STATISTICAL ANALYSIS PLAN	
Study Code	D589BC00027
Edition Number	4.0
Date	29-Jul-2024

CARE FOR ALL

Change Asthma Clinical Practice through Guideline Education and Implementation For All Patients with Asthma: an Evaluation of an Asthma Quality Improvement Program

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LIST OF ABBREVIATIONS

List abbreviations and definitions of specialized or unusual terms, measurements, or units. Examples are provided below. These can be modified at study level.

Abbreviation or Specialized Term	Definition
AE	Adverse Event
BPT	Bronchial Provocation Test
CRO	Contract Research Organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
eCRF	electronic Case Report Form
FeNO	Fractional exhaled Nitric Oxide
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
KPI	Key Performance Indicator
MCID	Minimum Clinical Important Difference
PEF	Peak Expiratory Flow
PFT	Pulmonary Function Testing
PHL	Potential Hy's Law
PI	Principal Investigator
QIP	Quality Improvement Program
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	10/21/2022	Initial approved SAP	Yes	N/A
N/A	7/4/2022	Add 2 interim analysis per Protocol v2.0	Yes	N/A
Exploratory Endpoints	7/4/2023	Add below exploratory endpoints per Protocol v2.0- ● ● ● ● ● ●	Yes	N/A

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
		characteristic and asthma control level		
N/A	2/18/2024	Add the baseline and analysis window for investigator analysis. Add scope of the interim analysis.	Yes	N/A
Exploratory Endpoints	2/18/2024	Add below exploratory endpoints per protocol V3.0 ●	Yes	N/A
NA	8/19/2024	Specify the visit windowing strategy for investigators in details, similar to subject's windows rule.	Yes	N/A
Subgroup Anlyses	8/19/2024	Move all subgroup analyses to a separate section 4.2.4. Specify the definition and cut-off threshold for subgroups.	Yes	N/A
Exploratory Endpoints - 3	8/19/2024		Yes	N/A
Exploratory Endpoints -5	8/19/2024		No	Prior and concomitant medication page does not collect the investigator ID number, so deleted.
NA	8/19/2024	Change wording "**partially** controlled" to "**partly** controlled" for ACQ-5 (0.75 to 1.5).	No	Based on comments from expert opinion, the word "partially" is

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
				not correct for ACQ-5 (0.75 to 1.5), so changed to "partly".
Safety analyses	8/19/2024	Deleted safety analysis part to be consistent with CSP V3.0 (with no safety objective or endpoints in CSP)	Yes	N/A

1 INTRODUCTION

This statistical analysis plan is for AstraZeneca "Change Asthma Clinical Practice through Guideline Education and Implementation For All Patients with Asthma: an Evaluation of an Asthma Quality Improvement Program (short title: CARE FOR ALL: an Evaluation of an asthma QIP)" (Study code: D589BC00027) and will give a detailed description of it. This version of SAP is for final analysis plan.

This is a real-world, multi-centre prospective study to bridge the gap that exists between GINA guideline recommendations and current clinical practice by demonstrating the benefits of an asthma quality improvement program (QIP), i.e. a standardized pulmonologist-targeted GINA guideline education and practice implementation. This is an evaluation on an asthma Quality Improvement Program (QIP, including GINA guideline education/training and implementation) to understand the change of physician behaviours, which leads to the change of patient outcomes.

This statistical analysis plan is based on the 3.0 version of the research protocol on February 22, 2023, the 5.0 version of the Case Report Form on September 26, 2023.

1.1 Study Objectives

Objectives	Endpoints
Primary	
• To evaluate the change in GINA guideline-recommended treatments after guideline education and implementation.	• Change from baseline in the proportion of participants with an ICS-based maintenance and/or reliever treatment at week 48
Secondary	
• To describe the asthma control after guideline education and implementation.	Secondary Endpoint 1 Change from baseline in the proportion of participant with well-controlled asthma (ACQ-5 ≤ 0.75) at week 48 • Distribution of ACQ-5 average scores [proportion of subjects well-controlled (ACQ-5 ≤ 0.75), partly controlled (0.75 to 1.5) and not well-controlled (ACQ-5 ≥ 1.5)] at weeks 12, 24, 36 and 48
• To describe the change in GINA guideline-preferred treatments during guideline education and implementation.	Secondary Endpoint 2 Change from baseline in the proportion of participants on the treatment of ICS-formoterol as reliever at week 12, 24, 36 and 48
• To describe the change in asthma control during guideline education and implementation.	Secondary Endpoint 3 Change from baseline in ACQ-5 average score at week 12, 24, 36 and 48 • Change from baseline in the proportion of participants achieving an improvement in ACQ-5 MCID of 0.5 units or more at week 12, 24, 36 and 48
• To describe the change in GINA guideline-recommended treatments during guideline education and implementation.	Secondary Endpoint 4 Change from baseline in the proportion of participants with an ICS-based maintenance and/or reliever treatment at week 12, 24 and 36
• To describe asthma related treatment patterns during the study duration.	Secondary Endpoint 5 Asthma related treatment patterns – Asthma treatment distribution at baseline and weeks 12, 24, 36, and 48, e.g., ICS-containing medications, ICS-LABA, ICS-formoterol, oral corticosteroids, leukotriene receptor antagonists,

	theophylline, Traditional Chinese Medicine
Exploratory •	•
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1.2 Study Design

