Objectives	Endpoints
	baseline) • Change from baseline in COPD assessment test (CAT) • Percentage of responders according to CAT (defined as a ≥2 unit improvement in score from baseline)
Other	
• To compare UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on other COPD efficacy measures	• Rate of mild, moderate or severe exacerbations • Time to first mild, moderate or severe exacerbation • Rate of moderate or severe exacerbation • Time to moderate or severe exacerbation • Time to severe exacerbations • Time to clinically important deterioration (CID) composite endpoint • Time to clinically important deterioration composite endpoint excluding FEV_1 • Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the electronic diary (eDiary) over 24 weeks • Inspiratory capacity (IC) • Full Vital capacity (FVC) • Change from baseline in trough FEV_1 • Change from baseline in global impression of disease severity

Objectives	Endpoints
	baseline) • Change from baseline in COPD assessment test (CAT) • Percentage of responders according to CAT (defined as a ≥2 unit improvement in score from baseline)
Other	
• To compare UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on other COPD efficacy measures	• Rate of mild, moderate or severe exacerbations • Time to first mild, moderate or severe exacerbation • Rate of moderate or severe exacerbation • Time to moderate or severe exacerbation • Time to severe exacerbations • Time to clinically important deterioration (CID) composite endpoint • Time to clinically important deterioration composite endpoint excluding FEV_1 • Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the electronic diary (eDiary) over 24 weeks • Inspiratory capacity (IC) • Full Vital capacity (FVC) • Change from baseline in trough FEV_1 • Change from baseline in global impression of disease severity

Subjects who experience a moderate or severe COPD exacerbation during the run-in period will be deemed run-in failures. Subjects who experience a mild COPD exacerbation, defined as worsening of symptoms that requires **no** treatment with antibiotics or steroids and is self managed by the patient by an increase of inhaled rescue medication, (Appendix 5), will be able to continue in the study based on the judgment of the investigator and agreement of the sponsor's medical monitor.

At the randomization Visit 2 (Day 1) those subjects who successfully complete the run-in period as well as meet the other pre-defined eligibility and randomization criteria will discontinue their inhaled COPD medications and will be randomized to one of the 3 treatment arms for 24 weeks.

During the run-in and treatment period, subjects will be completing PRO questionnaires in the eDiary and performing slow and forced spirometry at specific clinic visits.

In addition, a subset of subjects up to 150 per treatment arm will undergo assessment of their physical activity measured through a physical activity monitor (Actigraph GT9X) worn for 7 days from Screening (Visit 1), for 7 days from Randomisation (Visit 2), 7 days from Visit 3, and for 7 days prior to last clinic Visit (Visit 5).

Concurrent use of COPD maintenance medications including LAMAs, LABAs, oral beta-agonists, theophyllines, inhaled corticosteroids, inhaled corticosteroids and LABA combination and phosphodiesterase 4 inhibitors will not be allowed during the study (Section 6.11.2) .

The occurrence of adverse events (AEs) will be evaluated throughout the study beginning at Visit 2 (Day 1) and until the follow-up contact (Visit 6). Serious adverse events (SAEs) will be collected over the same time period as AEs. However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact (Appendix 4).

All subjects will be given an electronic diary (eDiary) for use during the run-in, and the treatment period to complete PRO questionnaires, record COPD daily symptoms, any medical problems experienced during the study and the time they take their COPD medications. Daily rescue medication usage (number of inhalations taken in the last 24h) will also be captured in the eDiary. In addition, and in some countries, rescue medication use will also be captured by the use of electronic metered dose inhaler (eMDI).

At Screening Visit 1, all subjects must be trained on the proper use of their existing COPD medications inhalation devices and instructed to strictly adhere to and record the time they take their COPD medications in the eDiary.

At the randomization Visit 2, all subjects must be trained on the proper use of the ELLIPTA and DISKUS inhalation devices and instructed to strictly adhere to and record the time they take their study medications in the eDiary.

