COLUMBIA UNIVERSITY MEDICAL CENTER

Herbert Irving Comprehensive Cancer Center Protocol

NCI·CC
A Cancer Center Designated by the National Cancer Institute

CUMC IRB#: AAAS9881
Version Date: 13 February 2023 NCT04347226

TITLE: A randomized phase 2 study of anti-IL-8 therapy versus standard of care in the treatment of hospitalized patients with severe COVID-19

Coordinating Center: Columbia University Medical Center

Principal Investigator: Mark Stein, MD
1130 St Nicholas Ave, 217A
New York, NY 10032
Phone: 212-305-5874
Fax: 212-304-6330
Mcd2187@cumc.columbia.edu

Co-Investigators: Matthew Baldwin, MD
Phone: 212-305-6539
mrb45@columbia.edu

Statistician: Cody Chiuzan, PhD
722 West 168th St, Room 646, New York, NY 10032
Phone: 212-305-9107
cc3780@cumc.columbia.edu

Regulatory Sponsor:	Columbia University Medical Center Division of Hematology and Oncology 177 Fort Washington Avenue Milstein Hospital Building, suite 6GN-435 New York, NY 10032 Phone: 212-305-2055 Fax: 212-305-3035
Funding Source:	Bristol-Myers Squibb Route 206 & Province Line Road Lawrenceville, NJ 08543 BMS reference number: CA025-013
Study Agents:	BMS-986253 (HuMax IL8, anti-IL8 mAb)
Other Agent:	None

IND Status:	**IND #:** [redacted] **IND Sponsor:** [redacted]

Affiliate Institutions:
N/A

Amendment: 13 February 2023
Amendment: 07 October 2020
Amendment: 24 April 2020
Amendment: 20 April 2020
Amendment: 14 April 2020
Amendment: 10 April 2020 (FDA Study May Proceed granted)
Amendment: 5 April 2020 (not approved)
Initial version: 31 March 2020 (not approved

Protocol Signature Page

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practices, and the applicable federal, state, and local laws, rules, and regulations relating to the conduct of the protocol. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I will promptly submit the protocol to the applicable IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modification made during the course of the study must first be approved by the IRB, prior to implementation except when such modification is made to remove an immediate hazard to the subject. I certify that I, and the study staff, have received the requisite training to conduct this research protocol. I agree to maintain adequate and accurate records in accordance with Columbia University and Herbert Irving Comprehensive Cancer Center policies, Federal, state and local laws and regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Instructions to Principal Investigator: Sign and Date this signature page and print your name. Return the original, completed and signed to the Clinical Protocol & Data Management Office. Retain a copy in the regulatory binder.

_____ _____
Signature of Principal Investigator Date

_____
Principal Investigator Name (Print)

_____
Name of Institution

Protocol Synopsis

Title	A randomized phase 2 study of anti-IL-8 therapy versus standard of care in the treatment of hospitalized patients with severe COVID-19
Short Title	Anti-IL-8 for patients with COVID-19
Protocol Number	AAAS9881
Phase	Phase 2
Methodology	Randomized, open label, phase 2 study
Study Duration	12 months (estimated)
Study Center(s)	single-center
Objectives	Primary: • To determine the **time to improvement in the 7-point ordinal scale** in patients treated with anti-IL-8 therapy compared to standard of care/controls. o Measured from baseline to 2 point or greater improvement in 7-point ordinal scale. Secondary: • To evaluate the **time to death** in patients treated with anti-IL-8 therapy compared to controls**.** • To evaluate the **mortality 1 month** after start of treatment in patients treated with anti-IL-8 therapy compared to controls. • To determine **the time to intubation** in patients treated with anti-IL-8 therapy compared to controls. o Measured from time of disease onset to time of intubation. • To estimate the **time to improvement in oxygenation** in patients treated with anti-IL-8 therapy compared to controls**..** o Measured as time from start of treatment until ≥ 30% decrease in oxygen requirement compared to baseline • To measure **the proportion of patients requiring ICU admission at 1 month** in patients treated with anti-IL-8 therapy compared to controls**.** o Measured as the number of patients requiring ICU admission over their hospitalization over the number of evaluable patients.

	• To compare the raw 7-point ordinal scale scores at day 14 in patients treated with anti-IL-8 therapy versus controls. • To assess the **safety and tolerability** defined as adverse events graded by CTCAE v5.0 in patients treated with anti-IL-8 therapy compared to controls. • To assess the **duration of hospitalization** in patients treated with anti-IL-8 therapy compared to controls. o Measured as time from admission to time of discharge. <u>Exploratory</u>: • To assess the **change in LDH, D-Dimer, CRP, ESR, NLR and absolute lymphocytes** before and after treatment and over time (every 2 days for duration of hospitalization). • To assess the **change in sIL-6** before and after treatment and over time. • To evaluate **radiological response** by comparing % of lung fields with infiltrates on chest imaging (CXR and CT) through independent radiology review. • To measure **time on ventilation** measured from time of intubation to time of definitive extubation • To measure time to improvement in **NEWS2 score to ≤ 2** • To evaluate the **change in NEWS2** from baseline. • To measure proportion of patients with **multi-organ failure at 1 month.** • To assess whether **IL-8 and other key cytokines (TNF, IL-1b, IL-6) at baseline and during treatment are predictive of treatment efficacy** by quantification of circulating IL-1b, IL8, TNFalpha and IL-6 levels over time. • To quantify **changes in humoral immune responses** by antibody profiling at baseline and following treatment. • To **characterize PK** of BMS-986253 in cancer patients with severe COVID-19.
Number of Subjects	This trial will enroll 138 patients randomized 2:1 (anti IL8: control).

