Clinical Study Protocol

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The cohort study for chronic obstructive pulmonary diseases (COPD) in China ---- Observation of the disease outcome and identification of prognostic biomarkers for the disease outcome

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Contents

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Events
ADR	Adverse Drug Reactions
BD	Bronchodilator
CAT	COPD Assessment Test
COPD	Chronic Obstructive Pulmonary Disease
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRQoL	Health-related Quality of Life
mMRC	Modified British Medical Research Council
SAE	Serious Adverse Events
SGRQ	the St George's Respiratory Quesionnaire

1. INTRODUCTION

1.1 Background

Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways, which is diagnosed based on chronic cough, sputum, wheeze & exposure to harmful factors, and confirmed by spirometry(1).

COPD is a leading cause of morbidity and mortality worldwide. In China, respiratory diseases (of which COPD is a major component) are the third leading cause of death in rural areas and the fourth leading cause of death in urban areas and rank second among the burdens of diseases.

The overall prevalence of COPD was 8.2%(men, 12.4%; women, 5.1%) (40 y) in China. It seems the prevalence is still growing concerning the high smoking rate, increasing aging population and serious air pollution in China(2).

Currently, COPD is largely treated symptomatically using bronchodilators to improve airflow, reduce dyspnea and prevent exacerbations. One major barrier to novel therapies is the heterogeneity of COPD pathogenesis. Although COPD is characterized by airflow limitation, the molecular processes that drive the airflow limitation are thought to be highly variable. To capture this heterogeneity, there has been a focused effort on finding simple biomarkers of disease activity.

1.2 Rationale

Chronic obstructive pulmonary disease (COPD) is a complex clinical entity. In contrast to previously limited diagnostic definitions, it is now apparent that COPD is a clinically and biologically heterogeneous disease process, overlapping with other airways diseases like chronic asthma. As such, symptomatic response to current standard treatment practices is variable. Thus phenotype and endotype are need to be identified to figure out the way to predict the disease course, treatment responses and prognosis. Recently, some big cohort studies about COPD have been conducted in the world, such as COPDgene, Eclipse and Spiromics(3-5). And some specific phenotypes and valuable biomarker have been identified in patients with strict definition of COPD.

However, currently there is few COPD studies to describe the biomarkers of the COPD patients longitudinally and few biological database established in China. Furthermore, there is very limited availability of emerging biomarker data (especially linked to other data types), which are key to understanding novel phenotypes and endotypes, disease mechanism, and disease progression, and to drive scientific discovery in obstructive lung disease.

Novelty, a Global sponsored study by AstraZeneca, aims to identify phenotypes and endotypes based on biomarkers and/or clinical parameters that are associated with differential outcomes over 3 years. But due to HGRAC restriction, China made the Specific Protocol

Amendment: No biobanking of any samples and remove collection of: DNA & RNA; urine; plasma.

In China, the phenotype / endotype of COPD patients might be unique for the following reasons, passive smoking is very common in China; air-pollution is public health issue in China; exposure to bio-fuel is not uncommon, especially in rural areas of China.

This study aims to clearly understand the Chinese COPD patients as below:

1. What's clinical outcome of COPD patients, including mortality, lung function decline, QOL, COPD exacerbation?

2. What's the different biomarkers to predict clinical outcomes in COPD patients?

3. What's the longitudinal clinical features and clinical practice of COPD patients to guide the future treatment pattern?

4. What's the relationship between high risk population (GOLD 0) with COPD patients and identify specific biomarkers to predict the disease progress?

This study is co-fuding with National Key Research and Development Program of China (No: 2016YFC0901102) and AstraZeneca's clinical research project (ESR-16-12485).

2. OBJECTIVES

2.1 Primary Objective & Outcome Measure

Primary Objective:	**Outcome Measure:**
● To observe the disease outcome and identify sub-populations (phenotype& biomarker) of COPD patients to know the clinical outcome	● COPD-related mortality and all-cause mortality in COPD individuals and GOLD 0 individuals respectively ● Clinical characteristics* and biomarkers* to identify phenotype* ● Use different phenotypes /biomarkers to predict clinical outcomes* of COPD ● Phenotypes and biomarkers of COPD patients to know the clinical outcome from specific treatment regimen*

