Reducing acute severe respiratory events in health care workers during the Covid-19 pandemic with OM85

Clinical Study Protocol

A phase 3, multi-centre study testing the reduction of acute severe respiratory events in health care workers during the Covid-19 pandemic with OM85

Study Number: BV-2020/19

Australia and New Zealand Clinical Trials Registry Number: ACTRN12620000473965p
NIH Clinical Trials Registry Number:
UTN: U1111-1250-2920

Date and Version of Protocol: 2.1 23 July 2020

Confidentiality Statement

This document is confidential and is to be distributed for review only to site investigators, potential site investigators, study staff and applicable Ethics Committees. It is understood that this information will not be disclosed to others without written authorization from the sponsor except to the extent necessary to obtain informed consent from those persons to whom the investigational product may be administered

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2. Investigator Signature Page

Reducing acute severe respiratory events in health care workers during the Covid-19 pandemic with OM85

I confirm that I have read **Protocol Version 2.0 dated 12th June 2020**. As the site investigator, I understand it, and I agree to adhere to the study conduct requirements and agree to conduct this protocol in accordance with International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), the Declaration of Helsinki, the United States (US) Food and Drug Administration (FDA), and local regulations and guidelines. I agree to report all information or data in accordance with the protocol and in particular I agree to report any serious adverse events. I will accept the monitors, auditors and regulatory inspector's oversight of the study. I will promptly submit the protocol to the applicable ethical review board.

Chief investigator signature

Professor Peter D Sly

Chief investigator printed name

Date

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3. Synopsis of Protocol

Title	A phase 3, multi-centre study testing the reduction of acute severe respiratory events in health care workers during the Covid-19 pandemic with OM85
Clinical phase	Phase Three
Protocol number	BV-2020/19
Principal Investigators	Prof Peter Sly Prof Patrick Holt Prof Adnan Custovic Assoc Prof Deborah Strickland Dr Anthony Bosco Prof John Upman Dr Emmanuelle Fantino Assoc Prof David Reid Prof Robert Ware Dr Adam Irwin
Statistical consultant	Prof Robert Ware
Study design	Parallel group, Wait-list design, with treatment delayed for 3 months Participants will be randomized on a 1:1 ratio with 500 participants per group in Australia and 500 per group in the UK. Group 1: Wait-list control. One capsule OM85 (7.0 mg) will be given daily for 3 months, commencing in Month 3, with 3 months follow-up off treatment. Group 2: Initial treatment. One capsule OM85 (7.0 mg) will be given daily for 3 months, commencing on day 0, with 3 months follow-up off treatment.
Accrual objective	2000 Health Care Workers (HCW):- 1000 from Brisbane Hospitals 1000 from UK Hospitals

Accrual period	4 weeks
Study duration	12 months
Countries	Australia, United Kingdom
Sites	Queensland Children's Hospital, Brisbane (Site Investigator: Dr Adam Irwin) Imperial College Hospital, London (Site Investigator: Prof Adnan Custovic) Prince Alexandra Hospital, Brisbane (Site Investigator: Prof John Upham) Princess Charles Hospital, Brisbane (Site Investigator: Assoc Prof David Reid)
Primary endpoint	The proportion of HCW contracting an ARI necessitating workforce removal.
Secondary endpoints	Secondary endpoints include: • The time to ARI necessitating workforce removal • The proportion of HCW contracting an ARI necessitating workforce removal at end of treatment and at the end of the follow-up period, overall and by department • The total number of days with respiratory symptoms (upper or lower) • The proportion of HCW with COV infection documented by PCR, seroconversion and/or COV ARI necessitating workforce removal. • The time to LRI necessitating workforce removal • The proportion of HCW contracting an LRI necessitating workforce removal at end of treatment and at the end of the follow-up period, overall and by department • The proportion of HCW with COV infection documented by PCR, seroconversion and/or COV LRI necessitating workforce removal.
Mechanistic endpoints	Mechanistic endpoints (Brisbane only) include: • Seroconversion to COV • Host immune cell profile grouped who test respectively positive or negative to COV during a ARI and stratified by treatment (COV^+/OM^+, COV^+/OM^-, COV^-/OM^+, COV^-/OM^-).

	• White blood cell transcriptomic profile by group (COV^+/OM^+, COV^+/OM^-, COV^-/OM^+, COV^-/OM^-). • White blood cell cytokine production profile by group (COV^+/OM^+, COV^+/OM^-, COV^-/OM^+, COV^-/OM^-).
Safety endpoints	Safety endpoints include: • Treatment-related adverse events • Routine haematology and clinical chemistry
Inclusion criteria	Participants who meet ***all*** of the following criteria are eligible for enrolment: 1. HCW "front line" clinical departments assessing or caring for patients with suspected or proven COV infection at one of the recruiting hospitals in Brisbane or London 2. Participants who, in the opinion of the investigator, are able to comply with the protocol for its duration 3. Written informed consent signed and dated by participant according to local regulations
Exclusion criteria	Participants who meet ***any*** of these criteria are ***not*** eligible for enrolment: 1. Staff with prior COV infection necessitating workforce removal.
Treatment description	Broncho-Vaxom adult capsules® (OM85)
Replacement of Participants	Participants who withdraw consent or who are prematurely terminated from the study for any other reason will not be replaced
Study procedures	Participants will be randomized to either Group 1 (waitlist control, delayed treatment group) or Group 2 (initial treatment) for treatment for a period of 3 months with 3 months follow-up off treatment
Statistical considerations	Participants will be randomised in blocks Group 1 (waitlist control, delayed treatment group) or Group 2 (initial treatment) using a one-to-one ratio
Stopping rules	Study enrolment may be stopped if any of the following occur: • Death of a participant that is related to study treatment • The study sponsor decides to terminate the study