Diagnosis and Main Inclusion Criteria	**Main Inclusion Criteria** • Confirmed diagnosis of SARS-CoV-2 infection • Inpatient hospitalization due to SARS-CoV-2 infection • Severe (oxygen saturation ≤93% on room air or requires ≥2L oxygen by NC in order to maintain SaO2 ≥93%) OR critical respiratory disease (ICU, ventilatory support, HFNC) • Non-COVID-related life expectancy > 2 months • Willingness to provide informed consent
Study Product, Dose, Route, Regimen	BMS-986253 2400mg IV at 0 and 2 weeks (if patient is still hospitalized) and then 4 weeks (only if continued severe respiratory disease).
Duration of administration	Every 2 weeks x 1-3 doses.
Reference therapy	Standard of care management
Statistical Methodology	This is a single center, randomized, open-label, phase 2 trial to evaluate the time-to-improvement in the 7 point ordinal scale following treatment with BMS-986253 compared to standard of care in hospitalized patients with COVID-19 respiratory disease. With a sample of 138 patients (N=92 patients randomized to the treatment arm and N=46 patients assigned to the control/standard of care arm), the study will have 80% power to detect an increase in the median time to improvement from 5 days (control) to 2 days (anti-IL-8 arm) with one-sided alpha of 0.025. The sample size was estimated based on a hazard ratio (HR) of 0.40 assuming an exponential survival.
Interim Analysis	One interim analysis is planned once 17 (40% of the total 41 events) have been observed using O'Brien and Fleming stopping boundary using the Lan-DeMets spending function and inflation for drop-outs. The intent-to-treat (ITT) principle is applied to the analysis, and therefore, we inflated the sample size by 5% to safeguard against drop-outs/lost-to-follow-up.

Protocol Schema:

Contents

1. INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Columbia University Medical Center institutional research policies and procedures.

2. STUDY OBJECTIVES

Primary Objective

- To determine the **time to improvement in the 7-point ordinal scale** in patients treated with anti-IL-8 therapy compared to standard of care/controls.
    - Measured from baseline to 2 point or greater improvement in 7-point ordinal scale.

Secondary Objectives

- To evaluate the **time to death** in patients treated with anti-IL-8 therapy compared to controls**.**

- To evaluate the **mortality 1 month** after start of treatment in patients treated with anti-IL-8 therapy compared to controls.

- To determine **the time to intubation** in patients treated with anti-IL-8 therapy compared to controls.
    - Measured from time of disease onset to time of intubation.

- To estimate the **time to improvement in oxygenation** in patients treated with anti-IL-8 therapy compared to controls.
    - Measured as time from start of treatment until ≥ 30% decrease in oxygen requirement compared to baseline

- To measure **the proportion of patients requiring ICU admission at 1 month** in patients treated with anti-IL-8 therapy compared to controls**.**
    - Measured as the number of patients requiring ICU admission over their hospitalization over the number of evaluable patients.

- To assess the **safety and tolerability** defined as adverse events graded by CTCAE v5.0 in patients treated with anti-IL-8 therapy compared to controls.

- To assess the **duration of hospitalization** in patients treated with anti-IL-8 therapy compared to controls.
    - Measured as time from admission to time of discharge.

- To compare the raw 7-point ordinal scale scores at day 14 in patients treated with anti-IL-8 therapy versus controls.

2.1 Exploratory Objectives

- To assess the **change in LDH, D-Dimer, CRP, ESR, NLR and absolute lymphocytes** before and after treatment and over time (every 2 days for duration of hospitalization).
    - To assess the **change in sIL-6** before and after treatment and over time.
    - To evaluate **radiological response** by comparing % of lung fields with infiltrates on chest imaging (CXR and CT) through independent radiology review.
    - To measure **time on ventilation** measured from time of intubation to time of definitive extubation
    - To measure time to improvement in **NEWS2 score to ≤ 2**
    - To evaluate the **change in NEWS2** from baseline.
    - To measure proportion of patients with **multi-organ failure at 1 month.**
    - To assess whether **IL-8 and other key cytokines (TNF, IL-1b, IL-6) at baseline and during treatment are predictive of treatment efficacy** by quantification of circulating IL-1b, IL8, TNFalpha and IL-6 levels over time.
    - To quantify **changes in humoral immune responses** by antibody profiling at baseline and following treatment.
    - To **characterize PK** of BMS-986253 in cancer patients with severe COVID-19.