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [UMEC/VI]		
Severe milk protein allergy	Anoro contains Lactose monohydrate (which contains milk protein) as an excipient.	Exclusion criteria have been set for subjects with milk protein allergy.
Cardiovascular effects such as cardiac arrhythmias *e.g.* supraventricular tachycardia and extrasystoles.	Class effects associated with LABAs and LAMA containing therapy. The clinical significance of these arrhythmias is unknown. Clinical experience with UMEC/VI to date in completed studies did not show any association with major cardiovascular events. Data available in the product label for UMEC/VI	Exclusion criteria have been set for subjects with uncontrolled or severe cardiovascular disease according to the principal investigation's (PI) opinion where the potential risk may outweigh the benefit. The PI should also determine the clinical significance of abnormal ECG findings at screening and exclude subjects who would be at undue risk by participating in the trial. Patients with the following abnormalities will be excluded from participation: atrial fibrillation with rapid ventricular rate >120bpm, sustained or nonsustained ventricular tachycardia, or second degree heart block Mobitz type II or third degree heart block (unless pacemaker or defibrillator had been inserted).
Beta agonists and risk of asthma-related death	Long-acting beta agonists such as vilanterol when used alone may increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including vilanterol. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.	Subjects with a current diagnosis of asthma are excluded from participation in the study.
Paradoxical bronchospasm	As with other inhaled medicines, UMEC/VI can produce paradoxical bronchospasm which may be life threatening.	If paradoxical bronchospasm occurs following dosing with UMEC/VI, this treatment should be discontinued immediately and alternative therapy should be instituted.
Use in patients with narrow-angle glaucoma or urinary retention	No association has been found to date, in completed studies with UMEC/VI or UMEC monotherapy, on glaucoma or urinary retention. However, glaucoma or urinary retention	Exclusion criterion states that subjects with medical conditions such as narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction should only be

7.1. Time and Events Table

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 ±2 days prior Visit 1**	**28 ± 2 days prior Visit 2**	**1± 2 days**	**28 ±2 days**	**84 ± 2 days**	**168 ±2 days**		**7± 2 days after V5 or EW Visit**
Screen/Baseline								
Written informed consent	X							
Demography	X							
Medical/COPD history		X						
Smoking history/status		X						
Smoking cessation counselling		X						
Concomitant medication assessment	X	X						
Cardiovascular History/family history of premature CV disease])		X						
Screening spirometry (including post bronchodilator testing)[3]		X						
CAT questionnaire		X	X					
Verify Inclusion/Exclusion Criteria		X						
Training on use of inhalers		X	X					
Training on use of eDiary and eMDI		X	X					
Verify randomization Criteria			X					
Register Visit in InForm	X	X	X	X	X	X	X	X
Register Visit in RAMOS NG	X	X	X	X	X	X	X	X

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 ±2 days prior Visit 1**	**28 ± 2 days prior Visit 2**	**1± 2 days**	**28 ±2 days**	**84 ± 2 days**	**168 ±2 days**		**7± 2 days after V5 or EW Visit**
Efficacy/HRQoL assessments								
Spirometry, including pre-dose FEV_1, trough FEV_1 and inspiratory capacity			X	X	X	X		
SAC BDI questionnaire [4]			X					
SAC TDI questionnaire [4]				X	X	X		
SGRQ-C questionnaire [4]			X	X	X	X		
CAT questionnaire [4]		X	X	X	X	X		
EXACT/ER-S: COPD [5]		→	→	→	→	→		
Patient Global Rating of COPD severity			X	X	X	X		
Patient Global Rating of Change in COPD				X	X	X		
Safety assessments								
Adverse events/Serious adverse events [6]	X	X	X	X	X	X	X	X
COPD exacerbation assessment	X	X	X	X	X	X	X	X
12-Lead ECG		X						
Urine pregnancy test [7]		X	X			X	X	
Pharmacogenetic sample[8]			←	→	X	←	→	
Medication/Supplies								
Dispense rescue albuterol/slabutamol. Dispense MDI[9]		X	X	X	X	X		
Assess COPD medication compliance[10] during run-in			X					
Dispense eDiary		X						
Assess compliance with eDiary during run-in			X					
Collect rescue albuterol/slabutamol.			X	X	X	X	X	
Collect eDiary						X	X	
Dispense study treatment[11]			X	X	X			
Collect study treatment				X	X	X	X	

- Train subject on the use of eDiary
- COPD assessment test (CAT) and patient global rating of COPD severity in eDiary
- Pre- and post-albuterol/salbutamol spirometry (reversibility, see Section 7.2.2.1)
- Inclusion/Exclusion criteria assessment
- Review exacerbations, AEs, (SAEs if related to study participation)
- Train subject on the proper use of their COPD medication inhalation devices
- Instruct subject to take their COPD medications as instructed and to enter the time they take their medication in the eDiary
- Dispense rescue medication

Medical history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.1 and Section 5.2.