4. Table of contents

5. Glossary of abbreviations

AE Adverse event

AGRF	Australian Genome Research Facility
AID	Australian Infectious Diseases Research
ARDS	Acute respiratory distress syndrome
ARI	Acute respiratory infection
CBC	Clinical blood count
COV	SARS-Cov-2
CHEP	Children's Health and Environment Program
CHQ	Children's Health Queensland
CRF	Case report form
DC	Dendritic cell
DSMB	Data safety monitoring board
EC	Ethics committee
ED	Emergency Department
GCP	Good clinical practice
HCW	Health Care Worker
ICH	International conference on harmonization
ICU	Intensive Care Unit
ITT	Intention to treat
LRI	Lower respiratory infection
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
mg	milligrams
MPV	Mean platelet volume
PA	Princess Alexandra Hospital, Brisbane
PPE	Personal protective equipment
QCH	Queensland Children's Hospital, Brisbane
QH	Queensland Health
SAE	Serious adverse events
SAP	Statistical analysis plan
sLRI	Severe lower respiratory infection
SPT	Skin prick test
TGA	Therapeutic Goods Administration
TKI	Telethon Kids Institute
TPCH	The Prince Charles Hospital, Brisbane
UQ	University of Queensland
UV	Unscheduled visit
WLC	Wait List Control

6. Introduction

6.1 Background

6.1.1 Covid-19

The Covid-19 pandemic has been characterised by acute respiratory distress syndrome (ARDS) accompanied by a systemic cytokine-storm resulting in severe illness, respiratory failure and death in some. SARS-Cov-2 (COV) infection *per se* is not the only underlying issue here, as it is becoming evident that ARDS is relatively rare amongst infected subjects, and appears to be associated with gross dysregulation of ensuing host-anti-viral responses resulting in collateral immune-inflammatory-mediated damage to host tissues. Rather than waiting for susceptible subjects to present with COV-associated ARDS, we propose treatment of healthy health care workers (HCW) with a therapeutic agent which simultaneously targets front-line innate anti-viral immune defences, together with the core mechanism that controls immune response intensity in the airways. This research addresses the hypothesis that resistance to development of severe COV-associated respiratory disease in front-line health workers, even in those who develop a primary infection, can be boosted via a regimen of daily dosing with the bacterial-derived immunomodulatory agent OM85.

6.1.2 Health Care Workers

HCW are at the forefront of the Covid pandemic. Figures from China show around 3300 HCW were infected, as were 20% of Italy's HCW[1]. Infected HCW who develop lower respiratory illnesses (LRI) are removed from frontline services putting additional pressure on system ability to provide patient care. Respiratory viruses, including COV, are initially encountered by the nasal epithelium where infection is initiated. An adequate anti-viral response can contain the virus in the upper airway, with cold-like symptoms. An inadequate response can see the infection spreading to the lower respiratory tract and induce a severe lower respiratory illness (sLRI). HCW in front line clinical departments, such as emergency departments, intensive care units, COV isolation wards and radiology departments, are at increased risk of COV infection.

6.1.3 Personal Protective Equipment

In theory, personal protective equipment (PPE) can protect HCW from infection. However, adequate PPE is in short supply and commonly used surgical masks are unlikely to protect HCW from virus-containing aerosols generated by infectious patients. Facemasks, originally introduced to protect patients from respiratory emissions from surgeons, can protect the wearer from inhaling particulate matter[2]. However, even the most efficient mask is unlikely to give adequate protection if not worn correctly, or if the mask does not fit[3]. Winter et al.[3] tested the fit of three versions of the high-efficiency N95 respirator (commonly known as P2 in Australia) to 50 health care workers. They found that only 18% of health care workers achieved an adequate fit without training, 40% achieved an adequate fit after training, and adequate mask fit was not possible in 28% of subjects. These data show that assuming that a mask will provide protection is likely to be false in many circumstances, especially in the absence of adequate training. N95 respirators are certified against national standards (USA), providing at least 95% protection against particles in the sub-micron (0.1 to 0.3μm) range[4]. N99 masks, that filter 99% of sub-micron particles, odours and gaseous pollutants, and >99% of bacteria and viruses are likely to be required to adequately protect HCW from COV-infected patients.

Most HCW rely on surgical masks that usually have a layer of 3-ply melt-blown material between layers of non-woven fabric. The melt-blown material acts as the filter that stops

microbes from entering or exiting the mask. Most surgical masks feature pleats or folds allowing the user to expand the mask to cover the area from the nose to the chin. The mask may have a metal strip the user moulds across the bridge of the nose to improve the fit, and is fixed to the face by elastic ear loops or ties secured behind the head. These masks are not designed to form a seal around the nose and mouth nor to protect the wearer from submicronic particulate matter[5], including viruses such as COV.

6.1.4 Therapeutic options

As the PPE available to HCW is unlikely to prevent COV infection, an alternative approach is required. OM85, variably known as Bronch-Vaxom®, Broncho-Munal®, Ommunal®, Paxoral®, or Vaxoral®, has been in widespread clinical use throughout Europe and South America since the early 1980s for protection of infants, children and adults from the inflammatory sequelae of lower respiratory diseases, in clinical settings ranging from infection-associated wheeze in infants and school children[6,7] to severe winter exacerbations occasioning hospitalization in adult COPD patients[8,9]. While its mechanism-of-action is not fully understood, the accumulating body of clinical and experimental/mechanistic data has been sufficient to attract major support from regulators and funding agencies, exemplified by the US NIH-funded ORBEX RCT (NCT02148796) and NHMRC-funded OMPAC RCT (ACTRN12612000518864)[7] which both target ARIs in children.

Evidence from numerous trials has demonstrated that OM85 treatment during periods of high infection risk can reduce the frequency of symptomatic ARI[10,11]. The mechanism-of-action appears to involve reduction in susceptibility to upper respiratory infection and attenuation of the intensity of inflammation-associated symptoms that accompany infection spread to the lower airways. Clinical experience with OM85 indicates it is active against a wide spectrum of microbial pathogens. As such, it is likely to target immunoregulatory pathways that are fundamental to anti-microbial immunity[10], particularly those which control the intensity of host defence-associated inflammatory responses. Accumulating evidence relating to COV pathogenesis suggests that primary infection followed by successful clearance represents the norm, with relatively rare severe infection-triggered events being associated with uncontrolled/excessive local and systemic inflammatory responses. Based on its performance in other infection-related settings[6,10], we hypothesize that OM85 pre-treatment has the capacity to enhance resistance to primary infection with COV, but more importantly to stabilize immunoregulatory mechanisms that maintain immune homeostasis during COV infection and lessen risk for progression to severe life-threatening symptoms.

