# Epstein-Barr Virus Suppression in Chronic Obstructive Pulmonary Disease (EViSCO)

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| Acronym: | EViSCO |
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| Study Sponsor: | Belfast Health and Social Care Trust |
| Chief Investigator: | Joe Kidney<br>Department of Respiratory Medicine<br>Mater Hospital<br>Crumlin Road<br>Belfast, BT14 6AB |

## PROTOCOL AUTHORISATION

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| Full Protocol Title: | Epstein-Barr Virus Suppression in Chronic Obstructive Pulmonary Disease (COPD) |
| Protocol Number: | 14143JK-AS |
| Protocol Version Number/Date: | Version 4.0 / 22/04/2020 |
| Protocol Amendments: | |

A review of the protocol has been completed and is understood and approved by the following:

| | | |
|---|---|---|
| Joe Kidney | | DD / MM / YYYY |
| Chief Investigator | Signature | Date |
| Christina Campbell | | DD / MM / YYYY |
| Statistician | Signature | Date |

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# LIST OF ABBREVIATIONS

| Abbreviation / Acronym | Full Wording |
|---|---|
| AE | Adverse Event |
| AR | Adverse Reaction |
| CAT | COPD assessment test |
| CD | Cluster designation (cell surface markers) |
| CI | Chief Investigator |
| COPD | Chronic Obstructive Pulmonary Disease |
| CRF | Case Report Form |
| CTA | Clinical Trial Authorisations |
| DMEC | Data Monitoring and Ethics Committee |
| EudraCT | European Clinical Trials Database |
| EBV | Epstein-Barr Virus |
| EQ-5D-5L | EuroQol quality of life questionnaire |
| FEV1 | Forced expiratory volume in 1 second |
| FVC | Forced vital capacity |
| GCP | Good Clinical Practice |
| GMCSF | Granulocyte Macrophage Colony Stimulating Factor |
| GOLD | Global initiative in Obstructive Lung Disease |
| HHV-4 | Human Herpes Virus 4 |
| ICAM-1 | Intra cellular adhesion marker 1 |
| IgA | Immunoglobulin A |
| ICH | International Conference of Harmonisation |
| IMP | Investigational Medicinal Product |
| ISRCTN | International Standard Randomised Controlled Trial Number Register |
| MHRA | Medicine and Healthcare Products Regulatory Agency |
| NICTU | Northern Ireland Clinical Trials Unit |
| PI | Principal Investigator |
| qPCR | Quantitative Polymerase Chain Reaction |
| REC | Research Ethics Committee |
| RSV | Respiratory Syncytial Virus |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| SOPs | Standard Operating Procedures |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMG | Trial Management Group |

# 1 STUDY SUMMARY

Chronic obstructive pulmonary disease (COPD) is a prominent disease associated with a downward spiral of progressive breathlessness and functional decline. This condition is projected to become the third most common cause of mortality worldwide within the next decade. The extensive pressure facing the health service behoves us to improve the outcome for this disease as the health system comes under increasing strain. There is no treatment that can meaningfully alter the course of deteriorating lung function or the time to death and future research urgently needs to focus on novel therapeutic measures for COPD sufferers. Only some smokers go on to develop COPD. Our research group and others have demonstrated high levels of Epstein-Barr virus (EBV) in the sputum and in the airway mucosa of patients with COPD using novel molecular diagnostic techniques. EBV is a gamma herpes virus. The virus usually has a latent phase, during which it resides in the B-lymphocytes. It has a shedding phase where it is released from the epithelium. This is generally uncommon in healthy subjects, however, it is frequently found in COPD. Other investigators have demonstrated EBV within bronchial epithelial cells using in-situ hybridisation techniques. Consequently it is hypothesised that persisting EBV infection in conjunction with cigarette smoke exposure could be implicated in the chronic airway inflammation seen COPD. EBV can be suppressed in a mouth ulcer condition called oral hairy leukoplakia (in immunocompromised patients). The medication used is valaciclovir which has been licenced for use since 1995. The aim of this study is to evaluate the safety of valaciclovir in subjects with COPD and whether EBV detected in the sputum of patients with COPD can be suppressed. We will also examine the effect of viral suppression on clinical symptoms, lung function and markers of airway inflammation in the blood and sputum.

The EBV suppression in COPD (EViSCO) study will be a randomised double-blind placebo-controlled clinical trial. The EViSCO trial will recruit subjects with COPD (GOLD classification 2 and 3) and EBV detectable in their sputum samples. Trial participants will receive either valaciclovir one gram three times daily or a matching placebo for a total of 8 weeks. Each participant will attend three separate clinic visits during the study (baseline assessment at 0 weeks followed by assessment at 4 and 8 weeks from enrolment). Participants will undergo measurement of lung function and provide blood and sputum samples during clinic visits. The study will recruit a total of 88 participants to the trial. We will also conduct an exploratory sub-study that will involve bronchoscopic evaluation of the airway epithelium before and after treatment. During flexible bronchoscopy washings, brushings and biopsies will be collected for analysis. Bronchial brushings will facilitate bronchial epithelial cell culture experiments. The exploratory bronchoscopy sub-study will recruit participants from the 88 patients already enrolled into the EViSCO trial on a voluntary basis.

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| Study Design: | Randomised Double Blind Placebo Controlled Trial |
| Study Aims and Objectives: | Safety of Valaciclovir in COPD |
| Study Intervention: | Valaciclovir |
| Concurrent Control: | Placebo |
| Primary Outcome: | 1. Safety: The incidence of serious adverse reactions (SARs)<br>2. Efficacy: EBV suppression measured by quantitative Polymerase Chain Reaction |
| Secondary Outcome: | 1. Change in Forced Expiratory Volume in 1 second (FEV1) from baseline to week 8<br>2. Participant compliance measured by total number of tablets administered as a proportion of total number of tablets supplied |
| Study Setting: | Belfast Health & Social Care Trust |
| Patient Population: | COPD patients (GOLD stage 2 &3) |
| Sample Size: | 88 (44 in each group) |
| Examination Points: | Baseline, 4 and 8 weeks<br>Bronchoscopy Sub-study Baseline and 8 weeks |
| Study Duration: | 4 years |

# 2 STUDY TEAM

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| Trial Sponsor: | Belfast Health and Social Care Trust |
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# 3 BACKGROUND AND RATIONALE

## 3.1 Background Information

**Introduction**
COPD is present in 10% of the population [1]. It is a disease occurring predominantly in smokers. Yet only one in four smokers become affected. Some people who never smoke develop the disease [2]. COPD is predicted to rise from the 6th commonest cause of death in the 1990's to the third commonest cause of death by 2020 [3]. In 2002 it was calculated that 12.5% of medical admissions were COPD[4]. In 2007 there were 9,500 hospital admissions in Northern Ireland, this rose to 12,000 admissions by 2011 (data from Dr Jenny Gingles, Public Health Agency NI). Mortality remains high and high 90-day-mortality and readmission rates are seen following COPD admissions [5].

A recent analysis of stakeholders in the COPD outcomes based Network for Clinical Effectiveness and Research Translation (CONCERT) highlighted that the impact on patient centred health outcomes was the most important criterion for prioritising future research projects. There were four aspects of care examined, chronic care, care coordination, acute exacerbations and transitions in care (mild to severe). In chronic care of COPD, effectiveness of care and pharmaceutical treatment were selected as priorities [6].

***Inflammation*:** COPD is characterised by inflammation with high levels of IL-8 and increased neutrophils in sputum. In previous studies it has been shown that IL-8 causes the neutrophils to cross the airway epithelium. The mechanism is by CD11b/CD18 on the neutrophils binding to epithelial ICAM-1 [7]. ICAM-1 is increased in COPD [8]. The airway mucosa is infiltrated with CD8+ T lymphocytes[9] (cytotoxic – suppressor cells).

