatment versus usual care in asthma exacerbation**	• Rate of moderate/severe asthma exacerbation over the 24-week treatment period

4. STUDY DESIGN

4.1. Overall Design



This is a prospective, multicentre, cluster-randomized, open-label study.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

4.2. Treatment Arms and Duration

- The study is planned to be a 24-week study.

- Baseline (week 0, visit 0): Subjects eligible for inclusion criteria will sign informed consent form at Visit 0. At this visit, investigators should collect baseline data, including demographic data (gender, age, height, weight, education level and smoking history), history of asthma (disease duration, disease severity and exacerbation history), and past and concurrent medical conditions and medication (both asthma and non-asthma). ACT, AQLQ(S) and lung function test will be completed as the baseline measurement in sequence.

- Treatment period (week 0-week 24): a 24 week treatment period. Subsequent scheduled visits occur as follows: Week 4 (Visit 1), Week 8 (Visit 2), Week 12 (Visit 3), Week 16 (Visit 4), Week 20 (Visit 5) and Week 24 (Visit 6).

- In this cluster-randomization design, each study centre, considered as a cluster, will be randomized to either ACT guided treatment group or control group (usual care group). The randomization will be stratified according to the hospital level (Tier 3 vs. Tier 2). The hospital level is determined in accordance with the uniform requirements of the government. And a Tier 3 hospital is on a larger scale and provides superior medical care than a Tier 2 hospital.

- For the subjects who are recruited in the ACT centres, they will be treated based on the ACT score. For subjects who are recruited in the control centres, they will be treated based on doctor's subjective judgment.

Table 1 ACT-guided treatment

ACT score	Treatment adjustment
ACT=25, ≥3 months	Step-down treatment
ACT≥20, <25 or ACT=25, <3 months	No change

ACT score	Treatment adjustment
ACT≤19	Step-up treatment

- During the treatment period, subjects should fill in the paper diary record card (DRC) every morning and evening, record their morning and evening PEF, symptom and medication. At each visit, subjects should complete the ACT at clinic. For the ACT guided group, the ACT must be completed prior to any other assessments are conducted. For the control group, subjects should complete the ACT after investigator making the treatment decision. This will ensure the investigators make treatment decision based on his/her clinical judgement, not based on ACT. For the control group, all subsequent assessments should be conducted in the same order as the ACT guided group. Investigators will be responsible for checking the subjects' DRC, including symptom score and evaluating therapeutic compliance.

4.3. Type and Number of Subjects

A total of 528 subjects are required including a total of 12 centres (6 centres per group) and around 44 asthma subjects per centre.

4.4. Design Justification

- We design our study to address the effectiveness of the intervention if implemented in a system without other enhanced healthcare options; we therefore use a usual care control group.

- Randomization by individual subjects may result the contamination due to the same investigator looking after both intervention and control group. Randomization by clusters (i.e., study centre) will reduce such bias.

4.5. Benefit:Risk Assessment

The following section outlines the risk assessment and mitigation strategy for this protocol:

4.5.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Patients' inappropriate understanding on ACT questionnaire	ACT is consisted of five questions, which each have a five-point rating scale and relate to the past month. It is not an objective tool.	Once a subject is enrolled into the study, the investigator is responsible for training the subject to understand and use the ACT.

4.5.2. Benefit Assessment

Usage of the ACT is beneficial for patients. The ACT as an easy and patient-friendly tool for asthma control assessment has been fully validated and used in interventional studies and routine clinical practice in many countries. The ACT empowers patients to take charge of their condition and work in partnership with their physicians, which could facilitate the achievement of guideline-defined asthma control.

4.5.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with inappropriate understanding on ACT questionnaire are justified by the anticipated benefits that may be afforded to subjects with asthma.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

Inclusion criteria for study centre (clusters):

A study centre (cluster) will be eligible for inclusion in this study only if all of the following criteria apply:

1. General practice;

2. Located in Shanghai;

3. Providing asthma care.

Inclusion criteria for subjects at Visit 0:

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

4. Age:18 to 70 years inclusive;

5. Gender: Male or Female;

6. Documented clinical history of asthma for at least 6 months prior to Visit 0;

7. At Visit 0, a demonstrable reversible increase in FEV1 of at least 12% (and ≥200 mL), 15 minutes after inhaling a short-acting bronchodilator or; at any time in the last 2 years documentary evidence of a reversible increase in FEV1 of at least 12% (and ≥200 mL) 15 mins after inhaling a short-acting bronchodilator; or demonstrable reversible increase in morning PEF of at least 15% (and ≥200 mL) either spontaneously or after inhalation of a short-acting bronchodilator;

8. History of using inhaled corticosteroids (ICS) alone or combined with an inhaled long-acting β2 agonist (LABA) treatment within 1 year prior to Visit 0;

9. Subjects must have an ACT score <20 at Visit 0;

10. Subject must have been able to read, comprehend, and record information in Chinese;

11. A signed and dated written informed consent must be obtained from the subject prior to study participation.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. History of Life-threatening asthma: Defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnea, respiratory arrest or hypoxic seizures within the last 6 months before Visit 0.

2. Subjects having severe and unstable asthma, with ACT score <12 at Visit 0, history of repeated severe exacerbations (3/year) and/or a severe exacerbation in the previous 6 weeks before Visit 0.