* Clinical characteristics: allergic history, smoking history/ passive smoking history, occupational exposure, bio-fuel exposure, current respiratory symptoms, pulmonary function test, presence or absence of emphysema or chronic bronchitis on CT scan
* Biomarkers: blood sample tested for biomarkers such as IL-4, IL-5, IL6, IL-8, IL-13, IL-33, TNF-α, CRP, EOS, etc.
* Phenotype: COPD without asthma/asthmatic characteristic population, COPD overlapping asthma/ asthmatic population, passive-smoking population, bio-fuel exposure population,

bronchitis-dominant COPD sub-population, emphysema-dominant COPD sub-population, more inflammatory COPD sub-population, less inflammatory COPD sub-population, neutrophilic inflammatory COPD sub-population, eosinophilic inflammatory COPD sub-population, etc.
* Clinical outcomes: COPD-related mortality and all-cause mortality, exacerbation rate, QOL, FEV_1, 6MWT decline.
* Specific treatment regimen: such as ICS+LABA vs LABA. e.g. inflammatory cytokine to predict clinical outcomes assessed by acute exacerbation rate, COPD-related mortality and all-cause mortality with different treatment regimen.

2.2 Secondary Objectives & Outcome Measure

Secondary Objective:	**Outcome Measure :**
● To identify the risk factor of progressing to COPD in population with high risk factors (GOLD 0). ● To describe the association between specified biomarkers, at enrolment and over time and evaluate their stability over time, factors affecting their variability, and their relationship with clinical features.	● Baseline summary of patients in GOLD 0 & COPD I~IV: demographic data, medical history, risk factors, acute exacerbation history in 12 months before the visit. Pulmonary function, CT results, QOL ● Longitudinal summary of patients in GOLD 0 & COPD I~IV: mortality, exacerbation* and treatment regimen modification* and reseasons for modifications, comorbidities morbidity, pulmonary function(FEV_1) , QOL and ability of activity ecaluated by 6MWT decline, biomarkers* at baseline and annually at each visit.

* Exacerbation: the number of exacerbations, severity of exacerbation: using systemic hormones/antibiotics/emergency /hospitalization and days of hospitalization or emergency room visit
* Treatment regimen modification: non-medicine treatment and medicine treatment including type/duration/dosage/frequency/discontinuation
* Biomarkers: blood sample tested for biomarkers such as IL-4, IL-5, IL6, IL-8, IL-13, IL-33, TNF-α, CRP, EOS, etc.

2.3 Exploratory Objectives & Outcome Measure

Exploratory Objective:	**Outcome Measure :**

• To investigate the factors of exacerbation of COPD patients. • To investigate the factors to predict treatment response.	• Multiple-factor analysis about the COPD exacerbation number (biomarkers, demographics data, drug compliance, visit compliance, smoking status, drug class, comorbidity, disease severity, QOL, etc.) • Treatment regimen modification and reseasons for modifications: medicine (type/duration/dosage/frequency/discontinuation) between each follow-up assessment. • Correlation between biomarkers, disease severity and/ or control and different measures of response to treatment. • Levels of biomarker parameters, lung function, and risk factors at each follow-up assessment, and variability in these measures

3. METHODOLOGY

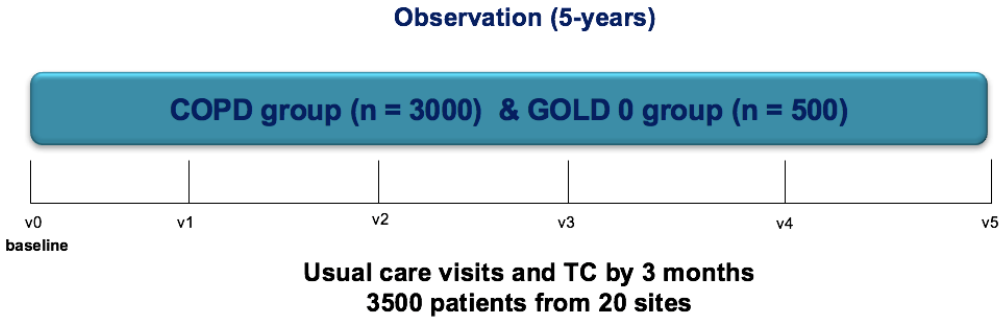
3.1 National Program ---- Co-Funding

This study is co-fuding with National Key Research and Development Program of China (No: 2016YFC0901102) and AstraZeneca's clinical research project (ESR-16-12485).

