A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with Acute Respiratory Distress Syndrome Associated with COVID-19

Appendix H2: Remdesivir

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This appendix provides detailed information pertaining to the study of remdesivir when studied alone and in combination with aviptadil. Although remdesivir is licensed for use in the United States and is standard of care for most hospitalized patients with COVID-19, the key registration trials[1] included insufficient patients in this subgroup to provide strong evidence in favor of remdesivir for critically ill patients. Thus, randomization to remdesivir versus placebo is a key component of this trial.

Remdesivir is not considered standard of care for this protocol: the protocol does not recommend routine initiation of remdesivir in this patient population. For patients who have already initiated remdesivir by the time of enrollment, this protocol makes no recommendation regarding whether to continue or discontinue remdesivir as part of background therapy. The core question being evaluated by this protocol is whether to start (or not to start) remdesivir among patients with ARDS from COVID-19.

Following a description of our rationale for studying remdesivir and description of the study agent, we state the objectives of the factorial study of aviptadil and remdesivir, describe the study design, and provide an overview of the planned analyses.

If not stated otherwise in this appendix, the text in the TESICO master protocol provides the approach that will be taken to study these agents

1. Introduction and rationale for studying remdesivir

Remdesivir is an adenosine nucleotide prodrug with antiviral activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Specifically, remdesivir triphosphate acts as an analog of adenosine triphosphate (ATP) and competes with the natural ATP substrate for incorporation into RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, which results in delayed chain termination during replication of the viral RNA.

COVID-19 is caused by infection with SARS-CoV-2, which requires viral replication. While such replication initially occurs in the upper respiratory tract, a transition to the lower respiratory tract and other tissues marks disease progression, which may develop into COVID-19 pneumonia. In the most severe stage of the disease, COVID-19 presents as ARDS; at this stage of illness, both ongoing viral replication and dysfunctional immune activation contribute to morbidity and mortality.[2] Importantly, RNA-emia is more prevalent in COVID-19 ARDS than in mild-to-moderate disease; in addition, levels of RNA in blood are prognostic among COVID-19 ARDS patients.[3] These observations suggest the possibility that anti-viral therapies may be of use in patients with COVID-19 ARDS.

In the Adaptive COVID-19 Treatment Trial 1 (ACTT-1) trial, remdesivir administered once daily for up to 10 days reduced time to recovery in hospitalized patients with COVID-19.[4] The rate ratio for recovery was largest in patients receive low flow rates of oxygen at baseline (ordinal category 5, rate ratio for recovery, 1.45; 95% CI, 1.18 to 1.79) and among patients without supplemental oxygen at baseline (ordinal category 4, rate ratio 1.29; 95% CI, 0.91 to 1.83). However, the clinical impact was uncertain for patients receiving baseline high flow oxygen or non-invasive ventilation (ordinal category 6, rate ratio for recovery 1.09; 95% CI, 0.76 to 1.57) and those receiving invasive mechanical ventilation or ECMO (ordinal category 7, rate ratio for recovery 0.98; 95% CI, 0.70 to 1.36). These

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subgroup comparisons were underpowered, though, and do not exclude clinically important benefit for patients with COVID-19 ARDS.

In the large, open-label, pragmatic SOLIDARITY trial, no survival benefit was observed with use of remdesivir, although the study design did not allow direct assessment of the effect on time to recovery.[5] In the subgroup of hospitalized patients without COVD-19 ARDS (no mechanical ventilation), the observed mortality favored remdesivir treatment (rate ratio for mortality 0.86; 95% CI 0.67-1.11), consistent with that observed in the ACTT-1, whereas for patients with COVID-19 ARDS (mechanical ventilation required) in the SOLIDARITY trial, the opposite was present (rate ratio for mortality 1.20; 95% CI 0.80-1.80). Given the pragmatic nature of the trial, the lack of blinding, and the requirement for longer hospital stay among treated patients, how best to interpret the SOLIDARITY results is not clear.

