GSK conducted a Phase III study comparing once-daily FF/UMEC/VI to twice-daily budesonide/formoterol (400/12 mcg) in COPD participants that were symptomatic and at risk of an exacerbation despite receiving maintenance therapy (CTT116853). FF/UMEC/VI demonstrated statistically significant improvements in trough FEV_1, a statistically significant reduction in the annual rate of moderate or severe COPD exacerbations, and a statistically significant reduction of COPD symptoms (using Exacerbations and Chronic Pulmonary Disease – Respiratory Symptoms [EXACT-RS]) when compared to budesonide/formoterol. Additionally, clinically meaningful improvements from baseline in St. George's Respiratory Questionnaire (SGRQ) total score were observed, with a statistically significant improvement compared to budesonide/formoterol. This Phase III study provided compelling efficacy data compared with an established ICS/LABA and demonstrated the clinical value of single inhaler triple-therapy compared to ICS/LABA therapy in patients with COPD.

As fixed dose combinations of LAMA/LABA therapy remain relatively new, and ICS monotherapy is not indicated for the treatment of COPD, the two most frequent treatment pathways that lead to 'open' triple therapy are the escalation of therapy from either an ICS/LABA fixed dose combination or from LAMA monotherapy. A prior study demonstrated that participants with COPD may remain symptomatic despite the use of LAMA or LABA monotherapy. Participants that remained symptomatic despite treatment with LAMA monotherapy, stepped up to 'open' triple therapy by the addition of ICS/LABA therapy, which resulted in greater improvements in lung function and HRQoL, compared LAMA monotherapy.

The primary purpose of this study is to evaluate lung function and HRQoL after 84 days of treatment with a single inhaler triple therapy combination of FF/ UMEC/VI (100/62.5/25 mcg) once daily via the ELLIPTA™ compared with tiotropium (18 mcg) once daily, in a patient population appropriate for triple therapy.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the effect of single inhaler triple therapy (FF/UMEC/VI) compared to tiotropium after 12 weeks of treatment on lung function	**Primary** • Change from baseline in trough FEV_1 at Week 12 (Day 85) **Secondary** • Change from baseline in trough FEV_1 on Day 28 and Day 84

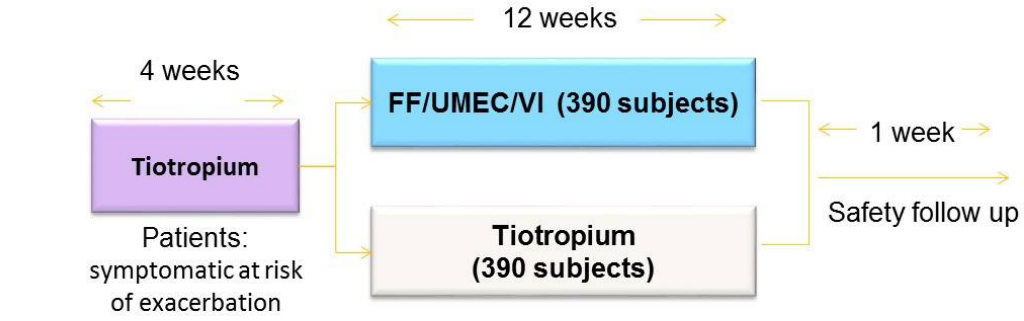
Protocol Activity	**Pre-Screen**	**Screen**		**Treatment**			**Follow-up**	
	Visit 0	**Visit 1 Screen/ Run-in**	**Visit 2 Randomisation**	**Visit 3**	**Visit 4**	**Visit 5**	**Study Treatment Discontinuation Visit**	**Visit 6 Safety Follow-up Contact**
Study Day	**-56 to -28**	**Day -28**	**Day 1**	**Day 28**	**Day 84**	**Day 85**		**Day 91**
Week	**-8 to -4**	**-4**	**0**	**4**	**12**	**12**		**13**
Window		**-3/+8d (Day -31 to -21)**		**-4/+2d (Day 24 to 30)**	**-4/+2d (Day 80 to 86)**			**-1/+4d (Day 90 to 95)**
Dispense run-in treatment		X						
Dispense study treatment			X	X				
Administer run-in treatment in clinic [m]		X						
Administer study treatment in clinic [n]			X	X	X			
Assess run-in treatment compliance			X					
Collect run-in treatment			X					
Assess study treatment compliance				X	X		X	
Collect study treatment				X	X		X	
Dispense albuterol/salbutamol		X	X	X	X			
Collect albuterol/salbutamol			X	X	X	X	X	
Dispense paper Medical Problems worksheet	X	X	X	X	X			
Review paper Medical Problems worksheet		X	X	X	X	X	X	

