A Pilot Study of Duvelisib to Combat COVID-19

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Protocol Revision History

Initial Version	**08/11/2020**
Amendment 1	**10/21/2020**
Amendment 2	**11/30/2020**

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

PROTOCOL SUMMARY

Title:	A Pilot Study of Duvelisib to Combat COVID-19
Study Description:	Patients with a diagnosis of COVID-19 with critical disease manifestations will be randomly assigned to receive duvelisib or placebo
Objectives:	Primary Objective: To evaluate the efficacy of duvelisib for the treatment of COVID-19 disease manifestations. Secondary Objectives: To evaluate the safety and tolerability of duvelisib for the treatment of COVID-19 disease manifestations.
Endpoints:	Primary Endpoint: • 28 day overall survival Secondary Endpoints: • Hospital and ICU length of stay • Duration of ventilator • Duration of vasopressors • Duration on renal replacement therapy • Viral kinetics • Adverse Events
Study Population:	Twenty-eight patients (approximately 14 per arm) over the age of 18 with a diagnosis of COVID-19 with advanced disease manifestations including one or more of the following: extensive lung involvement, respiratory failure, shock, or cardiac dysfunction.
Phase:	Pilot Phase 2
Description of Sites/Facilities Enrolling:	This is a multi-center study open at Washington University School of Medicine and Missouri Baptist Medical Center.
Description of Study Intervention:	Patients will receive either duvelisib 25mg or placebo for 10 days. Both participants and researchers will be blinded.
Study Duration:	18 months
Participant Duration:	6 months

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1.0 BACKGROUND AND RATIONALE

1.1 COVID-19 and Cytokine Release Syndrome

Coronavirus disease 2019 (COVID-19) is an unprecedented international pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The spread of the virus and the incidence of the disease are accelerating at exponential rates. Despite public health campaigns to quench the spread, delays in testing have allowed for dissemination that is undetected and unaccounted. Aggressive measures are being taken to develop vaccines and therapies, but even relaxation of regulatory measures are unlikely to expedite their development to allow for rapid widespread dissemination. Mortality in patients with severe and critical disease is exceedingly high. In Wuhan, mortality 28-day mortality for those admitted to the ICU was over 60%.[1] In New York City, initial mortality rates for those requiring mechanical ventilation was over 75% for those age 65 years and under, and 97% for those over 65 years-old.[2] These staggering statistics highlight a population with a significant unmet need. It is imperative that existing therapies be evaluated for repurposing in order to manage and potentially reverse the sequela of COVID-19.

Emerging evidence suggests that this novel coronavirus, like others, induces an overactive and ineffective immune cascade associated with acute lung pathology, acute myocarditis, and cytokine storm mediated by cytokines such as interleukins 2, 6, and 8, TNF-alpha, interferon-γ, and G-CSF.[3] This aberrant immune response is thought to be the principal contributor to the morbidity and mortality of COVID-19. Additionally, studies of viral kinetics suggest that viral peaking occurs a number of days prior to the apex of symptoms, further suggesting that decompensation is an immunopathogenic response related to innate immune cells.[4] Numerous anecdotal reports describe the onset of severe symptomatology with refractory pyrexia occurring one to two weeks after initial viral prodrome, consistent with this theory. As such, a number of agents, including IL-6 inhibitors and JAK inhibitors, are aiming to disrupt these immune pathways in COVID clinical trials.

1.2 Lessons and Preclinical Data from CART-releated CRS

Chimeric antigen receptor T-cell (CART) therapy has been limited by life threatening toxicities in over 50% of patients. Toxicities primarily manifest as cytokine release syndrome (CRS) characterized by an early phase with fever, hypotension, increasing oxygen requirements and elevations of cytokines including IFNγ, GM-CSF, TNF, IL-10, and IL-6 and a later phase associated with life-threatening or life-ending neurologic events. IL-6, unlike IFNγ, is often but not always elevated early during CRS and current management strategies rely on administration of the IL-6 receptor antagonist tocilizumab, which is effective at blocking the early events of CRS but ineffective at controlling life threating CNS CRS.[5] A clinical strategy to prevent CRS without attenuating CART mediated anti-tumor activity is essential for the safe use of CART as a curative therapy for hematological malignancies. Enhancing the safety and efficacy of CART therapy though the amelioration of CRS will dramatically improve outcomes and expand clinical

application of adoptive T cell therapy. The same processes may underlie the terminal clinical manifestations of COVID-19 where patients suffer from progressive fever, increasing oxygen requirements, bleeding and clotting due to the activation of the coagulation cascade and eventual respiratory failure.[6] These events are often associated with elevation of biomarkers such as elevated IL-6, CRP, D-Dimers and ferritin levels, which are comparable to those seen in CART-related CRS.[7]

1.3 Gene edited CART model for the Mitigation of CRS

We hypothesized that the generation of CART cells, engineered through CRISPR/Cas9 gene editing to delete IFNγ, or other selected genes known to mediate inflammatory interactions between CART and target cells and macrophages (source of IL-6 and other inflammatory cytokines) may ameliorate CRS, preventing downstream IL-6 secretion from macrophages. We had previously shown that inhibitors of JAK1/2 could block the production of IL-6 and CRS symptoms when immunocompetent mice were treated with anti-murine CD3 in vivo (**Fig 1**). We hypothesized that the generation of CART cells, engineered through CRISPR/Cas9 gene editing to delete IFNγ will completely ameliorate CRS, preventing downstream IL-6 secretion from macrophages and dendritic cells. To test this hypothesis we developed an in vitro assay to assess the effect of IFNy deletion in human T cells on the release of CRS related cytokines, specifically IL-6. Using CRISPR/Cas9, IFNy was genetically deleted in human primary T cells (>80% deletion). IFNy deficient T cells were stimulated in the presence of immature dendritic cells, prior to cytokine quantification by ELISA (+24hrs). Contrary to expectations, deletion of IFNy, significantly increased IL-6

