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## **PROTECT-CH TRIAL**

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### **IMP-APPENDIX A to Protocol version 1.0**

**IMP: Ciclesonide  
IMP type: Post-exposure prophylaxis (PEP)**

IMP-Appendix agreed by:

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# 1. Introduction and Rationale

Ciclesonide is an inhaled corticosteroid (ICS) used in the prophylaxis of asthma (80 µg od with maximum 320 µg bd; British National Formulary, accessed 28/12/2020); in North America it is also licensed for hay-fever and allergic rhinitis. It is a safe and effective inhaled corticosteroid (ICS) in asthma.[1-3] Potential advantages over other ICS are activation in the lung only with low oral and high pulmonary deposition, high first pass effect in the liver and high protein binding in the bloodstream.[4] As a result, it may cause less cortisol suppression [4] and systemic side effects than other ICS.

## 1.1 Corticosteroids in COVID-19

Emerging evidence suggests that the SARS-CoV-2 virus initially infects nasal and respiratory epithelial cells following which the infection is either cleared with minimal damage to the host, or inflammation becomes dysregulated with ongoing viral replication, particularly in alveolar macrophages. Ongoing inflammation in the lung causes further ingress of pro-inflammatory leukocytes and subsequent pulmonary tissue damage leading to endothelial and epithelial disruption, widespread organ damage, and activation of the complement cascade with consequent thrombosis and associated morbidity. Accompanying pulmonary damage, a systemic neutrophilia develops with evidence of systemic inflammation, widespread organ damage, activation of the complement cascade and thrombosis, with all contributing to morbidity and mortality. The use of corticosteroids in COVID-19 is well established as part of standard of care in severe disease. The RECOVERY trial data showed that dexamethasone was beneficial in late-stage disease.[5] Systemic corticosteroids such as dexamethasone suppress the immune system at the bone marrow level and their mechanism of action is outlined in the accompanying brief on oral steroids.

## 1.2 Rationale for ICS use in COVID-19

Implicit for the use of targeted ICS in the lung is that glucocorticoids will suppress inflammation and immune responses in the lung tissue without having significant systemic effects and allowing bone marrow-derived immune cell populations to continue being produced so leading to viral clearance. Further, the much wider therapeutic window seen with ICS as compared to systemic steroids may allow for a targeted lung approach, of relevance in earlier disease and prophylaxis. As a result, the ideal ICS in COVID-19 would include high affinity for the glucocorticoid receptor, a small particle size to avoid oropharyngeal deposition, minimal systemic bioavailability, a short plasma half-life, widespread availability and low acquisition cost.

## 1.3 Anti-inflammatory effects of ICS in lung

The anti-inflammatory effects of ICS are the same as that for systemic corticosteroids but just limited to the lung. There is relatively little direct research evidence comparing systemic steroid effects with inhaled glucocorticoid in lung inflammation other than in asthma specifically. In experimental models, ICS such as budesonide are biologically active reducing inflammatory markers in a rhinovirus infection model in bronchial epithelial cells and in studies of experimental adult respiratory distress syndrome (ARDS) where they also improved oxygenation. Nebulised budesonide reduced inflammatory markers in patients with ARDS.

## 1.4 Antiviral effects of ICS

Although most steroids do not exhibit activity against SARS-CoV-2, ciclesonide (and mometasone) does, as seen in laboratory studies where it block SARS-CoV-2 RNA replication by targeting the viral replication-transcription complex [6] and inhibited SARS-CoV-2 cytopathic activity.[7] Ciclesonide was specific for positive-strand RNA viruses suppressing viral growth in murine hepatitis virus type2 and several coronaviruses including human coronavirus 229E, MERS-CoV, SARS-CoV, and SARS-CoV-2 (but did not affect the replication of negative-strand viruses, e.g., respiratory syncytial virus (RSV) and influenza virus).[6] Ciclesonide had:



- EC50 values of <1 µM in primary human bronchial tracheal epithelial cells [7] and 1-10 µM in Vero-TMPRSS2 cells.
- EC90 values of 5.1 in VeroE6-TMPRSS2 cells, 6.0 µM in Calu-3 cells and 0.55 µM in differentiated primary human bronchial tracheal epithelial cells.[6]

Overall, ciclesonide suppressed SARS-CoV-2 viral RNA replication with efficacies similar to nelfinavir and lopinavir. In contrast, fluticasone and dexamethasone did not suppress viral replication, and budesonide had no effect on HCoV-229E replication in primary human nasal epithelial or human tracheal epithelial cells.