Despite the FDA approval for remdesivir, on the basis of the SOLIDARITY trial results, NIH treatment guidelines do not currently recommend remdesivir for patients receive invasive mechanical ventilation/ECMO and provides a weak recommendation (BIII) for remdesivir in combination with dexamethasone in patients receiving high flow oxygen or non-invasive ventilation.[6] The lack of definitive evidence for remdesivir in patients with COVID-19 ARDS provides motivation for this substudy.

1.1 Potential risk and benefits from remdesivir

Anticipated risk is considered low, based on the known mechanism of action and extensive clinical experience with the drug. The most common adverse reactions observed more commonly with treatment with remdesivir than with placebo are nausea, increase in ALT, and increase in AST.

The potential benefits of remdesivir include faster time to recovery, including earlier hospital discharge. There is no current evidence to suggest that remdesivir reduces mortality in hospitalized patients based on data from ACTT-1 and the WHO SOLIDARITY trial.[5]

Remdesivir is currently FDA approved and licensed in the United States for the treatment of hospitalized patients with COVID-19. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of remdesivir may be found in the Package Insert.[5] The overall benefit-risk assessment of this study is considered favorable.

1.2 Justification for dose chosen

Remdesivir will be administered as a 200 mg IV loading dose, followed by a 100 mg once-daily IV maintenance dose while hospitalized up to a 10-day total course. This regimen is the dosing recommended by the FDA (https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf) and evaluated in prior trials.

B2. Agent-specific exclusion criteria

1) Prior receipt of any dose of remdesivir during the present illness
2) GFR < 30 ml/min and not receiving dialysis
3) ALT or AST > 10 times upper limit of normal
4) Unwillingness to commit to avoid sex that may result in pregnancy for at least 7 days after completion of remdesivir vs. placebo

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B3. Description of investigational agent

3.1. Administration and duration

The prepared diluted solution should be administered through a separated/dedicated intravenous line and should not be infused simultaneously with other antimicrobials or antibody preparations (e.g., monoclonal antibodies, convalescent plasma, hyperimmune globin). The compatibility of remdesivir injection with IV solutions and medications other than 0.9% sodium chloride is not known. Administer remdesivir via IV infusion over 30 minutes. Slower infusion rates of up to 120 minutes can be considered to potentially prevent signs and symptoms of infusion-related reaction. See the PIM and Pharmacy Procedures for additional details.

The duration of study treatment will be 10 days. The initial loading dose is 200 mg, with all subsequent doses 100 mg. Treatment will be discontinued if the participant is discharged or transferred from the study hospital. In addition, the study treatment may be discontinued after at least 5 days, per discretion of the treating clinician, if the participant is no longer requiring respiratory support (high flow oxygen, noninvasive ventilation or invasive mechanical ventilation).

3.2. Formulation and preparation

Remdesivir is a sterile drug product. Remdesivir for injection, 100 mg, is a preservative-free, white to off-white to yellow, lyophilized solid containing 100 mg of remdesivir that is to be reconstituted with sterile water for injection and diluted into 0.9% saline prior to administration by IV infusion. Once prepared for infusion, remdesivir is colorless. In addition to the active ingredient, remdesivir for injection, 100 mg, contains the following inactive ingredients: sulfobutylether-beta-cyclodextrin (SBECD), water for injection, hydrochloric acid, and sodium hydroxide. Hydrochloric acid and sodium hydroxide are used to adjust the formulation to a pH of 3.0 to 4.0. Remdesivir for injection is supplied as a sterile product in a single-use, 30-mL Type I clear glass vial. Each vial is sealed with a rubber stopper and an aluminum overseal with a red, plastic flip-off cap.

The placebo to match remdesivir for injection, 100 mg, is 0.9% sodium chloride solution, commercially available and prepared locally in the research site pharmacy, as was true for the ACTT-1 trial.

3.3 Supply, distribution, and accountability

Procedures for ordering and accepting drug, for maintaining inventory of remdesivir, and for breaking the blind in the event of a medical emergency will be described in the Pharmacy Procedures.

3.4. Contraindicated medications

1) Hydroxychloroquine or chloroquine for any indication

3.5. Precautionary medications

The clinical site should have necessary equipment and medications for the management of any infusion-related or anaphylactic reaction.

