Reporting and Analysis Plan (RAP)

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

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RAP SIGNATURE PAGE

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol 201097.

Revision Chronology:		
201097	27-Jun-2016	Original

2. SUMMARY OF KEY PROTOCOL INFORMATION

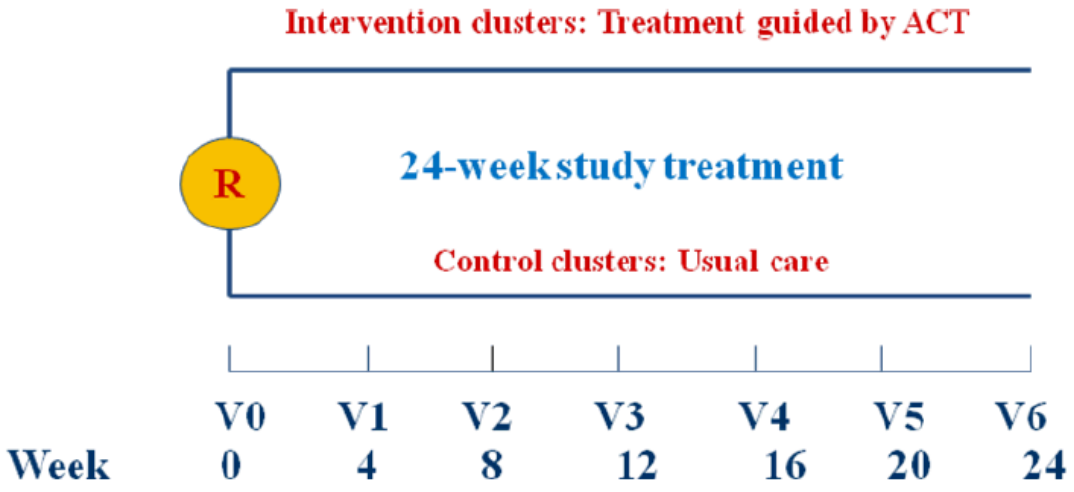
2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol, dated 27-Jun-2016. Some sensitivity and supportive analyses are added in the primary efficacy analysis in this RAP (See details in Section 7.1.3).

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To compare the effectiveness of ACT guided treatment versus usual care in achieving asthma control	• The percentage of subjects who have an ACT total score ≥20 or an improvement of more than 3 points in ACT total score in at least one post-baseline assessment during the 24-week treatment period
Secondary Objectives	**Secondary Endpoints**
• 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 total score ≥20 or improvement of more than 3 points in ACT over the 24-week treatment period • Time to first ACT total score ≥20 and improvement of more than 3 points in ACT total score over the 24-week treatment period
Exploratory Objectives	**Exploratory Endpoints**
• 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

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	• This is a prospective, multicentre, cluster-randomized, open-label study.
Dosing	• Not Applicable
Time & Events	• [Refer to Appendix 2: Schedule of Activities]
Treatment Assignment	• 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).
Interim Analysis	• No interim analysis is planned.

2.4. Statistical Hypotheses / Statistical Analyses

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 total score $\geqslant$20 or an improvement of more than 3 points in ACT total score in at least one post-baseline assessment 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 total score $\geqslant$20 or an improvement of more than 3 points in ACT total score in at least one post-baseline assessment during the 24-week treatment period for the ITT population.

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

3. PLANNED ANALYSES

3.1. Interim Analyses

There are no interim analyses planned for this study.

3.2. Final Analyses

The final planned analyses will be performed after all required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Intent-To-Treat (ITT)	• All subjects who signed informed consent form, were randomised and who had at least one post-baseline assessment on primary endpoints, second endpoints, and/or exploratory endpoints. The ITT population will be the primary population of interest.	Study Population Efficacy
Per-Protocol (PP)	• 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.	Efficacy
Safety	• All subjects who are enrolled into the study and who have at least one DRC assessment.	Safety

Refer to Appendix 8: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Important deviations, which result in exclusion from the analysis population, will also be summarised and listed. Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (refer to Appendix 1).

