An open label phase 1 trial of losartan for worsening respiratory illness in COVID-19

PROTOCOL

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Background

As of March 11, 2020, COVID-19 caused by the coronavirus SARS-CoV-2 reached pandemic status. Worldwide, there are 121,564 confirmed cases with 4,373 deaths and both numbers are rapidly rising. While our understanding of the disease continues to increase, the clinical picture in China can be summarized as follows:[1] median age is 47 years (41.9% females), most common symptoms are fever (88.7% during hospitalization) and cough (67.8%), radiographic findings include ground-glass opacities on CT scans (56.4%), and lymphocytopenia (83.2%), ICU admissions are required in 6.1% of the cases with 2.3% needing mechanical ventilation and 1.4% are dying. In Italy, the numbers are slightly different: median age 65, up to 15% ICU admissions, and current death rate up to 6%.

As the name of the virus indicates, death is usually associated with respiratory failure. Thus, the question is how to mitigate the development of lung disease in COVID-19 since no SARS-CoV-2, FDA approved therapeutics are available as yet. While trials with anti-viral and other therapies are being conducted, e.g., remdesivir[2] and chloroquine[3], additional safe and nontoxic therapies to prevent progression of lung disease are needed. We therefore propose a proof of concept clinical trial with **losartan** to block angiotensin II type 1 receptors (AT1R) in the lung of patients with worsening respiratory function due to SARS-CoV-2.

Arguments to use angiotensin receptor blockers (ARBs) for persons with COVID-19 were recently published in at least two opinion pieces.[4, 5] More importantly the premise is based on scientific data assembled over years in multiple models of viral pneumonia. Like other coronaviruses, SARS-CoV-2 infects cells by binding to angiotensin-converting enzyme 2 (ACE2),[6, 7] a protein highly expressed in the lung.[8] The enzyme is thereby downregulated in the setting of viral infection causing dysregulation of the renin-angiotensin axis that results in more angiotensin II[9] and less angiotensin 1–7, a vasodilator. This finding was confirmed in the systemic circulation of patients with H7N9 influenza in whom elevated plasma angiotensin II is associated with worse outcome.[10] Disproportionate AT1R stimulation has been shown to mediate pulmonary capillary leak and AT1R blockade or knockdown is associated with better outcomes in animal models.[11, 12] Furthermore, ACE2 null mice develop an angiotensin II-mediated cardiomyopathy through unopposed stimulation of AT1R.[13]

Since AT1R blockade increases ACE2,[14-16] one could be concerned about possibly worsening viral entry with worsening outcome. In this context, hypertension is a risk factor for severe COVID-19 disease and hypertension rates are high in China. However, ARBs are not commonly used in China to treat hypertension.[17] In addition and maybe paradoxically, ACE2 upregulation may still be beneficial in disease models,[18] possibly by increased angiotensin 1–7 production. Interestingly, upregulation of viral binding sites for HIV is also associated with a decrease rather than an increase in HIV virulence.[5, 19]

Thus, good evidence suggests that at least acute treatment with ARBs could ameliorate lung injury in COVID-19. We therefore propose to test losartan in a Phase I proof of concept and safety trial. The primary hypothesis to be tested is that losartan treatment is safe in the setting of acute SARS-CoV-2 infection. Secondarily, losartan can potentially reduce the length of respiratory failure due to SARS-CoV-2.

Significance

Importance of the problem: As outlined above, there is currently no data that supports specific treatment options for respiratory failure in COVID-19. There are active or soon to be active clinical trials that may show promise in this space such as blocking IL-6 with tocilizumab[20] or using hydroxychloroquine. None of these therapies are without side effects and alternative or additional approaches could lessen the burden of respiratory failure in this patient population.

Approach and Protocol

This is an open label, phase 1 clinical trial to evaluate the safety of losartan in respiratory failure due to COVID-19.

Clinical Trial setup:

Detailed inclusion and exclusion criteria are listed below. Briefly, 50 patients with COVID-19 and respiratory failure who meet criteria and agree to participation in the study will be placed on losartan 25 mg daily on study day 0. If parameters are met the dose of losartan will be increased to 50 mg on study day 3. Participants will continue losartan until they experience resolution of respiratory failure (normal oxygen levels on room air), are discharged from the hospital, meet stoppage criteria (detailed below) or complete 14 days of therapy.

