An open label, multi-centre, post marketing surveillance (PMS) to monitor the safety and efficacy of INCRUSE administered in Korean subjects with chronic obstructive pulmonary disease (COPD) in usual practice

Study No.: 205163

GlaxoSmithKline Korea

Sponsor Signatory:

_____ _____

[redacted] Date

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SUMMARY OF PROTOCOL

Title:	An open label, multi-centre, post-marketing surveillance (PMS) to monitor the safety and efficacy of INCRUSE administered in Korean subjects with chronic obstructive pulmonary disease (COPD) in usual practice
Protocol version:	2.0
Author(s):	[redacted] PMS associate [redacted] PMS team manager [redacted] Medical advisor
Background:	INCRUSE has been approved on 25, June, 2015 in Korea. We aimed to conduct PMS to monitor the safety and efficacy based on the data collected in a real world clinical practice according to PMS regulation.
Objectives:	Primary objective is to monitor adverse events, including unexpected adverse events and/or serious adverse events, reported after administrating INCRUSE. Secondary objective is to monitor efficacy after administrating INCRUSE. ● Minimum one follow-up after administrating INCRUSE for safety evaluation ● Minimum 24 weeks follow-up after administrating INCRUSE for efficacy evaluation
Design:	Open-label, single arm, multi-centre PMS
Eligibility criteria:	All subjects must satisfy the following criteria ● Adult subjects who have chronic obstructive pulmonary disease (COPD) -Pulmonary Function Test: Post bronchodilator, FEV1/FVC < 0.7 ● Subjects who will administer INCRUSE according to locally approved prescribing information
Evaluation variables:	● Primary: Incidence of adverse events, incidence of unexpected adverse events and incidence of serious adverse events after administrating INCRUSE ● Secondary: Efficacy after administrating INCRUSE, as determined by post BD FEV_1 on Treatment Week 24
Numbers of subjects:	600 COPD patients will be recruited. Each subject will be monitored for a maximum of 6 months.
Data analysis:	The number and percentage of subjects with an adverse event, including SAE and/or unexpected AE, after administration of INCRUSE will be presented. Cases with serious adverse events and/or unexpected adverse drug reactions will be described in detail. The percentage of subjects reporting adverse events will be analyzed using Chi-square test or Fisher's exact test stratified by potential confounding factors such as gender, age, smoking history, BMI, baseline lung function test(FEV_1)before administration, COPD treatment, disease history, and others for subgroup analysis. Efficacy evaluation will be stratified by potential confounding factors.

Key milestones:	- Surveillance period (planned): 01.Feb.2016~09 July.2020 - Submission period for periodic report : Every 6 months for 1.5years after approving the product, after that every 1 year (remaining period of Anoro) - Submission period of application form for PMS : 10 July.2020 ~ 09 October.2020

1. INTRODUCTION

1.1. Background

COPD is a major cause of poor health, resulting in millions of deaths annually worldwide[1] and contributing significantly to health care costs and morbidity[2,3]. As of 2001, COPD was the fifth leading cause of death and the eleventh leading cause of disability worldwide. By the year 2020, COPD is expected to be the third leading cause of death and the fifth leading cause of disability[4]. COPD is a preventable and treatable disease characterized by airflow limitation that is not fully reversible[5]. The airflow limitation of COPD is primarily due to small airways disease and parenchymal destruction associated with an abnormal inflammatory response of the lungs, mainly caused by cigarette smoking [5]. COPD is characterized by symptoms of chronic and progressive breathlessness (or dyspnea), cough and sputum production which can be a major cause of disability and anxiety associated with the disease.

COPD treatment guidelines recommend an incremental approach to pharmacological treatment as the disease state worsens, involving the use of combinations of drug classes with different or complementary mechanisms of action[1,5]. As disease progresses from mild to moderate, regular treatment with one or more long-acting bronchodilators is recommended. Treatment with muscarinic antagonists has been shown to significantly improve FEV1, resting and dynamic lung hyperinflation, symptoms, exercise capacity, health status[6.] However, approximately 50% of COPD patients treated with ICS/LABA combination treatment still have moderate-to-severe dyspnoea[7.].