3.2 Study Design

This is a multi-center observational prospective longitudinal cohort study. The study is designed to observe 3800 subjects for more than 5 years, including COPD subjects (n = 3000) and GOLD 0 subjects (n = 800) from 20 study sites, with baseline visit and Visit 1 in the first year and Visit 2 to Visit 5 in the next consecutive years. Each site will recruit about 150 COPD patients and 25 GOLD 0 subjects successively.

Blood sample will be collected at sites and transported to central lab to test for biomarkers such as IL-4, IL-5, IL6, IL-8, IL-13, IL-33, TNF-α, CRP, EOS, etc. Blood sample will then be preserved in central lab.



3.3 Study Population

The study population will recruit about 3800 subjects, men or women, between 40-75 yrs, with or without persistent airflow limitation (post-BD $FEV_1/FVC < 0.7$) in China. There are 2 cohorts in this study: COPD group and GOLD 0 group.

3000 patients will be recruited in COPD group. The post-bronchodilator FEV_1/FVC ratio < 0.70 was used as definition of COPD, which was proposed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). According to the real distribution of COPD patients, the sample size for different GOLD level was assigned as 500 (I), 2000 (II/III), 500 (IV).

800 individuals will be recruited in GOLD 0 group. GOLD 0 is defined as having chronic respiratory symptoms and/or high risk factors, but without airflow (post-BD $FEV_1/FVC \geqslant 0.7$). Chronic respiratory symptoms is defined as chronic cough, phlegm production, chest tightness, short of breath, dyspnea, wheeze, ect. High risk factors is defined as cigarette smoking, passive smoking, occupational exposures, bio-fuels exposures ect.

	GOLD 0	**GOLD I**	**GOLD II/III**	**GOLD IV**
Sample	800	500	2000	500
post-BD FEV_1/FVC	$\geqslant 0.7$	< 0.7	< 0.7	< 0.7
FEV_1 % Pred		$>$ 80%	80 – 30%	$<$ 30%

3.4 Data Sources

Sites must be tier 2 or tier 3 hospitals in China, with the equipment and ability to conduct pulmonary function test, HRCT. Investigators will be respiratory physicians working in the respiratory department of tier 2 or tier 3 hospitals. Physicians should have patients' spirometric data with 12 months before baseline in the patient's medical files (post-BD FEV_1%pred and post-BD FEV_1/FVC).

3.5 Inclusion Criteria

Subject population that will be observed in this study must meet all of the following criteria:

- Aged 40-75 years
- COPD group: baseline post-bronchodilator $FEV_1/FVC < 0.7$
- GOLD 0 group: individuals with chronic respiratory symptoms and/or high risk factors
- Signed informed consent obtained prior to participations with the ability to comply with protocol and be available for study visits over more than 5 years

3.6 Exclusion Criteria

Subject population that will be observed in this study must meet none of the following criteria:

- Acute exacerbation in the past 3 months
- Having other repiratory diseases with massive lung tissue destruction such as severe bronchiectasis and tuberculosis, etc
- The usual criteria of serious uncontrolled diseases
- thoracic or abdominal surgery in the last 3 months
- eye surgery in the last three months
- retinal detachment
- myocardial infarction in the last 3 months
- admission to hospital for any cardiac condition in the last month
- heart rate over 120 beats per minute
- antibacterial chemotherapy for tuberculosis
- pregnant or breast feeding

3.7 Study Plan

3.7.1 Intensive Follow-up Study Plan

	V0	**V1（12months±30d）**	**V2（24months±30d）**	**V3（36months±30d）**	**V4（48months±30d）**	**V5（60months±30d）**	**TC*（Every 3 months after enrolled）**
Informed consent	√						
Inclusion/exclusion criteria	√						
Demographics, medical history, etc	√						
Disease outcome		√	√	√	√	√	√

Physical examination	√	√	√	√	√	√	
Spirometry	√	√	√	√	√	√	
Lung volume measurement	√		√		√		
Diffusion function	√		√		√		
FENO	√	√	√	√	√	√	
Chest X-ray		√		√		√	
Chest CT(inspiratory and expiratory phase)	√		√		√		
6MWT	√	√	√	√	√	√	
Blood RT	√	√	√	√	√	√	
Phadiatop	√	√	√	√	√	√	
Total IgE	√	√	√	√	√	√	
Questionnaire (SGRQ/CAT/ mMRC/GERD Q/GAD-7/PHQ-9)	√	√	√	√	√	√	
Daily activities	√	√	√	√	√	√	
Blood samples	√	√	√	√	√	√	