Fig 1

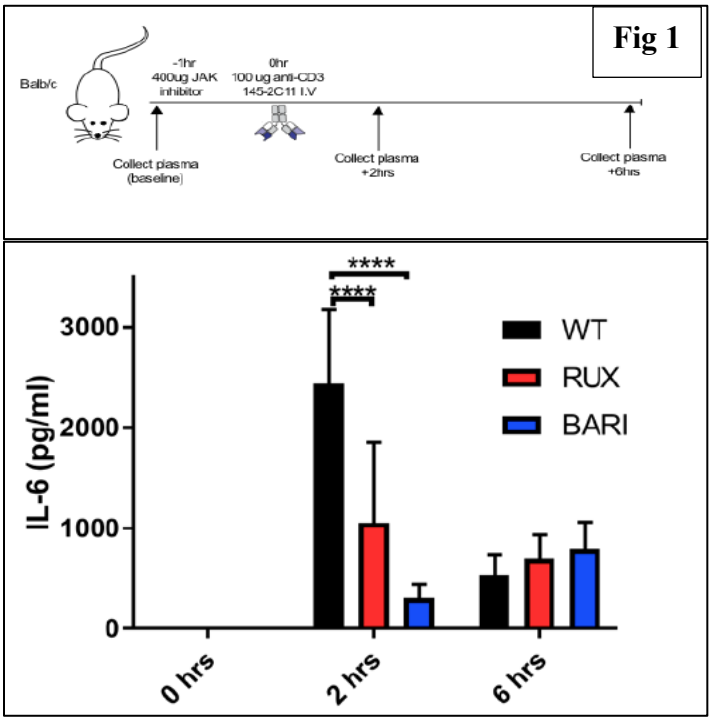
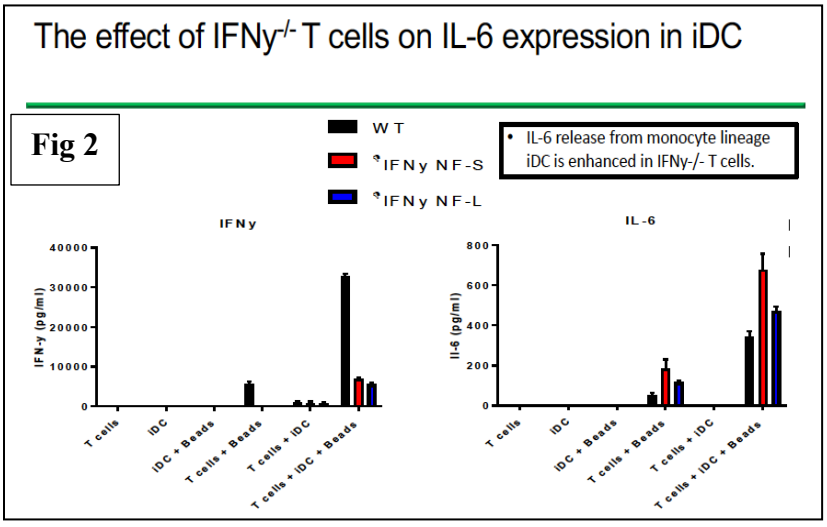


Fig 2

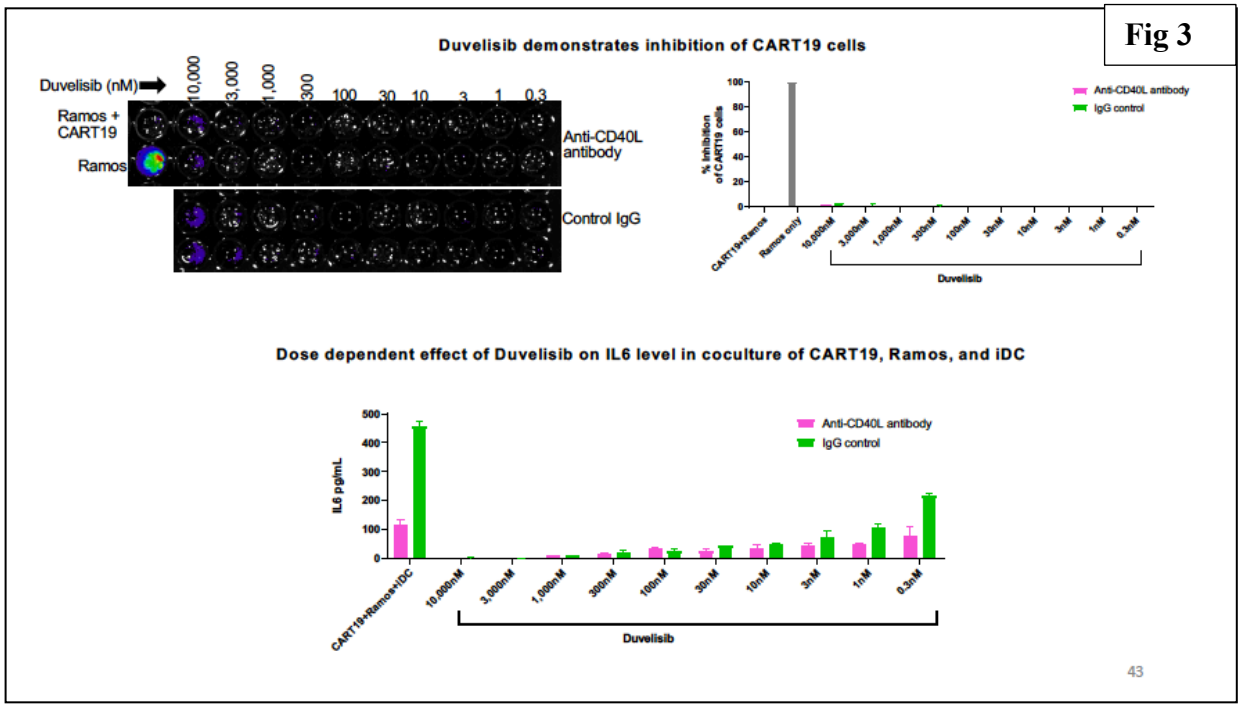


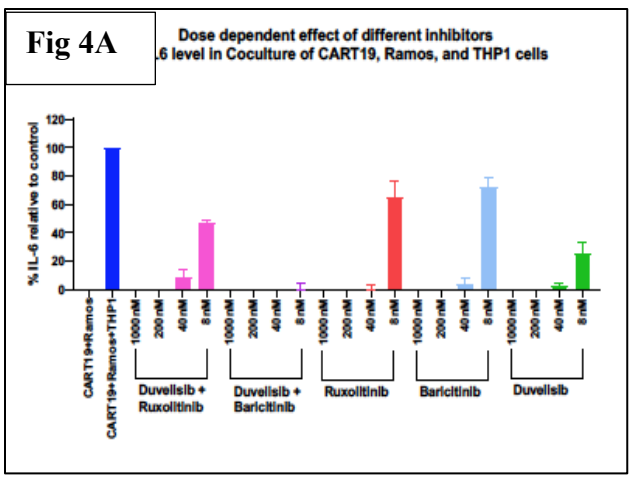
secretion from immature dendritic cells. These data suggest that IFNy is not the key mediator released by activated CART for the induction of IL-6 by iDCs/macrophages (**Fig 2**)

