CLARITY 2.0

An Investigator Initiated, International Multi-Centre, Multi-Arm, Multi-Stage Randomised Double Blind Placebo Controlled Trial of Angiotensin Receptor Blocker (ARB) & Chemokine Receptor Type 2 (CCR2) Antagonist for the Treatment of COVID-19

NHMRC CTC Protocol Number: CTC0312

Protocol Version Number and Date: v3.2 20 December 2021

ClinicalTrials.gov Identifier: NCT05122182

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Emergency Unblinding Please refer to Study Manual

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O'Hara DV, *et al. BMJ Open* 2024; 14:e081790. doi: 10.1136/bmjopen-2023-081790

ABBREVIATIONS

Acronym	Meaning
AE	Adverse Event
ACE2	Angiotensin-Converting Enzyme 2
ACEi	Angiotensin-Converting Enzyme Inhibitor
AKI	Acute Kidney Injury
AR	Adverse Reaction
ARB	Angiotensin Receptor Blocker
ARDS	Acute Respiratory Distress Syndrome
ARNi	Angiotensin Receptor-Neprilysin Inhibitors
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
CCR2	Chemokine Receptor Type 2
CDSCO	Central Drugs Standard Control Organisation
CLARITY	Controlled evaluation of Angiotensin Receptor Blockers for COVID-19 respiratory disease
COVID-19	Coronavirus Disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
DKD	Diabetic Kidney Disease
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
FSGS	Focal Segmental Glomerulosclerosis
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICMR	Indian Council of Medical Research
ICU	Intensive Care Unit
IL-6	Interleukin 6
IMP	Investigational Medicinal Product
LFT	Liver Function Test
MCP	Monocyte Chemoattractant Protein-1
NHMRC	National Health & Medical Research Council
NHMRC CTC	National Health & Medical Research Council Clinical Trials Centre
NSAID	Non-Steroidal Anti-inflammatory Drug
PCR	Polymerase Chain Reaction
PIS	Participant Information Sheet
RAS	Renin Angiotensin System
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SBP	Systolic Blood Pressure
SSI	Significant Safety Issue
SOC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TGI	The George Institute for Global Health
TMC	Trial Management Committee

TMF	Trial Master File
ULN	Upper Limit of Normal
USM	Urgent Safety Measure
VAP	Ventilator-Assisted Pneumonia

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SYNOPSIS AND SCHEMA

Background	The major cause of mortality from COVID-19 has been life-threatening pneumonia and acute respiratory distress syndrome (ARDS). Elevated levels of a number of pro-inflammatory cytokines, including interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1, also known as C-C Motif Chemokine Ligand 2 [CCL2]) have been reported in patients with severe COVID-19, suggesting involvement of a hyper-inflammatory immune response. MCP-1 is a chemokine with a key role in macrophage recruitment and activation and is the natural ligand for Chemokine Receptor Type 2 (CCR2). The utility of CCR2 antagonism in managing COVID-19 infection has not been tested, with most programs testing CCR2 in the setting of chronic disease such as renal disease. Alongside the role of chemokines in inducing the hyperinflammatory response, there is good evidence that the renin-angiotensin system (RAS) may also play a role in the pathophysiology of COVID-19. The RAS is responsible for regulating haemodynamic, inflammatory, and fibrotic processes, and includes two main cross-regulating axes: the vasoconstrictive, pro-inflammatory, pro-fibrotic ACE-Ang II-AT1R axis, and the vasodilatory, anti-inflammatory, anti-fibrotic ACE2-Ang1-7-MasR and ACE2-Ang1-9-AT2R axis. SARS-CoV-2 responsible for COVID-19 appears to bind and downregulate angiotensin converting enzyme type 2 (ACE2). Animal studies of the related SARS-CoV-1 suggest that this downregulation of ACE2 is sufficient for causing lung pathology and is reversed by treatment with an Angiotensin Receptor Blocker (ARB). Several randomised controlled trials are underway to assess the effectiveness of ARBs in limiting the severity of COVID-19. CLARITY 2.0 is an investigator-initiated trial that will evaluate the safety and efficacy of dual treatment with repagermanium, a CCR2 antagonist, and candesartan, an ARB, in patients hospitalised with COVID-19 disease.
Aim	The aim of this study is to evaluate the safety and efficacy of dual treatment with repagermanium and candesartan compared to placebo as treatment for patients hospitalised for management of COVID-19.
Primary Objective and Measures	To evaluate the safety and efficacy of dual treatment with repagermanium and candesartan in patients hospitalised with COVID-19 disease, assessed by the primary endpoint: 1. Clinical Health Score at day 14 This Clinical Health Score, is determined within an 8-point ordinal scale of health status, described as: 1. Not hospitalised, no limitations on activities. 2. Not hospitalised, limitation on activities. 3. Hospitalised, not requiring supplemental oxygen. 4. Hospitalised, requiring supplemental oxygen by mask or nasal prongs. 5. Hospitalised, on non-invasive ventilation or high-flow oxygen devices. 6. Hospitalised, requiring intubation and mechanical ventilation. 7. Hospitalised, on invasive mechanical ventilation and additional organ support (extracorporeal membrane oxygenation [ECMO]). 8. Death.
Secondary Objectives and Measures	To evaluate the safety and efficacy of dual treatment with repagermanium and candesartan in patients hospitalised with COVID-19 disease, assessed by: 1. Clinical Health Score at day 28. 2. ICU admission (incidence in days 0-28).

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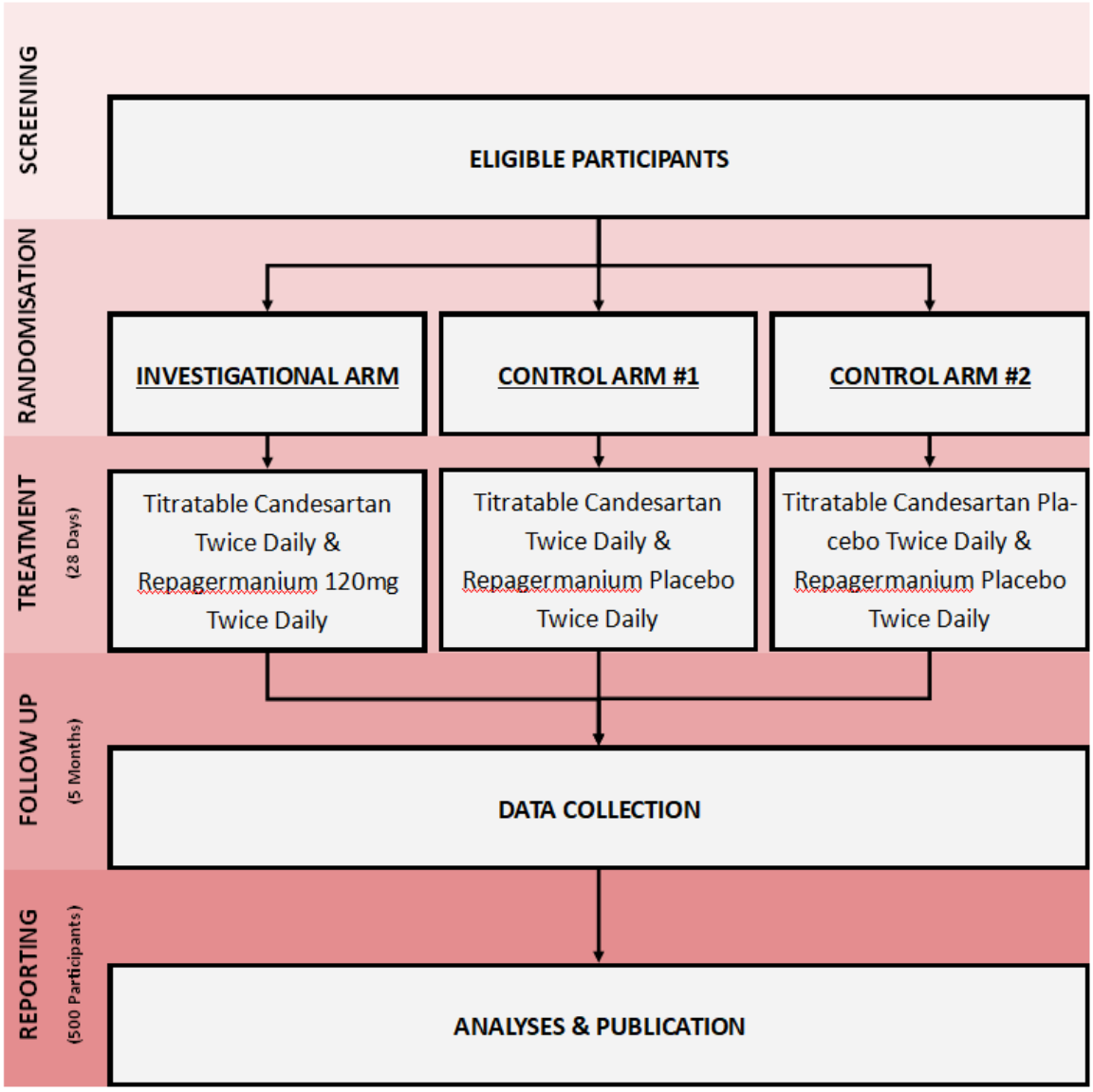
	3. Death (incidence in days 0-28). 4. Time to death, assessed from hospital admission to death. 5. Acute Kidney Injury (incidence in days 0-28). 6. Respiratory Failure (incidence in days 0-28). 7. Length of hospital admission (days of inpatient stay from admission to discharge or death). 8. Length of ICU Admission (days in ICU from admission to transfer to ward or death). 9. Requirement of ventilatory support (count of days with invasive ventilation in days 0-28). 10. Requirement of dialysis (count of days with dialysis in days 0-28). 11. Clinical Health Score at day 60. 12. Clinical Health Score at day 90. 13. Clinical Health Score at day 180.
Safety Objectives and Measures	To evaluate the safety of dual treatment with repagermanium and candesartan in patients hospitalised with COVID-19, assessed by incidence of pre-specified clinical events: 1. Hypotension, requiring an urgent or non-urgent intervention (e.g., reduction in dose or cessation of anti-hypertensive, vasopressors, intravenous fluids). Incidence in days 0-28. 2. Hyperkalaemia (defined as a K>5.5-6.0 mmol/L and requiring an intervention including hospitalisation, or K>6.0 mmol/L). Incidence in days 0-28. 3. Deranged Liver Function Tests (defined as Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) >Upper Limit of Normal (ULN) or >1.5 times baseline). Incidence in days 0-28. 4. Total SAEs.
Exploratory Objective and Measure	To evaluate the effect of dual treatment with repagermanium and candesartan in patients hospitalised with COVID-19 on hospital readmission rate, assessed by: 1. Incidence of hospital readmission. Admission for overnight stay up to day 90 following initial hospital discharge.
Design	This is a Prospective, Multi-Centre, Multi-Arm Multi-Stage Randomised, Double Blind, Placebo Controlled Trial, utilising adaptive sample size re-estimation. Stage 1 will include 80 participants from India for a Phase II safety analysis. Stage 2 will be completed globally, and will include an additional 520 participants for review of preliminary efficacy data. Expansion to Stage 3, a full Phase III study, will be subject to review of accumulated data in Stage 1 and Stage 2. Protocol Stage 1 will be conducted in India only. The rest of the world will initiate the study in Stage 2 regardless of the recruitment status of the Stage 1. Recruitment in India will not continue to Stage 2 until completion of the Stage 1 safety analysis. Participants in Stage 1 will be randomised into two arms in a 1:1 ratio (India only) 1. Candesartan (ARB) + repagermanium, 2. Candesartan (ARB) + placebo [repagermanium] Participants in Stage 2 and Stage 3 will be randomised into three arms initially in a 1:1:1 ratio (all countries) 1. Candesartan (ARB) + repagermanium, 2. Candesartan (ARB) + placebo [repagermanium], 3. Placebo [candesartan (ARB)] + placebo [repagermanium])
Population	Adults with laboratory-confirmed diagnosis of SARS-CoV-2 infection intended for hospital admission for management of COVID-19.