3. A current evidence of clinically significant uncontrolled medical condition or disease (e.g., psychological disorders, mental deficiency, severe hepatic and renal dysfunction, malignancy);

4. Current smoker or ex-smoker with a more than 10 pack-year history of smoking;

5. Current clinically significant respiratory diseases other than asthma, (e.g lung cancer, lung fibrosis, sarcoidosis, tuberculosis, chronic obstructive pulmonary disease [COPD]);

6. History of alcohol or medication abuse;

7. History of upper or lower respiratory tract infection within 4 weeks prior to Visit 0;

8. Enrolled in an asthma clinic or outpatient service in the past 12 months that provides comprehensive asthma management;

9. Subjects with a history of adverse reaction including immediate or delayed hypersensitivity to any intranasal, inhaled, or systemic corticosteroid and LABA therapy and to components of the inhalation powder (e.g., lactose) at Visit 0. In addition, subjects with a history of severe milk protein allergy that, in the opinion of the Investigator, contraindicates the subject's participation will also be excluded.

10. Females who are currently pregnant and lactating;

11. Subjects who have received any of the following medications in the 6 weeks preceding visit 0: oral/parenteral corticosteroids, oral β2-agonists or slow-release

bronchodilators, sodium cromoglycate or nedocromil sodium, ketotifen, anticholinergics, and anti-IgE treatment;

12. Subjects who comply poorly with asthma treatment in the opinion of the investigator/inability or unwillingness to take asthma medication (non-compliance), follow directions or unable to complete a written paper daily record card and self-rating questionnaires;

13. Concurrently participating in another clinical study in which the subject is or will be exposed to an investigational or a non-investigational medication or device, or has participated in a clinical trial and has received an investigational product within 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

14. Subjects with contraindications to any asthma medications they will be taking during the study period, or whom should be excluded on account of the special warnings and precautions within the label of the asthma medication they are to be treated with during the study period.

15. Affiliation with Investigator Site: Is an investigator, sub-investigator, study coordinator, employee of a participating investigator or study site, or immediate family member of the afore mentioned that is involved in this study.

16. Subjects who plan to move away from the geographical area where the study is being conducted during the study.

5.3. Withdrawal/Stopping Criteria

The primary reason for the subject discontinuing from the study will be recorded in the Case Record Form. The investigator must determine the primary reason for discontinuation. The end of study/early discontinuation procedures must be performed at the time of discontinuation from the clinical study.

The subject **must** be discontinued from the study for any of the following reasons:

1. A subject is significantly non-compliant with treatment or the requirements of the protocol;

2. Lost to follow up;

3. Subject's decision not to participate any further (withdrawal of consent);

4. In the investigator's opinion, it is in the subject's best interest;

5. Subjects experience a protocol-defined asthma exacerbation;

6. The study is terminated by the Sponsor or designee;

7. Pregnancy (Subject should notify investigator immediately on becoming pregnant).

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons.

The reason(s) for subjects not completing the study will be recorded in the Case Report Form (CRF), and that the investigator must document, if applicable, the reason (if specified by the subject) for withdrawal of consent. The end of study/early discontinuation procedures must be performed at the time of discontinuation from the clinical study.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study based on previous non-compliance.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last

known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

5.4. Subject and Study Completion

A completed subject is one who has completed all visits of the study.

The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Treatment Assignment

The study is a trial with the study centre as the unit of randomization. Computer generated randomization schedule for centres will be provided by GlaxoSmithKline (GSK) or its designee. Once a randomization number has been assigned, it is not re-assigned. Each centre will be randomized to either ACT guided treatment group or control group (usual care group). The randomization will be stratified according to the Tier of the hospitals (Tier 3 vs. Tier 2). Assignment to a treatment will not occur, as no treatment intervention is provided for this study. Each centre will be asked to recruit 44 consecutive patients with asthma attending the practice. For the subjects who are recruited in the ACT centres, they will be treated based on the ACT score. For subjects who are recruited in the control centres, they will be treated based on doctor's subjective judgment.

The subject number will be documented in the subject's clinic notes and in the CRF.

6.2. Blinding

This will be an open-label study.

6.3. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

7. STUDY ASSESSMENTS AND PROCEDURES

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1.

7.1. Time and Events Table

ACTIVITY	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 (or Early Withdrawal)
Study Week (Visit Window）	0	4w±1	8w±1	12w±1	16w±1	20w±1	24w±1
Informed consent	x						
Randomization/Allocation of clusters	x						
Subject Demography	x						
Medical history	x						
Verification of inclusion/exclusion criteria	x						
Efficacy Evaluation							
Verification of withdrawal criteria		x	x	x	x	x	x
Issue diary record cards	x	x	x	x	x	x	
Collect/Review diary record cards		x	x	x	x	x	x
Compliance assessment		x	x	x	x	x	x
Asthma control Test (ACT) score	x	x	x	x	x	x	x
AQLQ(S)	x						x
Lung function Test	x						x
Safety Evaluation							
Adverse event assessment[1]	x	x	x	x	x	x	x

1. Serious AEs will be recorded from the time the consent form is signed until the follow-up visit. All AEs will be recorded from the start of study treatment until the follow-up visit.