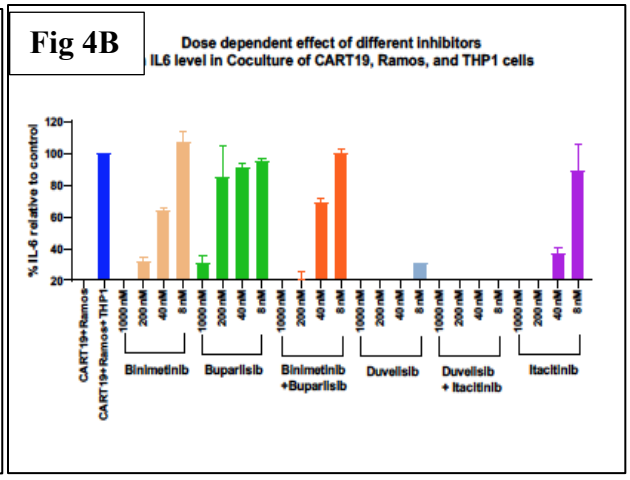
1.4 PI3K Inhibition Potently Mitigates CRS in Pre-clinical CART Model

Using unbiased CRISPR/Cas9 screens in which we have deleted several hundred genes involved in pathways of inflammation in CART19 cells, we have explored several other genes of interest.. Although these studies are still in progress we have identified several pathways/genes involving co-stimulatory pathways signaling through phosphoinositide 3-kinase (PI3K) in macrophages. One of these pathways includes the CD40-CD40L pathway. CRISPR/Cas9 genetic deletion of CD40L in CART resulted in normal CART function but no production of IL-6 when incubated with iDC (data not shown). We phenocopied these results by blocking both CD40L on CART and CD40 on iDC using antibodies to each. Of note is that one pathway of CD40 signaling in macrophages includes PI3K signaling specifically PI3Kγ signaling. We tested the pharmacologic inhibition of PI3K using a dual PI3K-δγ inhibitor duvelisib. Duvelisib, which is currently FDA approved for the treatment of chronic lymphocytic leukemia (CLL) had a potent effect on IL-6 production (even more potent that antibodies to CD40L) while having no impact on CART function, similar to CD40L-CD40 blockade and JAK1/2 blockade (**Fig 3**) Of interest is that the combination of a JAK1/2 inhibitor and duvelisisb completely a brogated IL-6 production in our in vitro CAR model (Fig 4).

Fig 3







1.5 PI3K Inhibition to Mitigate Pathogenesis of Advanced COVID-19

PI3K-δγ inhibition with duvelisib could potentially avert CRS related to COVID-19, while preserving cytotoxic T-lymphocyte, as we have seen in preclinical work on CART therapy.. Many of the cytokines reduced by duvelisib are ones demonstrated to be significantly elevated in patients with COVID-19, including IL-1beta, IL-6, IL-8, MIP-1α, MIP-1β, IL-10, and TNFα, supporting a potential role in mitigating CRS.[8, 9] Duvelisib may also positively impact the respiratory pathology associated with COVID-19 causing acute respiratory distress syndrome. In a murine model of acute pulmonary inflammation, PI3Kδ inhibition has been demonstrated to decrease IL-17 production and decrease pathogenic neutrophil recruitment to the lung.[10] Duvelisib has also demonstrated significant reductions in pro-inflammatory cytokines and neutrophil infiltration in in vivo models of asthma and pulmonary inflammation.[11] Lastly, duvelisib may potentiate the elimination of SARS-CoV-2 through preferential macrophage polarization and inhibiting viral persistence. Duvelisib has been demonstrated to polarize macrophages to the M1 phenotype which is responsible for pathogen elimination.[12] Such macrophage polarization has been demonstrated in primary samples from clinical trials of duvelisib.[13] Additionally, PI3K/Akt signaling has been shown to be a requirement for persistent SARS-CoV-1 infection in vitro in Vero E6 cells, which inhibition of PI3K can disrupt.[14, 15]

The exceedingly high mortality rates of severe and critical COVID-19 warrant the identification and evaluation of novel therapies that could potentially mitigate the advanced disease manifesations. Based on preclinical data from our institution and others,we hypothesize that PI3K inhibition with duvelisib could potentially quell aberrant hyperactivtation of the innate immune system, preferentially polarize macrophages, reduce pulmonary inflammation, and limit viral persistence, thereby improving patient outcomes.

2.0 OBJECTIVES

2.1 Primary Objective

To evaluate the efficacy of duvelisib for the treatment of COVID-19 disease manifestations.

2.2 Secondary Objectives

To evaluate the safety and tolerability of duvelisib for the treatment of COVID-19 disease manifestations.

2.3 Objectives and Endpoints Table

Objectives	Endpoints	Justification for Endpoints
Primary		
To evaluate the efficacy of duvelisib for the treatment of COVID-19 disease manifestations.	Primary: 28 day overall survival	The expected survival of these patients with advanced COVID-19 symptoms is poor and studies are currently needed.
	Secondary: Hospital and ICU length of stay and duration of ventilator, vasopressors, and renal replacement therapy	In addition to improving survival, duvelisib may reduce the need for these interventions.
Secondary		
To evaluate the safety and tolerability of duvelisib for the treatment of COVID-19 disease manifestations.	Viral kinetics	Duvelisib and similar treatments which modulate cytokine signaling have the potential to reduce immune function which could result in increasing viral loads.
	Adverse events	Adverse events are common with duvelisib for its indicated purpose. It is unclear if similar adverse events are observed in this population.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. A diagnosis of advanced COVID-19 as defined both of the following:
   a. as a positive test for SARS-CoV-2 RNA detected by RT-PCR collected from the upper respiratory tract (e.g. nasopharyngeal, nasal, oropharyngeal swab, or saliva) and, if possible, the lower respiratory tract (sputum, tracheal aspirate, or bronchoalveolar lavage), analyzed by a CLIA certified lab with an FDA approved assay. [11]
   b. Critical disease manifested by any of the following:
      i. Chest imaging with ≥ 50% lung involvement
      ii. Respiratory failure requiring invasive mechanical ventilation, non-invasive mechanical ventilation (eg. BiPAP, OptiFlow), supplementary oxygen with ≥ 6 LPM, or extracorporeal membrane oxygenation (ECMO)
      iii. Shock – defined as mean arterial pressure ≤ 65 mmHg unresponsive to 25ml/kg isotonic intravenous fluid resuscitation and/or requiring vasopressor support (See Appendix A)
      iv. Cardiac dysfunction defined by:
         1. New global systolic dysfunction with ejection fraction ≤ 40%
         2. Takotsubo cardiomyopathy

2. Patients who have received prior investigational or off-label agents for COVID-19 does not exclude eligibility.

3. At least 18 years of age at the time of study registration

4. Adequate hematologic function defined as absolute neutrophil count ≥ 1000/mm^3 and platelet count ≥ 50,000/mm^3 without growth factor or transfusion support for 7 days prior to screening.