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4. Clinical and laboratory evaluations

4.1 Timing of Assessments

All assessments are outlined in the relevant section of the master protocol.

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4.2. Pharmacokinetic Assessments
Relevant pharmacokinetics are outlined in the FDA-approved package insert for remdesivir (Veklury). After a 10-day course of remdesivir, it is anticipated that remdesivir will persist in the body for 5 days after completion of the course of therapy. No pharmacokinetic assessments will occur within this trial.

5. Clinical management issues
All participants should be monitored closely for infusion-related or anaphylactic reactions. eGFR and transaminases should be monitored during use as clinically appropriate, consistent with the Package Insert. Since remdesivir is approved in the United States, has been used extensively in clinical practice, and has a good safety protocol, specific additional monitoring for infusions is not required for this agent.

5.1. Symptoms and Signs
Hypersensitivity, including infusion-related and anaphylactic reactions, has been observed during and following administration of remdesivir, and hence it is required to monitor patients under medical supervision for hypersensitivity reactions during and following administration of remdesivir. This occurs as part of standard clinical practice. Symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering. Slower infusion rates (maximum infusion time ≤120 minutes) can potentially prevent these reactions if there are symptoms of infusion-related hypersensitivity reaction during the current or prior infusion. If a severe infusion-related hypersensitivity reaction occurs, remdesivir will be immediately discontinued and appropriate treatment initiated.

Transaminase elevations have been observed in healthy volunteers and in patients with COVID-19 who received remdesivir; frank hepatic failure has not been observed. Other minor side effects have been observed including constipation, nausea, vomiting, decreased appetite, and headache.

5.2. Site Needs
The clinical site should have necessary equipment, medications, adequately qualified and experienced staff with appropriate medical cover for the management of any infusion-related or anaphylactic reactions.

5.3. Management of Infusion Reactions including Discontinuation
Investigators will use their clinical judgement and standard of care to evaluate and manage all infusion reactions. Severe infusion-related hypersensitivity reaction should result in immediate discontinuation of remdesivir. Discontinuation should be considered if transaminases increase to >10x upper limit of normal or if transaminase elevation is accompanied by signs or symptoms of liver inflammation. If the complete infusion is not administered, all follow-up procedures and reporting outlined in the master protocol should be adhered to as indicated.

5.4. Factorial design features

5.4.1 Rationale for Studying Remdesivir and Aviptadil in a Factorial Study
Remdesivir and aviptadil have complementary mechanisms (pure anti-viral versus immune-modulator and pneumocyte stabilization combined with modest anti-viral effects) and no evidence to suggest an important drug-drug interaction. Notably, remdesivir has been commonly coadministered with aviptadil in the Expanded Access Program (EAP) and Phase 2 clinical experience with aviptadil. In neither experience was an important safety concern related to coadministration identified. Based on

this, we do not anticipate an interaction between aviptadil and remdesivir (i.e., the effect of aviptadil compared to placebo will be similar for those randomized to remdesivir and placebo for remdesivir).

If this assumption about the absence of an interaction is valid, there are substantial efficiencies gained by combining the study of remdesivir and aviptadil in a single 2x2 factorial study where possible.

Certain key assumptions and principles guide the approach to factorial study.

5.4.2 Severability of factors. Some patients will be eligible for aviptadil but not for remdesivir and vice versa. This may include patients with low GFR being ineligible for remdesivir as well as patients who have already received remdesivir. To accommodate such patients, randomization will be carried out in four distinct strata (see Figure 1). Considering the percentage of patients who enroll in each stratum, we estimated that approximately 800 patients will be randomized in order to achieve 640 participants for each of the two primary comparisons.

5.4.3 Primary objectives of the factorial study

- Primary objective 1. To determine whether aviptadil is superior to placebo when given with standard of care for the primary outcome of recovery based on a 6-category ordinal outcome evaluated at 90 days after randomization.
- Primary objective 2. To determine whether remdesivir is superior to placebo when given with standard of care for the primary outcome of recovery based on a 6-category ordinal outcome evaluated at 90 days after randomization.

