PROTOCOL TITLE: Duvelisib Ameliorates Manifestations of Pneumonia in Established Novel Coronavirus Infection (DAMPEN-CI)

NCT NUMBER: NCT04487886

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REVISION HISTORY

Revision #	Version Date	Summary of Changes
V2	26-MAY-2020	Responded to comments from FDA
V3	08-JUN-2020	Responded to comments from FDA Study May Proceed Correspondence
V3.1	19-DEC-2020	Logistical changes, sample collection updates, and small corrections
V3.2	25-APRIL-2021	Logistical changes and small corrections
V3.3	30-JUNE-2021	Added section on study-specific AE/SAE reporting

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1. Study Summary

1.1 Synopsis

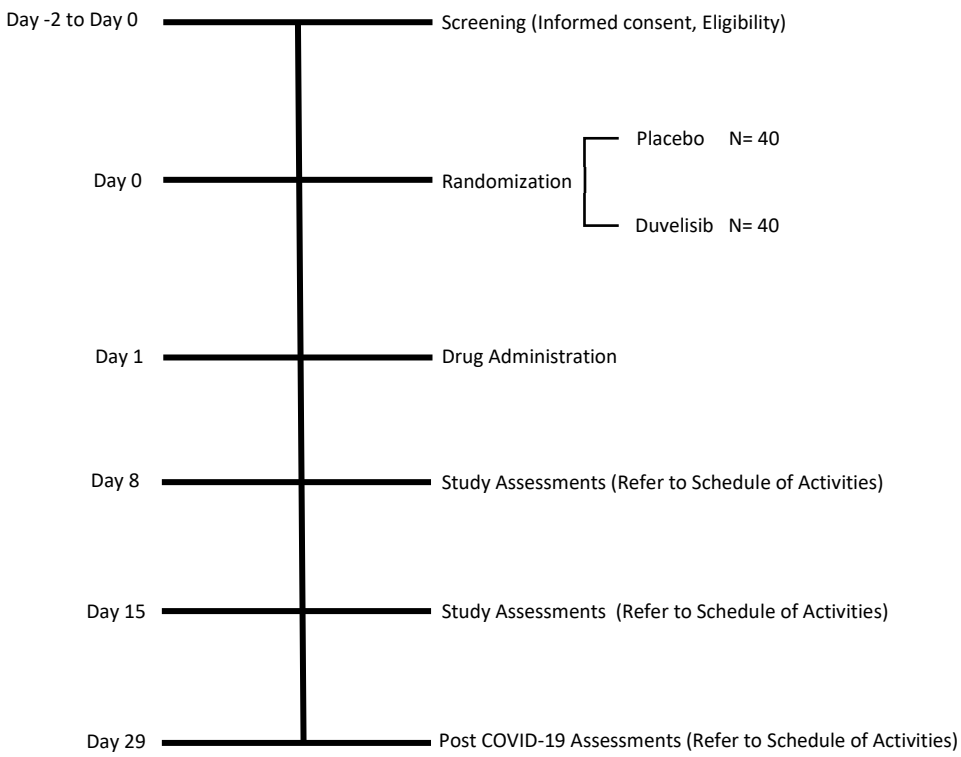
This randomized placebo-controlled phase 2 study will evaluate whether a two-week exposure to duvelisib, a gamma/delta PI3K inhibitor, reduces inflammation in the lungs in patients with severe SARS-CoV-2 infection and COVID-19 who do not require mechanical ventilation at study initiation. The primary objective of the study is to determine the efficacy of duvelisib treatment in preventing death or the need for mechanical ventilation among patients with WHO-defined severe COVID-19. Key secondary endpoints will be reductions in oxygen requirements of patients and improvements in their performance status, safety and tolerability of duvelisib in the setting of COVID-19, biomarkers of inflammation, and generation of IgG antibody responses to SARS-Cov-2 spike protein. The study will determine if a two-week exposure to duvelisib beginning soon after presentation with severe COVID-19 warrants further evaluation in a larger clinical study.

Title:	Duvelisib Ameliorates Manifestations of Pneumonia in Established Novel Coronavirus Infection (DAMPEN-CI)
Study Description:	This randomized placebo-controlled phase 2 clinical study will evaluate whether a two-week exposure to duvelisib in subjects with severe COVID-19 is safe and well tolerated, and whether exposure to the maximally effective dose of duvelisib will safely and favorably change inflammatory bio-markers and reduce the incidence of the composite end-point of mechanical ventilation or death following the diagnosis of severe COVID-19. We hypothesize that short term exposure to duvelisib in patients with severe COVID-19 will decrease the incidence of mechanical ventilation and death compared with placebo-treated control subjects. We also hypothesize that duvelisib will decrease inflammation and improve time to resolution of symptoms.
Objectives:	**Primary Objective**: 1) To compare the incidence of the composite end-point of mechanical ventilation or death within 29 days of randomization in subjects with severe COVID-19 given placebo or oral duvelisib **Secondary Objectives** are to compare the duvelisib cohort to the placebo cohort with respect to: 2) Days to recovery as assessed by ACTT endpoints as the time to recovery (Day 1 through Day 29) to satisfy one of the following eight categories from the NIAID ordinal scale. The scale is as follows: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 7) Not hospitalized, limitation on activities and/or requiring home oxygen; 8) Not hospitalized, no limitations on activities. 3) Duration of hospitalization 4) Death within 29 days of randomization

	5) ICU transfer within 29 days of randomization 6) Incidence of grade III-V adverse events or SAEs (as defined by NCI CTCAE version 5.0) 7) Documented secondary bacterial or viral infection within 29 days of randomization. 8) Mean frequencies of Th1 and Th17 T cells in blood mononuclear cells at 1, 2 and 4 weeks 9) Mean levels of inflammatory serum biomarkers at 1, 2 and 4 weeks 10) Gene expression profiles of T cells at 1, 2 and 4 weeks **11)** Median titers of IgG antibodies to SARS-CoV-2 at 4 weeks
Endpoints:	**Primary Endpoint**: 1. Composite endpoint of either mechanical ventilation or death within 29 days of randomization **Secondary Endpoints:** 2. Days to recovery as assessed by ACTT endpoints as the time to recovery (Day 1 through Day 29) to satisfy one of the following eight categories from the NIAID ordinal scale. The scale is as follows: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 7) Not hospitalized, limitation on activities and/or requiring home oxygen; 8) Not hospitalized, no limitations on activities. 3. Duration of hospitalization 4. Duration of hospitalization 5. Death within 29 days of randomization 6. ICU transfer within 29 days of randomization 7. ECOG performance status at day 15 and 29 of randomization 8. Incidence of grade III-V adverse events or SAEs (as defined by CTCAE version 5) *9.* Documented secondary bacterial or viral infection within 29 days of randomization. *10.* Mean frequencies of Th1 and Th17 T cells in blood mononuclear cells at 1, 2 and 4 weeks 11. Mean levels of inflammatory serum biomarkers at 1, 2 and 4 weeks *12.* Gene expression profiles of T cells at 1, 2 and 4 weeks *13.* Median titers of IgG antibodies to SARS-CoV-2 at 4 weeks
Study Population:	80 adults aged 18 years or older will be enrolled with severe, confirmed COVID-19
Phase:	Phase 2 randomized, placebo-controlled study
Description of Sites/Facilities Enrolling Participants:	This study will begin at Emory University and will seek to open at one or more secondary site institutions.

Description of Study Intervention:	Duvelisib is an oral PI3K inhibitor that is given at a dose of 25 mg BID
Study Duration:	We estimate that the duration of the study will be approximately 12 months. Participant duration will be approximately 1 month from the time of enrollment

1.2 Schema


Day -2 to Day 0
Screening (Informed consent, Eligibility)
Day 0
Randomization
Placebo N= 40
Duvelisib N= 40
Day 1
Drug Administration
Day 8
Study Assessments (Refer to Schedule of Activities)
Day 15
Study Assessments (Refer to Schedule of Activities)
Day 29
Post COVID-19 Assessments (Refer to Schedule of Activities)

1.2 Schedule of Assessments

Following screening, informed consent, and confirmation that a patient with severe COVID-19 meets all eligibility criteria, subjects will be randomized 1:1 to receive duvelisib 25 mg, po BID or a placebo pill, po BID. Randomization between duvelisib 25 mg po BID and placebo BID will be stratified by study site. The investigational pharmacy will supply coded study drug based upon the results of central randomization.

Procedures and Tests Study Tests DURING HOSPITALIZATION[#]	Days -2 to 0[@]	Day 1[@]	Day 8 (± 2)	Day 15 (± 2)	Day 29 (± 3)	Day 50-60
Randomization to duvelisib or placebo arm	X					
Study Drug Administration		Oral drug BID Days 1-14				
SARS-CoV-2 RT-PCR	X					
Immunophenotyping of immune cells in blood		X	X	X	X	
Whole blood for RNA gene expression [##]		X	X	X	X	
Mononuclear cells for mass cytometry [##]		X	X	X	X	
Plasma cytokines and chemokines [##]		X	X	X	X	
Anti-SARS Cov-2 IgG		X			X	
TSH	X				X	
Hepatitis Serologies if known history of treated Hepatitis B or C	X					

	Standard of Care Tests*					
	Days -2 to 0	Day 1	Day 8 (± 2)	Day 15 (± 2)	Day 29 (± 3)	Day 50-60
Physical Exam	X	Performed daily during hospitalization				
ECOG Performance Status	X	Performed daily during hospitalization				
Vital Signs	X	Performed daily during hospitalization				
	Clinical Labs: Record data in eCRF (REDCap) during hospitalization as shown below					
CBC with differential	X	Abstract data as available				
CMP	X	Abstract data as available				
Ferritin	Abstract data as available					
CRP, Troponin	Abstract data as available					
Coagulation Tests**	Abstract data as available					
Non-contrast Chest CT or Chest X-Ray	X	Abstract data as available				
Serum or Urine Pregnancy Test***	X					
Assessment of Survival Status						X

study procedures which are performed as part of the research protocol and covered by the study budget
Additional research blood samples will be obtained prior to discharge from hospital
@ Some overlap of procedures and tests performed for screening and Day 1 is expected.
* Standard of care procedures which are routinely performed on COVID-19 patients and the results of which will be recorded as part of study conduct
** PT/INR, PTT, Fibrinogen, D-Dimer, Heparin/Enoxaparin Anti Xa
*** Pregnancy test for WOCBP may be obtained after hospital admission but prior to study enrollment

2. Objectives (and Endpoints)

OBJECTIVES	ENDPOINTS
Primary	
To compare the incidence of mechanical ventilation or death in subjects with severe COVID-19 given placebo or oral duvelisib.	The primary end-point is a composite endpoint of mechanical ventilation or death within 4 weeks of randomization.
Secondary	
Secondary Objectives are to compare the duvelisib cohort to the placebo cohort with respect to: 1) Days to recovery as assessed by ACTT endpoints as the time to recovery (Day 1 through Day 29) to satisfy a score of ≥5 from the following eight categories from the NIAID ordinal scale. The scale is as follows: 1. Death; 2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3. Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4. Hospitalized, requiring supplemental oxygen; 5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 7. Not hospitalized, limitation on activities and/or requiring home oxygen; 8. Not hospitalized, no limitations on activities. 2) Duration of hospitalization 3) Death within 29 days of randomization 4) ICU transfer within 29 days of randomization 5) ECOG performance status at day 15 and 29 of randomization 6) Incidence of grade III-V adverse events or SAEs (as defined by CTCAE version 5) 7) Documented secondary bacterial or viral infection within 29 days of randomization. 8) Mean frequencies of Th1 and Th17 T cells in blood mononuclear cells at 1, 2 and 4 weeks 9) Mean levels of inflammatory serum biomarkers at 1, 2 and 4 weeks 10) Gene expression profiles of T cells at 1, 2 and 4 weeks	1) Days to recovery as assessed by ACTT endpoints as the time to recovery (Day 1 through Day 29) to satisfy one of the following eight categories from the NIAID ordinal scale (see to the left). 2) Comparing days of hospitalization between groups 3) Comparing incidence of death within 29 days of randomization in each group 4) Comparing the proportion of subjects in each group requiring ICU transfer within 29 days of randomization 5) Comparing median ECOG performance status in each group at day 15 and 29 after randomization 6) Comparing the incidence of grade III-V adverse events or SAEs (as defined by CTCAE version 5) 7) Comparing the incidence of documented secondary bacterial or viral infection within 29 days of randomization in each group. 8) Comparing the mean frequencies of Th1 and Th17 T cells in blood mononuclear cells at 1, 2 and 4 weeks in each group 9) Comparing mean levels of inflammatory serum biomarkers at 1, 2 and 4 weeks in each group 10) Description of gene expression profiles of T cells at 1, 2 and 4 weeks in each group 11) Comparing median titers of IgG antibodies to SARS-CoV-2 at 4 weeks in each group. 12) Overall survival is defined as days from randomization to death and censored at last follow up.