5. Creatinine-clearance ≥ 15 mL/minute or receiving renal replacement therapy (See Appendix B)

6. Aminotransferase (AST/ALT) levels <3x the upper limit of normal

7. Able to understand and willing to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable)

8. Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, or women who have had a tubal ligation) are required to have a negative pregnancy test and use two forms of acceptable contraception, including one barrier method, during participation in the study treatment period.

9. Male patients if engaging in sex with a women of childbearing potential are required to use two forms of acceptable contraception, including one barrier method, during participation in the study and throughout the evaluation period.

3.2 Exclusion Criteria

1. Known allergy or intolerance to duvelisib or another PI3K inhibitor.

2. Known or suspected active viral (including CMV, HIV, hepatitis B, and hepatitis C), bacterial, mycobacterial, or fungal infection other than COVID-19. CMV viral load will be assessed at screening and those with viremia will be excluded. Other virologic testing not required unless infection is suspected.

3. Pregnant and/or breastfeeding.

4. Any uncontrolled intercurrent illness that would put the patient at greater risk or limit compliance with study requirements in the opinion of the investigator.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial. The study is limited to adults over the age of 18 as the safety of duvelisib in minors has not been established.

4.0 REGISTRATION PROCEDURES

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to

respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

5.0 STUDY TREATMENT

5.1 Overview

Patients will be randomly assigned in a double-blind fashion to receive either duvelisib 25mg or placebo twice daily for up to 10 days. Patients who have significant clinical improvement prior to day 10 and are going to be discharged from the hospital may discontinue the treatment early with investigator permission.

Blocks of 10 patients will be used to allocate patients to duvelisib or placebo. Due to differences in color between the duvelisib and placebo capsules, we will employ methods in this trial to maintain the blinding of the investigator to the best of our ability (e.g. having the drug dispensed by alternative personnel). If this study were to lead to a pivotal trial, matched placebos would be manufactured for such a trial.

Treatment is dosed orally and can be administered with or without food. For patients unable to administer orally, a duvelisib suspension will be administered through a nasogastric/orogastric tube. In this event, the capsule(s) will be opened and the dose will be placed in 40mL water and stirred until dissolved. The suspension should be administered using an appropriate syringe within 6 hours after preparation. Following administration, the tube should be rinsed with approximately 75 mL of water.

If a dose is missed by fewer than 6 hours, administer the missed dose right away and take the next dose as usual. If a dose is missed by more than 6 hours, the patient should not take an additional dose, but should take the next usual prescribed dose.

5.2 Dose Modifications

Participants will be evaluated for toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) version 5.0. Dose modifications for treatment-emergent adverse events are listed in the table below. If the dose is reduced for toxicity, escalation may occur at the discretion of the treating physician following resolution/stabilization of the toxicity.

Treatment-Emergent Adverse Event	**Management for Duvelisib/Placebo**
Neutropenia	
Grade ≤ 3	No change.
Grade 4	Hold treatment until ≤ Grade 2. When resumed, reduce treatment by one dose level.
Thrombocytopenia	
Grade ≤ 3	No change.

Grade 4	Hold treatment until ≤ Grade 3. When resumed, reduce treatment by one dose level.
Anemia	
Any	Dose delay is not required for anemia, unless deemed necessary by the treating physician. Transfusions and/or erythrocyte stimulating agents are allowable.
Pneumonitis	
Grade 1	No change.
Grade 2	If suspected related to treatment, treat with systemic steroid therapy and hold treatment until ≤ Grade 1 OR patient returns to baseline (where patient had a predetermined abnormal baseline). When resumed, reduce treatment by one dose level. If unrelated to treatment, no change unless deemed necessary by the treating physician.
Grade ≥ 3	Discontinue.
Viral Load Elevation	
Increase in viral load of >0.5 log on two consecutive days, or >1 log increase in one day	See section 5.4. If viral load elevation is suspected to be related to treatment, hold treatment until patient returns to baseline (where patient had a predetermined abnormal baseline). Permission required from the principal investigator prior to re-treatment. If resumed, reduce treatment by one dose level.
All other events	
Grade ≤ 2	No change.
Grade 3	If suspected related to treatment, hold treatment until ≤ Grade 1 OR patient returns to baseline (where patient had a predetermined abnormal baseline). When resumed, reduce treatment by one dose level. When resumed, reduce treatment by one dose level. If unrelated to treatment, no change unless deemed necessary by the treating physician.
Grade 4	For Grade 4 lab abnormalities: Hold treatment until ≤ Grade 1 OR patient returns to baseline (where patient had a predetermined abnormal baseline). Permission required for the principal investigator prior to re-treatment. For Grade 4 treatment-related adverse events with clinical manifestation (eg. life-threatening colitis, cutaneous reactions, infections): Discontinue study treatment

5.2.1 Duvelisib/Placebo Dose Levels

1	25 mg twice daily
-1	15 mg twice daily
-2	Discontinue

5.3 Supportive Care

Patients should receive full supportive care, including but not limited to intravenous fluids, transfusions of blood and blood products, antibiotics, antivirals, antibacterial agents, and antiemetics, when appropriate at the discretion of the treating clinician.

5.3.1 Recommended Prophylaxis Medications

Patients should receive prophylaxis for Pneumocystis jirovecii (PJP) during study treatment. Following completion of study treatment, continue PJP prophylaxis until the absolute CD4+ T cell count is greater than 200 cells/μL.

CMV prophylaxis may be considered in patients deemed high risk per institutional guidelines, although is not mandatory. CMV viral load monitoring will occur for seropositive patients.

5.3.2 Prohibited/Discouraged Medications

Strong CYP3A inducers should be avoided as they decrease duvelisib area under the curve (AUC) which may reduce duvelisib efficacy.

Strong CYP3A inhibitors should be avoided as they increase duvelisib AUC which may increase the risk of duvelisib toxicities. If strong CYP3A inhibitors are clinically necessary, the dose of duvelisib should be reduced to 15 mg BID.

Other drugs that are sensitive CYP3A4 substrates should be avoided as administration of duvelisib increases AUC of these drugs which may increase the risk of toxicities. If sensitive CYP3A4 substrates are clinically necessary, it is recommended to reduce the dose of the sensitive CYP3A4 substrate and monitor for signs of toxicities.

5.3.3 Standard of Care Therapy

The standard of care for patients with severe or critical COVID-19 continues to evolve and may be defined differently due to local practice habits and the availability or shortage of therapies.

Ventilatory strategies and management of critical illness should proceed according to instutional standards, as should the use of remdesivir.

Patients who are not already receiving a corticosteroid should be started on a dose of at least dexamethasone 6mg daily oral or intravenously at the time of screening (Day -1) and continue through Day +10 or beyond, unless contraindicated, per results of the RECOVERY Trial.[19]

5.3.4 Investigational or Off-Label Treatments for COVID-19

Patients who have received other investigational or off-label agents previously are eligible for study and these agent(s) may be continued at the discretion of the treating physician.