Assessment of subject's health status will be made at screening using CAT. PRO questionnaires should be completed by subjects before any other assessments at a clinic visit, in the order specified in Section 7.3.1

7.2.2.1. Albuterol/Salbutamol Reversibility Assessment

At Visit 1, both pre- and post-albuterol/salbutamol spirometry will be obtained to determine subject eligibility. Reversibility assessment should be performed as follows:

- Perform pre-bronchodilator spirometry and record FEV_1 and FVC
- Subject to self-administer 4 Inhalations (4X100µg) of albuterol/salbutamol MDI
- Perform post-bronchodilator spirometry and record FEV_1 and FVC approximately 10 to 30 minutes after albuterol/salbutamol administration

  The results of the spirometry must meet the ATS/ERS criteria [Miller, 2005] for the subject to continue in the study.

7.2.3. Critical procedures performed at first treatment Visit (Baseline V2)

- Review and assess compliance with subject's COPD medications during the run-in period
- Review and assess compliance with completing the eDiary during the run-in period
- Review AEs, SAEs and exacerbations
- Urine pregnancy test, if applicable

impairment; magnitude of task, and magnitude of effort. SAC BDI/TDI should be completed before performing spirometry.

The SAC BDI/TDI was developed to address issues of potential bias in the interviewer administered (original) BDI/TDI [Mahler, 1984]. The SAC BDI/TDI provides a standardized approach to the measurement of dyspnea, equivalent to the original BDI/TDI with advantages over the interviewer method for grading dyspnea in patients with COPD by standardizing the process for each patient and eliminating individual judgment required by the interviewers when completing the original BDI/TDI. This also removes the need for the same investigator to conduct all interviews with a subject based on the patient's responses. SAC TDI provides a continuous measure of change in dyspnea using a visual analogue scale to record responses.

Details for the completion of the SAC BDI/TDI are provided in the SRM.

7.3.1.2. SGRQ-C

The St George's Respiratory Questionnaire-Chronic Obstructive Pulmonary Disease specific (SGRQ-C) will be completed by subjects at Randomisation (V2, Day 1), at Week 4, 12 and 24 or at the Early Withdrawal Visit (where applicable).

The SGRQ-C [Meguro, 2007] is a well established, disease-specific questionnaire. It was designed to measure the impact of respiratory disease and its treatment on a COPD patient's HRQoL. As well as producing an overall summary score, scores for the individual domains of symptoms, activity and impacts are also produced. It has been used in studies of COPD subjects and has been translated and validated for use in most major languages. The SGRQ-C is derived from the original SGRQ, and produces scores equivalent to the SGRQ instrument [Meguro, 2007].

7.3.1.3. COPD Assessment Test (CAT)

The COPD Assessment Test [Jones, 2009, Jones, 2012] is a validated, short and simple patient completed questionnaire which has been developed for use in routine clinical practice to measure the health status of patients with COPD. The CAT is an 8-item questionnaire suitable for completion by all patients diagnosed with COPD. When completing the questionnaire, subjects rate their experience on a 6-point scale, ranging from 0 (no impairment) to 5 (maximum impairment) with a scoring range of 0-40. Higher scores indicate greater disease impact.

The CAT will be completed in the eDiary by subjects at Screening Visit 1 and Randomisation Visit 2 to assess their eligibility to enter the study. CAT is also completed at Weeks 4, 12 and 24. Additional instructions for completion of the CAT are provided in the **SRM.**

7.3.1.4. EXACT and the Evaluating Respiratory Symptoms- COPD (E-RS: COPD)

EXACT-PRO is a 14 item patient reported outcome instrument designed to capture information on the occurrence, frequency, severity, and duration of exacerbations of

product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.4.1.3), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in (Appendix 4, Section 12.4.6)
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in (Appendix 4, Section 12.4.4 to Section 12.4.6)

7.4.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

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

7.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.5).