5.4.4 Randomization

As described in the master protocol, randomization will be stratified by study site pharmacy and receipt of mechanical ventilation at enrollment. Randomization will be further stratified by the strata shown in Figure 1.

Within each stratum, as indicated in the master protocol, mass-weighted urn randomization will be used to prepare randomization schedules. For the 2x2 factorial, patients will be equally allocated to four possible combinations of aviptadil, remdesivir, that the matching placebos for these drugs: 1) aviptadil + remdesivir placebo; 2) aviptadil placebo + remdesivir; 3) aviptadil + remdesivir; and 4) aviptadil placebo + remdesivir placebo. For strata 2 through 4 in Figure 1, treatment will also be equally allocated to either aviptadil or placebo (strata 2 and 4) or to remdesivir or placebo (stratum 3).

5.4.5 Analysis principles

For each primary objective the two treatments will be compared using a proportional odds model for the primary analysis. This analysis will pool results over the four strata shown in Figure 1 and by receipt of mechanical ventilation. Analyses will also be stratified by geographic region instead of site pharmacy to minimize the number strata. The effect of aviptadil and remdesivir, each compared to placebo will be estimated from a single proportional odds model. For example, just considering the strata in Figure 1, the comparison of aviptadil with placebo will be pooled over those assigned remdesivir and those given placebo for remdesivir in stratum 1, over those randomized in stratum 2, and over those randomized in stratum 4. The effect of remdesivir will be similarly estimated pooling

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results over those assigned aviptadil and those assigned placebo for aviptadil in stratum 1, and over those randomized in stratum 3.

An interaction test will be carried out for those randomized in stratum 1. In addition, an interaction test will be carried for aviptadil versus placebo for 4 subgroups defined by randomization to remdesivir or placebo in the factorial (2 subgroups in stratum 1), contraindications to remdesivir (stratum 2), and current or previous use of remdesivir (stratum 4). Similar subgroup analyses will be performed for 3 groups for remdesivir versus placebo, e.g., randomization to aviptadil or placebo (2 subgroups in stratum 1) and randomization to remdesivir or placebo only due to contraindication to aviptadil (stratum 3).

Analyses of secondary endpoints and of subgroups will follow the general plan described in the master protocol.