**Chronic viral infection in COPD**: The finding of CD8+ T cells has lead researchers to investigate if there is evidence of a chronic viral infection in these individuals. Some have proposed that a component of adenovirus (early antigen -E1A) may be left from early infections in childhood [10], but evidence has been unable to be demonstrated for either E1A or persistent adenovirus infection [11]. Two teams have proposed chronic and acute RSV infection in COPD [12,13]. However this research group and a separate team in the United States, have been unable to demonstrate significant amounts of RSV using different primers[14,15].

***Epstein Barr virus (EBV) and COPD***: In the search for chronic viruses in COPD Epstein Barr virus (EBV) has been found in the sputum of several groups of patients, with differing degrees of disease severity [16,17]. In the initial study, EBV was found in the sputum of half of the patients with severe COPD, a group of these patients were followed up at clinic after discharge and 20% lost their EBV and 20% who were negative for the virus began shedding EBV in their sputum [16]. In the second study patients with early COPD disease who had never been exposed to inhaled or oral steroids were examined. We used a more sensitive assay and found EBV in the sputum of 75% of those with COPD [17]. A third study by a separate research group

studied airway segments using antibodies against tissue samples (immunohistochemistry).
They found Epstein-Barr virus in the airway epithelium of patients with COPD [18]. When examined by severity of disease 68% of patients with GOLD stage I and II COPD (mild disease), whereas 84% of GOLD stage III and IV patients (moderate and severe disease) had EBV in their airway epithelium. A low secretory IgA was identified and this was attributed to the cause of EBV in the airway[18]. However, IgA is an anti-bacterial antibody- it is required for inoculation of EBV *into* lymphocytes [19]. Epstein-Barr virus is lymphotropic virus which affects the B-cells. The relationship of EBV and low IgA is therefore likely to be causal (rather than low IgA causing proliferation of EBV). Indeed, in x-linked aggamaglobulinaemia patients are not infected with Epstein-Barr virus [20].

Epstein-Barr virus is present in most people, however it is confined to the B-cells. Occasionally it escapes the B-cells and enters the epithelial cells. Here it is in its shedding phase. All the studies to date have focused on high levels of the virus being shed in the airway- the epithelial shedding phase (see below), or being in the epithelium itself. A study of seroprevalence in military recruits found Epstein-Barr virus is more common in poorer socioeconomic groups and in smokers [21]. Poorer smokers are the very group who go on to develop COPD [22]. Furthermore, cigarette smoke promotes viral replication [23].

***Mechanism of* Epstein Barr virus (EBV) *infection in the airway epithelium*;**
Epstein Barr virus is a gamma herpes virus. It has a complex relationship with the human immune system. The virus has a latent and a shedding phase. When latent, it resides in the B-lymphocytes for years at very low copies (20-100 copies per million B-cells) [24]. During the lytic phase, it infects the epithelial cells, which shed millions of viruses. Epstein-Barr virus latent membrane protein-1 induces CD54 (ICAM-1) on epithelial cells [25]. ICAM-1 is the principal ligand for transmigration of neutrophils into the airway by binding neutrophil CD18/CD11b [7]. ICAM-1 is also the receptor for human rhinovirus [26], which has been identified as the commonest cause of an acute exacerbation of COPD [14,13,26]. Indeed, infection with rhinovirus then further increases ICAM-1[28]. The bacterium H. Influenzae binds to ICAM-1 and is the most common pathogen in COPD [42]

Moreover, Epstein-Barr virus (EBV) infection is associated with increased GM-CSF synthesis by monocytes [29]. These monocytes are inhibited from maturing by EBV [29], adding insult to injury, as the mature pulmonary macrophages are responsible for antigen presentation, a key immune regulatory role for infection. The GM-CSF activates neutrophils which more readily migrate across the endothelium [29] and the airway epithelium (J Kidney unpublished observations). However, Epstein-Barr virus causes increased apoptosis of these neutrophils [32]. Thus, it is apparent that EBV, in its epithelial shedding phase, sets the scene for increased activation of the epithelium, propensity for further viral infection, adherence of H. Influenzae, failure of antigen presentation of bacteria and viruses as well as neutrophil recruitment to the airway followed by apoptosis. Furthermore, it has a deceptive technique to avoid appropriate antiviral responses by expressing LMP-1 (immediate early protein) and BZLF-1 which are located on the cell wall. These inhibit Interferon regulatory factor 7 (IRF-7) [33,34], subverting the synthesis of virus inhibiting interferon alpha and interferon beta.

### Evidence for Epstein-Barr virus suppression

#### Epstein-Barr virus suppression in Infectious mononucleosis

Tynell et al suppressed Epstein-Barr virus shedding in infectious mononucleosis by giving Aciclovir 800mg five times daily for 10 days in a placebo controlled trial [35]. Active treatment was accompanied by Prednisolone (to help the inflammatory reaction during infection). Several earlier studies had similarly shown suppression of EBV shedding. A meta-analysis of 5 RCTs of acyclovir in Infectious mononucleosis showed that acyclovir caused a significant reduction in viral shedding on active treatment. However, when treatment was withdrawn there was a recurrence of viral shedding. There was a trend towards clinical effectiveness [35].

#### Epstein-Barr virus suppression in oral hairy leukoplakia

EBV is associated with oral hairy leukoplakia. This infection in the oral mucosa occurs often in immunosuppressed patients, especially with HIV. The appearance of oral hairy leukoplakia is an AIDS defining illness. It is associated with a decrease in Langherhan's cells [37]. In an open labelled study Walling found that Valaciclovir 1g three times daily for 28 days suppressed viral shedding in 16 out of 19 cases (84%). There was a clinical and histological response of 89%. One patient failed treatment with Valaciclovir having recently failed high dose oral acyclovir treatment [38].

#### Epstein-Barr virus suppression in adults with normal immunity

A randomised trial in elite athletes compared Valaciclovir to placebo. There was an 82% reduction in virus shedding [39]. A further study examined Epstein-Barr virus (HHV-4) in the B-cells of patients being treated for Herpes Simplex virus 2 (HSV-2). Patients were routinely given an induction course of Valaciclovir followed by a maintenance daily dose of Valaciclovir to suppress their herpes infection. In this study EBV was suppressed in the B-cell population [24].

### 3.2 Rationale for the Study

#### Rationale for Epstein-Barr virus in COPD

EBV has been demonstrated in the airway of early and late COPD by the authors[16,17]. In a separate study, the virus has been found in the airway epithelium of patients with mild, moderate and severe COPD[18]. This is evidence of the virus being present across the spectrum of COPD. It is entirely reasonable to hypothesize that Epstein-Barr virus can be suppressed in the airway of patients with COPD.

#### Need for a trial now

COPD is a prominent disease with increasing prevalence [3]. It is associated with a downward spiral of breathlessness. There is a need to avert the progression of this disease. Moreover, the extensive pressure facing the health service in winter behoves us to improve the outcome for this disease not only on behalf of the patients with COPD, but also for patients with other illnesses which are present during 'winter pressures' as the health system comes under strain. There is no treatment that can meaningfully alter the course of deteriorating lung function or the time to death.