7.4.1.4. Pneumonia Events

Investigators will be required to fill out a pneumonia event specific eCRF within one week of when the pneumonia AE/SAE(s) is first reported.

mcg	Microgram
MCID	Minimal Clinically Important Difference
MDI	Metered Dose Inhaler
mL	Milliliter
mMRC	Modified Medical Research Council
MMRM	Mixed Models Repeated Measures
MSDS	Material Safety Data Sheet
NYHA	New York Heart Association
OTC	Over the Counter
PGx	Pharmacogenetic
PIL	Patient Information Leaflet
PK	Pharmacokinetic
PP	Per Protocol
prn	As required
QTc	QT interval corrected for heart rate
RAP	Reporting and Analysis Plan
SABA	Short Acting Beta-Agonist
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SRT	Safety Review Team
TDI	Transition Dyspnea Index
RAMOS NG	Randomization and medication ordering system new generation
ULN	Upper Limit of Normal
UMEC	Umeclidinium (GSK573719)
UMEC/VI	Umeclidinium & Vilanterol as a fixed dose combination
VI	Vilanterol Trifenate

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Liver Chemistry Stopping Criteria - Liver Stopping Event	
MONITORING: **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within normal ranges. • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within normal ranges.	hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best

condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.4.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

• This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.4.3. Definition of Cardiovascular Events

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

- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.4.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.
- Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

12.4.5. Evaluating AEs and SAEs

Assessment of Intensity

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

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

12.6.2. Documenting Medical Device Incidents

Medical Device Incident Documenting:
• Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 4. • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSK. • It is very important that the investigator provides his/her assessment of causality to the medical device provided by GSK at the time of the initial report, and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the design to prevent recurrence.

Objectives	Endpoints
Safety	
• To evaluate safety and tolerability of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5mcg once daily) and salmeterol 50mcg twice daily)	• Incidence of adverse events
Exploratory	
• To compare albuterol/salbutamol use captured in the eDiary with the electronic metered dose inhaler (eMDI) device	• Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the eMDI device over 24 weeks as data allow
• To explore the effect of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on physical activity	• Change from baseline in physical activity
• To investigate the CID composite endpoint ability to predict short term outcomes	• To compare physical activity levels, ER-S, rescue medication use, exacerbations and mortality in subjects with and without a CID

Overall Design

This is a multi-centre, randomized, double blind, double dummy, 3-arm parallel group study. Eligible subjects will be randomized in a ratio of 1:1:1 to UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA® dry powder inhaler (DPI), or UMEC (62.5 mcg once daily) administered via the ELLIPTA DPI or salmeterol (50 mcg twice daily (BID)) administered via the DISKUS® DPI.

Eligible subjects at Screening will enter a run-in period for 4 weeks during which they continue taking their inhaled COPD medications (excluding ICS and any exclusionary medications). In addition, subjects will be provided with short acting albuterol/salmeterol to be used on as needed basis (rescue medication) throughout the study.

Subjects who experience a moderate or severe COPD exacerbation during the run-in period will be deemed run-in failures. Subjects experiencing a mild exacerbation, defined as worsening of symptoms that requires **no** treatment with antibiotics or steroids and is self managed by the patient by an increase of inhaled rescue medication, will be allowed to continue in the study.

At the randomization Visit 2 (Day 1) those subjects who successfully complete the run-in period as well as meet the other pre-defined eligibility and randomization criteria will discontinue their inhaled COPD medications and will be randomized to one of the 3 treatment arms for 24 weeks.

Objectives	Endpoints
Safety	
• To evaluate safety and tolerability of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5mcg once daily) and salmeterol (50mcg twice daily)	• Incidence of adverse events
Exploratory	
• To compare albuterol/salbutamol use captured in the eDiary with the electronic metered dose inhaler (eMDI) device	• Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the eMDI device over 24 weeks as data allow
• To explore the effect of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on physical activity	• Change from baseline in physical activity
• To investigate the CID composite endpoint ability to predict short term outcomes	• To compare physical activity levels, ER-S, rescue medication use, exacerbations and mortality in subjects with and without a CID

4. STUDY DESIGN

4.1. Overall Design

This is a multi-centre, randomized, double blind, double-dummy, 3-arm parallel group study. Eligible subjects will be stratified based on long-acting bronchodilator usage during the run-in (none, one or 2 long-acting bronchodilators per day) and randomized in a ratio of 1:1:1 to UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA inhaler, or UMEC (62.5 mcg once daily) administered via the ELLIPTA or salmeterol (50 mcg BID) administered via the DISKUS.

There will be a total of 5 clinic visits and one follow-up phone call (Visit 6). The Pre-screening Visit (Visit 0) can occur on the same day as the Screening Visit (Visit 1) if subject does not take or has not taken any excluded protocol medications, but must be completed prior to initiating any Visit 1 procedures.