6.2 Investigational product

OM85 (commercial name Broncho-Vaxom adult capsule) consists of a capsule containing 7.0mg of active bacterial soluble fractions in one dose. Investigational product is to be taken orally daily for 3 months

6.3 Known and potential risks

Published clinical trials have reported OM85 to be well tolerated in children and adults. Reports of discontinuation of drug with an adverse event have been reported in three studies; two children from two separate studies discontinued drug due to rash or diarrhoea, and a study in adults with chronic obstructive pulmonary disease or chronic bronchitis reported 5 participants

in the active group (n=142) and 9 participants in the placebo group (n=131) discontinuing investigational product. In most clinical trials the number of participants experiencing adverse events were no different between the active (OM85) and placebo groups[12]. In adults, the most common reported adverse events were gastrointestinal, including nausea and diarrhoea. Six studies reported no adverse events. In elderly patients (>65 years), the most common adverse events were disease of the genitourinary (19/147, 13%), "symptoms, signs and ill-defined conditions" (11/147, 7%) and disease of the circulatory system (7/147, 5%).

6.4 Study population

The study population will include Health Care workers (adults) in emergency departments, radiology departments, isolation wards, intensive care units or other "front line" clinical departments of major Brisbane hospitals (CHQ, PA, TPCH) in Australia and at UK Hospitals

7. Study objectives and purpose

7.1 Primary objective

To reduce the proportion of HCW contracting an ARI necessitating workforce removal.

7.2 Secondary objectives

The secondary objectives of this study are to assess whether treating "front line" HCW at high risk of ARI, including LRI, with COV infection:

- Decreases time to ARI, including LRI, necessitating workforce removal
- Reduces the proportion of HCW contracting an ARI, including LRI, necessitating workforce removal at end of treatment and at the end of the follow-up period, overall and by department.
- Reduces the total number of days with respiratory symptoms (upper or lower)
- Reduces the proportion of HCW with COV infection documented by PCR, seroconversion and/or COV ARI, including LRI, necessitating workforce removal.

7.3 Mechanistic objectives

Mechanistic objectives of this study are to determine if OM85 modulates:

- Seroconversion to COV
- Host immune cell profile grouped who test respectively positive or negative to COV during an ARI, including LRI, and stratified by treatment (COV^+/OM^+, COV^+/OM^-, COV^-/OM^+, COV^-/OM^-).
- White blood cell transcriptomic profile by group (COV^+/OM^+, COV^+/OM^-, COV^-/OM^+, COV^-/OM^-).
- White blood cell cytokine production profile by group (COV^+/OM^+, COV^+/OM^-, COV^-/OM^+, COV^-/OM^-).

7.4 Safety objectives

The safety objective of this study is to determine if administration of OM85 is safe when treating front line HCW.

8. Study Design

8.1 Description

This study will be conducted as a multi-centre, parallel group, wait list design clinical trial testing the reduction of acute severe respiratory events requiring workforce removal in HCW with OM85. Health Care Workers who are eligible will receive daily OM85 for 3 months. Group 1 "Wait-list group" will be given daily OM85 for 3 months commencing in Month 3, with 3 months follow-up off treatment. Group 2 "Initial treatment group" will be given daily OM85 for 3 months commencing in on day 0, with 3 months follow-up off treatment

8.2 Efficacy Endpoints

8.2.1 Primary efficacy endpoint

The primary endpoint is the proportion of HCW contracting an ARI necessitating workforce removal

8.2.2 Secondary efficacy endpoints

Secondary endpoints include:

- The time to ARI necessitating workforce removal
- The proportion of HCW contracting an ARI necessitating workforce removal at end of treatment and at the end of the follow-up period, overall and by department
- The total number of days with respiratory symptoms (upper or lower)
- The proportion of HCW with COV infection documented by PCR, seroconversion and/or COV ARI necessitating workforce removal.
- The time to LRI necessitating workforce removal
- The proportion of HCW contracting an LRI necessitating workforce removal at end of treatment and at the end of the follow-up period, overall and by department
- The proportion of HCW with COV infection documented by PCR, seroconversion and/or COV LRI necessitating workforce removal.

8.2.3 Mechanistic endpoints

- Seroconversion to COV
- Host immune cell profile grouped who test respectively positive or negative to COV during an ARI, including LRI, and stratified by treatment (COV^+/OM^+, COV^+/OM^-, COV^-/OM^+, COV^-/OM^-).
- White blood cell transcriptomic profile by group (COV^+/OM^+, COV^+/OM^-, COV^-/OM^+, COV^-/OM^-).
- White blood cell cytokine production profile by group (COV^+/OM^+, COV^+/OM^-, COV^-/OM^+, COV^-/OM^-).

8.2.4 Safety endpoints

- Treatment-related adverse events.

- Routine haematology and clinical chemistry.

8.3 Stopping Rules

Study enrolment may be stopped if death of a participant that is related to the study treatment occurs.

Safety data will be presented by group in a blinded fashion to the Data Safety and Monitoring Board (DSMB) at scheduled DSMB meetings during the trial. The DSMB will have the authority to request un-blinded data if necessary. The DSMB may recommend that enrolment or study treatment be discontinued for the safety of participants.

Resumption of the study will be contingent upon a favourable decision by the Sponsor, and the DSMB after review of the adverse event data.

9. Selection and withdrawal of participants

Deviations from the eligibility criteria will not be permitted as they may potentially jeopardise patient safety and the scientific integrity of the study.

9.1 Inclusion criteria

Participants who meet ***all*** of the following criteria are eligible for enrolment:

1. HCW in front line clinical departments assessing or caring for patients with suspected or verified COV infection in one of the recruiting hospitals in Brisbane or the UK,
2. Participants who, in the opinion of the investigator, are able to comply with the protocol for its duration,
3. Written informed consent signed and dated according to local regulations.