The study will select a total of around 30 Tier 2 and Tier 3 hospitals across China and enrol approximately 1500 asthma patients ≥14 years old with all severities from the 30 participating hospitals. To represent the real-world situation of patients, pulmonologists and treatment practice, hospital selection will include as many as provinces or municipalities in mainland China, where the altitude is below 1,500 meters, while balancing hospital grade (e.g. 10 Tier 2 and 20 Tier 3). Patients will be recruited in hospital outpatient setting, where all potentially eligible asthma patients will be consecutively approached and invited to join the study, e.g., regardless of new patients or treated, exacerbation or regular follow-up.

The QIP (i.e., GINA 2021 guideline education/training and implementation) will be delivered to pulmonologists and specialist nurses in participating hospitals at hospital level, including pulmonologist-targeted initial comprehensive education based on GINA 2021, guideline implementation performance assessment and feedback, reinforcement learning, along with multiple online and offline approaches serving as reminders and supportive tools to ensure consistent education and to facilitate the asthma management in daily clinical practice in accordance with GINA 2021 recommendation.

Immediately after last patient has been enrolled at each site, the study intervention will be initiated, i.e., the initial comprehensive training on GINA 2021 will be offered to pulmonologists and specialist nurses in this hospital. All successfully enrolled participating patients will be followed up for up to 48 weeks and return to recruiting hospital for study

visits every 12 weeks. The total participating duration in this study for each participating patient will be approximately 60 weeks.

The study aims to bridge the gap between the recommendations from GINA 2021 and current clinical practice via an asthma QIP (including GINA guideline education/training and implementation).

Figure 1 Study Design

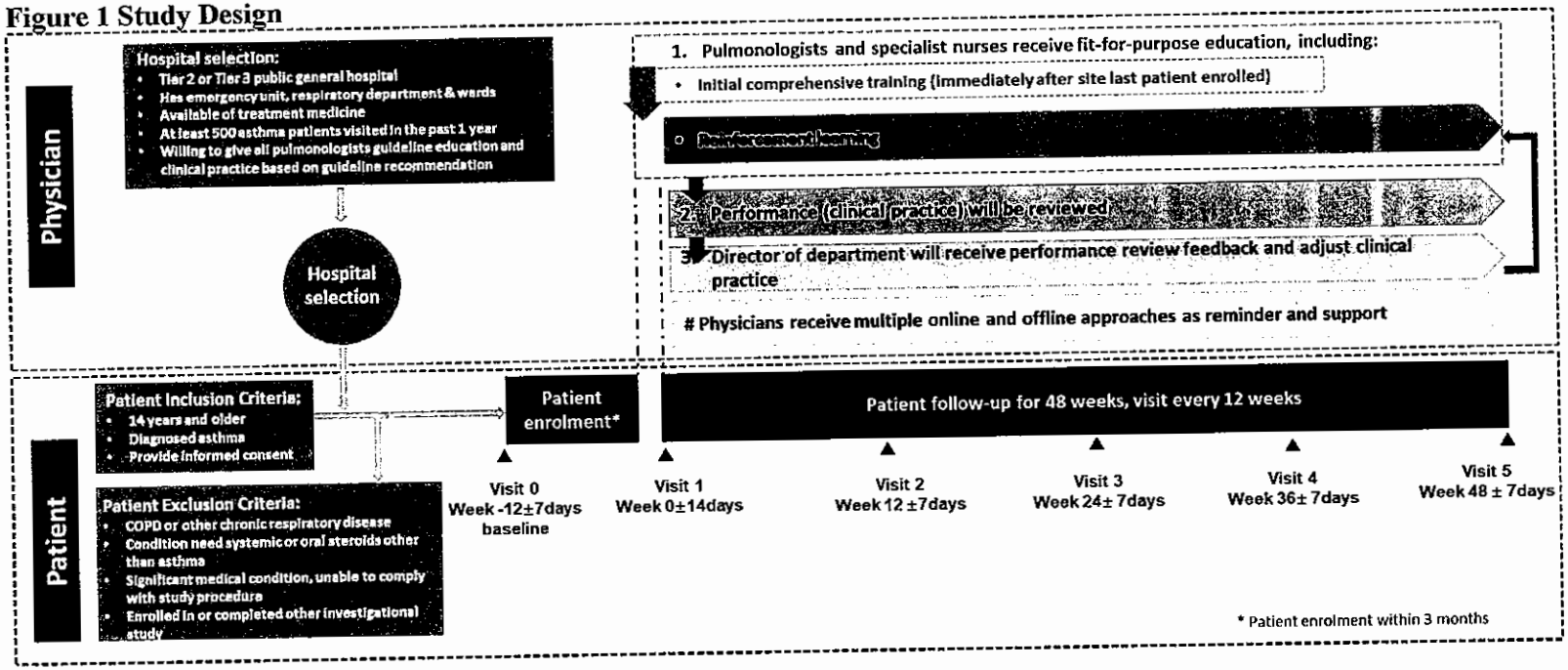

Table 1 Schedule of Activities (participating patients related)

