REMAP-CAP

Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Domain-Specific Appendix:

ACE2 Renin-Angiotensin System (RAS) Modulation Domain

Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP)

COVID-19 ACE2 RAS Modulation Domain-Specific Appendix Version 2 dated 14 October 2021

Summary

In this domain of the REMAP-CAP trial, participants meeting platform entry criteria with suspected or microbiological testing confirmed COVID-19 will be randomized to receive one of up to four renin-angiotensin system (RAS) modulation strategies, depending on availability and acceptability, or control:

- No RAS inhibitor (no placebo)
- Angiotensin converting enzyme inhibitor (ACEi)
- Angiotensin II receptor blocker (ARB)
- ARB in combination with DMX-200, a chemokine receptor-2 [CCR2] inhibitor (ARB + DMX-200)
- ACEi in combination with TRV-027, an angiotensin-(1,7) analogue (ACEi + TRV-027)

At this participating site the following interventions have been selected within this domain:

- ☐ No RAS inhibitor
- ☐ ACEi
- ☐ ARB
- ☐ ARB + DMX-200
- ☐ ACEi + TRV-027

This DSA applies to the following states and stratum:

Stratum	Pandemic infection suspected or proven (PISOP)			Pandemic infection neither suspected nor proven (PINSNP)
Core protocol documents	REMAP-CAP Core Protocol + Pandemic Appendix, or REMAP-COVID Core Protocol			REMAP-CAP Core Protocol
Illness Severity State	Moderate State		Severe State	Severe State
Interventions specified in this DSA	No RAS inhibitor ACEi ARB ARB + DMX-200 ACEi + TRV-027		No RAS inhibitor ACEi ARB ARB + DMX-200 ACEi + TRV-027	Not available
Interventions submitted for approval in this jurisdiction	☐ No RAS inhibitor ☐ ACEi ☐ ARB ☐ ARB + DMX-200 ☐ ACEi + TRV-027		☐ No RAS inhibitor ☐ ACEi ☐ ARB ☐ ARB + DMX-200 ☐ ACEi + TRV-027	Not available
Interventions offered at this site	Ward	ICU	ICU	ICU
	☐ No RAS inhibitor ☐ ACEi ☐ ARB ☐ ARB + DMX-200 ☐ ACEi + TRV-027	☐ No RAS inhibitor ☐ ACEi ☐ ARB ☐ ARB + DMX-200 ☐ ACEi + TRV-027	☐ No RAS inhibitor ☐ ACEi ☐ ARB ☐ ARB + DMX-200 ☐ ACEi + TRV-027	Not available

REMAP-CAP: COVID-19 ACE2 RAS Modulation Therapy Domain Summary	
Interventions	• No RAS inhibitor (no placebo) • Angiotensin converting enzyme inhibitor (ACEi) • Angiotensin receptor blocker (ARB) • ARB in combination with DMX-200 (a chemokine receptor-2 [CCR2] inhibitor) • ACEi in combination with TRV-027 (an angiotensin-(1,7) analogue)
Unit of Analysis and Strata	This domain is analyzed only in the pandemic statistical model. The pandemic statistical model includes only patients who are in the Pandemic Infection Suspected or Proven (PISOP) stratum. Within the stratum the unit-of-analysis is defined by illness severity state at the time of enrollment, defined as either Moderate State or Severe State. Unit-of-analysis may also be defined by SARS-CoV-2 infection strata. Borrowing is permitted between states and strata. Response Adaptive Randomization is not applied during the Phase 2 component (see below) but may be applied during the Phase 3 component and may be applied to all PISOP patients using probabilities derived from SARS-CoV-2 confirmed stratum.
Evaluable treatment-by-treatment Interactions	No interactions will be evaluated with any other domain.
Nesting	None.
Timing of Reveal	Randomization with Immediate Reveal and Initiation, or Randomization with Deferred Reveal if prospective agreement to participate is required.
Inclusions	Patients will be eligible for this domain if: • COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing • Microbiological testing for SARS-CoV-2 of upper or lower respiratory tract secretions or both has occurred or is intended to occur
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • If in the Moderate State, more than 96 has elapsed since hospital admission • If in the Severe State, more than 48 hours has elapsed since ICU admission, unless the patient has already been assigned a treatment in another domain in the Moderate state, in which case exclusion will occur if more than 48 hours has elapsed since commencement of sustained organ failure support in an ICU • Patient is already receiving, or a clinical decision has been made to commence, an ACEi, ARB, direct renin inhibitor, angiotensin-receptor-neprilysin inhibitor, or chemokine receptor modulator • Long-term therapy prior to this hospital admission with one or more of ACEi, ARB, direct renin inhibitor, angiotensin-receptor-neprilysin inhibitor, or chemokine receptor modulator • Hypersensitivity to ACEi or ARB, including any history of angioedema • Treating clinician believes that administration of ACEi or ARB is inappropriate because of risk for:

	o Clinically relevant hypotension or escalation of vasopressor requirements o Hyperkalemia • Known severe renal artery stenosis • Patient is known or suspected to be pregnant or breastfeeding • Renal impairment with creatinine clearance < 30 ml/min or receiving renal replacement therapy • Enrollment in another trial evaluating ACEi, ARB, or other RAS modulator, or any targeted chemokine receptor modulation for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial • If the domain is available at this site in the Moderate State and the patient is being assessed in the Severe state, prior assessment for this domain in the Moderate State • The treating clinician believes that participation in the domain would not be in the best interests of the patient
Intervention-Specific Exclusions	• Known severe liver disease or an alanine aminotransferase or an aspartate aminotransferase that is more than 5 times the upper limit of normal will result in exclusion from receiving combined ARB + DMX-200. • Known viral hepatitis will result in exclusion from receiving ARB + DMX-200 • Hypersensitivity to repagermanium will result in exclusion from receiving ARB + DMX-200 • Hypersensitivity to TRV-027 will result in exclusion from receiving ACEi + TRV-027
Outcome measures	This domain follows a seamless Phase 2-Phase 3 trial design using the primary REMAP end-point (refer to the REMAP-CAP Core Protocol + Pandemic Appendix and the REMAP-COVID Core Protocol). In the initial **Phase 2**, this primary end-point is evaluated using a statistical trigger for retention in the platform of a posterior probability of 0.5 or more that there is an improvement in odds ratio of at least 20% (for the ACEi and ARB interventions compared to no RAS inhibitor) or 30% (for the ARB + DMX-200 intervention compared to ARB alone and compared to no RAS inhibitor) or 30% (for the ACEi + TRV-027 intervention compared to ACEi alone and compared to no RAS inhibitor). Phase 2 will be evaluated with a fixed maximum sample size of 300 patients allocated to ACEi and ARB interventions, and 200 patients allocated to ARB + DMX-200 and ACEi + TRV-027 interventions. The decision to proceed to phase 3 is pre-specified, requiring both the phase 2 statistical trigger for retention and a satisfactory safety profile, as determined by judgement of the DSMB. The safety end-points to be evaluated by the DSMB are: • acute kidney injury defined as KDIGO Stage ≥2 acute kidney injury: o stage 2: serum creatinine increase 2-3x from baseline within 7 days and also within 14 days • stage 3: serum creatinine increase ≥3x from baseline within 7 days and also within 14 days, or increase in serum creatinine by ≥0.5 mg/dL (44 mmol/L) to ≥4 mg/dL (353.6 µmol/L), or initiation of renal replacement therapy • change from baseline to peak creatinine

	- angioedema - change in baseline to peak available AST, ALT, and bilirubin during the treatment period - administration of vasopressors (evaluated using vasopressor-free days at 21 days) - clinically relevant hypotension while admitted to a ward - in the ARB + DMX-200 and ACEi + TRV-027 interventions only: - occurrence of suspected unexpected serious adverse reactions (SUSAR). - Serious adverse events as defined in relevant core protocol documents and this DSA If the domain progresses to **Phase 3** the primary REMAP endpoint will be evaluated for superiority, efficacy, equivalence and futility will be evaluated using all patients randomized in Phases 2 and 3. Secondary REMAP endpoints: refer to REMAP-CAP Core Protocol + Pandemic Appendix and REMAP-COVID Core Protocol. Secondary domain-specific endpoints (during hospitalization censored 90 days from the date of enrollment): - Serious Adverse Events (SAE) as defined in relevant core protocol documents and this DSA

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1. ABBREVIATIONS

ACE	Angiotensin converting enzyme
ACEi	Angiotensin converting enzyme inhibitor
ARB	Angiotensin II receptor blocker
ARDS	Acute respiratory distress syndrome
CAP	Community acquired pneumonia
CCR2	Chemokine receptor 2
DSA	Domain-specific appendix
DSWG	Domain-specific working group
DSMB	Data safety and monitoring board
ICU	Intensive care unit
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
kg	Kilogram
LOS	Length of stay
MODS	Multiple organ dysfunction score
mg	milligram
OFFD	Organ failure free days
RAR	Response adaptive randomization
RAS	Renin-angiotensin system
RASi	Renin-angiotensin system inhibition
RCT	Randomized controlled trial
REMAP	Randomized, Embedded, Multifactorial Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
SAE	Serious adverse event

2. PROTOCAL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive, and the description of these adaptations is better understood and specified using a 'modular' protocol design. While all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example, by the introduction of new domains or interventions or both (see glossary, Section 1.2 Core Protocol for definitions of these terms) and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study), a Statistical Analysis Appendix (details of the current statistical analysis plan and models) and Simulations Appendix (details of the current simulations of the REMAP), multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain), and multiple Region-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol(s) contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s), within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions, within each domain, is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject of a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analysis model will change overtime in accordance with the domain and intervention trial adaptations, but this information is contained in the Statistical Analysis and Simulations Appendices. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the International Statistics Interest Group (ISIG) and the Data Safety and Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase

over time. Information that is specific to each region that conducts the trial is contained within a RSA. This includes information related to local management, governance, and ethical and regulatory aspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

The current version of the relevant Core Protocol (either REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol), DSAs, RSAs and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (www.remapcap.org).

3. COVID-19 ACE2 RAS MODULATION DOMAIN-SPECIFIC APPENDIX VERSION

The version of the COVID-19 ACE2 RAS Modulation Domain-Specific Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1:   Approved by the COVID-19 ACE2 RAS Modulation Domain-Specific Working Group (DSWG) on 8th November 2020

Version 2:   Approved by the COVID-19 ACE2 RAS Modulation Domain-Specific Working Group (DSWG) on 14 October 2021.

4. COVID-19 ACE2 RAS MODULATION DOMAIN GOVERNANCE

4.1. Domain members

Chair: Dr. Patrick R. Lawler

Co-Chair: Dr. Lennie Derde

Members:

Dr. Rebecca M. Baron

Dr. Slava Epelman

Prof. Justin Ezekowitz

Dr. Claudia Frankfurter

Dr. David Gattas

Dr. Frank Gommans

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Dr. Colin McArthur

Dr. Bryan McVerry

Prof. Danny McAuley

Dr. David Owen

Dr. Katrina Pollock

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5. ACE2 RAS MODULATION DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

The ACE2 RAS Modulation Domain-Specific Working Group have read the appendix and authorize it as the official COVID-19 ACE2 RAS Modulation Domain-Specific Appendix for the study entitled REMAP-CAP. Signed on behalf of the committee,

Chair   Date   14th October 2021
Patrick R. Lawler

6. BACKGROUND AND RATIONALE

6.1. *Domain definition*

This is a domain within the REMAP-CAP platform to test the effectiveness of strategies to reduce the potentially maladaptive secondary effects of SARS-CoV2-ACE2 binding by targeted inhibition of excessive angiotensin II activity, with or without concomitant inhibition of monocyte chemotaxis with chemokine receptor 2 (CCR2) inhibition, in patients with acute illness due to suspected or proven COVID-19.

6.2. *Domain-specific background*

6.2.1. SARS-CoV-2, ACE2, the renin–angiotensin-system, and its modulators

The pathogenesis of SARS-CoV-2 appears to critically involve an alteration in the host renin-angiotensin system (RAS) which is mediated by reduced bioavailability of angiotensin-converting enzyme 2 (ACE2) (Shang et al., 2020). The entry of SARS-CoV-2 into target host cells is mediated by the binding of its surface spike protein onto the ACE2 receptor, followed by fusion of viral and plasma membranes, endocytosis, and subsequent viral propagation (He et al., 2020, Hoffmann et al., 2020, Shang et al., 2020). Its binding affinity for ACE2 is 4-fold higher than its predecessor, SARS-CoV-1, with which it shares 76% of its viral genome (Li et al., 2003, Wang et al., 2020, Wrapp et al., 2020, Xu et al., 2020).

ACE2, and its 42% identical homologue ACE, are dipeptidyl carboxypeptidases which play contrasting roles in the RAS system (**Figure 1**) (Donoghue et al., 2000). ACE cleaves angiotensin I to generate

angiotensin II, which binds to the angiotensin type 1 (AT1) receptor, resulting in vasoconstriction, sodium retention, as well as a pro-inflammatory and pro-fibrotic state. To balance this vasoconstriction, angiotensin II can also bind to the angiotensin type 2 (AT2) receptor causing vasodilatation. ACE activity can also regulate bradykinin, a peptide that mediates vasodilation incrementally and stimulates both nitric oxide release and the synthesis of vasoactive prostaglandins (Messerli et al., 1996, Verdecchia et al., 2020). Conversely, ACE2 serves a protective function converting angiotensin II into angiotensin-(1-7) and cleaving angiotensin I into angiotensin-(1-9) (Donoghue et al., 2000, Verdecchia et al., 2020). Angiotensin-(1-7) exerts counter-regulatory effects to angiotensin II both by binding to the Mas receptor and by acting as a biased agonist of AT1, eliciting vasodilation as well as anti-inflammatory and anti-thrombotic effects (Mehta and Griendling, 2007, Santos et al., 2003, Santos et al., 2018, Galandrin et al., 2016, Gaidarov et al., 2018, Teixeira et al., 2017). ACE2 also catalytically inactivates bradykinin metabolites (Imai et al., 2008, Tolouian et al., 2020). These effects of ACE and ACE2 highlight that this system is highly balanced, and that a dysregulation of ACE2 would affect both the RAS and bradykinin system.