Primary hypothesis and endpoint:

- Losartan is safe in acute respiratory failure due to SARS-CoV-2.

Secondary endpoints:

- Losartan reduces the number of days on supplemental oxygen in respiratory failure due to COVID-19
- Incidence of mechanical ventilation use
- Days on mechanical ventilation
- Incidence of non-invasive positive pressure ventilation or heated high flow nasal cannula use
- Days on non-invasive positive pressure ventilation or high flow nasal cannula
- Incidence of transfer to ICU from non-ICU hospital bed
- ICU length of stay (days)
- In-hospital mortality
- Hospital length of stay (days)
- Cumulative incidence of severe adverse events
- Cumulative incidence of adverse events
- Change from baseline in oxygenation
- Incidence of medications with possible antiviral activity (hydroxychloroquine, lopinavir/ritonavir, ribavirin or remdesivir) or adjunctive therapy use (e.g., tocilizumab)
- Incidence (and length in days) of extracorporeal membrane oxygenation use
- Incidence (and length in days) of renal replacement therapy use
- Intolerance of high dose (50mg) losartan after tolerating 25mg
- Change in SARS-CoV-2 viral load determined by quantitative PCR

Inclusion criteria:

1.Age $\geq$18 years admitted to the University of Kansas Health System.
2.Confirmation of infection with SARS-CoV-2 by PCR testing.
3.Hypoxic respiratory failure
Requiring mechanical ventilation or oxygen OR a SpO2 ≤94% on room air or a P_aO_2/F_iO_2 (P/F) ratio <300 OR tachypnea (respiratory rate ≥24 breaths/min).
4.Other concomitant medications such as antivirals and hydroxychloroquine are allowed.
5.Participants prescribed standard of care (SOC) losartan (25mg QD) within 48 hours of consenting may be considered for enrollment if eligibility criteria are met based on EMR data assessment, i.e. no other ARB or ACE prior to SOC medication administration. If participant is eligible and signs consent form, investigational losartan 25mg QD will be ordered to replace SOC prescription on the following scheduled dose.

Exclusion criteria:

1.Pregnancy.
2.Respiratory failure due to a process other than COVID-19.
3.Intolerance to ARBs.
4.Previous treatment with an ARB or ACE inhibitor (see exception in inclusion criteria).
5.Current chronic use of medication with known interactions with losartan including NSAIDs (intermittent prior use is acceptable), potassium supplementation aliskiren.
6.Blood pressure less than 90 mm Hg systolic or 60 mm Hg diastolic recorded on at least two readings 30 min apart.
7.Need for vasopressors, unless norepinephrine ≤0.1 μg/kg/min
8.Hyperkalemia (serum K^+ >5.5 mM).
9.Known cardiac failure (left ventricular ejection fraction ≤35%), renal insufficiency (Cockcroft-Gault <30 mL/min/1.73 m^2 or urinary output <20 mL/h), hepatic failure (LFTs > 5x normal upper limit).
10.Known renal artery stenosis.
11.Neurological, psychiatric, endocrine or neoplastic diseases that are judged to interfere with participation in the study.
12.On another interventional trial (including one for COVID-19) that excludes participation.
13.Meeting all inclusion criteria for more than 48 hours prior to Day 0

Patients and/or surrogate decision maker who do not give consent to treatment will be asked to allow collection of data from their medical record for use as a control group. Patients or surrogate decision makers who cannot consent in person, will be consented in accordance to the KUMC remote consent guidelines.

Parameters to be collected:
General: Demographics, clinical symptoms, history of other medical conditions, routine blood work, and concomitant medications. Baseline characteristics will include age, sex, race, ethnicity and body mass index, Simplified Acute Physiology Score (SAPS) II, National Early Warning Signs (NEWS), Sequential Organ Failure Assessment (SOFA) and acute physiology and chronic health evaluation (APACHE) II. The APACHE II will be collected only for participants admitted in the ICU.