	Baseline Period	Intervention Period					Details in CSP Section or Appendix
Study Visit	**V0**	**V1**	**V2**	**V3**	**V4**	**V5 (Study completion/ withdrawal)**	
Weeks	-12 ±7	0 ± 14	12 ±7	24 ±7	36 ±7	48 ±7	
Informed consent [a]	X						
Inclusion and exclusion criteria	X						Sections 5.2.1 and 5.2.2
Demographics [b]	X						
Vital Sign [c]	X						
Subject status [d]	X						
Smoking status [e]	X						
Medical history (comorbidities) and medications [f]	X						
Asthma history & related treatment [g]	X						
Severe asthma exacerbation		X	X	X	X	X	
Hospitalization due to asthma exacerbation since last visit		X	X	X	X	X	Section 8.1.4
ACQ-5	X	X	X	X	X	X	Section 8.1.5.1
AQLQ(S)+12	X	X	X	X	X	X	Section 8.1.5.2
PFT	X					X	
MARS-A questionnaire	X		X	X		X	
Questionnaire of asthma knowledge for patient	X		X	X		X	
Inhale skill score for patient		X	X	X		X	
Patient's expectation for asthma treatment	X		X	X		X	

	Baseline Period	Intervention Period					Details in CSP Section or Appendix
Study Visit	**V0**	**V1**	**V2**	**V3**	**V4**	**V5 (Study completion/ withdrawal)**	
Laboratory assessments within prior 3 months (if available in medical records) [h]	X	X	X	X	X	X	
PFT/BPT/PEF/FeNO within prior 3 months (if available in medical records)	X	X	X	X	X	X	
Medical records on asthma related assessment and treatment	X	X	X	X	X	X	
Questionnaire for Asthma Patients during COVID-19[i]	X						Section 8.1.9
Patient evaluation on whose pulmonologists 1. assess symptom control, 2. watch the patient using their inhaler, educate their technique, 3. have a discussion about adherence, 4. develop or review the written asthma action plan, provide patient education, 5. had a PFT before dosage reduction	X	X	X	X	X	X	Section 6.1.2.3

PFT = Pulmonary Function Testing; BPT = Bronchial provocation test; PEF = Peak expiratory flow; FeNO = Fractional exhaled nitric oxide

a. Informed consent must be conducted prior to performing any study procedures including data collection.
b. Demographic includes patient age, gender, race, ethnicity and
c. Vital signs include body mass index (BMI, calculation by height and weight)
d. Subject Status education level, family monthly income, job, residence (urban communities or rural villages), etc
e. Smoking status include current smoker or stopping smoking or restarting smoking, smoking pack-years
f. Asthma related comorbidities, including allergic history, rhinitis, chronic rhinosinusitis, nasosinusitis, gastroesophageal reflux disease, obesity, obstructive sleep apnea, depression, anxiety, eczema, and atopic dermatitis according to ICD-10-CM.Medication includes drugs administered for these asthma related comorbidities within 4 weeks before enrolment
g. Historical data, e.g., the first diagnosed date of asthma and total asthma exacerbation, total number of prescription of systemic glucocorticoid treatment for at least 3 days or emergence visit or hospitalization due to asthma exacerbations during previous 12 months (an emergency room visit due to asthma that required use of systemic corticosteroids or hospitalization due to asthma), home PEF availability, asthma symptoms, severity class evaluated by self-assessment, asthma control level, first asthma-diagnose hospital and Tiers level, hospital numbers for asthma clinic visit in past 12month, medical insurance category, Patient's expectation for asthma treatment , etc
h. Clinical laboratory testing data include CBC with differentiation, blood gas analysis (pH, SaO2, PaO2, PaCO2, and HCO3-); C-reactive protein; skin allegen prick, total IgE or specific IgE

i: If the patient got COVID-19 infection, then answer the questionnaire, the uninfected patients are not necessary to response. Every subject if has a new infected with COVID-19 should answer one time.

1.3 Number of Subjects

Approximately 1500 participants will provide 80% power at a significant level of 0.05 to detect a change from baseline in the proportion of patients with an ICS-based maintenance and/or reliever treatment at week 48 of 5%. The baseline proportion is assumed to be 40% and a within-participants correlation is assumed to be 0.25. The proportion of missing postbaseline assessment at week 48 is assumed to be 30%.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

Not Applicable

3 DATA ANALYSIS CONSIDERATIONS

3.1 General Considerations

Unless otherwise stated, all statistical methods in the subsequent sections will be based on the following general methods. Statistical programming and analyses will be performed using SAS® (SAS Institute, Inc., Cary, NC, USA), version 9.3 or higher, and/or other validated statistical software as required

All categorical data will be presented in contingency tables, using absolute and relative frequencies. Percentages will be rounded to the first decimal place and, therefore, may not always add up to 100%. When applicable, 95% confidence intervals (CIs) will be presented with estimates of proportions. The percentages will not be presented for zero counts.