OBJECTIVES	ENDPOINTS
11) Median titers of IgG antibodies to SARS-CoV-2 at 4 weeks *12)* Survival at day 50-60 after randomization	

3. Background

3.1 Study Rationale

COVID-19 patients have a poor prognosis, especially in the setting of co-morbidities, the presence of inflammatory serum markers, and declining oxygenation levels, with reported frequency of ICU transfer up to 50% and death of 25% *(1, 2)*. Serum inflammatory markers in patients with severe COVID-19 including those that require ICU care and respiratory support with mechanical ventilation are reported to be higher than in patients with less severe disease *(1)*, and COVID-19 patients develop a pattern of interstitial pulmonary infiltrates *(3, 4)* that are similar to those seen among patients that develop auto-immune pneumonitis in the setting of treatment with monoclonal antibodies that block immune check-point signaling *(5)*. Taken together, these clinical and laboratory observations have led to the hypothesis that COVID-19 leads to hyper-immune activation, also termed "cytokine storm"*(6)*. Immunomodulatory clinical interventions that are currently being evaluated included antibodies that block IL6 signaling (22 trials), IL1 signaling (5 trials), and tyrosine kinase inhibitors to Bruton's tyrosine kinase (BTK) *(7)*, Janus2 Kinase (JAK) (2 trials). The common theme in these studies is the hypothesis that intra-cellular signaling pathways of immune cells are hyper-activated, that immune hyperactivation contributes to alveolar damage and impairments in gas exchange, and that clinical interventions to block intra-cellular tyrosine kinase-mediated signaling pathways activated during COVID-19 will prevent or reverse the alveolar damage and hypoxemia that characterizes this disease. Recently, clinical data from CLL patients treated with duvelisib, a dual PI3K gamma/delta inhibitor, indicate lower levels of serum inflammatory markers during PI3Ki exposure *(8)*. Addition of PI3K inhibitors, including duvelisib, during *ex vivo* expansion of T cells stimulated with anti CD3/CD28 beads indicates PI3K-inhibition appears to block differentiation of T cells from naïve/central memory to effector phenotypes, increases frequencies of CD8+ T cells, and improves in vivo persistence and anti-tumor activity when PI3Ki-expanded T cells are reinfused in vivo *(9)*. Paradoxically, continuous exposure to duvelisib over a period of months has been associated with both opportunistic infections *(10, 11)* as well as auto-immune toxicities *(12, 13)*, supporting the idea that duvelisib is an immunomodulatory drug, and indicating that short-term exposure to PI3Ki may have different immunological consequences than long-term exposure.

This study will examine if a 2-week exposure to duvelisib in patients with severe COVID-19, will favorably change their immune profile, decreasing alveolar inflammation and damage, and decrease the incidence of patients who require mechanical ventilation or who die.

3.2 SARS-CoV-2 and COVID-19

Severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) is a novel emerging pathogen that results in an illness called Coronavirus Disease 2019 (COVID-19). COVID-19 is an acute flu-like illness characterized by fever, dry cough and shortness of breath. In approximately 80-85% of individuals these symptoms will be mild to moderate, whereas in certain patient subgroups, such as the elderly and those with chronic cardiovascular disease, the illness may be severe, resulting in hypoxic respiratory failure and death *(1, 14)*. Prior to the development and after resolution of symptomatic disease, patients shed virus in mucosal surfaces, which facilitates spread of the disease. SARS-Cov-2 has a basic reproductive number of >2, meaning that the disease has the potential to expand at exponential rates. The outbreak started initially as 4 cases of severe pneumonia in Wuhan, China, but on March 11th, 2020, with over 118,000 cases spread across over 110 countries, the World

Health Organization (WHO) declared Covid-19 a pandemic. As of April 19, 2020, according to the Center for Disease Control and Prevention, there were over 690,000 confirmed cases and 35,000 deaths in the US due to this disease (https://www.cdc.gov/coronavirus/2019-ncov/casesupdates/cases-in-us.html), and experts predict that the number of individuals needing hospitalization and respiratory support may outpace existing capacity. Agents under investigation for treatment of COVID-19 include, but are not limited to, remdesivir, a nucleotide analogue, chloroquine and hydroxychloroquine, IL-6 blockers and lopinavir/ritonavir, as reviewed *(15)*.

3.3 Inflammation as part of lung pathology in COVID-19

Following initial infection of the nasal pharyngeal epithelium, SARS-Cov-2 infection can spread to the lungs where it causes viral pneumonia, producing symptoms of dyspnea secondary to hypoxemia *(2, 14)*, with radiographs showing interstitial infiltrates in the lung periphery *(3, 4)*, collectively creating a novel disease entity termed COVID-19. Severe pneumonia can progress to Adult Respiratory Distress Syndrome (ARDS) requiring intubation and mechanical ventilation *(1, 2)*.The development of severe pneumonia and respiratory failure leading to ARDS has been associated with elevated levels of serum cytokines *(1, 6)*, suggesting that SARS-CoV-2 pulmonary infection in these patients has led to a "cytokine storm", and that administration of drugs that inhibit cytokine release or block cytokine signaling may be of clinical benefit in patients with COVID-19. A recent report from Wuhan described 548 hospitalized patients with COVID-19, half of whom had severe disease (defined by the 2019 American Thoracic Society Guidelines *(16)*) of which one third required mechanical ventilation and one third died *(1)*. Age, male gender, elevated leukocyte counts, LDH, troponin and glucose levels were associated with an increased risk of death among COVID-19 patients with severe disease in a multi-variable model, and treatment with steroids, a non-specific immunosuppressive, were associated with an increased risk of death. Serum cytokine levels for IL-2R, IL-6, IL-10, and TNF-α were significantly higher in COVID-19 patients with severe disease than nonsevere patients *(1)*. These data and other reports of similar findings indicate that 1) patients with severe disease at a higher risk of death can be identified by simple clinical and laboratory assessments, 2) that disease severity is associated with a heightened inflammatory state, and 3) interventional studies to reduce inflammation in patients with high-risk disease could be of benefit to patients. A separate analysis of Wuhan patients with severe COVID-19 indicated that patients with severe disease had decreased numbers of total T cells, CD8+T cells and CD4+T cells, and that lower T cell numbers were negatively correlated with patient survival *(17)*. Of note, lower T cell numbers in patients were also associated with higher IL-6, IL-10 and TNF-α cytokine levels, and COVID-19 patients treated in the ICU had higher levels of expression of the coinhibitory markers PD-1, LAG-3 and TIM-3 *(17)*, suggesting that inflammation may cause quantitative and qualitative suppression of T cell function.

3.4 Phosphoinositide 3-Kinase (PI3K)

PI3K proteins are divided into three classes of which only Class IA PI3K molecules have been implicated in human cancers, prompting development of isoform-selective inhibitors to Class IA PI3K *(18)*. Analysis of evolutionary conservation across known class I PI3K signaling cascades reveals the greatest conservation in signaling along the insulin/IGF-1/AKT pathway, suggesting PI3K primarily evolved to regulate cellular proliferation and metabolic changes in response to glucose *(18)*.

PI3Ks are involved in the generation of lipid second messengers and contain eight catalytic subunits of PI3K, with the P110 gamma and the P110 delta subunits being expressed at much higher levels in immune cells *(19, 20)*. The PI3K p110 subunits work by phosphorylating phosphatidylinositol 4,5 bisphosphate (PIP2) into phosphatidylinositol 3, 4,5 triphosphate (PIP3), which enables anchorage and association of cytosolic proteins near the lipid bilayer, enabling complex signal transduction cascades to occur *(18)*. In the case of T cells, metabolism of glucose is closely linked to the replicative capacity of the cells, with T cells capable of oxidative phosphorylation exhibiting enhanced replicative capacity whereas T cells that rely upon glycolysis exhibit reduced replicative potential, as reviewed *(21)*.

PIP3 then goes on to function as a second messenger that initiates multiple signaling cascades, including the phosphorylation of AKT, a serine/threonine protein kinase, leading to downstream survival and differentiation signals for example through mechanistic target of rapamycin 1 (mTOR) also a serine/threonine kinase*(22)*. Upon T cell activation, there is an increase in uptake of amino acids and glucose leading to activation of mTOR1 and this activation is required to maintain the T cell effector functions *(23–26)*. Activation of mTOR1 also promotes induction of aerobic glycolysis, as well as assistance in maintaining it, which leads to increased differentiation and effector functions, which are shown to be less efficacious in terms of adoptive T cell therapies *(26)*. By inhibiting mTOR through inhibition of PI3K. PI3K inhibitors promote formation of a pool of T-cells with a memory phenotype by inhibiting aerobic glycolysis and preventing terminal differentiation *(26)*. Given that Daio et al. showed that CD8 and CD4 T-cells in COVID-19 patients increase expression of PD-1 and TIM-3 as their clinical symptoms worsen*(17)*, we propose that duvelisib may mitigate T-cell exhaustion to promote more effective anti-viral responses to COVID-19, thus preventing COVID-19 infection progression.

3.5 Pre-Clinical Pharmacology of duvelisib and T cell activation and expansion

Duvelisib is a highly potent, PI3K delta and gamma inhibitor with a whole blood IC_{50} of 0.36nM for inhibition of the delta subunit and whole blood IC_{50} of 19.6nM for inhibition of the gamma subunit *(11)*. We have seen that human T cells from healthy volunteers and chronic lymphocytic leukemia (CLL) patients show a doubling in net expansion at concentrations of duvelisib from to 40nM to 0.4 μM over a 9-14 day culture period (*(9)* and unpublished data). Of note, high dimensional profiling of T cells showed less effector T cells and a shift in the metabolic profile of T cells from dependency on glucose to glutamine and lower levels of expression of co-inhibitory markers PD-1, TIM-3 and LAG-3 (unpublished). Furthermore, models of the human CLL cell line OSU-CLL engrafted to NOG mice show that duvelisib-cultured chimeric antigen receptor (CAR) T-cells exhibit enhanced in vivo proliferation, greater CD8:CD4 CAR ratios, and enhanced efficacy (unpublished data). Taken together, this data indicates that a short-term exposure of T cells to duvelisib is not globally immunosuppressive but instead preserves qualitative measures of T cell function while reducing effector T cell differentiation and preserving naïve and memory subsets.