Subjects, who meet all the eligibility criteria at Screening, will enter a run-in period for 4 weeks in order to continue to assess the subject's eligibility for the study. During the run-in period subjects will continue with their inhaled COPD medications (excluding ICS and any exclusionary medications). In addition, subjects will be provided with short acting albuterol/salmeterol to be used on as needed basis for relief of COPD symptoms (rescue medication) throughout the study.

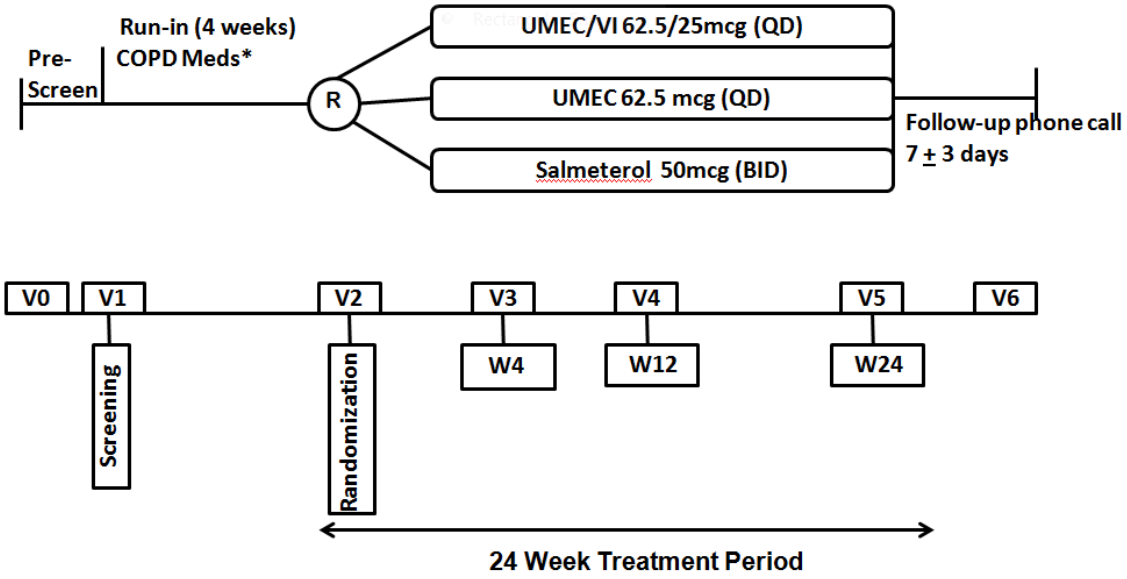
All subjects must be trained on the correct use of the eDiary and instructed to complete the eDiary during the run-in and treatment period.

Subjects will be considered to have completed the study upon completion of the follow – up contact by telephone.

There are no plans to routinely provide any of the study treatments for compassionate use following study completion as the study treatment are commercially available.

The study design schematic is illustrated in Figure 1

Figure 1 Study Schematic



*Inhaled COPD medications including LABAs, LAMAs or LABA/LAMA combination products are allowed in run-in. ICS alone or in combination with a bronchodilator or any exclusionary medications are not allowed.

4.2. Treatment Arms and Duration

Subjects will be stratified based on long-acting bronchodilator usage during the run-in (none, one or 2 long-acting bronchodilators per day) and randomized in a ratio of 1:1:1 to either

- UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA DPI) or
- UMEC (62.5 mcg once daily) administered via the ELLIPTA DPI or
- Salmeterol (50 mcg BID) administered via DISKUS