- Data will be reviewed prior to freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

4.2. Diary Compliance

Subjects' diary compliance will be assessed by the records of diary cards. For the subjects to be included in the PP population, there should be at least ≥80% expected diary counts in the diary cards according to the visits they have completed.

4.3. Treatment Compliance

Subjects' treatment compliance will be calculated as follow:

$$\text{Treatment compliance} = \frac{\text{Number of days that the subjects take asthma drugs following the doctor's advise}}{\text{The last assessment date in the diary cards} - \text{the first assessment date in the diary cards} + 1} \times 100\%$$

The number of days that the subjects take asthma drugs following the doctor's advice will be captured in the diary cards. For the subjects to be included in the PP population, the treatment compliance should ≥80%.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Continuous data will be summarized by treatment using descriptive statistics: number of subjects/observations (n), arithmetic mean values (Mean), median value (Median), standard deviation (SD), minimum value (Min), and maximum value (Max). Min and Max will be presented with the same number of decimal places as the raw data recorded in the database. Mean and Median will be presented using one more additional decimal place. SD will be presented with two more decimal places than the raw data recorded in the database.

Categorical data will be summarized by treatment using frequencies and percentages. Counts and percentages will be presented for each category. Percentages will be presented to one decimal place.

Statistical tests of treatment effects will be performed at a 2-sided significance level of 0.05, unless otherwise stated. And all p-values will be rounded up to 3 decimal places.

5.1. Study Treatment Display Descriptors

Code	Description	Order in TLF
ACT	Asthma Control Test	1
UC	Usual Care	2

Treatment comparisons will be displayed as follows using the descriptors as specified: ACT vs UC.

5.2. Baseline Definitions

For primary endpoint, baseline will be the measurements taken at visit 0. For secondary endpoints, baselines of FEV1 and AQLQ(S) will be the measurements taken at visit 0; for symptom score and PEF, baselines are unavailable since the data will be collected daily using diary cards from the first day of asthma treatment and baseline assessments before treatment will not be conducted.

Unless otherwise stated, if baseline data is missing, no derivation will be performed and baseline will be set to missing.

5.3. Multicentre Studies

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. Centre, as the unit of randomization, will be treated as a random effect in generalized linear mixed model (GLMM) used to analyse primary endpoints.

5.4. Examination of Covariates, Other Strata and Subgroups

The primary endpoints will be analysed using mixed effect logistic regression. In this study, generalized linear mixed model (GLMM) will be used to control for centre as a random effect since each centre is considered as a cluster in this cluster-randomization study. The statistical model on which the inference will be based will include terms for treatment, baseline ACT total score, baseline ACT total score squared, centre, type of baseline controller (inhaled corticosteroids [ICS] alone vs. ICS/long-acting β2 agonist [LABA]), gender and age. The primary endpoints will also be presented in the following subgroups: type of baseline controller (inhaled corticosteroids [ICS] alone vs. ICS/long-acting β2 agonist [LABA]), gender and age (<50 years old vs. >=50 years old).

5.5. Multiple Comparisons and Multiplicity

The primary comparison of interest is the comparison between ACT and usual care for the primary endpoint in the ITT population. Analyses of efficacy endpoints will not be subject to any multiplicity adjustment.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
10.3	Appendix 3: Study Phases and Treatment Emergent Adverse Events
10.4	Appendix 4: Derived and Transformed Data
10.5	Appendix 5: Reporting Standards for Missing Data
10.6	Appendix 6: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the ITT population, unless otherwise specified.

Study population analyses including analyses of subject's disposition, population, protocol deviations, demographic and baseline characteristics, subject's smoking history, alcoholism history, drug abuse history, asthma history, asthma exacerbation history, medical history (coded by MedDRA version 21.0 or above), asthma medications, and concomitant medications (coded by WHODrug version Global Mar 2018 or above), will be summarized and listed. Details of the planned displays are presented in Appendix 8: List of Data Displays.