* TC: Every 3 months after enrolled, interview participates by phone focusing on acute exacerbations, visits to hospitals, hospitalization and data about mortality

3.7.2 Extensive Follpw-up Study Plan

3.7.2.1 COPD Cohort Extensive Follpw-up

	V0	**V1（12months± 30d）**	**V2（24months± 30d）**	**V3（36months± 30d）**	**V4（48months± 30d）**	**V5（60months± 30d）**
Informed consent	√					

Inclusive/exclusive criteria	√					
Demographics, medical history, etc	√					
Disease outcomes		√	√	√	√	√
Physical examination	√	√	√	√	√	√
Spirometry	√	√	√	√	√	√
Chest X-ray	√	√	√	√	√	√
Blood RT	√					
Questionnaire (CAT/mMRC)	√	√	√	√	√	√
Blood samples	√					

3.7.2.2 GOLD 0 Cohort Extensive Follow-up

	V0（0 月）	**V1（12months± 30d）**	**V2（24months± 30d）**	**V3（36months± 30d）**	**V4（48months± 30d）**	**V5（60months± 30d）**
Informed consent	√					
Inclusive/exclusive criteria	√					
Demographics, medical history, etc	√					
Disease outcomes						√
Physical examination	√					√
Spirometry	√					√
Chest X-ray	√					√
Blood RT	√					
Questionnaire (CAT/mMRC)	√					√
Blood samples	√					

4. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

4.1 Exposures

The treatments will be determined by their treating physicians and no additional investigational drugs will be applied to the patients included in this study. Current medications and dosages to treat these diseases and some specific concomitant medications (steroids) will be collected at the visit.

4.2 Variables

- Demographic Data: gender, date of birth, height, weight, living environment, educational level/ years of formal education
- Medical history or Family history
- Allergic history
- Smoking history/ Passive smoking history
- Occupational exposure
- Bio-fuel exposure
- Current respiratory symptoms: breathlessness, chest tightness, coughing, wheezing, sputum production
- Years of COPD/chronic bronchitis/emphysema diagnosis and age of onset
- Acute exacerbation
  - × Acute exacerbation history in 12 months before the visit (the number of exacerbations, severity of exacerbation (using systemic hormones / antibiotics / emergency / hospitalization) and days of hospitalization or emergency room visit
  - × Acute exacerbation and treatment information during intervals of visits: the number of exacerbations, severity of exacerbation (using systemic hormones / antibiotics / emergency / hospitalization) and days of hospitalization or emergency room visit
- Comorbidities
  - × Fromer comorbidities before baseline
  - × New-developed comorbidities during intervals of visits
- COPD-related mortality and all-cause mortality during intervals of visits
- Teatment
  - × Current used medications prescribed by physicians to treat COPD/ chronic respiratory symptoms (type/duration/dosage/frequency)
  - × Treatment regimen modification and reseason for modifications during intervals of visits: medicine (type/duration/dosage/frequency) and non-medicine treatment
  - × Specific concomitant medications: steroids
- Pulmonary function:
  - × The latest pulmonary function results at non-acute stage in 12 months before baseline
  - × Spirometry and bronchial dilation test: pre/post/pred - FEV_1, pre/post/pred - FVC, post - FEV_1/FVC

  - × Lung volume measurement: absolute/pred - IC, absolute/pred - VCmax, absolute/pred - RV, absolute/pred - TLC
  - × Diffusion function: absolute/pred DLCO SB, absolute/pred VA
- Chest X-Ray
- HRCT scan: Chest high-resolution computed tomography at inspiratory and expiratory: presence or absence of emphysema /chronic bronchitis/pulmonary bulla or other abnormities; bronchial wall thickening
- Blood sample: IL-4, IL-5, IL6, IL-8, IL-13, IL-33, TNF-α, CRP, EOS
- Health-Related Quality of Life (QOL) evaluated by questionnaires: CAT*, mMRC*, SGRQ*
- Daily activity: monitored by pedometer for consecutive 7 days
- 6 minute walk test

*Patient Reported Outcomes(PRO) Measures

CAT / mMRC / SGRQ will be completed by patients themselves independently. If patients have any questions, investigator can help to explain the content of every item. The investigator should review the questionnaires to avoid any uncompleted responses. It is recommended that the investigators perform the clinical evaluation following completion of the questionnaire.