ACE2 receptors are abundantly expressed on type 2 pneumocytes, and can be found in epithelial cells, cardiomyocytes, and other tissues (Donoghue et al., 2000, Verdecchia et al., 2020, Zhao et al., 2020, Zhang et al., 2020a, Wysocki et al., 2010). The abundance of ACE2 in the lungs may explain why pneumonia is the prominent clinical feature of COVID-19, with the lungs serving as the primary site for viral invasion and replication (Zhao et al., 2020, Zhang et al., 2020a). ACE2 is present in two forms—both as a membrane-bound receptor and in soluble form, the latter of which normally circulates in scarce amounts. Of note, the gene coding for ACE2 lies on the X chromosome, and as such, there may be important sex differences in ACE2 levels influencing susceptibility to COVID-19 and its complications (Batlle et al., 2020, Crackower et al., 2002). There may also be ethnic differences in ACE2 levels (Batlle et al., 2020). In two independent cohorts of patients with heart failure receiving chronic RAS inhibitor (RASi) therapy — including ACE inhibitors (ACEis), angiotensin II receptor blockers (ARBs) – as well as aldosterone blockade with mineralocorticoid receptor antagonists—plasma ACE2 concentrations were higher in men compared to women (Sama et al., 2020). The clinical observation that men have higher rates of hospitalization and death due to COVID-19 relative to women has lent support to ACE2 as a critical mediator of disease course.

Figure 1. Schematic diagram of the engagement of SARS-CoV-2 with the renin-angiotensin system. Adapted from Vaduganathan et al. (2020), Zhang et al. (2020a), Burrell et al. (2004), and Verdecchia et al. (2020).
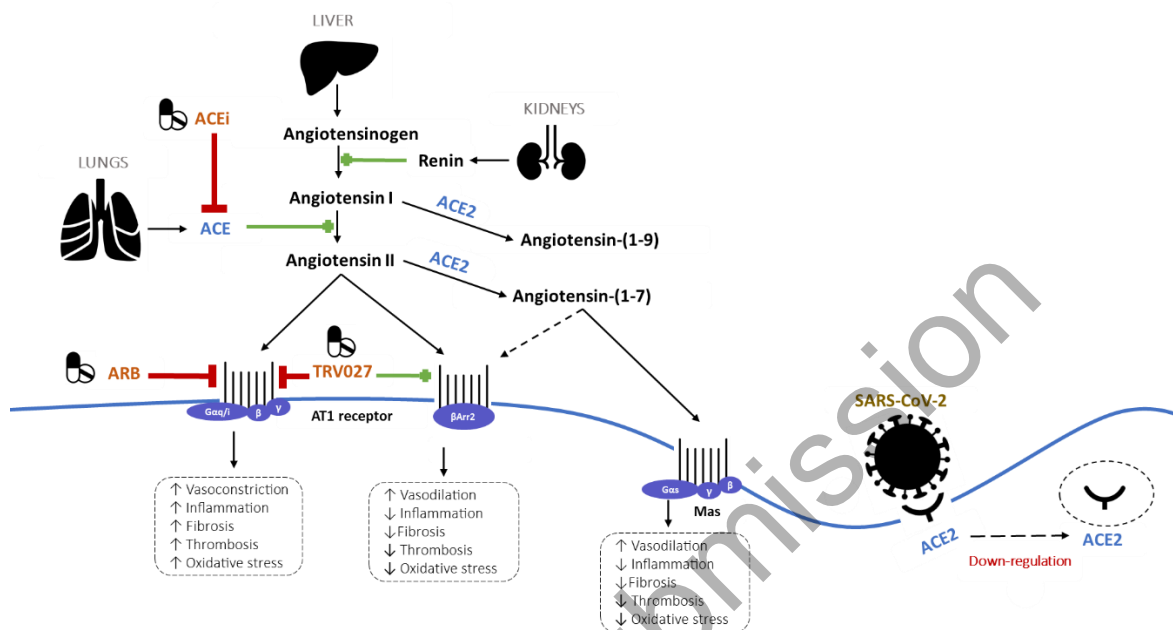
Figure 1. The renin-angiotensin system (RAS) is a hormonal system that regulates systemic vascular resistance and fluid/electrolyte balance. In the context of reduced renal blood flow, renin is released from the kidney and acts on angiotensinogen produced by the liver to convert it to angiotensin I. By the action of angiotensin-converting enzyme (ACE) in endothelial cells, predominantly in the lungs, angiotensin I is cleaved to angiotensin II, which subsequently binds to angiotensin II type 1 (AT1) receptor. Activation of the AT1 receptor by angiotensin II results in vasoconstriction, aldosterone release, as well as an increased inflammation, fibrosis, thrombosis, and oxidative stress, which precipitates tissue injury, notably in the lungs. ACE2, a homologue of ACE, cleaves angiotensin I into angiotensin-(1-9) and angiotensin II into angiotensin-(1-7) that acts on the Mas receptor. Activation of the Mas receptor results in vasodilation and decreases inflammation, fibrosis, thrombosis, and oxidative stress, in counterbalance to the negative effects of angiotensin II. The AT1 receptor can also be activated by angiotensin-(1-7), which acts as a biased agonist inducing a different (β-arrestin) signaling pathway from the angiotensin II G protein activation pathway (Teixeira et al., 2017); ACE inhibitors and angiotensin receptor blockers (ARBs) inhibit ACE and AT1 receptors, respectively. The surface spike protein of SARS-CoV-2 attaches to the ACE2 receptor, and subsequently downregulates expression of ACE2, which may induce acute lung injury. *Abbreviations:* ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AT1, angiotensin II type 1. Overall, this domain seeks to study several modulators of the RAS system, as well as related targets outlined below, overviewed in the **Box Insert**.

Box Insert: Summary of possible interventions in the domain. Not all sites offer all interventions.		
Intervention	Targeted mechanism of action	Possible beneficial effects
ACEi	Reduce levels of angiotensin II	Reduced inflammation, reduced fibrosis, reduced thrombosis
ARB	Block the receptor for angiotensin II	Reduced inflammation, reduced fibrosis, reduced thrombosis
TRV-027 + ACEi	TRV-027 stimulates the β-arrestin component of the angiotensin II receptor pathway as well as Mas receptor pathway; ACEi is given in combination to reduce levels of angiotensin II	Reduced inflammation, reduced fibrosis, reduced thrombosis, reduced oxidative stress
DMX-200 + ARB	DMX-200 inhibits chemokine receptor-2; ARB is given in combination to reduce angiotensin II signalling, as there is evidence that these two receptors communicate and that combined blockade of both receptors is more effective than blockade of only one receptor	Reduced macrophage-related inflammation, reduced fibrosis, reduced thrombosis

6.2.2. Adverse sequalae of unregulated angiotensin II activity and impaired angiotensin 1-7 activity

The entry of SARS virus via membrane fusion is believed to downregulate ACE2 abundance on cell surface membranes, resulting in subsequent loss of the enzyme's beneficial effect to regulate angiotensin II activity (Kuba et al., 2005). Reduced ACE2 expression may be associated with both an attenuation of the conversion of angiotensin II into angiotensin 1-7 and concomitant amplification of angiotensin II activity and reduction in angiotensin 1-7 activity. Unchecked angiotensin II, acting via the AT1 receptors, may incite a number of adverse effects, including increased pulmonary inflammation, endothelial dysfunction, myocardial dysfunction, and thrombosis (Zhang et al., 2020a). Angiotensin II has a pro-apoptotic action on alveolar epithelial cells, resulting in diffuse alveolar damage and cell death (Papp et al., 2002, Zhou et al., 2020a). Increased angiotensin II within the respiratory tree has been associated with the precipitation of severe pulmonary damage via alveolar wall thickening, edema, and inflammatory cell infiltration (Zhang et al., 2020a, Kuba et al., 2005, Imai et al., 2005). It likewise exerts pro-fibrotic effects via fibroblasts within the interstitial spaces surrounding the alveoli and activates macrophages, inducing inflammatory cytokines such as IL-6 and TNFα, and pathologic reactive oxidative species, further exacerbating edema and pulmonary epithelial injury, and potentially triggering the onset of acute respiratory distress syndrome (ARDS) (Verdecchia et al., 2020, Bernstein et al., 2018, Chuquimia et al., 2012, Meng et al., 2014, Sodhi et al., 2018, Uhal et al., 2012). Injured type II pneumocytes have a reduced ability to produce alveolar surfactant, resulting in reduced lung elasticity and an impaired ability to repair type I pneumocytes, hindering gas exchange (Rivellese and Prediletto, 2020). The blunting of the protective conversion of

angiotensin II by ACE2 into angiotensin-(1-7) precipitated by SARS-CoV-2 may enhance tissue injury, especially in patients with co-morbidities, notably cardiovascular and pulmonary disease (Sriram and Insel, 2020). In a cohort of patients from China, plasma levels of angiotensin II were significantly elevated after SARS-COV-2 infection, and were linearly correlated to viral load and lung injury (Liu et al., 2020). Much of the pathology associated with unregulated angiotensin II activity is also reproduced by angiotensin 1-7 depletion, as would be expected given angiotensin 1-7 functionally and pharmacologically antagonizes angiotensin II. Indeed, the animal models of angiotensin 1-7 depletion produce pathology which aligns with that seen in COVID-19 patients, including lung injury, lung inflammation, myocardial microinfarcts, characteristic glomerular thrombosis and coagulopathy.

6.2.3. RAS inhibition: possible mechanisms of benefit

As infection with SARS-CoV-2 results in down-regulation of ACE2 expression with concomitant amplification of local angiotensin II and reduced angiotensin 1-7, use of ACEi or ARB may mitigate the potentially deleterious effects of unchecked RAS activation (Kuba et al., 2005). The interplay between SARS-CoV-2 and use of RASi has been the focus of increasing attention both to attenuate disease virulence, as well as provide favorable lung-protective modulation of the angiotensin II axis (Diaz, 2020, Esler and Esler, 2020, Fang et al., 2020, Gurwitz, 2020, Sommerstein et al., 2020). As noted, increased pulmonary angiotensin II has been associated with the precipitation of severe pulmonary injury via alveolar wall edema and inflammation (Zhang et al., 2020a, Imai et al., 2005, Kuba et al., 2005). Blunting the effects of angiotensin-II-mediated AT1 receptor activation via ACE with ACEi to reduce angiotensin-II levels and AT1 receptor blockade with ARBs may potentially reduce the otherwise prominent pulmonary vascular permeability, inflammation, and vasoconstriction, and thereby attenuate acute lung injury and the risk of ARDS triggered by SARS-CoV-2-induced ACE2 downregulation (Gurwitz, 2020, Imai et al., 2005, Kim et al., 2017, Kuba et al., 2005). These potential lung protective effects of ACEi and ARB have been reflected in prior data noting their protective effect against ventilator-associated lung injury and ARDS (Arumugam et al., 2016, Wang et al., 2019, Wosten-van Asperen et al., 2010). In patients hospitalized with viral pneumonia, continued in-hospital use of ACEIs or ARBs is associated with a reduced risk of pneumonia (odds ratio [OR] 0.64, 95% confidence interval [CI] 0.34-1.19 for ACEIs; OR 0.48 95% CI 0.17-1.37 for ARBs) and in-hospital death and/or intubation (OR 0.25 95% CI 0.09-0.64 for ACEi; OR 0.75 95% CI 0.16-3.44 for ARB) (Henry et al., 2018).

Myocardial injury has likewise been documented in SARS-CoV-2 infection and is associated with a poor prognosis (Huang et al., 2020, Zheng et al., 2020). Underlying mechanisms for cardiovascular

injury are likely diverse, but may include ACE2-related cytokine activation and T cell dysregulation (Zheng et al., 2020). ACEis and ARBs confer robust cardiovascular protection in a number of conditions, and they may also do so during COVID-19 infection (Abraham et al., 2015, Vaduganathan et al., 2020).

A related physiologic alteration in COVID-19 may include bradykinin-dependent lung angioedema and vascular leakage. Use of RASi could potentially mitigate these effects by counteracting angiotensin II, which can incite vascular injury independent of its vasopressor actions (Williams et al., 1995). Via the AT1 receptor, angiotensin II potently induces a concentration-dependent increase in the expression of vascular permeability factor in human vascular smooth muscle cells (Williams et al., 1995). ACEis may reduce vascular permeability factor and hence pulmonary vascular leak, possibly conferring benefit in COVID-19 (Williams et al., 1995, Bodor et al., 2012). ACEi and ARB therapy may counter this process and improve vascular permeability.

6.2.4. RAS blockade in COVID-19: observational evidence

6.2.4.1. *Initial Safety Concerns*

Initial epidemiological data observed that hypertension, diabetes, and a history of cardiovascular disease are common co-morbidities in patients with SARS-CoV-2 (Grasselli et al., 2020, Wu et al., 2020, Yang et al., 2020). These risk factors, in conjunction with older age and male status, are associated with more severe COVID-19 infection, including a higher proportion of patients requiring intensive care, mechanical ventilation, and experiencing death (Grasselli et al., 2020, Jin et al., 2020, Yang et al., 2020). A similar risk factor profile was observed with the earlier SARS-CoV-1 pandemic (Booth et al., 2003). It is notable that these enriched comorbidities are often treated using ACEIs or ARBs, prompting concern about the role of these agents in increasing patients' susceptibility to initial infection and poor clinical outcomes (Diaz, 2020, Flack and Adekola, 2020). However, the confounding role of age and comorbidities such as hypertension, diabetes, and a history of cardiovascular disease may have influenced these risk patterns (Zhou et al., 2020a).

Concern was also raised that chronic ACEi/ARB therapy may be associated with an increase in ACE2 levels, and hence potential susceptibility to disease. In animal models, both lisinopril and losartan significantly increased cardiac ACE2 mRNA expression, 5-fold and 3-fold, respectively (Ferrario et al., 2005, Ishiyama et al., 2004). In patients with hypertension treated with olmesartan, increased urinary secretion of ACE2 has been detected (Furuhashi et al., 2015). Conversely, in two independent cohorts of patients with heart failure on RASi therapy, neither ACEi or ARB use was associated with higher plasma ACE2 concentrations (Sama et al., 2020). Robust data in humans on

the interplay of RASi, ACE2 levels, and COVID-19 clinical course are lacking. Additionally, there is an equilibrium between membrane-bound and soluble ACE2: The shedding of ACE2 from its membrane, mediated by metalloprotease ADAM17, may complicate the use of plasma ACE2 levels as a reliable indicator of ACE2 activity (Lambert et al., 2005). One canine model noted that once cleaved off into the circulation, ACE2 has decreased efficacy in its counter-regulatory functions, yet robust corroborating data in humans is lacking (Larouche-Lebel et al., 2019, Vaduganathan et al., 2020). Notably, despite being 42% somatically identical, ACE and ACE2 act on different enzyme sites, such that ACE inhibitors do not directly affect ACE2 levels (Rice et al., 2004).