7. EFFICACY ANALYSES

All hypothesis tests and confidence intervals will be two-sided. All efficacy measures over the course of the study will be presented and summarised. Continuous data will be summarised by means, standard deviations (SD), 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).

Unless otherwise specified, endpoints / variables defined in Section 7.1 and Section 7.2 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.1. Primary Efficacy Analyses

7.1.1. Endpoint / Variables

The ACT is a validated self-administered questionnaire utilising 5 questions to assess asthma control during the past 4 weeks on a 5-point categorical scale (1 to 5).

The total score is calculated as the sum of the scores from all 5 questions, provided all scores are non-missing; if any individual scores are missing then the overall score will be set to missing.

The primary endpoint for the study is the percentage of subjects who have an ACT total score $\geqslant$20 or an improvement of more than 3 points in ACT total score in at least one post-baseline assessment during the 24-week treatment period.

The calculation of percentage will base on the subjects with at least one post-baseline ACT assessment.

7.1.2. Primary Analysis Methods

The primary endpoints will be analysed using mixed effect logistic regression. In this study, generalized linear mixed model (GLMM) will be used to control for centre as a random effect since each centre is considered as a cluster in this cluster-randomization study. The statistical model on which the inference will be based will include terms for treatment, baseline ACT total score, baseline ACT total score squared, 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. Type of baseline controller (ICS alone vs. ICS/LABA) derives from the current asthma medication record in visit 0. The results of the primary analyses will be presented as adjusted odds ratios, 2-sided 95% confidence intervals, and associated p-values comparing ACT guided treatment with usual care. The adjusted odds ratios and 95% confidence intervals will be presented by a forest plot.

The example SAS codes are as below:

```
proc glimmix data=input_data method=quad;
class invsite rndgrp blcontrol gender;
model response= rndgrp actbl actblsq blcontrol gender age /s
dist=binomial oddsratio cl link=logit;
random intercept/subject= invsite;
lsmeans rndgrp /diff cl;
run;
```

where input_data is the name of the input dataset and response is the response variable. In terms of the covariates rndgrp, actbl, actblsq, blcontrol, gender and age are variables for randomised treatment code, baseline ACT total score, baseline ACT total score squared, type of baseline controller, gender and age respectively. For random effect, invsite is variable for centre.

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.

Analyses of the primary endpoints will be performed on the ITT population and the PP population; the ITT population is considered primary. The PP population will not be analysed if this population comprises more than 95% or less than 50% of the ITT population. Only the primary efficacy variables will be analysed using the PP population.

7.1.3. Sensitivity and Supportive Analysis Methods

- The primary endpoint will be repeatedly analysed in the following subgroups, using the same method used in primary analysis method:
  - ✓ Type of baseline controller (inhaled corticosteroids [ICS] alone vs. ICS/long-acting β2 agonist [LABA])
  - ✓ Gender (male vs. female)
  - ✓ Age (<50 years old vs. >=50 years old)

For subgroup analyses, the model will include all the covariates used in the primary analysis model except for the subgroup variable itself. Adjusted odds ratios and their 95% confidence intervals will be presented by a forest plot. These analyses will be performed for the ITT and PP populations.

- A supportive analysis of the primary endpoint will be performed using Generalised Estimating Equations (GEEs) if the model can converge.

All non-missing data from visits with scheduled ACT assessments (Weeks 4, 8, 12, 16, 20 and 24) will be included and an unstructured working correlation matrix will be implemented. The model will include terms for treatment, baseline ACT total score, baseline ACT total score squared, age, gender, visit and treatment-by-visit interaction. The number and percentage of subjects with a response within each treatment group will be presented by visit, together with the adjusted odds ratios, 2-sided 95% confidence intervals, and associated p-values between ACT guided treatment and usual care. The adjusted odds ratios and 95% confidence intervals will be presented by a forest plot.