### 1.5 Clinical antiviral effects of ciclesonide

In a case series, ciclesonide treatment was associated with higher blood lymphocyte counts, potentially important since lymphopenia is associated with severe COVID-19.[8] Several uncontrolled case series of ciclesonide use in COVID-19 have been reported but the lack of control groups, small size and concurrent testing of other potential antiviral agents limit their interpretation.[9-11] A large retrospective study linking inhaled ICS usage with subsequent death from COVID-19 suggested that ICS-users with COPD or asthma were at increased risk of death even after multiple covariate adjustment;[12] nevertheless residual indication bias and lack of adequate adjustment mean that ICS may yet have a protective effect.[13] Although unpublished, the COVIS Pharma Group recently announced the top-line results of a double-blind placebo-controlled phase III trial of inhaled ciclesonide (320 µg bd); the trial studied 400 non-hospitalised patients with symptomatic SARS-CoV-2 infection. Although ciclesonide did not alter the primary outcome - time to alleviation of COVID-19 symptoms, treatment was associated with reduced visits to the emergency department or hospitalisation (9% vs 30%, p=0.030).

The clinical evidence for ciclesonide lags that for budesonide which appeared to improve outcome in non-hospitalised patients with COVID-19.[14, 15] Since both ciclesonide and budesonide have comparable anti-inflammatory effects, the additional antiviral effects of ciclesonide raise the possibility that it may have even greater efficacy. Further, antiviral effects suggest that ciclesonide may have prophylactic effects and so prevent infection whilst anti-inflammatory effects may reduce the severity of infection.

## 2. Information on the Chemical and Pharmaceutical Properties

### 2.1 Active Substance

#### 2.1.1 Drug Structure

2-[(1S,2S,4R,8S,9S,11S,12S,13R)-6-cyclohexyl-11-hydroxy-9,13-dimethyl-16-oxo-5,7-dioxapentacyclicosa-14, 17-dien-8-yl]- 2-oxoethyl 2-methylpropanoate

C<sub>32</sub>H<sub>44</sub>O<sub>7</sub>

CAS: 141845-82-1

ATC: R01AD13 and R03BA08

Brand name: None

#### 2.1.2 Pharmacokinetic and Pharmacodynamic Properties



Ciclesonide is a nonhalogenated corticosteroid that is formulated as a solution for inhalation in a hydrofluoroalkane (HFA) pressurized metered-dose inhaler (MDI). This device delivers ciclesonide in fine particle spray (average particle size 1.1–2.1  $\mu\text{m}$ ) that yields a high fraction of respirable particles. Ciclesonide is converted to its clinically active metabolite, desisobutryl-ciclesonide, by esterases in the airways. Pharmacodynamic studies have shown that inhaled ciclesonide has potent anti-inflammatory activity in patients with asthma and does not appear to have clinically relevant systemic effects, even at high doses. It is highly protein-bound and rapidly metabolized by the liver, and thus has a low oral bioavailability. Ciclesonide is formulated as a solution for inhalation using a hydrofluoroalkane pressurized metered-dose inhaler. This formulation delivers a high fraction of respirable particles that yield high lung deposition with even distribution throughout the lungs and minimal oropharyngeal deposition. The favourable pharmacological properties of ciclesonide help explain the low incidence of adverse events, which are mostly mild to moderate in nature.