7.2. Screening and Critical Baseline Assessments

Baseline Assessments	
Demographic information	Gender ethnic origin date of birth, height weight education level smoking history
History of asthma including duration of asthma	
History of asthma exacerbations in the 12 months prior to Visit 0	
Concurrent medical conditions and concurrent medication	
Medical history	Use of corticosteroids for asthma in the 12 months prior to Visit 0 duration of inhaled corticosteroid treatment

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

7.3. Efficacy

7.3.1. Primary Endpoint (s)

- The primary endpoint for the study is the percentage of subjects who have an ACT score ≥20 or an improvement of more than 3 points in ACT during the 24-week treatment period.

Asthma control test (ACT)

ACT is a self-administered questionnaire comprising five questions [Nathan, 2004]. Each of the five items in the ACT is assessed on a five point scale and the scores are summed

to give a total score ranging from 5 to 25, with a score of ≥20 denoting 'well-controlled asthma', a score of 16-19 denoting 'not well-controlled asthma', and a score of ≤ 15 denoting 'very poorly controlled asthma'. The recall period of the questionnaire is four weeks. ACT must be completed by the subject at each visit. For the control group, subjects should complete the ACT after investigator making the treatment decision. Differences of 3 points in mean ACT scores between 2 groups or over time in an individual patient are clinically significant [Schatz, 2009]. An improvement of more than 3 points in ACT from baseline will also serve as primary endpoint.

The questionnaire will be attached separately.

7.3.2. Secondary Endpoint (s)

- Mean daytime symptom score over the 24-week treatment period
- Mean night-time symptom score over the 24-week treatment period
- Mean change from baseline to the end of study in FEV_1
- Mean morning(AM) PEF over the 24-week treatment period
- Mean evening(PM) PEF over the 24-week treatment period
- Mean change from baseline to the end of study in AQLQ(S) score
- Time to first ACT score ≥20 or improvement of more than 3 points in ACT over the 24-week treatment period

Asthma symptom score

Subjects will be instructed to record daytime and night-time asthma symptom scores prior to taking the morning or evening dose of study medication or rescue medication. Any asthma-related symptoms, such as wheeze, shortness of breath, cough or chest tightness experienced during the previous 12 hours will be rated as follows. The following will be recorded on DRC.

Daytime symptom score

0 = No symptoms during the day

1 = Symptoms for one short period during the day

2 = Symptoms for two or more short periods during the day

3 = Symptoms for most of the day which did not affect my daily activities

4 = Symptoms for most of the day which did affect my normal daily activities

5 = Symptoms so severe that I could not go to work or perform normal daily activities

Night-time symptom score

- 0 = No symptoms during the night
- 1 = Symptoms causing me to wake once or wake early
- 2 = Symptoms causing me to wake twice or more (including waking early)
- 3 = Symptoms causing me to be awake for most of the night
- 4 = Symptoms so severe that I did not sleep at all

FEV_1

FEV_1 will be measured at visit 0 and 6. Subjects should refrain from using short-acting bronchodilators for at least 6 hours prior to performing FEV_1 measurements. The highest of three technically acceptable measurements of FEV_1 will be taken.

Peak Expiratory Flow (PEF)

At Visit 0, the subject will be given a Mini-Wright Peak Flow Meter and taught how to measure and record their PEF. At each visit, the subjects' ability to measure their PEF will be checked and, if the investigator has any concerns, the subject will be retrained. The instructions for use will be provided with each Peak Flow Meter. PEF should be measured while subject is in the sitting position.

Subjects should record on diary card the best of three PEF measurements, using a mini-Wright peak flow meter in the morning (7:00-10:00 AM) and evening (6:00-9:00 PM) before taking any asthma drug. Bronchodilator therapy (e.g. salbutamol) is withheld, where possible, for 4 hours before recording PEF. Otherwise, the use of salbutamol will be recorded on diary card.

GSK will provide each centre with a supply of standard mini-Wright peak flow meters.

Standardised Asthma Quality of Life Questionnaire (AQLQ(S))

The Asthma Quality of Life Questionnaire (AQLQ) is a self-administered questionnaire consisting of 32 questions to measure the functional problem that are most troublesome to patients with asthma [Juniper, 1992]. There are 32 questions in 4 domains (symptoms, activity limitation, emotional function and environmental stimuli). Patients are asked to think about how they have been during the previous two weeks and to respond to each of the 32 questions on a 7-point scale (7 = not impaired at all - 1 = severely impaired). A change in score of greater than 0.5 can be considered clinically important [Juniper, 1994]. In the present study, the AQLQ(S) will be used with 5 standardised activities to replace the patient-specific ones in the AQLQ. These five generic activities incorporate the activities that were most frequently chosen by patients in studies in which the original AQLQ was used; Strenuous activities, Moderate activities, Social activities, Work-related activities, and Sleeping [Juniper, 1999]. At visit 0 and 6, the investigator will provide each subject with the AQLQ(S).

The questionnaire will be attached separately.

ACT, AQLQ(S) and lung function test should be completed in sequence at Visit 0 and 6.

7.3.3. Other Endpoint (s)

- Rate of moderate/severe asthma exacerbation over the 24-week treatment period

Asthma Exacerbations

Subjects who experience worsening of symptoms should:

- increase relief medication usage for relief of symptoms
- contact the investigator or primary physician immediately and report to the clinic as soon as possible (ideally within 24 hours)
- record their symptoms, PEF and relief medication usage in their DRC, as previously instructed

- if intervention therapy is required during a treatment period, subjects may receive oral corticosteroids (40-60 mg prednisolone daily, or equivalent, for 10 days), over and above their usual asthma medication.