The example SAS codes are as below:

```
proc genmod data= input_data descending;
class rndgrp gender visit subjid/ ref=first param=ref;
model response=rndgrp actbl actblsq blcontrol age gender visit
rndgrp*visit/dist=bin;
repeated subject=subjid /within=visit type=un corrw;
estimate "Treatment effect at Visit 1" rndgrp 1 visit 0 0 0 0 0
rndgrp*visit 0 0 0 0 0/exp;
estimate "Treatment effect at Visit 2" rndgrp 1 visit 0 0 0 0 0
rndgrp*visit 1 0 0 0 0/exp;
estimate "Treatment effect at Visit 3" rndgrp 1 visit 0 0 0 0 0
rndgrp*visit 0 1 0 0 0/exp;
estimate "Treatment effect at Visit 4" rndgrp 1 visit 0 0 0 0 0
rndgrp*visit 0 0 1 0 0/exp;
estimate "Treatment effect at Visit 5" rndgrp 1 visit 0 0 0 0 0
rndgrp*visit 0 0 0 1 0/exp;
estimate "Treatment effect at Visit 6" rndgrp 1 visit 0 0 0 0 0
rndgrp*visit 0 0 0 0 1/exp;
run;
```

where input_data is the name of the input dataset and response is the response variable. In terms of the covariates rndgrp, actbl, actblsq, blcontrol, gender, age and visit are variables for randomised treatment code, baseline ACT total score, baseline ACT total score squared, type of baseline controller, gender, age and visit number, respectively. For repeated measures, visit is variable for visit number and subjid is variable for subject's ID.

This analysis will be performed for the ITT and PP populations.

- Percentage of subjects who have an ACT total score $\geqslant$20 and an improvement of more than 3 points in ACT total score.

The following endpoints will be analysed as sensitivity analyses.

- ✓ Percentage of subjects who have an ACT total score ⩾20 and an improvement of more than 3 points in ACT total score at Week 12. Subjects with missing data at Week 12 will be set as non-responders.
- ✓ Percentage of subjects who have an ACT total score ⩾20 and an improvement of more than 3 points in ACT total score at Week 24. Subjects with missing data at Week 24 will be set as non-responders.
- ✓ Percentage of subjects who have an ACT total score ⩾20 and an improvement of more than 3 points in ACT total score at Weeks 16 and 20 and 24. Subjects with missing data at Weeks 16, 20 or 24 will be set as non-responders.

These endpoints will be analysed using the same model as defined for primary endpoint (GLMM). A supportive analysis will be conducted to analysis the percentage of subjects who have an ACT total score⩾20 and an improvement of more than 3 points in ACT total score, using the same GEEs method as mentioned above. All non-missing data from visits with scheduled ACT assessments (Weeks 4, 8, 12, 16, 20 and 24) will be used.

These analyses will be performed for the ITT and PP populations.

- Change from baseline in ACT total score in post-baseline visits.

A Mixed Model Repeated Measures (MMRM) will be used with covariates of treatment, baseline ACT total score, centre, type of baseline controller (ICS alone vs. ICS/LABA), gender, age, visit, treatment-by-visit interaction and treatment-by-baseline ACT total score, with centre as a random effect. The least squares (LS) mean and LS mean change from baseline for each treatment and the estimated LS mean change from baseline treatment difference will be presented at each visit together with the 95% confidence interval for the mean difference and P-value.

The example SAS codes are as below:

```
proc mixed data=input_data;
class invsite rndgrp visit subjid blcontrol gender;
model actchbl=rndgrp actbl blcontrol gender age visit rndgrp*visit
rndgrp*actbl/ ddfm =kr;
random intercept/subject= invsite;
repeated visit / subject=subjid type=un;
lsmeans rndgrp*visit / cl diff e;
ods output lsmeans=lsmeans;
ods output diffs=diffs;
run;
quit;
```

where input_data is the name of the input dataset and actchbl is change from baseline in ACT score. In terms of the covariates rndgrp, actbl, blcontrol, gender, age and visit are variables for randomised treatment code, baseline ACT total score, type of baseline controller, gender, age and visit number, respectively. For random effect, invsite is variable for centre. For repeated measures, visit is variable for visit number and subjid is variable for subject's ID.