The optimal strategy regarding ACEi/ARB therapy in patients with COVID-19 remains unknown. The American College of Cardiology, American Heart Association, Heart Failure Society of America, and Council on Hypertension of the European Society of Cardiology, among other international professional societies, have consistently recommended against discontinuation of ACEi and ARBs (when provided for other indications) both prophylactically and during COVID-19 disease (American Heart Association, 2020, European Society of Cardiology, 2020). Subsequently, initial results from the BRACE-CORONA randomized controlled trial (discussed in detail below) suggested that continuing ACEi or ARB therapy was safe in patients with COVID-19.

6.2.4.2. Concerns about Potential Harm Give Way to Hypotheses on Potential Efficacy

In the setting of initial hypothetical concerns, albeit increasingly tempered by emerging randomized controlled trial (RCT) evidence, several observational studies have been undertaken to determine if antecedent ACEi/ARB use is associated with differential outcomes among those with COVID-19 (**Table 1**). While most of these studies suggested that the use of ACEi/ARBs were safe in patients with COVID-19, some further identified beneficial signals associated with therapy, raising the possibility of therapeutic benefit.

Table 1. Observational data on the use of ACEi/ARB therapy and COVID-19

Study	Design	Population	Intervention	Control	Outcome	Outcome Measures
de Abajo et al. (2020)	Retrospective, case-population; multi-center with regional database	*Madrid, Spain* 1,139 patients hospitalized with COVID-19	RASi (ACEi/ARB/aldosterone antagonist) use based on prescription lasting until month prior to index date	Use of anti-hypertensive agent other than ACEi or ARB based on prescription lasting until	Hospitalization due to COVID-19	ACEi/ARB/aldosterone antagonist: OR 0.94 95% CI 0.77–1.15 ACEi: OR 0.80 95% CI 0.64-1.00 ARB: OR 1.10 95% CI 0.88-1.37

			month prior to index date		
Gao et al. (2020)	Retrospective, propensity-matched cohort; single-center	*Wuhan, China* 2,877 patients hospitalized with COVID-19	ACEi or ARB use based on pre-admission medication list	No ACEi or ARB use based on pre-admission medication list	All-cause mortality during hospitalization	HR 0.85 95% CI 0.28-2.58, p=0.774
Khera et al. (2020)	Retrospective, propensity-matched cohort; multi-center	*United States* 2,263 outpatients with hypertension, use of at least one anti-hypertensive agent, and positive test for SARS-CoV-2	ACEi or ARB use based on pharmacy claim for at least 30-day supply between July-August 2019	At least one anti-hypertensive other than ACEi or ARB based on pharmacy claim for at least 30-day supply between July-August 2019	Hospitalization	ACEi: HR 0.77, 95% CI 0.53-1.13, p=0.18 ARB: HR 0.88, 95% CI 0.61-1.26, p=0.48
					Hospitalization for patients enrolled in Medicare Advantage vs. commercial insurance	ACEi: HR 0.61, 95% CI 0.82-0.93, p=0.02 ARB: HR 0.88, 95% CI 0.61-1.26, p=0.12
		United States 7,933 in-patients with hypertension hospitalized with COVID-19	ACEi or ARB use based on pharmacy claim for at least 30-day supply between July-August 2019	At least one anti-hypertensive other than ACEi or ARB based on pharmacy claim for at least 30-day supply between July-August 2019	In-hospital mortality	ACEi: HR 0.97, 95% CI 0.81-1.16, p=0.74 ARB: HR 1.15, 95% CI 0.95-1.38, p=0.15
Fosbol et al. (2020)	Retrospective cohort; national registry	*Denmark* 4,480 patients with COVID-19 examined in a hospital	ACEi or ARB use based on 1 or more prescription filling in 6-month period preceding index date	No ACEi or ARB use prescription filling in 6-month period	All-cause death	ACEi or ARB: HR 0.83, 95% CI, 0.67-1.03, p=0.09
					Death or severe COVID-19	ACEi or ARB: HR 1.04, 95% CI, 0.89-1.23, p=0.61

				preceding index date	Severe COVID-19	ACEi or ARB: HR 1.15, 95% CI 0.95-1.41, p=0.15
	Nested case-cohort; national registry	*Denmark* 6,281 patients with hypertension tested for COVID-19	ACEi or ARB use based on 1 or more prescription filling in 6-month period preceding index date	Use of at least one anti-hypertensive other than ACEi or ARB based on prescription filling in preceding 6-month period	COVID-19 diagnosis	ACEi or ARB: HR 1.05, 95% CI, 0.80-1.36, p=0.67
Mehta et al. (2020)	Retrospective, propensity-matched cohort; multi-center	*Ohio and Florida* 18,472 patients tested for COVID-19	ACEi or ARB use documented in electronic medical record at time of SARS-CoV-2 testing	No ACEi or ARB use documented in electronic medical record at time of SARS-CoV-2 testing	Positive test for SARS-CoV-2 infection	ACEi or ARB: OR 0.97 95% CI 0.81-1.15
Reynolds et al. (2020)	Retrospective, propensity-matched cohort; single-center	*New York City* 12,594 patients who were tested for COVID-19	ACEi or ARB use documented within the last 18 months	No ACEi or ARB use documented within the last 18 months	Positive COVID-19 test	ACEi: Median difference 14.5%, 95% credible interval [CrI] 11.-17.6% ARB: 13.2%, 95% CrI 10.3-16.0% ACEi or ARB: 15.2%, 95% CrI 13.0-17.5%
					Severe COVID-19 illness	ACEi: 7.8%, 95% CrI 4.5%-11.3% ARB: 9.0%, 95% CrI 5.9-12.2% ACEi or ARB: 9.8%, 95% CrI 7.3-12.3%

| Zhang et al. (2020b) | Retrospective, propensity-matched cohort; multi-center | *Hubei province, China* 1,128 patients with hypertension and hospitalized for COVID-19 | ACEi or ARB use during hospitalization | No ACEi or ARB during hospitalization | 28-day all-cause mortality | HR 0.42 95% CI, 0.19–0.92, p=0.03 |

These observational studies suggest that ACEi/ARB use may be safe, and furthermore possibly beneficial, in patients with COVID-19, although these observational findings may be limited by uncontrolled confounding and bias. RCTs studying the efficacy and safety of ACEi and ARB in patients with COVID-19 are being undertaken, with initial results (discussed below) from BRACE-CORONA and REPLACE-COVID providing reassurance (Cohen et al., 2021, Lopes et al., 2021).

6.2.5. Safety of ACEIs/ARBs

ACEi and ARBs have a generally well-established safety profile as one the most prevalent drug classes prescribed globally. Their most commonly noted adverse effects include cough, hypotension, acute kidney injury, hyperkalemia, and rarely, angioedema. With respect to **ACEi**, c*ough*, typically dry and irritating, usually occurs within one to two weeks of therapy initiation and has an absolute incidence of 11.5% (95% CI 9.5% -13.4%), based on a meta-analysis of 125 RCTs, with a reported discontinuation rate secondary to cough of 2.6% (95% CI 2.4%-2.7%) (Bangalore et al., 2010). Onset of cough is 2.5 fold higher in patients of Asian descent (McDowell et al., 2006). *Hypotension* resulting in symptoms sufficient to discontinue the drug occurs in 1.7% of patients, based on a cohort of patients randomized to ramipril (The ONTARGET Investigators, 2008). Reduction in *glomerular filtration* rates, usually modest in the range of 5-25%, can be observed with ACEI therapy, accompanied by elevations in serum creatinine (The ONTARGET Investigators, 2008). Since ACEi causes vasodilatation of renal efferent arterioles, a reduction in glomerular filtration ratio may be an anticipated physiologic effect. *Hyperkalemia* with a serum potassium of greater than 5.5 mmol/L has an overall incidence of 2% with ACEi use, with a higher risk encountered in patients with chronic renal insufficiency and heart failure (Chang et al., 2016, Reardon and Macpherson, 1998, Sadjadi et al., 2009, The ONTARGET Investigators, 2008). The increase in serum potassium with ACEi is usually mild (0.1-0.3 mmol/L increase above baseline), and rates of drug discontinuation secondary to hyperkalemia are generally low (Weir and Rolfe, 2010). Its management can vary from serial

monitoring of serum potassium levels, down-titrating of ACEi dose, prescription of diuretics or agents to promote gastrointestinal elimination, to ACEI discontinuation (Chang et al., 2016). ACEi use may also rarely result in *angioedema*, with an overall absolute incidence of 0.10-0.70%, of which 20% of cases are life-threatening (Agostoni et al., 1999, Bavishi et al., 2016, Messerli et al., 2018, Miller et al., 2008). Angioedema can present as painless swelling of the face or upper aerodigestive tract with erythema and may occur more often in patients of African ancestry (Bernstein et al., 2017, Messerli et al., 2018). Importantly, its onset can be several hours to years following initial drug administration, and is believed to be incited by the accumulation of bradykinin and substance P (Israili and Hall, 1992, Makani et al., 2012). ACEi-induced angioedema usually resolves within 24-72 hours following ACEi cessation (Zuraw et al., 2013). Discontinuation of the drug alone resolves angioedema in 85% of patients (Cicardi et al., 2004). Management consists of acute upper airway management (including consideration of the need for intubation), and in cases of worsening angioedema, can include pharmacotherapy such as C1 inhibitor concentrate, ecallantide, icatibant, and in some settings, fresh frozen plasma (Bernstein et al., 2017).

ARBs also exhibit a generally robust safety profile (Deppe et al., 2010). The prevalence of *cough* with ARB therapy is an estimated 3.2%, based on meta-analysis of 29 studies examining ARB therapy, with a risk akin to that of placebo (RR 1.01, 95% CI 0.74-1.39) (Caldeira et al., 2012, Matchar et al., 2008). Cough severe enough to prompt drug discontinuation has been observed in 1.1% of patients (The ONTARGET Investigators, 2008). *Hypotension* warranting ARB discontinuation has been observed in 2.7% of patients (The ONTARGET Investigators, 2008). When compared to controls (placebo, usual care, or other antihypertensive agent), ARBs carry a higher risk of hypotension (RR 1.56, 95% CI 1.24–1.97) (Elgendy et al., 2015). G*lomerular filtration* may also be reduced, again due to reductions in efferent arterial tone. For example, elevations in serum creatinine 2-fold or higher have been found to occur in 1.7% in patients receiving telmisartan, with elevations severe enough to drug discontinuation occurring in 0.8% of patients (The ONTARGET Investigators, 2008). The rate of *hyperkalemia*, defined as serum potassium greater than 5.5 mmol/L, with ARB monotherapy was 1.5%, based on a meta-analysis of 2,900 patients with hypertension receiving losartan (Goldberg et al., 1995). A separate meta-analysis of seven RCTs in patients with mild-to-moderate hypertension demonstrated comparable rates of hyperkalemia between the ARB olmesartan and placebo (Puchler et al., 2001). ARBs do not carry an increased risk of angioedema compared to other anti-hypertensive agents, with a weighted incidence of 0.11% (95% CI 0.09-0.13) based on 19 RCTs of patients on ARB therapy, and are comparable in risk to placebo (RR 1.62, 95% CI 0.17-15.79) (Caldeira et al., 2012, Makani et al., 2012). ARBs are considered safe in patients with prior ACEi-related angioedema (Rasmussen et al., 2019).

Importantly, however, much of these safety data derives from ambulatory patients and may not be relevant to patients hospitalized with pneumonia. Among patients who are critically ill due to infection, including viral infection, there is limited safety profile and these agents are often/usually ceased in patients with hypotension due to infection (and the need for vasopressor therapy). These agents may contribute to occurrence of acute kidney injury, particularly in patients who are critically ill or at risk of becoming critically ill. As such, more safety data is needed prior to studying these agents in phase 3 trials of patients with COVID-19. This trial therefore follows a seamless phase 2-phase 3 design, first establishing the safety of ACEi (and other interventions) in this population before proceeding to study efficacy. However, recent safety data on the continuation of ACEi/ARB in patients with COVID-19 has emerged: The BRACE CORONA trial (Lopes et al., 2020) was a Brazilian randomized controlled trial conducted in 659 patients of temporarily stopping ACEi/ARB for 30 days (versus continuing) in patients taking these medications chronically who were hospitalized with confirmed COVID-19. The primary outcome was the number of days alive and out of hospital at 30 days. The average number of days alive and out of hospital was 21.9 days for patients who stopped ACEi/ARBs and 22.9 days for patients who continued (0.95 [95% CI] 0.90 to 1.01, p=0.09). The average difference between groups was -1.1 days (95% CI -2.33 to 0.17). The proportion of patients alive and out of hospital by the end of 30 days in the suspending ACEi/ARB group was 91.8% versus 95% in the continuing group. A similar 30-day mortality rate was seen for patients who continued and suspended the ACE inhibitor/ARB (2.8% versus 2.7%, respectively with a hazard ratio of 0.97). Overall, these data supported safety of ACEi/ARB, and may possibly even suggest a benefit of continuing them although the differences are small.

6.2.6. Concomitant AT1 and CCR2 inhibition

The beneficial anti-inflammatory effects of AT1 receptor blockade may be further potentiated by concomitant targeted blockade of monocyte recruitment in COVID-19. Part of the potentially maladaptive inflammatory cascade in COVID-19 includes the honing of large numbers of monocytes to injured tissue, including lung, via monocyte chemoattractant protein (MCP-1) (Merad and Martin, 2020). While monocytes play a critical role on host defense, there maybe be maladaptive consequences associated with excessive recruitment (Serbina and Pamer, 2006). Their egress from the bone marrow and recruitment in tissues is mediated by CC-chemokine receptor 2 (CCR2) (Merad and Martin, 2020). Higher blood and bronchial alveolar lavage MCP-1 levels are associated with more severe disease in COVID-19 (Huang et al., 2020, Xiong et al., 2020). This relationship was also observed in the 2003 SARS-CoV-1 pandemic (Wong et al., 2004). MCP-1 has previously been associated with severity of inflammatory response in ventilator-assisted pneumonia (VAP) (Li et al.,

2019). Plasma MCP-1 levels were significantly higher in VAP patients who developed ARDS when compared with patients without ARDS, healthy controls, and non-VAP subjects. Additionally, patients with severe COVID-19 have been found to exhibit BAL fluid enriched in CCL2 (MCP1), the ligand for CCR2 (Zhou et al., 2020b). These data suggest that monocyte chemotaxis may be associated with illness severity in COVID-19 pneumonia.