All continuous data will be summarized via relevant descriptive statistics, such as number of observations with available measurements, mean, standard deviation, median, first and third quartiles (Q1 and Q3) when applicable, minimum and maximum.

Missingness in the variables will also be presented.

Decimal points will be presented as follows: N will be presented without decimal, minimum/maximum in same precision as in the database, mean/median in one more decimal than minimum/maximum, and SD in one more decimal than mean/median. And the decimal places of SD should not be greater than 4.

3.1.1 General Study Level Definitions

The Electronic Data Capture (EDC) system will be used for data collection and query handling. Except for the questionnaires to be completed by participants, all data will be based on what have been generated during routine clinical practice, if available.

3.1.2 Baseline Definition

Unless otherwise stated, general baseline will be defined as the last non-missing evaluation on or prior to Visit 0. Baseline definitions of comorbidities and treatments are provided in the comorbidities, medications and prescriptions sections (refer to section 4.1.8 and 4.1.9).

3.1.3 Study Day

If the assessment date is on or after Visit 1 in intervention period, the study day will be calculated as: Assessment Date – Date of Visit 1 in intervention period + 1.

If the assessment or event date is prior to Visit 1 in intervention period, the study day will be calculated as: Assessment Date – Date of Visit 1 in intervention period.

3.1.4 Visit Window

A visit windowing strategy will be implemented for subjects as shown below.

Analysis visit	Target Day	Actual assessment day
Week 0	Day 1	Training day to D42
Week 12	Day 84	D43 to D126
Week 24	Day 168	D127 to D210
Week 36	Day 254	D211 to D294
Week 48	Day 336	D295 to D378

The visit will be missing if no assessment was reported within the specified visit window. If multiple assessments fall within one visit window, the scheduled visit takes priority, followed by the one closest to the target day. If two evaluations are equidistant from the scheduled time point, the earlier one will be used.

A visit windowing strategy will be implemented for investigator as shown below:

Analysis visit	Target Day	Actual assessment day
Baseline		<= Training day
Week 12	Day 84	Day2 to D126
Week 24	Day 168	D127 to D252

Week 48	Day 336	D253 to D378

The visit will be missing if no assessment was reported within the specified visit window. If multiple assessments fall within one visit window, the one closest to the target day. If two evaluations are equidistant from the scheduled time point, the earlier one will be used.

3.1.5 Handling of Unscheduled Visits

Listings will include scheduled and unscheduled data.

3.1.6 Handling of Protocol Deviations in Study Analysis

Criteria for protocol deviations will be established, and patients with protocol deviations will be identified and documented before the database lock.

3.1.7 Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in the SAP.

Missing dates or partially missing dates will be imputed conservatively for adverse events and prior or concomitant medications/procedures.

For comorbidities, medications and prescriptions sections, incomplete (i.e., partial missing) date will be imputed.

Incomplete End Date:

If missing day and month, then December 31 will be assigned to the missing field.

If missing day only, then the last day of month will be assigned to the missing field.

If the death date is complete and the imputed end date is after the death date, then the end date will be imputed using the death date.

Incomplete Start Date/Baseline Prescribed Date

If missing day and month, then January 1 will be assigned to the missing field.

If missing day only, then the first day of month will be assigned to the missing field.

If the imputed start date is after the end date, then the start date will be imputed using the end date.

If the imputed baseline prescribed date is after the planned start date, then the baseline prescribed date will be imputed using the planned start date.

Otherwise, do not impute.

For incomplete asthma symptoms start date or asthma diagnosed date, the imputation will follow as below:

If missing day and month, then January 1 will be assigned to the missing field.

If missing day only, then the first day of month will be assigned to the missing field.

Otherwise, do not impute.

By-visit endpoints will be analyzed using observed data, unless otherwise specified. For observed data analyses, missing data will not be imputed and only the observed records will be included.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation and analysis/data presentation per domain.

4.1 Study Population

The domain study population covers subject disposition, analysis sets, protocol deviations, demographics, baseline characteristics, medical history and prior and concomitant medication.

4.1.1 Subject Disposition and Completion Status

The number of subjects who signed the informed consent will be calculated.

The number and percentage of subjects who enrolled, completed the study, remained on study and withdrew early will be summarized. The number and percentage of subjects who withdrew early for various reasons will be summarized according to the categories in the CRF. Study follow-up time and primary reason for screen failure will be summarized. Listing will also be presented.

Study Follow-up Time = EOS – training date +1

4.1.2 Analysis Sets

Effectiveness analyses will be performed using an FAS population. Demographic and baseline characteristics will be presented for both all participants analysis set and FAS. The following populations are defined:

All Enrolled Participants Analysis Set: All participating patients enrolled for the study without screen failure will be included in the All Enrolled Participants population.

Full Analysis Set (FAS): All enrolled participants with at least one non-missing post-intervention GINA guideline treatment assessment.

Based on all enrolled subjects, the number and percentage of subjects in the FAS will be calculated and summarized. Listing will be provided for the reason of exclusion from analysis sets.