*CAT (COPD Assessment Test): CAT has been developed by Jones et al. CAT is a validated, short and simple questionnaire used to assess COPD symptom and the COPD impact on patients' daily life and well-being. It has good measurement properties, is sensitive to differences in state and should provide a valid, reliable and standardised measure of COPD health status with worldwide relevance. CAT comprises eight questions, each presented as a semantic six-point (0–5) differential scale, providing a total score out of 40. Scores of 0–10, 11–20, 21–30 and 31–40 represent mild, moderate, severe, or very severe clinical impact, respectively.

*mMRC (Modified British Medical Research Council): mMRC is a modified respiratory questionnaire designed by British Medical Research Council. It is used to assess the severity of breathlessness of COPD patients according to the different activities when dyspnea occurrs. mMRC is divided into 5 grades from 0 to 4 grade.

*SGRQ (the St George's Respiratory Quesionnaire): The SGRQ is designed to measure health impairment in patients with asthma and COPD. It is in two parts. Part I produces the Symptoms score, and Part 2 the Activity and Impacts scores. A Total score is also produced.

5. DATA PROCESSING

5.1 Sample Size Determination

This study is co-fuding with National Key Research and Development Program of China (No: 2016YFC0901102). The sample size has been determined as 3000 COPD individuals and 800 GOLD 0 subjects..

Sample size of the surney is 3800, including 3000 COPD patients and 800 GOLD 0 subjects. The sample size of COPD corhort was calculated considering the mortality of COPD as the primary outcome. With the assumption of average mortality in COPD population is 15%(6)，3000 enrolled subjects (assume a drop-out rate of 30%) will provide a precision of 1.5% for the estimate of the 95% confidence interval for the mortality rate.

According to the real distribution of COPD patients, the number of enrolled subjects for different GOLD level was assigned as 800 (GOLD I), 2000 (GOLD II/III) and 800 (GOLD IV). Assume the mortality for GOLD IV will be the highest, 25%, 800 subjects considering 30% drop-out rate still provide a precision of 4.5%. There's no exact assumption for the mortality rate in GOLD (0) population. It's assumed less than 25%, then 800 subjects will still provide a precision less than 4.5% which can fulfil the study need.

5.2 Statistical Analyses

Full analysis set (FAS) will be used for all analyses, which includes all enrolled subjects who fulfil the inclusion/exclusion criteria. Missing data will be analysed as it is, no imputation method will be utilized.

Statistical analysis will be conducted by epidemiology & statistics work group from Chinese Academy of Sciences, using SAS and SUDAAN software.

The analysis method will be primarily descriptive. For continuous variables, summary statistics including n, mean, median, standard deviation, min and max will be presented. For categorical variables, frequency and percentage of subjects at each category level will be presented. The variable with missing values will be analysed as is, that is, no imputation method will be utilized.

The primary variable, mortality rates inlucding COPD related mortality and all-cause mortality overall and by GOLD group will be summarized using the frequency and percentage, a 95% confidence interval for the percentage will be constructed. The mortality per patient-year (defined as the number of patients in whom an event occurs divided by the sum of person-time) may be provided if applicable

The other primary and secondary variables will be analysed descriptively overall and by sub-population: gender, year of birth, height, weight, living environment, educational level/ years of formal education, data of medical history, allergic history, smoking history/ passive smoking history, occupational exposure, bio-fuel exposure, current respiratory symptoms, pulmonary function test, HRCT scan (presence or absence of emphysema /chronic bronchitis/pulmonary bulla or other abnormities; bronchial wall thickening); blood sample (IL-4, IL-5, IL6, IL-8, IL-13, IL-33, TNF-α, CRP, EOS) .

The pre-planned sub-populations are: COPD without asthma/asthmatic characteristic population, COPD overlapping asthma/ asthmatic population, passive-smoking population, bio-fuel exposure population, bronchitis-dominant COPD sub-population, emphysema-dominant COPD sub-population, more inflammatory COPD sub-population, less

inflammatory COPD sub-population, neutrophilic inflammatory COPD sub-population, eosinophilic inflammatory COPD sub-population, etc.

Risk factor analyses will be performed using linear regression or logistic regression method to explore the relationship between phenotypes /biomarkers (IL-4, IL-5, IL-6, IL-8, IL-13, IL-33, TNF, CRP, EOS), different treatment regimen and clinical outcomes (COPD-related mortality and all-cause mortality, exacerbation rate, QOL, FEV_1 decline, 6MWT) in the whole population of COPD and different sub-populations mentioned above.