3.6 PI3K inhibitors in clinical settings

PI3-kinase (PI3K) inhibitors are FDA-approved for treatment of relapsed follicular lymphoma (FL) and CLL/small lymphocytic lymphoma (SLL). Orally bioavailable drugs are typically dosed once or twice a day with the goal of inhibiting signaling through the PI3K-AKT pathway causing reduction in the growth of malignant lymphoma cells and induction of apoptosis. PI3K inhibitors are generally well tolerated and can be given for weeks to months as continuous therapy without significant hematological toxicity. One common feature of treatment with PI3K inhibitors is the development of late autoimmune disease, typically after more than 1 month of drug exposure, including colitis, pneumonitis and rash, that appears to be a consequence of blocking differentiation and down-regulation of regulatory T cells *(12, 27)*.

4. Study Intervention/Investigational Agent

4.1 Description (duvelisib)

Duvelisib is an oral PI3K inhibitor. FDA approved duvelisib (Copiktra, IPI-145) on September 24, 2018. Duvelisib is approved for the treatment of adult patients with relapsed or refractory CLL/SLL after at least two prior therapies, and relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies. Refer to the approved labeling for more details on specific indications and for detailed information on duvelisib.

4.2 Drug handling

4.2.1 Acquisition and Accountability

Duvelisib and unmatched placebo capsule (same size and shape but slightly different shade of blue/green) will be provided by Verastem and will be packaged and labeled by Verastem. The study drug provided for this study will be used only as directed in the study protocol. The IDS (Investigational Drug Service) personnel at each site will account for all study drugs. Drug accountability should be performed until the patient stops study treatment completely. Study site personnel will account for all study drugs received at the site. Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels. The Investigator, pharmacist, or designee must maintain an accurate record of dispensing the study drug/s in a Drug Accountability Log.

The Drug Accountability Log may record specifics to study drug dispensation such as:
• Records of product delivery, inventory, temperature monitoring, destruction, and return.
• Dosages prepared, time prepared, doses dispensed.
• Doses destroyed.
• The Drug Accountability Log will be reviewed by the monitor during site visits and at the completion of the study.

The study drug supply will be disposed of as per Winship's Investigational Pharmacy (IDS) SOP. Duvelisib/study drug capsule should be taken at approximately the same times on each day. Duvelisib/study drug capsule should be taken with 8 oz of water if possible. Compliance will be assessed by the investigator and/or study personnel and information provided by the Hospital electronic medical record will be captured in the Drug Accountability Form. Dose changes and interruptions of study drug must be specifically documented in the patient source documents and eCRF. The time of each dose should be reported in the Hospital electronic medical record. Patients will not be allowed to make up missed doses and a missed dose should also be recorded in the Hospital electronic medical record. Damaged medication will be replaced.

4.2.2. Formulation, Appearance, Packaging and Labeling

Duvelisib comes in two strengths: 15mg and 25mg capsules. A placebo capsule matched in size and shape with similar color to the 25 mg duvelisib capsule will be provided by Verastem. Twenty-eight (28) 25mg duvelisib tablets or placebo capsule will be dispensed to the in-patient unit for each enrolled patient. 15mg duvelisib tablets are also available if needed for dose reduction. All duvelisib and placebo capsules will be over-encapsulated at the Emory Investigational Pharmacy so that they appear identical, to avoid unblinding due to differences in duvelisib and placebo capsule color.

4.2.3. Product Storage and Stability

Duvelisib/placebo will be stored at the Emory Investigational Pharmacy. Duvelisib/study drugs will be stored at room temperature between 20-25 degrees Celsius.

4.2.4. Study Drug Administration:

Duvelisib/placebo is an oral medication that will be taken twice a day. The intent of the study design is to conduct a placebo-controlled double-blinded/double-masked administration of duvelisib or placebo in hospitalized

patients with severe COVID-19. All efforts will be undertaken to maintain ignorance among clinical and study staff as to allocation of each individual patient to active drug versus placebo. Subjects, the clinical team (physicians, nurses, advanced practice providers (nurse practitioner/physician assistant), clinical pharmacists) will not be informed as to whether an individual subject is receiving active drug or placebo.

4.2.5 Interruption/Disruption of Treatment:

Duvelisib/placebo is a BID medication. Medication doses that are missed or not absorbed (i.e., vomiting) will not be made up with additional dosing.

Duvelisib can be stopped if any of the following are observed:

- Grade 3 or 4 hematologic toxicity (19) as defined by the NCI CTCAE v5.0.
- Grade 3 or 4 non-hematological toxicity

Study drug (duvelisib or placebo) will be stopped at the time of hospital discharge if that occurs prior to day 15.

Grades 1-2 AEs as defined by the NCI CTCAE, version 5.0 will not result in any dose modifications and will be treated with supportive care. If study drug is stopped due to an AE, it will not be resumed.

5. Study Procedures

5.1 Study Design

This is a prospective placebo-controlled, double-blinded/double-masked phase 2 clinical trial study of treating patients with severe COVID-19 disease who do not require mechanical ventilation at randomization with the FDA-approved dose of duvelisib for a maximum of 14 days.

Rationale for study design

Duvelisib is proposed as an immunomodulatory drug that can reduce the generation of inflammatory cytokines in patients with severe COVID-19 while preserving quantitative and qualitative T cell function. A two-week exposure to duvelisib has been chosen because clinical deterioration of patients with severe COVOD-19 typically occurs within this time frame, and we have demonstrated enhanced T cell expansion and decreased expression of markers associated with T cell exhaustion and senescence in T cells co-cultured with duvelisib for 14 days in both healthy controls, CLL and DLBCL patients. While longer exposure to duvelisib might be considered, it is appropriate for an initial study to limit the duration of exposure to reduce the risk of secondary opportunistic infections associated with long-term exposure and to potentially preserve B cell function and humoral responses to SARS-CoV-2.

Justification for Duvelisib Dose

In the phase I study with duvelisib in hematological malignancies, the maximum tolerated dose (MTD) was 75 mg BID. However, peak inhibition of the p-AKT pathway was not dose dependent among the doses tested and was maximally inhibited at 25mg BID, and this is the FDA approved dose (8). We will initiate treatment of critically ill patients with COVID-19 at an initial dose of 25 mg duvelisib BID, and dose-deescalate to 15 mg BID if patients receive concomitant drug that is a strong CYP3A4 inhibitor.

5.2 Dosing and Administration

Regimen Description					
Agent	**Premedication/Precautions**	**Dose**	**Route**	**Schedule**	**Treatment Course**
Duvelisib/ placebo	Take with 8 oz of water food	25 mg capsule	PO	BID	14 days

5.3 Dose Modification

The investigator will decide whether any AE that occurs is related to study drugs and determine whether dose modification or discontinuation of duvelisib/placebo is required. Treatment of critically ill patients with COVID-19 will be started at an initial dose of 25 mg duvelisib/placebo BID, and dose-deescalate to 15 mg BID if patients receive concomitant drug that is a strong CYP3A4 inhibitor.

5.4 Concomitant medication

Acceptable Concomitant Medications

Patients with severe COVID-19 are ill and will require treatment with standard-of-care drugs or procedures to treat existing signs and symptoms of their disease and to prevent the development of additional disease manifestations. All concomitant medication (including prescribed, over the counter, herbal or vitamin supplements) used by the patient prior to 7 days to enrollment are permitted to be continued under the supervision and discretion of the treating physician. The use of FDA-approved drugs in an "off-label" situation to treat or prevent signs or symptoms of COVID-19 are permitted if they are given under the direction of the treating physician as local standard-of-care. Any drug with known anti-viral activity that has been accepted by the FDA/CDC/NIH/WHO in published clinical guidance documents as having activity against SARS-CoV-2, or an anti-viral drug that has been approved by a regulatory agency for use as an anti-viral against SARS-CoV-2 is permitted as standard-of-care or as part of a formal clinical study. Co-enrollment in randomized or non-randomized clinical studies of drugs with potential anti-viral activity against SARS-CoV-2 are permitted. For example, the FDA has authorized the unapproved product remdesivir for treatment of suspected or confirmed COVID-19 in adults and children hospitalized with severe disease. As new drugs are developed and introduced into the treatment paradigm for patients with COVID-19, the toxicity profile of these drugs will be compared with the toxicity profile of duvelisib by the study pharmacist. Treatment with an agent (investigational or standard of care) with a toxicity profile that overlaps significantly with that of duvelisib will be an exclusion criterion for subject enrollment. Co-enrollment on a clinical study testing another immune-modulatory drug (i.e., tociluzumab, baracitinib) is not permitted. Determination of whether the mechanism of action of drugs being tested in COVID-19 patients have an immune-modulatory effect as their primary proposed mechanism of action will be made monthly by the study pharmacist based upon a review of data available in www.clinicatrials.gov, and an updated list of non-permitted immune-modulatory drugs will be provided to the research staff for the purposes of subject screening. All medications should be reported to the investigators and recorded in the concomitant medications page.

It is anticipated that participants may be treated with antibacterial agents, either for concomitant infection, or bacterial superinfection, anti-coagulants, and passive antibody treatment (immune plasma or purified antibodies reactive to SARS-CoV-2 epitopes). The final decision for antibiotics (need, drug[s] and dose) and other medications will be made by the treating physician (except as noted below under Prohibited Medications). Concomitant use of medications that are sensitive CYP450 substrates (Appendix C) are prohibited, unless

absolutely necessary. If concomitant use of a medication which is a CYP450 substrates is required, then adverse events (AEs) should be monitored every 2 days.

Pneumocystis jirovecii pneumonia (PJP) and CMV prophylaxis.

Since duvelisib or placebo exposure is only 14 days, the risk of developing PJP of CMV viremia in this study is low, and specific antimicrobial prophylaxis with Bactrim (PJP) and valganciclovir (CMV) for a 14 period would be of limited clinical benefit given the short time of exposure to duvelisib, and prophylaxis with Bactrim and/or valganciclovir could lead to a higher incidence of blood cytopenia which might trigger stopping the study drug. Given the short term exposure to duvelisib, no PJP or CMV prophylaxis is mandated by the protocol, although treating physician may prescribe such medications if deemed to be in the interests of the subject.

Prohibited Medications and Food

Concomitant medications will be tracked daily during duvelisib administration. Patients on strong inhibitors of CYP3A (Appendix B) will receive a reduced dose of duvelisib of 15 mg PO BID (or matched placebo). Initiation of medications known to be strong inducers or inhibitors of CYP3A should be avoided unless deemed to be necessary by the PI. In this instance, patients should be carefully monitored and the duvelisib dose reduced to 15 mg PO BID if the patient was started on a CYP3A inhibitor. Please see Appendix B for known potent inhibitors and inducers of CYP3A. Other anti-neoplastic drugs, radiotherapy and other investigational drugs other than anti-viral and other non-immunomodulatory drugs to treat signs and symptoms of COVID-19, as described above, are prohibited during the study period. Concomitant use of an immunomodulator or immunosuppressant (Appendix E) such as IL-6 inhibitors, TNF inhibitors, anti-IL-1 agents, and JAK inhibitors while on study or within 5 half-lives or 30 days (whichever is longer) prior to randomization is prohibited.

5.5 Study Procedures

Before randomization, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate **safety and tolerability assessments**. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments during the screening and treatment period is provided following the Protocol Synopsis. Please see Section C, Schedule of Activities, Table 1, for the schedule for screening phase and treatment phase procedures. Screening assessments will be completed within two days of initiation of duvelisib/placebo.