4.1.3 Protocol Deviation

Major protocol deviations will be summarized for all patients in FAS. They will also be listed by each category. No patients will be excluded from analysis from the FAS due to protocol deviations.

4.1.4 Demographics

Demographics will be summarized using descriptive statistics for both all enrolled participants analysis set and FAS.

Continuous demographic variables include age, weight, height, and BMI (in kg/m^2); categorical variables include age group (>65 years, ≥18 to ≤65 years, <18 years), sex, race, ethnicity, BMI group (≥24 kg/m^2, <24 kg/m^2), education level, household per capita monthly income, occupation, residence, and source of drug purchase.

4.1.5 Baseline Characteristics

Baseline characteristics will be summarized using descriptive statistics for both all enrolled participants analysis set and FAS.

Continuous baseline variables include number of pack years (current usage only); categorical variables include nicotine usage frequency (current, former, never), temporarily stop nicotine use for more than 6 months (current usage only).

4.1.6 Disease Characteristics

Disease characteristics will be summarized using descriptive statistics for both all enrolled participants analysis set and FAS.

Disease characteristics includes Asthma history and Historical asthma exacerbation.

Continuous Asthma history variables include asthma duration since symptom start, asthma duration since diagnosed and hospital numbers for asthma clinic visit in past 12 months; categorical variables include SABA usage within one year before enrolment, Allergen Asthma Trigger, Any symptoms within the past 12 months, Most frequent symptoms within past 12 months and other symptom related questions in Asthma history CRF page.

*Asthma duration since symptom start (in months) = (ICF date – asthma symptoms start date +1)/365.25*12*

*Asthma duration since diagnosed (in months) = (ICF date – asthma diagnosed date +1)/365.25*12*

Continuous Historical asthma exacerbation variables include Historical Asthma Exacerbation number, number of exacerbations resulted in emergency room treatment, number of exacerbations resulted in hospitalization, medication number; categorical variables include Historical Asthma Exacerbation to Record within the past 12 months.

A subject data listing of disease characteristics will be provided.

4.1.7 Medical History and Concomitant Disease

Respiratory Medical History (Comorbidities) will be coded using MedDRA codes of the version currently in effect at the time of database lock. The number (percentage) of patients reporting a history of any medical condition, as recorded on the CRF, will be summarized by system organ class and preferred term in FAS. A listing of respiratory medical history will be provided.

4.1.8 Prior and Concomitant Medications

Prior and concomitant medications for asthma, and prior medications for asthma related comorbidities will be coded using the World Health Organization Drug Dictionary (WHO DD) of the version currently in effect at the time of database lock. The number and percentage of patients who took prior and concomitant medications for asthma, prior medications for asthma related comorbidities will be summarized respectively by ATC medication class 2 and WHO DD preferred term (PT) in the FAS. Prior and concomitant medications will also be presented in a listing.

Prior medications are defined as those medications with an end date prior to enrolment. Concomitant medications are defined as those medications which are taken on or after Visit 1 (Week 0). This includes medications which start prior to Week 0 but continue after Week 0. Multiple drug usage in the same classification and preferred term by a subject will be counted only once.

4.1.9 Prescriptions

Prescribed medication for asthma will be coded using the World Health Organization Drug Dictionary (WHO DD) of the version currently in effect at the time of database lock. The number and percentage of patients who are prescribed for asthma will be summarized respectively by ATC medication class 2 and WHO DD preferred term (PT) and visit in the FAS. Prescriptions will also be presented in a listing.

If treatment is prescribed at least once within 3months before Visit 0 (week -12), the subjects will be regarded as receiving this treatment at baseline. For Visit 2 (week 12), if treatment is prescribed at least once on or after Visit 1 and on or before Visit 2, the subjects will be regarded as receiving treatment at this visit. For Visit 3 -Visit 5 (week 24, 36 and 48), if treatment is prescribed at least once after last visit and on or before this visit, the subjects will be regarded as receiving treatment at this visit.

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, other endpoints including sensitivity and supportive analyses.

4.2.1 Primary Endpoint

4.2.1.1 Definition

The primary endpoint is the proportion of patients with an ICS-based maintenance and/or reliever treatment, which is indicated by whether or not the treatment option includes ICS-containing medication. Change from baseline in the proportion of patients with an ICS-based maintenance and/or reliever treatment at week 48 will be analysed.

Doctor's prescription will be used to define this endpoint. The baseline and following analysis visits' definitions refer to section 4.1.9.

4.2.1.2 Primary Analysis of Primary Endpoint

Proportion of patients with an ICS-based maintenance and/or reliever treatment will be described using the frequency with ICS and corresponding percentage at baseline and week 48.

The primary analysis will use mixed effect logistic regression model, taking the measurement timepoint (baseline/post-baseline) as the fixed effect, hospital, pulmonologist and patient as the random effects. Logit link function will be used, and the model parameters will be estimated by maximum likelihood approach. The compound-symmetry variance-covariance structure will be used. In case of lack of convergency, hospital and prescriber factors will be removed from the model.