Exacerbations will be assessed by the physician at each scheduled visit by reviewing the DRC, as well as specific questioning on adverse events (AEs).

Exacerbations will be defined based on one or more of the following characteristics:

Definition of asthma exacerbation(s)

Moderate

A moderate asthma exacerbation is defined as a deterioration in asthma requiring treatment with an oral corticosteroid.

Individual courses of oral corticosteroids are classified as separate exacerbations only if they are administered >1 week apart. Any course started within one week of finishing the previous course is considered part of the previous exacerbation.

Severe

A severe asthma exacerbation is defined as a deterioration in asthma which requires hospital admission.

Time/date of resolution

Time/date at which the exacerbation has resolved, in the opinion of the investigator and/or subject.

Details of exacerbations must be collected in the Asthma Exacerbations page of the CRF and DRC as follows at the Visit immediately following the exacerbation:

Date of onset and resolution, daily morning PEF during the exacerbation; details of management of the exacerbation (e.g. clinic or emergency room visit, self-managed, hospital admission etc.); restriction/prevention from continuing usual activities. An exacerbation resulting in hospitalization will be recorded as a serious adverse event (SAE) in the Serious Adverse Event pages of the CRF. However, it is not only these exacerbations resulting in hospitalization which require collection as SAEs, but those that meet any of the definitions of Seriousness, listed in Section 7.4.

7.3.4. Guidance for Questionnaires Administration

All questionnaires in the study are self-administered. It is recommended that a subject completes all questionnaires before the physical examination and lung function. For the ACT guided group, the ACT should be completed first followed by the AQLQ (at visits during which the AQLQ is measured) and the treatment decision. The remaining assessments should be conducted after the AQLQ has been completed. This order should be used throughout the study. For the control group, the ACT must be completed after the treatment decision has been made, but the remaining assessments should be conducted in the same order as for the ACT guided group.

It is important that in the ACT guided group, the patients are blinded to the treatment decision to prevent any potential bias when the patients complete the AQLQ.

The following guidance is applicable to all questionnaires for the present study.

Subjects should be requested to perform the questionnaire as completely and accurately as possible. Regardless of when the questionnaire is completed, the subject should be given adequate time to complete all questions. No stated or implied time limit for completing the questionnaires should be given. The subject should be given a quiet area in which to complete the questionnaire.

If a subject has difficulty in completing the questionnaire, a third party (an investigator or study personnel) can help the subject to understand and answer the questions. If the subject should request help or clarification of any question in the questionnaire, the investigator or the study personnel is to instruct the subject to reread the instructions and to give the best answer possible to each question. The investigator or study personnel will not provide the subject with any possible answer to any question.

A subject may use a black or blue pen to complete the questionnaire. If the subject wishes to change a response, the original response should be crossed out with a single line, and then dated and initiated by the subject, as applicable and the alternative response should be marked. Once the subject returns the questionnaire to the investigator or the study personnel, no changes will be allowed except for incomplete items.

After a subject has completed the questionnaire, the investigator may review the questionnaire for completeness. If any portion of the questionnaire is not complete, the subject should be given the opportunity to complete any missing items prior to the physician evaluation. The investigator or the study personnel is under no obligation to review or to validate the accuracy of the completed questionnaire.

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1).

7.4.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 2.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.4.1.1. 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.
- Serious AEs will be recorded from the time the consent form is signed until the follow-up contact. All AEs will be recorded from the start of study treatment until the follow-up contact.
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 2.

- Once the investigator determines that an AE is identified as explicitly attributed to any GSK product (including products not covered in the specific study objective), the adverse drug reactions (ADR) page should be completed and reported to GSK China within 5 calendar days. Any follow-up information on a previously reported ADR will also be reported to GSK China within 5 calendar days.
- 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.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 2.

7.4.1.2. 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?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.4.1.3. 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 SAE will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.3).

7.4.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 2 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV medical dictionary for regulatory activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

7.4.1.5. Regulatory Reporting Requirements for SAEs and ADRs

Prompt notification by the investigator to GSK of SAEs and non-serious AEs related to the use of any GSK products (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.4.2. Pregnancy

- Any pregnancy exposure to GSK products that is notified during study participation must be reported using a pregnancy notification form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.
- In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to GSK as described above.

7.4.3. Physical Exams

- A brief physical examination will include, at a minimum assessments of the lungs, cardiovascular system, and nose.

7.4.4. Vital Signs

- Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate.

8. DATA MANAGEMENT

- For this study subject data will be collected using GSK defined CRFs and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events will be coded using MedDRA and concomitant medications terms will be coded using the World Health Organisation (WHO) Drug system.

- 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.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The null hypothesis for this study is that there is no difference between ACT guided treatment and usual care in the percentage of subjects who have an ACT score ≥20 or an improvement of more than 3 points in ACT during the 24-week treatment period for the intention-to-treat (ITT) population.

The alternative hypothesis for this study is that there is a difference between ACT guided treatment and usual care in the percentage of subjects who have an ACT score ≥20 or an improvement of more than 3 points in ACT during the 24-week treatment period for the ITT population.