During study treatment, screening through Day 10, the addition of investigational or off-label agents for patients on the study is discouraged. However, physicians who believe use of such agents is warranted should discuss with the principal investigator. If such agents are administered, patients are permitted to continue on duvelisib.

5.4 Viral Load Monitoring

All patients will have three consecutive days of viral load monitoring prior to receiving duvelisib, on Screening day, Day -1, and Day 1 (see Section 7.0), to establish the baseline viral load and trend. For patients with an increase in viral load of >0.5 log on two consecutive days, or >1 log increase in one day, clinical judgement should be used to determine if any continued rising viral load is susprected to be related to study treatment. If suspected to be related to study treatment, follow dose modifications as outlined in section 5.2. If thought to be unrelated to study treatment, i.e. keeping with baseline trend, no change unless deemed necessary by the treating physician.

5.5 Worsening COVID-19 Symptomology

Patients with clinically worsening symptoms of COVID-19 may be removed from study treatment at any time per discretion of the treating physician and additional treatments may be commenced. However, patients should continue to be followed as per the protocol calendar in section 7.0.

5.6 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient/surrogate no longer wishes continuation of the protocol therapy, the protocol therapy should be discontinued and the reason(s) documented in the case report forms.

Patients will be removed from the study for any of the following reasons:

- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of the study drug
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious noncompliance with the study protocol

- Lost to follow-up
- Patient/surrogate withdraws consent
- Investigator removes the patient from study
- Investigator decides to close the study

5.7 Duration of Follow-up

All patients will be followed as according to the protocol calendar in Section 7.0 for the duration unless the patient withdraws consent or is lost-to-follow-up. Following the safety follow-up visit, patients will continued to be monitored for survival and late-onset toxicity every 3 months for up to 6 months. For these long-term follow-up visits, a telephone visit can be made in lieu of a physical visit.

5.8 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study team.

The following actions must be taken if the participant fails to return to clinic for a required study visit:

- The study team will attempt to contact the participant and reschedule the missed visit within 1 week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6.0 PHARMACEUTICAL INFORMATION

6.1 Duvelisib

6.1.1 Description

Duvelisib is a dual inhibitor of phosphatidylinositol 3-kinases PI3K-δ and PI3K-γ. Duvelisib is a white-to-off-white crystalline solid with the empirical formula C22H17ClN6O•H2O and a molecular weight of 434.88 g/mol. Hydration can vary with relative humidity. Duvelisib contains a single chiral center as (S) enantiomer. Duvelisib is soluble in ethanol and practically insoluble in water. Duvelisib is

described chemically as a hydrate of (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2- phenylisoquinolin-1(2H)-one.

6.1.2 Dose Forms and Strengths

Duvelisib capsules are for oral administration and are supplied as white to off-white opaque and Swedish orange opaque capsules (25 mg, on anhydrous basis) or pink opaque capsules (15 mg, on anhydrous basis), and contain the following inactive ingredients: colloidal silicon dioxide, crospovidone, magnesium stearate, and microcrystalline cellulose. Capsule shells contain gelatin, titanium dioxide, black ink, and red iron oxide.

Plaebos are supplied as matching size white to off-white opaque capsules containing the inactive aboves.

6.1.3 Storage and Stability

Store at room temperature 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F).

6.1.4 Availability

Duvelisib is commercially available by prescription. For this study, duvelisib or placebo will be supplied without charge to the participants by Verastem Oncology, the maker of duvelisib.

6.1.5 Preparation

Not applicable for capsule administration. For nasogastric/orogastric tube administration see Section 5.1.

6.1.6 Administration

Please see Section 5.1.

6.1.7 Warnings and Precautions

Fatal and/or serious diarrhea or colitis occurred in 18% of duvelisib-treated patients. Monitor for the development of severe diarrhea or colitis.

Fatal and/or serious cutaneous reactions occurred in 5% of duvelisib-treated patients.

Fatal and/or serious pneumonitis occurred in 5% of duvelisib-treated patients. Monitor for new/evolving pulmonary symptoms and interstitial infiltrates.

7.0 SCHEDULE OF ASSESSMENTS

	Screening[1]	Study Treatment Days											Safety Follow-Up[11]	
		-1	1	2	3	4	5	6	7	8	9	10	15	29
Informed Consent	X													
Medical History	X													
Physical Exam w/ vital signs and O2 saturation[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
APACHE II Score		X										X		
SOFA Score		X										X		
CBC[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CMP[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ferritin[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
D-Dimer[10]	X		X	X		X				X			X	X
aPTT and PT/INR[10]	X		X	X		X				X			X	X
Fibrinogen[10]	X		X	X		X				X			X	X
C-reactive peptide[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SARS-CoV-2 viral load [3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quantitative immunoglobulins (IgA, IgG, IgM)	X													
Immune competence assessment	X													X
CMV IgG	X													
CMV DNA PCR (CMV seropositive pts)	X									X[8]				
Serum βhCG[4]	X													
Chest X-ray[5]	X													
Electrocardiagram[5]	X													
ECHO or MUGA[5]	X													
Plasma troponin and NT-proBNP[5]	X													
Duvelisib/placebo[6]			X	X	X	X	X	X	X	X	X	X		
PJP prophylaxis[7]			X	X	X	X	X	X	X	X	X	X	X	X

Correlative studies[9]	X[12]			X		X				X		X	X	X
Adverse event monitoring			Continuously											

1 – Within 7 days of registration
2 – Performed daily while inpatient or per local SOC. If outpatient, visits may occur within +/- 2 days from schedule
3 – Performed daily through Day +10 then weekly thereafter by NP or OP
4 – Women of childbearing potential only
5 – Not required at Screening if patient meets Inclusion Criterion 1 by other measures. Repeated on study if clinically indicated.
6 – Duvelisib or placebo will be administered twice daily for up to 10 days. See section 5.0 for treatment administration details.
7 - Continued until CD4+ T cells >200 cells/μL. Choice of agent per institutional guidelines and patient tolerance.
8 – CMV viral load monitoring should occur at screening, and on D8 in patients who are CMV seropositive (positive IgG at screening). CMV prevention/treatment should follow institutional guidelines.
9 – Collected on the first 10 patients enrolled onto study. A variance of +/- 2 days for correlative collection will be permitted.
10 – Performed as scheduled or more frequently if clinically indicated for coagulopathy monitoring
11 – Outpatient follow-up visits may be performed by telemedicine/telephone encounter without lab assessment in situations that preclude in-person visits (eg. discharge to skilled nursing facility, lack of transportation, persistent COVID precautions)
12 – May occur anytime from screening through Day 1 pre-dose.

8.0 CORRELATIVE STUDIES

Correlative studies will be collected and analyzed for the frist 10 patients enrolled onto the trial.