9.2 Exclusion criteria

Participants who meet ***any*** of these criteria are ***not*** eligible for enrolment:

- Staff with prior COV infection necessitating workforce removal

9.3 Criteria and procedures for participant withdrawal

9.3.1 Withdrawal of participants from study

Participants will be withdrawn from the study if any of the following conditions are met:

- The participant withdraws their consent
- The participant fails to return to the clinic (i.e., they are lost to follow-up or death)
- The site investigator or his/her designee believes that continuation in the study is no longer in the participant's best interests (which may be as a result of the occurrence of adverse events (AE) or clinically relevant laboratory results)
- The participant is unable to comply with the protocol, including completing required study treatments, procedures, tests and/or examinations
- The Sponsor reserve the right to terminate the entire study or any participants involvement at any time

Participants who prematurely discontinue investigational product will be encouraged to continue with the study visit schedule and assessments. For further information regarding Early Withdraw Visits refer to Section 10.4.

Those participants that cease the investigational product before the end of the study, but continue to be assessed for all other aspects of the study, will be regarded as members of the intention to treat (ITT) sample. All remaining study medication (including used and unused medication and packaging) will be collected.

In all cases, the reason and date of withdrawal from the study, or investigational product, will be completed in the source documentation and the CRF. If the withdrawal is due to an adverse event or a clinically significant laboratory result, the participant will be followed until the AE is resolved or is clinically stabilised. The AE or laboratory result must be recorded in the CRF.

If a participant tests positive to a clinical test (not part of the study) they will follow the hospital isolation protocol. The study Covid testing is done by measuring antibodies, which are not suitable for acute surveillance as it detects past infection. Results (positive or negative) will be returned to participant for their own information

9.3.2 Premature termination of study/closure of centre

The Sponsor or the Therapeutic Goods Administration (TGA) may stop the study for any reason. They may also prematurely close any study centre following consultation with the parties involved.

In the event that the study is terminated prematurely, written notification must be sent to the ethics committee (EC), according to local regulations. The site investigator must also promptly inform all study participants and if appropriate, should assure appropriate medical follow-up. All study materials, except those documents that must remain on site, should be returned to the sponsor.

9.4 Replacement of participants

Participants who withdraw consent or who discontinue the study for any reason will not be replaced.

10. Study procedures

The study procedures are listed in the Schedule of Assessments and Procedures in Appendix 1.

10.1 Description of assessments and procedures

Procedures conducted as a part of the participant's routine clinical management and obtained prior to informed consent may be used for screening purposes or assessing eligibility. However, the procedure must meet the protocol-defined criteria and have been performed within the timelines permitted by the protocol.

10.1.1 Informed consent

A signed, written informed consent must be obtained from the participant and will be undertaken prior to any study-specific assessments or procedures. In accordance with Good Clinical Practice (GCP) guidelines, informed consent is an ongoing process throughout the study.

10.1.2 Eligibility criteria

To be eligible for enrolment into the study, participants must meet ***all*** the inclusion criteria and ***none*** of the exclusion criteria.

10.1.3 Medical/ work history

A comprehensive general medical history will be taken by the site investigator to determine significant previous and current medical conditions, diseases, procedures and surgeries that may increase the risk of developing a ARI necessitating workforce removal. Exposure data, including time on the front line, also be collected.

10.1.4 Demographic history

Participant's date of birth, ethnicity, sex, smoking information will be collected at Visit 1.

10.1.5 Nasal swab

Nasal swab will be collected at four time points (shown in Figure 1).
One swab will be collected from each nostril. Nasal swab will be used for viral detection and identification, including COV.

10.1.6 Blood tests

Venous blood samples will be collected at four time points (shown in Figure 1) for viral serology and immune profiling.

10.1.7 Patient daily symptom data

Following randomisation, the process will be explained to participants concerning their documentation of /response to daily SMS regarding any respiratory symptoms. These symptoms and/or condition related to the symptoms will be recorded as adverse events. Unclear or missing entries will be clarified with the participant and any correction annotated by site staff as appropriate. Annotations made by site staff will be clearly identified and initialled and dated.

10.1.8 Telephone calls

Telephone calls may be conducted during the study to ensure patient compliance with investigational product and completion of daily symptom data. If required, telephone calls will be conducted to assess adverse event data and review of concomitant medications and therapies will be undertaken. These may be conducted via SMS or email if participant prefers.

10.1.9 Adverse events

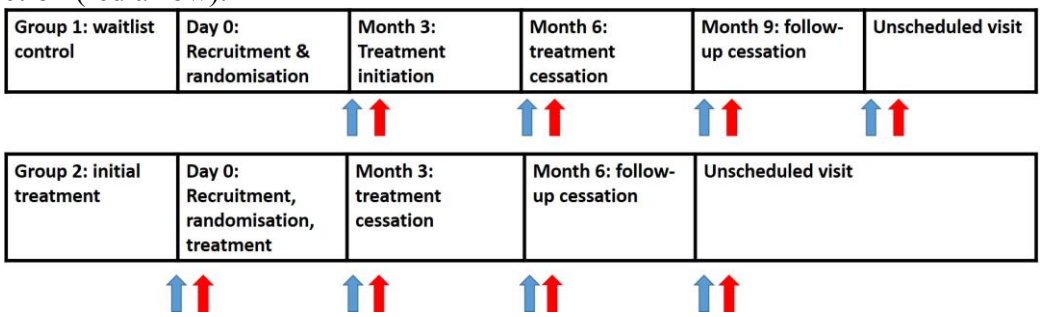
AEs will be collected from the time the medicinal product is administered. Further information regarding the collection and reporting of AEs can be found in Section 12.

10.2 Scheduled visits

This study consists of 5 visits (Group 1 - WLC) or 4 visits (Group 2 – initial treatment) over 6 or 9 months respectively (see Figure 1) Study procedures to be performed at each visit are detailed in the Schedule of Assessments and Procedures in Appendix 1.

Visits should be conducted within the specified visit windows where possible.

Figure 1: Study timeline and procedures. Nasal swab collection (blue arrow), blood collection (red arrow).



Group 1 (WLC)

Visit 1 – Screening and randomisation

The following assessments and procedures will be performed and recorded at this visit:

- Obtain written informed consent
- Evaluate inclusion and exclusion criteria
- Obtain demographic history
- Obtain medical history
- Vital signs
- Explain daily respiratory symptom data collection and assist with collection for Day 0

Once all screening procedures have been completed and eligibility confirmed, the participant will be registered with the Sponsor. Further information on the registration process is provided in the Study Reference Manual.