Physical examination: We will record vital signs such as highest and lowest temperatures (˚C), highest respiratory rate, highest heart rate, lowest mean arterial pressure (mmHg), highest oxygen requirements and body mass index (BMI).

Confirmation of infection with SARS-CoV-2 by PCR testing by chart. Also, documentation of other infections if present.

Blood samples: We will collect laboratory values throughout the study (hemoglobin, platelet count, white blood cell count, lymphocyte count, liver enzymes, glucose, blood urea nitrogen, creatinine, creatine kinase, lactate, and arterial blood gas) and as indicated (LDH, ferritin, troponin), potassium and other values available in EMR.
Store plasma at beginning and at the end of study for later analysis (possibly IL-6 etc.).

Nasopharyngeal swabs: We will collect nasopharyngeal swabs at study enrollment and end of study to determine SARS-CoV-2 viral load by quantitative PCR.

Radiographic imaging will be recorded upon presentation and subsequently thereafter as indicated.

Monitor for deteriorating acute respiratory failure and determine the indication the need for mechanical ventilation.

Study procedures (see schematic)
Day 0
- Labs collected for routine clinical care and the medical record will be reviewed to screen for eligibility. Assuring pre-menopausal women have a negative pregnancy test.
- Consenting participants who meet enrollment criteria will be started on losartan 25 mg once daily per mouth.
- Treatment group will have nasaopharyngeal swab and research plasma collected for analysis.
- Control group will be followed only for data collection until study completion.

Day 1-2;
- Monitor subject for safety and losartan stoppage criteria.
- For participants following inclusion criteria #5: Day 0 assessments should be performed on enrollment day as well as day 1 **or** day 2 based on first dose of SOC losartan administration.

Day 3:
- Dose escalation: On study day 3 if none of the parameters listed below are met the dose of losartan will be increased to 50 mg once daily.

Day 4 until study completion:
- Monitor subject for safety and losartan stoppage criteria.
- Treatment group will have nasopharyngeal swab and research plasma collected at end of study.

Stoppage criteria for losartan
- Hyperkalemia (persistent values >5.5 mM recorded on at least 2 readings).
- Worsening renal function (Cockcroft-Gault <30 mL/min/1.73 m^2) or urinary output <20 mL/h.
- Skin rashes, palpitations or other moderate or severe adverse events (interference with usual daily activities) without clear explanation should warrant immediate cessation of treatment and notification of study personnel.
- Development of sustained hypotension defined as SBP <90 mmHg, DBP <60 mmHg recorded on at least two readings 30 min apart or use of norepinephrine >0.1 µg/kg/min.