	The diagnosis (i.e., date of test result) for SARS-CoV-2 infection within 10 days prior to randomisation. Diagnosis must be confirmed through Reverse Transcription Polymerase Chain Reaction (RT-PCR) method. Participants must have Systolic Blood Pressure (SBP) ≥ 120 mmHg OR SBP ≥ 115 mmHg and currently treated with a non-RAASi Blood Pressure (BP) lowering agent that can be ceased. Participants must not be currently treated with an ACE inhibitor (ACEi), ARB or aldosterone antagonist, aliskiren, or angiotensin receptor-neprilysin inhibitors (ARNi).
Study Treatments	**Investigational Arm**: Titratable candesartan with commencing dose 4mg tablets twice daily (daily dose 8 mg) + fixed dose repagermanium one x 120mg immediate release capsule twice daily (total daily dose 240mg). **Control Arm #1:** Titratable candesartan with commencing dose 4mg tablets twice daily (daily dose 8 mg) + matched placebo repagermanium one capsule twice daily. **Control Arm #2 (in Stage 2 and Stage 3 only):** Titratable matched placebo candesartan one tablet twice daily + matched placebo repagermanium one capsule twice daily. Treatment for will continue for 28 days.
Assessments	Participants will be followed up daily for 28 days then on day 60, day 90 and day 180 post randomisation.
Statistical Considerations	Stage 1 of the trial will conclude following recruitment of 80 participants in India. An interim assessment of the Safety Objectives and Measures will be presented to the relevant regulatory bodies to inform on whether there is any reason not to proceed with the trial in its current format. Stage 2 of the trial will conclude following recruitment of an additional approximately 520 participants. An interim assessment will be performed on all accumulated data to inform decisions on whether to progress to a Stage 3 of the trial. Information from other trials will be incorporated into CLARITY 2.0 interim analyses for decisions on the relative randomisation allocations to control. The primary endpoint is assessed at day 14. Stage 3 of the trial will be conducted using Bayesian methods, with rules determined from simulated analyses for stopping rules on efficacy, futility, and harm. The primary endpoint will be analysed using a proportional odds logistic regression model. The effect of the intervention will be estimated as the common odds ratio, corresponding to the decrease in odds of worse outcomes on the 8-point ordinal scale of health status. Comparisons will be made between all participants randomised to the different treatment arms, irrespective of whether they received their allocated treatment under the planned intention-to-treat analyses.

Figure 1. Trial Schema (Stage 2 and Stage 3)



1 BACKGROUND

1.1 COVID-19 and need for treatments

The COVID-19 pandemic has now affected more than 200 million people globally and caused over 4.5 million deaths, with the number of daily new cases continuing to rise.[1] In this context, pharmacotherapeutic agents that limit the severity of COVID-19 will be imperative.

While there is an international effort to vaccinate against COVID-19, this approach is limited by vaccine stock issues, vaccine hesitancy, and evolving virus variants, and does not offer complete immunity against infection. As such, it is crucial to continue to build the evidence portfolio for treatments for the reduction of length of infection and severity of disease.

1.2 MCP-1 and inflammation in COVID-19

The major cause of mortality from COVID-19 has been life-threatening pneumonia and ARDS.[3] While the exact mechanisms of COVID-19-induced ARDS are still being elucidated, several reports have demonstrated elevated levels of a number of pro-inflammatory cytokines, including interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1, also known as C-C Motif Chemokine Ligand 2 [CCL2]) in patients with severe COVID-19, suggesting involvement of a hyper-inflammatory immune response. One observational study of 41 patients with COVID-19 reported higher concentrations of MCP-1 in hospitalised patients compared to non-hospitalised, with the highest concentrations observed in ICU patients.[4] Other studies have reported similar patterns, including those of SARS patients as well as patients with ventilator-assisted pneumonia (VAP).[5,6]

MCP-1 is a chemokine with a key role in macrophage recruitment and activation and is the natural ligand for CCR2. In humans, CCR2 has been identified on the surface of monocytes, activated memory T cells, B cell, and basophils.[7,8]

1.3 RAS and inflammation in COVID-19

Alongside the role of chemokines in inducing the hyperinflammatory response, there is also good evidence that the renin-angiotensin system (RAS) may also play a role in the pathophysiology of COVID-19. The RAS is responsible for regulating haemodynamic, inflammatory, and fibrotic processes, and includes two main cross-regulating axes: the vasoconstrictive, pro-inflammatory, pro-fibrotic ACE-Ang II-AT1R axis, and the vasodilatory, anti-inflammatory, anti-fibrotic ACE2-Ang1-7-MasR and ACE2-Ang1-9-AT2R axis. SARS-CoV-2 responsible for COVID-19 binds and downregulates ACE2. Animal studies of the related SARS-CoV-1 suggest that this downregulation of ACE2 is sufficient for causing lung pathology and is reversed by treatment with an ARB.

Two of the mechanisms through which ACE2 is downregulated are endocytosis of the ACE2/SARS-CoV-2 complex during infection and virus-mediated proteolytic cleavage of the catalytically active ACE2 ectodomain. Importantly, both these processes have been shown to depend on the AT1R in the non-COVID-19 setting. It is therefore possible that inhibition of the AT1R by ARBs may not only help to limit overactivation of the ACE/Ang II/AT1R axis, but also attenuate the downregulation of ACE2 and prevent viral entry.

1.4 The interface between MCP-1 and the RAS

Pre-clinical studies have shown that CCR2 and AT1R functionally interact at the cell surface to amplify the pro-inflammatory effects of the MCP-1/CCR2 and ACE/Ang II/AT1R signalling pathways.[9] Importantly, previous studies have shown that simultaneous inhibition of CCR2 and AT1R when both their ligands are present results in a synergistic effect in reducing markers of inflammation.[10]

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1.5 CCR2 and AT1R Inhibitors

DMX-200 is a CCR2 antagonist known as repagermanium. ARBs are widely used medications with a robust safety profile. When administered concurrently with an ARB, the CCR2 antagonist, DMX-200 (repagermanium), is designed to inhibit recruitment of monocytes via both the AT1R and CCR2 pathways implicated in the inflammatory cytokine environment of respiratory distress.

1.5.1 Efficacy Experience in Human Studies

Controlled studies of DMX-200 have been limited to patients with proteinuric chronic kidney disease.

A 28-week open-labelled Phase 2a dose-escalation trial study of DMX-200 was conducted investigating the safety and efficacy of 30-240 mg/day repagermanium administered to N=27 patients with proteinuria on a stable dose of irbesartan. The primary endpoint was safety, and the secondary endpoint was change in proteinuria (PCR), an assessment of efficacy. Treatment with 30 to 240 mg of repagermanium daily was well tolerated, with no concerning safety signals identified at any dose. There was a general trend to reducing PCR for all patients, but the effect was not statistically significant. However, a subgroup analysis showed that there was statistically significant reduction of PCR by 34% from baseline in patients with diabetes.

A 16-week placebo-controlled Phase 2a cross-over trial of DMX-200 was conducted investigating the safety and efficacy of 240 mg/day repagermanium administered to N=10 patients with Focal Segmental Glomerulosclerosis (FSGS) on a stable dose irbesartan. The primary endpoint was safety, and the secondary endpoint was PCR. Treatment was well tolerated, and the mean decrease (improvement) in 24-hour urine PCR from baseline was greater in the repagermanium group (−84.3 mg/mmol) compared with the placebo group (−5.1 mg/mmol). In addition, DMX-200 reduced the inflammatory biomarker MCP-1, suggesting the proposed anti-inflammatory mechanism of action of repagermanium may be effective in diseases where active inflammatory processes are driving disease progression[11].

A 12-week placebo-controlled Phase 2 cross-over trial of DMX-200 was conducted investigating the efficacy of 240 mg/day repagermanium administered to N=45 diabetic kidney disease patients on a stable dose of irbesartan. The mean decrease (improvement) in urine ACR (Treatment Periods 1 and 2 combined) from baseline was moderately greater in the repagermanium group (−9.17 mg/mmol) compared with the placebo group (−6.92 mg/mmol), with a mean difference of −2.24 mg/mmol, but the difference was statistically significant.[12] Subsequent subgroup analysis showed a statically significant 18% decrease of PCR in patients with higher baseline values.

1.5.2 Safety Experience in Human Studies

An alternative crystal packing of repagermanium is named propagermanium. The structures of propagermanium and repagermanium are identical when in solution, and both have been available as a nutritional and dietary supplement since the 1970s in Japan and in other countries including the United States and Australia since the 1980s[16]. When used for treatment of patients with chronic hepatitis, propagermanium has a warning related to exacerbation of liver damage related to hepatitis B infection. Given differences in the proposed duration of use and indication in respiratory conditions, prior data on this adverse effect from long term use may not have direct relevance to short-term treatment of patients with COVID-19.

Propagermanium has been available as a drug in the prescription product Serocion® in Japan since 1994 where it is approved for the treatment of chronic hepatitis B [13]. Adverse reaction (AR) onset rate at the time of Serocion® approval was 6.56% (49/747 subjects). The most frequently occurring ARs were elevated AST in 38 subjects (1.89%), elevated ALT in 40 subjects (1.99%), languor in 27 subjects (1.34%), and decreased appetite in 18 subjects (0.89%). Exacerbation of chronic to acute hepatitis B was reported as a severe AR, and the Serocion® label contains the warning: “Acute exacerbation of chronic hepatitis and patient death have been reported with respect to use of this product”. Due to the possibility of propagermanium to exacerbate hepatitis-related hepatic damage, the Serocion® product is contraindicated for patients: (1) patients with

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jaundice (chronic hepatitis B may become severe), (2) patients with actual or suspected liver cirrhosis (chronic hepatitis B may become severe), and (3) patients with a history of hypersensitivity to this product. Post-marketing studies of Serocion® including 32,700 individuals have identified a 4% risk of moderate-to-severe hepatic toxicity in patients with hepatitis B treated with propagermanium [13].

In response to the finding that CCL2 is overexpressed in the tumour microenvironment, two early phase studies of propagermanium in oncology have been performed. A study of 5 healthy volunteers exposed to 30mg/day of propagermanium for 8 weeks, and 23 patients with refractory gastric or oral carcinomas who were treated with 30mg/day for up to 12 months, found no evidence of drug-related toxicity or dose-limiting adverse events (AEs)[14]. A dose escalation study of 12 women with breast cancer found doses up to 90mg/day of propagermanium to be well tolerated with no severe or dose-limiting side effects over 36 days [15].

In several completed and ongoing phase 1 and 2 clinical studies of DMX-200 in volunteers and renally-impaired patients (without hepatitis B) receiving an ARB, there have been no reports of acute hepatic damage and the product has demonstrated a favourable safety profile to date (Table 2). Again, additional disease-relevant safety data is needed before larger outcomes trials may be undertaken.