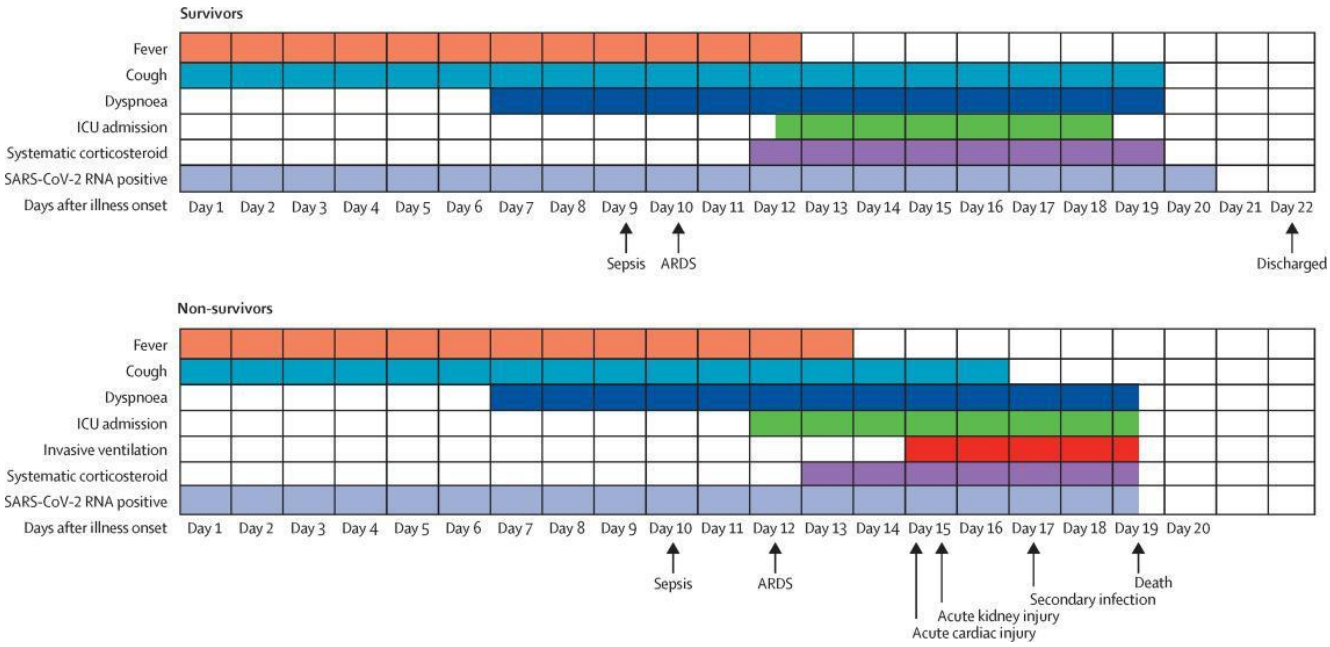
3. BACKGROUND

3.1 Disease Background

Coronavirus disease 2019 (COVID-19) represents an emerging public health crisis that is caused by infection with the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is associated with high transmissibility and mortality.[1] The World Health Organization (WHO) has defined COVID-19 as a pandemic. Symptoms include fever, cough, myalgias, shortness of breath and are most commonly mild in severity. However approximately 14% of patients with COVID-19 will develop severe disease (defined as dyspnea, respiratory frequency ≥30/minute, blood oxygen saturation ≤93%, PaO2/FiO2 ratio <300, and/or lung infiltrates >50% of the lung field within 24-48 hours).[2] Although the overall mortality appears <1%, patients with severe disease have a mortality of approximately 20-25% across multiple studies reported to date.[3-5] Medical co-morbidities also appear associated with particularly poor outcomes.[3] Particular, in cancer patients, reports suggest a mortality as high as 7%. Cancer patients also appear to have a dramatically increased rate of severe events (invasive ventilation or

death), with a rate of 40% in a small study from China.[6] Novel strategies to address respiratory failure in COVID patients generally and cancer patients in particular represents an urgent and critical need.

Figure 1 Clinical Course of Patients with COVID-19



3.2. <u>IL-8 is a key cytokine in the pathogenesis of coronavirus-associated ARDS</u>

The primary causes of death in patients infected with SARS-CoV-2 is acute respiratory distress syndrome (ARDS), which is primarily a cytokine-mediated process that leads to profound lung injury. **In addition, coronavirus spike protein-encoding plasmids can induce IL-8 production in lung cells.**[7] Innate immunity with neutrophil, macrophage and dendritic cell mediated lung injury plays a central role in the pathophysiology of ARDS. In ARDS, alveolar macrophages can trigger a robust pro-inflammatory response and secretion of interleukin-8 (IL-8) recruits neutrophils.[8,9] This aberrant inflammatory response results in the accumulation of alveolar edema with resultant hypoxia and respiratory failure. Numerous clinical studies demonstrate that IL-8 is dramatically increased in both bronchoalveolar fluid and plasma in patients with ARDS compared to healthy controls and is associated with poor clinical outcomes.[10-13] In particular, prior data show that elevated IL-8 is associated with increased mortality rate in patients developing ARDS after infection with a similar virus (MERS-CoV).[14] Neutrophil-lymphocyte ratio (NLR) also appears to be associated with poor outcomes in ARDS and NLR is known to correlate with IL-8 levels.[15] Therefore, IL-8 may represent a key upstream mediator of inflammation in ARDS that makes it an attractive therapeutic target.

3.3. Rationale for anti-IL-8 therapy in hospitalized patients with severe COVID-19

BMS-986253 (also referred to as anti-IL8 mAb or HuMax IL8) is a fully human-sequence IgG1κ mAb directed against human interleukin-8 (IL-8) also known as CXCL8. IL-8 is a well-described pro-inflammatory cytokine orchestrating the recruitment of neutrophils in tissue injuries. BMS-986253 potently binds to and neutralizes the various biological activities of IL-8. BMS-986253 was initially investigated for the treatment of inflammatory skin diseases and demonstrated an excellent tolerability and safety. More recently, BMS-986253 has been developed as a cancer immunotherapy and is currently in late-stage phase 1 testing. Results from these studies show excellent safety and tolerability at a dose of 2400mg every 2 weeks in a cancer patient population.

Given the central role of IL-8 in the pathophysiology of ARDS, the increased morbidity and mortality of patients who develop severe COVID pneumonia and the excellent safety profile of BMS-986253, we believe there is an urgent need to evaluate this agent in patients who develop respiratory failure in the setting of SARS-CoV-2 infection. As a New York City based hospital, we believe we are well placed to rapidly evaluate BMS-986253 in this patient population.

INVESTIGATIONAL AGENTS

3.4 BMS-986253

3.4.1 Pharmaceutical and Therapeutic Background

BMS-986253 (also known as Humax-IL8 and formerly referred to as Humax-Inflam) is a fully human immunoglobulin subclass G1 kappa monoclonal antibody (mAb) directed against IL-8, also known as CXCL8. IL-8 is a well-described proinflammatory cytokine. BMS-986253 potently binds free IL-8. Disruption of the IL-8:CXCR1/2 signaling axis may inhibit recruitment of neutrophils to sites of injury.