  The total duration of subject participation in the study will be approximately 29 to 31 weeks consisting of 2 weeks pre-screening if necessary, 4 weeks run-in, 24 week treatment and one week follow-up.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	have been observed with other antimuscarinic agents, and could potentially be due to the pharmacology.	included if, in the opinion of the principal investigator, the benefit outweighs the risk.
Use of beta blockers	Beta-adrenergic blockers may weaken or antagonize the effect of $beta_2$-agonists such as vilanterol.	The study permitted medications and non drug therapies section states that concomitant administration with beta-blockers is only permitted if, in the Investigator's opinion, the likely benefit outweighs the potential risk.
Pregnancy	There is no experience to date of pregnancy during the use of UMEC/VI.	The study inclusion criteria ensures that female subjects of child bearing potential must have a negative pregnancy test at screening, and agree to a reliable contraceptive method, used consistently and correctly (i.e. in accordance with the approved product label and the instructions of the physician for the duration of the study). Exclusion criteria include **Pregnancy:** Women who are pregnant or lactating or are planning on becoming pregnant during the study.
Severe hepatic impairment	UMEC/VI has not been studied in severe hepatic impairment.	Exclusion criterion states that subjects severe hepatic impairment should only be included if, in the opinion of the study physician, the benefit outweighs the risk.
Investigational product (IP) [UMEC]		
Cardiovascular effects such as cardiac arrhythmia, e.g. atrial fibrillation and tachycardia	A potential class effect associated with anti-muscarinic therapies. Data available to date in the IB for UMEC [GlaxoSmithKline Document Number RM2006/00835/09	Screening electrocardiogram (ECG) criteria to exclude subjects potentially at risk
Narrow-angle glaucoma, urinary retention	A class effect associated with anti-muscarinic therapies. Data available in the IB for UMEC [GlaxoSmithKline Document Number RM2006/00835/09	Exclusion criterion states that subjects with medical conditions such as narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction should only be included if, in the opinion of the study physician, the benefit outweighs the risk.
Paradoxical bronchospasm that may be life threatening	Known effect associated with inhalation therapy	A short-acting inhaled bronchodilator (albuterol/salbutamol) will be provided for use as needed throughout the study. The investigators will be instructed to assess subject's condition to determine their eligibility to

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mizatio n 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 ±2 days prior Visit 1**	**28 ± 2 days prior Visit 2**	**1± 2 days**	**28 ±2 days**	**84 ± 2 days**	**168 ±2 days**		**7± 2 days after V5 or EW Visit**
Assess study treatment compliance during treatment[10]				X	X	X	X	
Study sub-set								
Physical activity monitor[12]		X	X	X		X		
Collect Physical activity monitor						X	X	

1. Pre-screen Visit 0 must be completed prior to Screening Visit1. It can be completed 2 weeks prior or on the same day of V1, if no wash out of exclusionary medications is required.
2. Early Withdrawal Visit: Subjects that withdraw should return to the clinic as soon as possible to complete the Early Withdrawal Visit procedures.
3. Spirometry at screening should be performed as described in (Section 7.2.2.1).
4. SAC BDI, SAC TDI, SGRQ-C, CAT questionnaires will be completed at clinic visits and in the eDiary
5. EXACT/ER-S: COPD is completed daily in the eDiary approximately 2 hours before bed-time, starting on Day 1 of the run-in period.
6. For the start date of collecting AEs and SAEs see (Appendix 4)
7. Pregnancy test: for females for child bearing potential only.
8. Pharmacogenetic sample may be drawn at visit 2 or any visit after.
9. Rescue medication use to be recorded in the eDiary daily **and** in some sites in the eDiary and the eMDI
10. Sites are requested to call subjects every 2 weeks to remind them to take study treatment regularly and to record the time of the morning and evening dose in the eDiary.
11. In order to ensure subjects have sufficient doses of study treatment, they must return to clinic within 30 days from V2 and within 60 and 90 days from V3 and V4 respectively
12. The Actigraph GT9X should be worn for 7 days from Visit 1, for 7 days from Visit 2, for 7 days from Visit 3 and for 7 days prior to Visit 5.

- Baseline dyspnea Index, BDI, patient global rating of COPD severity, patient global rating of change in COPD, SGRQ-C and CAT questionnaires in eDiary
- Review randomization criteria (Section 5.3)
- Register and randomize subject in RAMOS NG
- Pre-dose spirometry; IC and FEV_1
- Train subject on the proper use of ELLIPTA and DISKUS inhalers
- Dispense study medication
- Dispense rescue medication
- Optional pharmacogentic sample can be collected at V2 or any visit after.

7.3. Efficacy Assessments

7.3.1. HRQoL assessments: Completion of PRO questionnaires in the Electronic Diary

All subjects will be completing PRO questionnaires in the eDiary.

It is requested that questionnaires are completed before any procedures are performed on the subject.