The study is designed to show superiority of ACT guided treatment over usual care.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The study will be powered to demonstrate superiority of ACT guided treatment over usual care from baseline over Week 24 in the primary endpoints.

We assume an intra-cluster correlation coefficient (ICC) of ρ=0.01, 29% well-control rate for usual care group, and 44% for ACT guided treatment group. It is required to have 6 centres for each treatment group and a minimum of 35 subjects for each centre (a total of 420 evaluable subjects) to achieve a power of 80% with two-sided α=0.05. We anticipate a dropout rate of 20% and therefore planned to recruit 44 subjects in each centre (a total of 528 randomized subjects). These sample size calculations are produced based on Donner [Donner, 1981].

An ACT score ≥20 indicates controlled asthma. The assumed rate of subjects with an ACT score ≥20 for usual care group is based on a nationwide epidemiologic survey in

China [Nan, 2013], which reported a 29% asthma control rate. The rate for ACT guided treatment is assumed based on GOAL study [Bateman, 2004], which reported a 80% rate for salmeterol/fluticasone group. An additional adjustment has been made to reduce it to 44% to account for real life practice. A 15% difference between ACT guided treatment group and usual care group is considered clinically meaningful.

Study centres will be randomly assigned to the 2 groups using a computer generated randomization list. The randomization will be stratified according to the Tier of the hospitals (Tier 3 vs. Tier 2).

9.2.2. Sample Size Sensitivity

The robustness and sensitivity of the sample size calculation has been considered in order to assess the impact on the power of the study should the observed well-control rates for the primary endpoints be higher or lower than expected. Table 2 displays the estimated sample size and power for a variety of rates with other assumptions unchanged.

Table 2 Sample Size and Power Calculation by Efficacy Rates

Well-control rate ACT guided treatment	Well-control rate usual care	Total sample size to achieve 80% power	Power if 528 subjects are enrolled
40%	27%	680	69%
40%	29%	970	54%
40%	31%	1474	39%
44%	27%	404	89%
44%	29%	528	80%
44%	31%	718	67%
48%	27%	268	98%
48%	29%	332	94%
48%	31%	422	88%

9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation is currently planned for this study. However, if during the course of the study, new information becomes available about clinically meaningful differences for the primary endpoints, a sample size re-estimation may be conducted. Full details of the procedure used would be specified in the reporting and analysis plan (RAP) and any subsequent change to the target sample size would be documented in a protocol amendment.

9.3. Data Analysis Considerations

All statistical analyses will be conducted by GSK or its designee.

In general, descriptive statistics including the number of observations, mean, standard deviation (SD), median, minimum and maximum will be provided for continuous data, frequency counts and percentages will be used in tabulation for categorical variables. Unless specified otherwise, the percentage calculation will not take the missing values into account.

If not specified otherwise, all data will be summarized/listed as observed. Missing values will not be imputed.

All tests will be two-tailed, the general two-sided significance level will be $\alpha = 0.05$.

A complete description of data handling rules and planned statistical analyses are provided in a separate RAP. The RAP will be finalized before the database lock.

9.3.1. Analysis Populations

Three populations are defined for this study.

- Intent-to-Treat (ITT) Population: all subjects who signed informed consent form, were randomised and who had at least one post-baseline assessment. The ITT population will be the primary population of interest.
- Per Protocol (PP) Population: all subjects in the ITT population with no major protocol deviations and with ≥80% treatment compliance and diary compliance. The PP population will not be analyzed if this population comprises more than 95% or

less than 50% of the ITT population. Only the primary efficacy variables will be analyzed using the PP population.

- Safety Population: all subjects who are enrolled into the study and who have at least one DRC assessment.

9.3.2. Consideration on Missing Data Handling

Missing values will not be considered when calculating the ACT score for primary endpoint, symptom score and/or PEF over 24-week treatment period. If not specified otherwise, missing values will not be imputed.

9.3.3. Interim Analysis

There are no interim analyses planned for this study.

9.4. Key Elements of Analysis Plan

All hypothesis tests and confidence intervals will be two-sided. Except where otherwise stated, the estimation of treatment effect will be adjusted for the effects of centre, type of baseline controller (ICS alone vs. ICS/LABA), gender, and age. Centre, as the unit of randomization, will be treated as a random effect.

All efficacy measures over the course of the study will be presented and summarised in graphs and tables. Continuous data will be summarised by means, standard deviations, medians, minimum and maximum; categorical data will be summarised by counts and percentages.

All outcomes will be pertained to the individual participant's level and the analysis model will be adjusted for the effect of centre (cluster).

9.4.1. Primary Analyses

The primary endpoints will be analyzed using logistic regression. The statistical model on which the inference will be based will include terms for treatment, centre, type of baseline controller (ICS alone vs. ICS/LABA), gender and age. Centre, as the unit of randomization, will be treated as a random effect. The results of the primary analyses will be presented as point estimates, 95% confidence intervals and associated p-values for the adjusted mean differences between ACT guided treatment and usual care.

Analyses of the primary endpoints will be performed on the ITT population and the PP population; the ITT population is considered primary.

9.4.2. Secondary Analyses

All secondary endpoints will be confined to the ITT population.