Visit 2: Treatment initiation 3 months post randomisation (±5 days)

- Update demographic & medical history
- Vital signs

- Nasal swab
- Collection of blood samples
- Dispense study medication and explain administration
- Adverse event assessment

Visit 3: Treatment cessation 6 months post randomisation (±5 days)
- Vital signs
- Nasal swab
- Collection of blood samples
- Clarify any missing data (daily respiratory symptoms) with participant, if not previously addressed by email/SMS
- Adverse event assessment
- Collect used investigational product packaging and unused investigational product

Visit 4: Follow up cessation 9 months post randomisation (±5 days)
- Vital signs
- Nasal swab
- Collection of blood samples
- Clarify any missing data (daily respiratory symptoms) with participant, if not previously addressed by email/SMS
- Adverse event assessment

Unscheduled Visit: at time of ARI necessitating workforce removal
- Vital signs
- Nasal swab
- Collection of blood samples
- Clarify any missing data (daily respiratory symptoms) with participant, if not previously addressed by email/SMS
- Adverse event assessment

Group 2 (Initial Treatment)

Visit 1 – Screening, randomisation, and treatment initiation
The following assessments and procedures will be performed and recorded at this visit:
- Obtain written informed consent
- Evaluate inclusion and exclusion criteria
- Obtain demographic history
- Obtain medical history
- Vital signs
- Nasal swab
- Collection of blood samples
- Drug delivery
- Dispense study medication and explain administration
- Explain daily respiratory symptom data collection and assist with collection for Day 0

- Adverse event assessment

Once all screening procedures have been completed and eligibility confirmed, the participant will be registered with the Sponsor. Further information on the registration process is provided in the Study Reference Manual.

Visit 2: Treatment cessation 3 months post randomisation (±5 days)
- Vital signs
- Nasal swab
- Collection of blood samples
- Clarify any missing data (daily respiratory symptoms) with participant, if not previously addressed by email/SMS
- Adverse event assessment
- Collect used investigational product packaging and unused investigational product

Visit 3: Follow up cessation 6 months post randomisation (±5 days)
- Vital signs
- Nasal swab
- Collection of blood samples
- Clarify any missing data (daily respiratory symptoms) with participant, if not previously addressed by email/SMS
- Adverse event assessment

Unscheduled Visit: at time of ARI necessitating workforce removal
- Vital signs
- Nasal swab
- Collection of blood samples
- Clarify any missing data (daily respiratory symptoms) with participant, if not previously addressed by email/SMS
- Adverse event assessment

10.3 Early withdrawal visit

Participants who discontinue from the study for reasons other than ARI necessitating workforce remove, will be asked to attend an Early Withdrawal Visit. Where practicable, the study procedures scheduled for the current visit should be completed, or in the case of early withdrawal between visits, the procedures scheduled for the next study visit should be completed if the participant is agreeable.

For safety follow-up, participants should be encouraged to provide a blood sample. All used and unused study medication (including packaging) should be collected or arrangements made for its return to the clinic at this visit. Where possible, stop dates for ongoing AEs should be obtained.

11. Study treatment

11.1 Enrolment and randomisation

Once all required screening assessments are completed and eligibility is confirmed, participants will be registered with the Sponsor. Upon approval of registration, participants will be assigned a unique participant number that will remain consistent for the duration of the study.

Participants who sign an informed consent form, but do not fulfil the inclusion/exclusion criteria, will not be allocated a participant identification number.

Participants will be randomised into one of the following two groups on a 1:1 ratio with 500 participants per group:

- Group 1 (WLC): OM85 7.0 mg will be given daily for three months from Month 3

- Group B (Initial Treatment): OM85 7.0 mg will be given daily for three months from Day 0

Please see the Study Reference Manual for randomisation instructions.

11.2 Dosing, formulation and storage

OM85 (as Broncho-Vaxom adult capsules) is presented in a box with blister packs, containing 7.0 mg (30 doses). 7.0mg of OM85 is administered orally each day for 3 months.

Excipients: each capsule contains pregelatinised starch, magnesium stearate, anhydrous propyl gallate (E 310), monosodium glutamate, and mannitol.

The investigational product used throughout the study will be stored at the site's pharmacy in accordance with the instructions supplied by the Sponsor. Access to the investigational product will be restricted to authorised study staff only. OM85 (as Broncho-Vaxom adult capsules) will be kept below a temperature of 30°C. The product must not be frozen or refrigerated. The product should not be used for more than 3 months after opening.

11.3 Accountability for investigational product

Under Title 21 of the Code of Federal Regulations (21CFR 312.62), the site investigator is required to maintain adequate records of the disposition of the investigational product, including the date and quantity of product received, to whom the product was dispensed (participant-by-participant accounting) and a detailed accounting of any investigational product accidentally or deliberately destroyed.

All records regarding the disposition of the investigational product will be available for inspection by the monitor.

Participants will be requested to return all unused drug and empty blister packs & boxes at each visit. All efforts should be made by the site to follow up any bottles not returned.

11.4 Treatment adherence

The site will record the number of boxes dispensed to participants. Each box will have a unique identifying number. To enable the site to perform accountability, the participants will be asked to return all used and unused investigational product at each study visit. In the case where a participant is withdrawn from the study or becomes non-compliant with their allocated treatment, all efforts should be made to collect each previously dispensed study medication bottles. Dispensing and treatment compliance information will be recorded in the CRF.

11.5 Prohibited medications during study

There are no prohibited medications.

11.6 Permitted medications during study

During the study, participants will be allowed to take medications routinely used in the management of fever, cough or wheezing attacks, including inhaled and oral steroids. All medications will be recorded in the source documentation and CRF.

12. Assessment of safety

The site investigator is responsible for the assessment and documentation of any event that meets the criteria of an AE (see Section 12.1) or an SAE (see Section 12.2).

AEs and SAEs will be collected from the time of first dose of investigational product until the participant has completed the study at their final visit, even if the participant ceases the investigational product prematurely.

12.1 Adverse events

In accordance with the TGA GCP guidelines (CPMP/ICH/135/95), an AE is any untoward medical occurrence in a participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the investigational product, whether or not considered related to the investigational product.

All AE should be well documented in the participant's source notes and CRF. Start and stop dates, outcome and whether the participant required treatment will be recorded. The site investigator will determine the title of the AE, severity, relationship to investigational product and seriousness.