The drug was initially investigated for the treatment of inflammatory skin diseases under the name Humax-Inflam. HuMax-Inflam was in a Phase 1/2 dose-escalation, safety, and efficacy trial in patients with palmoplantar pustulosis (PPP). The antibody demonstrated a tolerable profile and sign of activity based on a reduced inflammation index at doses up to 8 mg/kg weekly.

Subsequently, the product is now being developed for the treatment of cancer under the product code BMS-986253. The clinical development strategy for BMS-986253 as an anticancer agent will be in combination with other therapeutic approaches such as immune checkpoint inhibitors.

The transition from hybridoma-derived to Chinese hamster ovary (CHO) cell-derived BMS-986253 was accomplished by the cloning and expression of the heavy and light chains of the antibody cDNAs in CHO cells to produce BMS-986253. A comparability exercise between CHO cell-derived material and hybridoma material has not revealed any significant differences in antigen-binding fragment (Fab) to IL-8 and other critical quality attributes, but has demonstrated a more complete processing and decreased heterogeneity in isoelectric point with the CHO cell-derived BMS-986253. Based on molecular characterization, the main difference between the hybridoma-derived and CHO cell-derived materials is glycosylation patterns.

BMS-986253 was tested as monotherapy in 15 participants with advanced solid tumors (Study CA027-001) and demonstrated a tolerable profile at doses up to 32 mg/kg Q2W. Of these 15 participants, 11 had a best overall response of stable disease (SD) and 4 had a best overall response of progressive disease. **In an ongoing Phase 1/2a study of BMS-986253 in combination with nivolumab in advanced cancers (N=92 treated as of Jan 2020), safety data from patients treated to date suggest that the drug is extremely well tolerated at the maximum dose tested (2400mg Q2W) and does not lead to significant neutropenia.**

3.4.2 Pre-clinical and Clinical Data

Pre-clinical Data:

The pharmacokinetics (PK) of BMS-986253 and HuMax-Inflam evaluated in cynomolgus monkeys showed that BMS-986253 and HuMax-Inflam have similar PK upon intravenous (IV) administration.

After a single IV dose of HuMax-Inflam in monkeys (2 and 20 mg/kg doses), HuMax Inflam exhibited typical antibody PK characteristics: low total body serum clearance (CLTs, 0.001 to 0.003 mL/min/kg), limited volume of distribution at steady-state (Vss,

0.041 to 0.067 L/kg), and a long apparent elimination half-life (T-HALF) of 249 to 672 hours. HuMax-Inflam exhibited a generally dose-proportional increase in exposure between 2 and 20 mg/kg doses. The exposure was generally similar in males and females at the 2 mg/kg and 20 mg/kg dose levels.

After IV dosing of BMS-986253 to monkeys, the systemic exposure of BMS-986253 increased in a dose-proportional manner between 20 and 160 mg/kg. The T-HALF was 204 and 286 hours at 20 and 160 mg/kg, respectively.

The nonclinical safety of BMS-986253 and HuMax-Inflam was evaluated in vitro in a human tissue cross-reactivity study, and in vivo was evaluated in exploratory single-dose and repeat IV dose studies in cynomolgus monkeys.

In a Good Laboratory Practice (GLP)-compliant tissue cross reactivity study in normal human tissues, there was no specific staining of biotin labeled HuMax-Inflam (produced in hybridoma cells) indicating that BMS-986253 did not demonstrate cross reactivity with the human tissues examined.

The cynomolgus monkey was selected as the toxicology species because 1) HuMax-Inflam stained intracellular IL-8 in lipopolysaccharide (LPS) stimulated whole blood cells from cynomolgus monkeys and rhesus monkeys, 2) amino acid sequence of cynomolgus IL-8 is identical to rhesus IL-8, and 3) BIAcore analysis confirmed that HuMax-Inflam cross reactivity to rhesus IL-8 (K_D= 2.56 x 10^{-10} M) is comparable to human IL-8 (K_D = 1.68 x 10^{-10} M). BIAcore analysis of BMS-986253 to cynomolgus IL-8 has not been performed.

Single dose IV tolerability studies demonstrated tolerability up to the highest doses tested of 20 mg/kg HuMax-Inflam (sex combined mean AUC[0-T] = 162,196 µg·h/mL) and 160 mg/kg BMS-986258 (mean male AUC[INF] = 709,000 µg·h/mL). In GLP-compliant repeat-dose toxicity studies in cynomolgus monkeys, based on the lack of BMS-986253-related adverse effects, the NOAEL was considered to be the highest HuMax-Inflam dose of 20 mg/kg QW x 4 (sex combined mean AUC[0-T] = 93,500 µg·h/mL) in the 4-week study and the highest BMS-986253 dose of 160 mg/kg QWx12 (sex combined mean AUC[0-T] = 569,500 µg·h/mL) in the 12-week study. This dose was 5x higher than the proposed maximum dose tested in humans (32 mg/kg) with a corresponding AUC multiple of 3.6x the projected human AUC (approximately 159,934 µg·h/mL).