Table 1. Adverse Event Profile of DMX-200 from completed studies

Completed DMX-200 Studies	Adverse Event Profile
DMX-200-101 N=14 healthy volunteers. A phase I pharmacokinetic study investigating the administration of repagermanium in immediate release capsules and extended-release capsules.	The most frequently reported treatment-emergent adverse events (TEAEs) were gastrointestinal disorders with 8 events in 6 (40.0%) participants. The majority of TEAEs were mild, and the only TEAEs of moderate severity were deemed unrelated to study drug. There were no serious adverse events (SAEs) or TEAEs leading to study drug withdrawal, life-threatening TEAEs, or TEAEs leading to death reported during the study.
DMX-200-201 N=27 patients with chronic kidney disease receiving irbesartan. A phase 2a study investigating the safety and efficacy of DMX-200 capsules (increasing doses from 30-240 mg/day for a total period of 28 weeks).	At doses from 30-240 mg/day over 28 weeks, 22 (81.5%) patients reported at least 1 TEAE with 121 events reported. The maximum severity of TEAEs in the majority of patients treated with repagermanium was moderate. The most frequently reported TEAEs by SOC were metabolism and nutrition disorders with 9 (33.3%) patients reporting at least 1 TEAE including gout (n=5) and hyperkalaemia (n=2). Overall, 21 events in 7 (25.9%) patients were deemed treatment related. Overall, 10 events in 5 (18.5%) patients were classified as SAEs, the majority of which were reported during treatment with 240 mg repagermanium. Of those patients that reported an SAE, 3 were withdrawn from the study. One patient received study drug but was immediately withdrawn due to a non-related SAE (decreased haemoglobin), one patient had study drug temporarily withheld at 2 events (cholelithiasis and pancreatitis) but went on to complete the study. One SAE (suicidal depression) was deemed possibly related to treatment. The annualised rate (events/days) for the total number of TEAEs was roughly equivalent across TEAE type and at each propagermanium dose level.
DMX-200-202 N=10 patients with FSGS receiving irbesartan. A Phase 2a, double blinded, randomised, placebo-controlled crossover study evaluating the	Ten patients were enrolled, seven were evaluable and included in the final analysis. The primary endpoint was safety. DMX-200 doses were 240mg daily. Repagermanium was safe and well tolerated when added to irbesartan treatment in patients with FSGS. None of the TEAEs assigned to repagermanium or placebo were considered related. There were no clinically significant trends associated with treatment-related TEAEs.

safety and efficacy of repagermanium in patients with FSGS who are receiving irbesartan	The most frequently reported TEAEs (≥2 patients in any treatment group) during the study were hypertension and decreased appetite; the frequencies of these events were comparable between PPG and placebo groups. The maximum severity of TEAEs (assigned and unassigned) for the majority of patients was mild. One patient in the repagermanium group had a severe TEAE of chest pain, which was considered not related to repagermanium or irbesartan by the investigator. One SAE (tendonitis) was reported in the repagermanium group during the study. This event was considered as unrelated to repagermanium or irbesartan by the investigator. No TEAEs leading to study treatment or study discontinuation and no TEAEs leading to death occurred during the study.
DMX-200-203 N=45 patients with diabetic kidney disease receiving irbesartan. A phase 2, double blinded, randomised, placebo controlled, crossover study evaluating the safety and efficacy of repagermanium in patients with diabetic kidney disease who are receiving irbesartan	45 patients were enrolled, 40 qualified for the final analysis and 26 for the sub-analysis. DMX-200 doses were 240mg daily. Overall, the addition of repagermanium 240 mg/day to stable irbesartan treatment in patients with DKD was well tolerated when administered over 12 weeks of treatment. The reported TEAEs were consistent with natural history of DKD and events seen in a general patient population. No concerns were identified relative to the known safety profile of repagermanium. The nature, severity, and frequency of TEAEs following repagermanium administration were similar to those observed following placebo administration. The most frequently reported TEAEs during the study were oedema peripheral, nasopharyngitis, upper respiratory infection and hypertension; the frequencies of these events were comparable between repagermanium and placebo groups except for nasopharyngitis which had a higher frequency in the placebo group. The maximum severity of TEAEs (assigned and unassigned) for the majority of patients was mild or moderate. More patients in the repagermanium group had severe TEAEs (6 patients [13.3%]) compared with the placebo group (2 patients [4.4%]). All severe TEAEs were considered not related to the IP or irbesartan by the investigator. Overall, 6 patients in each group reported at least 1 IP-related TEAE. No severe IP-related TEAEs were reported. Ten patients experienced a total of 13 SAEs during the study. The frequency of SAEs during the study following repagermanium administration were similar to those observed following placebo administration and all SAEs were considered to be not related to IP by the investigator. Two patients (1 in the repagermanium group and 1 in the placebo group) withdrew from IP following TEAEs of moderate erythema multiforme and severe anaphylactic reaction, respectively. The TEAE of erythema multiforme was considered IP-related. The anaphylactic reaction was considered as a SUSAR not related to IP.

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	No TEAEs leading to death occurred during the study. There were no clinically significant findings in the laboratory data including no changes in liver function enzymes (ALT or AST) following treatment. There were also no clinically significant changes in vital signs, ECGs, or physical examination during the study.

1.6 Current Evidence for the use of ARBs and CCR2 in COVID-19

Several randomised controlled trials are underway to assess the effectiveness of ARBs in limiting the severity of COVID-19. One other trial is assessing the effectiveness of combination ARB and CCR2 antagonist as part of a master protocol trial in patients with ARDS, as a result of COVID-19.
No group has yet tested the capacity of CCR2 in the setting of COVID-19.

2 AIM AND OBJECTIVES

2.1 Aim

The aim of this study is to evaluate the safety and efficacy of dual treatment with repagermanium and candesartan compared to placebo for patients hospitalised for management of COVID-19.

2.2 Objectives

2.2.1 Primary Objective

The primary objective is to evaluate the safety and efficacy of dual treatment with repagermanium and candesartan in patients hospitalised with COVID-19 disease, assessed by:

1. Clinical Health Score at day 14.

This Clinical Health Score is determined within an 8-point ordinal scale of health status which is a modified version of the 9-point score developed by the WHO for Coronavirus Disease 2019 (COVID-19) trials. A single score will be reported with higher values corresponding to worse symptoms. The ordinal scale is an assessment of the clinical status of the participant at the first assessment for the day, measured at Day 14 after the date of randomisation.

8-point ordinal scale of health status:
1. Not hospitalised, no limitations on activities.
2. Not hospitalised, limitation on activities.
3. Hospitalised, not requiring supplemental oxygen.
4. Hospitalised, requiring supplemental oxygen by mask or nasal prongs.
5. Hospitalised, on non-invasive ventilation or high-flow oxygen devices.
6. Hospitalised, requiring intubation and mechanical ventilation.
7. Hospitalised, on invasive mechanical ventilation and additional organ support (ECMO).
8. Death.

2.2.2 Secondary Objectives

The secondary objectives are to evaluate the safety and efficacy of dual treatment with repagermanium and candesartan in patients hospitalised with COVID-19 disease, assessed by:

2. Clinical Health Score at day 28.
3. ICU admission (incidence in days 0-28).
4. Death (incidence in days 0-28).
5. Time to death, assessed from hospital admission to death.
6. Acute Kidney Injury (incidence in days 0-28).

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7. Respiratory Failure (incidence in days 0-28).
8. Length of hospital admission (days of inpatient stay from admission to discharge or death).
9. Length of ICU Admission (days in ICU from admission to transfer to ward or death).
10. Requirement of ventilatory support (count of days with invasive ventilation in days 0-28).
11. Requirement of dialysis (count of days with dialysis in days 0-28).
12. Clinical Health Score at day 60.
13. Clinical Health Score at day 90.
14. Clinical Health Score at day 180.

The specific safety objectives are to evaluate the safety of dual treatment with repagermanium and candesartan in patients hospitalised with COVID-19 disease, assessed by incidence of pre-specified clinical events:

15. Hypotension, requiring an urgent or non-urgent intervention (e.g., reduction in dose or cessation of anti-hypertensive, vasopressors, intravenous fluids). Incidence in days 0-28.
16. Hyperkalaemia (defined as a K>5.5-6.0 mmol/L or requiring an intervention including hospitalisation; K>6.0 mmol/L). Incidence in days 0-28.
17. Deranged Liver Function Tests (defined as Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) >Upper Limit of Normal (ULN) or >1.5 times baseline). Incidence in days 0-28.
18. Total SAEs.

2.2.3 Exploratory Objective

The exploratory objective is to evaluate the effect of dual treatment with repagermanium and candesartan in patients hospitalised with COVID-19 disease on hospital readmission rate, assessed by:

19. Incidence of hospital readmission. Admission for overnight stay up to day 90 following initial hospital discharge.

3 DESIGN

CLARITY 2.0 is a prospective, Multi-Centre, Multi-Arm Multi-Stage Randomised, Double Blind, Placebo Controlled Trial, utilising adaptive sample size re-estimation. Stage 1 will include 80 participants for a Phase II safety analysis to be conducted in India. Stage 2 will be completed globally, and will include 520 participants for review of preliminary efficacy data. Expansion to Stage 3, a full Phase III study, will be subject to review of accumulated data in Stage 1 and Stage 2.

Protocol Stage 1 will be conducted in India only. The rest of the world will initiate the study in Stage 2 regardless of the recruitment status of the Stage 1. Recruitment in India will not continue to Stage 2 until completion of the Stage 1 safety analysis and review and approval of the Indian Central Drugs Standard Control Organization Subject Expert Committee on COVID-19 related proposals.

Participants in Stage 1 will be randomised into two arms in a 1:1 ratio (India only)

1. Candesartan (ARB) + repagermanium,
2. Candesartan (ARB) + placebo [repagermanium]

Participants in Stage 2 and Stage 3 will be randomised into three treatment arms (all countries) initially in a 1:1:1 ratio

1. Candesartan + repagermanium, (Investigational Arm)
2. Candesartan + placebo [repagermanium], (Control Arm #1)
3. Placebo [candesartan] + placebo [repagermanium] (Control Arm #2)

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4 STUDY POPULATION

Participants must meet all the inclusion criteria, and none of the exclusion criteria, to be eligible for this trial. No exceptions will be made to these eligibility requirements at the time of randomisation. All enquiries about eligibility should be addressed by contacting the sponsor prior to randomisation.

4.1 Target Population

Adults with laboratory-confirmed SARS-CoV-2 infection intended for hospital admission for management of COVID-19.

4.2 Eligibility

4.2.1 Inclusion Criteria

1. Adults aged ≥ 18 years. *Refer to Appendix 1 for age requirement in India.*
2. Laboratory-confirmed diagnosis of SARS-CoV-2 infection within 10 days prior to randomisation. (*Confirmation must be through Reverse Transcription Polymerase Chain Reaction [RT-PCR] method)*
3. Intended for hospital admission for management of COVID-19.
4. Patients with moderate (respiratory rate of ≥ 24/minute or SPO2: 90% to ≤ 93% on room air) or severe (respiratory rate of ≥ 30/minute or SPO2: <90% on room air) COVID-19.
5. Systolic Blood Pressure (SBP) ≥ 120 mmHg ***OR*** SBP ≥ 115 mmHg and currently treated with a non-RAASi BP lowering agent that can be ceased.
6. Willing and able to comply with all study requirements, including treatment, timing and/or nature of required assessments.
7. Documented informed consent.