An excessive and dysregulated monocyte response in COVID-19 may be associated with adverse clinical outcomes through several mechanisms such as cytokine release, macrophage activation syndrome, and hypercoagulation (**Figure 2**). Activated macrophages that infiltrate the lung and other target organs arise from circulating monocytes that require CCR2 to mediate their chemotaxis (Merad and Martin, 2020, Serbina and Pamer, 2006). Once activated by CCR2, monocytes differentiate into hyperactivated macrophages that elicit a cytokine release including tumor necrosis factor and interleukin-1 (IL-1), IL-6, and IL-8 amongst others, and consequently, precipitate acute lung injury (Merad and Martin, 2020). Moreover, in such a highly inflammatory milieu, natural anticoagulants such as antithrombin and tissue factor pathway inhibitor are impaired, creating a nidus for the initiation and amplification of local thrombosis (von Bruhl et al., 2012). Pathogen-induced circulating pro-inflammatory stimuli result in the induction of tissue factor membrane expression in both monocytes and organ endothelial cells. This expression of tissue factor initializes the extrinsic coagulation pathway such that fibrin deposition and blood clotting ensues (Merad and Martin, 2020). Taken together, these results suggest that CCR2 inhibition may blunt excessive monocyte recruitment and mitigate associated injurious maladaptive sequalae of tissue inflammation and thrombosis, engendering calls for such therapeutic targeting of monocyte inhibition in COVID-19 (Merad and Martin, 2020).

Figure 2. Proposed mechanisms for monocyte-derived macrophage hyperactivation and hyperinflammation in COVID-19. Reproduced from Merad and Martin (2020).
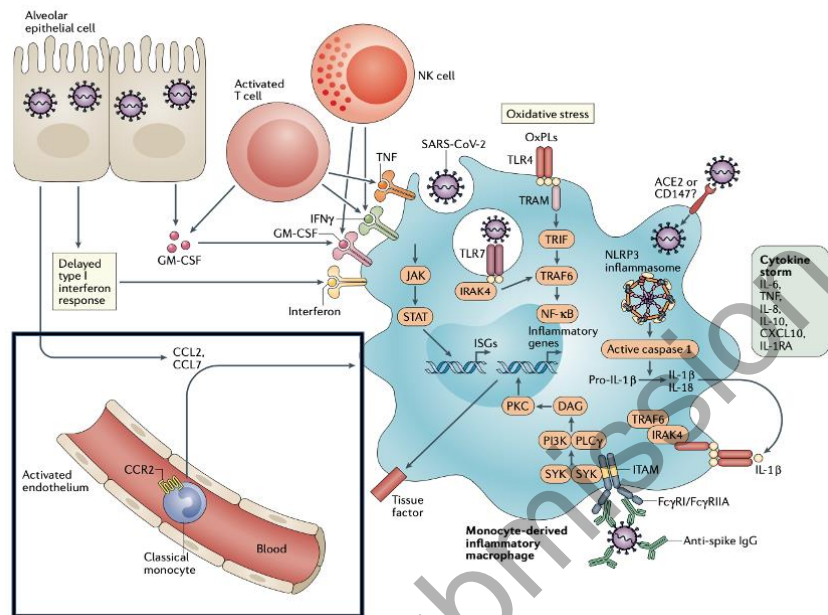
Figure 2. Binding of SARS-CoV-2 to entry receptors on alveolar epithelial cells results in delayed type 1 interferon responses that enhance release of monocyte chemoattractants, thereby promoting monocyte recruitment into the lungs. Via activation of the Janus-kinase signal transducer and activator of transcription (STAT) pathways, monocytes differentiate into macrophages. The macrophages precipitate a cytokine storm via liberation of pro-inflammatory cytokines such as IL-6, TNF, IL-8 and IL-10. *Abbreviations*: CCL, CC-chemokine ligand; CXCL10, CXC-chemokine ligand 10; ISG, interferon-stimulated gene; ITAM, immunoreceptor tyrosine-based activation motif; TRAM, TRIF-related adaptor molecule.

Pre-clinical studies suggest that AT1 receptor and CCR2 may functionally interact on the cell surface, and that concomitant inhibition of these parallel pathways may reduce inflammation and possibly fibrosis in vasculopathy and inflammatory nephropathy models (Ayoub et al., 2015, Ohshima et al., 2012). These receptors can form functional dimer complexes on the cell surface, potentially promoting signaling cross-talk between receptors. The activation G-protein recruitment required for receptor signaling cannot be eliminated unless both receptors are antagonized simultaneously. **DMX-200** (repagermanium; Dimerix) is an oral CCR2 inhibitor currently in phase 2 development for the treatment of diabetic kidney disease and focal segmental glomerulosclerosis. This domain seeks to repurpose DMX-200 to benefit from expected synergy between concomitant blockade of CCR2 and AT1 receptors.

6.2.6.1. *Safety of DMX-200*

The drug substance in DMX-200 is the small molecule known as repagermanium. This is an alternative crystal packing of the same compound propagermanium. Both propagermanium and repagermanium have known existing safety profiles from their use as medicinal products. 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. In short-term treatment of healthy volunteers (N=14) and longer-term treatment (up to 24 weeks) of patients with chronic kidney diseases already receiving an ARB (N=80), no significant safety signals of concern have been observed (**Table 2**).

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 (Hirayama et al., 2003). Adverse reaction onset rate at the time of Serocion® approval was 6.56% (49/747 subjects). The most frequently occurring adverse reactions were elevated aspartate aminotransferase (AST) in 38 subjects (1.89%), elevated alanine aminotransferase (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 adverse reaction, 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 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 (Hirayama et al., 2003).

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 favorable safety profile to date (Table 2). Again, additional disease-relevant safety data is needed before larger outcomes trials may be undertaken.

Table 2. Summary of clinical studies conducted on DMX-200.

Study number & population	Study title	Adverse event profile	Status
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 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 treatment-emergent adverse events (TEAEs) leading to study drug withdrawal, life-threatening TEAEs, or TEAEs leading to death reported during the study.	Complete
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.	Complete
DMX-200-202 N=8 patients with FSGS receiving irbesartan	A Phase 2a, double blinded, randomised, placebo-controlled crossover study evaluating the safety and efficacy of repagermanium in patients with FSGS who are receiving irbesartan	As this study is still ongoing and has not yet been unblinded AEs cannot at this point be attributed to the investigational product. However, safety data has been reviewed by an independent safety monitoring committee throughout the study and the committee has unanimously voted for the study to continue without change to the protocol.	Ongoing (due to be completed in 2020)

DMX-200-203 N=46 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	As this study is still ongoing and has not yet been unblinded AEs cannot at this point be attributed to the investigational product. However, safety data has been reviewed by an independent safety monitoring committee throughout the study and the committee has unanimously voted for the study to continue without change to the protocol.	Ongoing (due to be completed in 2020)

Repagermanium has also been available as a nutritional or dietary supplement since the 1970s in Japan and in other countries including the US and Australia since the 1980s (Kaplan et al., 2004). Incorrect manufacture of repagermanium may lead to a product containing impurities that cause nephrotoxicity and death when used chronically. In 1998 the US Food & Drug Administration (US FDA) introduced an Import Alert to prevent human use of poor-quality germanium containing products. In the following years, an extensive body of evidence has been generated on the safety of pure repagermanium. The developer of DMX-200 has subsequently received confirmation from the US FDA that the method of manufacture, testing, and impurity profile of the US-made pharmaceutical grade repagermanium manufactured at an FDA approved facility and used in the DMX-200 clinical program is appropriate for registration of a drug for chronic use in humans.

6.2.7. Concomitant angiotensin II inhibition with an angiotensin 1-7 analogue (TRV027)

Whilst ACEi and ARB treatment antagonize angiotensin II accumulation, either by inhibiting its production or blocking its access to AT1, they may contribute to angiotensin 1-7 deficiency, as ACEi may further deplete angiotensin 1-7 production as it is a product of angiotensin II, and ARBs may prevent angiotensin 1-7 from binding ATR1, and hence block its beneficial biased agonist actions at this receptor. However, a combination of ACEi with an angiotensin 1-7 analogue may plausibly mitigate both angiotensin II activity and angiotensin 1-7 depletion. An ACEi would reduce angiotensin II formation, and although it would further deplete endogenous angiotensin 1-7, co-administration with an angiotensin 1-7 analogue would restore the beneficial bias agonist signaling at AT1.

TRV027 is a similar peptide to angiotensin 1-7, but is a more potent biased agonist at AT1R than angiotensin 1-7, potently and selectively recruiting β-arrestin to the AT1 while antagonizing Ang II-stimulated Gq activation (Violin et al., 2010). This β-arrestin bias of the ligand translates into unique

downstream signaling, including extracellular signal-regulated kinases 1 and 2 (ERK1/2) phosphorylation and AT1 internalization. Recruitment of β-arrestin by TRV027 stimulates the activation of endothelial cell nitric oxide synthase (eNOS) and prostacyclin production. The combination of inhibition of Ang-II-mediated G-protein activation and activation of eNOS and prostacyclin production may contribute to the in vivo vasodilatory properties of TRV027.

6.2.7.1. *Safety of TRV027*

Nonclinical safety pharmacology and toxicology studies have shown that TRV027 is compatible with blood, non-genotoxic, and that continuous IV infusions up to 14 days duration are well tolerated. The no observed adverse effect level (NOAEL) in 2-week continuous IV infusion studies in rats and dogs was 500 µg/kg/min, the highest dose tested. Measured TRV027 plasma concentrations at the NOAEL dose in rats and dogs were approximately 20-times higher than extrapolated steady-state plasma concentrations in humans administered the highest Phase 2 clinical dose of 25 mg/hr.

TRV027 has been studied in healthy volunteers (n=20) and in three studies in patients with heart failure. In the FTIH study (NCT01514578), a dose range of 0.01 to 20 µg/kg/min for 4 hours (2.4 to 4800 µg/kg) was studied in 20 healthy subjects; the highest dose was expected to be approximately 20-fold higher than the efficacious dose in acute decompensated heart failure (ADHF) patients. All AEs reported were mild and transient. There were three AEs, in two subjects, that were considered possibly related to study drug: mild fatigue, and mild dizziness and paresthesia. All resolved within 2 hours without medical intervention. There were no deaths, no SAEs, and no AEs that led to discontinuation from the study. There were no clinically significant changes in laboratory findings, vital signs (heart rate, blood pressure, oxygen saturation, respiratory rate and temperature), ECGs or physical examinations.

Study CP120027.1002 enrolled 17 patients with heart failure and renal dysfunction. Each patient received both placebo and a dose (1.25-31.25 mg/hr) of TRV027 as a 6.5 hr continuous infusion (NCT01444872). All AEs reported in this study were mild or moderate in nature. There were no serious adverse events or clinically significant adverse events reported.

In CP120027.2001, 33 patients with NYHA class 3-4 heart failure and a clinical indication for right-heart catheterization received either a dose regimen of TRV027 or volume-matched placebo (NCT01187836). The doses studied were as follows:

- Cohort 1: 0.1, 0.2, 0.4, 0.7 µg/kg/min each for 1 hour over hours 1-4, followed by 1 µg /kg/min for 10 hours

- Cohorts 2 and 4: 0.3, 0.6, 1.2, 2.4 µg/kg/min each for 1 hour over hours 1-4, followed by 3 µg/kg/min for 10 hours

- Cohort 3: 1, 2, 4, 8 µg/kg/min each for 1 hr over hours 1-4, followed by 10 µg/kg/min for 10 hours.

There were no serious adverse events attributed to TRV027 treatment. In the first cohort, one subject experienced hypotension necessitating dose reduction and then discontinuation of the study drug infusion. No other TRV027-related clinically significant adverse events were reported.

In the CP120027.2002 study (n= 621 patients with ADHF) which used doses ranging from 1-25 mg/hr for 48-96 hours, no safety issues were identified that affected the safety of trial subjects (NCT01966601). There was no difference from placebo in non-serious and serious treatment-emergent adverse events, events leading to discontinuation, or deaths.

In a small (n=29) experimental medicine study in hospitalized patients admitted with COVID-19 comparing 7 days treatment with TRV027 (12mg/hr continuous IV infusion) or placebo (NCT04419610), there was no difference from placebo in non-serious and serious treatment-emergent adverse events, events leading to discontinuation, or deaths.

6.2.7.2. Pharmacokinetics and Dose Rationale of TRV027

The pharmacokinetics of TRV027 has been studied in healthy volunteers, in patients with stable mild/moderate heart failure, patients with stable NYHA class III/IV CHF, and in 621 adults with ADHF. The clearance of TRV027 is rapid (ranging between 51.3-127 L/hr) and exhibits a short half-life (4.2-15.8 minutes). Heart failure, sex, or renal dysfunction had no significant effect on the clearance of TRV027. TRV027 is not metabolized by, nor does it inhibit any of the CYP450 enzymes. The plasma protein binding of TRV027 is low at 53.4%.