Continuous efficacy endpoints will be analyzed using analysis of covariance (ANCOVA) and adjusted for centre as a random effect. For daytime and night-time symptom score, the same method (ANCOVA adjusted by centre) will be used if the parametric model assumptions hold. The assumptions of normality and homogeneity of variance will be assessed by inspection of normal probability plots and residual plots. If these assumptions are not met, alternative methods (e.g., nonparametric methods) may be performed in order to assess the robustness of the conclusions from the primary analysis.

For time to event endpoint, stratified log-rank test and Cox regression analysis will be performed with centre, type of baseline controller (ICS alone vs. ICS/LABA), gender and age as the stratification factors. Kaplan-Meier methodology will be used to estimate median time for each treatment arm. Kaplan-Meier curves will be constructed to provide a visual description of the difference between the two treatment arms.

9.4.3. Other Analyses

Asthma exacerbation rate will be analyzed using logistic regression as described for the primary endpoints.

Interactions between treatment and each of the covariates will be investigated in turn, with all main effects in the model regardless of their statistical significance. Any

interaction terms found to be statistically significant will be explored and if necessary results will be reported for each level of the covariate. Investigation of interactions will be confined to the primary endpoints. The effect of interactions (e.g., treatment by centre) will be assessed at the 10% level of significance.

Adverse events

The number (%) of subjects in each treatment group with treatment emergent AEs will be produced. Counts and percentages will also be presented of subjects with serious adverse events (SAEs), AEs leading to withdrawal, AEs by severity and AEs by relationship to study drug.

Other safety measures

Reason for withdrawal will be summarised.

Summary statistics for vital signs evaluations at each visit will be presented by treatment group. In addition, summary statistics for change from baseline for vital signs evaluations will be presented by treatment group.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

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 Council for 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 to be obtained for each subject 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.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- 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 multicentre 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 IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time

will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

ACT	Asthma Control Test
ADR	Adverse Drug Reactions
AE	Adverse Event
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
AQLQ	Asthma Quality of Life Questionnaire
AQLQ(S)	Standardised Asthma Quality of Life Questionnaire
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CV	Cardiovascular
DRC	Daily Record Card
ECG	Electrocardiogram
FEV1	Forced Expiratory Volume in one second
GCP	Good Clinical Practice
GINA	International Guidelines for Asthma Management
GSK	GlaxoSmithKline
IB	Investigator Brochure
ICC	Intra-cluster Correlation Coefficient
ICH	International Council for Harmonisation
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention-to-Treat
LABA	Long-acting β2 agonist
Mg	Milligram/s
mL	Millilitre/s
PEF	Peak Expiratory Flow
PP	Per Protocol
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
ULN	Upper Limit of Normal
WHO	World Health Organisation

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ACT

Trademarks not owned by the GlaxoSmithKline group of companies
AQLQ(S)
Mini-Wright

12.2. Appendix 2 : Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.2.1. Definition of Adverse Events

Adverse Event Definition:
• An 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. • NOTE: 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.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., Electrocardiograms (ECGs), radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment 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 study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • 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.

- 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.

12.2.2. Definition of Serious Adverse Events

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).

Serious Adverse Event (SAE) is defined as 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 hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization 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 hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

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, diarrhea, 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 situations: • Medical or scientific judgment 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 hospitalization but may jeopardize 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 hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: • Alanine Transaminase (ALT) ≥3x upper limit of normal (ULN) and total bilirubin* ≥2xULN (>35% direct), **or** • ALT ≥3xULN and International normalized ratio (INR)** >1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥3xULN and total bilirubin ≥2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.2.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack

- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.2.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.2.5. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.2.6. Reporting of SAEs/ADR to GSK

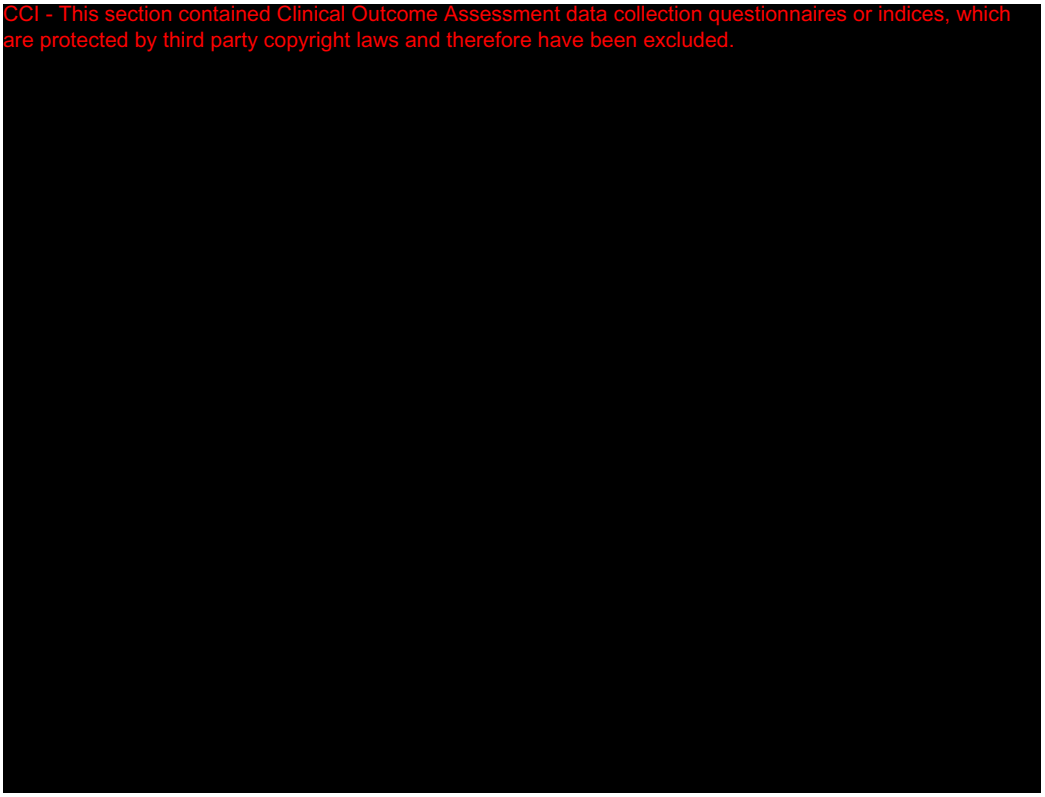
SAE/ADR reporting to GSK via paper CRF
• Facsimile transmission of the SAE/ADR paper CRF is the preferred method to transmit this information to the SAE/ADR coordinator • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE/ADR data collection tool sent by overnight mail • Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE/ADR CRF pages within the designated reporting time frames. • Contacts for SAE/ADR receipt can be found at this beginning of the protocol on the Sponsor/Medical Monitor Contact Information page.