An AE does not include:

- Pre-existing disease or condition that was present prior to the first administration of the investigational product, and that does not have a clinically significant increase in severity and/or frequency during the study
- Medical or surgical procedures. The disease or condition that led to the procedure should be recorded as the AE, not the procedure itself.

AEs will be followed up until they have returned to baseline status or stabilised. Follow-up of AEs should continue until the overall clinical outcome has been ascertained or the final visit completed.

If an AE later escalates to meet the criteria for a SAE (see Section 12.2), then it must be reported to the Sponsor as an SAE. See Section 12.3 for Investigator's responsibilities for reporting SAEs.

12.1.1 Grading of adverse events

The severity of AEs experienced by study participants will be graded as mild, moderate, severe, life threatening or death by the site investigator.

12.1.2 Attribution of adverse events

The relationship, or attribution, of an AE to the investigational product will be determined by the site investigator. The relationship of the AE to the investigational product will be coded according to the following definitions:

Unrelated: The AE is due to an underlying or concurrent illness or effect of another drug and is clearly not related to the investigational product (e.g. has no temporal relationship to study drug or has a much more likely alternative aetiology).

Unlikely: The AE has little or no temporal relationship to the investigational product and a more likely aetiology exists.

Possibly: The AE has a strong temporal relationship to the investigational product and an alternative aetiology is equally or less likely compared to the potential relationship to the investigational product.

Probably: The AE has a strong temporal relationship to the investigational product or recurs on re-challenge. Another aetiology is unlikely or significantly less likely.

The site investigator should attempt to provide an alternative aetiology for all AEs considered to be unrelated, unlikely or possibly related to the investigational product. This will be recorded in the source documentation.

For the purposes of reporting to the relevant regulatory agencies, unrelated and unlikely AEs will be classified as Not Related, while possible and probably related will reported as Related.

12.2 Serious adverse events

12.2.1 Definition of serious adverse events

A SAE or reaction is any untoward medical occurrence that results in one or more of the following:

- results in death
- is life-threatening
- requires inpatient hospitalization or results in prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a medically important event or reaction

12.2.2 Clarification of serious adverse events

Death is an outcome of an AE and not an AE in itself.

A “life threatening” event is any adverse therapy experience that, in the view of the site investigator, places the participant at immediate risk of death from the reaction as it occurred.

An “inpatient hospitalisation” occurs when a participant is formally admitted to hospital for any length of time. It does not refer to Emergency Department or Accident & Emergency visits where the patient is observed and not admitted.

“Hospital in the home” or equivalent programs are not considered inpatient hospitalisations, and therefore do not need to be recorded as SAE’s.

Hospitalisations considered to be "routine" and therefore not SAEs will include hospitalisation for procedures unrelated to respiratory system or to the trial. Site staff will notify the Sponsor of routine hospitalisations within one week of the admission. Reporting instructions are provided in the Study Reference Manual.

If a routine hospitalization is prolonged due to an AE or results in any of the other definitions in Section 12.2.1, it should be reported to the Sponsor as a SAE.

Medical and scientific judgment should be exercised in deciding whether other situations than those listed in Section 12.2.1 should be considered serious. This may include important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardise the participant or might require intervention to prevent one of the other outcomes listed in Section 12.2.1.

Regardless of the relationship of the event to the investigational product, the event must be reported as a SAE if it meets any of the definitions listed in Section 12.2.1.

12.3 Investigator's responsibility for reporting serious adverse events

All SAEs will be reported within 24 hours of the site staff becoming aware of the event. The SAE (Initial) Form will be completed and faxed to the Sponsor on +**61 7 3609 7159** using all information known at the time. A minimum of the SAE title, onset date and date the last investigational product was delivered should be provided, and if possible, the form should be reviewed and signed by the site investigator prior to faxing.

Further guidance on SAE reporting, including instructions for completion of the SAE form can be found in Study Reference Manual.

If site staff becomes aware of new information regarding an SAE, a SAE (Follow Up) form should be completed and forwarded to the Sponsor within five days. New information may include recurrent episodes, complications, or progression of the initial SAE, acquisition of relevant hospital records, reports and/or laboratory results. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

SAEs, regardless of suspected causality, occurring after the patient had provided informed consent and until 30 days after the patient has stopped study participation/ withdrawn, must be reported. Any SAEs experienced after this 30 day period should only be reported if the Investigator suspects a causal relationship to the study drug. SAEs that are ongoing at the end of the study should be followed up until a final assessment is possible, and until all queries from the Sponsor have been resolved.

In accordance with local requirements, the site investigator must also notify their local EC of any SAEs.

12.4 Reporting to regulatory authorities

It is important that all known information at the time of the SAE is forwarded to the Sponsor within the protocol required time frame, as expedited reporting to the appropriate regulatory authorities may be required based on the following criteria:

No Reporting

This requirement applies if the SAE is deemed not serious by the Principal Investigators.

Standard Reporting

This requirement applies if the SAE is classified as any of the following:

- Serious, expected, and related to the investigational product
- Serious, expected and *not* related to the investigational product
- Serious, *unexpected* and *not* related to the investigational product

Expedited Reporting

This requirement applies if the SAE is classified as serious, unexpected and related to the investigational product. During these circumstances, the Sponsor must notify the appropriate health authorities within 15 days, however fatal or life-threatening events must be reported within 7 days.

13. Statistical considerations

13.1 Randomisation, stratification and blinding

Participants will be randomised to the wait list group (Group 1) or the initial intervention group (Group 2) using a one-to-one ratio, stratified by Country (Australia, UK), hospital (QCH, PA, TPCH) and department [High risk (ED, ICU, isolation wards), lower risk (radiology, general wards, other)].

13.2 Sample size calculations

There are no data in the literature on use of OM85 for the primary prevention of ARI, in relation to COV. However, 20% of Italy's HCW are infected with COV[1] If we assume 20% infection in Gp 1, then with 500 HCW in each group we will be able to detect a reduction in ARI in Gp 2 by 32.5% (to 13.5%) with 80% power (alpha=0.05). Combined with 1000 UK-recruited HCW, we will be able to detect a 25% reduction (80% power, alpha=0.05).