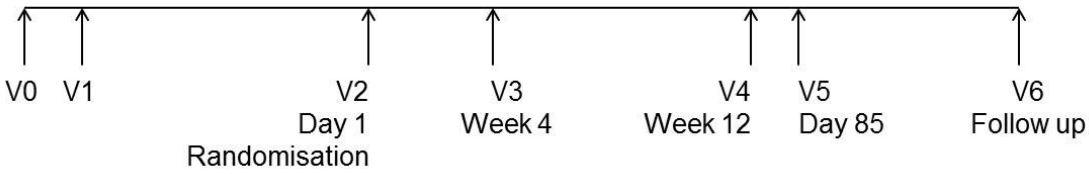
5. STUDY DESIGN

5.1. Overall Design

This is a Phase IV, 12-week, randomised, double-blind, double-dummy, parallel group, multicentre study evaluating once-daily single inhaler triple therapy (FF/UMEC/VI) delivered via the ELLIPTA, compared to once daily tiotropium, in participants with COPD.

Study design schema





Eligible participants at Screening (Visit 1) will be current or former smokers, with an established clinical history of COPD, receiving daily maintenance therapy with tiotropium alone for at least 3 months (no ICS or LABA maintenance therapy is allowed during the 3 months prior to screening), with a post-bronchodilator FEV_1 of <50 % predicted (or <80 % predicted with a documented history of at least 2 moderate or 1 severe [hospitalized] exacerbation in the last 12 months) and a CAT score of ≥10. Participants will be requested to participate in the study for approximately 17 weeks, consisting of a 4-week run-in period, 12-week treatment period and a 1-week follow-up period.

- **Pre-screening:** Details about the study and procedures will be explained through the informed consent process. The Pre-screening Visit (Visit 0), including the informed consent process, must be completed prior to any protocol-required changes to a participant's usual COPD treatment and the initiation of any Visit 1 procedures. Participants will continue treatment with their regular (i.e. pre-study) tiotropium monotherapy during the pre-screening period.

- **Screening/run-in:** Eligible participants will be allowed to continue their usual tiotropium monotherapy COPD medication until the day before Screening (Visit 1). On the morning of the Screening Visit participants will refrain from taking their morning dose of tiotropium. Participants who meet all of the eligibility criteria at Visit 1, will enter the 4-week run-in period.

  Participants will discontinue existing tiotropium medication and will take open-label tiotropium 18 mcg once daily via the HandiHaler plus placebo via the ELLIPTA. Participants will not use any other COPD medications (except for those allowed per protocol).

  During the run-in period participants will also take placebo via the ELLIPTA in addition to open-label tiotropium. This will familiarise participants with the use of the ELLIPTA device and will help ensure participants are compliant and use both devices as instructed.

  Participants will be provided with short-acting albuterol/salbutamol to be used on an as-needed basis (rescue medication) throughout the study. At Screening, each participant will be instructed on the proper use of the ELLIPTA and HandiHaler and will self-administer their first doses of their run-in treatment during the Screening Visit. On the morning of the other study visits (Visit 2 onwards), participants will refrain from taking their morning dose of study treatment until instructed to do so by clinic personnel.

- **Randomisation/treatment:** On the morning of the day before the Randomisation Visit (Visit 2), participants will take their last dose of run-in treatment and will not use any other COPD medications (except for those allowed per protocol) until the end of the study. Rescue albuterol/salbutamol can be used throughout the study as-needed but must be withheld for at least 4 hours prior to conducting spirometry.

  At Visit 2 (the Randomisation Visit), participants who meet all of the randomisation criteria (see Section 6.3) will be randomised 1:1 to receive one the following double-blind study treatments for 84 days:

  - FF/UMEC/VI 100/62.5/25 mcg via the ELLIPTA once daily in the morning
    + placebo to match tiotropium via HandiHaler once daily in the morning

  - Tiotropium 18 mcg via HandiHaler once daily in the morning
    + placebo via the ELLIPTA once daily in the morning

  Participants may continue their study-supplied rescue albuterol/salbutamol. On the morning of Visits 3 and 4, participants will refrain from taking their morning dose of study treatment until instructed to do so by clinic personnel. At Visits 2, 3, and 4 participants will self-administer study treatment whilst at the clinic. Participants will take their last dose of study treatment in the clinic on Day 84 and then return to the clinic on Day 85 (Visit 5) for their final clinical assessments. Participants are expected on non-clinic visit days to take their study

5.5. Dose Justification

The FF/UMEC/VI (100/62.5/25 mcg) dose was selected based on the doses that have been licensed for COPD for the FF/VI (100/25 mcg) and UMEC/VI (62.5/25 mcg) dual combinations through extensive studies in the mono and dual therapy programmes. It is the dose which is currently under regulatory review based on the Phase IIIa FF/UMEC/VI registration programme.