Umeclidinium is an orally inhaled, potent, pan-active LAMA in development for use as an inhaled product in the treatment of COPD as a monotherapy once-daily product and also in combination with the long acting beta agonist (LABA), vilanterol, as a once-daily treatment of COPD.

A once-daily LAMA has the potential to optimize bronchodilator therapy and improve patient compliance and, as a result, improve overall disease management.

INCRUSE was approved on 25, June, 2015 in Korea. We aim to conduct a PMS study to monitor the safety and efficacy based on the data collected in a "real world" clinical practice according to PMS regulation.

2. OBJECTIVES

2.1. Primary

Primary objective is to monitor adverse events, including unexpected adverse events and/or serious adverse events, reported after administrating at least 1 dose of INCRUSE.

- Minimum of one follow-up visit after administration of INCRUSE in order for safety evaluation

2.2. Secondary

Secondary objective is to monitor efficacy after administrating INCRUSE, as determined by following items at the follow up visit on Treatment Week 24.

- physician's evaluation(improved, no change, worsening, not able to determine) based on the variation of post BD FEV_1 following GOLD guideline after administrating INCRUSE for 24weeks

① Improved: improvement of symptom or maintenance effect

② No change: no change compared to pre-administration and no maintenance effect

③ Worsening: worse of symptom than before the medication

④ Not able to determine: in case physician cannot evaluate the efficacy e.g. lost to follow up, in case of no result of Post BD FEV_1

※Maintenance effect: potential of symptom worsening in case of stop administration or similar effect after administrating alternative drug or others

- Post BD FEV_1.

① Lung function test results will be collected through physician

3. DESIGN OF SURVEILLANCE

3.1. Design

Open-label, single arm, multi-centre PMS. No comparator cohort will be included in this study.

3.2. Surveillance period

- Surveillance period (planned) : 01.Feb.2016~09 July.2020
- Submission period for periodic reports : Every 6 months during 1.5 years after approving the product, after that every 1 year
- Submission period of application form for PMS : 10 July.2020 ~ 09 October.2020

3.3. Surveillance site

Division of Pulmonary medicine in the internal medicine department, whole country general-hospital

4. OUTCOME DEFINITIONS

The following outcomes will be collected:

Safety

- Adverse event (AE): All AE will be collected. See Section 9.1 for the definition of AE.
- Adverse drug reaction (ADR): All ADR will be collected. See 9.2 for the definition of ADR
- Serious AE (Serious Adverse Event), Serious ADR (Adverse Drug Reaction): All Serious AE (Serious Adverse Event), Serious ADR (Adverse Drug Reaction) will be will be collected. See Section 9.3 for the definition of Serious AE (Serious Adverse Event), Serious ADR (Adverse Drug Reaction)
- Unexpected ADR: All unexpected ADR will be collected. See Section 9.4 for the definition of unexpected ADR

- Safety evaluable population: All subjects who received at least one dose of INCRUSE and at least one safety assessment

- Safety assessment: All subjects who received at least one dose of INCRUSE will have a safety assessment completed by the treating physician. The safety assessment will indicate whether the subject experienced any adverse events (e.g. unexpected adverse events and/or serious adverse events) post-administration of INCRUSE. All adverse events will be reported according to the processes described in Section 9: Adverse Events and Serious Adverse Events.

Efficacy

Physician's evaluation with post BD FEV_1 on Treatment Week 24. Measure on Treatment Week 24 is defined as the value obtained on Treatment Week 24 (± 14 days).

- Efficacy evaluable population: Subjects who complete physician's evaluation (improved, no change, worsening, not able to determine based on the variation of post BD FEV_1 following GOLD guideline after administrating INCRUSE for 24 weeks and who are able to collect the value of post BD FEV_1

5. SUBJECTS

5.1. Number of subjects

Category	NUMBER OF SUBJECTS	RELEVANT	REFERENCE
New drug - New drug domestically developed first in the world -New drug developing in foreign countries (not approved) - New drug developed in foreign countries and within 3 years from international birth date - New drug developed and approved in foreign country and launched only in that country	More than 3000		
Other new drugs, etc.	**More than 600**	**O**	**Incruse is a LAMA monotheraphy, and one of the component of Anoro, which was approved 10 July 2014.**

* It will not be included in the safety/efficacy evaluable population for subject who did not administer according to prescribing information; however, it will be analyzed separately.