**Rationale for the study population**
Previous studies have shown that the majority of patients with mild, moderate and severe COPD have EBV in their airway, either in the epithelium or in the sputum. EBV has the ability to cycle from a shedding to a latent phase (where it stays in tiny amounts in the B-cells) [24]. This study will evaluate the suppression of EBV shedding and we will therefore only study patients who are actively shedding with detectable virus in the sputum. We will study patients with COPD and moderate or severe airflow limitation on spirometry according to the current GOLD criteria (i.e. FEV1 <80% and >30% predicted). There is considerable overlap between patients with mild COPD and those with normal lung function. We will therefore not study patients with mild COPD. At the other end of the spectrum, very severe disease is associated with significant established organ damage, including hypoxia and often the cardiac complications of respiratory disease such as cor pulmonale. This cohort of patients may encounter significant difficulty enduring the rigors of the clinical trial. Consequently we will confine study participation to those with moderate and severe COPD.

**Rationale for the Drug**
A meta-analysis has shown that aciclovir can suppress EBV shedding in Infectious Mononucleosis [35]. Valaciclovir is the valine ester of aciclovir and is converted into acyclovir after absorption. Because of it's altered structure, absorption of valaciclovir is much higher than equivalent doses of aciclovir. The serum levels of acyclovir are 3-5 times higher after equivalent doses of valaciclovir compared to acyclovir. Oral valaciclovir achieves serum levels of acyclovir similar to high dose intravenous aciclovir [40].

**Rationale for the Dose**
This is the first trial of valaciclovir in COPD. Previous studies which have used this drug to suppress Epstein-Barr virus in oral hairy leukoplakia and infectious mononucleosis have used a dose of 1 gram three times daily [39,40]. Because of this precedent, this study will use the same dose.

**Rationale for the duration**
The virus is usually suppressed after 2 weeks of treatment. In this study we will also examine the effect on inflammation in the airway. The duration of inflammation with a scar or with an asthma exacerbation is 6 weeks. This study will use 8 weeks treatment to firstly, suppress the virus, and secondly, to alter the inflammation.

# 4 STUDY AIMS AND OBJECTIVES

## 4.1 Study Hypothesis

The primary hypothesis is that treatment with valaciclovir is safe and will suppress Epstein-Barr virus in the sputum of patients with COPD.

## 4.2 Study Aim

This study seeks to establish if an antiviral therapy (valaciclovir) used to treat other herpes viruses is safe in patients with COPD. We will also examine whether it is possible to supress EBV in the airways of patients with COPD and examine important outcome measures including lung function and markers of airway inflammation in the blood and sputum.

In a sub-study airway samples will be obtained from patients with COPD by bronchoscopy before and after treatment with either valaciclovir or placebo.

## 4.3 Study Objectives

**The primary objective:**

- To evaluate the safety of valaciclovir (1 gram three times daily for 8 weeks) for the suppression of Epstein-Barr virus in patients with COPD.
- To suppress Epstein-Barr virus shedding in COPD.

**The secondary objective**:

- To determine the effect of Epstein-Barr virus (EBV) suppression on lung function (FEV1) in patients with COPD.

- To assess the tolerability of valaciclovir (1 gram three times daily for 8 weeks) by measuring participant compliance.

**The exploratory objectives**:

- To measure the effect of EBV suppression on sputum and blood markers of inflammation in patients with COPD.

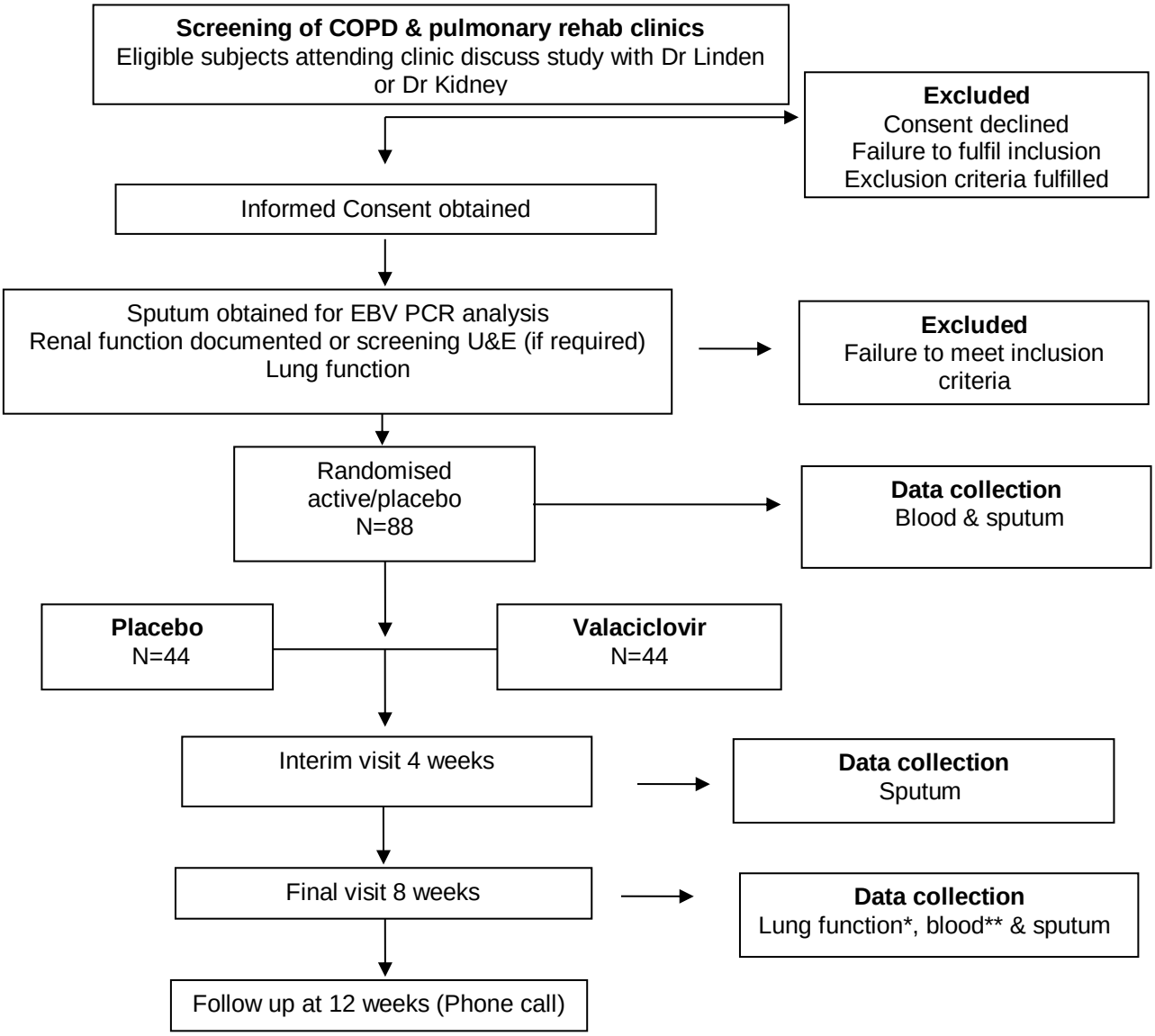
- To evaluate quality of life following EBV suppression in patients with COPD.

# 5 STUDY DESIGN

## 5.1 Study Design

The EViSCO trial is a randomised double-blind, placebo-controlled trial of 1 gram three times daily of valaciclovir or placebo for 8 weeks in COPD patients with Epstein-Barr virus. Patients will be randomised with an allocation ratio of 1:1 valaciclovir to placebo.

## 5.2 EViSCO Study Schematic Diagram




## 5.3 Outcome Measures

### 5.3.1 Primary Outcome Measure

- The primary safety outcome is the incidence of serious adverse reactions (SARs).

- The primary efficacy outcome is suppression of Epstein-Barr virus in the sputum of subjects with COPD assessed using quantitative PCR at baseline and 8 weeks.