Screening Phase:

All screening evaluations must be conducted and reviewed by the primary investigator to confirm that patients meet the eligibility criteria. The following procedures will be performed during the screening visit:

- Informed Consent
- Medical History, Physical Exam, Assessment of Performance Status
- Nasopharyngeal swabs for SARS-CoV-2 RT-PCR test, with Ct values for positive tests. Note: saliva SARS-CoV-2 PCR test will be added once available.
- Electrocardiogram (EKG) (if ordered by the primary care team)
- Labs: Complete Blood Count (includes hemoglobin, platelets, and white blood cell count with differential), Comprehensive metabolic panel (includes sodium, potassium, chloride, creatinine, AST, ALT total bilirubin and alkaline phosphatase), Thyroid Stimulating Hormone (TSH), and Covid-19 IgG. Other labs typically (but not always) ordered by the primary care team at the time of screening include: ferritin, D-dimer, CRP, Coagulation Testing (PT/INR, PTT)

- Non-contrast Chest CT and/or Chest X-ray
- Pregnancy Test (for pre-menopausal women)
- Hepatitis C antibody and Hepatitis B antibodies and viral antigen testing (if known history of treated Hepatitis B or C).

Treatment Phase:

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Activities (Section C).

- Randomization to duvelisib or placebo arm
- Study drug administration (BID Days 1-14)
- Brief medical history
- Symptom-directed physical exam
- ECOG Performance Status
- Vitals signs, weight, requirement for supplemental oxygen
- Review of prior/concomitant medications
- EKG as ordered by attending physician
- Labs: Complete Blood Count (includes hemoglobin, platelets, and white blood cell count with differential), Comprehensive metabolic panel (includes sodium, potassium, chloride, creatinine, AST, ALT, total bilirubin, and alkaline phosphatase), ferritin, D-dimer, CRP, troponin (abstract from SOC labs daily or as available), Thyroid Stimulating Hormone (TSH, Day 29)
- Immune phenotyping of leukocytes (days 1, 8, 15, and 29)
- Whole blood for RNA – gene expression analyses (days 1, 8, 15, and 29)
- Mononuclear cells for mass cytometry (CyTOF) (days 1, 8, 15, and 29)
- Plasma for cytokine/chemokine analyses (days 1, 8, 15, and 29)
- Serum for antibodies to SARS-CoV-2 (screening and 29)

Follow-up Phase:

- Survival status on day 50 - 60

5.6 Description of Data Collection

Definition of Study Assessments

All patients will be closely monitored for safety and tolerability throughout the study. Patients will continue dosing until they experience intolerable AE's, discharge from hospital,patient withdrawal or termination of the study. Subjects may be discontinued from study treatment in the following situations: 1) subject has decided to withdrawal from the study, 2) Intolerable adverse events, 3) mechanical ventilation (e.g. intubation, high-flow 0_2 Bi-PAP or AIRVO) or death, 4) pregnancy, or 5) severe noncompliance. The schedule of activities is listed in section C.

Medical History

Medical history and demographics will be collected at screening. Medical history will include other significant co-morbidities, previous surgeries, history of hypertension, chronic obstructive lung disease, asthma, diabetes, cancer, previous chemotherapy and outcomes, prior immunosuppressive drug therapy including

steroids, use of tobacco, alcohol and recreational drugs and any known toxin exposure. Demographics data will include age, sex and self-identified race/ethnicity.

Performance Status

The ECOG performance status will be assessed at screening and on days 1 [baseline, prior to study drug], 8, 15, and 29.

Physical Exam

Physical exam will include focused examination of body systems, including assessment of ECOG performance status, weight, heart, lungs, abdomen, skin and nervous system. A targeted physical exam will be performed on screening and on days 1 [baseline, prior to study drug], 8, 15, and 29.

Clinical Assessments

Vital signs will be recorded daily including maximal and minimal blood pressure, heart rate, temperature, oxygen saturation. Daily weights will be recorded. The maximum level of supplemental oxygen delivered in each 24-hour period will be recorded. Results from imaging studies of the lung ordered as part of the standard-of-care management of COVID-19 patients will be extracted from the electronic medical record and entered into case report forms. Positive results from microbiological tests of blood, sputum, and bronchial lavage ordered as part of the standard-of-care management of COVID-19 patients will be extracted from the electronic medical record and entered into case report forms.

Clinical Laboratory Data

Blood samples for chemistry, hematology, viral serologies, leukocyte immunophenotyping and pregnancy (for pre-menopausal patients) will be analyzed at Emory or secondary site clinical laboratories. The chemistry panel will include sodium, potassium, chloride, bicarbonate, glucose, BUN, AST, ALT, total bilirubin, total protein, ferritin, D-dimer, CRP will be tested at screening and on days 1, 8, 15, and 29. TSH will be tested at screening and at day 29. Hematology panel includes complete blood count, including white blood cell count with differential (neutrophils, lymphocytes, eosinophils, basophils), red blood cell count, hemoglobin, hematocrit and platelet count will be tested at screening and days 1, 8, 15, and 29. Hepatitis viral serologies will be tested at screening if a patient has a prior history of treated hepatitis B or C, and include:

- Hepatitis B Panel (HBsAg, HBsAb, HBcAb and HBV DNA PCR)
- Hepatitis C Panel (HCV Ab and HCV PCR)

Correlative Laboratory Data

- SARS-CoV-2 RT-PCR test from nasopharyngeal swabs will be ordered at screening [baseline, prior to study drug]. Results are returned as positive or negative, with Ct values for positive tests. Note: saliva SARS-CoV-2 PCR test will be added once available.
- Leukocyte immunophenotyping (via flow cytometry/fluorescence-activated cell sorting) will be done at days 1, 8, 15, and 29. This will determine the amount of B/T/NK cells and more specifically, the phenotypes and frequencies of these immune cell populations pre and post duvelisib exposure (Th1 and Th17 T cells).
- Mononuclear cells collected at days 1, 8, 15, and 29 will be stored for CyTOF analyses for more in-depth immune-phenotyping in follow-up studies.
- Blood cells collected at days 1, 8, 15, and 29 will also be collected in RNA stabilization tubes for immunological gene expression analyses.

- Mean levels of inflammatory serum biomarkers will be measured by ELISA at day 1 [baseline, prior to study drug], during and following 2 weeks of study drug exposure in each cohort, using samples at days 1, 8, 15, and 29
- Median titers of neutralizing antibodies to SARS-CoV-2 will be determined at days 1 and 29.

6. Data and Specimen Banking

Specimens will be obtained and used for medical research by the investigators of this study. Data and specimens from this study may be useful for other research being done by investigators at Emory or elsewhere. To help further science, Investigators may provide de-identified data and/or specimens to other researchers. Any information that could identify participants will not be included. If data or specimens are labeled with study ID, we will not allow other investigators to link that ID to identifiable information.

Samples and data collected under this protocol may be used to study **COVID-19**. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

The results of some study tests and procedures will be used only for research purposes and will not be placed in subject's medical record.

7. Sharing of Results with Participants

In general, study staff will not provide any individual results to subjects (ex. outcome trial results or results from subject's samples studies). If something of urgent medical importance to the participating subjects will be found, the PI (or co-Is) will inform the subject, although we expect that this will be a very rare occurrence. Samples and data will only be used for research.

8. Study Timelines

8.1 Duration of therapy and follow up

In the absence of treatment delays due to adverse event(s), subjects will be treated for 14 days with duvelisib/placebo. A subject will be considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the schedule of activities. Subjects who have signed consent, are deemed eligible and are randomized to receive study drug (duvelisib/placebo) will be considered evaluable for efficacy endpoints on an intent-to-treat basis. Subjects who receive at least one dose of study drug (duvelisib/placebo) will be evaluable for toxicity. The end of the study is defined as completion of the last visit or procedure in SOA (Day 29) and an assessment of survival status on day 50 - 60. In the event of a subject's withdrawal, the Investigator will make every effort to complete the End of Treatment procedures specified in the Schedule of Events. Subjects who withdraw from the study will be encouraged to permit follow-up for clinical end-points, including death, mechanical ventilation (e.g. intubation, high-flow 0_2 Bi-PAP or AIRVO), hospital discharge, and need for supplemental oxygenation. Subjects will be assessed daily while hospitalized. If the subjects are discharged from the hospital, they will have phone follow-up calls with a study team member at

day 15 (window d13 – 25), and at day 29 (window d27 - 39) for clinical outcomes data. Arrangements will be made for an outpatient phelebotomy appointment after day 29 (day 30 - day 60 if possible, but up to day 100) to obtain safety laboratory tests and blood samples for secondary research. Patients will receive $100 compensation for the in-person follow-up phlebotomy visit. However, travel distance, infection control or other restrictions may limit the ability of the subject to return to the clinic. In such cases, only clinical data will be obtained via the d27 - 39 call.

Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event and for key clinical end-points including death, mechanical ventilation (e.g. intubation, high-flow 0_2 Bi-PAP or AIRVO), hospital discharge, and need for supplemental oxygenation. Survival status of each subject will be assessed by reference to documentation in EMR of non-protocol specified in-person or tele-medicine visits that occurred on or following day 50 - 60, contacting the patient by phone or text, contacting know associate of the patient, or through a search of vital records.

8.2 Study termination

This study may be suspended or terminated if there is sufficient reasonable cause. The Sponsor/Investigator will notify the co-investigators and Verastem if he/she decides to discontinue the study. If the study is prematurely closed, the clinical investigators will notify the study participants, and the Sponsor/Investigator will notify the IRB/IEC, and the FDA. Reasons for suspension and termination of the study include:

- Determination of unexpected or unacceptable risk to patients
- Demonstration of efficacy that would warrant stopping
- Determination of futility
- Insufficient compliance to protocol requirements
- Determination that the primary endpoint has been met

The study may resume once concerns about safety and compliance have been addressed and are satisfactory with sponsor and IRB/IEC.

9. Inclusion and Exclusion Criteria

9.1 Inclusion Criteria

1. Hospitalized in participating facility.
2. Documentation of pneumonia with radiographic evidence of infiltrates by imaging (e.g., chest x-ray or CT scan).
3. Laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other authorized or approved assay in any specimen collected within 72 hours prior to enrollment. Note – An exception must be requested to the Sponsor if ≥72 hours since positive test.
4. Symptoms suggestive of severe systemic illness with COVID-19, such as respiratory rate $\geq$ 30 breaths per minute, heart rate >125 beats per minute, oxygen saturation (O_2 sat) in the blood of <93% on room air at sea level or PaO_2/FiO_2< 300 (see Appendix A).
5. 18 years of age or older
6. Patients with hematological parameters at screening consistent with $\leq$ grade 2 NCI CTCAE v5.0 toxicity: hemoglobin $\geq$8 g/dL, platelet count $\geq$50,000 K/mcl, an absolute neutrophil count (ANC) $\geq$1,000/mm3, and an absolute lymphocyte count (ALC) $\geq$500/mm3.

7. Patients with laboratory measurements of liver function at screening consistent with ≤ grade 2 NCI CTCAE v5.0 toxicity: alanine aminotransferase (ALT) ≤ 5X ULN; aspartate aminotransferase (AST) ≤ 5X ULN; and bilirubin ≤ 3X ULN.
8. The effects of duvelisib on the developing human fetus are unknown. For this reason, women of child-bearing potential (WOCBP) must have a negative serum or urine pr5egnancy test prior to starting therapy. WOCBP and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) from enrollment into this study until at least 60 days after the first dose of duvelisib. A woman of childbearing potential (WOCBP) is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 2 months after completion of duvelisib administration. WOCBP must have a negative pregnancy test after admission to the hospital, prior to the first dose of study drug.