The dose selected for tiotropium (18 mcg, once daily) is the dose licensed in the US for use in COPD.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. **Informed consent:** capable of giving signed informed consent prior to study start which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
2. **Type of participant**: Outpatient.
3. **Age**: Participants 40 years of age or older at Screening (Visit 1).
4. **Gender**: Male or female participants.

Female participants:

A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP)

OR

- A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and until the safety follow-up contact after the last dose of study treatment.

5. **COPD Diagnosis**: An established clinical history of COPD in accordance with the definition by the American Thoracic Society/European Respiratory Society [Celli, 2004].
6. **Smoking History**: Current or former cigarette smokers with a history of cigarette smoking of ≥10 pack-years at Screening (Visit 1) [number of pack years = (number of

- Medical history including COPD history (comprised of COPD type [emphysema and/or chronic bronchitis]), smoking history, COPD exacerbations history, smoking status and previous and/or current medical conditions.
- Demography
- Concomitant Medications
- COPD exacerbation assessment (documented history of exacerbation(s))
- Cardiovascular medical history/risk factors
- Inclusion/Exclusion criteria
- Physical examination (including oropharyngeal examination)
- Pulse rate, blood pressure measurements
- 12-lead ECG
- Pre- and post-albuterol/salbutamol spirometry (reversibility)
- SAE assessment (if related to study participation)
- Chest X-Ray or (historical radiograph obtained within 3 months prior to screening)
- Laboratory assessments (chemistry and hematology, hepatitis and pregnancy testing)
- CAT
- Administer and dispense run-in study treatment

In addition the following procedures must be completed at Screening (Visit 1):

- Smoking cessation counseling
- Register visit in IWRS
- Dispense albuterol/salbutamol

9.1. Efficacy Assessments

The timings of all efficacy assessments are specified in the SoA (Section 2).

9.1.1. Spirometry

Spirometry measurements will be obtained using spirometry equipment that meets or exceeds the minimal performance recommendations of the American Thoracic Society (ATS) [Miller, 2005]. All sites will use standardised spirometry equipment provided by an external vendor. All participants will have spirometry performed at screening and each scheduled clinic visit 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 start of test and end of test (*e.g.* a plateau in the volume-time curve) and be free from artifacts due to cough,

early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reasons [Miller, 2005].

The largest FEV_1 and FVC from the 3 acceptable efforts should be recorded, even if they do not come from the same effort.

Spirometry must be performed as follows:

- Started approximately between 6:00AM and 11:00AM.
- If applicable, after completing the health outcomes assessments (CAT should be administered first followed by SGRQ-C)
- After withholding albuterol/salbutamol for ≥4 hours.
- At Screening (Visit 1), before the morning dose of their usual COPD medication.
- At Randomisation (Visit 2) and all treatment visits, before the morning dose of study treatment.
- Participants should refrain from smoking for 1 hour prior to each pulmonary function test.
- Participants should abstain from drinking beverages with high levels of caffeine such as tea and coffee for 2 hours prior to each pulmonary function test.

A full description of the timing and conduct of spirometry procedures is provided in the SRM.

9.1.1.1. Reversibility

At Visit 1, both pre- and post-albuterol/salbutamol spirometry will be obtained. Post-albuterol/salbutamol FEV_1 and FEV_1/FVC findings will be used to determine participant eligibility.

Reversibility testing will be completed as follows: Following pre-albuterol/salbutamol spirometry (three acceptable spirometry efforts), the participant will self-administer 4 puffs of albuterol/salbutamol MDI using a spacer/valved-holding chamber. Three acceptable spirometry efforts will be obtained approximately 10 to 30 minutes after albuterol/salbutamol administration.