TRV027 has been studied in patients with acute heart failure in doses ranging from 1.25 – 31.25 mg/hr. Using in vitro-derived AT1 receptor binding data as well as population PK data in healthy volunteers, simulations were performed to explore a range of doses of TRV027 which might be expected to result in at least 80% receptor occupancy, correcting for protein binding. The results (**Figure 3**) suggest that 12 mg/hr will result in median receptor occupancy well in excess of 80%. This dose is in the mid-range of what has been studied clinically and is expected to be well-tolerated.
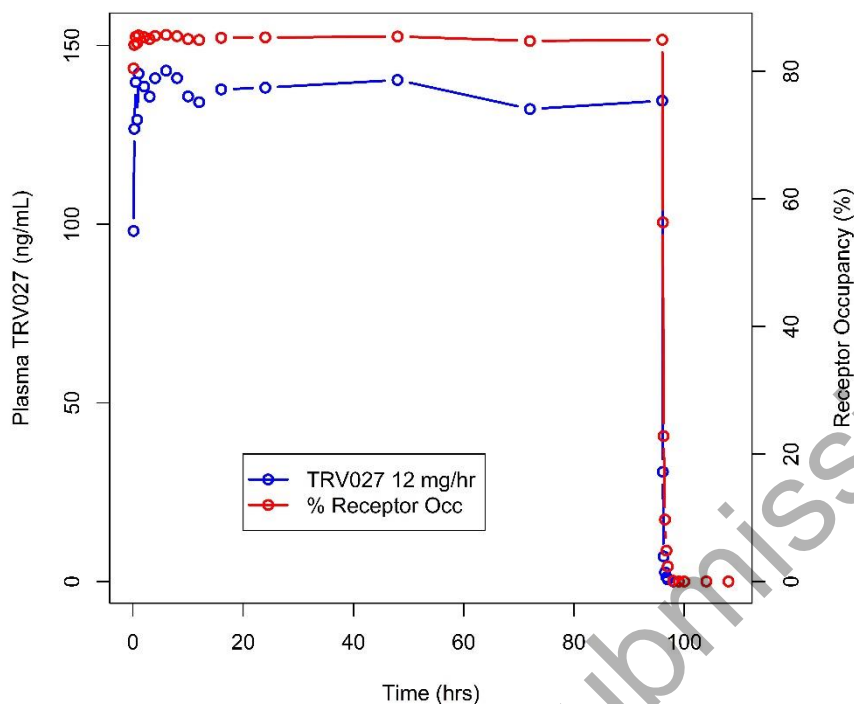
Figure 3. Estimation of the median AT1R receptor occupancy resulting from TRV027 given at a dose of 12 mg/hr for 96 hours.

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of strategies inhibiting the renin-angiotensin system, including in combination with CCR2 inhibition, for patients with acute illness due to suspected or proven COVID-19 infection.

We hypothesize that the probability of occurrence of the primary endpoint specified in the relevant core protocol documents will differ based on the allocated RAS inhibition strategy. The following interventions will be available:

- No RAS inhibitor
- ACEi
- ARB
- ARB + DMX-200
- ACEi + TRV-027

We hypothesize that the treatment effect of RAS inhibition is different depending on whether SARS-CoV-2 infection is confirmed to be present or absent.

We hypothesize that the treatment effect of RAS inhibition is different depending on the illness severity state at the time of enrollment.

8. TRIAL DESIGN

This domain will be conducted as part of the REMAP-CAP trial. Treatment allocation proportions will not be adaptive, although this may be revised if the ARB + DMX-200 and ACEi + TRV-027 interventions are withdrawn from the domain.

8.1. *Phases of evaluation*

This domain permits a seamless Phase 2-Phase 3 design using the same REMAP primary end-point (a composite of in-hospital mortality and provision of organ failure support while admitted to an ICU in the 21 days following randomization). In the initial Phase 2, evidence of efficacy and safety will be evaluated during enrollment of a fixed sample size (which varies between interventions). A decision to proceed from phase 2 to phase 3 will be dependent on meeting a pre-specified statistical trigger, comprising a greater than 0.5 probability of a more than 20% (for the ACEi and ARB interventions compared to no RAS inhibitor) or 30% (for the ARB + DMX-200 intervention compared to ARB alone and compared to no RAS inhibitor; and also for the ACEi + TRV-027 intervention compared to ACEi alone and compared to no RAS inhibitor) improvement in odds ratio for the primary endpoint in the absence of an unsatisfactory safety profile, as judged by the DSMB. The lower threshold for graduation and larger maximum sample size for the ACEi and ARB interventions reflects these agents being widely available, and as such, even a small clinical benefit may be practice changing. One or more active interventions may graduate into the subsequent Phase 3 component in which interventions are evaluated using the primary end-point for superiority, efficacy, equivalence, and futility.

The domain will commence using open-label administration of all active interventions. Blinding of one or more interventions may be considered later but, if this occurs, this will be specified by a protocol amendment. If blinding is applied, this may be instituted before or after graduation of an intervention to phase 3. While it is not intended that Public Disclosure of outcome of phase 2 will occur (unless an intervention stops for futility in phase 2), this is not precluded. However, if Public Disclosure of one or more intervention occurs, recommencement in phase 3 will occur with a

noninformative prior and without incorporation of patients enrolled to this intervention being included in the statistical model used to evaluate the intervention at phase 3.

8.2. *Population*

REMAP-CAP enrolls patients with acute illness due to suspected or proven COVID-19 admitted to hospital, including patients admitted to ICU.

8.3. *Eligibility Criteria*

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria as specified in either the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID protocol. Patients otherwise eligible for REMAP-CAP may have conditions that exclude them from the COVID-19 ACE2 RAS Domain.

This domain is available for patients who have acute illness due to suspected or proven pandemic infection in both the Moderate State and the Severe State.

8.3.1. Domain inclusion criteria

Patients are eligible for this domain if:

- COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing (i.e., PISOP stratum)
- Microbiological testing for SARS-CoV-2 of upper or lower respiratory tract secretions or both has occurred or is intended to occur

8.3.2. Domain exclusion criteria

Patients will be excluded from this domain if they have any of the following:

- If in the Moderate State, more than 96 hours has elapsed since hospital admission.
- If in the Severe State, more than 48 hours has elapsed since ICU admission, unless the patient has already been assigned a treatment in another domain in the Moderate State in which case exclusion will occur if more 48 hours has elapsed since commencement of sustained organ failure support in an ICU.

- Patient is already receiving, or a clinical decision has been made to commence, an ACEi, ARB, direct renin inhibitor, angiotensin-receptor-neprilysin inhibitor, or chemokine receptor modulator.

- Long-term therapy prior to this hospital admission with one or more of ACEi, ARB, direct renin inhibitor, or angiotensin-receptor-neprilysin inhibitor, or chemokine receptor modulator.

- Hypersensitivity to ACEi or ARB, including any history of angioedema.

- Treating clinician believes that administration of ACEi or ARB is inappropriate because of risk for:
  - Clinically relevant hypotension or escalation of vasopressor requirements
  - Hyperkalemia

- Known severe renal artery stenosis

- Known or suspected pregnancy or breast feeding

- Renal impairment with creatinine clearance <30ml/min or receiving renal replacement therapy.

- Enrollment in a trial evaluating ACEi, ARB, or other RAS modulator, or any targeted chemokine receptor modulation for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial.

- If the domain is available at this site in the Moderate State and the patient is being assessed in the Severe State, prior assessment for this domain in the Moderate State.

- The treating clinician believes that participation in the domain would not be in the best interests of the patient.

8.3.3. Intervention exclusion criteria

Patients may also be excluded from receiving one or more interventions within the domain for patient-specific reasons. Patients are eligible for this domain if, after application of intervention-level exclusions, the patient is eligible to receive at least one active intervention. In such cases, patients will be randomly allocated to a remaining intervention from among those available at that site. Patients in whom all interventions are contraindicated will be treated according to the current standard of care at the clinician's discretion.

Criteria that exclude a patient from one or more interventions are:

- Known severe liver disease or an alanine aminotransferase (ALT) or an aspartate aminotransferase (AST) that is more than five times the upper limit of normal will result in exclusion from receiving ARB + DMX-200.

- Known viral hepatitis will result in exclusion from receiving ARB + DMX-200.

- Hypersensitivity to repagermanium will result in exclusion from receiving ARB + DMX-200.

- Hypersensitivity to TRV-027 will result in exclusion from receiving ACEi + TRV-027.

8.4. *Interventions*

8.4.1. Domain interventions

Patients will be randomly assigned to receive one of the following open-label strategies. All interventions will be commenced immediately after allocation status is revealed.

□ No RASi

□ ACEi

□ ARB

□ ARB + DMX-200

□ ACEi + TRV-027

8.4.2. No RAS inhibition

Patients allocated to the *no RAS inhibition* intervention are not to receive any RAS inhibitor (no ACEi or ARB) up until the end of study day 10. There is no administration of placebo. Should patients in the control group develop hypertension necessitating treatment during the study period, the preference is for non-ACEi/ARB interventions where deemed clinically appropriate. Initiation of an ACEi/ARB if deemed the most clinically appropriate is permitted but will be considered a protocol deviation. The open label design is better suited to the domain than a placebo control group given difficulties blinding ACEi or ARB due to the readily observable physiologic effects (most notably on blood pressure) of these drugs and for the clinician to know the treatment assignment so as to interpret occurrence of one or more of hypotension, hyperkalemia, and renal impairment. Furthermore, the titration tables (below) are proposed to optimize therapeutic efficacy and participant safety; such a titration algorithm would be impractically paired with a placebo control.

8.4.3. ACEi intervention

Patients may be randomly assigned to receive one of several ACEi. This is a pragmatic trial and several agents are permitted to match the varying patterns of local drug availability. However, within a site, the preferred agent must be pre-specified. Furthermore, a hierarchy of choices is specified in **Table 3**; study sites will consider the agent with which they have the greatest local familiarity and access, choosing from options in descending order in **Table 3**. The agent selected by a study site should not change, unless drug supply or other considerations compel this. Sites will also be asked to provide a back-up agent, in the event that the first choice becomes unavailable during the trial.

8.4.3.1. *ACEi Dosing*

ACEi are widely used and clinician familiarity should be high. Initial and subsequent dosing of ACEi should be determined clinically, but is generally titrated to the maximally-tolerated dose based on hemodynamics. A table of possible dosing schedule is provided as guidance (**Table 3**), but final dose titration strategy is left to the treating physician. Consideration of dose-reduction or holding other prior antihypertensive agents to facilitate hemodynamic margin for ACEi up-titration may be undertaken, at the discretion of the treating team. The following reasons should prompt consideration of discontinuation of therapy, with recommencement when clinically appropriate:

- Hyperkalemia (serum potassium >5.5 mmol/L). However absolute and relative change in serum potassium should be interpreted in conjunction with urine output and change in serum creatinine.

- Significant renal impairment (eGFR < 15 ml/min/1.73 m2 or the new initiation of renal replacement therapy/dialysis), or deteriorating renal function (>50% increase in creatinine in 48 hours)

- Significant exposure to other nephrotoxic agents (including intravenous iodinated contrast medium), noting that exposure to other nephrotoxic agents should only occur if no acceptable alternative exists

- Clinically-relevant hypotension, including need for significant escalation in therapies (e.g., initiation of vasopressor when not previously required)

- Occurrence of angioedema

The below provides a hierarchy for possible ACEi. Each site should select the agent, from the descending hierarchy, with the greatest local familiarity and access. Example dosing schedules and titration is provided. These criteria are largely intended for titration in patients in the Moderate State. In patients in the Severe State receiving vasopressors, ACEi may be administered and titrated based on physician judgement including accepting the use of vasopressors or adjustment of vasopressor dose to permit administration of the ACEi. Physician concern that the administration of an ACEi at any time in any patient may result in clinically-relevant hypotension associated with an increased risk of death or the need for significant escalation of care should prompt the holding of the study drug.

Table 3. Hierarchy of choice, and example dosages for available ACEi therapy (Dalpoas and Samal, 2017, Dalpoas et al., 2017, Bicket, 2002).

		Starting dosage	Titration				
		SBP <120 mmHg	If SBP >120 mmHg ***	Physician concern that ACEi will result in clinically relevant hypotension†	If SBP >95 but <105mmHg	If SBP >105mmHg, but <120mmHg	If SBP >120mmHg	Maximum dose
ACEi								
First Choice								
Ramipril	2.5 mg daily	5 mg daily	Hold dose*	Decrease dose by 50%	Continue same dose	Increase dose by 100%*	10 mg daily
Second Choice								
Lisinopril	5 mg daily	10 mg daily	Hold dose*	Decrease dose by 50%	Continue same dose	Increase dose by 100%*	20 mg daily
Third Choice								
Perindopril	2 mg daily	4 mg daily	Hold dose*	Decrease dose by 50%	Continue same dose	Increase dose by 100%*	8 mg daily
Fourth Choice								
Enalapril	2.5 mg daily	5 mg daily	Hold dose*	Decrease dose by 50%	Continue same dose	Increase dose by 100%*	20 mg daily
Fifth Choice								

Trandolapril	1 mg daily	2 mg daily	Hold dose*	Decrease dose by 50%	Continue same dose	Increase dose by 100%*	4 mg daily
Optional Consideration							
Captopril**	6.25 mg three times daily	12.5 mg three times daily	Hold dose*	Decrease dose by 50%	Continue same dose	Increase dose by 100%*	50 mg three times daily

SBP: systolic blood pressure. All medications administered orally.

Note: Intravenous enalapril (enalaprilat) is not considered an acceptable study drug.

† Clinically relevant hypotension or hypotension requiring a major escalation of intensity of treatment (e.g., the initiation of vasopressors).

*Up to maximum dose.

**Captopril may be favored in patients in the ICU given that its shorter half-life may allow more frequent titration, although more first-dose hypotension may be a theoretical concern.

***A patient with hypertension may receive a higher dose on the first day than specified in the table.

8.4.4. ARB intervention

Patients may be allocated to receive one of several ARBs. This is a pragmatic trial and several agents are permitted to match the varying patterns of local drug availability. However, within a site, the preferred agent must be pre-specified. Furthermore, a hierarchy of choices is specified in **Table 4**; study sites will consider the agent with which they have the greatest local familiarity and access, choosing from options in descending order in **Table 4**. The agent selected by a study site should not generally change, unless drug supply or other considerations compel this. Sites will also be asked to provide a back-up agent, in the event that the first choice becomes unavailable during the trial.

8.4.4.1. *ARB Dosing*

ARBs are widely used and clinician familiarity should be high. Initial and subsequent dosing of ARB should be determined clinically, but is generally titrated to the maximally-tolerated dose based on hemodynamics. A table of possible dosing schedule is provided as guidance (**Table 4**), but final dose titration strategy is left to the treating physician. Consideration of dose-reduction or holding other prior antihypertensive agents to facilitate hemodynamic margin for ARB up-titration may be undertaken, at the discretion of the treating team. The following reasons should prompt consideration of discontinuation of therapy, with recommencement when clinically appropriate:

- Hyperkalemia (serum potassium >5.5 mmol/L). However absolute and relative change in serum potassium should be interpreted in conjunction with urine output and change in serum creatinine.