This analysis will be performed for the ITT and PP populations.

7.2. Secondary Efficacy Analyses

7.2.1. Endpoint / Variables

- 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 AQLQ(S) score
- Time to first ACT total score $\geqslant$20 or improvement of more than 3 points in ACT total score over the 24-week treatment period
- Time to first ACT total score $\geqslant$20 and improvement of more than 3 points in ACT total score over the 24-week treatment period

7.2.2. Analysis Methods

All secondary endpoints will be confined to the ITT population. The continuous efficacy endpoints will be summarized by mean, standard deviation (SD), median, minimum and maximum according to scheduled visits. Time to event endpoint will be summarized by median time, 95% confidence interval of median time, lower and upper quantiles and range.

Continuous efficacy endpoints will be analysed using analysis of covariance (ANCOVA) and adjusted for centre as a random effect.

For mean daytime and night-time symptom score and mean morning and evening PEF, the mean values will be based on the available data on the diary card over each visit assessment period. No imputations will be performed on missing data. The mean values will be considered missing if less than 14 days are recorded in each visit assessment period. A Mixed Model Repeated Measures (MMRM) will be used with covariates of treatment, centre, type of baseline controller (ICS vs. ICS/LABA), gender and age, with the centre as a random factor. The results will be presented as LS mean (SE), 95% confidence interval for LS mean, treatment difference, 95% confidence interval for treatment difference and P-value by visit.

The example SAS codes are as below:

```
proc mixed data=input_data;
class invsite rndgrp visit subjid blcontrol gender;
model endpoint=rndgrp actbl blcontrol gender age/ ddfm =kr;
random intercept/subject= invsite;
repeated visit / subject=subjid type=un;
lsmeans rndgrp*visit / cl diff e;
ods output lsmeans=lsmeans;
ods output diffs=diffs;
run;
quit;
```

where input_data is the name of the input dataset and endpoint is the endpoint variable. In terms of the covariates rndgrp, actbl, blcontrol, gender and age are variables for randomised treatment code, baseline ACT total score, type of baseline controller, gender and age respectively. For random effect, invsite is variable for centre. For repeated measures, visit is variable for visit number and subjid is variable for subject's ID.

The AQLQ(S) contains 32 items in four domains: activity limitation (11 items), symptoms (12 items), emotional function (5 items) and environmental stimuli (4 items). The following items are included in each of the 4 domains:

- Symptoms: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
- Activity Limitation: 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
- Emotional Function: 7, 13, 15, 21, 27
- Environmental Stimuli: 9, 17, 23, 26

The response format consists of a seven-point scale where a value of 1 indicates "total impairment" and a value of 7 indicates "no impairment". The total AQLQ(S) score is the mean of all 32 items in the questionnaire and each individual domain score is calculated as the mean of the items within that domain. Hence, the total and domain scores are also each defined on a range from 1 to 7 with higher scores indicating a higher quality of life.

For the total AQLQ(S) score, the score for a subject at any time point will only be calculated if at least 90% of the questions were answered (calculated as the mean of those non-missing questions). If fewer than 90% of the questions were answered then the mean score for that subject at that time point will be considered missing.

For each individual domain of the AQLQ(S) score, the score for a subject at any time point will only be calculated if at least 90% of the questions for that domain were answered (calculated as the mean of those non-missing questions). If fewer than 90% of the questions were answered for that domain then the mean score for that subject and domain at that time point will be considered missing.

The analysis of changing from baseline to the end of study in FEV1 and AQLQ(S) score will only include those who complete the study and change from baseline will be calculated as the difference between baseline visit and Visit 6.