EBV is a DNA virus that may be suppressed beyond detection, however, it may be reverse transcribed and so it is possible that there will some detectable virus. For this this reason we will define EBV suppression as a 90% reduction in the viral load.

### 5.3.2 Secondary Outcome Measures

- Lung function measured by spirometry, the principal component will be the change in FEV1 from baseline to week 8*.

Participant compliance measured by total number of tablets administered as a proportion of total number of tablets supplied.

*In light of the COVID19 lockdown lung function will not be measured in order to prevent unnecessary risk of exposure to study participants.

** Blood samples will no longer be taken in order to prevent unnecessary risk of exposure to study participants.

### 5.3.3 Exploratory Outcomes

**Clinical Exploratory Outcomes**

- Symptoms measured by CAT score and EQ-5D-DL from baseline to week 8

**Biological Exploratory Outcomes**

- Neutrophil activation biomarkers that may include but are not limited to measurement of neutrophil elastase and ICAM-1.

- Inflammatory response biomarkers that may include but are not limited to measurement of proteins, metabolites, cytokines (including but not limited to TNFα, IL-1β, IL-6, IL-8), proteases and anti-proteases.

- Nucleic acid analysis in sputum and blood including, viral/bacterial nucleic acid detection and gene expression. RNA sequencing, mRNA analysis and methylation analysis.

## 5.4 Exploratory Bronchoscopy Sub-study

EViSCO trial participants will be recruited to the sub-study on a voluntary basis and will indicate their consent to have a bronchoscopy at baseline and following 8 weeks treatment during the initial study visit. Participants undergoing bronchoscopy will have bronchial washings and tissue specimens taken via bronchial biopsies and brushings. This will allow bronchial epithelial cell culture and pathological assessment of the airway epithelium before and after treatment.

### 5.4.1 Exploratory Bronchoscopy Sub-study Outcome Measures

- Measurement of epithelial ICAM-1 and airway neutrophilic inflammatory markers.

- Bronchial biopsy histology and immunohistopathology.

- Indices of nucleic acid expression in sputum and blood including viral and genomic DNA, viral RNA, microRNA and mRNA analysis & methylation analysis.

### 5.5 Proposed Study Milestones

The study will be conducted over four years. There will be a 9-month set up period to allow regulatory applications, site set up and training. Patient recruitment has been estimated at 4 patients per month over a period of 22 months. As there is an 8-week (2 months) treatment period and 4 weeks (1 month) follow up, it is anticipated that patient recruitment and follow up will be completed within a 25-month period. Analysis of the primary and secondary outcomes and dissemination of the study results will take place following trial completion. The projected trial milestones are shown below in Table 1.

**Table 1 EViSCO Trial Milestones**

| **Year** | **1** | | | | **2** | | | | **3** | | | | **4** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Quarter** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** | 1 | **2** | **3** | **4** | **1** | **2** | **3** | **4** |
| Management meetings | x | x | x | x | x | x | x | x | x | x | x | x | | | | |
| Trial set up | x | x | x | | | | | | | | | | | | | |
| Ethical approval | | | x | | | | | | | | | | | | | |
| Trial staff recruitment & training | x | x | x | | | | | | | | | | | | | |
| Drug source & label | x | x | x | | | | | | | | | | | | | |
| Patient recruitment | | | | x | x | x | x | x | x | x | x | | | | | |
| Follow up, monitoring & review | | | | x | x | x | x | x | x | x | x | x | | | | |
| Data cleaning & analysis | | | | | | | | | | | | | x | x | | |
| Dissemination | | | | | | | | | | | | | | | x | x |

### 5.6 Study Duration

The estimated duration of the study will be four years.

### 5.7 End of Study

The trial will end when 88 study participants have completed the 12-week follow-up and database closure occurs for the final study analysis. The trial will be stopped prematurely if:

- Mandated by the Research Ethics Committee (REC)
- Mandated by the Medicines & Healthcare products Regulatory Agency
- Mandated by the Sponsor (e.g. following recommendations from the Data Monitoring and Ethics Committee (DMEC)
- Funding for the trial ceases

The REC that originally gave a favourable opinion of the trial and the MHRA who issued the Clinical Trial Authorisation (CTA) will be notified in writing once the trial has been concluded or if terminated early.

# 6 PATIENT SELECTION CRITERIA

Eligibility to participate in the trial will be confirmed by a medically qualified person who is named on the delegation log and documented on the eligibility checklist. Patients will be eligible to participate in the study if they fulfil all of the following inclusion criteria and none of the exclusion criteria.

## 6.1 Inclusion Criteria

1. Age over 18 years.
2. Clinical diagnosis of COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease criteria (FEV1/FVC <70%) with GOLD 2 and GOLD 3 airflow obstruction (FEV1 30-80% predicted) with significant symptoms
3. Presence of Epstein-Barr virus on sputum PCR analysis.

## 6.2 Exclusion Criteria

1. Respiratory failure (defined as long-term oxygen therapy).
2. An acute exacerbation of COPD in the previous month (defined as an acute, sustained worsening of symptoms that is beyond normal day-to-day variations).
3. A diagnosis of asthma.
4. Patients with known hypersensitivity to valaciclovir or aciclovir.
5. Patients unable to swallow study drug capsules.
6. Established diffuse interstitial lung disease (e.g. Idiopathic Pulmonary Fibrosis).
7. Established diagnosis of symptomatic bronchiectasis*.
8. Patients known to be pregnant or breastfeeding.
9. Patients with an estimated creatinine clearance less than 50ml/minute**.
10. Known participation in investigational medicinal product trials within 30 days.
11. Patients who do not adequately understand verbal or written information.
12. Concomitant use of nephrotoxic medicinal products or medicines associated with altered renal tubular secretion. These inlcude aminoglycosides, organoplatinum compounds, methotrexate, pentamidine, foscarnet, ciclosporin, tacrolimus,tenofovir, cimetidine and probenecid. As iodinated contrast used in radiological examinations can be nephrotoxic any patients with planned radiological contrast studies will be deferred for a reasonable time until after their contrast.
13. For the exploratory bronchoscopy sub-study patients will require adequate oxygen saturations, FEV1 >0.5 L and will not be performed while patients are taking aspirin or clopidogrel (BTS guidelines 2013).

** Patients with a primary respiratory diagnosis of established symptomatic bronchiectasis will be excluded. In order to fulfil this exclusion criteria patients must exhibit the clinical bronchiectasis phenotype and demonstrate computed tomography (CT) evidence of established multi-lobar bronchiectasis.*

*** Documented eGFR values from within the past 4 months will be used to confirm eligibility. If not available screening U&E will be completed.*

# 7 PATIENT SCREENING AND CONSENT

## 7.1 Screening Procedure

Potentially eligible subjects with COPD will be identified and screened by members of the direct care team based on the inclusion/exclusion criteria as specified in the study protocol (section 6). Eligible subjects will receive REC approved written study information sheets and have the opportunity to review this document in advance of the consent process. An appropriately trained doctor within the study team will seek informed consent from eligible participants following their routine scheduled clinic appointment. Appropriate signatures and dates must be obtained on the informed consent documentation prior to collection of trial data and administration of the trial drug. If no consent is given a patient cannot be randomised into the trial. At the screening visit, an appropriately trained doctor within the study team will discuss the study with the patient to determine their interest in participating and address any queries the patient may have. Informed consent, screening sputum and blood samples (if required) will be obtained at this initial screening visit. The Northern Ireland Clinical Trials Unit (NICTU) will provide screening logs which will be completed by the Chief Investigator (CI) or designee to document all patients screened for the study. Patients screened and not recruited on to the study should also be documented on the screening log, including the reason for not being enrolled on the trial. Sites will be required to submit screening data to the CTU monthly.