Overall, the nonclinical toxicology assessment of BMS-986253 has demonstrated an acceptable safety profile with a lack of BMS-986253-related adverse effects, supporting clinical use in oncology patients

Clinical Data:

The clinical experience with BMS-986253 is based on the 4 completed and 1 ongoing clinical studies outlined in **Table 2.** In the HuMax-Inflam-001 study administration of HuMax-Inflam in a single dose of up to 8 mg/kg and up to 4 mg/kg in 4 weekly doses was safe and well tolerated by participants with PPP. Approximately 50% of reported AEs (45

of 85) were judged attributable to the study drug. The most frequent AEs were nausea, nasopharyngitis, and headache. In cancer patients, experience is based on the completed Phase 1 dose escalation study CA027-001, in which BMS-986253 monotherapy was assessed in a classical 3+3 design, as well as preliminary data from 92 participants in the ongoing Phase 1/2a study CA027-002 treated with varying doses of BMS-986253 in combination with a flat dose of 480-mg nivolumab Q4W: 600 mg Q4W (N = 16), 1,200 mg Q4W (N = 15), 2,400 mg Q4W (N = 18), 1,200 mg Q2W (N = 12), and 2,400 mg Q2W (N = 31). In the CA027-001 study, AEs leading to discontinuation were reported in 3 (20.0%) participants, and all were considered not related to BMS-986253. AEs leading to discontinuation included Grade 3 increased blood alkaline phosphatase (ALP), Grade 2 increased blood creatinine, Grade 3 hypertension, Grade 3 fall, and Grade 3 back pain**. 1 patient reported "white blood cell decreased" (grade 1) at a dose of 16mg/kg Q2W.** In the CA027-002 study combining BMS-986253 with nivolumab**, 1 participant treated with Q2W BMS-986253 2,400mg experienced Grade 3 neutropenia on Cycle 2 Day 1; this participant was asymptomatic without evidence of infection, and the episode resolved without intervention in < 2 weeks.** Overall, based on the available data as of 16-Jan-2020, no significant safety trends were identified. In CA027-001, BMS-986253 reduced baseline serum IL-8 levels at all dose levels. The PD effect in tissue was not analyzed, and PK analysis showed an approximate linear correlation between increasing dose and exposure.

Previously, three clinical studies were conducted with HuMax-Inflam. In the Humax Inflam-001 trial, intravenous infusion of repeated doses up to 4 mg/kg weekly for 4 weeks after single dose up to 8mg/kg were safe and well tolerated by 6 patients diagnosed with PPP, the MTD was not reached. The study indicated biologic and clinical activity, achieving reduction of IL-8 in the targeted tissue along with decrease in inflammatory scores. In the two subcutaneous studies, HuMax-Inflam-302 and -303, the drug was well tolerated with one injection site reaction noted in Study HuMax-Inflam-303 (n=7) as moderate pruritus. Overall these studies have not elicited any strong evidence for any adverse events of concern with an anti-IL8 antibody and are in support of further clinical development. See **Table 2** below for summary of anti-IL8 clinical studies (see Investigator's Brochure for additional details). **Of note there was no clinically significant neutropenia in any of the trials conducted to date, including an ongoing study at Columbia testing BMS-986253 in patients with high-risk prostate cancer.**

Table 2 anti-IL8 Clinical Trials

Study/ Country /Status	Study Design	Primary Objective(s)	Endpoints	Dose/Route/Duration	Subject Population	Study Report Status
CA027-001, US, LPLV Complete	Phase 1, single arm, ascending multiple-dose study	Assess safety and tolerability of multiple doses of BMS-986253	Safety, PK, and PD	Doses: 4, 8, 16, and 32 mg/kg/ IV/ Q2W	Participants with advanced cancer. (Male – 9, Female – 6)	Final
CA027-002	Phase 1/2a, open label study investigating the combination of BMS-986253 and nivolumab	Assess safety and tolerability of multiple dose combinations of BMS-986253 and nivolumab	Safety, PK, and PD	Doses: 600, 1200, or 2400 mg Q4W IV in combination with nivolumab 480 mg IV Q4W. Other dosing regimens/frequencies of BMS-986253 may be explored.	Participants with advanced/ metastatic solid tumors	Ongoing
HuMax-Inflam-001, Denmark, Finland Complete	Phase 1/2, A single dose escalation study followed by a 4-week multiple dose extension.	Assess safety and tolerability of single and multiple doses of HuMax-Inflam.	Safety, PK, and PD	Single dose of 0.15, 0.5, 1, 2, 4, and 8 mg/kg/ IV followed by a weekly dose of 0.15, 0.5, 1, 2, and 4 mg/kg/IV for 4 weeks	Participants with PPP. (Male – 6, Female – 25)	Final
Hx-Inflam-302, Denmark, Complete	Phase 2, open-label, non-randomized investigating of the effect HuMax-Inflam for psoriasis	Investigate whether treatment with HuMax-Inflam induced regression or reduced progression of inflammatory, progressive psoriasis in comparison with isotonic saline solution.	Investigator's overall assessment of disease activity in the treated areas	Part A- 5mg/mL fixed dose of HuMax-Inflam was injected 4 times at 1-week intervals. Part B- 5mg/mL fixed dose of HuMax-Inflam was injected 5 times a week for 3 consecutive weeks	Participants with inflammatory progressive psoriasis or actively expanding plaque psoriasis (Male = 4, Female = 3)	Final
Hx-Inflam-303, Denmark, Complete	Phase 2, open label, non-randomized trial in health volunteers with local injection of HuMax-Inflam to prevent	Investigate the capacity of locally injected HuMax-Inflam to prevent follicular rash induced by locally injected HuMax-EGFR.	Investigators assessment of the degree of follicular rash at injection sites	A 1.25 mg fixed dose of HuMax-Inflam was injected, 1 time weekly for 7 weeks (Parts 1 and 2) or 5 times weekly for 5 weeks (Part 3)	Normal Healthy Volunteers (Male = 13, Female – 0)	Final