12.3. Appendix 3 - Country Specific Requirements

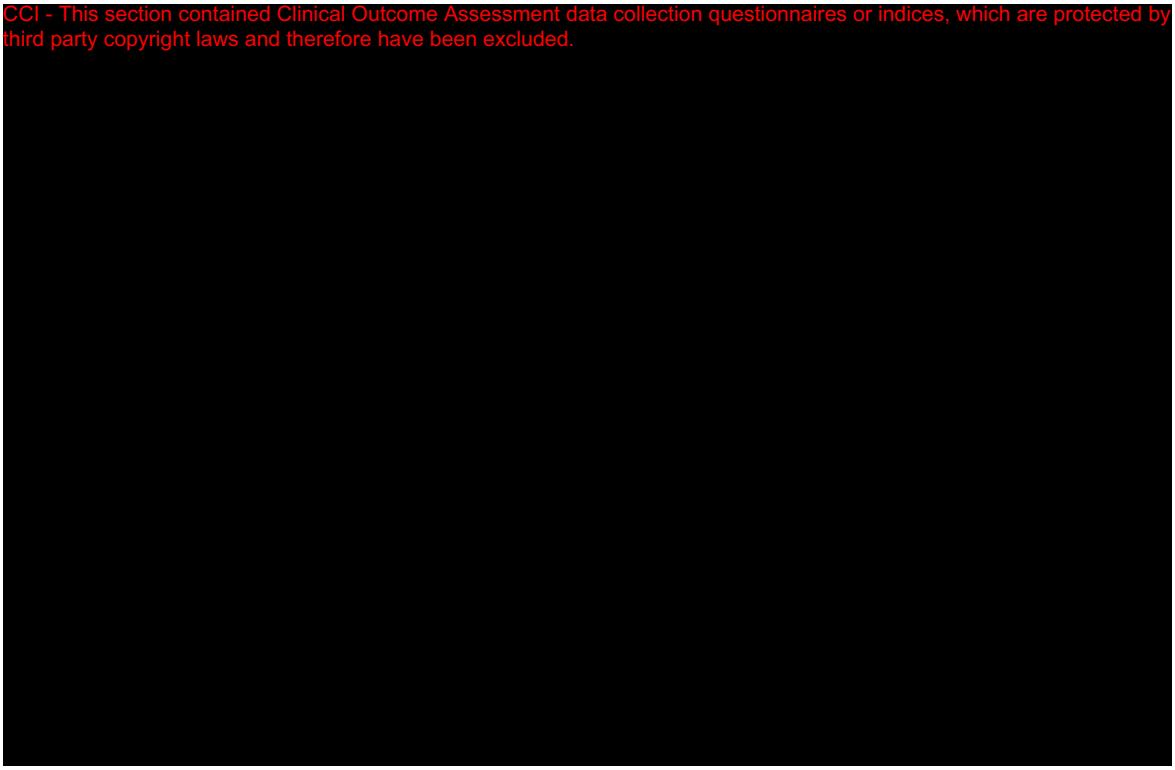
This requirement applies to China studies only.