13.2.1 Analysis sample

All participants randomised who receive at least one dose of study treatment will be included in the "intention-to-treat" group for statistical analyses.

Participants who complete the treatment period and take at least 80% of scheduled doses will be included in the "per protocol" group for statistical analyses.

13.2.2 Statistical analyses

The ***interim analysis***, undertaken at month 1 on both the "intention-to-treat" and "per protocol" groups, will examine the primary outcome: if the treatment difference is statistically significant in favour of OM85 the DSMB will consider immediately switching WLC participants to OM85.

Between-group differences in the primary outcome at 3 months will be assessed using log-binomial regression. Secondary outcomes measured to follow-up cessation will be assessed using mixed-effects models with group and stage (treatment/follow-up) (main effects and interaction) as fixed effects and HCW as random effect. Time-to-ARI analyses will use the log-rank test. Analyses will be undertaken on both the "intention-to-treat" and "per protocol" groups.

13.3 Study endpoint assessments

Study endpoint analyses will be conducted 3 months after enrolment and at completion of the study, with an interim analysis planned at month 1.

13.3.1 Primary efficacy endpoint

The primary endpoint, defined in Section 7.2.1, will be analysed 3 months after enrollment using data collected prior to the WLC group commencing treatment, by comparing between-group differences in rates of ARI that necessitated workforce removal. The primary analysis will be conducted using log-binomial regression on both the "intention-to-treat" and "per protocol" groups.

13.3.2 Secondary efficacy endpoints and mechanistic endpoints

The secondary endpoints, defined in Section 7.2.2, and mechanistic evaluations, defined in Section 7.2.3, will be assessed using mixed-effects models with group and stage (treatment/follow-up) (main effects and interaction) as fixed effects and HCW as random effect. Time-to-ARI, including LRI, analyses will use the log-rank test.

These analyses will be undertaken, on both the "intention-to-treat" and "per protocol" groups, regardless of the outcome of the primary endpoint analysis.

13.3.3 Safety endpoints

All participants will be included in all safety analyses. All AEs reported during the study will be included in the analysis. The goal of the statistical evaluation of all AE data will be evaluated using a standardised tabulation of frequency and incidence rates of all observed AEs. The frequencies and incidence rates will be calculated on a per patient basis and not on an even basis.

13.4 Reporting deviations from the original statistical plan

Any deviations from the statistical analysis plan will be described and a justification given in the final clinical study report.

14. Direct access to source data/documents

It is the responsibility of the site investigator to maintain adequate and accurate source documentation to record all observations and other data pertinent to the study. All CRFs should be completed in their entirety to ensure accurate interpretation of the data.

The Investigator's Study Site File should include, but not limited to, approved Protocols and any subsequent Amendments, staff curricula vitae, sample Patient Information and Consent Forms, and other appropriate documents and correspondence used for the study.

14.1 Identification of source data

Data entered into the CRF should be consistent with and substantiated by original source documentation. Source documentation should be legible, complete and attributable to an originator.

14.2 Direct access to source data

The study sites will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from the participants in this study. All medical and research records will be maintained in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of any study, the sites must permit authorised representative of the Sponsor and health authorities to examine (and when required by applicable law) to copy clinical records for the purpose of quality assurance reviews, audits, and evaluations of the study safety and progress.

14.3 Case report forms

Study data will be captured in a Case Report Form (CRF). Each participant will have their own CRF. All participant study records will be completed by site study staff in a timely manner.

Throughout the study the site may receive queries from the monitor to clarify discrepancies or request further data. It is important for the data validation process of the study that all queries are resolved in a timely manner and completed as accurately as possible.

15. Quality control and quality assurance

The site investigator must retain all study records in a secure facility for 15 years after the study closes. Approval to destroy a study-specific documentation should be obtained from the Sponsor prior to the destruction of any study records.

15.1 Study monitoring

The Sponsor monitor (or designee) will regularly inspect the various records of the study, including source documents, CRFs and other pertinent documents.

The monitor will confirm the completeness, consistency, and accuracy of all documented data and verify that all study activities are carried out by the appropriate designated staff. The average monitoring frequency will be determined according to the rate of participant recruitment. In accordance with Good Clinical Practice, the monitor will visit the study site frequently enough to assure that the facilities used by the site investigator continue to be acceptable for the purposes of the study as well as tracking that the study protocol is being adhered to and has been approved by the EC.

15.2 Information to study personnel

It is the investigator's responsibility to ensure that all study personnel who are listed on the Site Responsibility Log receive training on the protocol and are qualified to carry out their delegated study tasks. Evidence of training on the study protocol must be provided for any new personnel that become involved in the study after site initiation has taken place.

It is the monitor's responsibility for initiating the site, ensuring that all study procedures are adhered to according to the approved protocol and for closing out the site at the end of the study.

15.3 Termination of study

The Sponsor reserves the right to terminate the study at any time. If the study is terminated for any reason, the Sponsor will promptly inform the site investigator. The site investigator should provide appropriate follow-up and/or therapy for their study participants. Site investigators should inform their local EC.

15.4 Protocol amendments, violations and deviations

The protocol may be amended by the Sponsor if there are changes that may significantly affect the safety of the participants, scope of the investigation, or the scientific quality of the study. Any protocol amendments must be signed by the site investigator. It must also be submitted to the local EC, with any changes from the final approved protocol not initiated at the study site until appropriate written approval is received by the EC, except when necessary to eliminate an immediate safety risk to the participants, or when the change only involves logistics or administration.

A protocol violation is any failure to comply with the final study protocol as approved by the EC. This includes but is not limited to, the final detailed protocol, patient information and consent form, questionnaires, and other study-related documents. Circumstances which may impact participant safety, affect the integrity of the study data and/or affect a participant's

willingness to participate in the study may be deemed as protocol violations. All protocol violations must be immediately reported to the Sponsor as well as the local EC in accordance with local regulations. A protocol violation page must also be completed.

A protocol deviation involves any modification or alteration to the final study protocol as approved by the EC, but does not fulfil the criteria above for a protocol violation. Examples of protocol deviations may include inappropriate documentation of the informed consent document, implementation of unapproved recruitment procedures, study visits outside of set windows and missing tests and/or laboratory values. All deviations from the protocol and the reason for the deviation will be documented in the source documentation.