3.4.3 Rationale for Dose Selection/Regimen

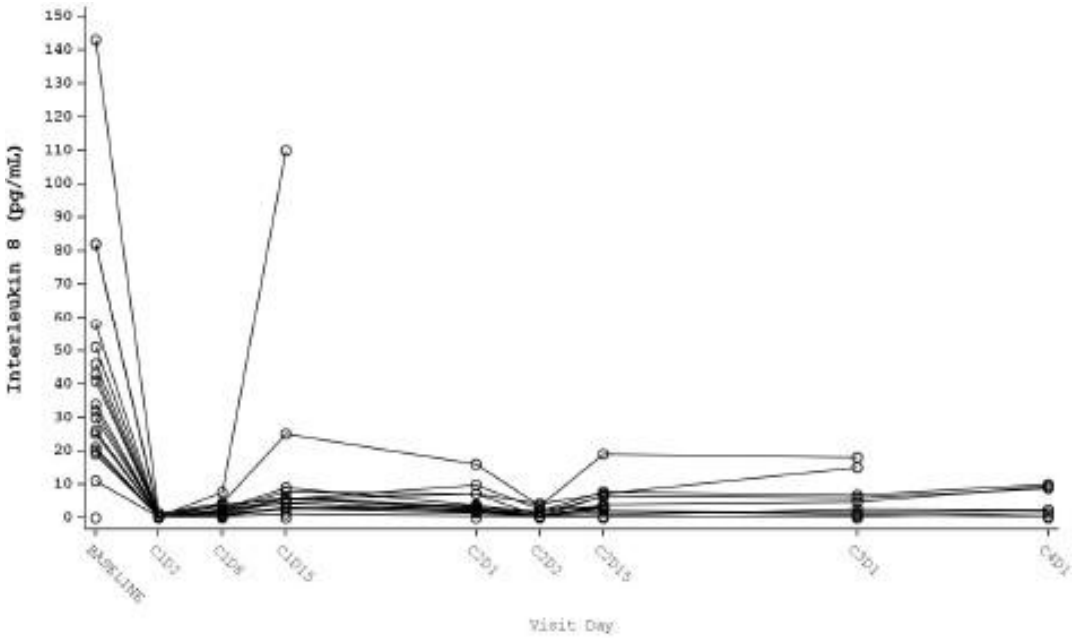
Based on safety, PK, and PD findings, a combination of BMS-986253 2400mg Q2W was selected for testing.

BMS-986253 trough serum concentrations in oncology subjects who received a 32 mg/kg Q2W (equivalent to 2400 mg flat dose) dose exceeded the IC90 concentrations for both CXCR1 and CXCR2 binding of IL-8 resulting in target engagement and the mean Cmax of this dose was 300 times higher than the IC50 for chemotaxis in vitro (IC50 of 0.3 µg/ml). Based on the safety data observed in oncology subjects as well as from healthy subjects, and PPP subjects, doses up to 2400mg Q2W were well tolerated with no MTD reached.

In the ongoing Phase 1/2a Study CA027-002, the combination of BMS-986253 and nivolumab is being evaluated in advanced cancers. An ELISA assay is being used to detect serum free IL-8 (IL-8 that is not bound to therapeutic antibody). The serum free IL-8 results (as of the data cut-off date 16-Jan-2020) for 17 participants who were treated with BMS-986253 at a dose of 2400mg Q2W in combination with nivolumab 480 mg Q4W are presented in Figure 3. All participants displayed a rapid decrease in free serum IL-8 at the earliest time point assessed (Cycle 1 Day 2). **The data suggest that BMS-986253**

Figure3 Free serum IL-8 concentration after treatment with BMS-986253

decreases free serum IL-8 in a dose and frequency dependent manner. The 2.400 mg O2W dosing provides the deepest and most durable free serum IL-8 suppression as well as robust suppression of IL-8 in tumor tissue.



4. STUDY DESIGN

4.1 General Design

This is a single-center, randomized, open-label phase 2 study comparing the time-to-improvement in 7 point ordinal scale in hospitalized patients with severe COVID-19 treated with BMS-986253 (anti-IL-8) to standard of care/control. Patients will be recruited from the inpatient hospital at NYP/Columbia University Irving Medical Center.

Study Interventions: Eligible patients will be randomized 2:1 to receive BMS-986253 IV every 2 weeks x 1-3 doses (with 2nd dose given if patient still hospitalized and 3rd dose optional for patients with continued severe COVID-19 requiring hospitalization) versus standard of care.

Schedule of Evaluations: During treatment patients will have safety assessments including routine bloodwork and routine physical examinations daily. (See **Section 10** for detailed study evaluations and the study schedule). Safety evaluations will also occur by phone monthly following discharge until 100 days after the last treatment doses.

The primary endpoint is time to improve in clinical status: the time (days) required from the start of treatment to the improvement of clinical status (2 points) assessment from baseline based on the 7-point ordinal scale.

Laboratory assessments including CBC with differential, basic metabolic panel, hepatic panel and coagulation studies will be performed daily during hospitalization. Inflammatory markers including D-Dimer, LDH, s-IL-6, neutrophil-to-lymphocytes ratio (NLR) and absolute lymphocyte count will be measured every other day during hospitalization. Imaging with CXR or CT scan will be done at baseline and after 7 days of treatment as clinically indicated. Serum for research purposes will be collected at baseline and then weekly during hospitalization if feasible. For patients ready for discharge prior to day 8, a serum sample should be collected, when feasible, prior to discharge. Post-discharge follow up will be conducted by phone and will be done monthly until 100 days following the last dose of treatment and then every 3 months for up to 1 year. Toxicity evaluation will utilize CTCAE v5.0 criteria.

Duration of Treatment: Subjects randomized to receive BMS-986253 will receive treatment for up to 4 weeks while hospitalized or intolerable toxicity or side effects. Patients who are discharged prior to 2 weeks after the first treatment, will not receive additional doses of therapy. Patients still with severe respiratory symptoms and hospitalized at 4 weeks may receive an additional treatment dose. Subjects randomized to the control arm will receive standard of care therapy as determined by their treating physician.

PK assessments and Correlative Studies: Serum will be collected at baseline and then weekly during hospitalization if feasible. For patients ready for discharge prior to day 8, a serum sample should be collected, when feasible, prior to discharge.