5.2. Eligibility criteria

5.2.1. Inclusion criteria

All subjects must satisfy the following criteria

- Adult subjects (19 years and older) who have chronic obstructive pulmonary disease (COPD)

  -Pulmonary Function Test: Post bronchodilator, FEV1/FVC < 0.7

- Subjects who will administer INCRUSE according to locally approved prescribing information

5.2.2. Exclusion criteria

- Subject who has medical history of hypersensitivity to the active substances or main substances or atropine derivative(i.e. ipratropium,tiotropium, oxitropium, glycopyrronium, aclidinium)

- Subject with severe hypersensitivity to milk proteins
- Subject with hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption

6. SURVEILLANCE ITEMS AND METHODS

6.1. Items

- Information of site: Name of site, Department, Physician name, Centre agreement execution date
- Basic information of subjects: Gender, Age, Height, Weight, Pregnancy and/or Breast-feeding
- COPD disease profile: Disease diagnosis (year), Smoking history (Current smoker/quit smoker/Non smoker, smoking amount(P/Y))
- Disease history of subjects: Cardiovascular disease, Diabetes mellitus, Metabolic syndrome, Osteoporosis, Depression, Lung cancer and others
- INCRUSE information: Dose, Frequency, Starting date, Stop date, Frequency change, Change reason
- COPD related prior medication (4 weeks before the initiation of treatment): Name of prior medication, Dose, Frequency, Starting date, Stop date
- COPD related concomitant medication: Name of concomitant medication, Dose, Frequency, Starting date, Stop date
- Non-COPD related concomitant medication: Name of concomitant medication, Dose, Frequency, Starting date, Stop date, Reason
- Safety: Adverse event, Onset date, Stop date, Severity, Causality(related and non-related), Results

  Efficacy: Physician's evaluation, post BD FEV_1

  [Table 1] Time and Events Table

	At enrollment (Month 0)	Any visits	End of surveillance (Month 6) Or discontinuation
Written Informed Consent	O		
Inclusion/Exclusion	O		
Demography	O		
Medical History	O		
COPD History	O		
Therapy History	O	O	O
Adverse Events		O	O
Evaluation by physicians			O
post BD FEV_1	O*		O*

*Collect the data, if applicable in real practice

6.2. Collection Methods

- Data collection method: Physician collects consecutively all contracted number of subjects who was first administered with the drug after the initiation of surveillance among subjects who consent to participate in the surveillance.

- The cases will be collected using case report form.

7. INVESTIGATIONAL PRODUCT

7.1. Overview

7.1.1. Active pharmaceutical ingredients

Refer to local prescription information

7.1.2. Image

Refer to local prescription information

7.1.3. Indication

Maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)

7.1.4. Dosage and administration

INCRUSE should be administered as 1 inhalation once daily by the orally inhaled route only. INCRUSE should be taken at the same time every day. Do not use INCRUSE more than 1 time every 24 hours.

7.2. Administration schedule

All subjects must administer INCRUSE according to information of prescription. This surveillance doesn't affect the subject's history of care as this is an observational study conducted in real world clinical practice.

8. SUBJECT COMPLETION AND DISCONTINUATION

8.1. Subject completion

It is recommended that physicians follow-up the subjects for at least 24 weeks to assess the safety and efficacy of INCRUSE.

If the subject does not return to a follow-up visit for the safety assessment, the physician can contact subjects by message or call to check for report of any adverse events which occurred 7 days after the last administration.

8.2. Subject drop-out

Subjects who are discontinued because of AEs must be clearly distinguished from subjects who are discontinued for other reasons. For subjects who discontinue INCRUSE during the surveillance, physicians should check AEs which occurred at least 7 days after the last administration. A Subject is considered a 'drop-out' from the surveillance when subject is lost to follow-up after receiving at least one dose of INCRUSE. If no surveillance and follow-up has been performed or no further information has been collected, this subject would be considered as 'drop-out' or lost to follow-up and excluded from the subject of safety evaluation.

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9. ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENS (SAE)

9.1. Definition of AE (Adverse Event)

AE represents the undesirable, unintended signs (i.e. abnormal laboratory results), symptoms, or diseases that occur after the administration / use of pharmaceuticals, etc., and a causal relationship with the concerned pharmaceutical is not necessarily required.