- Significant renal impairment (eGFR < 15 ml/min/1.73 m2 or the new initiation of renal replacement therapy/dialysis), or deteriorating renal function (>50% increase in creatinine in 48 hours)

- Significant exposure to other nephrotoxic agents (including intravenous iodinated contrast medium) noting that exposure to other nephrotoxic agents should only occur if no acceptable alternative exists

- Clinically-relevant hypotension, including physician-perceived risk of death or risk of need for significant escalation in therapies (e.g., initiation of vasopressor when not previously required)

The below provides a hierarchy for possible ARB. Each site should select the agent, from the descending hierarchy, with the greatest local familiarity and access. Example dosing schedules and titration is provided. These criteria are largely intended for titration in patients in the Moderate State. In patients in the Severe State receiving vasopressors, ARB may be administered and titrated based on physician judgement, including accepting the use of vasopressors or adjustment of vasopressor dose to permit administration of the ARB. Physician concern that the administration of an ARB at any time in any patient may result in clinically-relevant hypotension associated with an increased risk of death or the need for significant escalation of care should prompt the holding of the study drug.

Table 4.Hierarchy of choice, and example dosages for commonly used ARB therapy (Bicket, 2002, Dalpoas and Samal, 2017, Dalpoas et al., 2017).

	Starting dosage		Titration based on every other day SBP assessment				
	SBP <120 mmHg	If SBP >120 mmHg	Physician concern that ARB will result in clinically relevant hypotension†	If SBP >95 but <105mmHg	If SBP >105mmHg, but <120mmHg	If SBP >120mmHg	Maximum dose
ARB							
First Choice							

Losartan	25mg daily	50mg daily	Hold dose*	Decrease dose by 50%	Continue same dose	Increase dose by 100%*	50mg daily
Second Choice							
Valsartan	80 mg daily	160 mg daily	Hold dose*	Decrease dose by 50%	Continue same dose	Increase dose by 100%*	160mg daily
Third Choice							
Candesartan	4mg daily	8mg daily	Hold dose*	Decrease dose by 50%	Continue same dose	Increase dose by 100%*	16mg daily
Fourth Choice							
Irbesartan	75mg daily	150mg daily	Hold dose*	Decrease dose by 50%	Continue same dose	Increase dose by 100%*	150mg daily
Fifth Choice							
Telmisartan	20mg daily	40mg daily	Hold dose*	Decrease dose by 50%	Continue same dose	Increase dose by 100%*	40mg daily
Sixth Choice							
Olmesartan	10mg daily	20mg daily	Hold dose*	Decrease dose by 50%	Continue same dose	Increase dose by 100%*	20mg daily

SBP: systolic blood pressure. All medications administered orally.

†Clinically relevant hypotension or hypotension requiring a major escalation of intensity of treatment (e.g., the initiation of vasopressors).

*Up to maximum dose.

8.4.5. Combination CCR2 inhibition and ARB intervention

Patients allocated to the ARB+CCR2 inhibitor intervention arm will receive the DMX-200 (repagermanium) investigational medicinal product administered concurrently with an ARB as per the ARB inhibition treatment arm (8.4.4) with concurrent DMX-200.

8.4.5.1. *Combination CCR2 inhibitor (DMX-200) and ARB dosing*

DMX-200 will be administered by the enteral route at a dose of 120 mg twice daily. The preferred method of administration is oral capsules but if oral delivery is not possible the contents of the

capsule can be dissolved in water and administered via an enteral tube. No titration of DMX-200 is required. Dosing of the ARB is as above (**Table 4;** Section 7.3.4.1). Consideration of temporary discontinuation of ARB therapy should occur as in the ARB intervention above (section 7.3.4.1); in these circumstances, the ARB should be discontinued, but DMX-200 should continue to be administered (without ARB). By contrast, the development of liver failure, or if the ALT or AST are more than 5 times the ULN, or other SUSAR felt attributable to the study drugs, should prompt the permanent discontinuation of both the ARB and DMX-200.

8.4.6. Combination angiotensin 1-7 and ACEi intervention

Patients allocated to the ACEi+TRV-027 intervention arm will receive the TRV-027 investigational medicinal product administered concurrently with an ACEi as per the ACEi inhibition treatment arm (8.4.3).

8.4.6.1. *Combination ACEi and TRV027 dosing*

TRV-027 will be prepared by dilution in normal saline. To prepare the infusion, withdrawal of 28.8 mL of normal saline from a 250 mL normal saline bag is undertaken, followed by replacement with 28.8 mL of TRV-027. This is then administered by continuous intravenous infusion at 11 mL/hour (corresponding to 12 mg/hour). No titration of the TRV-027 infusion is required. Dosing of the ACEi is as above (section 8.4.3.1). Consideration of temporary discontinuation of ACEi therapy should occur as in the ACEi intervention above (section 8.4.3.1); in these circumstances, the ACEi should be discontinued, but TRV-027 may continue to be administered (without ACEi). If hypotension continues or worsens then consideration of temporary discontinuation of TRV-027 should also be considered. By contrast, the development of a SUSAR felt attributable to the study drugs should prompt the permanent discontinuation of both the ACEi and TRV-027.

8.4.7. Duration of RAS inhibition therapy

The duration of all interventions is the same. Patients assigned to an active intervention are to receive the allocated intervention until the end of study day 10 or hospital discharge, whichever occurs first.

Temporary or permanent cessation of the study interventions for any of the reasons specified above is not a protocol deviation.

Guidance for the clinical approach to the management of hypotension, hyperkalemia, and renal impairment will be provided in an operational document.

8.4.8. COVID-19 RAS strategy in patients negative for COVID-19 infection

In patients with suspected COVID-19 infection who receive an allocation status to receive an active intervention but who subsequently test negative for COVID-19 infection may have treatment ceased unless the treating clinician believes that doing so is not clinically appropriate. This decision should take into account the known or suspected local population incidence of COVID-19 infection among hospitalized patients and sensitivity of testing for COVID-19 infection.

8.5. *Concomitant care*

Additional agents, other than those specified in the platform, that are intended to modify the patient's renin-angiotensin system function as a treatment for COVID-19 should not be administered. All other treatment that is not specified by assignment within the platform will be determined by the treating clinician.

8.6. *Endpoints*

8.6.1. Primary endpoint

The primary endpoint for this domain is the REMAP primary outcome as specified in the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol. This will serve as the primary endpoint for both the Phase 2 and Phase 3 components.

8.6.2. Secondary endpoints

All secondary endpoints as specified in the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol.

The domain-specific secondary outcome measures (from randomization, during the index hospitalization, censored 90 days after enrollment) will be:

- acute kidney injury defined as KDIGO Stage ≥2 acute kidney injury:
  - stage 2: serum creatinine increase 2-3x from baseline within 7 days and also within 14 days
  - stage 3: serum creatinine increase ≥3x from baseline within 7 days and also within 14 days, or increase in serum creatinine by ≥0.5 mg/dL (44 mmol/L) to ≥4 mg/dL (353.6 µmol/L), or initiation of renal replacement therapy
- change from baseline to peak creatinine
- angioedema

- change in baseline to peak available AST, ALT, and bilirubin during the treatment period (14-day peak; these should be performed at a minimum once within blocks of post-randomization days 1-5, 6-10, and 11-14; preferably these should be from standard of care labs, and if not available should be checked at least once within each of these time blocks)

- clinically relevant hypotension while admitted to a ward (defined as one or more episodes of clinically relevant hypotension while admitted to a ward; clinically relevant hypotension includes hypotension that triggers medical emergency/rapid response team activation, hypotension that requires ICU admission, > 500mL fluid administration in less than one hour, or administration of vasopressor or inotrope) through 14 days after randomization

- in the ARB + DMX-200 and ACEi + TRV-027 interventions only:

  o occurrence of suspected unexpected serious adverse reactions (SUSAR).

- serious adverse events as defined in relevant core protocol documents and this DSA

It is noted that Organ Failure Free Days (OFFDs), which includes both vasopressor and renal replacement free days, censored at 28 days are a platform-level secondary end-point that will be available in this domain and applied as a specific safety secondary end-point in this domain.

Regarding potential for hypotension and resultant potential need for vasopressors, the investigators hypothesize that there may be a treatment-related increase in exposure to vasopressors, particularly in severe patients, but that this hazard may be offset by other benefits of the therapy in regards to reduction in exposure to other organ failure support and death such that there remains a net clinical benefit.

9. TRIAL CONDUCT

9.1. *Microbiology*

Sites that are participating in this domain are encouraged to also participate in the Clinical Characterization Protocol (CCP) for patients with COVID-19 that has been established by the International Severe Acute Respiratory and Emerging Infectious Consortium (https://isaric.tghn.org/CCP/). This protocol specifies the collection of biological samples from patients with COVID-19. Samples collected in patients who are enrolled in the CCP may be made available to REMAP-CAP investigators to evaluate aspects of host or pathogen biology associated with assignment in this domain. Ethical approval at such sites and agreement from patients to undertake the CCP will be obtained separately.

9.2. *Domain-specific data collection*

Additional domain-specific data will be collected:

- Administration of ACEi, ARB, ARB + DMX-200, and ACEi + TRV-027 as per study protocol (including daily doses)
- Baseline and peak creatinine
- Occurrence of angioedema
- Baseline and peak AST, ALT, and bilirubin
- Clinically relevant hypotension while admitted to a ward
- SUSARs (for patients allocated to the ARB + DMX-200 and ACEi + TRV-027 interventions)

9.3. *Criteria for discontinuation*

Refer to relevant core protocol documents for criteria for discontinuation of participation in the REMAP-CAP trial.

9.4. *Blinding*

9.4.1. Blinding

All medications will be administered on an open-label basis.

9.4.2. Unblinding

Not relevant.

10. STATISTICAL CONSIDERATIONS

10.1. *Domain-specific stopping rules*

This domain permits a seamless phase 2 to phase 3 design with pre-specified 'stop-go' rules to determine if the domain progresses from phase 2 to phase 3. The same primary REMAP end-point (a composite of in-hospital mortality and days of provision of organ-failure support while admitted to an ICU in the 21 days following randomization), is used in both phase 2 and phase 3.

10.1.1. Stopping and graduation rules during phase 2

During phase 2, a 'stop-go' decision for efficacy will be applied at series of interim analyses; for each intervention, the first of these interim analyses will occur as soon as possible after a minimum of 50 patients have been assigned to that intervention, and then will occur at the time of regular adaptive analyses, with the aim of occurring approximately monthly thereafter. These 'stop-go' rules are applied separately within patients in the Moderate and Severe States, although borrowing across states will permit statistical sharing of observations between states if treatment effects are similar. There are three mutually exclusive outcomes at each interim analysis:

- Graduate to phase 3. For the ACEi and ARB interventions, graduation can only occur after assignment of at least 100 patients to that intervention and will occur if the posterior probability of a greater than 20% improvement in odds ratio is higher than 0.5 compared with the 'no RAS inhibitor' control (i.e., efficacy not domain superiority). For the ARB + DMX-200 intervention, graduation can only occur after assignment of at least 100 patients and will occur if the following are true: 1) posterior probability of a greater than 30% improvement in odds ratio is higher than 0.5 in the ARB + DMX-200 compared with the ARB intervention as a control (i.e., efficacy compared to ARB alone, not domain superiority) AND 2) posterior probability of a greater than 30% improvement in odds ratio is higher than 0.5 in the ARB + DMX-200 compared with the 'no RAS inhibitor' intervention. For the ACEi + TRV-027 intervention, graduation can only occur after assignment of at least 100 patients and will occur if the following are true: 1) posterior probability of a greater than 30% improvement in odds ratio is higher than 0.5 in the ACEi + TRV-027 compared with the ACEi intervention as a control (i.e., efficacy compared to ACEi alone, not domain superiority) AND 2) posterior probability of a greater than 30% improvement in odds ratio is higher than 0.5 in the ACEi + TRV-027 compared with the 'no RAS inhibitor' intervention.

- Withdraw intervention and not proceed to phase 3. Withdrawal of an intervention will occur if there is evidence of futility, defined as the posterior probability of a more than 20% improvement in odds ratio being less than 0.05 or, if at the maximum available sample size for that intervention, the posterior probability of a more than 20% (ACEi/ARB) or 30% (ARB + DMX-200/ACEi + TRV-027) improvement in odds ratio is less than 0.5 compared with the pre-specified paired control group (lack of efficacy).

- Retain intervention. At any interim that occurs prior to the sample size cap for an intervention being reached, if neither the criteria for graduation nor the criteria for withdrawal are met, then the intervention is retained.

The 'stop-go' rules are applied at the level of an intervention (i.e., one or more interventions may have graduated from phase 2 to phase 3, while other interventions active in the domain remain at phase 2).

In the event that the ARB or 'no RAS inhibitor' interventions are withdrawn when ARB + DMX-200 is in phase 2, the graduation criteria for the ARB + DMX-200 intervention will be based only on comparison with the retained comparator (ARB or 'no RAS inhibitor' – but no longer both). In the event that the ACEi or 'no RAS inhibitor' interventions are withdrawn when ACEi + TRV-027 is in phase 2, the graduation criteria for the ACEi + TRV-027 intervention will be based only on comparison with the retained comparator (ACEi or 'no RAS inhibitor' – but no longer both). Decisions to graduate from phase 2 to phase 3 are hence based only on the treatment effect relative to the relevant concurrently active comparator. The use of a single comparator only arises in the event that one of the two comparators is dropped. In the event of graduation from phase 2 to phase 3, the treatment effect in phase 3 is evaluated as per below. In the unlikely event that both either the ARB or ACEi *and* no RAS inhibitor control groups are dropped (the latter of which could only happen in phase 3 for efficacy or superiority of ARB or ACEi), then the remaining intervention would be implied as the new standard of care based on the phase 3 evaluation and the results of the remaining ARB + DMX-200 or ACEi + TRVB-027 interventions compared with this active new standard of care comparator. It is also acknowledged that, although the above represents the framework for graduation decisions, analyses with all available comparators, possibly accounting for the effects of time, will be presented in the final report.

The following sample size caps will be applied with the cap being operationalized at the first adaptive analysis that occurs after the maximum sample size has been attained:

- ACEi = 300 patients
- ARB = 300 patients
- ARB + DMX-200 = 200 patients
- ACEi + TRV-027 = 200 patients

It is noted that if one or more of these sample size caps are applied, that the total sample size will be slightly larger than the specified cap and may also include patients who continue to be randomized until the results of the first adaptive analysis that occurs after the cap is attained are available to the DSMB.

The selection of these sample sizes is based on simulations which are available as an appendix. The rationale for a larger maximum sample size for the ACEi and ARB interventions is that these drugs are not expensive and are widely available, providing a rationale for tolerating a smaller risk of type II error.