9.1.2. SGRQ-C

The St George's Respiratory Questionnaire-Chronic Obstructive Pulmonary Disease specific (SGRQ-C) will be completed by participants at Randomisation (Visit 2), Day 28 (Visit 3), and Day 84 (Visit 4). When the SGRQ-C and the COPD Assessment Test (CAT) are collected at the same visit, the CAT should be collected prior to the SGRQ-C.

The SGRQ-C [Meguro, 2007] is a disease-specific questionnaire designed to measure the impact of respiratory disease and its treatment on a COPD participant'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 participants and has been translated and validated for use in most major languages. The SGRQ-C is

9.2.1. Time Period and Frequency for Collecting AE and SAE Information

- Any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study up to and including the safety follow-up contact at Visit 6.
- All AEs will be collected from the start of study treatment (Visit 2) until the safety follow-up contact at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 6. The Investigator will submit any updated SAE data to the sponsor or designee within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the sponsor or designee.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 6.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Participants will be issued with a paper Medical Problems worksheet to record any medical problems experienced during the study. This paper worksheet will be used to assist participant recall in discussions with the Investigator (or designee), for site staff to then enter as appropriate in the eCRF.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 6.

9.2.7. COPD exacerbations should not be recorded as an adverse event, unless they meet the definition of an SAE (Appendix 6).Pneumonia

All suspected pneumonias will require confirmation as defined by the presence of new infiltrate(s) on chest x-ray AND at least 2 of the following signs and symptoms:

- Increased cough
- Increased sputum purulence (colour) or production
- Auscultatory findings of adventitious sounds (*e.g.* egophony, bronchial breath sounds, rales, etc.)
- Dyspnoea or tachypnea
- Fever (oral temperature >37.5 °C)
- Elevated white blood cells (WBC) (>10,000/mm^3 or >15 % immature forms)
- Hypoxemia (HbO_2 saturation <88 % or at least 2 % lower than baseline value)

All pneumonias must be captured on the AE/SAE page of the eCRF and on the pneumonia page of the eCRF.

The Investigators and site staff should remain vigilant for the possible development of pneumonia in participants with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in participants with COPD receiving FF/VI included current smokers, participants with a history of prior pneumonia, participants with a body mass index <25kg/m^2 and participants with an FEV_1 <50 % predicted. For all suspected cases of pneumonia, Investigators are strongly encouraged to confirm the diagnosis (this includes obtaining a chest x-ray) and to initiate appropriate therapy as promptly as possible. All diagnoses of pneumonia (radiographically confirmed or unconfirmed) must be reported as an AE or SAE (if applicable).

Note: Pulse oximetry should be measured at any time a moderate or severe exacerbation is reported or pneumonia is suspected and recorded in the source documents and on the pneumonia page of the eCRF if applicable.

9.2.8. Sentinel Events

A Sentinel Event is a GSK-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. Medical monitor review of all SAEs for possible Sentinel Events is mandated at GSK. The medical monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:

- Acquired Long QT Syndrome
- Agranulocytosis/Severe Neutropenia

- Anaphylaxis & Anaphylactoid Reactions
- Hepatotoxicity
- Acute Renal Failure
- Seizure
- Stevens Johnson Syndrome/Toxic Epidermal Necrolysis

9.2.9. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and until the safety follow-up contact/visit.
- If a pregnancy is reported, the Investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 3.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2.10. Medical Device Incidents (Including Malfunctions)

Medical devices (spacers/holding chambers) are being provided for use in this study. In order to fulfil regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 7

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 9.2 and Appendix 6 of the protocol.

9.2.10.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the Investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify the Sponsor.
- The method of documenting Medical Device Incidents is provided in Appendix 7.

9.2.10.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 9.2). This applies to all participants, including those who discontinue study treatment or the study.

9.4.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height,weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

- Vital signs will be performed at the time points specified in the SoA table (Section 2) prior to conducting spirometry and prior to taking study treatment.
- Blood pressure (systolic and diastolic) and pulse measurements will be assessed in the sitting position after approximately 5 minutes rest.
- A single set of values will be collected and recorded in the source documentation and eCRF.

9.4.3. Electrocardiograms

- A single 12-lead ECG and rhythm strip will be recorded after measurement of vital signs and prior to spirometry. Recordings will be made at the time-points defined in the SoA table (Section 2). All ECG measurements will be made with the participant in a supine position having rested in this position for approximately 5 minutes before each reading.
- For participants who meet the QTc, protocol defined stopping criteria, triplicate ECGs (over a brief period of time) should be performed (Section 8.1.1).
- The Investigator, a designated sub-Investigator or other appropriately trained site personnel will be responsible for performing each 12-lead ECG. The Investigator must provide his/her dated signature on the original paper tracing, attesting to the authenticity of the ECG machine interpretation.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 8 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 5 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are

no longer considered significantly abnormal by the Investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 8, must be conducted in accordance with the laboratory manual and the SoA.