All questionnaires will be completed using the eDiary at clinic and at home. Adequate time should be allowed to complete all items of the questionnaires and the questionnaires must be reviewed by the investigator or designated study staff for completeness and, if necessary, the subject must be encouraged to complete any missing items. Where more than one questionnaire is to be completed at a visit the order should be as follows:

1. Baseline dyspnea index (Visit 2) then Transient dyspnea index at subsequent visits
2. Patient global rating of COPD severity and global rating of change in COPD
3. St George's respiratory questionnaire
4. COPD Assessment Test

Instructions for completing the questionnaires can be found in the **SRM.**

7.3.1.1. Self Administered Computerised Baseline Dyspnea Index/Transitional Dyspnea Index (SAC BDI/TDI)

The BDI is used to measure the severity of dyspnea in patients at baseline. The TDI measures changes in the patient's dyspnea from baseline. The self-administered computerized version of the BDI/TDI (SAC BDI/TDI)[Mahler, 2004] is used to measure severity of dyspnea in patients at baseline (SAC BDI) on Day 1 (Visit 2) of treatment and change from the baseline (SAC TDI) at Week 4, 12 and 24 (Visits 3, 4 and 5). The scores in both indexes depend on ratings for three different categories: functional

disease in patients with COPD [Leidy, 2011]. EXACT captures information on the severity of the respiratory and systemic manifestations of a COPD exacerbation as reported by the patient. The instrument is to be completed daily (typically 2 hrs before bedtime) using the electronic diary. The daily recording of information allows an assessment of the underlying day to day variability of a patient's symptoms and facilitates the detection of symptom worsening indicative of a COPD exacerbation. The total score for EXACT ranges from 0-100. The entire instrument is intended to be completed in about 3 minutes or less (typically the time required for completion decreases as the patient becomes more familiar with the tool and the electronic diary).

The E-RS: COPD consists of 11 items from the 14 item EXACT instrument [Leidy, 2014]. E-RS: COPD is intended to capture information related to the respiratory symptoms of COPD, i.e. breathlessness, cough, sputum production, chest congestion and chest tightness. The E-RS: COPD has a scoring range of 0-40 higher scores indicate more severe symptoms.

Three subscales of the E-RS are used to describe different symptoms; dyspnea, cough and sputum and chest symptoms.

The EXACT questionnaire will be completed by subjects in the eDiary, at home every night throughout the entire study, starting from Screening V1

7.3.1.5. Subject Global Rating of COPD Severity and Global Rating of Change in COPD

Subjects will complete the Global Rating of COPD Severity at Randomization Visit 2 and visits 3, 4 and 5 or Early Withdrawal Visit. This single global question will ask subjects to rate their severity of COPD on a four point scale (mild, moderate, severe, and very severe).

This question should be used immediately before the patient completes other visit specific questionnaires but after completion of SAC TDI questionnaire.

Subjects will also complete a Global Rating of Change in COPD (overall disease) question at Visits 3, 4 and 5 or Early Withdrawal Visit. Response options will be on a 7 point Likert scale ranging from much better to much worse. Completing the question at each Visit allows for early detection of response as well as continued response.

7.3.2. Spirometry

Spirometry measurements will be obtained using spirometry equipment that meets or exceeds the minimal performance recommendations of the ATS [Miller, 2005]. All sites will use standardized spirometry equipment provided by an external vendor.

All subjects will have spirometry performed at Screening to assess eligibility (see Section 7.2.2.1) and at Visits 2, 3, 4 and 5 during the treatment period.

For FEV_1 and FVC determinations, at least 3 acceptable spirometry efforts (with no more than 8) should be obtained. Acceptable spirometry efforts should have a satisfactory

7.4.1.5. Cardiovascular and Death Events

For any cardiovascular events detailed in (Section 12.4.3) and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

7.4.1.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The following disease related events (DREs) are common in subjects with COPD and can be serious/life threatening:

- COPD exacerbation

COPD exacerbations are associated with the disease to be studied and will not be recorded as AEs unless the exacerbation meets the definition of a 'serious' AE. Exacerbations that meet the definition of 'serious' AEs will be recorded on the appropriate eCRF section and should be reported to GSK for all subjects regardless of whether or not they are randomized to study medication. Signs and symptoms of COPD included on the electronic diary will not be considered AEs and will not be recorded in the eCRF

7.4.1.7. Regulatory Reporting Requirements for SAEs

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

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

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

12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

Phase III-IV liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• Immediately discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve , stabilize, or return to within normal ranges. baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment. Permanently discontinue stud**y treatment and may continu**e subject in the study for any protocol specified follow up assessments	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5]. • Blood sample for pharmacokinetic (PK) analysis, obtained within a week after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or

approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

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

Assessment of Causality

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

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health

12.7. Appendix 7: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

12.7.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.7.2. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.