    The patient must be willing to comply with fertility requirements as below:

    - Total abstinence (when this is in line with the usual practice and lifestyle of the patient) will be accepted. Periodic abstinence (i.e., calendar, ovulation, post-ovulation methods) and withdrawals are not acceptable forms of contraception. All other patients must comply with the measures described below.
    - If a female participant is of reproductive potential, the participant (and her partner) must agree to use of one of the following combinations of birth control during the study and for 2 months after the last dose of study drug (or tubal ligation as a single method):
        1) Use of a double-barrier method of contraception: condoms (male or female) and a diaphragm or cervical cap with spermicide;
        2) Use of an IUD and a barrier method: condoms (male or female, with or without spermicide) or a diaphragm or cervical cap with spermicide;
        3) Tubal ligation.
    - Women who are post-menopausal, defined as age greater than 45 and no menses for at least 24 consecutive months, or who have had a hysterectomy, are considered not of reproductive potential.
    - Males must agree to using contraception during the study and for 2 months after the last dose of study drug or have undergone a male sterilization procedure (at least 6 months prior to screening.
    - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception, or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of contraception that comparable efficacy (failure rate <1%). In case of oral contraception, the woman should be stable on the same pill for a minimum of 3 months prior to enrollment on the study.
5. Patients must agree not to donate blood, sperm/ova or any other organs while taking protocol therapy and for at least 2 weeks after stopping treatment.
6. Willingness and ability of the patient to comply with scheduled visits, drug administration plan, protocol specified laboratory tests, other study procedures and study restrictions
7. Evidence of personally signed informed consent indicating that the subject is aware of the life-threatening nature of the disease and has been informed on the procedures to be followed, the experimental nature of the therapy, alternative, potential risks and discomforts, potential benefits and other pertinent aspects of study participation.

9.2 Exclusion criteria

1. Patients requiring mechanical ventilation (e.g. intubation, high-flow 0_2 Bi-PAP or AIRVO) at the time randomization.
2. Patients receiving any investigational drugs other than drugs or therapies to treat COVID-19, with the exception of investigational immune-modulatory drugs as per section 5.4.
3. Pregnant women are excluded from this study because duvelisib is agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with duvelisib, breastfeeding should be discontinued before starting study drug and breastfeeding should not be resumed until at least 1 month after last dose of study drug.
4. Clinical suspicion that the etiology of acute illness (acute decompensation) is primarily due to a condition other than COVID-19
5. Known contraindication to duvelisib
6. Patients with hepatic cirrhosis as defined by symptomatic liver dysfunction; liver fibrosis by biopsy; ALT > 5X ULN, AST> 5X ULN, or bilirubin > 3XULN.
7. Patients with autoimmune diseases or patients on chronic immunosuppressive medications at the time of hospital admission or screening.
8. Active Hepatitis B or C infection, as determined by FDA-approved serology testing.

10. Number of Participants

We will be recruiting a total of 80 participants at Emory Healthcare and potential secondary sites, combined. We are expecting to have to consent 100 number of participants to reach our recruitment goal of 80. Patients will be registered after signing of the informed consent document and meeting all entry requirements.

11. Recruitment Methods

Investigators, nurses, and/or data managers review lists of patients who have COVID-19 and will determine if there are patients who might be eligible for a clinical trial. The nurse/data manager reviews accessible medical records to screen further for eligibility. Subjects will be identified by their treating physicians. Clinical care team at Winship will inform potential subjects about the known benefits and potential risks of a clinical trial as well as other available treatment options. Some of the subjects recruited for this protocol will be patients being treated at Emory and under the care of one or more of the study investigators.

No incentives are provided to patients for trial participation.

Study personnel will notify Winship Central Subject Registration (WCSR) by email at winshipcsr@emory.edu, once subject has been consented for a trial. Email notification must be done within 24 hours after consent has been obtained and it will include scanned copies of:

- Signed patient consent form
- HIPAA authorization form
- Emory Research Management System (ERMS; *https://erms.emory.edu*) Enrollment Fax Cover

The WCSR will enter the subject into the OnCore Research Management System, which is the system of record for Winship Cancer Institute Clinical Trials.

Participating Site (s)

A site- specific Central Subject Registration (CSR) form will be provided to Participating Site.
After each subject signs consent, the Central Subject Registration form is to be completed and sent to Winship within 24 hours of consent. This form, along with the valid, signed informed consent form/HIPAA authorization form, is to be faxed or emailed to Winship's Central Subject Registrar per instructions on the form. Once a subject is registered, each participating site will be notified via e-mail.

Enrolling a subject requires careful screening and determination of eligibility.
Eligible patients will be enrolled on study centrally at Winship Cancer Institute by the Study Coordinator.
When all required test results are available, complete the eligibility checklist and provide the checklist and the supporting documentation to the IRB approved investigator for review and sign-off. Once the investigator (sub-investigator, Co-Investigator) has signed the eligibility checklist, randomization and enrollment may proceed. Oncore and ERMS must be updated to reflect eligibility and on treatment status.
Following enrollment, patients should begin protocol treatment within 3 days. Issues that would cause treatment delays should be discussed with the Principal Investigator.

Screen failures:

After the screening evaluations have been completed, the investigator or designee is to review the inclusion/exclusion criteria and determine the participant's eligibility for the study.

Only the reason(s) for ineligibility will be collected on screen failures. Participants who are found to be ineligible will be told the reason(s) for ineligibility.

Individuals who do not meet the criteria for participation in this study (screen failure) because of an abnormal laboratory finding may be rescreened once

Participating site

The Eligibility checklist is to be printed from OnCore and verified by 2 people, of which one must be a clinical investigator or co-investigator. The completed and signed eligibility checklist along with all redacted supporting source documentation must be submitted to the Winship Multi-site Coordinator (MSC) or designee (fax 404-778-0417) within 14 days after pre-registration but no later than 2 business days before the scheduled treatment visit. Eligibility will be confirmed by the site investigator or co-investigator and the MSC or designee within 1 business day of receipt of all eligibility documentation and confirmation will be sent to the participating site along with cohort assignment, if subject meets criteria. The Participating Site will enter all subject enrollment data in OnCore following eligibility confirmation, including subject 'on treatment date'. If a consented subject does not meet eligibility criteria (screen failure), the MSC will update the enrollment status in OnCore. The Participating Site is responsible for entering data for all procedures subject completed prior to eligibility determination.

Randomization between duvelisib 25 mg po BID and placebo BID will be stratified by study site. The investigational pharmacy will supply coded study drug based upon the results of central randomization.

12. Withdrawal of Participants

All study patients have the right to withdraw from the study at any time. The reasons for withdrawal must be documented in the case report form. Final study evaluations will be done at the time of withdrawal. The following are examples of early withdrawal from the study:

- Patient withdrawal of consent at any time

- Any medical condition that the primary investigator believes may jeopardize the patient's health or safety if they continue in the study
- Pregnancy
- Initiation of mechanical ventilation (e.g. intubation, high-flow O_2 Bi-PAP or AIRVO)
- Termination of the study by the Sponsor/Investigator, IDMC, the IRB, or the FDA

13. Risks to Participants

Safety of duvelisib:

Immune related toxicities are the most common non-hematological adverse event (AE) with duvelisib. Elevated AST/ALT and diarrhea are the most common non-hematological AEs. The rates of diarrhea ranged from 42-51% in clinical trials with a median onset of 2.2-4 months (*28, 8*). The median time of onset for AST/ALT elevation was 1.2 months and occurred in 39% of patients in one phase I clinical trial (*28*). Other non-hematological AE's that have been reported include:

1) risk of infection (reported in 61-69% of patients with upper respiratory tract infections and pneumonia being the most common infections (*8, 29*).) There have also been reports of Pneumocystis jirovecci with the use of duvelisib.
2) risk of pneumonitis,
3) risk of intestinal infection and colitis,
4) risk of severe skin reactions (maculopapular rash)
5) Neutropenia (the most common hematological AE, occurring in 29%-39% of patients in clinical trials)
6) pyrexia

Other Risks:

Risk of Phlebotomy- The primary risks of phlebotomy include local discomfort, occasional bleeding or bruising of the skin at the site of needle puncture, and rarely hematoma, infection, or fainting. At the time of enrollment and during study visits, each participant will be asked about participation in other research studies to ensure that blood draws do not exceed the following amounts for all research protocols combined: 10.5 mL/kg or 550 mL, whichever is smaller, over any 8-week period for adults, and no more than 5 mL/kg may in a single day (no more than 9.5 mL/kg may be drawn over any 8-week period) for persons under the age of 18.

Risk of Nasopharyngeal Swab- The primary risk of a nasal swab is local discomfort. Rarely, there can be local bleeding from the nasal mucosa, which is controlled with local measures such as pressure or packing with gauze.

Risk of Oropharyngeal Swab- The primary risk of an oropharyngeal swab is local discomfort. This swab can stimulate the gag reflex, and very rarely vomiting.

Risk of Endotracheal Aspirate- The primary risk of endotracheal aspirate is cough, and rarely can cause a small amount of bleeding.

Data security- Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will

see the subjects' PHI. All records will be kept in a locked file cabinet or maintained in a locked room at the participating sites. Electronic files will be password protected behind an academic institutional firewall. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Any publications from this study will not use information that will identify subjects. Organizations that may inspect and/or copy research records maintained at the participating sites for quality assurance and data analysis include groups such as the Food and Drug Administration (FDA).

14. Potential Benefits to Participants

There is no guarantee of benefit to subjects who enroll in this protocol.

15. Data Management and Confidentiality

15.1 Statistical considerations

The proportion of patients that did not require mechanical ventilation or die within 29 days of randomization will be recorded as a preliminary assessment of the efficacy of duvelisib in this setting.

Definition of subjects evaluable for efficacy response

Subjects who completed screening and enrollment procedure and who are randomized to receive duvelisib/placebo will be evaluable for efficacy endpoints on an intent-to-treat basis.

Definition of NIAID scale

The clinical response to study drug is defined as the first day on which the subject satisfies the criteria of a score of 5 or greater in the following categories from the NIAID ordinal scale. The NIAID ordinal scale is an assessment of the clinical status at the first assessment on a given study day. The scale is as follows: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 7) Not hospitalized, limitation on activities and/or requiring home oxygen; 8) Not hospitalized, no limitations on activities.

Definition of the primary efficacy endpoint

The proportion of patients who do not require mechanical ventilation (e.g. intubation, high-flow 0_2 Bi-PAP or AIRVO) and who survive to 4 weeks after randomization will be used as the primary measure of efficacy.

Study design

This is a randomized placebo-controlled double blind/double masked phase 2 study to explore the efficacy of exposure to a PI3K inhibitor in patients with severe COVID-19. Subjects who are randomized to receive duvelisib or placebo will be evaluable for the primary and secondary efficacy analyses. All subjects with any exposure to duvelisib will be evaluable for toxicity (please see section 13.3 on grading of toxicities). A total of 80 subjects will be planned for analysis of the primary and secondary endpoints. We estimate that five subjects will be enrolled every month. One interim analysis is planned upon 50% (n=40) of subjects enrolled, which allows us the

opportunity to stop the trial early due to futility or safety concerns. The only groups that will have access to unblinded interim data: (a) an independent data monitoring committee (IDMC); and (b) an independent statistical team whose role will be to generate the reports to be reviewed by the IDMC. The responsibility of any data-informed recommendations regarding continuing/stopping the study or modifying the study design/protocol be restricted to the IDMC.