Duration of Follow up: Toxicity and laboratory tests will be graded using the NCI CTCAE v5.0 scoring system. Adverse events will be assessed continuously from the inpatient medical record during the study and for **100 days** after the last dose of treatment. Laboratories as outlined in **Section 11** will be collected daily during hospitalization. Post-discharge medical history and survival will be assessed monthly until 100 days following the last dose of therapy and then every 3 months for up to 1 year.

4.2 Number of Subjects

This study will enroll a total of 138 subjects randomized 2:1 (anti-IL-8: standard of care).

5. SUBJECT SELECTION AND WITHDRAWAL

Subjects will include patients hospitalized with confirmed SARS-CoV-2 who have developed severe COVID-19. Both patients with severe disease defined as oxygen saturation ≤ 93% on room air or critical disease defined as requiring non-rebreather, non-mechanical/mechanical ventilation, high-flow nasal cannula, or ICU admission will be recruited. Subjects will be identified and recruited through inpatient units at NYP/Columbia University Irving Medical Center.

5.1 Inclusion Criteria

- Male or female adult ≥ 18 years of age at time of enrollment.
- Confirmed diagnosis of SARS-CoV-2 infection ≤ 14 days prior to registration.

- Inpatient hospitalization (or documentation of a plan to admit to the hospital if the patient is in the emergency department)
- Evidence of pneumonia by chest radiographs, chest CT **OR** chest auscultation (rales, crackles).
- Severe respiratory disease (oxygen saturation ≤93% on room air or requires ≥2L oxygen by NC in order to maintain SaO2 ≥93%) OR critical respiratory disease (requiring non-rebreather, non-mechanical/mechanical ventilation, high-flow nasal cannula, ICU admission).
- Patients can continue their anti-cancer therapy at the discretion of the treating physician.
- *Adequate laboratory tests including:*
    - ANC >500 cells/mm^3
    - Platelet count >20,000 cells/mm^3
    - Serum total bilirubin <1.5 × ULN
    - ALT <5 × ULN
    - AST <5 × ULN

- *Age and Reproductive Status*

    a) Males and females, aged at least 18 years old

    b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study treatment.

    c) Women must not be breastfeeding.

    d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment plus for a total of 155 days post treatment completion. Local laws and regulations may require use of alternative and/or additional contraception methods.

    e) WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, but should still undergo pregnancy testing as described in this section.

    f) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception during study treatment with BMS-986253 for a total of 215 days post-treatment completion.

    g) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

- Willingness to provide written informed consent and HIPAA authorization for the release of personal health information, and the ability to comply with the study requirements

(***note***: HIPAA authorization will be included in the informed consent). In cases of partial impairment, impairment that fluctuates over time, or complete impairment due to dementia, stroke, traumatic brain injury, developmental disorders (including mentally disabled persons), serious mental illness, delirium, medical sedation, or intubation, a subject may be enrolled if the subject's legally authorized representative consents on the subject's behalf.

5.2 Exclusion Criteria

- Treatment with anti-IL-6, anti-IL-6R antagonists or Janus kinase inhibitor (JAKi) within 48 hours of first dose of study treatment.
- No other investigational therapies as part of another clinical trial with the intent to treat the patient's COVID-19 can be administered while the patient is enrolled in the study.
    - Exception is remdesivir, hydroxychloroquine, convalescent plasma or other treatments being used as compassionate use or under Emergency Use Authorization (EUA) for COVID-19 per Investigator discretion.
- Expected non-COVID-related survival of < 2 months.
- Receipt of non-oncology vaccines containing live virus for prevention of infectious diseases within 4 weeks prior to first dose of study treatment
- History of severe hypersensitivity reaction to any mAb
- Multi-organ failure requiring vasopressors or continuous veno-venous hemofiltration (CVVH) or extracorporeal membrane oxygenation.
- No active systemic bacterial or fungal infection
    - Excludes patients with positive blood cultures not infections like empiric pneumonia, antibiotic coverage, UTIs, etc.
    - Patients with a history of positive bacterial or fungal cultures but on enrollment do not have suspected or known active systemic bacterial or fungal infections are permitted.

5.3 Inclusion of Women and Minorities

All genders, races and ethnic groups are eligible for this trial.

5.4 Subject Recruitment

Subjects will be recruited from the inpatient units at NYP/Columbia University Irving Medical Center. Patients will not receive payment or reimbursement for participation. Every effort will be made to include patients of racial and ethnic minorities who fulfill the eligibility criteria.

A member of the patient's treatment team, the protocol investigator, or research team at NYP/Columbia University Irving Medical Center will identify potential research

participants. If the investigator is a part of the treatment team, s/he will screen the patient as to eligibility, and will discuss the study and the possibility of enrollment in the research study with the patient. The preliminary screen of eligibility will be inpatient hospitalization and confirmed SARS-CoV-2 infection.

Potential subjects that meet these basic criteria will be referred by their treating physician to the investigator, co-investigators, or research staff of the study. Minority patients are well represented at NYP/Columbia University Irving Medical Center, and we expect that they will be well represented in the trial accrual. The principal investigator, Mark Stein, MD will be available to all patients for further questions and information through the contact number that will be provided on the consent form.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patients during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes

5.5 Early Withdrawal of Subjects

5.5.1 When and How to Withdraw Subjects

- If at any time the patient develops unacceptable toxicity (e.g. a severe infusion reaction), as determined in consultation with the PI, he/she will be removed from the study treatment but should continue to be followed on the study for clinical outcomes including safety, intubation and mortality.
- If the patient withdraws consent for continued participation, he will be removed from study.

5.5.2 Data Collection and Follow-up for Withdrawn Subjects

If subjects withdraw prematurely from the study, follow-up will continue for all subjects. Subjects withdrawn because of unacceptable adverse events will be followed until resolution or stabilization of the adverse event. An attempt will be made to obtain survival information for all subjects for a period of at least 1 year following the time of registration or until death, whichever comes first. This will include attempts to contact subjects via telephone and by certified letter using information available to the investigators and the study team. When possible, at least two attempts will also be made to contact the subject's next of kin to obtain such information while observing relevant privacy laws, when applicable.