9.2. Definition of ADR (Adverse Drug Reaction)

ADR represents adverse, unintended reactions from normal administration / use of the pharmaceuticals, etc. for which the causal relationship with the particular pharmaceutical cannot be excluded. Of the voluntarily reported adverse events, those with no known causal relationship with the pharmaceutical are deemed to be adverse drug reactions.

9.3. Definition of Serious AE / ADR (Adverse Drug Reaction)

Serious AE/ADR represents the adverse events / adverse drug reactions that correspond to one of the following.

A. Event which results in death or is life-threatening

B. Event which results in or prolongs hospitalization

C. Event which is disabling or incapacitating

D. Event of Congenital Anomaly/Birth Defect

E. Other medically significant conditions

9.4. Definition of Unexpected ADR

Unexpected ADR represents an adverse drug reaction where the nature, severity, specificity, or the outcome shows a difference from that reported in the product approval (this hereinafter includes product declaration)

9.5. Recording of AEs and SAEs

Every AE or SAE which occurs during the PMS should be documented at medical record and relevant page of CRF for the subject. Each AE or SAE should be documented separately.

When an AE/SAE occurs, it is the responsibility of the physician to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The physician will then record all relevant information regarding an AE/SAE on the CRF. It is not acceptable for the physician to send photocopies of the subject's medical records to GSK in lieu of completion of the appropriate AE/SAE CRF pages. However, there may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK.

The physician will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

9.6. AEs and SAEs Evaluation

9.6.1. Assessment of severity

Physician assesses the severity of AE and/or SAE reported during surveillance. The assessment is based on the physician's medical judgement. The severity of each AE/or SAE on the case report table assesses as following.

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities

Severe: An event that prevents normal everyday activities

An AE that is assessed as severe will not be confused with an SAE.Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in "the definition of an SAE" (Section 9.3).

9.6.2. Assessment of causality

The physician has the obligation to assess the causality of the investigational product and each of adverse event/serious adverse event. The physician should determine the causality in a clinical judgment. The investigation should be based upon other optional reason, such as the natural history of the underlying disease, concomitant therapy, other risk factors and temporary causality of the adverse event with the investigational product. In addition, the physician can refer to Product Information in determining his/her assessment.

Should a serious adverse event occur the physician must have the minimum information (subject no, product, AE term, onset date, causality, etc.) that is included in the initial report to GSK. However, it is very important that the physician always assesses the causality of the adverse event before sending a case report form about a serious adverse event. The physician can correct a case report form about a serious adverse event with follow up information and change the assessment of the causality. The assessment of the causality is one of the standards to be used to decide whether to report to the relevant authorities.

The physician should assess the causality according to the guidelines described in a serious adverse event form of a case report form. For detailed assessment of causality, refers as following.

① Certain:

The relationship of the administration and use of the drug is reasonable and it is not able to be explained by other medication, chemical substances or concomitant disease, it shows clinically reasonable response on discontinuation of the drug, the decisive case in the pharmacological or phenomenological aspect on re-challenge of the drugs if needed

② Probable/Likely:

The temporal sequence of the administration and use of the drug is appropriate and it does not seem that it is accompanied by other medications, chemical substances or concomitant disease, in the case that shows clinically appropriate response on discontinuation of the drug (no information for re-challenge)

③ Possible:

The temporal sequence of the administration and use of the drug is appropriate but it is also able to be explained by other medications, chemical substances or concomitant disease, and information related to discontinuation of the drug is insufficient or vague

④ Unlikely:

It is a transitory case which may not have causality with the administration and use of the drug, it is also able to be explained reasonably by other medications, chemical substances or latent disease

⑤ Conditional/Unclassified:

In the case that more information is needed for a proper evaluation or additional information is under review

⑥ Unassessible/Unclassifiable:

In the case that could not be judged due to insufficient or conflicting information and no way to complement or validate (e.g. Subjects do not complete follow up visits or do not have the result of Post BD $FEV_{1)}$

9.7. Follow-up of AEs and SAEs

After the initial AE/SAE report, the physician is required to proactively follow each subject and provide further information to GSK on the subject's condition.