15.5 Data safety monitoring board

Prior to the start of the study a DSMB will be assembled consisting of appropriate clinical and statistical experts who are independent of the conduct of the study. The DSMB will provide an ongoing independent review of data from the study to address any safety concerns. The DSMB will review whether the study data are properly collected, analysed and reported. The DSMB will review blinded study results at regular intervals, but may also request unscheduled analysis or additional analysis during the course of the study. They will evaluate periodic assessments of data quality and timeliness, as well as details such as participant recruitment, accrual and retention. The DSMB will make recommendations concerning the continuation or conclusion of the study and will notify the Sponsor accordingly.

15.6 Audits and inspections

All source documents for this study must be made available to staff from the Sponsor or its designees or to health authority inspectors after the appropriate notification. The verification of CRF data will be by direct inspection of source documents.

16. Ethics

16.1 Statement of compliance

This study will be conducted in compliance with the criteria specified in this study protocol, the ethical principles stated in the current revision of the "Declaration of Helsinki", the International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP) or with the laws and regulations of the country in which the research is conducted, whichever represents the greater protection of the individual.

16.2 Informed consent form

The informed consent form is a means of providing information about the study to a prospective participant and allows for an informed decision about participation in the study. In accordance with GCP, informed consent remains an ongoing process throughout the study.

It is the responsibility of the site investigator, or a person designated by the site investigator (if acceptable by local regulations), to obtain written informed consent from each participant after adequate explanation of the study. After ample time to have all their questions answered by the site investigator or designee, the participant must read, sign and date the informed consent form before they may enter the study, take study treatment, or undergoe any study-specific procedures.

The site investigator or designee must also explain to the prospective participant that enrolling in the study is entirely voluntary and that he, she or they may withdraw from the study at any time, for any reason.

A copy of the informed consent form will be given to the prospective participant for review.

The informed consent form must be revised whenever important new safety information is available that results in significant changes in the risk/benefit assessment or whenever any new information becomes available that may affect participation in the study. The prospective participant (including those already being treated) should be informed of the new information, given a copy of the updated informed consent form and give their consent to continue their participation in the study.

16.3 Ethics committee

This protocol, informed consent form (including the participant information sheet and any other material provided to the participant) and any advertising material must be approved by the local EC and the appropriate written approvals made available to the Sponsor before the site may begin screening potential participants.

Any modifications made to the protocol or informed consent form after receipt of the EC's original approval must be submitted by the site investigator to the committee in accordance with local procedures and regulatory requirements. Approval must be awaited before any changes can be implemented, except for changes necessary to eliminate immediate hazards to study participants.

The site investigator will ensure that prior to the initiation of the study, and also whenever subsequent modifications to the protocol and informed consent form are made, that copies of all EC approvals are sent to the Sponsor.

16.4 Participant confidentiality

The site investigator must ensure that a participant's anonymity will be respected throughout the study and that their identities are protected from unauthorised parties. A participant's privacy and confidentiality will be maintained by the assignment of a unique identification number. On participant records and other documents submitted to the Sponsor, participants should not be identified by their names, rather their unique identification number. These numbers will be used to collect, store and report participant information. The site investigator should keep a Subject Enrolment Log showing codes, names and date of birth of the participants. Confidentiality and protection of data will be maintained according to local regulatory requirements.

All information disclosed or provided by the Sponsor, including, but not limited to, the protocol, participant records, and the results obtained during the course of the study, is confidential, prior to the publication of the results.

The site investigator and any person under his/her authority must maintain this confidentiality and must not disclose the information to any third party without the prior written approval of the Sponsor.

17. Administrative procedures

17.1 Curriculum vitae

A current copy of the curriculum vitae describing the experience, qualification and training of each site investigator, pharmacist and study personnel listed on the Site Responsibility Log will be provided to the Sponsor prior to the beginning of the study. Other relevant documentation such as current medical or professional licenses should also be forwarded at the request of the Sponsor.

17.2 Participant reimbursement

Participants will not receive payment for taking part in this study.

17.3 Archiving

The site investigator shall retain all study related material including study site folders and participants' case histories. This includes, but is not limited to, signed and dated consent forms, medical records and physician progress notes. These study materials must be maintained by the site investigator for the appropriate period of time as determined by local regulations and ICH-GCP.

18. Finance and insurance

An application for funding for this study has been submitted to the Medical Research Future Fund 2020 Respiratory Medicine Clinical Trials on COVID 19 Funding commencing 2020.

OM Pharma has agreed to supply investigational product.

Insurance will be provided by The University of Queensland.

All site investigators at the study site may be asked to complete a financial disclosure form at the discretion of the Sponsor.

19. Publication policy

The results of this study will be published and/or presented at scientific meetings. The site investigators participating in this study will not have the right to publish or present any finding from this study without prior written consent from the Sponsor.

20. References

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Appendix 1: Schedule of Assessments and Procedures
Group =1 (Wait List Control)

	Recruitment and Randomisation	Treatment initiation	Treatment Cessation	Follow-up Cessation	Unscheduled visit
Visit	1	2	3	4	5
Day	0	90	180	270	
Visit Window		±5 days	±5 days	±5 days	
Informed consent	x				
Eligibility criteria	x				
Randomisation	x				
Medical history	x	x			
Demographic history	x				
Vital signs	x	x	x	x	x
Nasal swab		x	x	x	x
Study bloods		x	x	x	x
Drug delivery		x			
Drug distribution		x			
Drug collection			x		
Daily symptom data explained & first day completed	x				
Diary Daily symptom data reviewed		x	x	x	x
Adverse events		x	x	x	x

Group 2 (Initial Treatment)

	Recruitment Randomisation and Treatment	Treatment Cessation	Follow-up Cessation	Unscheduled visit
Visit	1	2	3	4
Day	0	90	120	
Visit Window		±5 days	±5 days	
Informed consent	x			
Eligibility criteria	x			
Randomisation	x			
Medical history	x			
Demographic history	x			
Vital signs	x	x	x	x
Nasal swab	x	x	x	x
Study bloods	x	x	x	x
Drug delivery	x			
Drug distribution	x			
Drug collection		x		
Daily symptom data explained & first day completed	x			
Diary Daily symptom data reviewed		x	x	x
Adverse events		x	x	x