12.4. Appendix 4: Asthma Control Test

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

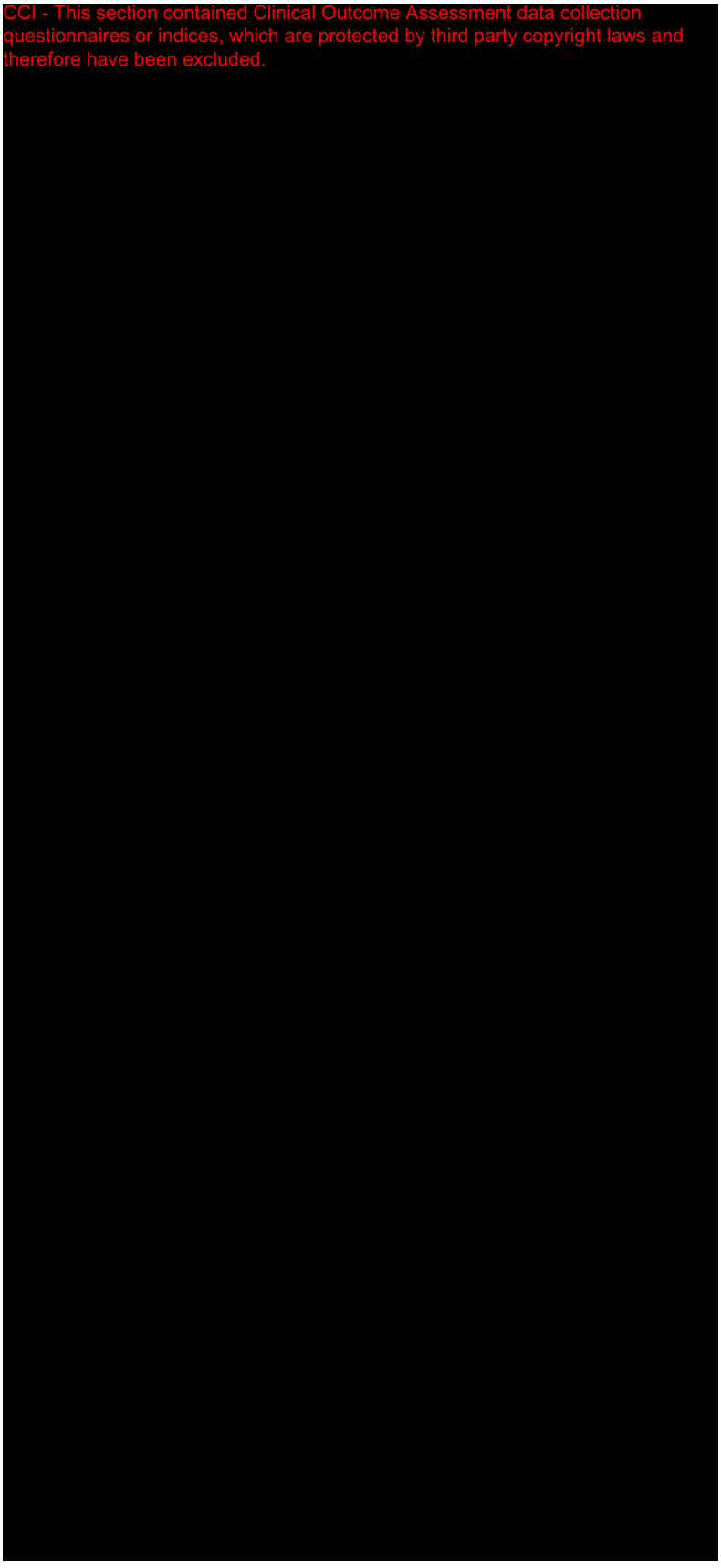


CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



12.5. Appendix 5: Standardised Asthma Quality of Life Questionnaire (AQLQ(S))

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.


CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Appendix: Asthma quality of life questionnaire (interviewer)

The questionnaire includes 32 questions. Each has one of four sets of seven response options, identified by the colour of the card (see next page). First subjects are asked to identify activities in which they are limited by their asthma. If more than five activities are identified they are asked to choose the five most important. To ensure that all possible relevant items are considered subjects are presented with the following prompts:

- Bicycling
- Clearing snow off your car*
- Dancing
- Doing home maintenance
- Doing housework
- Gardening*
- Hurrying
- Jogging, exercising, or running
- Laughing
- Mopping or scrubbing the floor
- Mowing the lawn*
- Playing with pets
- Playing with children
- Playing sports
- Shovelling snow*
- Singing
- Doing regular social activities
- Having sexual intercourse
- Talking
- Running upstairs or uphill
- Vacuuming
- Visiting friends or relatives
- Going for a walk
- Walking upstairs or uphill
- Woodwork or carpentry
- Carrying out your activities at work

*Included only in studies conducted in the appropriate season.

When five activities have been identified subjects are asked about the extent to which they have been limited in each of the activities as follows:

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CCI

RESPONSE OPTIONS

Green card

1 Totally limited, couldn't do activity at all
2 Extremely limited
3 Very limited
4 Moderate limitation
5 Some limitation
6 A little limitation
7 Not at all limited

Red card

1 A very great deal of discomfort or distress
2 A great deal of discomfort or distress
3 A good deal of discomfort or distress
4 A moderate amount of discomfort or distress
5 Some discomfort or distress
6 Very little discomfort or distress
7 No discomfort or distress

Blue card

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

Yellow card

1 Severely limited—most activities not done
2 Very limited
3 Moderately limited—several activities not done
4 Slightly limited
5 Very slightly limited—very few activities not done
6 Hardly limited at all
7 Not limited at all—have done all activities that I wanted to do

DOMAINS

The items were grouped into four domains:
Activity limitations (items 1 to 5, 11, 19, 25, 28, 31, 32)
Symptoms (items 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30)
Emotional function (items 7, 13, 15, 21, 27)
Exposure to environmental stimuli (items 9, 17, 23, 26).