The multiple-factor analyses will be further performed to explore if different phenotypes /biomarkers (IL-4, IL-5, IL-6, IL-8, IL-13, IL-33, TNF, CRP, EOS) , different treatment regimen are pragnostic factors of clinical outcomes (COPD-related mortality and all-cause mortality, exacerbation rate, QOL, FEV_1 decline, 6MWT) in the whole population of COPD and different sub-populations mentioned above.

The analyses will be further detailed in a statistical analysis plan (SAP).

5.3 Data Management

An electronic data capture (EDC) system will be used in this study. A password-protected web-based data entry platform was used to enter data of each site. Meanwhile, paper-based questionnaire administration was also used in order to ensure the validity of the computer-based system. The PFTs data from spirometry was transmitted daily to the web-based data entry platform. Researchers in each site graded the quality of PFTs (FEV_1, FVC, and diffusing capacity of the lung for carbon monoxide) in 48 hour intervals according to a scholastic-type grading system: A, B, C, D, or E. Researchers at the central site checked the quality grade among 20% of PFT data selected randomly each week. If more than 10% of PFT data in a sample site was graded D or E, PFTs was conducted again. If researcher grading differs between a site and central site, PFTs was also conducted again at that site.

Questionnaire variables was checked for completeness and accuracy. Any apparent errors and omissions in the data that require clarification will be resolved with the interviewer before data entry. All paper questionnaire administration was transmitted to the central site and was entered into the electronic database as well. Currently, double-entered data needed to be checked for consistency before statistical analysis, while the paper questionnaires needed to be scanned and properly documented.

6. MONITORING OF THE STUDY

During the study, PI will be in charge of the monitoring of the whole procedure. Two working group will be recruited, focusing on data cleaning and data analysis respectively. They will be led by Prof. Kewu Hang from Beijing Institute of Respiratory Medicine. The leader will report the progress of the study to the PI every week.

7. COLLECTION AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS

7.1 Definition of Adverse Events (AE)

An AE is any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs.

7.2 Definition of Serious Adverse Events (SAE)

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is life-threatening (life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe)
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event that may jeopardise the subject or may require intervention to prevent one of the outcomes listed above. Medical and scientific judgement should be exercised in deciding whether other situations should be considered an SAE.

Any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and may be subject to expedited reporting requirements in some countries. Any organism, virus or infectious particle (for example Prion Protein Transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

7.3 Definition of Adverse Drug Reactions (ADR)

An Adverse Drug Reaction (ADR) is an Adverse Event suspected to be causally related to the medicinal product.

An ADR is a response to a medicinal product which is noxious and unintended. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure.

The term ADR is used to include both serious and non-serious ADRs.

7.4 Reporting of Adverse Events

The investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

The investigator is responsible for reporting adverse events to regulatory authorities according to China related regulation.

The investigator is also responsible for reporting serious ADRs related to AZ products within 24 hours after awareness to AZ Data Entry Site and copy to AZ China pharmacovigilance department, and reporting non-serious ADRs related to AZ products to AZ Data Entry Site and copy to China pharmacovigilance department within the same timeline as investigator reports to ADR center.

Contact information of AZ Data Entry Site:

Fax: +1 302 886 4114;

Email: AEmailboxclinicaltrialTCS@astrazeneca.com;

Contact information of AZ China Pharmacovigilance department:

Fax: +86 21 38683551;

E-mail: China.AZDrugSafety@astrazeneca.com;

Tel: +86 21 52929866.

For ADRs related to non-AZ products, the investigator can report to the marketing authorisation holder of the products if he/she consider it is appropriate.

8. STUDY TIMETABLE

The study is expected to start in 2017-Q3 and to be completed by 2025-Q4.

The end of the study is definite as “completing all related analysis of the study”

Study period	**Estimated Time**
Protocol approved	Dec. 2016
First subject in	Mar. 2017
Last subject in	Feb. 2020
Last subject last visit	Mar. 2025
Database lock	Jun. 2025

Study period	Estimated Time
Completion of Final Study Report	Sep. 2025
Final Study Report to Publication	Dec. 2025

9. STUDY AGREEMENT

The principal investigator must comply with all the terms, conditions and obligations of the protocol for this study. In the event of any inconsistency, the study protocol shall prevail.

10. LIST OF REFERENCES

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