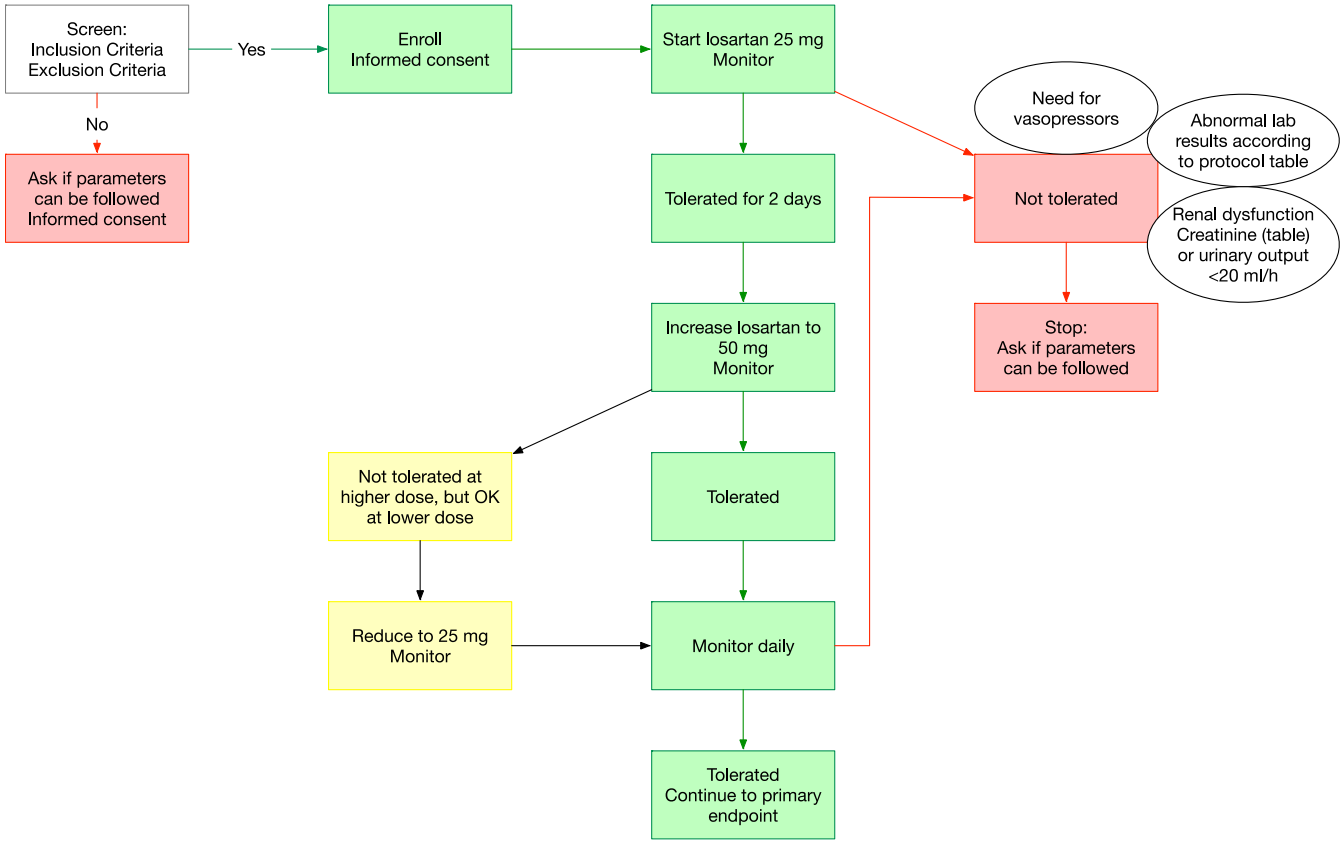
- Any change in monitor lab parameters deemed significant and potentially related to study drug by the Investigator.

Dose de-escalation criteria

- Any change in monitoring parameter after dose increase from 25 mg to 50 mg that is considered significant by the investigator will trigger a decrease dose back to 25 mg
- If abnormal parameter is resolved and, in the opinion of the investigator, is unlikely to be related to losartan will increase dose back to 50 mg
- If de-escalation criteria is met after re challenging 50mg dose, the dose will be once more decreased to 25mg until the end of the study.

Criteria for resuming after stopping

- If stoppage criteria have resolved and reason for stoppage is felt to be unlikely or possibly related to losartan, discussion of resumption of losartan with medical monitor
- Dose resumption will start at 25 mg. If stopped at 25 mg → the dose will be continued for three days followed by increase to 50 mg if tolerated. If stopped at 50 mg, 25 mg will be started and escalated to 50 mg the day after if tolerated.



Control

Patients that request to not be treated with Losartan will be approached by the study team to request permission for their standard of care treatment and data be followed and recorded by the research team for this study. Patients that agree, will sign the consent form, but will not provide a blood sample for research. We will also collect medical information relating to safety criteria on historical controls treated at the University of Kansas Hospital in the 30 days prior to the study start date (3/25/2020) and during the study period. These controls will be retrospectively identified through query of the electronic health record. We will attempt to include controls that meet all criteria for enrollment into the study but to achieve a ratio of controls to study participants of 2:1 may need include some with exclusion criteria (excluding prior ACE inhibitor or ARB use). Controls identified retrospectively will not undergo informed consent as this represents minimal risk.

Losartan

Losartan is an FDA-approved ARB widely prescribed for treatment of hypertension, heart failure, and for renal protection in patients with diabetes. The doses proposed in this study are well tolerated by non-hypertensive patients without significant effect on blood pressure. The proposed starting dose of losartan is 25 mg orally per day with increase to 50 mg orally per day on day 3 if tolerated until they patient is discharged from the hospital, met stoppage criteria (above) or completed 14 days of therapy.