9.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

Information regarding genetic/ pharmacogenetic (PGx) research is included in Appendix 9. The IEC/IRB and, where required, the applicable regulatory agency must approve the PGx and genetic assessments before these can be conducted. The approval(s) must be in writing and will clearly specify approval of the PGx and genetic assessments (i.e., approval of Appendix 9).

In some cases, approval of the PGx and genetic assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx and genetic assessments is being deferred and the study, except for PGx and genetic assessments, can be initiated. When PGx and genetic assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx and genetic assessments will not be conducted.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9.10. Smoking Cessation Counselling

During Visits 1 and 4, or Study Discontinuation, participants will be given smoking cessation counselling. This will include advice regarding the following:

- the health effects that smoking may cause
- the health benefits that may result with smoking cessation

HIV	Human Immunodeficiency Virus
HPA	Hypothalamic-Pituitary-Adrenal
HPLC	High-Performance Liquid Chromatography
HRQoL	Health related quality of life
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
Kg/m^2	Kilograms per meter squared
LABA	Long-Acting Beta-2-Agonists
LAMA	Long-Acting Muscarinic Antagonist
LRTI	Lower Respiratory Tract Infection
LTOT	Long-term oxygen therapy
MACE	Major Adverse Cardiac Event
MAOI	Monoamine Oxidase Inhibitors
MedDRA	Medicinal Dictionary for Regulatory Activities
mcg	Microgram
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDI	Metered Dose Inhaler
min	Minute
mL	Milliliter
mMRC	Modified Clinical Research Council
MMRM	Mixed-Model Repeated Measures
mPP	Modified Per Protocol
MSDS	Material Safety Data Sheet
msec	Millisecond
NA	Not Applicable
NYHA	New York Heart Association
PDE4	Phosphodiestrase 4 inhibitor
PGx	Pharmacogenetic
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red Blood Cell
RNA	Ribonucleic acid

study treatment unless allowed per protocol • If restart/rechallenge **not allowed per protocol** , permanently discontinue study treatment and may continue participant in the study for any protocol specified follow up assessments **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 participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • 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 participants weekly until liver chemistries resolve, stabilize or return to within baseline	dehydrogenase. • Fractionate bilirubin, if total bilirubin≥2x ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or 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 participants 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 eCRF 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 partcipant if ALT ≥ 3x ULN **and** bilirubin ≥ 2x ULN. 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 ≥ 3x ULN **and** bilirubin ≥ 2x ULN (>35% direct bilirubin) or ALT ≥ 3x ULN **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 participants 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)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which 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.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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 inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant 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 outpatient setting. Complications that occur during hospitalization are AE. 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 persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct

12.9. Appendix 9: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a 6 mL blood sample will be collected for DNA analysis.
- DNA samples may be used for research related to study treatment or COPD and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to study treatment or study treatments of this drug class and indication. Genetic research may consist of the analysis of one or more candidate genes (including but not limited to: *PIK3CD*, *PIK3CA*, *IL10*, *CHRNA3*, *CHRNA5*, *DNAH5*, *SUMF1*, and *CELSR1*) or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate)
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study treatment or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on study treatment (or study treatments of this class) or indication continues but no longer than 15 years after the last participant last visit or other period as per local requirements.
- **Withdraw Process**: If a participant withdraws consent, the Investigator must complete the Genetic Sample Destruction Request Form, which will be provided to the site in the Investigator Site File.
- **Destruction Process**: After the specified storage period of 15 years or on withdrawal of consent, samples will be destroyed by incineration. Samples that are sent for testing to vendors are returned or destroyed as part of the formal agreement and a full record of chain of custody is maintained. A laboratory information management system (LIMS) is used to track and identify samples for destruction.