An intervention can be withdrawn for safety end-points, at the discretion of the DSMB, at any time including after any interim analysis. The safety end-points that will be evaluated are:

- commencement of renal replacement therapy (dialysis)

- administration of vasopressors (evaluated using vasopressor-free days at 21 days)

- clinically relevant hypotension while admitted to a ward

- reported SAEs

- In the ACEi intervention only:
  - angioedema

- in the ARB + DMX-200 intervention only:
  - change in baseline to peak available AST, ALT, and bilirubin during the treatment period

- in the ARB + DMX-200 and ACEi + TRV-027 intervention:
  - occurrence of SUSARs

The decision to withdraw an intervention for safety reasons is not pre-specified but is based on recommendation by the DSMB which should take into account the clinical significance of the safety end-point and be interpreted in conjunction with any observed treatment effect on the primary end-point.

For example, as noted above, the investigators hypothesize that there may be a treatment-related increase in exposure to vasopressors, particularly in severe state patients, but that this hazard may be offset by other benefits of the therapy in regards to reduction in exposure to other organ failure support and death such that there remains a net clinical benefit; the DSMB will review the totality of evidence at each interim. The safety end-points are of particular importance during phase 2, but continue to be relevant to considerations of the DSMB during phase 3.

During phase 2, the 'stop-go' criteria are the only criteria that are evaluated as statistical triggers, i.e. statistical triggers that would otherwise lead to a platform conclusion are not permitted during phase 2 and only become evaluated following the first interim analysis after an intervention graduates from phase 2 to phase 3. However, all patients recruited to an intervention during phase 2 contribute to the phase 3 analyses (unless there is Public Disclosure of phase 2 results for an

intervention, in which case no patients from the phase 2 component are included in the statistical model used to evaluate that intervention at phase 3 and the intervention will commence with a non-informative prior).

10.1.2. Stopping rules during phase 3

Within this domain the following Platform Conclusions are possible during phase 3:

- Inferiority (No RAS inhibitor only)

- Efficacy (all active interventions in comparison with no RAS inhibitor, ARB + DMX-200 in comparison with ARB alone, and ACEi + TRV-027 in comparison to ACEi alone); however, if the 'no RAS inhibitor' or ARB is dropped, then efficacy of the ARB + DMX-200 intervention is primarily evaluated relative only to the retained comparator intervention ('no RAS inhibitor' or ARB), while if the 'no RAS inhibitor' or ACEi is dropped, then efficacy of the ACEi + TRV-027 intervention is evaluated relative only to the retained comparator intervention ('no RAS inhibitor' or ACEi)

- Superiority (among all interventions)

- Futility (all active interventions in comparison with no RAS inhibitor and, if the no RAS inhibitor intervention was dropped, ARB + DMX-200 in comparison with ARB alone and ACEi + TRV-027 in comparison with ACEi alone)

- Equivalence (among all active interventions)

If a Platform Conclusion of equivalence in the primary endpoint is demonstrated the DSMB and the ITSC may consider continuation of randomization if clinically relevant differences in secondary endpoints have not been demonstrated and it is considered plausible that clinically relevant differences in one or more secondary endpoints may be capable of being demonstrated. In all other respects the stopping rules for this domain are those outlined in the relevant core documents.

10.2. *Unit-of-analysis and strata*

Response adaptive randomization will not be conducted in this domain, as long as the ARB + DMX-200 and ACEi + TVR-027 interventions are retained. All interventions will be assigned equally but response adaptive randomization may be instituted if the ARB + DMX-200 and ACEi + TRV-027 interventions are dropped. The blinded International Trial Steering Committee will determine whether response adaptive randomization is implemented if the ARB + DMX-200 and ACEi + TRV-027 interventions are dropped from the domain. Such a decision may take into account the possible

inclusion of additional interventions in the domain for which current interventions may serve secondarily as active comparators.

With respect to strata, the unit-of-analysis, for treatment effect, will be the PISOP stratum, as specified from PAtC and corresponding to the eligibility criteria specified in the REMAP-COVID Core Protocol. Within this stratum, the unit-of-analysis is defined by illness severity state at time of enrollment, defined as either Moderate State or Severe State. Unit-of-analysis may also be defined by SARS-CoV-2 infection strata.

At the time of a Platform Conclusion, results will be reported for all randomized patients, patients in whom COVID-19 infection is confirmed by microbiological testing, microbiological tests do not detect or isolate COVID-19 infection, and testing is not performed.

The shock strata will not contribute to unit-of-analysis for this domain, as this strata is not applied in the Pandemic Statistical Model.

The influenza strata will not contribute to unit-of-analysis for this domain.

10.3. *Timing of revealing of randomization status*

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal and Initiation or Randomization with Deferred Reveal if prospective agreement to participate is required for this domain (see relevant core protocol documents).

10.4. *Interactions with interventions in other domains*

Interactions with other domains are either not evaluable or not considered possible and will not be incorporated into the statistical model or models in which this domain is evaluated. If an interaction is specified with a future domain, it is sufficient for the interaction to be specified only in the DSA of such a future domain.

10.5. *Nesting of interventions*

Nesting is not applicable to this domain.

10.6. *Threshold odds ratio delta for equivalence and futility*

The threshold odds ratio for equivalence and futility in this domain are those specified above for phase 2 and those in the relevant core protocol documents for phase 3.

10.7. *Post-trial Subgroups*

Domain-specific *post hoc* sub-groups will be used in analysis following the conclusion of one or more interventions within the domain. The *a priori* patient sub-groups of interest are:

- sex at birth
- all other potentially evaluable treatment-by-treatment interactions with other domains and treatment-by-strata interactions

11. ETHICAL CONSIDERATIONS

11.1. *Data Safety and Monitoring Board*

The DSMB should be aware that the superiority, inferiority, or futility of different interventions with respect to the primary endpoint is possible, and if equivalence is demonstrated, determination of the optimal intervention may be based on secondary endpoints.

11.2. *Potential domain-specific adverse events*

Potential domain-specific harms related to ACEi and ARBs relate to hypotension, renal failure, and allergic reaction including angioedema (angioedema with ACEi only). These have been identified as domain-specific secondary end-points (see above). While the incidence of angioedema is known to be low, its incidence in patients with COVID-19, in whom bradykinin may be more active, is unknown, and hence this will be collected. Potential intervention-specific adverse events related to DMX-200 relate to acute liver dysfunction. These four potential adverse events will be collected. In addition, these severe events may have an influence on the primary and secondary trial outcomes which would be evident between the treatment arms. Other unexpected serious adverse events, including suspected unexpected serious adverse reactions (SUSARs), should be reported only where, in the opinion of the site investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see Core Protocol Section 8.13).

11.3. *Domain-specific consent issues*

The use of DMX-200 (repagermanium) and TRV-027 are as Investigational Medicinal Products and should not be used outside a clinical research study. The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) for Investigational Medicinal Products and must adhere to ICH GCP guidelines.

12. GOVERNANCE ISSUES

12.1. *Funding of domain*

Funding sources for the REMAP-CAP trial are specified in the relevant core protocol documents. This domain has not received any additional domain-specific funding but funding, from any source, may be obtained during the lifetime of the domain.

12.2. *Funding of domain interventions and outcomes measures*

Dimerix will provide DMX-200 through a centrally-regulated and overseen process. All other study drugs will come from local supply. Dimerix may also contribute to platform-level and site-level costs. Dimerix have had input into the design of the domain but analysis and reporting will be conducted independently of Dimerix. Trevena will provide TRV-027 through a centrally-regulated and overseen process. Trevena may also contribute to platform-level and site-level costs. Trevena will review the study design prior to initiation of this intervention in the domain and may provide feedback, subject to approval of the investigators and ITSC. Analysis and reporting will be conducted independently of Trevena.

12.3. *Domain-specific declarations of interest*

All investigators involved in REMAP-CAP maintain a registry of interests on the REMAP-CAP website. These are updated periodically and publicly accessible on the study website.

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14. APPENDIX 1. ACE2 RAS MODULATION DOMAIN SIMULATION REPORT

14.1.   *Introduction*

This report is an appendix to the ACE2 RAS Modulation Domain-Specific Appendix. This report details the clinical trial simulations that have been conducted for the ACE2 RAS Modulation Domain of REMAP-CAP. The goal of the simulations is to understand the operating characteristics of this domain. The analysis model is described briefly in this report, with the ACE2 RAS Modulation DSA, REMAP-CAP COVID-19 Protocol, Statistical Analysis Plan, and the Current Model report providing the full details.

14.1.1. Primary endpoint

The primary endpoint is organ support-free days (OSFD). This endpoint is a composite of in-hospital mortality and the number of days free of organ support in the 21-day period following the time of enrollment. A value of –1 is for any patient that dies within the first 21 days or during their in-hospital stay. For patients that do not die, the outcome is the number of days (rounded to the nearest integer) out of the ICU with 0 as the worst non-death outcome. The best possible outcome of 22 is reserved for patients who survive and never have organ support in ICU. We label the outcome for a patient as Y. This endpoint is an ordinal outcome with 24 possible outcomes (integers –1 to 22) where higher values correspond to better patient outcomes.

14.1.2. Arms

In this domain, subjects are randomized equally between each active intervention and the 'no RAS inhibitor' control.

14.1.3. States

There are two states in this analysis based on the baseline disease severity: severe and moderate. We label the disease severity as s = 1 (severe) and s = 2 (moderate). Since the severe state is defined as receiving organ support at baseline, the outcome of 22 is not possible in this state.

14.1.4. Trial status

In this report, we do not simulate the fixed effects in the model for sex, age, site, or time. Let $Y_i \in \{-1, 0, 1, \ldots, 21, 22\}$ denote the ordinal outcome for subject i. We denote the probability of subject

i observing y number of ICU free days or less as $\pi_{iy} = \Pr(Y_i \leq y)$. Then, for $y = \{-1, 0, 1, \ldots, 21\}$, the primary analysis model is formulated as follows for this report:

$$\log\left(\frac{\pi_{iy}}{1 - \pi_{iy}}\right) = \alpha_{y,s} - \theta_{a,s}$$

The model is a proportional odds model, where the log odds-ratio parameters in the model (θ_a) are structured so that a value > 0 implies treatment benefit, and an odds-ratio > 1 implies treatment benefit.

1. The "arm" to which a patient is randomized is labeled as a where a=1 is the 'no RAS inhibitor' control. The treatment effect for intervention a in state s is modeled with the $\theta_{a,s}$ parameter.

2. The $\alpha_{y,s}$ parameters determine the baseline rates of the ordinal outcome, which are modeled separately by disease state.

The treatment effect parameters are relative to the 'no RAS inhibitor' control. The treatment effect for the 'no RAS inhibitor' control, labeled as arm a = 1, will be set to 0 for $s = 1,2$:

$$\theta_{1,s} \equiv 0$$

The effect of the other interventions, a, is modeled with a hierarchical prior that borrows information on the treatment effect across states:

$$\theta_{a,s} \sim N(\mu_a, \sigma_a^2), \qquad s = 1,2$$

where the hyperparameters μ_a and σ_a^2 are given the following prior distributions:

$$\mu_a \sim N(0, 1)$$

$$\sigma_a^2 \sim IGamma(0.25, 0.1)$$

Where *IGamma(a,b)* denotes an inverse gamma distribution with shape *a* and scale *b*. Small values of σ_a^2 result in a fit approximately equivalent to assuming intervention *a* has the same effect in each state. Large values of σ_a^2 result in a model with differential treatment effects by state. The prior on σ_a^2 was selected to place mass across both small and large values to allow the posterior distribution to be based on the consistency of the data with pooled or differential effects.

The ordinal endpoint rates are modeled using a Dirichlet prior where the individual probabilities for the 24 outcomes are based on 1 patient's weight on real-world evidence-based outcomes.

$$logit(\alpha_{y,s}) \sim Dirichlet(P)$$

For the severe state, the model is constrained so that the probability of an OSFD of 22 is zero (*i.e.,* $\alpha_{21,1} = \infty$).

14.1.5. Domain design and simulation assumptions

The following are the domain design rules and thresholds:

- For the ACEi and ARB interventions, respectively:
  - The maximum sample size is 300.
  - Graduation will occur if the following is true within a state:
    - The posterior probability of an odds-ratio greater than 1.2 relative to the 'no RAS inhibitor' control exceeds 50%
- For the ARB + DMX-200 intervention:
  - The maximum sample size is 200.
  - Graduation will occur if the following are true within a state:
    - The posterior probability of an odds-ratio greater than 1.3 relative to the ARB intervention exceeds 50%.
    - The posterior probability of an odd-ratio greater than 1.3 relative to the 'no RAS inhibitor' intervention exceeds 50%.

There are additional assumptions made in the simulations that are not specific to the trial design. The following assumptions are made for the simulations:

- We assume there are no dropouts or missing data.
- We assume fixed, equal randomization of subjects to the active interventions and the 'no RAS inhibitor' control.
- We simulate fixed trials with no interim analysis.
- We simulate three scenarios for the distribution of patients across disease states. For these three scenarios, we assume the breakdown of patients across states is 50/50, 30/70, and 70/30 for severe/moderate states.
- We simulate the ordinal outcome with five levels: –1 (death), 0 OSFD, 1-10 OSFD, 11-21 OSFD, and 22 OSFD. This simplification was made for both computational efficiency and statistical model stability, and we believe the impact on operating characteristics is minimal. We retain the proportional odds assumption made in the primary analysis model. Table

2.5.1 includes the baseline scenarios for the distribution of the ordinal outcome in the severe and moderate control groups.

Table 2.5.1: Control Rate Scenarios

Outcome	State	
	Severe	Moderate
−1 (Death)	0.295	0.090
0	0.224	0.071
1-10	0.150	0.040
11-21	0.330	0.099
22	0.000	0.700

- For computational ease and numerical stability, the simulations incorporate an informative prior on the $\alpha_{y,s}$ parameters. Rather than a Dirichlet prior with a weight of 1 patient, this informative prior has a weight of 50 patients.

- For simplicity, these simulations define graduation of ARB + DMX-200 based on a single comparison to a control instead of the two criteria listed above. For the purposes of these simulations, this "control" intervention can be interpreted as either the 'no RAS inhibitor' control or the ARB intervention.