For FEV1 and AQLQ(S) changing from baseline, a mixed model will be used with covariates of treatment, centre, type of baseline controller (ICS vs. ICS/LABA), gender and age, with the centre as a random factor. The results will be presented as LS mean (SE), 95% confidence interval for LS mean, treatment difference, 95% confidence interval for treatment difference

The example SAS codes are as below:

```
proc mixed data=input_data;
class invsite rndgrp blcontrol gender;
```

```
model epchbl=rndgrp actbl blcontrol gender age/ ddfm =kr;
random intercept/subject= invsite;
lsmeans rndgrp/ cl diff e;
ods output lsmeans=lsmeans;
ods output diffs=diffs;
run;
quit;
```

where input_data is the name of the input dataset and epchbl is the endpoint variable changing from baseline. In terms of the covariates rndgrp, actbl, blcontrol, gender and age are variables for randomised treatment code, baseline ACT total score, type of baseline controller, gender and age respectively. For random effect, invsite is variable for centre.

For time to event endpoint, Cox regression analysis will be performed with treatment, baseline ACT total score, centre, type of baseline controller (ICS alone vs. ICS/LABA), gender and age as the adjusted factors. The results will be presented as hazard ratio (SE), 95% confidence interval and P-value. Log-rank test and 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.

The example SAS codes are as below:

```
proc phreg data=input_data;
class rndgrp actbl invsite blcontrol gender;
model timeto1*eventflag(0)= rndgrp actbl invsite blcontrol gender age /
risklimits ties=exact;
hazardratio rndgrp/ diff=all;
run;

proc lifetest data=input_data outsurv=survest;
time timeto1*eventflag(0);
strata rndgrp;
run;
```

where input_data is the name of the input dataset, timeto1 is the variable for time to response and eventflag is the variable for sensor. In terms of the covariates rndgrp, actbl, invsite, blcontrol, gender and age are variables for randomised treatment code, baseline ACT total score, centre, type of baseline controller, gender and age respectively.

7.3. Exploratory Efficacy Analyses

Moderate/severe asthma exacerbations will be summarized, including number of subjects with moderate/severe exacerbations, number of moderate/severe exacerbations and characteristics of moderate/severe exacerbations. Exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation

The moderate/severe exacerbation rate will be analyzed using a generalized linear model, assuming the number of exacerbations has a negative binomial probability distribution and that its mean is related to covariate factors with a ‘log link’ function. The logarithm of time (year) on study will be used as an offset variable. All moderate/severe

exacerbations observed during the study, with the onset date of event from date of baseline visit to the end of study visit date or early withdrawal (from study) visit date, will be included in the analysis. Missing data due to early withdrawal from the study will not be imputed. The model will include covariates for treatment, baseline ACT total score, type of baseline controller (ICS alone vs. ICS/LABA), gender and age. The annual moderate/severe exacerbation rates and 95% confidence interval for each treatment will be presented. The rate ratio and 95% confidence interval, percent reduction in rate and 95% confidence interval and P value will also be presented.

The example SAS codes are as below:

```
proc genmod data= input_data;
   class rndgrp blcontrol gender;
   model no_exac = rndgrp actbl blcontrol gender age / dist=negbin
link=log offset=logtime wald type3;
   lsmeans rndgrp / cl diff OM exp;
run;
```

where input_data is the name of the input dataset and no_exac is the number of moderate/severe asthma exacerbations per subject during the study. In terms of the covariates rndgrp, actbl, blcontrol, gender and age are variables for randomised treatment code, baseline ACT total score, type of baseline controller, gender and age respectively. For offset, logtime is logarithm of time (year) on study.

8. SAFETY ANALYSES

The safety analyses will be based on the Safety population, unless otherwise specified.

8.1. Adverse Events Analyses

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, AEs by relationship to study procedure/study drug, asthma exacerbation and death.

Adverse events will be coded by MedDRA version 21.0 or above. Adverse events will be summarized and presented by system organ class (SOC) and preferred term (PT) by treatment group. Adverse events analyses including the analysis of AEs, SAEs, non-serious AE and other significant AEs will be summarized. All AEs and SAEs will be listed. The details of the planned displays are provided in Appendix 8: List of Data Displays.