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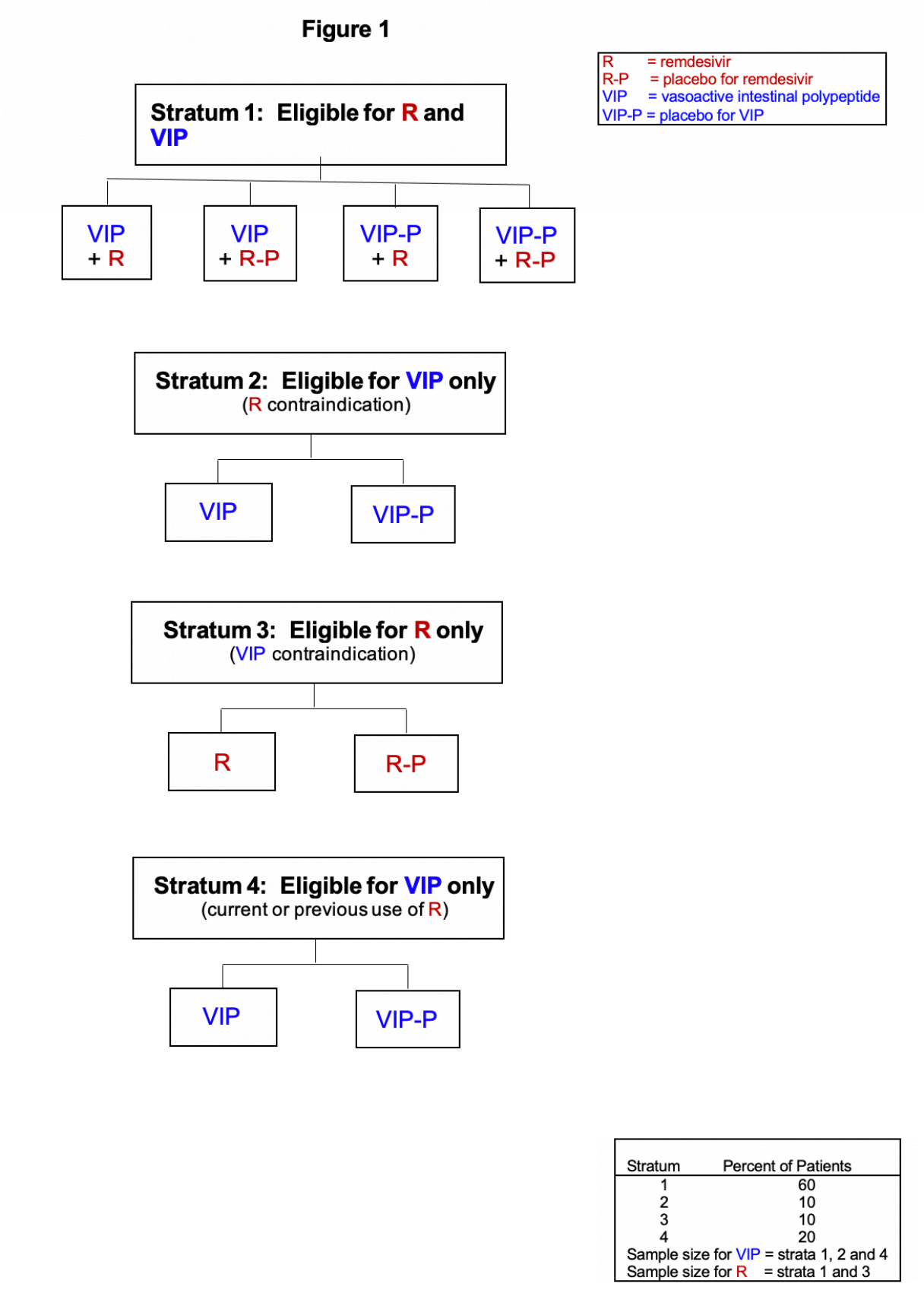

Figure 1. Schematic of approach to factorialization of aviptadil and remdesivir

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6. Specific safety-monitoring activities

Because remdesivir is already approved for the treatment of hospitalized patients with COVID-19 and has been administered to very large numbers of patients without significant safety concerns, remdesivir safety monitoring is simpler than for an investigational agent with limited human safety data. Specifically, no additional infusion monitoring beyond standard clinical monitoring will be required during remdesivir infusions. All other safety monitoring will occur as directed by the master protocol.

No additional components will be added to the safety outcome outlined in the master protocol.

The safety monitoring table (Table 1) from the master protocol has been reproduced here with the appropriate modifications relevant to remdesivir. Specifically, the requirement for additional infusion monitoring has been removed.

Table 1 Overview of Safety Data Collection Specific to Remdesivir

	Day 0–7	Day 14	Day 28	Day 90
All grade 3 and 4 clinical AEs (new or increased in severity to Grade 3/4)	X	X[a]	X[a]	
Protocol-specified exempt serious events[b]	Collected through Day 90			
SAEs that are not PSESEs	Collected through Day 90			
Unanticipated problems	Collected through End of Subject Participation (Day 180)			
Hospital admissions and deaths	Collected through End of Subject Participation (Day 180)			
Any SAE related[c] to study intervention	Collected through End of Subject Participation (Day 180)			

[a]Participants will be asked about all new relevant adverse events which have occurred since the last data collection, up to that time point. On these visits, AEs of Grade 1 or 2 that are present on the day of the visit will also be collected.
[b]These are collected on designated forms and consist of events most likely occurring due to the underlying disease. Hence they are study endpoints and will be reviewed by the DSMB regularly, but will be "exempt" from additional collection and reporting as adverse events for safety. See section 10.2.3 of the master protocol for further details
[c]Relatedness determined as per protocol rules in section 10.

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7. References

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