Animal [16] and in vitro [17] studies showed that ciclesonide is converted by esterases in lung tissue to the pharmacologically active metabolite, desisobutryl-ciclesonide (des-CIC), which has a 100-fold greater glucocorticoid receptor binding affinity than ciclesonide.[18] An in vitro study in human lung tissue slices showed a high proportion of des-CIC conjugation with fatty acids.[17] These lipid conjugates of des-CIC may explain the prolonged local anti-inflammatory action of ciclesonide in the lung and its clinical efficacy with once-daily dosing.

Ciclesonide and des-CIC are highly protein-bound (~99%), which is an advantage over other ICS because it results in a low proportion of free, unbound drug in the systemic circulation.[4] In vitro studies show that ciclesonide is metabolized by hepatocytes to des-CIC within the first hour of exposure.[19] Des-CIC is, in turn, extensively metabolized to inactive metabolites.[17, 19] Elimination of des-CIC and other metabolites is predominantly in faeces.[17] Because of extensive first-pass metabolism, the systemic bioavailability of des-CIC after oral ingestion is < 1%.[17] Thus, any ciclesonide swallowed after oral inhalation does not contribute to the systemic availability of the drug or its active metabolite. In addition, low systemic exposure to unbound des-CIC suggests a low potential for systemic adverse events after oral inhalation.

## 2.2 Manufacture and licensing status

Ciclesonide is not licensed for COVID-19 prophylaxis. Ciclesonide (by inhalation of aerosol) is currently licensed in the UK as a treatment to control persistent asthma in adults and adolescents (12 years and older). It is a pressurised solution, intended for inhalation use and commercialised under the brand Alvesco. The recommended dose of ciclesonide is 160ug once daily, which leads to asthma control in the majority of patients. However, this may be increased if necessary to 320ug twice daily, in severe asthma.

Ciclesonide will be manufactured and supplied by Ayrtons Saunders Ltd (UK) for use in the PROTECT-CH trial. The product being supplied for use in the trial is an unlicensed formulation identical to that of the UK licensed formulation,

Ayrton Saunders will distribute supplies of the product to a central pharmacy/manufacturing unit who will be responsible for the labelling and final packaging of the product into clinical trial supplies.

## 2.3 Stability and Storage

Store below 25°C out of direct sunlight in accordance with the manufacturer's instructions. Temperature monitoring will not be carried out for the purpose of the trial and storage should be



managed and handled in accordance with the care homes own guidelines for the management of medicines.

Individual prescriptions to be stored for each resident as per usual care home practice.

Do not use or store near open flame or heat; do not puncture canisters. Exposure to temperatures >49°C (120°F) may cause canister to burst; do not throw canister into fire or incinerator.

### **3. Dosage and Administration**

#### **3.1 Prescription**

Following randomisation, all participants within a care home randomised to receive ciclesonide will be prescribed trial treatment by a PROTECT-CH doctor. Trial prescriptions will be sent directly to the central pharmacy. Upon receipt, the central pharmacy will apply approved trial-specific labelling (containing the participant's name) to the IMP. This will be packaged together with a spacer with attached face mask for administration of the IMP into a treatment pack. The central pharmacy will distribute trial medication directly to the care home who will be asked to confirm receipt.

Each individual participant IMP treatment pack will contain 2 inhalers sufficient for the 6 week treatment period.

#### **3.2 Dosage**

Participants will be prescribed ciclesonide once daily, administered as follows:

- Two puffs (320 µg) inhaled via mouth sequentially. Participants who are unable to tolerate a face mask will use the spacer mouthpiece taking two puffs.
- One puff (160 µg) inhaled via nose. Participants who are unable to tolerate a face mask will not receive the intranasal puff.

#### **3.3 Administration/dispensing and return**

By registered nurses or care assistants trained to administer or assist in the administration of the inhaler. Ciclesonide will be administered via an AeroChamber Plus spacer and mask using the multiple breathing technique.

Any unused drug should be returned to a local pharmacy for destruction.