Objectives	Endpoints
Other	
• To evaluate the effect of single inhaler triple therapy (FF/UMEC/VI) compared to tiotropium after 12 weeks of treatment on Health Status	• Proportion of responders based on the St George's Respiratory Questionnaire (SGRQ) Total Score at Week 4 and Week 12 • Change from baseline in SGRQ Total Score at Week 4 and Week 12
• To evaluate the effect of single inhaler triple therapy (FF/UMEC/VI) compared to tiotropium after 12 weeks of treatment on Health Status	• Proportion of responders based on the COPD Assessment Test (CAT) Total Score at Week 4 and Week 12 • Change from baseline in CAT Total Score at Week 4 and Week 12
• To evaluate the effect of single inhaler triple therapy (FF/UMEC/VI) compared to tiotropium after 12 weeks of treatment on COPD exacerbations	• Moderate or severe exacerbation event
Safety	
• To evaluate the safety profile of single inhaler triple therapy (FF/UMEC/VI) compared to tiotropium over 12 weeks of treatment	• Incidence of adverse events • Vital signs

Overall Design:

This is a Phase IV, 12-week, randomised, double-blind, double-dummy, parallel group, multicentre study evaluating once-daily single inhaler triple therapy (FF/UMEC/VI) delivered via the ELLIPTA, compared to once daily tiotropium, in participants with COPD.

a. Informed consent must be conducted at the Pre-screen Visit prior to performing any study procedures including the changing or withholding of medications. The informed consent may be given at Screening Visit 1 if the participant does not take or has not taken any protocol excluded medications. The Pre-screen and Screening Visits can occur on the same day.
b. Genetics research consent may be obtained at the same time as the study informed consent and must be obtained prior to obtaining a genetic blood sample. The sample can be collected at any time after Visit 2, providing consent is obtained.
c. Demography may be captured at either the Pre-screen Visit or Screening Visit.
d. SGRQ-C and CAT will be completed electronically, and should be conducted in the following order and before other study assessments: CAT, SGRQ-C.
e. At Screening Visit 1 both pre and post-bronchodilator spirometry will be conducted. Participants are required to withhold their usual morning doses of their COPD meds including rescue albuterol/salbutamol for the protocol designated period prior to reversibility testing.
f. Pre-bronchodilator spirometry will be performed pre-dose at 30 mins and 5 mins prior to taking the morning dose of study treatment, between 6am and 11am and after withholding rescue albuterol/salbutamol for ≥4 hours. On Day 85, study drug will not be administered following spirometric assessments.
g. Physical examination may include height, weight, blood pressure and temperature
h. Vital signs must be performed prior to spirometry and prior to taking morning dose of study treatment.
i. Chest X-ray is required at Screening (or historical x-ray obtained within 3 months prior to Screening) and at anytime there is a suspected pneumonia or a mod/severe exacerbation
j. Genetic consent must be obtained prior to obtaining a blood sample.
k. Hematology and chemistry panels will include full and differential blood count and liver chemistry. See Appendix 8.
l. All female Participants of child bearing potential will have a urine pregnancy test at Visits 1, 4 and Study Treatment Discontinuation Visit (if applicable).
m. Participants must withhold their morning dose of existing COPD medication/study treatment and not take their treatment until instructed to do so by study staff
n. Participants must withhold their morning dose of study treatment at each clinic visit and not take their study treatment until instructed to do so by study staff

When multiple assessments and procedures are performed suggested order is CAT, SGRQ-C, vitals, ECG, spirometry, clinical lab assessments.

3. INTRODUCTION

3.1. Study Rationale

Chronic obstructive pulmonary disease (COPD) guidelines advocate the use of long-acting muscarinic receptor antagonists (LAMA) added to the combination of an inhaled corticosteroid (ICS) plus a long-acting β_2-adrenergic receptor agonists (LABA) as second line therapy for the most advanced patients with significant symptoms and a high risk of exacerbations. Regular treatment with ICS-containing regimens has been reported to improve respiratory symptoms, lung function, health related quality of life (HRQoL) and reduce the frequency COPD exacerbations in patients with a forced expiratory flow in 1 second (FEV_1) <60 % predicted [Aaron, 2007; Cazzola, 2007; Hanania, 2012; Jung, 2012; Siler, 2015; Welte, 2009].

Population based studies of COPD treatment patterns demonstrate that 'open' triple therapy (use of ICS/LAMA/LABA delivered via multiple inhalers) is already widely used in the real-life management of COPD. In 2011, 26 % of patients in the United States (US) who were taking controller medicines for the treatment of COPD were taking an 'open' triple therapy, typically by adding fluticasone propionate/salmeterol (ICS/LABA) to

treatment at home in the morning at approximately the same time each day, as directed by the clinic.