4.2.2 Exclusion Criteria

1. Currently treated with an ACEi, ARB or aldosterone antagonist, aliskiren, or ARNi
2. Intolerance of ARBs
3. Serum potassium >5.5 mmol/L
4. An estimated Glomerular Filtration Rate (eGFR) <30ml/min/1.732m
5. Known biliary obstruction, known severe hepatic impairment (Child-Pugh-Turcotte score 10-15)
6. Known viral hepatitis
7. High sensitivity Troponin (hsTn) ≥ 2 ULN or new (or previously undocumented) ECG changes
8. Pregnancy, lactation, or inadequate contraception.
    - Female participants must be either post-menopausal, infertile or use a reliable means of contraception for during the treatment period and for at least 60 days after the last dose of investigational product or refrain. Where they are of childbearing potential, female participants must also have a negative pregnancy test result within 7 days prior to randomisation.
    - Male participants must have been surgically sterilised or use a (double if required) barrier method of contraception during the treatment period and for at least 60 days after the last dose of investigational product or refrain from donating sperm during this period.
9. Participation in a study of a novel investigational product within 28 days prior to randomisation.
10. Plans to participate in another study of a novel investigational product during this study.

4.3 Study Enrolment

4.3.1 Screening

Screening of potential participants will occur in hospitals participating in the trial. Participants will be recruited through participating hospitals at the time of, or soon after, their admission for management of COVID-19.

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Potential participants will be screened to ensure they meet all the inclusion criteria and do not meet any of the exclusion criteria.

4.4 Consent

Once an eligible patient has been identified, the treating team will discuss the trial with the patient. The Participant Information Sheet (PIS) will be read out to the participant word for word by trial staff (the treating team or embedded research staff), either in person or by phone. The PIS will describe in detail the information needed for a patient to decide whether they would like to participate in the trial. The PIS includes but is not limited to information on the exact nature of the trial, the implications and constraints of the protocol and any risks involved in taking part.

The treating team will discuss the trial with the patient in detail and allow them sufficient time for reflection and consultation with family, friends, their local doctor, or other. All participants must provide verbal consent, prior to randomisation and the commencement of any trial-related procedures. Consent to participate in the trial will include consent for the study team to have access to the participant's medical record throughout the duration of the trial for the sole purpose of trial data extraction and/or verification.

Consent will be taken by the principal investigator or delegate. Consent will be documented in writing by the participant, or observed and documented in writing by a witness, where quarantine measures prevent the prior from occurring. Consent should be documented in the participant's medical record.

Participants have the right to withdraw their consent to participate in the trial at any time, and it will not affect their rights as a patient, including the health care they receive outside of the trial. To document this process, withdrawals will be documented in the medical record and notified to the sponsor.

4.4.1 Randomisation

Participants will be randomised by their treating team. Randomisation will be performed and will be accessed online by participating hospitals. The randomisation will be performed according to the instructions in the Study Manual.

Through the randomisation process, the participant will be assigned a treatment arm. Written confirmation of randomisation will be provided to the site. Treatment should be commenced as soon as possible and within one day after randomisation. Participants will be encouraged to continue in the trial, even if they withdraw from the randomised treatment allocation, to enable intention-to-treat analyses. Individuals may only be randomised once in this trial.

Initially, treatment allocation will be with a 1:1 randomisation between two arms in Stage 1 (India only), and a 1:1:1 block randomisation between three arms in Stage 2, stratified by centre.

The treatment allocation may be altered based on findings from this study protocol and other protocols investigating the effect of ARBs on health outcomes in COVID-19.

5 TREATMENT PLAN

5.1 Treatments

The intervention being investigated in this trial is a dual therapy of candesartan and repagermanium.

Candesartan is an ARB. ARB treatment is commonly used in the management of hypertension, or for the prevention of progression of diabetic kidney disease or secondary prevention of cardiovascular events. ARBs are widely used medications with an excellent safety profile.

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Repagermanium is a CCR2 antagonist with an extensive safety database and, unlike many immune modulators, has a low AE profile. When administered concurrently with an ARB, repagermanium is designed to inhibit recruitment of monocytes via both the AT1R and CCR2 pathways implicated in the inflammatory cytokine environment of respiratory distress.

5.1.1 Study Treatment

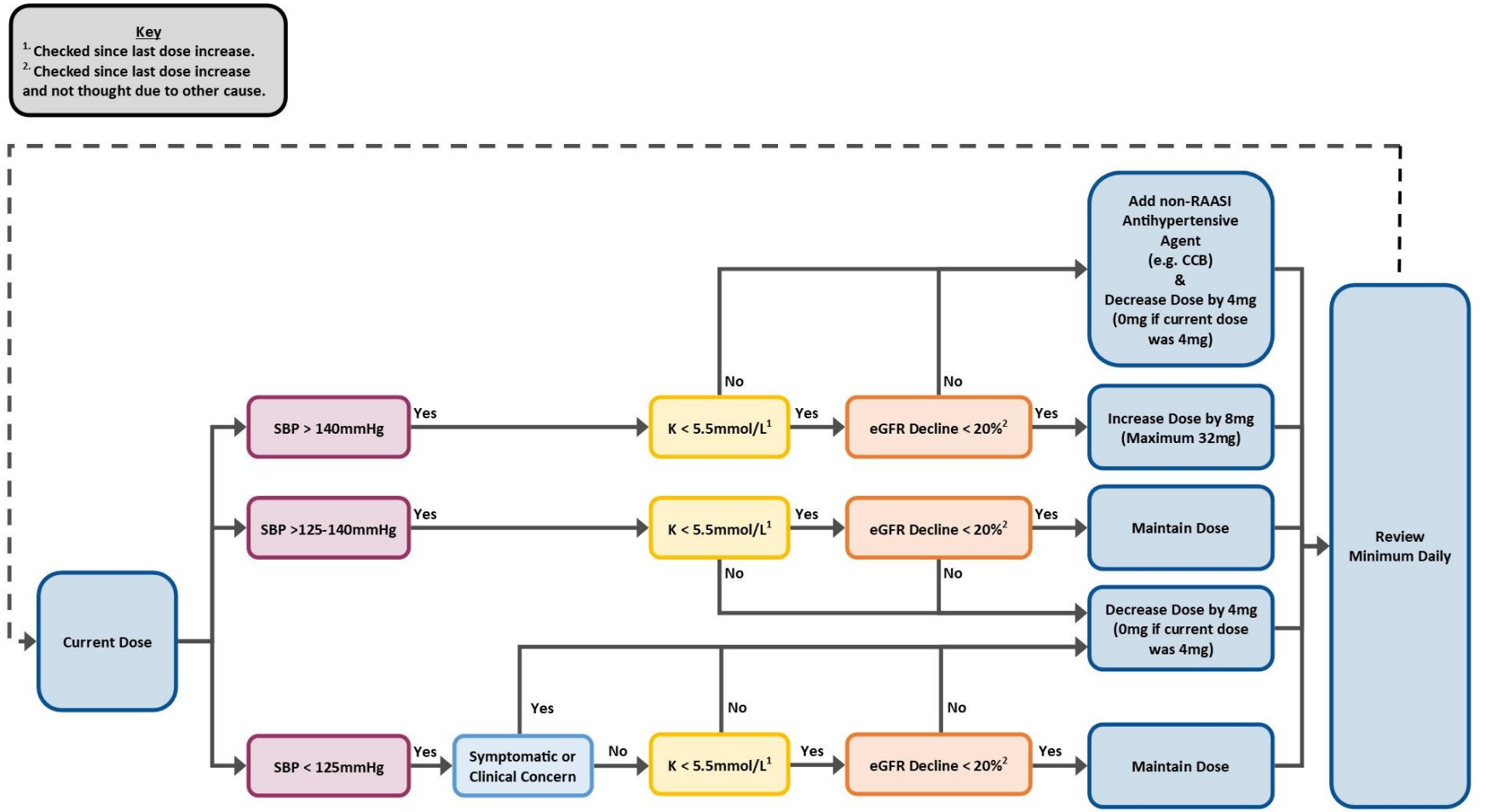
Participants will be randomised to one of three arms described in Table 1, including repagermanium, or matched placebo, and candesartan, or matched placebo.

Table 2. Trial Arms treatment

Agents	Commencing Dose	Route	Duration
Investigational Arm Interventions			
Candesartan	Titratable commencing dose 4mg tablets twice daily *(daily dose 8 mg)*	Oral	28 days
Repagermanium	120mg immediate release capsule twice daily. *(daily dose 240mg)*	Oral	
Control Arm #1 Interventions			
Candesartan	Titratable commencing dose 4mg tablets twice daily *(daily dose 8 mg)*	Oral	28 days
Placebo [repagermanium]	Matching capsules twice daily	Oral	
Control Arm #2 Interventions (in Stage 2 and Stage 3 only)			
Placebo [candesartan]	Titratable tablets twice daily	Oral	28 days
Placebo [repagermanium]	Matching capsules twice daily	Oral	

The dose of repagermanium will be delivered as 120mg capsules given twice a day. The dose will not be changed during the trial. The starting dose of candesartan will be 4mg given twice a day. The dose will be titrated in accordance with the algorithm presented in Figure 2.

Figure 2. Candesartan dose titration algorithm (NOTE: dose increase/decrease refers to the total daily dose)



5.1.2 Required Background Treatment

5.1.2.1 Respiratory & COVID-19 Care

For participants within this trial, background care and respiratory management will be according to local site regulations, recommendations and protocol in the setting of the pandemic. Sites are free to make changes as new evidence comes to light. COVID-19 directed treatments must be appropriately documented and reported within the trial database.

5.1.2.2 COVID-19 Associated Myocardial Dysfunction Care

Australian guidelines recommend routine monitoring for COVID-19 associated myocardial dysfunction with appropriate therapy in detected cases. Further information is outlined in the guidelines of the Cardiology Society of Australia and New Zealand and in Section 15.2.1.

5.1.2.3 Trial Specific Care

For participants within this trial, background care must include local investigations of Blood Pressure, Potassium and Renal Function as directed within the schedule of assessments. Participants are not permitted to participate in another clinical trial of a novel investigational product.

5.2 Management of Toxicities

Participant safety is the primary responsibility of the treating clinician, as such their discretion should determine the course of action for the management of toxicities. In general, treatment should be withheld during AEs of severity Grade 3-4 (according to the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5)), and not restarted until the AE has resolved to Grade 0-1, at the investigator's discretion. Where guidance is requested from the treating clinician on management of toxicities, the following guidance is provided.

5.2.1 Candesartan

The safety profile of candesartan has been researched comprehensively. The most common adverse drug reactions (>1%) observed within those treated with candesartan are hypotension, hyperkalaemia, and increased creatinine.

Table 3. Management of toxicities associated with candesartan

Toxicity	Grade	Range	Management
Hypotension	All Grades		Managed as per Figure 2.
Hyperkalaemia	1	>ULN - 5.5 mmol/L	Managed as per Figure 2.
	2	>5.5 - 6.0 mmol/L ***or*** intervention initiated	Treating clinician should consider ceasing other hyperkalaemia-inducing medications (e.g., beta blockers) prior to study medication. Ensure not taking Non-steroidal anti-inflammatory drugs (NSAIDs) (including selective COX-2 inhibitors) or potassium supplementation.
	3	>6.0 - 7.0 mmol/L ***or*** hospitalisation indicated	Pause study medication and reintroduce when reduced to grade 1 or 0.
	4	>7.0 mmol/L ***or*** life-threatening consequences	Study medication permanently stopped.
	1	>ULN – 1.5xULN	Manage according to local practice.