The most common side effects are fatigue and dizziness. Serious adverse events that are rare include angioedema, hypotension, renal dysfunction or failure, blood dyscrasias, hepatitis, or rhabdomyolysis. The following are meant to mitigate risk to the subjects: Dosing will be done in an inpatient setting with clinically indicated close observations of blood pressure and organ dysfunction (blood work). Subjects with hyperkalemia, renal dysfunction, or who are taking potassium supplements will not be enrolled into the study. Participants will be given written descriptions of potential side effects and potential responses to the side effects.

Sample size and Statistics

Since there is no information on the effects of losartan in human beings suffering from COVID-19, a statistical analysis based on efficacy is not possible. From a safety perspective, we would accept considering losartan equivalent or superior to the comparison group not receiving losartan (historical or no consent) if there is a ±20% difference in total AE/SAEs. Historical controls will be matched with study participants based on upon age, sex and disease severity in a 2:1 ratio for safety comparison. From a safety perspective, losartan's long track record as a safe medication is reassuring. See section on DSMB for further details on safety monitoring and analysis.

Confidentiality

All information provided by the subject to the investigators, and all information that is collected about the subjects by the investigators, shall be kept confidential to the extent that is provided by law. Computer data files will be stored and backup up to secure, HIPPA compliant, password protected computers and servers. Electronic data capture into REDCap system will be used. Access to these databases will be restricted to individuals associated with the study who require access to the data to perform their duties. These individuals will be named by the principal investigator prior to initiation of the clinical trial. The subject's actual identity cannot be ascertained exclusively from these data and the subject's name shall not be used in any publications. All investigators and staff involved in the research protocol will be bound by this agreement of confidentiality.

Adverse Event and Serious Adverse Event Documentation

Definition of an Adverse Event

For the purpose of this protocol, an AE will be defined as any untoward medical occurrence in a subject during the study listed under DMSB - Anticipated Adverse Events and Grading Scale section of this protocol as well as safety monitoring data listed on table 1 as well as stoppage criteria for losartan.

The event does not necessarily have a causal relationship with the treatment. AEs will be collected for both study groups, treatment and control from the time the ICF is signed until the subject completes study participation.

Definition of a Serious Adverse Event

An SAE is any AE that meets any of the following outcomes:

- Fatal (death, regardless of cause, that occurs during participation in the study or occurs after participation in the study and is suspected of being a delayed toxicity due to administration of the study drug)
- Life-threatening, such that the subject was at immediate risk of death from the reaction as it occurred
- Inpatient hospitalization or prolongation of hospitalization

- Persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)

- Congenital anomaly or birth defect

- Important medical event that, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above (e.g., an allergic bronchospasm requiring intensive treatment)

Data Safety and Monitoring Plan and Internal DSMB

Anticipated Adverse Events and Grading Scale

Losartan side effects: The most common side effects are fatigue and dizziness. Serious adverse events that are rare include angioedema, hypotension, renal dysfunction or failure, blood dyscrasias, hepatitis, or rhabdomyolysis (clinical assessment of muscle pain). Skin rashes, palpitations or other moderate or severe adverse events without other clear explanation warrants immediate cessation of treatment and notification of study personnel, who will take appropriate reporting actions.

Grading Scale

Grade 1:
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2
Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*Grade 3
Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

Grade 4
Life-threatening consequences; urgent intervention indicated.