## 7.2 Informed Consent Procedure

The study will be performed in accordance with the ethical principles that have their origin in the Declaration Helsinki. The Chief Investigator is responsible for ensuring that informed consent for trial participation is given by each patient. An appropriately trained doctor or nurse may take consent. Signatures and dates must be obtained on the informed consent documentation prior to collection of trial data and administration of the trial drug. If no consent is obtained a patient cannot be randomised into the trial. The patient will be informed about the trial by the responsible clinician or a member of the trial team and given a copy of the Patient Information Sheet. Informed patients will be given an adequate amount of time to consider their decision on trial entry. If the patient decides to enter the trial, they will be asked to sign two copies of the Patient Consent Form, which will be countersigned by the responsible doctor or designee. The patient will retain one copy of the signed consent form. The second copy will be photocopied and the photocopy will be placed in the patient's medical records, while the original will be retained in the Investigator Site File. Study participant's GPs will be informed via written letter when they are randomised.

## 7.3 Withdrawal of Consent

Patients may withdraw or be withdrawn from the trial at any time without prejudice. Data recorded up to the point of withdrawal will be included in the trial analysis. If a

patient requests termination of the trial drug during the treatment period, the study drug will be stopped, but the patient will continue to be followed-up as part of the trial. If a patient withdraws consent during trial treatment, the trial drug will be stopped, but permission will be sought to access medical records for data related to the trial.

# 8 RANDOMISATION

## 8.1 Randomisation Procedure

Eligible participants will be randomised using a 1:1 allocation ratio into the two groups. All researchers will be blinded to the sequence. After informed consent has been obtained and eligibility has been confirmed, the next sequential number on the randomisation schedule will be assigned to the patient as the unique patient identifier.

The pharmacist will also confirm the study pack numbers to be dispensed at visit 1 and visit 2.

## 8.2 Co-enrolment Guidelines

Patients who are already enrolled in observational studies will be eligible for co-enrolment with the EViSCO study. Patients who have been recruited to the EViSCO study are eligible for co-enrolment in other observational studies. The Co-enrolment Form within the Case Report Form (CRF) should be completed and submitted to the CTU. Participants who have been enrolled in other IMP trials within the last 30 days will not be eligible for co-enrolment in EViSCO. Co-enrolment with other interventional studies will not be permitted.

## 8.3 Unblinding Procedure

As a placebo controlled, double-blind trial, patients, clinicians and the CI will be blinded to treatment allocation. Patients will be given a Patient Study Card when they are enrolled in the trial. This will include 24-hour contact details of their treating clinician in the event that the patient needs to contact their clinician. Emergency unblinding may be requested on safety grounds, or if the treatment decision for a patient could be influenced by the knowledge of what the patient is taking as part of the trial. If there is justification to unblind a patient, emergency unblinding will be performed by the Belfast Trust on call pharmacist. In the event unblinding occurs, the patient may discontinue study drug but will remain on the trial unless they decide to withdraw. Where unblinding has occurred this should be fully documented by the site and the Sponsor and NICTU informed.

# 9 STUDY DRUG

## 9.1 Treatment Regimen

Patients will be randomised to receive valaciclovir 1 gram to be taken 3 times daily or matching placebo for 8 weeks. Patients will continue on treatment until they attend for visit 3 (Week 8 +/- 7 days) assessment.

## 9.2 Concomitant Therapy

Patients will be allowed to continue their COPD therapy which usually consists of inhaled short acting beta agonist, inhaled antimuscarinic therapy- typically a long acting agent, an inhaled long acting bronchodilator and an inhaled steroid. Medication for other conditions will be continued provided they are not interacting with the investigational medication. If there is an interacting drug as outlined in the exclusion criteria they will not be included in the trial.

### 9.3 Study Drug Supply

Study drug packs will be packaged and labelled by Victoria Pharmaceuticals, The Plenum Building, The Royal Hospitals, Grosvenor Road, Belfast, BT12 6BA. Study drug packs consist of:

Valaciclovir 500mg capsules in bottles containing 210 capsules

Matched placebo (Avicel®PH) capsules in bottles containing 210 capsules

Study drug packs of valaciclovir 500mg or placebo capsules will be labelled in compliance with the applicable regulatory requirements. Study drug packs will be dispatched to the responsible site pharmacist under the instruction of the CI or designee. The CI or designee will monitor the quantity of study drug packs at site to ensure study drug packs are available to facilitate the supply of study drug to patients at the time of recruitment/randomisation and at subsequent study visits.

### 9.4 Study Drug Accountability

Pharmacy will maintain accurate records of all Investigational Medicinal Product (IMP) received (including date of receipt, batch numbers, expiry date, quantities of drug shipments), dispensed and returned on the Drug Accountability Log. Records must be available to the study monitors on request. Unallocated, unused and used study drug will be destroyed at site with permission from the CTU and in accordance with site pharmacy procedure for destruction of IMP and hospital waste management policies. A record of the destruction will be maintained.

### 9.5 Storage of Study Drug

Site pharmacies must ensure all study drugs are stored in a secured area and held separately from normal hospital stock and under the manufacturer's recommended storage conditions as detailed on the study drug pack label.

### 9.6 Study Drug Dispensing

When a patient is recruited at visit 1 (baseline) and subsequently at visit 2 (week 4) the clinician will complete a trial prescription form and present this to pharmacy. At visit 1 and 2 (baseline and week 4), patients will receive a four week supply (plus one week overage) of valaciclovir 500mg or placebo capsules

### 9.7 Study Drug Administration

Patients will take valaciclovir 1 gram (2 x 500mg capsules) or matching placebo capsules orally three times daily for 8 weeks .

### 9.8 Study Drug Termination Criteria

Prior to the maximum treatment period of 8 weeks (after randomisation), study drug will be discontinued if any of the following conditions are met:

- Patient request termination of study drug
- Patient withdraws consent for the study
- Non-compliance with study drug as determined by the PI
- PI decision that study drug should be discontinued on safety grounds.

The reason for study drug termination should be recorded on the CRF and arrangements will be made for any unused medication to be returned to pharmacy.

### 9.9 Study Drug Compliance

Patients will be asked to store the medication according to the manufacturer's instructions as detailed on study drug pack label. Patients will be asked to bring all unused medication and empty bottles to visit 2 and visit 3. Research staff will perform a count and return any unused medication and empty bottles to the site pharmacy. Patients who have taken 80% or more of the expected number of tablets will be considered compliant. Non-compliance should be discussed with the PI to determine the appropriateness of continuing/discontinuing the medication.

# 10 STUDY ASSESSMENTS

## 10.1 Study Visits and Procedures

Study visits must be accurately recorded in participants medical notes i.e. screening and baseline visits. All details to confirm eligibility should be retained in the participant's medical notes. Medical notes are source documents.

### 10.1.1 Screening Visit Procedures

The consent process will be conducted at the screening visit. Screening blood U&E samples will be taken (if required). Medical and Medication history will be reviewed, demographic data and screening sputum samples will be obtained. Patients in whom the screening sputum sample is found to be positive for EBV (measured by quantitative PCR) will be advised and invited to return for measurement of lung function. Those patients found to be eligible will then be invited to take part in the study. Patients who suffer an exacerbation of COPD in the interim period between the screening and baseline visits will be invited to be re-screened following clinical resolution of the exacerbation. Patients in whom sputum EBV qPCR is negative may be given the opportunity to return to be re-screened at a later date.