Creatinine Increased	2	>1.5-3.0 x Baseline ***or*** >1.5-3.0 x ULN	
	3	>3.0 x Baseline ***or*** >3.0 – 6.0 x ULN	Pause study medication and reintroduce 4mg daily when reduced to grade 1 or 0. Further adjustment managed as per Figure 2.
	4	> 6.0 X ULN	Manage according to local practice.

If participants experience a suspected drug related AE, the treating clinician, at their discretion, can interrupt candesartan until the symptoms resolve. At the investigator's discretion, candesartan may then be reintroduced at same/reduced dose at any time throughout the treatment period. If the reaction reappears then candesartan is to be discontinued permanently.

Based on pharmacological considerations, the main manifestation of an overdose is likely to be symptomatic hypotension and dizziness. These symptoms would be expected to resolve as per the half-life of candesartan.

Where any toxicity continues while candesartan is not administered, it should be managed according to local practice.

5.2.2 Repagermanium

The safety profile of repagermanium continues to be updated as noted in the DMX-200 Investigators Brochure. Prior data on AEs from long term use of repagermanium may not have direct relevance to short-term treatment of patients with COVID-19.

No titration of repagermanium is required for toxicity management. Consideration of temporary discontinuation of candesartan should occur first as in the above (section 5.2.1); in these circumstances, candesartan should be paused, but repagermanium should continue to be administered (without candesartan).

By contrast, in the development of liver failure, or if the ALT or AST are more than 5 times the ULN, or other suspected unexpected serious adverse reaction (SUSAR), the treating clinician should permanently discontinue both candesartan and repagermanium.

Table 4. Management of toxicities associated with repagermanium.

Toxicity	Grade	Range	Management
ALT increased	1	1.5 - 3.0 x Baseline ***or*** >ULN - 3.0 x ULN	Manage according to local practice
	2	>3.0 - 5.0 x Baseline ***or*** >3.0 - 5.0 x ULN	
	3	>5.0 - 20.0 Baseline ***or*** >5.0 - 20.0 x ULN	Study medication permanently stopped
	4	>20.0 x Baseline ***or*** >20.0 x ULN	Study medication permanently stopped
AST increased	1	1.5 - 3.0 x Baseline ***or*** >ULN - 3.0 x ULN	Manage according to local practice
	2	>3.0 - 5.0 x Baseline ***or*** >3.0 - 5.0 x ULN	
	3	>5.0 - 20.0 Baseline ***or*** >5.0 - 20.0 x ULN	Study medication permanently stopped
	4	>20.0 x Baseline ***or*** >20.0 x ULN	Study medication permanently stopped

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If participants experience a suspected drug related AE, the treating clinician, at their discretion, can interrupt repagermanium until the symptoms resolve. At the investigator's discretion, repagermanium may then be reintroduced at the protocol dose at any time throughout the treatment period. If the reaction reappears then repagermanium is to be discontinued permanently.

Where any toxicity continues while repagermanium is not administered, it should be managed according to local practice.

5.3 Unblinding

Unblinding is not generally necessary for the management of a participant with an AE and, as it has an impact on the study's validity, it is strongly discouraged. However, if required, it should be done centrally after discussion with the Study Chair and NHMRC CTC Clinical Lead using the emergency unblinding process outlined in the Study Manual.

5.4 Concomitant Medications

5.4.1 Prohibited

The following medications should not be used during this study:

- Other novel investigational treatments – patient is ineligible.
- Any ACEis – patient is ineligible.
- Any other ARBs – patient is ineligible.
- Aldosterone antagonist – patient is ineligible.
- Aliskiren – patient is ineligible.
- ARNi – patient is ineligible.
- NSAIDs – patients should be advised not to take NSAIDs whilst they are receiving treatment in the trial. This includes ibuprofen (e.g. Ibugesic, Intafen, Nurofen or Advil), diclofenac (Voltaren or Voveran) or meloxicam (Mobic or Movac). Use of Paracetamol or Aspirin is permitted.

Participants who require treatment with any of these agents will usually need to discontinue study treatment. This should be discussed with the Medical Monitor by contacting the NHMRC CTC.

Any other BP-lowering medication can continue except in the setting of hypotension.

5.4.2 Reporting

All concomitant medications will be reported within the trial electronic case report forms (eCRFs).

5.5 Compliance

Participants and trial sites are encouraged to maintain appropriate treatment with the study intervention without interruption. Where treatment is missed or discontinued for any reason, relevant information should be documented within the participant's medical record and reported within the trial eCRF. The participant should be counselled appropriately if significant non-compliance is determined. Any unused study medication should be returned to the study site for destruction.

An intention-to-treat analysis will be performed on this trial data.

5.6 Discontinuation & Post-Study Treatment

Study treatment will be permanently discontinued for any of the following reasons:

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- Unacceptable toxicity as determined by the participant or site investigator or as defined in section 5.2.
- The investigator determines that continuation of treatment is not in the participant's best interest.
- Occurrence of an exclusion criterion affecting participant safety, e.g., pregnancy.
- Required use of a concomitant treatment that is not permitted, as defined in section 5.4.
- Failure to comply with the protocol, e.g., repeatedly failing to attend scheduled assessments.
- The participant declines further study treatment or withdraws their consent to participate in the study.

The reasons for discontinuing treatment will be documented in the participant's medical record and eCRF.

Participants who stop study treatment prior to the time recommended in the protocol will be requested to continue follow-up visits according to the protocol and included within the intention-to-treat analysis.

If a participant wishes to stop the study visits, they will be requested to allow their ongoing health status to be periodically reviewed via continued study visits or phone contact or from their general practitioner, or medical records.

Treatment after discontinuation of study treatment is at the discretion of the participant's clinician.

6 ASSESSMENT PLAN

6.1 Schedule of Assessments

Table 5. Schedule of Assessments

Time Point	S	B	1º Follow Up & Treatment Period															2º Follow Up		
Day	<B	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-28	21[7]	28[7]	60[+]	90[+]	180[+]
Eligibility	X																				
Consent	X																				
Demographics[1]		X																			
Medical History		X																			
Randomisation		X																			
Con-Meds		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Initial IMP Supply		X																			
Health Status Assessment[2]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Pressure		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X			
Blood Pathology[3]		X[5]		X		X		X		X					X		X	X			
Safety Events[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECG and Troponin Assessment		X																			
Vaccination Status		X[6]																			

S = Screening, B = Baseline, 1º = Primary, 2º = Secondary, Con-Meds = Concomitant Medications, IMP = Investigational Medicinal Product

[+] Telephone follow up accepted.

[1] Demographics includes: Date of Birth, Sex, Ethnicity, Weight, Height, and Smoking Status

[2] Health Status Assessment includes: Hospital Admission status, Ventilation status, Supplemental Oxygen Status, Intensive Care Unit Admission status, and Mortality status

[3] Blood Pathology includes: Potassium, Serum Creatinine, Creatinine Kinase (in selected sites), estimated Glomerular Filtration Rate, White Blood Cell Count, Neutrophil Count, Lymphocyte Count, D-Dimer (in selected sites), C-Reactive Protein, Aspartate Aminotransferase, Alanine Aminotransferase, Alkaline Phosphatase, Gamma-Glutamyl Transferase and Bilirubin.

[4] Reportable from initiation of trial treatment until Day 60 or 30 days following permanent discontinuation of all trial IMP.

[5] Within 7 days prior to randomisation.

[6] COVID-19 vaccination status can be updated at any time while the participant is on trial, and must include: brand, number of doses, and date of vaccination.

[7] Visit to be conducted if participant is an inpatient on the visit day.

6.2 Details of Assessments

6.2.1 Screening

Potential participants will be screened within the 10 days prior to randomisation to ensure they meet all the inclusion criteria and do not meet any of the exclusion criteria as described in section 4.2. Assessments necessary to ascertain eligibility include SARS-CoV-2 test within 10 days prior to randomisation, blood pressure, serum potassium (test performed or on record within the 3 months prior to randomisation) and eGFR (test performed or on record within the 3 months prior to randomisation).

Within the screening period consent will be taken according to section 4.4.

6.2.2 Baseline Assessment

Demographics and medical history assessment including details of the SARS-CoV-2 test and results, blood pressure, date of birth, sex, weight, height, smoking history, pregnancy test status (for women younger than 51 years), comorbidities, concomitant medications, ECG and troponin assessment, and most recent blood test results. Ethnicity will be recorded. COVID-19 vaccination status will also be recorded and can be updated at any time while the participant is on the trial.

6.2.3 Primary Follow Up & Treatment Period (Day 1 to 28)

Participants will be provided with their randomised interventions following randomisation. Treatment will continue for 28 days. Additional candesartan may be supplied at any time in the first 28 days via resupply to accommodate for up-titration in dose.

Participants will be followed up daily for 28 days after randomisation. This follow-up includes:

- Health status assessment including assessment of hospital admission status, ventilation status, supplemental oxygen status, intensive care unit status, and mortality status and collection of concomitant medications will be undertaken from baseline to day 28 from commencement of study treatment.
- Blood pressure will be assessed from baseline to day 14 from commencement of study treatment.
- Blood tests will be undertaken at baseline, then days 1, 3, 5, 7, 9 and 14 from commencement of study treatment. Blood tests will include Potassium, Serum Creatinine, Creatinine Kinase (in selected sites), estimated Glomerular Filtration Rate (using CKD-EPI creatinine equation), White Blood Cell Count, Neutrophil Count, Lymphocyte Count, D-Dimer (in selected sites), C-Reactive Protein, Aspartate Aminotransferase, Alanine Aminotransferase, Alkaline Phosphatase, Gamma-Glutamyl Transferase and Bilirubin.
- Safety events will be reportable from initiation of trial treatment until day 60 or 30 days following permanent discontinuation of all trial IMP.
- Days 21 and 28 visits will be conducted if participant is an inpatient on the visit days.

6.3 Secondary Follow-Up (Day 29 to 180)

Participants will be followed up for 180 days after randomisation to reach the study endpoint. The health status assessment measurement will be undertaken at 60 days, 90 days and 180 days and can be done by phone or clinic visit. Each visit will occur within a 7-day window of the scheduled visit date. Safety events will be reportable from initiation of trial treatment until day 60 or 30 days following permanent discontinuation of all trial IMP.