All AEs and SAEs documented at a previous visit/contact and that are designated as ongoing, will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once they are resolved, the information should be updated in the AE/SAE CRF page. The physician will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

GSK may request that the physician perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The physician is obligated to assist. If a subject dies during participation in the study or during a recognized follow-up period, the physician will provide GSK with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded in the originally completed SAE data collection tool. The physician will submit the updated SAE data with the signature to GSK within the designated reporting time frames in section 9.8.

9.8. Expedite Reporting of SAEs to GSK

SAEs will be promptly reported to GSK as described in the following table once the physician determined that the event meets the protocol definition of an SAE.

9.8.1. Timeframe of SAE reporting to GSK

	Initial SAE Reports		Follow-up Information on a Previously Reported SAE	
Type of SAE	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hrs	"SAE" CRF PAGES	24 hrs	UPDATED "SAE" CRF PAGES

9.8.2. Completion and transmission of the SAE REPORTS

Once the physician is aware of a serious adverse event that the subject experienced, he/she should report to GSK within 24 hours. The physician (or his/her designee) should record as all detailed information obtained about the serious adverse event as possible in the section for serious adverse event of a case report form completely and send to GSK within the defined timeline. If the physician does not have all information about the serious adverse event, he/she does not wait for additional information before completing the form and notifies to GSK. When obtaining additional information, the report form should be updated.

The physician should always provide the assessment of the causality at the time of the initial reporting as described in Section 9.6.2 “Assessment of Causality”.

The physician sends “Serious Adverse event” report form to the GSK staff (or designee) that collects a serious adverse event by fax or e-mail. Below are the fax number, telephone number and address of the GSK staff (or designee) collecting a serious adverse event.

Name: [redacted]
Fax : [redacted] Phone : [redacted] Email : [redacted]
Address : PMS team, GSK, 9 Floor LS Yongsan Tower, 191, Hangang ro 2 ga, Yongsan gu, Seoul

9.9. Adverse Drug Reaction reporting to GSK

Once the physician is aware of an adverse drug reaction that the subject experienced, he/she should report to GSK.

The physician (or his/her designee) should record as all detailed information obtained about the adverse drug reaction as possible in the section for adverse drug reaction report form completely and send to GSK. If the physician does not have all information about the adverse drug reaction, he/she does not wait for additional information before completing the form and notifies to GSK. When obtaining additional information, the report form should be updated.

The physician sends “Adverse Drug Reaction” report form to the GSK staff (or designee) that collects an adverse drug reaction by fax or e-mail. Below are the fax number, telephone number and address of the GSK staff (or designee) collecting an adverse drug reaction.

Name: [redacted]
Fax : [redacted] Phone : [redacted]
Email : [redacted]
Address : PMS team, GSK, 9 Floor LS Yongsan Tower, 191, Hangang ro 2 ga, Yongsan gu, Seoul

9.10. Regulatory Reporting Requirements for AEs

The physician should report all serious adverse events to GSK according to the procedures described in Section 9.8 “Expedite Reporting of SAEs to GSK”.

The physician should comply with regulations regarding the adverse event report to regulatory authorities, IRB (Institutional Review Board) and IEC (Independent Ethics Committee).

GSK is liable to report the safety of the investigational product to local regulatory authorities. The physician’s expedite reporting of a serious adverse event to the applicable project contact is essential in meeting legal and ethical responsibilities for the safety of other subjects.

In case of serious AE/ADR, GSK should report to KIDS (The Korea Institute of Drug Safety and Risk Management) within 15days of getting report or noticing events from the physician. GSK has responsibility that report serious AE/ADR that was not expedited of reported AE to KIDS when submit periodic report (re-examination as substitute for final report).

10. REPORTING OF PREGNANCY

If there is a subject in person or his or her partner who becomes pregnant while participating in this surveillance, the physician should inform the GSK personnel within 24 hours. This inform should be with the Pregnancy Report Form and for initial and follow up report, both should be done.

Name: [redacted]
Fax : [redacted] Phone : [redacted]
Email : [redacted]
Address : PMS team, GSK, 9[th] Floor LS Yongsan Tower, 191, Hangang ro 2 ga, Yongsan gu, Seoul

Once a pregnant subject is identified, it is needed to contact GSK personnel and get the Pregnancy Report Form and be guided to complete the form with guidance.