8.1 Sample Collection

Peripheral blood (20 ml) will be collected into EDTA (pink or lavender top) vacutainer tubes and 10 mL will be collected into serum (red top) vacutainer tubes at the following time points (a variance of +/- 2 days will be permitted for correlative collections):

- Screening (May occur anytime from screening through Day 1 pre-dose)
- Day 2
- Day 4
- Day 8
- Day 10
- Day 15
- Day 29

8.2 Sample Processing

EDTA tubes will be processed to obtain double-spun plasma and peripheral blood mononuclear cells (PBMCs); serum tubes will be processed to obtain serum.

8.3 Planned Correlative Studies

8.3.1 Monitoring anti-SARS-Cov2 antibody responses in Duvelisib-treated COVID-19 patients

Rationale of the study

The production of neutralizing antibodies represents an important host defence mechanism against systemic dissemination of SARS-CoV2. Our understanding of the molecular determinants controlling in B cells the strength and quality of the antibody response against SARS-CoV2 during the acute phase of infection remains largely unknown. Also, we have limited information on the molecular effectors that control in B cells the production of specific classes (ie. IgM, IGG, IGA) and subclasses (IGG1, IGG2, IGG3, IGG4) of antibodies during SARS-CoV2 infection. The latter information is crucial to understand which factors trigger the production of antibody classes and subclasses with neutralizing activity rather than those exerting pro-inflammatory functions by binding to Fc receptors on macrophages and natural killer cells, or by complement fixation. Finally, the identification of molecular determinants contributing to the establishment of long-lived antigen-specific memory B cells and antibody-secreting plasma cells during the acute phase of SARS-Cov2 infection represents a key step to possibly modulate the duration of anti-viral responses.

PI3K signalling is a strong candidate for controlling key functions of B cells related to the production of antigen-specific antibodies during both T-cell dependent and independent anti-viral immune responses. Therefore, Duvelisib inhibition of PI3K catalytic function offers the opportunity to understand whether such treatment can influence the quality and quantity of the antibody response raised against SARS-CoV2 during the acute phase of the infection. Specifically, Duvelisib may influence the extent of B cell activation in response to SARS-CoV2 recognition, by modulating B cell receptor (BCR) signalling, which in turn controls B cell proliferation and terminal differentiation [16.17). Duvelisib exposure may also influence immunoglobulin isotype switching [17] This effect may lead to a substantial shift in the classes and subclasses of antibodies produced during the viral infection. In particular, Duvelisib treatment may change the ratio between neutralizing IGG1 antibodies and pro-inflammatory IGG3 antibodies produced during the acute phase of SARS-CoV2 infection. Duvelisib interference of PI3K signalling may enhance the process of antibody somatic hypermutation in antigen-specific B cells recruited into germinal centers (GC), in the frame of a conventional T-cell dependent anti-SARS-Cov2 immune response [17]. Whether enhanced antibody diversification ignited in GC B cells by Duvelisib, positively impacts on the average affinity of antibodies raised against SARS-Cov2 remains to be determined. Finally, Duvelisib treatment, during the acute phase of SARS-Cov2 infection, could exert a crucial impact on the net output of germinal centers represented by the generation of long-lived memory B cells and plasma cells producing high-affinity anti-virus antibodies [17,18].

Aim of the investigations and experimental plan

The proposed studies aim to obtain a comprehensive understanding of the effects of Duvelisib treatment on the antibody response raised against SARS-CoV2 in the acute phase of infection. Specifically, we will measure the effects of Duvelisib treatment on the concentration of all classes (IGM, IGG, IGA) and subclasses (IGG1, IGG2, IGG3, IGG4), IGA1 and IGA2) of serum anti-SARS-CoV2 Spike RBD-specific antibodies, respectively at Day-2, Day-4, Day-8, Day-15, and Day-29 of infection. Through serum neutralization tests, we will also estimate at the same time points, the effects of Duvelisib on the extent of production of anti-SARS-Cov2 neutralizing antibodies. Finally, flow cytometric determinations will establish whether Duvelisib treatment impacts. on the frequency of circulating RBD-binding long-lived $CD27^+$ IgM- and Ig-switched memory B cells and $CD38^+CD138^+$ plasma cells/plasma blasts, assessed at the different time points after the infection.

Methods

The laboratory of Dr S. Casola (The FIRC Institute of Molecular Oncology, IFOM, Milan) has developed an in-house ELISA-based serological assay to measure serum/plasma levels of the entire spectrum of antibody classes and subclasses (IGM, IGG1, IGG2, IGG3, IGG4, IGA1/A2) raised against the Receptor Binding Domain (RBD) of the SARS-CoV2 Spike protein, produced in recombinant fashion. In particular, the assay will ensure the measurement of absolute amounts

(i.e concentration) of IGM- and IGG1-specific anti-RBD antibody titers. An ELISA-based competition assay will be employed to quantify the neutralizing activity of the serum of SARS-Cov2-infected patients. To perform the serological tests mentioned above, we will need between 0.5 and 1.0 ml of fresh or -20°C - stored serum (or plasma). One-two ml of fresh or cryopreserved peripheral blood mononuclear cells will be needed to estimate by flow cytometry the frequency of antigen-specific memory B cells and plasma cells revealed after staining the cells with a tetramer form of fluorescent labelled recombinant RBD.

8.3.2 Additional analyses

Analysis will include, but are not limited to, the evaluation of cytokine expression via multiplex cytokine array or other markers/predictors of response.

9.0 DATA SUBMISSION SCHEDULE

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Registration Form Eligibility Form Medical History Form Treatment History Form Medical Assessment Form Lab Form	At Baseline
Medical Assessment Form Lab Form	As Scheduled in Section 7.0
28 Day Overall Survival Form	At Day 28 or Death
Adverse Events	Continuous from baseline through safety follow-up visit
MedWatch Form	See Section 10.0 for reporting requirements
SAE / CIOMS Form	See Section 10.0 for reporting requirements for Canada
End of Treatment Form	At the completion of study follow-up
Death Form	At time of death

Any queries generated by Washington University must be responded to within 28 days of receipt by the participating site. The Washington University research team will conduct a regular review of data status at all secondary sites, with appropriate corrective action to be requested as needed.

10.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix C for definitions and Appendix D for a grid of reporting timelines.

Adverse events will be tracked from start of treatment through Day 29. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF

Refer to the data submission schedule in Section 9 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 10.1. Reporting requirements for secondary site study teams participating in Washington University-coordinated research may be found in Section 10.2.

10.1 Sponsor-Investigator Reporting Requirements

10.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

10.1.2 Reporting to Verastem

All initial and follow-up SAEs to include unanticipated problems and pregnancies, must be reported to Verastem, Inc. Safety and Pharmacovigilance via PPD at rtpsafety@ppdi.com within 24 hours of knowledge of the event concerning the Verastem, Inc. product. Reports should be submitted in English via the sponsor-investigator internal SAE/pregnancy forms, MedWatch or CIOMS forms.