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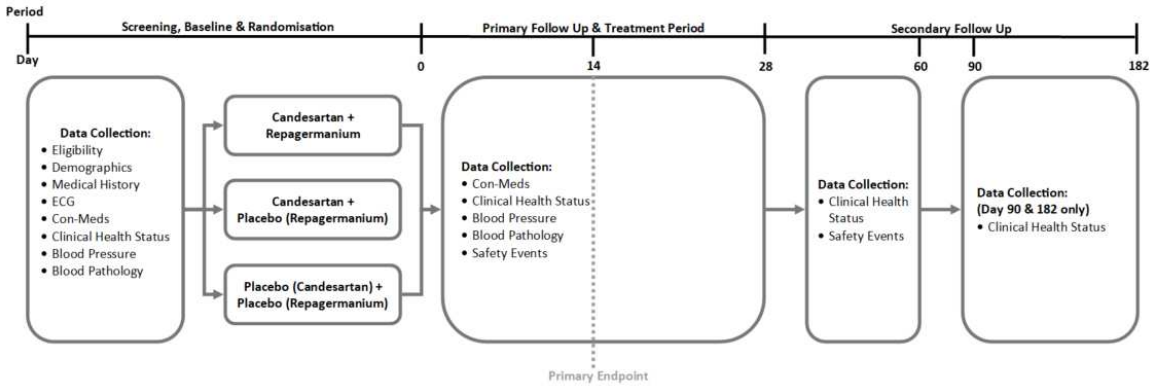
Figure 3. Participant assessment and data collection



7 OUTCOMES, ENDPOINTS AND OTHER MEASUREMENTS

7.1 Primary Endpoint Definition

The primary endpoint is a Clinical Health Score, determined within an 8-point ordinal scale of clinical health status which is a modified version of the 9-point score developed by the WHO for Coronavirus Disease 2019 (COVID-19) trials. A single score will be reported with higher values corresponding to worse symptoms. The ordinal scale is an assessment of the clinical status of the participant at the first assessment for the day, measured at Day 14 after the date of randomisation.

Clinical Health Score at day 14

1. Not hospitalised, no limitations on activities.
2. Not hospitalised, limitation on activities.
3. Hospitalised, not requiring supplemental oxygen.
4. Hospitalised, requiring supplemental oxygen by mask or nasal prongs.
5. Hospitalised, on non-invasive ventilation or high-flow oxygen devices.
6. Hospitalised, requiring intubation and mechanical ventilation.
7. Hospitalised, on invasive mechanical ventilation and additional organ support (ECMO).
8. Death.

Clinical assessment includes review of hospital medical records, following admission by the investigator, for Clinical Health Score events at day 14 (including hospitalisation, use of oxygen, ventilation, ECMO or death due to any cause). Where the participant has been discharged, Clinical Health Score events will be confirmed by the participant (by phone or clinic visit) or local General Practitioner. Community-based death events will be confirmed with the participant's local General Practitioner in local medical records.

7.2 Secondary Endpoint Definitions

Clinical Health Score at day 28

Clinical assessment includes review of hospital medical records, following admission by the investigator, for Clinical Health Score events at day 28 (including hospitalisation, use of oxygen, ventilation, ECMO or death due to any cause). Where the participant has been discharged, Clinical Health Score events will be confirmed by the participant (by phone or clinic visit) or local General Practitioner. Community-based death events will be confirmed with the participant's local General Practitioner in local medical records.

Intensive Care Unit (ICU) admission

Incidence in days 0-28. Clinical assessment includes review of hospital medical records following admission by the investigator or notification of admission by the participant or local General Practitioner for ICU admission (for any reason).

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Death
Incidence in days 0-28. Clinical assessment includes review of hospital medical records following admission by the investigator or notification of death (due to any cause) by the participant's local General Practitioner. Community-based death events will be confirmed with the participant's local General Practitioner in local medical records.

Time to death
Assessed from hospital admission to death. Clinical assessment includes review of hospital medical records following admission by the investigator or notification of death (due to any cause) by the participant's local General Practitioner. Community-based death events will be confirmed with the participant's local General Practitioner in local medical records.

Acute Kidney Injury (AKI)
Incidence in days 0-28. Clinical assessment includes review of hospital medical records following admission by the investigator or notification of AKI by the participant or local General Practitioner. AKI is defined by the KDIGO criteria as an increase in serum creatinine by ≥ 0.3mg/dL within 48 hours or an increase in serum creatinine ≥ 1.5 times from baseline within the last 7 days or urine output <0.5 mL/kg/h for 6 hours. Community-based AKI events will be confirmed with the participant's local General Practitioner in local medical records.

Respiratory Failure
Incidence in days 0-28 defined as receipt of non-invasive or invasive mechanical ventilation. Clinical assessment includes review of hospital medical records following admission by the investigator or notification of respiratory failure events by the participant or local General Practitioner.

Length of hospital admission
Days of inpatient stay from admission to discharge or death. Clinical assessment includes review of hospital medical records following admission by the investigator or notification of hospital admission by the participant or local General Practitioner.

Length of ICU admission
Days in ICU from admission to transfer to ward or death. Clinical assessment includes review of hospital medical records following admission by the investigator or notification of overnight admissions to ICU by the participant or local General Practitioner.

Requirement of ventilatory support
Count of days with ventilation in days 0-28. Clinical assessment includes review of hospital medical records following admission by the investigator or notification of episodes of ventilatory support by the participant or local General Practitioner. Ventilatory support is defined as the delivery of oxygen via invasive ventilation.

Requirement of dialysis
Count of days with dialysis in days 0-28. Clinical assessment includes review of hospital medical records following admission by the investigator or notification of episodes of dialysis support by the participant or local General Practitioner. Dialysis support is defined as any occurrence of haemodialysis or peritoneal dialysis. Community-based dialysis will be confirmed with the participant's local General Practitioner in local medical records.

Clinical Health Score at day 60
Clinical assessment includes phone or clinic visit for Clinical Health Score events at day 60, including hospital admission (for any reason) or death (due to any cause). Community-based death events will be confirmed with the participant's local General Practitioner in local medical records.

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Clinical Health Score at day 90
Clinical assessment includes phone or clinic visit for Clinical Health Score events at day 90, including hospital admission (for any reason) or death (due to any cause). Community-based death events will be confirmed with the participant's local General Practitioner in local medical records.

Clinical Health Score at day 180
Clinical assessment includes phone or clinic visit for Clinical Health Score events at day 180, including hospital admission (for any reason) or death (due to any cause). Community-based death events will be confirmed with the participant's local General Practitioner in local medical records.

7.3 Safety objectives and measures

Hypotension
Incidence in days 0-28. Clinical assessment includes review of hospital medical records following admission by the investigator or notification of hypotensive events (requiring an urgent or non-urgent intervention) by the participant or local General Practitioner. Hypotension is defined as blood pressure readings <90 mmHg systolic or <60 mmHg diastolic; urgent or non-urgent intervention includes, but is not limited to, reduction in dose or cessation of anti-hypertensives, vasopressors, intravenous fluids. Community-based hypotensive events will be confirmed with the participant's local General Practitioner in local medical records.

Hyperkalaemia
Incidence in days 0-28. Clinical assessment includes review of hospital medical records following admission by the investigator or notification of hyperkalemic events by the participant or local General Practitioner. Hyperkalaemia is defined as a K>5.5-6.0 mmol/L and requiring an intervention including hospitalisation, or K>6.0 mmol/L. Community-based hyperkalemic events will be confirmed with the participant's local General Practitioner in local medical records / pathology reports.

Deranged Liver Function Tests (LFTs)
Incidence in days 0-28. Clinical assessment includes review of hospital medical records following admission by the investigator or notification of deranged LFTs by the participant or local General Practitioner. Deranged LFTs is defined as ALT or AST >ULN or >1.5 times baseline. Community based LFT derangement will be confirmed with the participant's local General Practitioner in local medical records / pathology reports.

Serious Adverse Events (SAEs)
Please refer to section 8.

7.4 Exploratory Objective and Measure

Incidence of hospital readmission
Admission for overnight stay up to day 90 following initial hospital discharge. Clinical assessment includes review of hospital medical records to day 90 from primary admission at randomisation.

8 SAFETY REPORTING

8.1 Definitions

An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether considered related to the medicinal product, or not.

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AEs include the following:

- All suspected adverse drug or device reactions
- All reactions from drug or device – overdose, abuse, withdrawal, sensitivity, toxicity, or failure of expected pharmacological action (if appropriate)
- Apparently unrelated illnesses
- Worsening (severity, frequency) of pre-existing illnesses or symptoms
- Injury or accidents
- Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination)
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test). Any untoward event that occurs after the protocol-specified reporting period which the Investigator believes may be related to the drug or device.

A SERIOUS ADVERSE EVENT (SAE) is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (i.e., the participant is at risk of death at the time of the event),
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
- other important medical events which, in the opinion of the investigator, are likely to become serious if untreated, or as defined in the protocol

NOTES:

(i) The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

(ii) Important medical events which may not be immediately life-threatening or result in death or hospitalisation, but which may jeopardize the patient or may require intervention to prevent one of the listed outcomes in the definition above should also be considered serious.

A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) is an SAE that is related to the drug or device and is unexpected, i.e., not listed in the investigator brochure or approved Product Information; or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the Participant Information Sheet or elsewhere in the protocol. An event is causally related if there is a reasonable possibility that the intervention caused the AE, i.e., there is evidence to suggest a causal relationship between the drug and the event within the reference safety information (RSI).

For the purposes of this study, the following AEs are not reported to the responsible coordinating centre as SAEs:

- Hospitalisations related to management of the disease under study
- Deaths related to disease under study
- Elective hospitalisations to facilitate the administration of treatment, e.g., Porta-Cath insertion
- Elective hospitalisations for other procedures, e.g., screening colonoscopy, stent change, cardiac catheter, etc.

The following definitions are used for reporting of safety events:

- A SIGNIFICANT SAFETY ISSUE (SSI) is defined as is a safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. These events may be in addition to the current SAE/SADR/SUSAR reports and generally have a consequence related to patient safety within the current study protocol, which thus requires some type of amendment.

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- An URGENT SAFETY MEASURE (USM) is one type of significant safety issue where sponsors or trial investigators act immediately to protect participants from an immediate hazard to their health and safety. USMs are often instigated before the regulatory body and ethics committee are notified. In these cases, it is strongly recommended that the sponsor contact the regulatory body within 24 hours of the measure being taken. Examples include:
  - an SAE that could be associated with the trial procedures and that requires modification of the conduct of the trial
  - a hazard to the patient population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease
  - a major safety finding from a newly completed animal study (such as carcinogenicity)
  - a temporary halt/termination of a trial for safety reasons
  - recommendations of the Data Safety Monitoring Board, where relevant for the safety of participants, such as an increase in frequency or severity of an expected AR
  - single case events (e.g., toxic epidermal necrolysis, agranulocytosis, hepatic failure) that lead to an urgent safety measure)

SSIs or USMs do not necessarily meet all criteria to be considered an SAE. For purpose of safety reporting, these events are to be reported as SAE with a note that this concerns an SSI or USM.

8.1.1 Other Important Medical Conditions

Pregnancy

In the event of a pregnancy occurring during a study, the participant must be withdrawn from study interventions immediately. The investigator should counsel the participant; discuss the risks of continuing with the pregnancy and the possible effects on the foetus.

The sponsor must be notified within 24 hours and the participant followed during the entire course of the pregnancy and postpartum period. Parental and neonatal outcomes must be recorded even if they are completely normal. Pregnancies occurring up to 6 months after the completion of the study drug must also be reported. Pregnancy occurring in the partner of a participant and up to 60 days after the completion of the study drugs should also be reported. The partner should be counselled and followed as described above.

Within the trial, pregnancy will be recorded in the same manner as an SAE outlined in section 8.2.

8.2 Recording Adverse Events

The investigator is responsible for recording all SAEs occurring during the study from the date of IMP supply up until day 60 following randomisation, or 30 days following permanent discontinuation of all trial IMP, whichever is sooner.

Information to be collected for SAEs includes event description, date of onset, investigator assessment of severity, investigator assessment of relationship to study treatment, date of resolution of the event, seriousness, and outcome.