Grade 5
Death related to AE.
Activities of Daily Living (ADL)

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Table 1

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hemoglobin	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L Follow up	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L ; follow up	Hgb <8.0 - 6.5 g/dL; <4.9 - 4.0 mmol/L; <80 - 65 g/L; transfusion indicated; stop losartan, follow up	Life-threatening consequences; urgent intervention indicated; stop losartan	Death
Leukocytes	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L; follow closely	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L; stop losartan; follow up	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L; stop losartan; follow up and further investigation	<1000/mm3; <1.0 x 10e9 /L; stop losartan; follow up and further investigation	
Platelets	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L; follow closely	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L; follow closely, stop losartan	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L; follow closely, stop losartan,	<25,000/mm3; <25.0 x 10e9 /L; follow closely, stop losartan, transfer to ICU	
Angioedema	N/A	N/A	Angioedema occurs – mild: stop losartan, transfer to ICU	Angioedema occurs – severe tongue swelling: stop losartan, transfer to ICU	Death
Hypotension (for participants in ICU on sedation for mechanical ventilation ONLY)	Initiation of vasopressors	Increase in vasopressor dose to >0.1; stop losartan, follow up	Persistent hypotension without alternative cause; stop losartan, follow up	Irreversible end organ damage related to hypotension; stop losartan, follow up	Death
Hypotension (for participants NOT in ICU on sedation for mechanical ventilation)	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated; stop losartan, follow up	Urgent medical intervention or transfer to ICU indicated; stop losartan, follow up	Life-threatening and urgent intervention indicated; losartan, follow up	Death

Creatinine	>1 - 1.5 x baseline; >ULN - 1.5 x ULN; follow up	>1.5 - 3.0 x baseline; >1.5 -3.0 x ULN; close follow up	>3.0 baseline; >3.0 - 6.0 x ULN; stop losartan, nephrology intervention	>6.0 x ULN; stop losartan, nephrology intervention	
Potassium[&]	>ULN to 5.5 mmol/L; monitor	>5.5 - 6.0 mmol/L, stop losartan, close follow up	>6.0 - 7.0 mmol/L; urgent intervention indicated, stop losartan, intervention	>7.0 mmol/L; life-threatening consequences; stop losartan, intervention	
AST, ALT, alkaline phosphatase	>ULN - 3.0 x ULN; monitor closely	Asymptomatic with AST,ALT, alk.P. >3.0 -5.0 x ULN; >3 x ULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia or bilirubin elevation; stop losartan, monitor	>5.0 - 20.0 x ULN; >5 x ULN for >2 weeks; stop losartan, monitor	>20.0 x ULN; stop losartan, monitor, other interventions	
CPK[#]	>ULN - 2.5 x ULN; monitor closely	>2.5 x ULN - 5 x ULN; stop losartan, monitor closely	>5 x ULN - 10 x ULN; stop losartan, monitor closely	>10 x ULN; stop losartan, monitor closely, possible admission with other abnormalities	

[&] Given that hyperkalemia occurs with patients on Losartan and there could be patients with renal dysfunction that falls just under the 1.5 mmol/L creatinine exclusion point, the DMC would recommend a modification to the reporting of abnormal results of serum potassium. We suggest that upon receipt of a level greater than 5.5 mM, the blood draw be repeated within 24 hours and that the PI for the study respond to the repeat level by either reassuring the patient that all is well or if the level is still rising discontinuing the study drug. Since there will be blood draws frequently during this study, we feel that continuing the study subject on study drug if the level returned to normal on repeat testing is safe, especially in the expected monitored setting.

[#] Only done when clinically indicated

Pregnancy

Female subjects will be tested for pregnancy by hospital policy. If pregnant they will be excluded.

It is not expected that a female subject becomes pregnant while participating in the study. In the rare case this does occur, study drug must be stopped immediately and permanently discontinued. Losartan does not have effects on a fetus in the 1st trimester but could later on. The investigator must notify the DSMB and IRB within 24 hours of the site's knowledge of the subject's pregnancy and other agencies as by law. Pregnancy itself does not constitute an AE. Pregnancy test will be performed at all site visits.

Data monitoring plan will be implemented as follows:

- Safety monitoring will be done:
    - All SAEs attributable to study drug will be reported to the study investigator(s) and discussed with an internal safety and monitoring group of 5 experts consisting of an intensivist(s), infectious disease specialist(s), ethicist and biostatistician. These experts may not report to the PI directly.
    - Any serious AE or SAE attributable to study drug will be shared with the medical monitor and safety and monitoring group within 24 hrs. The members will make the decision whether or not to stop the trial.
- All SAEs will be reported to the safety and monitoring group and the appropriate agencies including FDA and IRB as required.
- All adverse effects will be reported according to the rules to the FDA, the IRB and our internal DMSB
- Initial interim analysis on safety will be done after the first 5 patients and reviewed by the internal DSMB.
- The DSMB may stop the study due to safety or futility.
- All DSMB reports will be shared with the IRB.