10.1. Initial report

The physicians will record pregnancy information on the Pregnancy Report Form and submit it to GSK within 24 hours of learning of a subject's pregnancy.

10.2. Follow-up report

Follow the subject to determine the outcome of the pregnancy and forward the outcome information to GSK no later than 6 to 8 weeks following the estimated delivery date. The result about the follow up report should be reported to GSK within 24 hours.

10.3. Timeframe

	Initial Pregnancy Reports		Follow-up Information on a Previously Reported Pregnancy	
Type of Pregnancies	Time Frame	Documents	Time Frame	Documents
All Pregnancies	24 hrs	"PREGNANCY" REPORT FORM	24 hrs	UPDATED "PREGNANCY" REPORT FORM

11. DATA ANALYSIS AND STASTICAL CONSIDERATION

11.1. Evaluation variable

- ✓ Primary : Incidence of adverse events, incidence of unexpected adverse events, and incidence of serious adverse events after administrating INCRUSE
- ✓ Secondary: Physician's evaluation based on the variation of post BD FEV_1 following GOLD guideline after administrating INCRUSE for 24 weeks, the value of post BD FEV_1

11.2. Interim analysis

The Interim analysis is restricted to subjects who have completed data analysis according to PMS regulation, and the interim PMS report is submitted to MFDS as a form of periodic report.

11.3. Number of subjects

The number of subjects to be included in this surveillance was determined to be 600 patients as per PMS regulation.

11.4. Data analysis

11.4.1. Analysis population

We plan to summarize the number of enrolled cases and identify subjects evaluated for safety, evaluated for efficacy, and drop-out cases.

- Safety population: All subjects who receive at least one dose of INCRUSE and complete at least one safety assessment will be included in the evaluable safety population.

- Efficacy population: Subjects who complete physician's evaluation(improved, no change, worsening, not able to determine) based on the variation of post BD FEV_1 following GOLD guideline administrating INCRUSE for 24 weeks and who are able to collect the value of post BD FEV_1 Drop-out cases will be analyzed separately for safety and efficacy

11.4.2. Analysis method of safety

Safety analyses will be based on the evaluable safety population, defined as subjects who receive at least one dose of the INCRUSE and completed at least one safety assessment. In general, data summaries will be presented overall and by the subgroups of interest. Categorical outcomes will be summarized by the number and percentage in each category. Baseline characteristics will be summarized using descriptive statistics.

The number and percentage of subjects reporting adverse event after administration of INCRUSE will be tabulated. Cases with serious adverse events and/or unexpected adverse drug reactions will be described in detail. The distribution of adverse events by severity, outcome, and physician's causal assessment will be tabulated. The percentage of subjects reporting adverse events will be analyzed using Chi-square test or Fisher's exact test stratified by potential confounding factors for subgroup analysis.

For re-examination, safety analyses will be analyzed by sub-group analysis, potential confounding factors and considered baseline using a logistic regression model. If clinical significance is found through analysis, clinical/medical opinion will be detailed..

11.4.3. Efficacy Analysis

Efficacy analyses will be based on the evaluable population, defined as subjects who receive INCRUSE for 24 weeks and have a completed post BD FEV_1 on Treatment Week 24. In general, data summaries will be presented overall and by the subgroups of interest. Categorical outcomes will be summarized by the number and percentage in each category. Continuous outcomes will be summarized by the number of non-missing values, mean, standard deviation, median, lower and upper quartiles and minimum and maximum values. Baseline characteristics will be summarized using descriptive statistics.

Efficacy endpoint, physician evaluation result and post BD FEV_1 (the mean value before administration and on Treatment week 24) will be presented in a summary table of baseline data and stratified by potential confounding factors. Efficacy will be analyzed using Chi-square test or Fisher's exact test stratified by potential confounding factors for subgroup analysis.

For re-examination, efficacy analyses will be analyzed by sub-group analysis, potential confounding factor and considered baseline using a logistic regression model. If clinical significance is found through analysis, clinical/medical opinion will be described.

11.4.4. Safety and efficacy analysis for specific population

The percentage of subjects reporting adverse events among special care population (the elderly-65 years old and above, hepatic impairment, renal impairment, child and pregnant women) will be tabulated respectively. The difference of the incidence of adverse events by each factor will be analyzed. The efficacy test results will be tabulated for efficacy analysis and the difference each factor will be analyzed.