All AEs will be managed as per usual local clinical care practice and the treatment specific guidance provided within the protocol. Non-serious AEs will not be reported unless it leads to permanent stoppage of investigational product. Reports of these events will be recorded in the eCRF.

8.3 Reporting of Serious Adverse Events (including SUSARs, SSIs and USMs)

The investigator is responsible for reporting all SAEs (including SUSARs), SSIs and USMs occurring during the study to the sponsor within 24 hours of investigational site staff becoming aware of the event according to the procedure documented in the Study Manual.

The sponsor will be responsible for providing reports to the lead ethics committee. These reports will include SUSAR, SSI and USM reports and SAE line listings as required.

The sponsor will submit 'reportable safety events' to the relevant regulatory authority in time to comply with the requisite specified regulatory time windows.

9 STUDY TREATMENT SUPPLY AND ACCOUNTABILITY

9.1 Investigational Arm Treatment

Participants will receive candesartan 4mg tablets and repagermanium 120mg capsules in the study. Candesartan will be provided by the sponsor in tablet form and repagermanium will be provided by Dimerix in capsule form.

Candesartan will be commenced at a daily dose of 8mg, titrated in accordance with the algorithm presented in Figure 2. Repagermanium will be commenced at a fixed daily dose of 240mg.

9.2 Control Arms Treatment

Participants will receive:

1. Candesartan 4mg tablets and placebo repagermanium capsules. Candesartan will be commenced at a twice daily dose of 4mg, titrated in accordance with the algorithm presented in Figure 2. Placebo repagermanium capsules will be commenced at the fixed twice daily regimen. OR
2. Candesartan placebo tablets and repagermanium placebo capsules. Candesartan placebo tablets will be commenced at a twice daily regimen, titrated in accordance with the algorithm presented in Figure 2. Repagermanium placebo capsules will be commenced at the fixed twice daily regimen.

Candesartan and candesartan placebo will be provided by the sponsor in tablet form. Repagermanium and repagermanium placebo will be provided by Dimerix in capsule form.

9.3 Treatment Administration

The investigational medicinal product (IMP) will be self-administered, within an hour of eating food, by participants who will be directed to take the IMP each day at approximately the same time (e.g., 9:00am and 7:00pm ± 1 hour).

9.4 Labelling

All IMP will be labelled according to applicable local and legislative requirements. For all IMP, a numbering system that meets all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of IMP can be traced back to a specific batch number. A complete record of batch numbers and expiry dates of all study treatment, as well as the labels, will be maintained in the Sponsor's Trial Master File (TMF).

The packaging and labelling will be designed to maintain blinding to the study team and to participants (double-blind).

9.5 Drug Accountability, Storage and Handling

The IMP will be stored at the Pharmacy Department at participating sites, in accordance with Good Clinical Practice (GCP) and GMP requirements. The responsible pharmacy staff will maintain a record of IMP receipt and dispensing for each participant. Participants will be asked to return unused IMP and empty IMP

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containers after day 28 to the Pharmacy Department or via mail return. IMP return and destruction (if applicable) must be properly documented by pharmacy staff as per the Sponsor's guidance.

All IMP will be kept in a locked area with limited access and stored at 15°- 25°C. Mean kinetic temperature should not exceed 25°C. Excursions between 15°C and 30°C that may be experienced in pharmacies, hospitals, or warehouses, and during shipping are allowed.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size

Stage 1 of the trial will recruit 80 participants from India for a safety analysis.

An interim assessment of the Safety Objectives and Measures will be presented to the relevant regulatory bodies to inform on whether there is any reason not to proceed with the trial in its current format.

The safety pre-specified clinical events to be analysed in Stage 1 will be:

1. Hypotension, requiring an urgent or non-urgent intervention (e.g., reduction in dose or cessation of anti-hypertensive, vasopressors, intravenous fluids). Incidence in days 0-28.
2. Hyperkalaemia (defined as a K>5.5-6.0 mmol/L or requiring an intervention including hospitalisation; K>6.0 mmol/L). Incidence in days 0-28.
3. Deranged Liver Function Tests (defined as Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) >Upper Limit of Normal (ULN) or >1.5 times baseline). Incidence in days 0-28.
4. SAEs.

Stage 2 of the trial will recruit an additional 520 participants. Information from other relevant trials will be utilised to inform the decision for dropping one of the two control arms.

A review of the accumulated safety and efficacy data following Stage 2 of the trial, together with data accumulated in other trials, will inform the decision to transition into Stage 3 of the full Phase III trial. Stage 2 will use the accumulated evidence to support selection of the primary comparator.

Stage 3 of the trial will be conducted using Bayesian methods, with rules determined from simulated analyses for stopping rules on efficacy, futility, and harm. Adaptive sample size estimation will be employed and detailed within an updated statistical considerations section, following completion of trial simulations.

10.2 Statistical Analysis

This study will use Bayesian principles and Monte Carlo methods to evaluate the outcomes of interest. All inferences will be based on posterior distributions of the model parameters. Trial decisions will be based on the posterior and predictive distributions.

Stage 1 analysis of the Safety Objectives and Measures will evaluate the safety of combination ARBs and CCR2a compared to ARBs and placebo.

The estimated treatment effect on the primary endpoint will be expressed as the common odds ratio, corresponding to the odds of a better outcome in the investigational arm versus each comparator arm on the 8-point ordinal scale at Day 14, and its 95% credible interval. This will be modelled using a proportional odds logistic regression model. Details will be provided in the statistical analysis plan which will be completed prior to any analysis of the data.

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The assessment of the primary endpoint at Day 14 reflects the timeframe within which most SARS-CoV-2-positive patients have either developed severe disease or begun to recover.

The primary analysis will be an ITT analysis, whereby comparisons will be made between all participants randomised to the treatment arms and who have passed the primary endpoint, irrespective of whether they received their allocated treatment.

To explore the power achieved with the sample size, extensive simulations will be performed under various assumptions. Details of these simulations and their underlying assumptions will be provided in the statistical analysis plan.

11 STUDY ORGANISATION AND COMMITTEES

11.1 Study Coordination

The study is a locally developed and led, investigator initiated international study. Overall coordination, data acquisition and management will be performed by the NHMRC CTC.

This international study will be conducted at a number of regions, with each regional coordinating centre responsible for their own ethics and regulatory approvals, medical oversight and facilitation of data collection and query resolution.

The international sponsor is responsible for developing and maintaining charters for all involved committees/boards, including those listed below. These charters provide further details on the composition, roles, and responsibilities of each committee

11.2 Trial Steering Committee

The international sponsor of the trial is responsible for convening, chairing, and reporting to the Trial Steering Committee (TSC) who, in turn, is responsible for oversight of the study. The TSC will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g., ethics committees).

The TSC will consider recommendations from the Data Safety Monitoring Board (DSMB) about whether to continue the study as planned, modify, or stop it, based on accumulated data or other information.

The TSC will make recommendations to the funder whether to extend from Stage 2 to Stage 3 of the study based on a planned review at following Stage 2 and recommendations from the DSMB.

11.3 Data Safety Monitoring Board

An independent DSMB has been convened by the international sponsor and will operate in accordance with the DSMB Charter. This DSMB Charter describes the Board's structure, roles, and responsibilities, including their remit to protect the safety of trial participants and the scientific integrity of the trial by monitoring accumulating safety and operational data. The DSMB will make appropriate recommendations to the TSC regarding trial continuation and participant safety. The TSC will retain sole decision-making responsibility.

11.4 Consumer and Community Advisory Committee (CCAC)

A CCAC will be convened by the NHMRC Clinical Trials Centre, University of Sydney to provide consumer perspective and input on consumer engagement and recruitment for this study, as well as provide valuable connections with the target population to assist in educating and informing the community on trial activities relevant to them.

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12 ADMINISTRATIVE ASPECTS

12.1 Ethics and Regulatory Compliance

This protocol has been developed by sponsor staff and the TSC, in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement and in accordance with relevant guidelines. This protocol and, where appropriate, other trial documents, including all future versions, will be reviewed, and approved by the applicable Ethics Committee, with respect to scientific content and compliance with applicable regulations.

This study will be conducted according to the Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) dated 9 November 2016 and local regulations.

To this end, no patient will be recruited to the study until all the necessary approvals have been obtained and the patient has provided informed consent. Further, the investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a participant. In this circumstance, the sponsor, principal investigator and ethics committee must be advised immediately.

12.2 Confidentiality

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the NHMRC CTC, University of Sydney and will only be available to people directly involved with the study.

The investigator and trial staff must ensure that participants' anonymity is maintained, that their identities are protected from unauthorised parties, and that measures are taken to prevent accidental or premature destruction of study documents.

Participants' records and the data generated by the trial will be confidential, in line with the recommendations of the NHMRC and the 2001 privacy legislation and ICMR, National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017. All documents will be stored securely and only accessible by trial staff and authorised personnel. With the exception of the trial consent recordings, which will be kept separate from all other trial documentation, a unique trial-specific ID will be used on all trial-specific documents and databases in place of the participant's name. Information linking participants' medical data to database materials will be maintained in a secure location at the participating site. The key to code and re-code participant identifiers will only be accessible to local site investigators (i.e., the research nurse and PI) and not to members of the central study team.

Any information that may identify a participant will be excluded from data presented in the public arena. When archiving or processing data pertaining to the investigator and/or to the participants, the sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorised third party.

12.3 Data Handling and Record Keeping

All trial data required for the monitoring and analysis of the study will be recorded on the eCRFs provided. All required data entry fields must be completed. Data corrections will be done according to the instructions provided. The investigator will be asked to confirm the accuracy of completed eCRFs by signing key eCRFs as indicated.

Source documents pertaining to the trial must be maintained by investigational sites. Source documents may include a participant's medical records, hospital charts, clinic charts, the investigator's participant study

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files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the eCRF serves as part of the investigator's record of a participant's study-related data.

The following information should be entered into the participant's medical record:

a. The participant's protocol identification.
b. The date that the participant entered the study, and participant number.
c. A statement that informed consent was obtained (including the date)
d. Relevant medical history
e. Dates of all participant visits and results of key trial parameters.
f. Occurrence and status of any SAEs
g. The date the participant exited the study, and a notation as to whether the participant completed the study or reason for discontinuation.

All study-related documentation at sites will be maintained for local regulatory mandated period after the completion of the trial, or submission to the regulatory agency; whichever is later.

12.4 Study Monitoring

Data from this study will be monitored by Clinical Trials Program staff from the NHMRC CTC and regional coordinating centres (or their delegates). Monitoring will include centralised review of eCRFs and other study documents for protocol compliance, data accuracy and completeness. Monitoring may include monitoring visits to investigational sites during the study for source data verification, review of the investigator's site file and drug handling records. The NHMRC CTC and the regional coordinating centres (or their delegates) will be given direct access to source documents, eCRFs and other study-related documents. By signing the informed consent form, the participant gives authorised NHMRC CTC staff and the regional coordinating centres' staff (or their delegates) direct access to their medical records and the study data.

12.5 Audit and Inspection

This study may be participant to audit or inspection by representatives of Dimerix, the University of Sydney, the NHMRC CTC, regional coordinating centres (or their delegates), relevant ethics committees, or representative of regulatory bodies in each region.

Trial related documentation should be kept in a secure location and held for 15 years after the end of the trial or longer if required according to local regulation. During this period, all data should be accessible, with suitable notice, as it may be subject to audit or inspection from any of the above.