### 10.1.2 Visit 1 (Baseline) Procedures

Medical history, medication history, vital signs and BMI will be recorded at the baseline visit. Participants will complete CAT and EQ-5D-5L assessments.. FBC, research blood and sputum samples will be taken. Participants will be asked regarding exacerbation status and if applicable exacerbations will be documented. Four weeks supply of the study drug or placebo will be given and an appointment for follow up will be made. The GP will be informed via written correspondence. Sub-study volunteers will undergo diagnostic bronchoscopy.

### 10.1.3 Visit 2 (Week 4 +/- 7days) Procedures

Participants will undergo assessment via telephone call (including medication review and recording of adverse events). CAT and EQ-5D-5L assessments will be completed remotely via telephone call. Participants will be asked regarding exacerbation status and if applicable exacerbations will be documented. A sputum sample will be left for collection by the participant .Participants will count surplus medication and advise the researcher of the tablet count . A new 4-week supply of medication will be dispensed.

### 10.1.4 Visit 3 (Week 8 +/- 7 days) Procedures

Participants will undergo assessment via telephone call (medication review and recording of adverse events).. Participants will complete CAT and EQ-5D-5L assessments remotely via telephone call. Participants will be asked regarding exacerbations. . A sputum sample will be left for collection by the participant

.Participants will count surplus medication and advise the researcher of the tablet count.

### 10.1.5 Follow Up (Week 12 +/- 7 days) Procedures

For those patients who withdraw from the trial / discontinue the study drug prior to 8 weeks or following the completion of 8 weeks of treatment, the CI or designee will contact the patient by telephone 4 weeks post study drug termination to assess if the patient is experiencing any adverse events. Participants will be asked regarding exacerbation status and if applicable exacerbations will be documented.

## STUDY PROCEDURES AMENDMENT SUMMARY

The study assessments and procedures have been amended in order to observe national Coronavirus lockdown guidelines and to ensure appropriate shielding of the vulnerable participant population. The researcher will conduct the remaining study visits via telephone (including review of online health records) in order to collect data regarding adverse events, safety data, study drug compliance and complete the study questionnaires. It will no longer be possible to measure lung function or collect blood samples.

**Table 2: Schedule of Assessments EViSCO study**

| Table 2 | Screening | Visit 1 | Visit 2 week 4 (+/-7days) | Visit 3 week 8 (+/-7days) | Follow up week 12 |
|---|---|---|---|---|---|
| Informed Consent | X | | | | |
| Inclusion/Exclusion Criteria | X | | | | |
| Demographic Data | X | | | | |
| Medical History | X | X | | | |
| Medications | X | X | X | X | |
| Vital signs & BMI | | X | | | |
| Documentation of exacerbations | X | X | X | X | X |
| Randomisation/ Registration | | X | | | |
| CAT | | X | X | X | |
| EQ-5D-5L | | X | X | X | |
| Drug administration | | X | X | | |
| Sputum sample | X | X | X | X | |
| Adverse events | | X | X | X | X |

*In some cases it may not be possible to facilitate lung function testing at the screening visit. In such cases patients who otherwise meet the trial eligibility criteria will be invited to return to have lung function measurement in order to complete the screening procedures. Confirmation of lung function indices must occur prior to trial enrolment.

**At the screening visit a U&E sample will only be sent if there are no previous U&E results from the previous 4 months. A screening U&E sample may be repeated at the discretion of the researcher if there is clinical concern that historic values are borderline.

***Bronchoscopy will only be performed in participants that consent to the sub-study. In addition bronchoscopy may not be undertaken on the same day as visit 1 and visit 3 but ideally will be facilitated within the bronchoscopy list.

## 10.2 Study Procedures

### 10.2.1 Sputum sampling

Sputum will be obtained via spontaneous sputum production. Sputum will be transferred to BHSCT for EBV qPCR in line with current infection control measures. .

### 10.2.2 Research Blood Sampling
Research blood samples will no longer be taken.

### 10.2.3 Bronchoscopy

No further research bronchoscopy will take place.

### 10.2.4 EQ-5D-5L
EQ-5D-5L is a standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. Patients will complete the EQ-5D-5L 3 via telephone.

### 10.2.5 COPD Assessment Test (CAT)
The COPD Assessment Test (CAT) is a patient-completed assessment index that is designed to measure and quantify health related outcomes in patients with chronic airflow limitation. This assessment index is a short (8 point) and simple questionnaire that patients should complete independently. It has been shown to correlate well with symptoms, disease activity and disability. Patients will complete the CAT via telephone.

### 10.2.6 Pharmacy (prescribing, randomisation and dispensing)

Prescriptions must not be signed prior to eligibility being confirmed. The date that the prescription form is signed (i.e. requested) cannot be prior to date on which eligibility is confirmed. the date of study drug dispensed by Pharmacy is the randomisation date. The eligibility checklist and stickers cannot be signed off until all results of the tests required to confirm eligibility are completed and available. The study drug start date cannot be before prescription pick up date and must be accurately recorded as this relates to study drug compliance.

# 11 DATA MANAGEMENT

## 11.1 Data Collection and management

All data for an individual patient will be collected by the CI or designee and recorded in source documents/electronic case report form (CRF) for the study. For routinely collected clinical data the NHS record will be the source document. Patient identification on the CRF will be through their unique trial identifier, allocated at the time of randomisation. Data will be collected and recorded on the electronic CRF by the CI or designee as per the CRF submission guidelines. Following the entry of patient data into the study database, the data will be processed as per the CTU Standard Operating Procedures (SOPs) and the study specific Data Management Plan (DMP). Data queries will be generated electronically for site staff to clarify data or request missing information. The designated site staff will be required to respond to these queries. All queries will be responded to/resolved within the study database and amended in the study database.

## 11.2 Data storage

All documentation and trial records will be stored in conformance with the applicable regulatory requirements. Access to stored information will be restricted to authorised personnel. The trial master file will be managed according to Sponsor SOP.

## 11.3 Data archiving

Trial documentation and data will be archived after completion of the trial in keeping with the applicable regulatory requirements.

# 12 PHARMACOVIGILANCE

## 12.1 Definition of Adverse Events

The EU Clinical Trials Directive 2001/20 provides the definitions given in table 3

**Table 3: Terms and Definitions for Adverse Events**

| Term | Definition |
|---|---|
| Adverse Event (AE) | Any untoward medical occurrence in a participant to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product. |
| Adverse Reaction (AR) | Any untoward and unintended response in a participant to an investigational medicinal product, which is related to any dose administered to that participant. |
| Unexpected Adverse Reaction (UAR) | An adverse reaction the nature and severity of which is not consistent with the Reference Safety Information. |
| Serious Adverse Event (SAE) Serious Adverse Reaction (SAR) | An adverse event or adverse reaction that: results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, consists of a congenital anomaly or birth defect, or any other important medical event(s) that carries a real, not hypothetical, risk of one of the outcomes above. |
| Suspected Serious Adverse Reaction (SSAR) | 12.1.0.1 Any adverse reaction that is classed in nature as serious and **is consistent** with the Reference Safety Information (RSI) |
| Suspected Unexpected Serious Adverse Reaction (SUSAR) | 12.1.0.2 Any adverse reaction that is classed in nature as serious and **is not consistent** with the Reference Safety Information (RSI) |

Hospitalisation is defined as an inpatient admission regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation.

## 12.2 Eliciting Adverse Event Information

The CI or designee will record all directly observed AEs and all AEs spontaneously reported by the patient. In addition the patient will be asked about AEs at each visit following initiation of treatment.