Pregnancy per se is not considered an AE unless there is cause to believe that the study interventions may have interfered with the effectiveness of a contraceptive medication or if the outcome of the pregnancy meets SAE criteria (miscarriage or congenital anomaly/birth defect, etc.), in which case it should be reported in the same manner and timelines as an SAE. In addition, any infant death or congenital anomaly occurring after 30 days that the Investigator suspects is related to the in-utero exposure to the study interventions should also be reported as an SAE. Hospitalization for normal delivery of a healthy newborn is not an SAE.

Since duvelisib has not been evaluated in pregnant or nursing women, the treatment of pregnant women or WCBP who are not using highly effective contraception is contraindicated.

Pregnancies occurring in subjects or partners of male subjects during the study intervention period and until 30 days after the subject's last dose of study interventions are considered immediately reportable events. If a pregnancy occurs in a subject, study interventions must be discontinued immediately. The pregnant woman should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. The Investigator will observe the pregnant woman until completion of the pregnancy and must notify Verastem of the outcome within 24 hours of the Investigator's knowledge of the pregnancy outcome using a Pregnancy Outcome Form. This notification includes pregnancies resulting in live, "normal" births.

SAE reports must contain the following minimum information:

- At least one identifiable reporter
- One single identifiable patient
- At least one suspect adverse reaction
- At least one suspect medicinal product
- The sponsor-investigator's assessment of causality for the event

All such occurrences listed in this section shall be reported to Verastem using an approved local regulatory form and/or SAE form provided by Verastem and sent by facsimile or email to the following:

Facsimile: 888-529-3580
Email: rtpsafety@ppdi.com

FDA submissions of IND safety reports should be reported to the contact information provided above and reported to Verastem in the same timeframe as the submission. Copies of any correspondence or telephone conversation logs with the applicable Regulatory Authorities regarding all SAE(s), irrespective of association with the Study Drug(s), within a reasonable time frame must be provided to Verastem, Inc. Safety and Pharmacovigilance. The sponsor-investigator will provide additional information about SAEs or Safety Information upon request.

An aggregate listing of all SAEs and pregnancies reported by the site will be sent monthly by Verastem to the sponsor-investigator site for the site's reconciliation. Discrepancies between Verastem and sponsor-investigator site's records will be investigated by the sponsor-investigator site. The sponsor-investigator will send an updated SAE/pregnancy forms, MedWatch or CIOMS to Verastem or designee to resolve identified discrepancies.

10.1.3 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It

is the responsibility of the Washington University Sponsor-Investigator to report to the FDA as follows:

- Report any unexpected fatal or life-threatening suspected adverse reaction (refer to Appendix C for definitions) no later than **7 calendar days** after initial receipt of the information.
- Report a suspected adverse reaction that is both serious and unexpected (SUSAR, refer to Appendix C) no later than **15 calendar days** after it is determined that the information qualifies for reporting. Report an adverse event (refer to Appendix C) as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
  - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
  - One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug
  - An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group
- Report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any findings from animal or in vitro testing that suggest significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any clinically important increase in the rate of a serious suspected adverse reaction of that listed in the protocol or IB within **15 calendar days** after it is determined that the information qualifies for reporting.

Submit each report as an IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. Study teams must notify the Siteman Cancer Center Protocol Development team of each potentially reportable event within 1 business day after initial receipt of the information, and must bring the signed 1571 and FDA Form 3500A to the Siteman Cancer Center Protocol Development team no later than 1 business day prior to the due date for reporting to the FDA.

Each notification to FDA must bear prominent identification of its contents ("IND Safety Report") and must be transmitted to the review division in the Center for Drug Evaluation and Research (CDER) or in the Center for Biologics Evaluation and Research (CBER) that has responsibility for review of the IND. Relevant follow-up information to an IND safety report must be submitted as soon as the

information is available and must be identified as such ("Follow-up IND Safety Report").

10.1.1 Reporting to Secondary Sites

The Washington University Sponsor-Investigator (or designee) will notify the research team at each secondary site of all unanticipated problems involving risks to participants or others that have occurred at other sites within **10 working days** of the occurrence of the event or notification of the Sponsor-Investigator (or designee) of the event. This includes events that take place both at Washington University and at other secondary sites, if applicable. Refer to Section 16.0 (Multicenter Regulatory Requirements) for more information.

10.2 Secondary Site Reporting Requirement

The research team at each secondary site is required to promptly notify the Washington University Sponsor-Investigator and designee of all serious adverse events (refer to Appendix F, Section D) within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report (using a FDA Form 3500a (MedWatch) and Washington University's cover sheet (Appendix H)). A formal written report must be sent to the Washington University Sponsor-Investigator and designee within **4 calendar days** (for fatal or life-threatening suspected adverse reactions) or **11 calendar days** (for serious unexpected adverse reactions) of the occurrence of the event or notification of the secondary site's PI of the event.

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines. The research team at Washington University is responsible for reporting all applicable events to the FDA and AstraZeneca as needed.

10.3 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 10.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

11.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, an independent Data and Safety Monitoring Board (DSMB) will be specifically convened for this trial to review toxicity data. A DSMB will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. DSMB members must be employed by Washington University, Barnes-Jewish Hospital, or St. Louis Children's Hospital. Like investigators, DSMB members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMB will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMB must also be disclosed.

The DSM report for the DSMB will be prepared by the study team with assistance from the study statistician and will be reviewed by the DSMB. The first DSM report will be completed 3 months or following the completion of the 10^{th} enrollment, whichever comes first. Subsequent reports will be completed every 3 months thereafter or after completion of the 20^{th} and 28^{th} enrollments, whichever is sooner for as long as patients are actively receiving treatment on study. The DSM report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual including numbers from participating sites
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date and accrual by site
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities at all participating sites
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

Further DSMB responsibilities are described in the DSMB charter.

12.0 STATISTICAL CONSIDERATIONS

This is a double-blinded randomized pilot phase II study. The purpose of this study is to provide hypothesis generating data on the efficacy and toxicity duvelisib for the treatment of COVID-19. The total accrual goal is 28 patients, approximately 14 in each arm. Blocks of 10 patients will be used to allocate patients to either duvelisib or placebo. The projected enrollment time frame is 3 months (approximately 9 patients per month).