As soon as the site investigator is notified of a planned inspection by the authorities, they will inform the sponsor, and request their participation in this inspection. Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the sponsor. The Investigator shall take appropriate measures required by the sponsor to rectify the areas of opportunity identified during the audit or inspections.

12.6 Clinical Study Report & Publication Policy

A Clinical Study Report which summarises and interprets all the pertinent study data collected will be issued which may form the basis of a manuscript intended for publication. The Clinical Study Report or summary thereof will be provided to the study investigators, regional coordinating centres, Dimerix, and relevant ethics and regulatory bodies as required. A lay summary of the results will be prepared for participants and other interested parties.

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The Trial Management Committee will draft manuscript(s) based on the trial data. Manuscript(s) will be submitted to peer-reviewed journal(s). The first publication will be the report of the full trial results based on the main protocol. The sponsor will develop a publication plan, including authorship, target journals and expected dates of publication. All publications must receive prior written approval from the TMC prior to submission.

12.7 Insurance and Indemnity

The sponsor certifies that it has a liability insurance policy which covers the liability of the Chief Investigator. This insurance policy is in accordance with local laws and requirements. The insurance of the sponsor does not relieve the sites, investigators, or manufacturers of the study interventions of any obligation to maintain their own liability insurance policy as required by applicable law.

13 PROTOCOL AMENDMENTS

Any modifications to the protocol which may impact on the conduct of the trial, potential benefit of the participant or may affect participant safety, including changes of core trial objectives, platform design, patient population, trial procedures or significant administrative aspects will require a formal amendment to the protocol. Such amendments will be agreed upon by the TMC and approved by the relevant ethics committee prior to implementation, and then notified to the health authorities in accordance with local regulations.

The full history of modifications to the Protocol is described in table 6 below.

Table 6. Version Control

Version	Changes from Prior Version
1.0	N/A
2.0	• Update to CTC contact information. • Update Section 1. Background. • Update of the following typos: 1) Synopsis and Schema - Safety Objectives and Measures The original text for Hyperkalaemia *(defined as a K>5.5-6.0 mmol/L and requiring an intervention including hospitalisation or K<6.0 mmol/L. Incidence in days 0-28*. This has been updated to correct to K>6.0mmol/L 2) Section 2.2.2 Secondary objectives. This section was missing the third safety objective of deranged liver function test. The following has been added: 17. Deranged Liver Function Tests (defined as Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) >Upper Limit of Normal (ULN) or >1.5 times baseline). Incidence in days 0-28. Epagermanium has been updated to Repagermanium in section 2.2.2 secondary objectives • Update to the Clinical Health Score. • Update to the Inclusion Criteria #1 and #2. • Additional Inclusion Criteria defining moderate and severe COVID-19. • Update to the design of the study. Changed from 2 stage to 3 stage design (India only). • Update to statistical analysis section. Update to the sample size analysis for a 3-stage sample. Updates to the main analysis section, outlining the stage 1 safety analysis. • Update to Figure 1. Clarification on Candesartan dose frequency.

	• Update to Figure 2. Candesartan titration dose algorithm. • Section 6.1 (Schedule of assessments). Merged Baseline and Day 1 assessments in one visit. • Section 6.1 (Schedule of assessments). Removal of the ECG assessment at Baseline • Section 6.2.3. Update to laboratory test (Creatinine Kinase and D-dimer) requirements. • Section 7.2. Addition of the Respiratory Failure incidence definition.
3.0	• Moved information specific to India to Appendix 1 and added Australian-specific Appendix; • Updated Statistician on page 1. • Added instructions to refer to Study Manual for emergency unblinding process; • Updated age requirement in Section 4.2.1 Inclusion Criteria and added the Indian-specific age requirement to Appendix 1; • Updated Section 5.2 by adding version of CTCAE (Version 5.0); • Updated Sections 11.1 and 12.4-12.6 to include regional coordinating centres and their delegates; • Administrative updates.

3.1	• Addition of ClinicalTrials.gov identifier on page 1;
	• Addition of Inclusion Criterion 6 – "known viral hepatitis";
	• Addition to Section 6 Assessment Plan:
	  ○ addition of Alkaline Phosphatase, Gamma-Glutamyl Transferase and bilirubin as markers of acute cholestasis, to the blood pathology requirements;
	  ○ addition of ECG and troponin assessment at Baseline;
	  ○ addition of COVID-19 vaccination status;
	  ○ addition of follow-up visits at Days 21 and 28 if participant is an inpatient during those visits.
	• Update of the typographical error in Section 10.1 – "Stage 2" amended to "Stage 3";
	• Addition of Section 11.4 – Consumer and Community Advisory Committee (CCAC);
	• Addition of Section 15.2.1 for guidance on cardiac monitoring in COVID-19 patients;
	• Clarified definition of "Respiratory failure" as receipt of non-invasive or invasive mechanical invasive ventilation;
	• Clarified definition of "Requirement of ventilatory support" as receipt of invasive ventilation;
	• Administrative updates.

3.2	• Addition of Exclusion Criterion #7 – "*High sensitivity Troponin (hsTn) ≥ 2 ULN or new (or previously undocumented) ECG changes*"; • Addition of Section 5.1.2.2 to refer to Australian-appendix regarding COVID-19 associated myocardial dysfunction care; • Update of Section 15.2.1 to include guidance on detection and treatment of COVID-19 associated myocardial dysfunction care, based on the CSANZ Position Statement.

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15 COUNTRY SPECIFIC APPENDICES

The country-specific appendices provide additional information about trial conduct specific to the country and therefore it supersedes entirely or partially the corresponding information in the protocol.

15.1 Appendix 1 – INDIA

India Sponsor:	The George Institute, New Delhi, 110025, India
India Coordinating Centre:	The George Institute for Global Health India 308-309, Third Floor, Elegance Tower, Plot No. 8, Jasola District Centre New Delhi 110025 India Telephone: +91 11 415 880 91-93 Fax: +91 11 415 880 90
Medical Monitor Contact:	Prof Vivekanand Jha +91 11 415 880 91-93

15.1.1 Eligibility

The age requirement for inclusion of participants from India in this trial is as follows:

Inclusion Criteria

1. Adults aged between 18 and 65 years.

15.1.2 Ethics and Regulatory Compliance

This protocol has been developed by sponsor staff and the TSC, in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement and in accordance with the Indian Council of Medical Research (ICMR)relevant guidelines.

15.2 Appendix 2 – AUSTRALIA

Australia Sponsor:	The University of Sydney, NSW 2006, Australia
Australia Coordinating Centre:	NHMRC Clinical Trials Centre, University of Sydney 92-94 Parramatta Road Camperdown NSW 2050, Australia Telephone: +61 2 9562 5000 Fax: +61 2 9565 1863
Medical Monitor Contact:	Prof Meg Jardine +61 2 9562 5000

15.2.1 Detection and Treatment of COVID-19 Associated Myocardial Dysfunction

The Cardiac Society of Australia and New Zealand (CSANZ) Position Statement[1] on "*COVID-19 and Acute Heart Failure: Screening the Critically Ill"* is concerned with the identification and management of people with COVID-19 at risk for severe heart failure.

The latest version of the statement is available at: https://www.csanz.edu.au/for-professionals/position-statements-and-practice-guidelines/. Clinicians are urged to review the full advice and to seek specialist cardiology advice if considering enrolling a patient with acute heart failure into the CLARITY 2.0 study.

The Statement presents a screening "algorithm to better identify COVID-19 patients at risk for severe heart failure and circulatory collapse, whilst balancing the need to protect health care workers and preserve personal protective equipment (PPE)." It outlines the significance of serum troponin levels and the role of telemetry and targeted transthoracic echocardiography (TTE) in patient investigation and management. Management of acute heart failure in COVID-19 patients is also outlined, including the role of mechanical circulatory support. "Endomyocardial biopsy is not recommended; further, inpatient cardiac MRI should be avoided."

It outlines a comprehensive approach to a range of clinical scenarios, including what to do in response to raised troponin or an abnormal ECG in a person with COVID-19 and how these patients should be appropriately managed. A summary of this advice is outlined below.

"Patients with an elevated hsTn (greater than 99th centile for the assay) should be considered for telemetry, preferably in the high dependency or intensive care unit (HDU/ICU). Useful adjunct tests include serum d-dimer, C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, and brain natriuretic peptide (BNP) (or N-terminal pro hormone BNP [NT-proBNP]) although the availability of the latter may vary between institutions. *If there are also* ECG changes (see below) then this should trigger a transthoracic echocardiogram (TTE) [13], with limited views (see below). Otherwise, a hsTn should be undertaken daily and an ECG second daily (see caveat below) in the HDU/ICU."

"For patients in the HDU/ICU/telemetry setting, an elevated hsTn (greater than 99th centile for the assay), which *continues to rise* (in the absence of chest pain) over three consecutive days with or without ECG changes (see below) should trigger a targeted TTE [13] (see below). Haemodynamic instability (e.g., increasing vasopressor requirement), or any inotropic requirement or clinical evidence of heart failure should be independent triggers for a targeted TTE."

"Patients who develop acute heart failure should be managed in an ICU environment according to established guidelines with the use of intravenous diuretics and inotropic/vasopressor support for those who develop hypotension. In patients with progressive cardiogenic shock, who fail to respond to inotropic support, consideration of mechanical circulatory support (e.g., veno-arterial extracorporeal membrane oxygenation

O'Hara DV, *et al. BMJ Open* 2024; 14:e081790. doi: 10.1136/bmjopen-2023-081790

[VA ECMO] or Impella) may be appropriate, however, this requires careful evaluation of the overall clinical picture. Given the potential risk posed to healthcare staff from aerosol generation during high-flow nasal oxygen, non-invasive ventilation or positive pressure ventilation without an adequate seal, institutional and departmental preparation is required for the management of acute respiratory failure [15].

The underlying pathophysiology in these critically ill patients is a likely fulminant myocarditis, so consideration should be given for therapies such as high dose corticosteroids, intravenous immunoglobulin and even selective cytokine blockade that target hyperinflammation [16], although these are not yet proven. Novel markers of inflammation and emerging therapies should also be considered as the evidence comes to hand.

While endomyocardial biopsy is considered the 'gold standard' for diagnosis of acute myocarditis, experience with this procedure in COVID-19 patients is extremely limited. Isolated case reports have suggested that the findings on endomyocardial biopsy are nonspecific and are non-contributory to patient management. Furthermore, the procedure carries risks for both the patient and proceduralist. Based on these considerations endomyocardial biopsy is not recommended."

We recommend that inpatient cardiac MRI should also be avoided as the risks of the prolonged scan time and magnet contamination are substantial and immediate management is unlikely to be changed by its use."

Reference:

[1] *Lal S, Hayward CS, De Pasquale C, Kaye D, Javorsky G, Bergin P, Atherton JJ, Ilton MK, Weintraub RG, Nair P, Rudas M, Dembo L, Doughty RN, Kumarasinghe G, Juergens C, Bannon PG, Bart NK, Chow CK, Lattimore JD, Kritharides L, Totaro R, Macdonald PS. COVID-19 and Acute Heart Failure: Screening the Critically Ill - A Position Statement of the Cardiac Society of Australia and New Zealand (CSANZ). Heart Lung Circ. 2020 Jul;29(7):e94-e98. doi: 10.1016/j.hlc.2020.04.005. Epub 2020 May 1. PMID: 32418875; PMCID: PMC7252099.*