- **Safety/follow-up:** A safety follow-up telephone contact or clinic visit (Visit 6) will be conducted approximately 7 days after the participant completes all of the protocol-defined procedures for Visit 5/End of Study (EOS) or, if applicable, the Study Treatment Discontinuation Visit. A participant will be considered to have completed the study when they have completed all phases of the study including screening, run-in, the randomised treatment phase, and safety follow-up.

Participants who permanently discontinue double-blind study treatment are not required to withdraw from the study. Participants who have permanently discontinued study treatment and have not withdrawn consent are encouraged to continue in the study and complete all remaining protocol specified clinic visits (see Section 8.1).

5.2. Number of Participants

Approximately 848 participants with advanced COPD will enter the run-in, in order to randomise approximately 780 participants, in order to achieve an estimated 702 evaluble participants. See Section 10 for further details.

Approximately 100 centres globally will be required to recruit the study.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including pre-screening, screening, run-in, the randomised treatment phase and the safety follow-up.

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities (SoA) table (see Section 2) for the last participant in the trial globally.

5.4. Scientific Rationale for Study Design

This study will use a multicenter, randomised, double-blind, double-dummy, parallel-group design. A placebo arm is not included because the primary comparison of interest is FF/UMEC/VI vs. tiotropium and it is not considered appropriate to include a placebo arm in a study in patients with advanced COPD. Eligible participants must have been on daily maintenance tiotropium for at least 3 months, and those randomised to tiotropium will be essentially continuing their therapy prior to enrollment. Although LAMA monotherapy in severe patients is not designated a preferred treatment option, it continues to be listed as a treatment option for these patients (GOLD B or D) in the 2017 GOLD strategy document, and is commonly used in clinical practice. The 4-week run-in period is necessary in order to assess participant compliance with and ability to use all of the medications together and allow sufficient time for the results of screening assessments to be returned to the site, in order to establish participant eligibility.

cigarettes per day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)]. Previous smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1. ***Note**: Pipe and/or cigar use cannot be used to calculate pack-year history*.

7. **Severity of COPD symptoms:** A score of ≥10 on the COPD Assessment Test (CAT) at Screening (Visit 1).

8. **Severity of Disease:**

   Participants must demonstrate at Screening:

   - a post-bronchodilator FEV_1 <50 % predicted normal

   OR

   - a post-bronchodilator FEV_1 <80 % predicted normal and a documented history of ≥2 moderate exacerbations or one severe (hospitalized) exacerbation in the previous 12 months

   Participants must also have a measured post albuterol/salbutamol FEV_1/forced vital capacity (FVC) ratio of <0.70 at screening.

   Note: *Percent predicted will be calculated using the European Respiratory Society Global Lung Function Initiative reference equations [*Quanjer*, 2012]*.

   Note: *A documented history of a COPD exacerbation (e.g., medical record verification) is a medical record of worsening COPD symptoms that required systemic/oral corticosteroids and/or antibiotics (for a moderate exacerbation) or hospitalization (for a severe exacerbation). Prior use of antibiotics alone does not qualify as an exacerbation history unless the use was associated with treatment of worsening symptoms of COPD, such as increased dyspnoea, sputum volume, or sputum purulence (colour). Participant verbal reports are not acceptable.*

9. **Existing COPD maintenance treatment:** participant must have been receiving daily maintenance treatment with tiotropium alone (via the Handihaler or Respimat) for their COPD for at least 3 months prior to Screening.

   Note: *Participants taking only as-needed tiotropium are not eligible.*

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. **Pregnancy**: Women who are pregnant or lactating or are planning on becoming pregnant during the study.

2. **Asthma**: Participants with a current diagnosis of asthma. (Participants with a prior history of asthma are eligible if they have a current diagnosis of COPD).

derived from the original SGRQ, and produces scores equivalent to the SGRQ instrument [Meguro, 2007].

9.1.3. COPD Assessment Test (CAT)

The CAT will be completed by participants at Screening (Visit 1), Randomisation (Visit 2), Day 28 (Visit 3), and Day 84 (Visit 4). CAT should be collected prior to SGRQ-C when collected at the same visit.

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, participants 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.

9.1.4. COPD Exacerbations

COPD exacerbation data will be collected from the start of the randomised double blind treatment period (Visit 2) until the safety follow up contact at Visit 6. Participants will complete a paper Medical Problems worksheet to record medical problems experienced during the study. This paper worksheet must be reviewed by the Investigator (or designee) at each visit to the study site to assist in the identification of new COPD exacerbations.