Within the framework of this model, first predict for all patients the probability of ICS usage at baseline/ post-baseline and then take the average over baseline/ post-baseline patients to get an estimate of proportion, and finally take the difference between the two proportions as the risk difference estimate, the 95% confidence interval of risk difference in proportion by bootstrapping method will be estimated and presented. Besides, Odds Ratio and P value from the model will also be estimated and presented. The analysis will be performed in FAS. Reference SAS code is shown in section 7.

If medication is taken at least once within 3 months before Visit 0 (week -12), the patients will be regarded as taking this medication at baseline. For Visit 2 (week 12), if medication is taken at least once on or after Visit 1 and on or before Visit 2 (within 3 months before this visit), the subjects will be regarded as taking medications at this visit. For Visit 3 -Visit 5 (week 24, 36 and 48), if medication is taken at least once after last visit and on or before this visit (within 3 months before this visit), the subjects will be regarded as taking medication at this visit.

4.2.1.3 Sensitivity Analyses of the Primary Endpoint

Sensitivity analysis will be conducted with generalized estimating equations (GEE) model using measurement timepoint (baseline/post-baseline) as the fixed effect, and subject ID is used to identify individual subjects. Reference SAS code is shown in section 7. Logit link function will be used for binary distribution. The model parameters are estimated by generalized estimating equations. Compound-symmetry working correlation matrix will be used to model the correlation of the responses from subjects.

4.2.1.4 Supplementary Analyses of the Primary Endpoint

Not applicable.

4.2.2 Secondary Endpoints

4.2.2.1 Secondary Endpoint-1

The ACQ-5 is a shortened version of the full 7-item ACQ (Juniper et al 1999) that assesses asthma symptoms (night-time awakening, symptoms on awakening, activity limitation, shortness of breath, and wheezing) but omits the FEV1 measurement and SABA use from the original ACQ assessment. Patients are asked to recall how their asthma has been during the previous week by responding to 5 symptom questions. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-5 score is the mean of the responses. Mean scores of ≤ 0.75 indicate well controlled asthma, scores between >0.75 and <1.5 indicate partly controlled asthma, and a score ≥ 1.5 indicates not well controlled asthma (Juniper et al 2006). Individual changes of ≥ 0.5 are considered to be clinically meaningful (Juniper et al 2005).

The change from baseline in the proportion of well-controlled asthma evaluated by ACQ-5 score at week 48 will be derived using the percentage of patients with ACQ-5 score $\leqslant 0.75$, its 95% confidence interval (95% CI) will be summarized descriptively. Normal approximation method will be used to calculate 95% CI.

Distribution of ACQ-5 average scores at baseline and weeks 12, 24, 36 and 48 will be described as summary and listing, using the frequency and percentage at each category listed below, a shift table will also be generated:

- Well controlled: ACQ-5 $\leqslant$ 0.75
- Partly controlled: 0.75 <ACQ-5< 1.5
- Not well-controlled: ACQ-5 $\geqslant$ 1.5

4.2.2.2 Secondary Endpoint-2

One secondary endpoint is the proportion of patients on the treatment of ICS-formoterol as reliever, without concomitant SABA. Change from baseline in the proportion of patients on the treatment of ICS-formoterol as reliever at week 12, 24, 36 and 48 will be summarized with its 95% confidence interval (95% CI). Normal approximation method will be used to calculate 95% CI. Doctor's prescription will be used to define this endpoint. The baseline and following analysis visits' definitions refer to section 4.1.9.

4.2.2.3 Secondary Endpoint-3

The ACQ-5 overall score will be calculated as the average of the non-missing 5 symptom questions. At least 4 out of the 5 symptom items are needed to provide an ACQ-5 overall score. Change from baseline in ACQ-5 average score at week 12, 24, 36 and 48 will be summarized.

Responder status will be descriptively summarized by visit as the number (%) of responders and non-responders. A responder status at post-baseline will be calculated as

- Responder: (post-baseline – baseline) $\leqslant$ -0.5
- Non-responder: (post-baseline – baseline) > -0.5

Proportion of participants achieving an improvement in ACQ-5 MCID of 0.5 units or more at Week 12, 24, 36 and 48 will be summarized.

4.2.2.4 Secondary Endpoint-4

Change from baseline in the proportion of patients with an ICS-based maintenance and/or reliever treatment at week 12, 24 and 36 will be summarized with its 95% confidence interval (95% CI). Normal approximation method will be used to calculate 95% CI.

4.2.2.5 Secondary Endpoint-5

Asthma related treatment patterns will be evaluated by treatment distribution at baseline and at weeks of 12, 24, 36 and 48, e.g., ICS-containing medications, ICS-LABA, SABA, ICS-formoterol, oral corticosteroids, leukotriene receptor antagonists, theophylline, Traditional Chinese Medicine and combination.