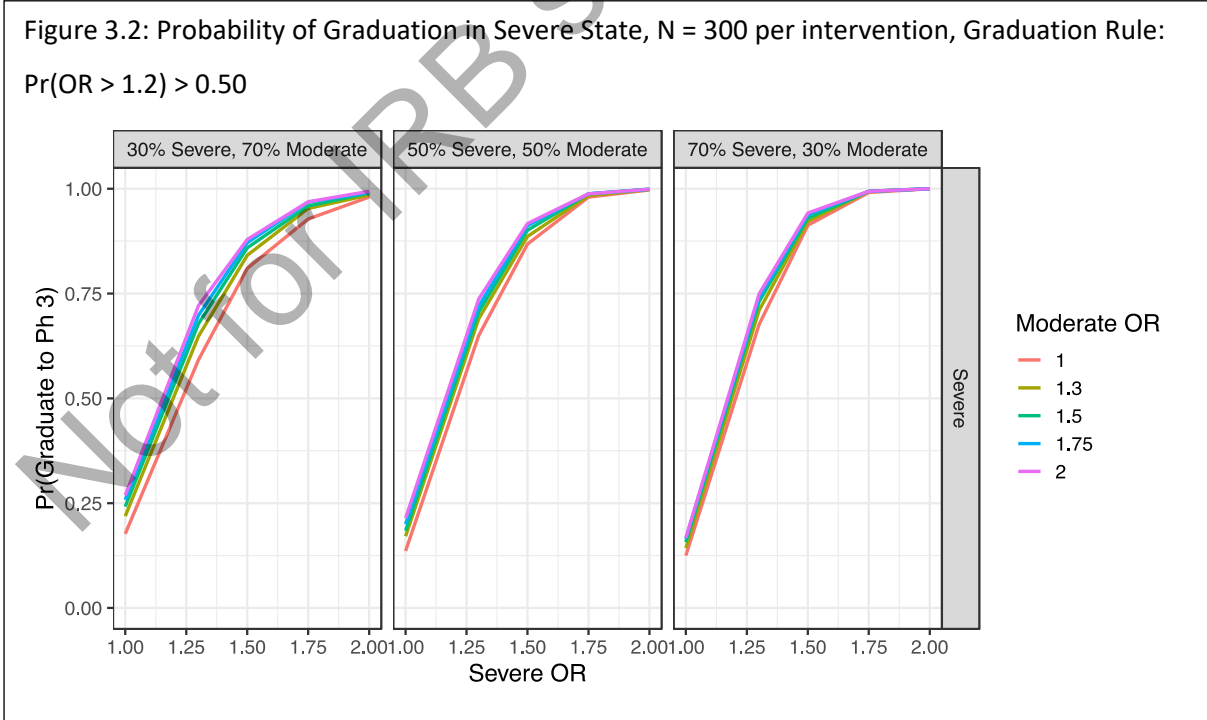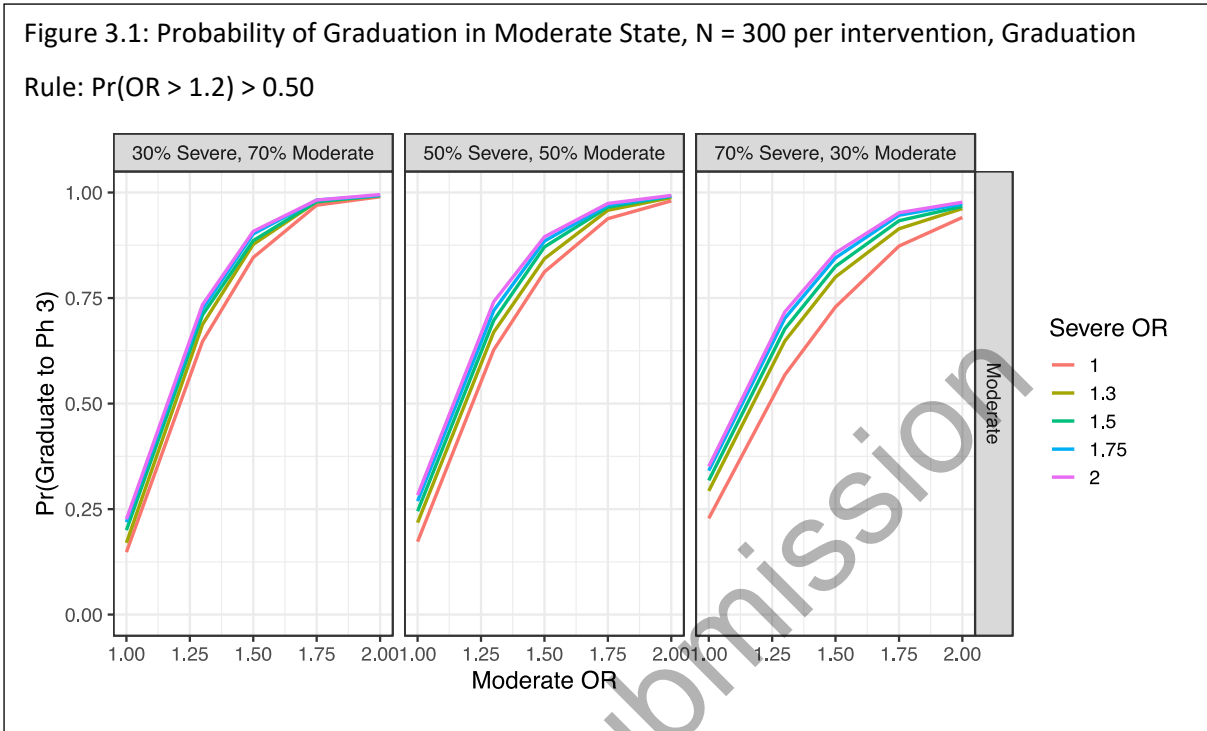## 14.2.   *Domain operating characteristics*

In this section, we report the probability of graduation for the active interventions within this domain. Since graduation rules are applied separately to the moderate and severe states, we present the probability of graduation separately by state. For each intervention and state, we will plot the probability of graduation within that state based on the odds-ratios (OR) within each state and the distribution of patients across states. Since this domain includes borrowing of information across states, the probability of graduation within one state depends on the OR within both states. When we present the probability of graduation within the moderate state for an intervention, the plot shows the moderate state odds-ratio on the x-axis and the color of the lines indicates the severe state odds-ratio. When we present the probability of graduation within the severe state for an intervention, the plot shows the severe state odds-ratio on the x-axis and the color of the lines indicates the moderate state OR. Each figure below includes three panels representing the different assumptions for the distribution of patients across severe/moderate states.

14.2.1. ACEi and ARB intervention operating characteristics

In this section, we report the probability of graduation of ACEi and ARB interventions within each state. Since these interventions have the same maximum sample size and statistical triggers for graduation, the operating characteristics are the same for each intervention.

Figure 3.1 reports the probability of graduation within the moderate state based on the moderate state OR, the distribution of patients across states, and the severe state OR. The probability of graduation in the moderate state increases as: 1) the proportion of patients in the moderate state increases, 2) the moderate state OR increases, or 3) the severe state OR increases. The impact of the severe state OR on the moderate state probability of graduation increases as the moderate sample size decreases. Additionally, the impact of the severe state OR on the moderate state probability of graduation decreases as the moderate state OR increases.

Figure 3.2 reports the probability of graduation within the severe state based on the severe state OR, the distribution of patients across states, and the moderate state OR. The probability of graduation in the severe state increases as: 1) the severe state OR increases, 2) the proportion of patients in the severe state increases, or 3) the moderate state OR increases. The impact of the moderate state OR on the severe state probability of graduation increases as the severe sample size decreases. Additionally, the impact of the moderate state OR on the severe state probability of graduation decreases as the severe state OR increases.

Figure 3.1: Probability of Graduation in Moderate State, N = 300 per intervention, Graduation Rule: Pr(OR > 1.2) > 0.50

Figure 3.2: Probability of Graduation in Severe State, N = 300 per intervention, Graduation Rule: Pr(OR > 1.2) > 0.50

14.2.2. ARB + DMX-200 intervention operating characteristics

In this section, we present the probability of graduation for the ARB + DMX-200 intervention in the moderate and severe states.

Figure 3.3 shows the probability ARB + DMX-200 graduates within the moderate state based on the OR within each state and the distribution of patients across states. Given the smaller sample size and more stringent graduation rules, the probability of graduation is lower for ARB + DMX-200 than ARB/ACEi interventions. Additionally, the severe state OR appears to have a larger impact on the probability of graduation within the moderate state for ARB + DMX-200 than the other interventions.

Figure 3.3: Probability of Graduation in Moderate State, N = 200 per intervention, Graduation Rule: Pr(OR > 1.3) > 0.50
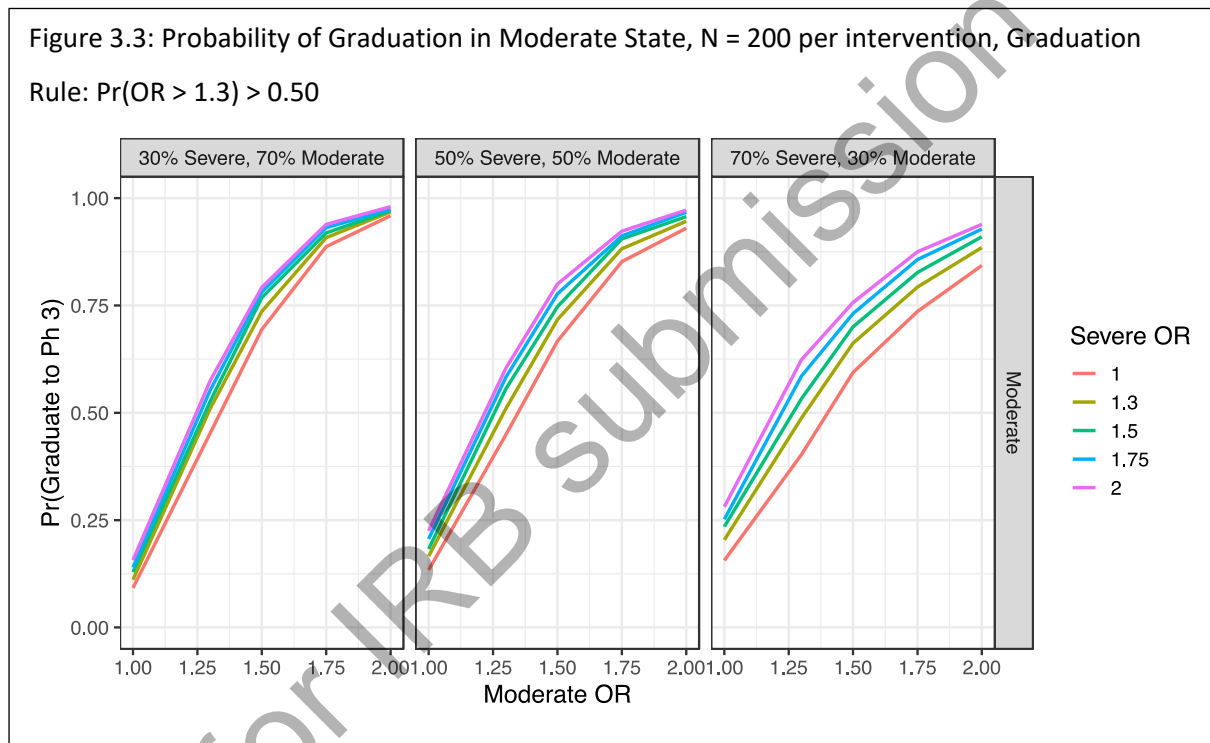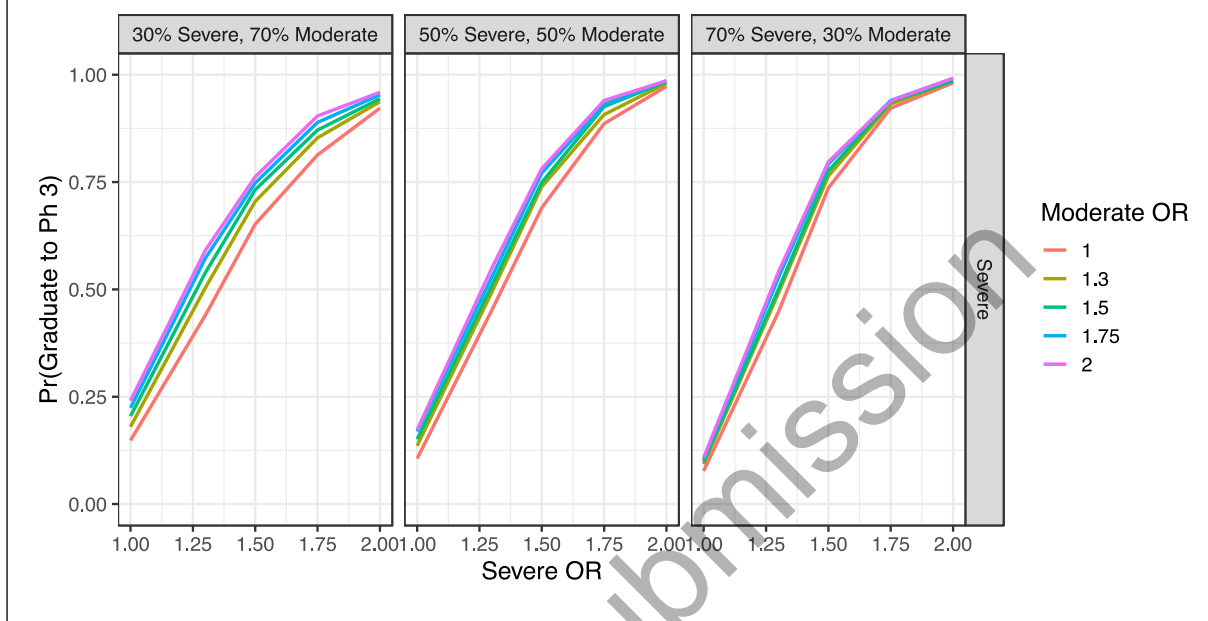
Figure 3.4 shows the probability ARB + DMX-200 graduates within the severe state based on the OR within each state and the distribution of patients across states.

Figure 3.4: Probability of Graduation in Severe State, N = 200 per intervention, Graduation Rule: Pr(OR > 1.3) > 0.50

Simulations were not updated at the time of addition of the ACEi + TRV-027 intervention but simulations that apply to the ARB + DMX-200 intervention can reasonably apply to ACEi + TRV-027 intervention.