Safety Reporting

Data monitoring plans will be implemented as follows: The study will be closely monitored by the PI and Co-PIs. Any relevant AE or SAE will be reported to the medical monitor and to the DSMB (separate charter).

- DSMB meeting will occur after the first 5 patients, 25 patients and at end of study, or more frequently if needed.
    - Safety monitoring will be done by the DSMB. Safety monitoring will be done as follows: The investigators will continuously monitor the study for side effects. If any AE or serious adverse events (SAEs) occur, the physicians will assess the event and report them to the appropriate authorities if needed as per Good Clinical Practice. Subjects might be withdrawn from the study if they experience intolerance to the study medication, initially based on the investigators' discretion.
    - All adverse effects will be discussed among the investigators
        - If deemed severe the data will be shared with the medical monitor and the safety and monitoring group. The group will make the decision whether or not to stop the trial based on safety data.
- All SAEs will be reported to the IRB and the appropriate agencies including FDA as required.

- All adverse effects will be reported according to the rules to the FDA (if needed), the IRB and the DSMB.

Safety Reviews

Safety review will occur at least every month and/or if a SAE occurs. The internal safety and monitoring group will meet after the first 5 patients, 25 patients and at end of study or more frequently if needed. If needed, the biostatics core will assist in data analysis for adverse events as well (fee for service basis). However, this is a small study.

Removal of Subjects from Study

A subject withdrawal is defined as a discontinuation from the study for any reason. Subjects may withdraw or be withdrawn from this study for the following reasons:

- At their own request or at the request of their authorized representative at any time for any reason
- If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being

Subjects must be withdrawn from the study for the following reasons:

- Subjects with an occurrence of any medical condition which, either because of its severity or duration or necessary change in treatment, contravenes the condition of the study or puts the patient at unnecessary risk or harm.
- Subjects with an occurrence of an AE/SAE, which in the opinion of the investigator and/or subject requires termination of treatment
- Subjects who are noncompliant with the protocol per the investigator's discretion
- Pregnancy

In all cases, the reason for withdrawal will be recorded in the subject's medical records and case report forms. Subjects who terminate the clinical study prematurely, either at their own request or on the recommendation of the clinical investigator, will be considered early terminations. Subjects who withdraw from the study will not be replaced but asked that their progress off drug can be followed as well. The DSMB should be notified of all early withdrawals and/or termination in the trial.

REGULATORY CONSIDERATIONS

The protocol will be submitted to the KUMC IRB. The study was registered on clinicaltrials.gov.

ADMINISTRATIVE SECTION

Protocol Amendments

Any amendments to the protocol will be approved by the PI and co-investigators and the independent Data Monitoring Committee and the DSMB. All amendments will be submitted to the IRBs for review and approval prior to implementation unless the amendment details changes related to safety.

Protocol Deviations

The investigator will only make changes to the protocol procedures when necessary to protect the safety, rights, and welfare of the subjects. In such an event where protocol procedures are changed, the investigators are responsible for notifying the IRBs and the internal DSMB.

In the event that an isolated, unforeseen instance occurs resulting in a protocol deviation, the investigators are to document this deviation and notify IRBs as by the rules at KUMC.

Case Report Form (CRF)

All clinical data will be recorded on the CRFs for this study, including their electronics versions (Red Cap and Velos databases).

Study Documentation and Records Retention

The Good Clinical Practice guidelines issued by the Committee for Proprietary Medicinal Products state that "The investigator must arrange for retention in strict confidence of the subjects' identification codes, names and addresses for at least 15 years after the completion or discontinuation of the trial." Subjects' files and other pertinent documentation (i.e., study protocol, signed informed consent forms, drug dispensing logs, correspondence, and other documents pertaining to the conduct of the study) must be kept for the maximum

period permitted by the hospital or private office in accordance with the local requirements, but not less than 15 years.

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