4.2.3 Other Endpoint

4.2.3.1 Exploratory Endpoint-1

4.2.3.2 Exploratory Endpoint-2

4.2.3.3 Exploratory Endpoint-3

4.2.3.4 Exploratory Endpoint-4

4.2.3.5 Exploratory Endpoint-5

4.2.3.6 Exploratory Endpoint-6

4.2.3.7 Exploratory Endpoint-7

4.2.3.8 Exploratory Endpoint-8

4.2.3.9 Exploratory Endpoint-9

4.2.3.10 Exploratory Endpoint-10

4.2.3.11 Exploratory Endpoint-11

4.2.3.12 Exploratory Endpoint-12

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4.2.3.13 Exploratory endpoint-13

4.2.4 Subgroup analyses

Subgroup analyses as below will be performed as appropriate for the primary endpoint, selected secondary endpoints and exploratory endpoints. Any subjects with a missing value for the defined subgroup will be excluded from the analysis of that subgroup. The subgroups to be explored may include as needed:

- Age be category: >65 years, ≥18 to ≤65 years, <18 years old
- Age of onset: <20 years old, <40 years old, ≥40 years old
- Phenotype of asthma: allergic or non-allergic
- Hospital Tier: Tier 2, Tier 3
- Job: related to asthma, no-related to asthma (occupational exposure Y or N)
- Nicotine usage frequency (current, former, never)
- Sex (Male, Female)

- BMI (≥24 kg/m^2, <24 kg/m^2)
- Education level (elementary school and below, high school, university degree and postgraduate)
- Questionnaire with response and non-response subjects (if the subject performed ACQ and AQLQ at Visit 5 and had any questionnaire performed in each visit, the subject is defined as responder; otherwise, the subject is a non-response subject)
- Adherence (Good adherence or not)
- Patient expectation of asthma treatment
- Asthma severity class: Mild, Moderate, Severe (based on Patient Self-Assessment of Asthma Severity)
- Symptoms: Symptoms less than twice a month; Symptoms twice a month or more, but less than 4-5 days a week; Symptoms most days, or waking with asthma once a week or more; Daily symptoms, or waking with asthma once a week or more, and low lung function
- Hospital Type: PCCM, non-PCCM
- Geographic region: North, South
- ICS containing change: with-to-with, with-to-without, without-to-with, without-to-without ICS containing (From ICS containing to ICS containing, from ICS containing to no-ICS-containing, from no-ICS-containing to ICS-containing, from no-ICS containing to no-ICS-containing.)
- ICS-formoterol as reliever: with-to-with, with-to-without, without-to-with, without-to-without ICS-formoterol as reliever (From ICS-formoterol as reliever to ICS-formoterol as reliever, from ICS-formoterol as reliever to no-ICS-formoterol as reliever, from no-ICS-formoterol as reliever to ICS-formoterol as reliever, from no-ICS-formoterol as reliever to no-ICS-formoterol as reliever.)
- Participants complete status: Missing at Week 24, not Missing at Week 24.
- Participants complete status: Missing at Week 48, not Missing at Week 48.

These analyses are exploratory and the result from these subgroup analyses will not affect the choice of the model for the primary analysis.

5 INTERIM ANALYSIS

There will be two interim analyses, first interim analyses will mainly focus on the baseline when all subjects enrolled and finish baseline assessment, and the other will happen when all subjects complete week 12 visit.

First interim analysis includes the following parts:

1. Subject disposition
2. Demographics
3. Substance use – nicotine
4. Asthma history
5. Historical asthma exacerbation
6. Prior and concomitant medications – asthma/asthma related comorbidities
7. Prescribed medication – asthma
8. ICS-based maintenance and/or reliever treatment
9. ACQ-5 average scores
10. Distribution of ACQ-5 average scores (Well controlled/Partly controlled/Not well-controlled) and its subgroup listed in Section 4.2.3.12
11. ICS-formoterol as reliever
12. Asthma treatment patterns
13. Numbers of severe asthma exacerbation
    a. With ICS containing vs. without ICS containing
    b. Good adherence vs. not
14. Health-related quality of life evaluated by Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(S)+12) score
15. MARS-A average score
16. Hematology

17. Blood Gas
18. IgE
19. FeNO
20. Pulmonary Function Test (PFT)
21. Pulmonary Function Test-Post-BDT (PFT)

Second interim analysis includes the following parts:

1. Subject disposition
2. Demographics
3. Substance use – nicotine
4. Asthma history
5. Historical asthma exacerbation
6. Prior and concomitant medications – asthma/asthma related comorbidities
7. Prescribed medication – asthma
8. ICS-based maintenance and/or reliever treatment
9. ACQ-5 average scores
10. Distribution of ACQ-5 average scores (Well controlled/Partly controlled/Not well-controlled) and its subgroup listed in Section 4.2.3.12
11. ICS-formoterol as reliever
12. Asthma treatment patterns
13. Patient evaluation on whose pulmonologists (whether their pulmonologists develop or review the written asthma action plan and watch the patient using their inhaler, checking their technique)
14. Numbers of severe asthma exacerbation
    a. With ICS containing vs. without ICS containing
    b. Good adherence vs. not