Power Calculation

The reported incidence of death or mechanical intubation for patients with severe COVID-19 is approximately 40% (1). Local experience with COVID-19 patients at the Emory hospitals is consistent with this estimate, as 29% of all SARS-CoV-2 positive patients (n=800) are admitted to the ICU with COVID-19, and that 22% of all admitted patients are intubated, and 37% of intubated patients die in hospital. A favorable and clinically significant result from treatment with duvelisib in high-risk COVID-19 patients would be to reduce the composite incidence of death/mechanical ventilation from 40% to 15%. A sample size of 40 subjects for each treatment group will have >80% power to detect a 25% absolute reduction in the proportion of subjects who experience death or mechanical ventilation, comparing a predicted proportion of 40% death or intubation in the control arm to 15% death or intubation in the experimental arm receiving duvelisib treatment. The calculation is based on 10% type 1 error rate and two-sided Mantel-Haenszel test with one planned interim analysis when approximately 50% of sample enrolled (N=20/treatment). For

Analysis of Primary Endpoints

Analysis of the primary end-point will be based upon an intent-to-treat analysis of all subjects who are randomized to receive duvelisib/placebo. The primary endpoint is the proportion of patients who will require mechanical ventilation or experiencing death within 4-weeks (29 days) after randomization, which will be estimated with the corresponding 95% Clopper-Pearson confidence interval for the two arms separately. Fisher's Exact test will be used to test the difference between the two arms. In addition, a logistic regression will be used to estimate the odd ratio between the two arms controlling for the baseline covariattes for an improved precision of the estimation *(30).*

Analysis of Secondary Endpoints

Evaluable subjects will be all subjects who were randomized to receive duvelisib or placebo. The definition of secondary endpoints are listed in section 2. The descriptive statistics will mainly be applied to all secondary endpoints by treatment arms separately, such as frequency and percentage for categorical endpoints and mean, median, and standard deviation for numerical endpoints. They will be compared between treatment arms by Fisher's Exact test for categorical endpoints and Wilcoxon Rank-Sum test for numerical endpoints. For biomarkers measured repeated over time, generalized estimating equation (GEE) model will be used to test the difference in change pattern over time by two treatment groups using a nonlinear model. P-value will be adjusted for multiple comparison if necessary. Time to recovery is as the days from randomization to reach the desired NIAID ordinal scale >=5, a log-rank test will be used to compare the difference between the two arms. Survival rate at day 50 - 60 will be estimated by Kaplan-Meier method with log-rank test.

Interim Analysis for futility

The responsibility of any data-informed recommendations regarding continuing/stopping the study or modifying the study design/protocol be restricted to the independent data monitoring committee (IDMC), which is a part of the Winship data safety monitoring committee (DSMC). Upon 20 enrolled for each arm, an interim analysis will be carried out by two-sided Mantel-Haenszel test. O'Brien-Fleming boundary for futility is 2.373 on the Z score (equivalently: 0.991 on the fixed sample p-value scale). The trial may be terminated due to futility, or

following review by the IDMC of clinical and laboratory immune-monitoring data. Otherwise, the trial will continue enrolling patients until all 80 patients enrolled.

Stopping Rule for Safety

At the interim analysis (20 patients/arm), the incidence of death or mechanical ventilation, grade ¾ elevations in liver transaminases, or neutropenia will be estimated. We assume that the underline rate is 40%, 10%, or 24% for the three incidences in placebo group respectively, and if the rate in duvelisib group is >=15% higher than that in the placebo group in either of the three incidences, the trial may be stopped due to the safety concern. It also translates to stop the study if 3 or more excess events in duvelisib group are observed in either of the three incidences. Operating Characteristics, the probability of trail stopping due to >=3 excess events based one simulation study, is listed in the below table.

AEs	Underline event rate in Placebo arm	Underline event rate in Duvelisib arm						
		5%	10%	20%	30%	40%	50%	60%
death or mechanical ventilation	40%	0%	0.02%	0.7%	4.8%	16.6%	37.4%	62.7%
grade ¾ elevations in liver transaminases	10%	0.79%	5.7%	32.8%	65.8%	87.9%	97.2%	99.7%
neutropenia	24%	0.07%	0.6%	7.3%	26.1%	52.7%	77.3%	92.6%

In addition to the study stopping rules based an interim analysis, the Independent Data Monitoring Committee (IDMC) will review, on a monthly basis, the number of Grade 3 and/or Grade 4 adverse events in each arm, including neutropenia and elevated transaminases, and consider stopping or suspending accrual to the study if the frequencies of Grade 3 or Grade 4 adverse events are significantly higher among subjects in the duvelisib arm compared with subjects in the control arm.

Analysis of Safety Data

The primary safety endpoints include death or mechanical ventilation, grade ¾ elvation in liver transminases, and neutropenia within 4 weeks. The cumulative incidence rate of each safety endpoint will be calculated with 95% confidence interval by randomized arms, and compared by Fisher's exact test.

Handing of Missing Data

For the safety endpoints and secondary endpoints, missing data will not be imputed, summaries and analyses will be based on the observed cases. For the primary efficacy analysis, every effort will be made from the informed consent form design to clinical follow up to reduce the missing data. Patients withdraw consent before the primary endpoint can be measured will be replaced.

Demographics and Baseline Characteristics

Summary statistics and frequencies for the following characteristics will be described by randomized arms:
ECOG, Race, Ethnicity, Age, Sex, Body mass index (BMI), Medical history of hypertension, diabetes, asthma, chronic obstructive pulmonary disease, History of and treatment for cancer, History of coronary artery disease (prior MI, CABG, coronary artery stent, or medical management), History of prior pulmonary infections (TB, pneumonia, influenza), Allergies

Subgroup analyses

None

15.2 Data/specimens:

Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples include medical records (hospital records, office charts), laboratory results, imaging scans and reports, EKGs, patient diaries, videos, photographs, pharmacy dispensing, and other records, investigator or patient completed questionnaires involved in the clinical trial.

Case Report Forms

The case report form (CRF) will be the primary data collection instrument for the study. All data requested on the CRF will be recorded and all entries will be recorded into an electronic data capture system by authorized personnel. The principal investigator is responsible for assuring that the data entered into the CRF are complete, accurate and that entries are updated in a timely fashion. Data will be entered in the clinical research data management system – REDCap - per Winship SOP 4.2 Data Completion Metrics. REDCap will be used to record all study related information and data for all registered subjects, including their assigned patient ID. All data submitted must be accompanied by supporting source documents, where applicable and as outlined in the protocol-specific monitoring plan. Data completion will be reviewed monthly. In situations where there are significant delays of data completion, the Associate Director of Clinical Research or the Director of Clinical Trials may temporarily suspend enrollment. All data must be entered in the timeframe required at each site, but no later than 30 days following registration and each visit completion. All queries are to be resolved within 4 weeks of issue. The coordinating center multi-site coordinator will provide REDCap training and request access to the appropriate staff at the participating site.

Procedures to Ensure Capturing Data for the Primary End-point

All patients who maintain consent to be followed for additional outcome information will remain in the study through the end of the double-blind period collection of safety and efficacy assessments. Subjects discharged from the hospital prior to the last protocol-specified assessment on day 29 will be followed as out-patients with in-person or telehealth visits. Survival status at day 50 - 60 will be captured in all subjects who have not withdrawn consent for follow-up by contacting the patient via a telehealth visit or other approaches (e.g., telephone calls, texts, and emails to the patient and close contacts). In the absence of direct or indirect contact with the subject, a vital records search will be performed to assess survival status of each subject.

Data Retention

All study documents will be retained for at least two years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country.

Transmission of Data:

Blood samples for T-cell phenotyping from secondary sites will be cryopreserved and shipped to Emory University in real-time. Patient samples will be cryopreserved by using Crystor Media (please see Appendix F). Emory University will cover the cost of shipment of blood samples. All patient samples for T-cell phenotyping will be analyzed at Emory University to ensure uniform analysis. Clinical data (ORR and rates of CRS, neurotoxicity, ICU

transfers) will be captured with chart review at Emory University and secondary sites. Data will be uploaded into RedCap. There will be monthly meetings (tele-conference) with each site's PI to review the study, enrollment and reporting of data.

Publication Plan

The results of the study should be available within 12 months of completion of the study. The end of the study is the time point at which the last data items are to be reported or after the outcome data are sufficiently mature for analysis. A full report of the outcomes will be made public no later than three years after the end of the study.

16. Provisions to Monitor the Data to Ensure the Safety of Participants

16.1 Safety Analyses

Adverse event data will be described and graded per the NCI CTCAE v5.0 guidelines. For AE that are not listed in the NCI CTCAE v5.0 guidelines, grade 3 AEs are defined as events that interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating. For each adverse event, information to be collected includes event description, time of onset, clinician assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. Regardless of relationship, all AEs will be recorded with start dates occurring any time after patient receives any duvelisib/placebo. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. Adverse events will be summarized and described within each cohort. They will initially be reviewed regardless of attribution, but also whether they are possibly, probably, or definitely related to treatment. In addition, we will review all adverse event data that are graded as 3, 4, or 5 and classified as either "unrelated" or "unlikely to be related" to study treatment in the event of an actual relationship developing. The incidence of severe adverse events or toxicities will be described. We will assess the proportion of patients who experience grade 3 or higher non-hematologic toxicity. To assess tolerability, we will also capture the proportion of patients who go off treatment due to adverse events.

16.2 Adverse Event and Serious Adverse Event Reporting

Definition of Adverse Events (AE)

The ICH defines an adverse event as any unfavorable and unintended sign, including laboratory findings, symptoms or diseases temporally associated with the use of an investigational product. Adverse event severity will be graded per the using the CTCAE version 5 for toxicity and adverse event reporting.

Any adverse events, either observed by the investigator or reported by the patient, should be documented, including the intensity and duration of the AE, what steps were taken in regard to duvelisib and the outcome.

The principal investigator must review any laboratory abnormality for clinical significance. If the abnormality is deemed to be clinically significant, then the adverse event will be reported along with the actions taken in regard to duvelisib and the outcome of the event. All AE's will began recording at the beginning of enrollment until withdrawal and/or completion of the clinical trial.

Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- 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, or a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Study-Specific AE/SAE Reporting

- Due to the wide array of symptoms experienced by patients hospitalized with COVID-19, it is not feasible or informative to record and assess all possible symptoms and lab test results for AE/SAE grading in this study. Hence AE/SAE grading and reporting will be limited to lab tests that might reflect effects of study drug exposure including bilirubin, ALT, ALK PHOS, AST, leukopenia, lymphopenia, anemia, and thrombocytopenia. Symptomatic AE/SAE grading and reporting will focus on the following: diarrhea, bradycardia, symptoms requiring ICU admission and mechanical ventilation, symptoms requiring repeat hospitalization, or death. Non-clinically relevant AEs (Grade 1) will not be included on AE logs or AE reporting documents.

Classification of an Adverse Event

Severity of Event

For both AE's and SAE's the investigator must assess the severity of the event. The severity of the event will be graded based off the patient's symptoms using the Common Terminology Criteria for Adverse Events (CTCAE Version 5.0):
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations

Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

Expectedness

Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected.

An ***expected*** adverse event is those that have previously identified resulting from administration of the study drug. These include, but not limited to, AE's that are listed in the AE list, stated on the informed consent document or listed on the investigator's brochure.

An ***unexpected*** adverse event occurs when the nature or severity or frequency of the event is not consistent with the risk product's information (i.e., investigator's brochure, not listed on the informed consent document).