### 12.3 Assessment of Seriousness

The CI or designee should make an assessment of seriousness. This is an adverse event that:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is any other important medical event(s) that carries a real, not hypothetical, risk of one of the outcomes above

### 12.4 Assessment of Causality

Adverse Events (AE) will be clinically assessed by the CI or designee for causality based on the available information, i.e. the relationship of the AE to the study drug. Causality assessment decisions must be made by a medically qualified doctor. For the purposes of this trial the causality should be assessed using the categories below.

- **Not related**: Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event.

- **Unlikely**: Temporal relationship of the onset of the event, relative to administration of the product, is likely to have another cause which can by itself explain the occurrence of the event.

- **Possibly***: Temporal relationship of the onset of the event, relative to administration of the product, but the event could have been due to another, equally likely cause.

- **Probably***: Temporal relationship of the onset of the event, relative to administration of the product, is reasonable and the event is more likely explained by the product than any other cause.

- **Definitely***: Temporal relationship of the onset, relative to administration of the product, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

*Where an event is assessed as possibly, probably or definitely related to the study drug the event is an AR.

### 12.5 Assessment of Severity

The CI or designee should make an assessment of severity for each AE according to the following categories:

- Mild: A reaction that is easily tolerated by the trial participant, causing minimal discomfort and not interfering with every day activities.

- Moderate: A reaction that is sufficiently discomforting to interfere with normal everyday activities.
- Severe: A reaction that prevents normal everyday activities.
- Life Threatening: A reaction that has life threatening consequences; urgent intervention indicated.
- Death: A reaction that results in death.

### 12.6 Assessment of Expectedness

The sponsor is required to make an assessment of expectedness and this is delegated to the CI or designee. The CI or designee is required to make an assessment of expectedness of any ARs based on the relevant Reference Safety Information (RSI).

The reference safety information for this study is the version of the Summary of Product Characteristics (SPC) for Valaciclovir (section 4.8 undesirable effects) as approved by the Medicines and Healthcare Products regulatory Agency.

Adverse reactions may be classed as either:

- Expected: The AR is consistent with the toxicity of the study drug listed in the SPC.
- Unexpected: The AR is not consistent with the toxicity in the SPC.

An AR may be described as 'unexpected' if it has occurred with greater frequency or severity that might otherwise have been expected.

### 12.7 Adverse Event Reporting Period

The AE reporting period for this trial begins on enrolment into the trial and ends 28 days following the administration of the study drug. All AEs assessed as possibly, probably or definitely related to the study drug and all SAEs that occur during this time will be followed until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

### 12.8 Adverse Event Reporting

Adverse events (AEs) associated with the patient's underlying medical condition should not be reported. However if the clinician responsible for the patients care determines that the patients change in health is related to the trial this should be reported. AEs that are not related to the underlying medical condition should be recorded within the CRF. The investigator should attempt to establish a diagnosis based on the subjects signs and symptoms and if possible record the diagnosis in the CRF as opposed to reporting the individual symptoms. All AEs should be treated appropriately and the action taken should be recorded in the CRF. Once an AE is detected it should be followed up until resolution or stabilisation, or the events are otherwise explained and the outcome recorded in the CRF.

An adverse reaction (AR) (i.e. an AE which is related to the administration of the study drug must be reported on the AE Form within the CRF. An unexpected adverse reaction (UAR) is an AE which is related to administration of the study drug and that is unexpected, in that it has not been previously reported in the approved RSI All UARs must be reported on the AE form within the CRF.

### 12.9 Serious Adverse Event Reporting

A Serious Adverse Event (SAE) is defined as an AE that fulfils one or more of the criteria for seriousness as defined in section 12.3. A serious adverse reaction (SAR) is a SAE which is related to the administration of the study drug. Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are considered to be caused by the study drug and are unexpected, i.e. their nature or severity is not consistent with the RSI.

If a SAE occurs, reporting will follow the regulatory requirements as appropriate and all SUSARs will be the subject of expedited reporting.

SAEs should be reported using the Serious Adverse Event Report Form to the Sponsor within 24 hours of becoming aware of the event using the dedicated email address clinical.trials@belfasttrust.hscni.net. Information not available at the time of the initial report should be documented on a follow-up SAE Report Form and submitted to the Sponsor. The SAE Form and any follow up report should also be submitted to the NICTU at the dedicated email address clinicaltrials@nictu.hscni.net.

The Chief Investigator or designee is responsible for reporting SAEs to the Sponsor, ethics committee and MHRA within the required time lines as per the regulatory requirements.

The CI or designee should contact the Sponsor immediately if the decision is taken that a SAR is a SUSAR using the dedicated email address, Clinical.Trials@belfasttrust.hscni.net.

**For fatal or life-threatening SUSARs (7 day reporting),** the Sponsor in collaboration with the CI will submit the SUSAR report as soon as possible but, within **7 calendar** days of becoming aware of the event.

**For non-fatal or life-threatening SUSARs (15 day reporting),** the Sponsor in collaboration with the CI will submit the SUSAR as soon as possible but within **15 calendar** days of becoming aware of the event.

### 12.10 Recording and Reporting of Urgent Safety Measures

If the CI becomes aware of information that necessitates an immediate change in study procedure to protect clinical trial participants from any immediate hazard, they can implement this immediately prior to approval by REC/MHRA. The CI should phone the Clinical Trials Unit at the MHRA and discuss the issue with a medical assessor once an urgent safety measure is taken. Urgent safety measures should be reported to the Sponsor immediately, using the dedicated email address, clinical.trials@belfasttrust.hscni.net

The MHRA and the main REC will be informed in writing providing full details of the measures taken, the reason for them, the medical assessor contacted and any supporting documentation within 3 days.

Details of the urgent safety measure should also be submitted to the NICTU at the dedicated email address clinicaltrials@nictu.hscni.net.

### 12.11 Pregnancy Reporting

Pregnancy is not considered an AE or a SAE however, an abnormal outcome would be. Therefore, the CI or designee must collect pregnancy information for female participants, and for females who become pregnant while their partners are participating in the trial. Consent should be obtained to follow up the pregnancy from the female partners of male participants.

The pregnancy reporting period for the trial is from the commencement of the study drug until 28 days post administration of the final dose of study drug. The CI or designee should complete and submit the Pregnancy Reporting Form to the Sponsor as soon as they are aware of the event using the dedicated email address clinical.trials@belfasttrust.hscni.net.

Any pregnancy that occurs in a participant or participant's partner during the trial should be followed to outcome. Follow up/outcome information should be provided to the Sponsor as soon as it becomes available. Any outcomes assessed as a SAE should be reported as per the SAE reporting procedure. The Pregnancy Reporting Form should also be submitted to the NICTU at the dedicated email address clinicaltrials@nictu.hscni.net.

## 13 STATISTICAL CONSIDERATIONS

### 13.1 Sample Size

A sample size of 31 subjects per group will have 90% power at a two-tailed significance level of 0.05 to detect a difference in the primary efficacy outcome EBV shedding of 70% in the treated group to 30% in the control group. With a dropout rate of approximately 30%, this study will require a total of 44 patients per group.

**Sample Size in Bronchoscopy sub study**

The exploratory bronchoscopy sub-study will be voluntary for participants recruited to the EViSCO trial and thus no formal sample size calculation has been performed.

### 13.2 Data Analysis

Analyses will be on an intention-to-treat basis and all statistical tests will be at the 2-sided p-value of 0.05.

Comparison between groups for the primary safety outcome measure, incidence of SARs will be carried out using Fisher's exact test.

The primary efficacy outcome, suppression of EBV shedding will initially be analysed using chi-square test. Logistic regression will be used for adjusting for covariates if required. The comparison of continuous secondary/exploratory outcomes will be initially by t-tests followed by analysis of covariance or any other appropriate methodology if required. Statistical diagnostic methods will be used to check for violations of the assumptions, and transformations will be performed where required.