11.4.5. Potential confounding factor

- Basic information of subjects: Gender, Age, Weight, Height

- COPD disease profile: Disease diagnosis (year), Smoking history (Current smoker/quit smoker/Non smoker, smoking amount(P/Y))

- Disease history of subjects: Cardiovascular disease, Diabetes mellitus, Metabolic syndrome, Osteoporosis, Depression, Lung cancer, etc.

- COPD related concomitant medication (SABA, SAMA, LABA, LAMA, ICS, ICS/LABA, LAMA/LABA, PDE4-I, oral steroid, methylxanthine): Name of concomitant medication, Dose, Duration

- Prior treatment for COPD (before observation start): (SABA, SAMA, LABA, LAMA, ICS, ICS/LABA, LAMA/LABA, PDE4-I, oral steroid, methylxanthine): Name of medication, Dose, Duration

12. CONSIDERATION

12.1. Disclosure of PMS at GSK-Clinical Study Register

The information of this PMS will be posted on *http://www.gsk-clinicalstudyregister.com/*

12.2. Quality Control

If applicable, in accordance with applicable regulations and GSK procedures, GSK monitors will contact the site prior to the start of the PMS to review with the site staff the protocol, PMS requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

GSK will monitor the surveillance to ensure that the:

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

The physician and the head of the medical institution (where applicable) agree to allow the monitor direct access to all relevant documents.

12.3. Quality Assurance

To ensure compliance with all applicable regulatory requirements, GSK may conduct a quality assurance audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the surveillance. In the event of an audit or inspection, the physician (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

12.4. Surveillance and Site Closure

Upon completion or termination of the PMS, the GSK monitor will conduct site closure activities with the physician or site staff (as appropriate), in accordance with applicable regulations and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the PMS at any time for reasons including (but not limited to) safety issues, ethical issues, or serious non-compliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the physician or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the physician or head of the medical institution of the impending action.

If a PMS is suspended or terminated for safety reasons, GSK will promptly inform all physicians, heads of the medical institutions (where applicable), and/or institutions conducting the PMS. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the physician or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

12.5. Records Retention

Following closure of the PMS, the physician or head of the medical institution (where applicable) must maintain all site PMS records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The physician must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if

required. The physician must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the physician of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention period will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

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

12.6. Provision of Study Results and Information to Physicians

After the PMS completed and analyzed, the physician will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

For the surveillance evaluate the efficacy of GSK drug, GSK will disclose the results via the GSK Clinical Trials Register within 8 months upon completion of data analysis (if Pediatric study, within 6months) according to the GSK SOP and provide the physician with the full summary of the PMS results. In addition, the manuscript would be submitted within 18 months upon completion of data analysis. The physician is encouraged to share the summary results with the surveillance subjects, as appropriate.

13. PUBLICATION

13.1. Ownership

All data generated during this PMS and provided to GSK are the property of GSK.

13.2. Confidentiality

The physicians and site staff will keep any information provided by GSK confidential. The information includes this protocol, all data and records generated during PMS. The physicians and site staff will not use the information, data, or records for any purpose other than conducting the PMS. These restrictions do not apply to:

- Information that becomes publicly available through no fault of the physician of site personnel;
- Information that is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study;
- Information that is necessary to disclose in order to provide appropriate medical care to a patient; or
- Study results that may be published, as described in the next paragraph.

13.3. Publication

For any multi-centre study, data from any individual centre must not be published or presented until the complete multi-centre study has been published or presented in full. Any subsequent publications should refer to the published multi-centre findings.

Prior to submitting for publication, presenting, using for instructional purposes or otherwise disclosing the results of the study, the physician shall allow GSK a period of at least thirty (30) days [or, for abstracts, at least five (5) working days] to review the proposed publication or disclosure prior to its submission for publication or other disclosure. Publications or disclosures of PMS results shall not include other confidential information of GSK's. If the proposed publication/disclosure risks GSK's patent any invention related to the PMS, the publication or disclosure will be modified or delayed a sufficient time to allow GSK to seek patient protection of the invention. This statement does not give GSK any editorial rights over the content of a publication or disclosure, other than to restrict the disclosure of GSK's confidential information.

14. REFERENCES

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