Documenting Adverse Events

From the time of treatment until 14 days following cessation of duvelisib/placebo all adverse events, that begin or worsen after informed consent, **must be recorded** by the investigator or designee at each examination on the Adverse Event case report forms (CRF)/worksheets

The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF/worksheet.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1 to 5 will be used to characterize the severity of the Adverse Event. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected. The occurrence of adverse events should be sought by non-directive questioning of the patient (patient) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (patient) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes) or Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 16.1 and which seriousness criteria have been met).
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4. For phase I studies any AE that constitutes a DLT should be reported like a grade 3 and 4 adverse event. All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome. Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events.

A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose-hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such. Any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the study drug, must be **submitted on an SAE form** and assessed by PI in order to determine reporting criteria to regulatory authorities, IRB, DSMC, FDA.

All serious adverse events collected during this time frame will also be reported to Verastem.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. The sponsor-Investigator will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

All subjects with serious adverse events must be followed up for outcome.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode **within 24 hours** of the investigator receiving the follow-up information.
An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.
Any SAEs experienced after the reporting period described above should only be reported to FDA/IRB if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the **Serious Adverse Event Report Form**; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and submit the completed form.
Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved

or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

Reporting Requirements for IND holder

For Investigator-sponsored IND studies, reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR, Part 312.32. Events meeting the following criteria need to be submitted to the FDA as Expedited IND Safety Reports.

7 Calendar-Day Telephone or Fax Report

The Sponsor-Investigator is required to notify the FDA of a fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of *investigational agents*. An unexpected adverse event is one that is not already described in the most recent Guidance for Investigator section of the Investigator's Brochure. Such reports are to be telephoned or faxed to the FDA, within 7 calendar days of the first learning of the event.

15 Calendar-Day Written Report

The Sponsor-Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious unexpected adverse event that is considered reasonably or possibly related to the use of investigational agent.

Written IND Safety Reports with analysis of similar events are to be submitted to the FDA, within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 Form but alternative formats (e.g., summary letter) are acceptable.

SAE must be recorded on a MedWatch 3500 Form. SAE reports and any other relevant safety information are to be forwarded to the following

MedWatch 3500 Reporting Guidelines:

Note: MedWatch 3500 forms and other information related to MedWatch reporting are available at http://www.fda.gov/medwatch/index.html.

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA. Investigators will cross reference this submission according to local regulations to the Investigational Compound Number (IND, CSA, etc.) at the time of submission.

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

FDA Fax number of IND Safety Reports: 1-(800)-FDA-1078.

The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

Participating subsites

For participating subsites, adverse events collected are to be entered into OnCore no later than 14 calendar days after data collection. Subsites are not permitted to report directly to the coordinating center IRB or FDA. All external site SAEs are to be reported to the coordinating center multi-site regulatory specialist. The coordinating center multi-site regulatory specialist will facilitate submission of external site SAEs to the coordinating center IRB and FDA. All serious adverse events (SAEs) and other adverse events must be recorded on case report forms. In addition, all SAEs must be reported to the coordinating center principal investigator and coordinating center multi-site regulatory specialist within 24 hours of knowledge of the event using the FDA MedWatch 3500A mandatory reporting form. Copies of de-identified source documentation pertaining to the SAE must be submitted to the coordinating center. If a patient is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up form. All SAEs must be submitted to the local IRB per local IRB and institutional policy. Upon request of additional data or information that is deemed necessary must be reported to the coordinating center as soon as possible but no later than 5 calendar days.

16.3 The Data and Safety Monitoring Committee (DSMC)/Independent Data Monitoring Committee (IDMC)

The Independent Data monitoring Committee (IDMC) for this study is a part of the Winship Data Safety Monitoring Committee (DSMC). The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP). The DSMC will provide oversight for the conduct of this study based upon access to unblinded study data and will continuously monitor cumulative SAE provided by the PI on a monthly basis. A planned analysis for futility will be submitted to the DSMC after accrual of 40 subjects. The DSMC will meet in closed session with access to unblinded data that will be provided by the study statistician.

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify, using blinded data, informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data. The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

Multisite Monitoring Plan

At the time of study initiation at a non-Emory site, the Emory Sponsor-Investigator, Winship regulatory specialist, and Winship MSC will perform a site initiation teleconference. During this teleconference, the Emory team will review the study, enrollment, reporting, and regulatory compliance. Winship will have internal monitoring meetings. These meetings, which will include the participating site investigator, the clinical research coordinator and the regulatory affairs coordinator, will meet at least on a monthly basis to review and discuss study data to ensure subject safety. The research coordinators will maintain a spreadsheet which will be de-identified and will summarize all the patient data for subjects actively being treated on the trial as well as a roadmap detailing pending tests/treatments for each individual subject. The spreadsheet will be shared with the Emory PI via e-mail.

Winship's MSC will perform an on-site or remote monitoring visit within the first three months of enrollment of the first subject. Quarterly monitoring visits will occur (once annually onsite and three times remotely) until subject follow-up is terminated. Monthly reviews of data in OnCore will be conducted to ensure compliance or identify discrepancies; specifically, to assess compliance with the protocol, verify informed consent forms, verify compliance with SAE reporting procedures, monitor the tracking of study drug (pharmacy visit, storage and accounting of study drug), retrieve regulatory documentation, and perform quality control by comparing data from the CRF to the source documents of the center.

Study updates will occur at least once monthly between the PI at Emory and the research team at the participating site(s). The purpose of the meetings is to discuss the enrollment, regulatory updates, monitor toxicities, and evaluate the progress of the trial. Scheduled teleconferences may stop after all patients have completed assigned protocol therapy. The coordinating center (or designee) will communicate with participating sites via monthly email. The minutes from the teleconference will be maintained in the regulatory binder for the study. In addition, electronic copies will be sent via email to the principal investigators at each site.

17. Provisions to Protect the Privacy Interests of Participants

Participants will be assured of their voluntary participation in the study, their choice to answer or not answer any question, and the protocol for maintaining confidentiality.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The

study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived

18. Economic Burden to Participants

The study supporter will provide or pay for certain items and services the subject may receive in this study. Subjects will have to pay for the items or services for which the study supporter does not pay. The sponsor will not pay for regular medical care. If subjects have insurance, Emory will submit claims to the insurance for items and services that the sponsor does not cover. Emory will send in only those claims for items and services that it reasonably believes the insurance will pay and that the sponsor has not paid. The actual amount that participants have to pay depends on whether or not they have health insurance and whether or not that insurance will pay for any research study costs. Generally, insurance companies will not pay for items and services that are required just for a research study. Some insurance companies will not pay for regular medical treatment or treatment for complications if in a study. If subject do not have insurance, Emory will review that particular case as part of its program for low-income patient care. The standard policies of that program will apply. The program will figure out if subjects have to pay any costs for taking part in the study and what those costs will be.

19. Consent Process

The initial informed consent discussion will occur in one of the Emory Healthcare Hospitals or the Emory Clinic. The consent discussion may take place in person, or by phone or video call. The informed consent is an ongoing, interactive process rather than a one-time information session. The consent form document is designed to begin the informed consent process, which provides the patient with ongoing explanations that will help them make educational decisions about whether to begin or continue participating in the trial. The research team knows that a written document alone may not ensure that the patient fully understands what participation means. Therefore, the research team will discuss with the patient the trial's purpose, procedures, risks and potential benefits, and their rights as a participant. The team will continue to update the patient on any new information that may affect their situation.

Consent will be obtained prior to any research-driven procedures. The investigator will assess the patient's capacity during his/her encounters with him or her. The investigator will give the person providing consent (the patient or a legally authorized representative) adequate opportunity to read the consent document before it is signed and dated. It will be explained to prospective participants that the study involves research, the purpose of the research, the expected duration of participation, as well as the approximate number of participants to be enrolled. The study procedures, and identification of research procedures v. non-research will also be thoroughly discussed. It will be explained to participants that participation is voluntary and that the subject may discontinue at any time.

Refusal to participate or withdraw will not involve a penalty or loss of benefits to which the participant is otherwise entitled. Refusal will in no way affect the participant's future are. The participant will also be told of the possible consequences of the decision to withdraw from the research, and procedures for orderly termination of participation.

Any significant new findings developed during the course of the research that may affect the participant's willingness to continue to participate will be provided. Also explained will be anticipated circumstances under which the subject's participation may be terminated by the investigator without the participant's consent. Prospective participants will be provided with a description of any reasonably foreseeable risks or discomforts as

well as a description of any benefits to the participant or to others that might be reasons expected from the research. Alternative procedures or courses of treatment will also be thoroughly discussed. Prospective participants will also be given detailed information describing the extent to which confidentiality of records identifying the participant will be maintained and what records may be examined by the research staff, IRBs, sponsor, their representatives, and possibly the FDA or OHRP.

Also communicated to the participant will be an explanation that emergency medical care will be arranged for a study-related illness or injury, and an explanation of whether funds are set aside to pay for this care and/or compensation, and if so by whom (e.g., sponsor, subject, insurer). The participant is told the source of the study's funding. All participants will be told of any additional costs that may result from participation in the research.

Non-English-Speaking Participants

A certified translator/interpreter will be present during the consenting process and this will be documented. All questions and concerns will be answered by one of the study physicians with the aid of a certified translator/interpreter.

An IRB-approved Short Form in that specific language will be used. We will use what's available on Emory IRB website. For the languages that are not available, we will have the short form translated to that language and submit the IRB for review and approval prior to use. Process to Document Consent in Writing: Winship SOP 2.1: ”Obtaining Informed consent for Interventional clinical trial” will be followed.

Participants who are not yet adults (infants, children, teenagers)

N/A

Cognitively Impaired Adults

A legally authorized representative may take part in the informed consent discussion and sign the consent form on behalf of the patient

Adults Unable to Consent

A legally authorized representative may take part in the informed consent discussion sign the consent form on behalf of the patient

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

N/A

20. Setting

The study will begin at Emory University and will seek to open at one or more secondary site institutions.

21. Resources Available

Emory University was founded in 1836 and is a national center for teaching, research, and service. Emory University has been named as one of the nation’s top 25 universities for more than a decade by the U.S. News and World Report. Emory University research partners include the Georgia Institute of Technology, the University

of Georgia, Morehouse School of Medicine, the US Centers for Disease Control and Prevention, Children's Healthcare of Atlanta, and the Georgia Clinical and Translational Science Alliance (GACTSA). Emory University researchers received $734 million from external funding agencies in fiscal year 2018, including approximately $441 million in funding from federal agencies, $359 million of this from the National Institutes of Health (NIH).

Winship Cancer Institute (Winship) is Georgia's first and only National Cancer Institute (NCI)-designated Comprehensive Cancer Center (P30CA138292) and is dedicated to the integration of innovative clinical and basic science research with outstanding patient care for the prevention, treatment and control of cancer. First designated in 2009, Winship's NCI designation was renewed in 2012 and 2016, achieving an "outstanding" rating. Winship earned the prestigious Comprehensive Cancer Center designation from the NCI in 2016, after demonstrating that its outstanding programs are reducing the cancer burden on the state of Georgia through research conducted in its laboratories, its clinical trial program, and its population-based science. The institutional support for Winship was rated as 'exceptional' by the review panel.

The **Winship Clinic Building C** houses the primary offices and clinical space for cancer services including the medical oncology, hematology, and surgical oncology clinics, the radiation oncology program, and the Winship Ambulatory Infusion Center. In summer 2017, Emory Healthcare completed the expansion of **Emory University Hospital Tower** on Clifton Road. This nine-floor facility adds 144 inpatient beds to the hospital, of which more than 80% are dedicated to cancer care. The hospital expansion also accommodates cancer patient-specific intensive care units, an expanded BMT Unit with peri-transplant clinics to facilitate continuity of care, and a 24-hour cancer urgent care center, which serves as both a triage facility and short stay treatment center for patients with cancer-related medical concerns.