Correlations between changes in the biological markers measured and physiological and clinical outcomes will be assessed by appropriate graphical and statistical methods including Pearson's (or Spearman's) correlation coefficient.

A single final analysis is planned at the end of the trial. A detailed statistical analysis Plan will be written prior to the final statistical analysis.

# 14 STUDY MONITORING

## 14.1 Data Access

The agreement with the CI or designee will include permission for trial related monitoring, audits, ethics committee review and regulatory inspections, by providing direct access to source data and trial related documentation. Consent from patients and informants for direct access to data will also be obtained. The patients' confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

## 14.2 Monitoring Arrangements

On-site monitoring visits will be undertaken by the CTU and conducted in accordance with the study-monitoring plan. On-site monitoring will be an ongoing activity from the time of initiation until study closeout and will comply with the principles of GCP and EU directive 2001/20/EC.
The frequency and type of monitoring will be detailed in the monitoring plan and agreed by the trial Sponsor.

Before the study starts a pre-initiation visit will take place to ensure that all relevant essential documents and trial supplies are in place and that site staff are fully aware of the study protocol and SOPs. During the study, on site monitoring visits will check the completeness of patient records, the accuracy of entries on CRFs, the adherence to the protocol, SOPs and GCP, and the progress of patient recruitment. Monitoring will also ensure that the study drug is being stored, dispensed and accounted for according to specifications. The CI or designee should ensure that access to all trial related documents including source documents (to confirm their consistency with CRF entries) are available during monitoring visits. The extent of source data verification (SDV) will be documented in the monitoring plan.

# 15 TRIAL COMMITTEES

The Chief Investigator (CI) will have overall responsibility for the conduct of the study. The Northern Ireland Clinical Trials Unit (NICTU) will undertake data management, statistics and monitoring. The CI will be responsible on a day-to-day basis for overseeing and co-ordinating the work of the multi-disciplinary trial team and will be the main point of contact across the study team.

## 15.1 Trial Management Group (TMG)

Trial Management Group (TMG) will be established and chaired by the CI. The TMG will have representation on it from NICTU and other investigators or members of collaborating groups who are involved in the study and provide trial specific expertise. This group will have responsibility for the day-to-day operational management of the trial, and regular meetings of the TMG will be held to discuss and solve problems and monitor progress. The discussions of the TMG will be formally minuted and a record kept in the TMF.

### 15.2 Data Monitoring and Ethics Committee (DMEC)

A DMEC will be appointed with responsibility for safeguarding the interests of trial patients, they will monitor the main outcome measures including safety and efficacy so as to protect the validity and credibility of the trial. The committee members will be independent of the study team and will comprise of at least two respiratory specialists and one statistician. The DMEC Charter will outline the terms of reference of the DMEC including roles/responsibilities, membership, organisation of meetings, reporting, decision-making and the relationship with the other trial committees.

The DMEC will discuss trial progress as and when required, but at least every 9 months, meetings will be held and will be formally minuted. The Trial Statistician will produce reports for the DMEC including recruitment, baseline, adverse event, compliance and outcome data to enable them to monitor the trial and guide overall progress. An interim analysis of efficacy is not planned, although this can be requested by the DMEC as required.

The DMEC will function primarily as a check for safety reviewing adverse events (AEs). They will specifically review the incidence of ARs, SAEs and SUSARs and produce a recommendation following each meeting. They will report any issues pertaining to safety to both the study sponsor and the Chief Investigator. If concerns exist about participant safety it will be the responsibility of both to take appropriate action to halt the trial immediately.

### 15.3 User Involvement

Patient and Public Involvement (PPI) will be integrated during the study through working closely with patients who attend the COPD patient meetings at the Mater Hospital.

# 16 REGULATIONS, ETHICS AND GOVERNANCE

## 16.1 Sponsorship

The Belfast Health and Social Care Trust (BHSCT) will act as Sponsor for the study and the CI will take overall responsibility for the conduct of the trial. Separate agreements will be put in place between the Sponsor, CI and each organisation who will undertake delegated Sponsor duties in relation to the management of the study.

## 16.2 Regulatory and Ethical Approvals

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by a Research Ethics Committee (REC). The trial will be conducted in accordance with the EU Directive 2001/20/EC and adhere to the appropriate regulatory requirements. A CTA will be obtained from the MHRA before the start of the trial. The trial will be registered with the International Standard Randomised Controlled Trial Number (ISRCTN) register and the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database.

## 16.3 Good Clinical Practice

The trial will be carried out in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines (www.ich.org). All members of the trial team will complete GCP training**.**

## 16.4 Protocol Compliance

The CI or designee will conduct the study in compliance with the protocol given approval/favourable opinion by the Ethics Committee and the appropriate regulatory authority. Changes to the protocol may require competent authority/ethics committee approval/favourable opinion prior to implementation, except when modification is needed to eliminate an immediate hazard(s) to patients. The CI in collaboration with the sponsor will submit all protocol modifications to the competent authority/research ethics committees for review in accordance with the governing regulations. Protocol compliance will be monitored by the CTU who will undertake site visits to ensure that the trial protocol is adhered to and that necessary paperwork (e.g. CRF's, patient consent) is being completed appropriately. Any deviations from the protocol will be fully documented on the protocol deviation form in the CRF.

## 16.5 Patient Confidentiality

Due care will be taken to ensure data safety, integrity and compliance with the Data Protection Act. The patient's trial identifier, name, address and other contact details of all patients will be kept separate. The CI or co-investigator will keep these details in a locked filing cabinet. All documentation regarding the study will identify the patients by the assigned unique trial identifier. Computers where information will be stored will be password protected. Patient confidentiality will be maintained at every stage and will not be made publicly available to the extent permitted by the applicable laws and regulations.

### 16.6 Record retention

On completion of the trial the TMF and study data will be archived by the CI and CTU according to the applicable regulatory requirements and as required by the Sponsor.

### 16.7 Indemnity

The BHSCT will provide indemnity for any negligent harm caused to patients by the design of the research protocol and the management of the trial through the Clinical Negligence Fund in Northern Ireland.

### 16.8 Finance

The study is funded by the YP Trustees, a charity associated with the Mater Hospital. Dr Joe Kidney will manage the grant.

# 17 DISSEMINATION/PUBLICATIONS

The intention is to publish the results of this study in high quality peer-reviewed scientific journal(s). The TMG (and where appropriate collaborators) will take an active part in the preparing and reviewing of all manuscripts and reports generated during/on completion of the study. Any papers reporting the study outcome will be provided to collaborators and/or the Sponsors for advisory review and comment prior to submission for publication. The trial will be reported in accordance with the CONSORT guidelines (Schulz et al, 2010; www.consort-statement.org).

**Definition of authorship**

An author is considered to be someone who has made substantive intellectual contribution to a study. Many journals consider it best practice that everyone who is listed as an author should have made a substantial, direct, intellectual contribution to the work. All investigators will potentially be co-authors and collaborators will be acknowledged. Honorary or guest authorship is not acceptable.

**Dissemination Policy**

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).

Dissemination will be achieved in several ways: (1) the findings will be presented at national and international meetings with open access abstracts on-line e.g. the American Thoracic Society annual meeting; and (2) in accordance with the open access policies proposed by the leading research funding bodies we aim to publish the findings in high quality peer-reviewed open access (via Pubmed) journals. This will secure a searchable compendium of these publications and make the results readily accessible to the public, health care professionals and scientists

At the end of the trial, all subjects will be written to thanking them for their participation in the study and provided with a short summary of the trial findings. Further details about the trial may be obtained on request.

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