8.2. Adverse Events of Special Interest Analyses

Except for study indication Asthma, there is no other adverse event of special interest.

8.3. Clinical Laboratory Analyses

Clinical laboratory data is not collected and analysed in this study.

8.4. Other Safety Analyses

The analyses of non-laboratory safety test results including vital signs and physical examination will be summarized and listed by descriptive statistics. The details of the planned displays are presented in Appendix 8 List of Data Displays.

9. REFERENCES

Zhu, Sammy; Liu, Lian. 3.1 Clinical Study Protocol_201097_20160627_ EN,2016

Zhu, Sammy; Liu, Lian. 3.2 Clinical Study Protocol _201097_20160627_CN,2016

10. APPENDICES

10.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

Refer document “PDMP201097 final.docx”

10.2. Appendix 2: Schedule of Activities

10.2.1. Protocol Defined Schedule of Events

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.

10.3. Appendix 3: Study Phases and Treatment Emergent Adverse Events

Assessments and events will not be classified by study phase. All the adverse events and concomitant medications are collected during the study as treatment emergent adverse events.

10.4. Appendix 4: Derived and Transformed Data

10.4.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of “Any visit post-baseline” row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day
• Not Applicable.

10.5. Appendix 5: Reporting Standards for Missing Data

10.5.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as who has completed all visits of the study. • Withdrawn subjects were not replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will be slotted as per Appendix 2: Schedule of Activities or will be summarised as withdrawal visits.

10.5.2. Handling of Missing Data

Element	Reporting Detail

General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument:
	  • These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table.
	  • Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

10.5.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• Completely missing start or end dates will remain missing, with no imputation applied. • Also no imputation applied for Partial dates. • The recorded partial date will be displayed in listings.
Concomitant Medications/ Medical History	• Completely missing start or end dates will remain missing, with no imputation applied. • Also no imputation applied for Partial dates. • The recorded partial date will be displayed in listings.

10.6. Appendix 6: Values of Potential Clinical Importance

10.6.1. Laboratory Values

Laboratory values are not collected in this study.

10.6.2. ECG

ECG values are not collected in this study.

10.6.3. Vital Signs

Vital Signs Values are only collected at Visit 0 as baseline characteristics, will be listed and summarized by descriptive statistics, normal range and clinical concern range will not be collected and summarized.

10.7. Appendix 7: Abbreviations & Trade Marks

10.7.1. Abbreviations

Abbreviation	Description
ACT	Asthma Control Test
AE	Adverse Event
ANCOVA	Analysis of Covariance
AQLQ	Asthma Quality of Life Questionnaire
AQLQ(S)	Standardised Asthma Quality of Life Questionnaire
CRF	Case Report Form
DRC	Daily Record Card
ECG	Electrocardiogram
FEV1	Forced Expiratory Volume in one second
GINA	International Guidelines for Asthma Management
GSK	GlaxoSmithKline
ITT	Intention-to-Treat
LABA	Long-acting β2 agonist
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram/s
mL	Millilitre/s
PEF	Peak Expiratory Flow
PP	Per Protocol
PT	Preferred Term
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event
SOC	System Organ Class
SD	Standard Deviation

Abbreviation	Description
WHO	World Health Organisation

10.7.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
ACT

Trademarks not owned by the GlaxoSmithKline Group of Companies
AQLQ(S)
MedDRA
SAS
WHODrug

10.8. Appendix 8: List of Data Displays

10.8.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures	Listings
Study Population	1.01 to 1.09		1.01 to 1.10
Efficacy	2.01 to 2.28	16	2.01 to 2.04
Safety	3.01 to 3.11		3.01 to 3.03

For Details of Mock Shells for Data Displays, please refer document "C_012_RESP_201097_TFL Template_Mock-ups.doc".