22. Multi-Site Research when Emory is the Lead Site

All sites will have the current protocol document and each IRB will review each site's consent form and all required approvals will be obtained at each site. Any protocol modifications will be communicated to all sites with the appropriate regulatory agencies notified for their respective reviews and approvals. All engaged participating sites will safeguard date, including secure transmission of data, as required by local information security policies. All local site investigators will conduct the study in accordance with applicable federal regulations and local laws. All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

Site initiation at subsites

At the time of study initiation at a subsite, the coordinating center multi-site coordinator (with additional staff as needed) will perform a site initiation teleconference. During this teleconference, the Emory team will review the study, enrollment, reporting, and regulatory compliance.

Subsite data collection

Subsite data must be submitted to the coordinating center multi-site coordinator as outlined in the protocol-specific monitoring plan. The protocol-specific monitoring plan will be provided by the coordinating center multi-site coordinator to external participating prior to site activation. Access to the coordinating center OnCore database will be provided to external participating sites for direct electronic data entry. All data submitted must be accompanied by supporting source documents, where applicable and as outlined in the protocol-specific monitoring plan. All data must be entered in the timeframe required at each site, but no later than 14 days following registration and each visit completion. All queries are to be resolved within 4 weeks of issue. The coordinating center multi-site coordinator will provide OnCore training and request access to the appropriate staff at the participating site.

Monthly investigator conference calls

The subsite research coordinators will maintain a spreadsheet which will be de-identified and will summarize patient data for subjects actively being treated on the trial well as a roadmap detailing pending tests/treatments for each individual subject. The spreadsheet will be shared with the coordinating center PI / IND sponsor (or designee) via e-mail. Teleconferences will be conducted at least once monthly between the PI (or designee) at Emory and the research team at the participating site(s).

The purpose of the meetings is to discuss the enrollment, regulatory updates, monitor toxicities, and evaluate the progress of the trial. Scheduled teleconferences may stop after all patients have completed assigned protocol therapy. The coordinating center (or designee) will communicate with participating sites via monthly email.
The minutes from the teleconference will be maintained in the regulatory binder for the study. In addition electronic copies will be sent via email to the research teams at subsite.

Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial follows the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

Subsite self-monitoring: The participating site will have internal monitoring meetings. These meetings which will include the participating site investigator (or designee), the clinical research coordinator and the regulatory affairs coordinator as applicable, will meet at least on a monthly basis to review and discuss study data to ensure subject safety. Chart reviews will be performed on selected cases by participating site staff to confirm that the data collection is accurate regarding study conduct, data collection, documentation and completion.

Central monitoring: Study-specific monitoring plans are specified per site, with the only difference between sites whether the site submits source data on paper or provides the coordinating center multi-site team remote access to that site's local electronic medical record. Centralized monitoring will occur minimally quarterly, no more frequently than monthly. Monitoring will be centralized, including data reporting and research sample acquisition. The coordinating center multi-site coordinator will perform on-site and/or remote monitoring visit within the first three months of enrollment of the first subject. Quarterly monitoring visits will occur (on site up to once per year and at least three times remotely) until subject follow-up is terminated. Monthly reviews of data will be conducted to ensure compliance or identify discrepancies; specifically, to assess compliance with the protocol, verify informed consent forms, verify compliance with SAE reporting procedures, monitor the tracking of study drug (pharmacy visit, storage and accounting of study drug), retrieve regulatory documentation, and perform quality control by comparing data from the CRF to the source documents of the center.

Auditing

For sites with an auditing mechanism in place that are able to share documentation of their auditing standards and processes followed, an agreement may be requested for the site to perform local auditing and provide formal audit reports to the coordinating center.

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APPENDIX A: Clinical diagnosis of severe acute respiratory infection (SARI) when COVID-19 disease is suspected - Interim guidance(16)

Validated definition for severe disease (https://covid19treatmentguidelines.nih.gov/overview/management-ofcovid-19/) is based on the following:

Confirmed SARS-CoV-2 infection (by PCR test) with fever or suspected respiratory infection, plus one of the following:

a. respiratory rate > 30 breaths/min;
b. severe respiratory distress; or
c. SpO2 ≤ 93% on room air at sea level or PaO_2/FiO_2< 300.

APPENDIX B: POTENT INHIBITORS AND INDUCERS OF CYP3A4 (FDA reference 2014)

Effect on CYP3A	Drug Class	Medications
Moderate to Strong CYP3A Inhibitors	Antibiotics	chloramphenicol, ciprofloxacin, clarithromycin, erythromycin, telithromycin
	Antiemetic	aprepitant
	Antifungals	ketoconazole, fluconazole, itraconazole, posaconazole, voriconazole
	Antiviral protease inhibitors	amprenavir, atazanavir, boceprevir, cobicistat, darunavir, elvitegravir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, tenofovir, tipranavir
	Calcium-channel blockers	diltiazem, mibifradil, verapamil
	Foods/herbs	grapefruit, grapefruit juice, Seville oranges
	Serotonin antagonist	nefazodone
	Tyrosine kinase inhibitor	imatinib
	Vasopressin antagonist	conivaptan
Moderate to Strong CYP3A Inducers	Antibiotics	nafcillin, rifampin
	Anticonvulsants	carbamazepine, phenobarbital, phenytoin
	Antiviral reverse transcriptase inhibitors	efavirenz, etravirine
	Endothelin receptor antagonist	bosentan
	Foods/herbs	St. John's wort
	Wakefulness-promoting agent	modafinil

APPENDIX C: CYP450 Substrates (FDA reference 2019)

CYP enzyme	Sensitive substrates	Moderately sensitive substrates
CYP1A2	alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, tizanidine	clozapine, pirfenidone, ramosetron, theophylline
CYP2B6	bupropion	efavirenz
CYP2C8	repaglinide	montelukast, pioglitazone, rosiglitazone
CYP2C9	celecoxib	glimepiride, phenytoin, tolbutamide, warfarin
CYP2C19	S-mephenytoin, omeprazole	diazepam, lansoprazole, rabeprazole, voriconazole
CYP2D6	atomoxetine, desipramine, dextromethorphan , eliglustat, nebivolol, nortriptyline, perphenazine, tolterodine, R-venlafaxine	encainide, imipramine, metoprolol, propafenone, propranolol, tramadol, trimipramine, S-venlafaxine

APPENDIX D: CYP3A Substrates (FDA reference 2019)

CYP enzyme	Sensitive substrates	Moderately sensitive substrates
CYP3A	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil	alprazolam, aprepitant, atorvastatin, colchicine, eliglustat, pimozide, rilpivirine, rivaroxaban, tadalafil

APPENDIX E: Immunomodulator and Immunosuppressant

Class	Medication
IL6 inhibitors	Tocilizumab, sarilumab, siltuximab
TNF inhibitors	Adalimumab, certolizumab pegol, etanercept, golimumab, infliximab
Anti-IL-1 agents	Anakinra, canakinumab, rilonacept

JAK inhibitors	Baricitinib, fedratinib, ruxolitinib, tofacitinib, upadacitinib

APPENDIX F: Drug Accountability Form

Study ID:

[*Drug*] Pill Record

Subject Initials:___ Subject ID: _____

Instructions:
Planned Daily Dose: **__mg**

Day	Date	Time	# of Tablets taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				

APPENDIX G: Procedure protocol for analysis of T cells

Procedure Protocol for Analysis of T-Cells for Protocol Duvelisib Antagonizes Manifestations of Pneumonia in Established Novel Coronavirus Infection (DAMPEN-CI)

Cryopreservation with CryoStor Media:

1. Suspend cells to be cryopreserved using mechanical or enzymatic dissociation.
2. Centrifuge cells to obtain cell pellet.
3. Remove supernatant.

Note: Remove as much culture medium as possible to reduce dilution of the CryoStor medium.

4. Isolation - Add **cold (2–8 °C) CryoStor medium** to a cell concentration range of 0.5–10x10^6 cells/ml for standard cell culture protocols. A higher cell concentration is possible with testing.

Note: CryoStor media contain DMSO, no additives are necessary.

5. Pre-freeze - Incubate cell suspension at 2–8 °C for ~10 minutes.
6. Nucleation – Lower sample temperature to –80 °C.
   a. Use a controlled rate freezer (–1 °C /minute) or similar procedure for most mammalian cell systems.
   b. The freezer should be pre-cooled to 2–8 °C.
   c. Ice nucleation within the sample (seeding) should be initiated at approximately –5 °C using a liquid nitrogen burst program setting on the controlled rate freezer or mechanical agitation (flick or tap) of the cryovial/sample container after 15–20 minutes at –80 °C.

Alternative Nucleation Procedures – cells can be frozen using stepwise freezing procedures.

Stepwise freezing procedures include:

   a. 2 hours at –20 °C followed by 2 hours at –80 °C or
   b. 3–4 hours at –80 °C in an isopropanol freezing container. The isopropanol container should be pre-cooled to 2–8 °C

   Ice nucleation - mechanical agitation (flick or tap) of the cryovial/sample container after 15–20 minutes at –80 °C.

7. Storage – Store the samples at liquid nitrogen temperatures (below –130 °C).

Note: Sample storage at –80 °C is only recommended.

8. Thawing - Thaw samples quickly in a 37 °C water bath. Sample should be thawed with gentle swirling of the sample until all visible ice has melted. Thaw time for a 1 ml sample in a cryovial is ~3 minutes. Note: DO NOT allow sample to warm above chilled temperatures (0–10 °C). Cryovials should be cool to the touch when removed from the water bath. Passive thaw is **not** recommended.
9. Dilute cell/CryoStor mixture immediately with appropriate culture medium. This can be performed in a single step. The dilution medium should be between 20–37 °C. A dilution ratio of 1:10 (sample: medium) or greater is recommended.
10. Plate cells appropriately.
11. Culture the cells or use immediately.

Shipment:

Patient samples from secondary sites will be shipped in real-time overnight on Monday-Wednesday so that samples will be received no later than Friday. Each sample will be shipped on adequate amounts of dry ice. Emory University will cover the cost for shipment of the patient samples

APPENDIX H: Table to guide the IDMC during review of potential toxicity in the duvelisib arm at the time of the interim safety analysis

Table 1: Approximate probability of observing excess instances of mechanical ventilation or death in the duvelisib treatment arm at the time of the interim analysis.

		True Underlying Duvelisib Rate								
		20%	**25%**	**30%**	**35%**	**40%**	**45%**	**50%**	**55%**	**60%**
Approximate probability of observing ≥ X excess instances of mechanical ventilation or death in the duvelisib arm compared to placebo	**X = 0**	7.9%	15.2%	25.2%	37.2%	50.0%	62.6%	73.9%	83.2%	90.2%
	X = 1	3.9%	8.6%	15.9%	25.7%	37.3%	50.0%	62.5%	73.9%	83.4%
	X = 2	1.7%	4.4%	9.1%	16.3%	25.9%	37.4%	50.0%	62.6%	74.1%
	X = 3	0.7%	2.0%	4.8%	9.5%	16.6%	26.1%	37.5%	50.0%	62.7%
	X = 4	0.2%	0.8%	2.3%	5.1%	9.8%	16.8%	26.1%	37.4%	50.0%

Note: The true underlying placebo rate is assumed to be 40% in this table