#### **3.4 Training**

Care home staff will be trained on the use of inhalers and spacers, and specific risks of bleeding including central serous chorioretinopathy, risk of airway obstruction from aspiration of loose objects (e.g. dentures) and adrenal crisis. Prior to administration of IMP all staff involved in the administration of ciclesonide will be required to complete a training module on the administration of the IMP.

#### **3.5 Length of treatment**

6 weeks.



### 3.6 Primary Endpoint

Day 60 from the point of randomisation. Care homes will be requested to enter primary endpoint data within 60+7 days.

## 4. Additional Eligibility Criteria

In addition to the inclusion/exclusion criteria detailed within the current version of the PROTECT-CH trial protocol, the following ADDITIONAL criteria will be used to assess a participant's eligibility to take ciclesonide as an IMP in the trial:

### 4.1 Inclusion criteria

No additional criteria. Inclusion criteria as per protocol.

### 4.2 Exclusions and contraindications

1. Already taking, or definite need for, an inhaled or intranasal corticosteroid: beclometasone dipropionate (aerosol inhaler and dry powder inhaler), budesonide (dry powder inhaler and single-dose units for nebulization), ciclesonide (aerosol inhaler), fluticasone propionate (dry powder inhaler, aerosol inhaler, and single-dose units for nebulization), mometasone furoate (dry powder inhaler).
2. Known allergy/hypersensitivity to ciclesonide or any incipient.
3. Received a live vaccine within last 14 days - ciclesonide increases risk of generalised infection: influenza, MMR, rotavirus, typhoid, varicella-zoster (shingles), yellow fever.
4. Severe liver impairment.

### 4.3 Exceptions

The following are usually considered contraindications. However, in this patient population and for the duration of time that the IMP will be taken, it is expected that these will not be of significance. However, each resident's medical records will be taken into consideration before the IMP is prescribed,

1. Daily use of non-steroidal anti-inflammatory drugs - increased risk of bleeding when given with ciclesonide: aceclofenac, aspirin, bromfenac, celecoxib, dexibuprofen, dexketoprofen, diclofenac, etodolac, etoricoxib, felbinac, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, nepafenac, nicorandil, parecoxib, piroxicam, sulindac, tenoxicam, profenic acid, tolfenamic acid
2. Daily use of oral anticoagulants - increased risk of bleeding when given with ciclesonide: acenocoumarol, phenindione, warfarin

## 5. Safety and Adverse Event Monitoring

### 5.1 Reference Safety Information

The reference safety information is taken from section 5 of the SmPc for ciclesonide as manufactured by COVIS for inhalation.

### 5.2 Adverse Events



The following are known side-effects (taken from Summary of Product Characteristics for ciclesonide inhaler and aerosol) and will be collected within the case report form:

Incidence	Side-effect
Uncommon (>1/1,000, <1/100)	Nausea, vomiting*, bad taste, application site reactions, application site dryness, oral fungal infections*, headache*, dysphonia, cough after inhalation*, paradoxical bronchospasm*, eczema and rash, nasal discomfort, epistaxis
Rare or very rare (>1/10,000 – 1/1,000)	Palpitations**, abdominal pain*, dyspepsia*, angioedema, hypersensitivity, hypertension
Unknown	Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural changes (predominantly in children)

\* similar or lower incidence when compared with placebo

\*\* palpitations were observed in clinical trials in cases mostly confounded with concomitant medication with known cardiac effects (e.g. theophylline or salbutamol)

Details of other adverse events (AEs) will not be collected unless they meet the criteria for a serious adverse event (see below).

### 5.3 Serious Adverse Events

Serious Adverse Events (SAE), including Serious Adverse Reactions (SAR) and Suspected Unexpected SAR (SUSAR), will be recorded except where they constitute part of the primary outcome (all cause death, all cause hospitalisation and SARS-CoV-2 positivity).

Reporting will be via the on-line encrypted REDCap database. Please refer to the main trial protocol for further information on the general SAE reporting procedure.

## 6. Label

A trial-specific IMP label will be applied to the IMP by the central pharmacy prior to distribution to the care home.

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