15. Health-related quality of life evaluated by Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(S)+12) score

16. MARS-A average score

17. Inhaler skill score of subjects

18. Asthma knowledge score of subjects

19. Patient expectations of asthma treatment

20. Asthma knowledge questionnaire score of investigators

21. Adverse event

22. Hematology

23. IgE

24. FeNO

25. Pulmonary Function Test (PFT)

26. Pulmonary Function Test-Post-BDT (PFT)

27. Branchial Provocation Test

6 REFERENCES

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2. 中国医学装备协会呼吸病学专委会吸入治疗与呼吸康复学组,中国慢性阻塞性肺疾病联盟. 稳定期慢性气道疾病吸入装置规范应用中国专家共识[J]. 中华结核和呼吸杂志,2019,42(4):241-253.
3. Allen RM, Jones MP. The validity and reliability of an asthma knowledge questionnaire used in the evaluation of a group asthma education self-management program for adults with asthma. J Asthma. 1998;35(7):537-45.
4. 田庆秀,余丽君. 中文版支气管哮喘用药依从性量表的信效度检验[J]. 中华护理杂志,2014,49(5):621-624.
5. Mancuso CA, Rincon M, Robbins L, et al. Patients' expectations of asthma treatment. J Asthma. 2003 Dec;40(8):873-81.

7 APPENDIX

7.1 SAS sample code for proc GLIMMIX

```
proc GLIMMIX data=ics;

class visit (ref='0') hosp doct;

model mpd = visit /dist=binary link=logit oddsratio solution;

contrast 'week 48 vs baseline' time [1,4][-1,5] ;

random subjid hosp doct;

run;
```

7.2 SAS sample code for proc GENMODE

```
proc genmod data=ics;

class subjid hosp doct visit (ref='0')/ param=ref;

model mpd = visit / dist=bin link=logit;

repeated subject=subjid / corr=cs covb corrw;

run;
```

7.3 ASTHMA QUALITY OF LIFE QUESTIONNAIRE WITH STANDARDISED ACTIVITIES (AQLQ(S))

Self-administrated (≥12 years)

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

Please complete all questions by circling the number that best describes how you have been during the **last 2 weeks as a result of your asthma.**

HOW **LIMITED** HAVE YOU BEEN **DURING THE LAST 2 WEEKS** IN THESE ACTIVITIES **AS A RESULT OF YOUR ASTHMA?**

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
1. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
2 MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
3. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
4. WORK/SCHOOL-RELATED ACTIVITIES* (tasks you have to do at work/in school)	1	2	3	4	5	6	7
5. SLEEPING	1	2	3	4	5	6	7

*If you are not employed or self-employed, these should be tasks you have to do most days.

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS?**

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
6. How much discomfort or distress have you felt over the last 2 weeks as a result of CHEST TIGHTNESS?	1	2	3	4	5	6	7

Modified September 2010
AQLQ(S) ≥12 years SA North American English Version

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
7. Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7
8. Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
9. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO CIGARETTE SMOKE?	1	2	3	4	5	6	7
10. Experience a WHEEZE in your chest?	1	2	3	4	5	6	7
11. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF CIGARETTE SMOKE?	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS?**

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
12. How much discomfort or distress have you felt over the last 2 weeks as a result of COUGHING?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
13. Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
14. Experience a feeling of CHEST HEAVINESS?	1	2	3	4	5	6	7

Modified September 2010
AQLQ(S) ≥12 years SA North American English Version

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
15. Feel CONCERNED ABOUT THE NEED TO USE MEDICATION for your asthma?	1	2	3	4	5	6	7
16. Feel the need to CLEAR YOUR THROAT?	1	2	3	4	5	6	7
17. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO DUST?	1	2	3	4	5	6	7
18. Experience DIFFICULTY BREATHING OUT as a result of your asthma?	1	2	3	4	5	6	7
19. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF DUST?	1	2	3	4	5	6	7
20. WAKE UP IN THE MORNING WITH ASTHMA SYMPTOMS?	1	2	3	4	5	6	7
21. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
22. Feel bothered by HEAVY BREATHING?	1	2	3	4	5	6	7
23. Experience asthma symptoms as a RESULT OF THE WEATHER OR AIR POLLUTION OUTSIDE?	1	2	3	4	5	6	7
24. Were you WOKEN AT NIGHT by your asthma?	1	2	3	4	5	6	7
25. AVOID OR LIMIT GOING OUTSIDE BECAUSE OF THE WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7

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ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
26. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
27. Feel AFRAID OF GETTING OUT OF BREATH?	1	2	3	4	5	6	7
28 Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
29. Has your asthma INTERFERED WITH GETTING A GOOD NIGHT'S SLEEP?	1	2	3	4	5	6	7
30. Have a feeling of FIGHTING FOR AIR?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS?**

	Severely Limited Most Not Done	Very Limited	Moderately Limited Several Not Done	Slightly Limited	Very Slightly Limited Very Few Not Done	Hardly Limited At All	Not Limited Have Done All Activities
31 Think of the OVERALL RANGE OF ACTIVITIES that you would have liked to have done during the last 2 weeks. How much has your range of activities been limited by your asthma?	1	2	3	4	5	6	7

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AQLQ(S) ≥12 years SA North American English Version

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

HOW LIMITED HAVE YOU BEEN DURING THE LAST 2 WEEKS?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
32. Overall, among ALL THE ACTIVITIES that you have done during the last 2 weeks, how limited have you been by your asthma?	1	2	3	4	5	6	7

DOMAIN CODE:

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

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