Every effort should be made to conduct a chest x-ray within 48 hours of identification of a moderate or severe exacerbation.

All COPD exacerbations will be recorded on the exacerbation page of the eCRF.

Details on COPD Exacerbation Identification, Categorization and Treatment Guidelines are provided in Appendix 5.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 6

The Investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment or withdraw from the study (see Section 8).

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information eg, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 6 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs 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 eCRF within one week of receipt of a CV Event data query prompting its completion.

The Death eCRF 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.

9.2.6. Disease-Related Outcomes – COPD exacerbations

COPD exacerbations are an expected disease-related outcome.

- The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

9.2.10.3. Prompt Reporting of Medical Device Incidents to Sponsor

- Medical device incidents will be reported to the sponsor within 24 hours after the Investigator determines that the event meets the protocol definition of a medical device incident.
- The Medical Device Incident Report Form will be sent to the sponsor electronically.
- The same individual will be the contact for the receipt of medical device reports and SAE.

9.2.10.4. Regulatory Reporting Requirements for Medical Device Incidents

- The Investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The Investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

9.3. Treatment of Overdose

An overdose is defined as a dose greater than the total doses described above which results in clinical signs and symptoms. These should be recorded by the Investigator on the AE/SAE eCRF pages. In the event of an overdose of study treatment, the Investigator should use clinical judgment in treating the overdose and contact the GSK medical monitor.

GSK is not recommending specific treatment guidelines for overdose and toxicity management. The Investigator is advised to refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the study drug being used in this study. Such documents may include, but not be limited to, the IB or equivalent document provided by GSK.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 2).

- discuss anti-smoking strategies that primary care physicians may be able to provide if participants do not feel capable of discontinuing smoking

- participants may discontinue smoking at any time during the study and will not have to be withdrawn from the study if they do so.

The specific information to be discussed with each participant is provided in the SRM.

10. STATISTICAL CONSIDERATIONS

10.1. Hypotheses

The primary objective of this study is to compare single inhaler triple therapy (FF/UMEC/VI) with tiotropium in participants with COPD who have received tiotropium and continue to have symptoms as measured by CAT ≥10. The primary endpoint is trough FEV_1 at Week 24 (Day 85). The primary analysis is the comparison of this endpoint between FF/UMEC/VI and tiotropium.

The null hypothesis is that there is no difference between treatment groups.

H0: T1 – T2 = 0

The alternative hypothesis is there is a difference between treatment groups.

H1: T1 – T2 ≠ 0

Where T_1 and T_2 are the treatment means for FF/UMEC/VI and tiotropium, respectively.

10.2. Sample Size Determination

Sample size calculation is based on the primary endpoint of trough FEV_1 at Week 12 (Day 85) and assumes 90 % power, a two-sided 1 % significance level, an estimate of residual standard deviation of 240 mL (based on mixed model repeated measures [MMRM] analyses of closed triple Phase IIb study CTT116853 in COPD participants) and a treatment difference of 70 mL. Under these assumptions, in total 702 evaluable participants (351 per treatment group) will be required.

It is estimated that approximately 10 % of participants will withdraw during the treatment period without providing a Day 85 trough assessment and approximately 8 % of participants will drop out from the 4 week run-in (including those not meeting randomisation criteria). Therefore approximately 848 participants will be enrolled to 4-week run-in in order to have 780 participants randomised.

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

SAE	Serious Adverse Event
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SGRQ-C	St. George's Respiratory Questionnaire for COPD patients
SMQ	Standardised MedDRA Query
SoA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reaction
TIO	Tiotropium
TQT	Thorough QT
UK	United Kingdom
ULN	Upper Limit of Normal
UMEC	Umeclidinium
US	United States
VI	Vilanterol
WBC	White Blood Cell
WOCBP	Woman of child-bearing potential

Trademark Information

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Respimat
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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 participants 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 eCRF. If the date or time of the last dose is unclear, provide the participant's best 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 SPM.

Phase III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5x ULN and <8x ULN **and** bilirubin <2x ULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3x ULN and <5x ULN **and** bilirubin <2x ULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5x ULN and <8x ULN to ≥3x ULN but <5x ULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3x ULN and bilirubin <2x ULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, et al. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, et al. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43:2363-2369.

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 (eg, sprained ankle) which may interfere with 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 SAE 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include 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.

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the eCRF 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

12.10. Appendix 10: Country-specific requirements

There are currently no country specific requirements.