12.1 Determination of Sample Size

The primary endpoint is 28 day overall survival (OS). While outcomes data are still developing, observational studies in other areas demonstrate 28-day OS to be poor but highly variable, from approximately 10-40%. [12–14] The variability is outcomes makes a priori sample size calculations difficult, but as this pilot study is designed to generate hypotheses rather than show superiority, sample size considerations were based largely on feasibility and detecting a clinically meaningful effect rather than statistical significance. For duvelisib to have clinically meaningfully efficacy, we estimate that 28-day OS is >60% in this patient population. Based on this assumption, a sample size of 28, 14 in each arm, would allow us to detect an improvement in 28-day OS from approximately 20% to 60%, with >80% power at a one-sided type I error of <0.20. If 28 day survival in the placebo cohort is considerably higher, for example 40%, we would only have approximately 40% power in detecting a statistical-significant difference. In either event, additional confirmatory studies that are adequately powered would be needed to more accurately assess the efficacy of duvelisib for the treatment of COVID-19.

12.2 Statistical Analysis Plan

The primary endpoint is 28 day overall survival (OS) and will be treated as a binary outcome for the purposes of the primary analysis and will be described using descriptive statics with the corresponding 95% confidence intervals. This will be an intent-to-treat analysis, and all patients randomized will be included in the analysis. The assumption is that all patients will be followed for at least 28 days. Patients who are lost to follow-up for any reason prior to this point will be included in the analysis and considered treatment failures and treated the same as a death. The 28 day OS of each cohort, duvelisib versus placebo, will be compared using Fisher's exact test of independence.

In addition to the primary analysis, OS will be treated as a time-to-event variable and will be described using Kaplan-Meier product limit estimators of event time curves and, if reached, medians with 95% confidence intervals. Cox proportional hazards models may be used to adjust for potential confounding effects. These analyses are considered exploratory, and we acknowledge that the proposed sample size will have low power for such adjustment.

The analyses of secondary end points are all exploratory in nature. Secondary endpoints of efficacy include: hospital and ICU length of stay and duration of ventilator (for those on a ventilator at the time of randomization), vasopressors, and renal replacement therapy. Kaplan-Meier product limit estimators of event time curves and, if reached, medians with 95% confidence intervals, and compared between cohorts using the Log-Rank test. For these analyses, patients will be censored at Day 28 or at death, whichever is earlier. Secondary end points of toxicity are viral kinetics and adverse events. The rate of viral load elevation and other adverse events of interested will be summarized using descriptive statistics and compared using Fisher's Exact tests.

Demographic and clinical characteristics of the sample and of each cohort will be summarized using descriptive statistics. For continuous variables, the number of patients, mean, standard deviation, median, minimum, maximum, and quartiles will be provided. For categorical variables, the number and percent of patients in each demographic/characteristic category will be summarized with 95% confidence intervals.

12.3 Study Termination

Early stopping criteria for virologic failure are described above. In addition, at any time the study may be discontinued by the sponsor due to excessive toxicity, enrollment issues, etc. In this event, all participating sites, physicians, and patients will be notified and alternative treatment plans will be arranged.

13.0 MULTICENTER REGULATORY REQUIREMENTS

Washington University requires that each participating site sends its informed consent document to be reviewed and approved by the Washington University Regulatory Coordinator (or designee) prior to IRB/IEC submission.

Site activation is defined as when the secondary site has received official written documentation from the coordinating center that the site has been approved to begin enrollment. At a minimum, each participating institution must have the following documents on file at Washington University prior to study activation:

- Documentation of IRB approval of the study in the form of a letter or other official document from the participating institution's IRB. This documentation must show which version of the protocol was approved by the IRB.
- Documentation of IRB approval of an informed consent form. The consent must include a statement that data will be shared with Washington University, including the Quality Assurance and Safety Monitoring Committee (QASMC), the DSMC (if applicable), and the Washington University study team.
- Documentation of FWA, signed FDA Form 1572 (if applicable), and the CVs of all participating investigators.
- Protocol signature page signed and dated by the investigator at each participating site.

The coordinating center Principal Investigator (or designee) is responsible for disseminating to the participating sites all study updates, amendments, reportable adverse events, etc. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites within 4 weeks of obtaining Washington University IRB approval. Activated secondary sites are expected to submit protocol/consent/IB modifications to their local IRBs within 4 weeks of receipt unless otherwise noted. Upon the secondary sites obtaining local IRB approval, documentation of such shall be sent to the Washington University study team within 2 weeks of receipt of approval.

Documentation of participating sites' IRB approval of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be kept on file at Washington University.

The investigator or a designee from each institution must participate in a regular conference call to update and inform regarding the progress of the trial.

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Appendix A: Mean Arterial Pressure (MAP) Formula

$$\text{Mean Arterial Pressure} = \frac{\text{Systolic blood pressure} + (2 \times \text{Diastolic blood pressure})}{3}$$

Appendix B: Creatinine Clearance (Cockcroft-Gault) Formula

$$eC_{Cr} = \frac{(140 \text{ - Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

APPENDIX C: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death

- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX D: Reporting Timelines

Expedited Reporting Timelines			
Event	**HRPO**	**FDA**	**Verastem Oncology**
Serious AND unexpected suspected adverse reaction		Report no later than 15 calendar days after it is determined that the information qualifies for reporting	Report to Verastem at the same time as the FDA.
Unexpected fatal or life-threatening suspected adverse reaction		Report no later than 7 calendar days after initial receipt of the information	Report to Verastem at the same time as the FDA.
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.		Report to Verastem at the same time as the FDA.
Pregnancy (within 30 days after last dose)			Report to Verastem at the same time as the FDA.
Overdose			Report to Verastem at the same time as the FDA.
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.		
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.		
Protocol exception	Approval must be obtained prior to implementing the change		
Clinically important increase in the rate of a serious suspected adverse reaction of that list in the protocol or IB		Report no later than 15 calendar days after it is determined that the information qualifies for reporting	Report to Verastem at the same time as the FDA.
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH,		

Expedited Reporting Timelines			
Event	**HRPO**	**FDA**	**Verastem Oncology**
	report within 1 working day. Otherwise, report at the time of continuing review.		
Breach of confidentiality	Within 10 working days.		
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.		

Routine Reporting Timelines			
Event	**HRPO**	**FDA**	**Verastem Oncology**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	The most current toxicity table from the DSM report is provided to the FDA with the IND's annual report.	
Minor deviation	Report summary information at the time of continuing review.		
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.		
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.		

APPENDIX E: Washington University Serious Adverse Event Reporting Cover Sheet

SAE COVER SHEET- Secondary Site Assessment

Washington University HRPO#:	Sponsor-Investigator:
Subject Initials:	Subject ID:
Treating MD:	Treating Site:
EVENT TERM:	Event Start Date:
EVENT GRADE:	Date of site's first notification:

Treating MD Event Assessment:

Is this event **possibly, probably, or definitely** related study treatment?

☐ yes ☐ no

If yes, please list which drug (if more than one)_____

Explain _____

_____

_____ _____ _____

Physician's Name **Physician's Signature** **Date**