6. REGISTRATION PROCEDURES

6.1 CUMC Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures, along with applicable institutional policies and federal regulations.

Only Investigators/Research personnel properly trained and delegated to consent subjects for this protocol will participate in the consenting process. Furthermore, properly delegated/trained Physician Investigators (e.g., MD, MD PhD) are required to sign/verify a protocol specific Eligibility Checklist for each subject enrolled on the study, in addition to providing the relevant source documentation confirmation subject eligibility.

All participants must be centrally registered through the Central Registration Office within Herbert Irving Comprehensive Cancer Center at CUMC prior to initiation of study treatment.

Registration hours are available Monday through Friday from 9:00am – 5:00pm EST (excluding holidays and weekends). Same day patient registrations (and after hour registrations) will be accommodated on a case by case basis provided that the study team has expressed all time sensitive registration concerns/cases in a timely manner to the Central Registration Office.

CPDM Central Registration Procedures:
Within 48 hours of obtaining consent (excluding holidays and weekends), a completed/signed IRB approved informed consent HIPAA form, and demographics forms must be submitted to the CPDM Central Registration Office via an email to CPDMRegistration@cumc.columbia.edu or fax to 212.304.6330, with the subject line "AAAS9881 Pending Subject Registration Request (PHI)". Upon receipt, applicable subject information as well as a "pending eligibility" status will be entered into HICCC's institutional database. This status will remain until further source documentation is made available to confirm overall patient eligibility. Required materials for all pending registration submissions are as follows:

- Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable.
- The completed/signed IRB approved HIPAA Authorization form
- Completed/signed CPDM ICF checklist
- Completed/signed HICCC personal census form
- Completed/signed CPDM Demographics Note to File

In order to confirm eligibility status, Investigators/designees (e.g., study specific Clinical Research Coordinator/Research Nurse, etc.) must submit the following documentation to the Central Registration Office via email or fax:

- The completed/signed study specific Eligibility Checklist (signed by a Physician level Investigator)

- Copies of source documentation necessary for each item to be verified on the CPDM specific Eligibility Checklist, including but not limited to:

  - Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)

  - Copy of pathology and surgical reports

  - Copy of clinic note(s) or other appropriate medical records capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)

  - Protocol deviation/waiver approvals (if applicable)

- **Please note**: subject line of email or fax should include the following: "AAAS9881 Complete Subject Registration Request (PHI)".

Upon receipt of the above mentioned documentation, participant eligibility information will be verified by a qualified Central Registration Registrar. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable study team personnel for clarification prior to enrollment. All applicable finalized registration/eligibility information will then be entered into HICCC's institutional CTMS database by the Central Registration Registrar. Upon completion, an official subject registration notification email will be sent to the PI/research team which will include eligibility/enrollment status, as well as subject ID information. Protocol therapy may not be initiated prior to receipt of this notification from the Central Registration Office.

All screen fail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

6.2 Informed Consent Procedures

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must review the IRB/PB-approved consent form and indicate their consent to participate. This consent form meets the requirements of the Code of Federal

Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature, objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

The participant must receive a copy of the signed informed consent form.

Remote Consenting
Patient will be consented remotely as part of this study either by phone.

During this phone call, or subsequent phone calls if necessary, the PI/treating physician will perform remote consent. The remote consent discussion will be documented in the medical record. Upon receipt/confirmation of the signed/dated consent form (if applicable), the authorized consenter will subsequently sign/date the scanned copy of the consent/HIPAA document, and provide documentation regarding the delay in signature, so documentation is clear and self-evident upon any audit or QA review. Further guidance regarding the consent process can be found in Appendix E: Consent Guidance.

7. TREATMENT PLAN

7.1 Agent Administration

Treatment will be administered on an inpatient basis. Reported adverse events and potential risks for BMS-986253 are described in **Section 10**. Appropriate dose modifications for BMS-986253 are described in **section 9**. No investigational therapies other than those described below may be administered with the intent to treat the patient's COVID-19 while the patient is enrolled in the study.

REGIMEN DESCRIPTION					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**[+]	**Cycle Length**
BMS-986253	No specific premedications or precautions	2400mg	IV over 120 minutes (+/- 10 minutes)*	Days 1, 15, 29	6 weeks

*Infusion time will be 180 minutes (+/- 10 minutes) for patients <35kg.
+ Day 15 dose will be given if still hospitalized; day 29 dose is optional and will be given if patient hospitalized with severe respiratory symptoms.

7.2 Management of Infusion Reactions:

Since BMS-986253 contains only human Ig protein sequences, it is unlikely to induce hypersensitivity reactions. In the CA027-001 study, an infusion reaction (Grade 1) was observed in 1 patient and in the CA027-002 study 2 patients experienced infusions reactions (1 patient with Grade 2; 1 patient with Grade 4). If such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All serious infusion reactions should be reported to BMS. All Grade 3 or 4 infusion reactions should be reported within 24 hours (excluding holidays and weekends) to the CUMC Sponsor-Investigator and BMS Medical Monitor and reported as an SAE. Infusion reactions should be graded according to NCI CTCAE v5.0 guidelines.

Treatment recommendations for infusion reactions are provided below and may be modified based on local treatment standards and guidelines, as appropriate.

For Grade 1 symptoms (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg at least 30 minutes before study treatment administrations.

For Grade 2 symptoms (moderate reaction requiring therapy or infusion interruption but responding promptly to symptomatic treatment such as antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids, or prophylactic medications indicated for ≤ 24 hours):

- Stop the study treatment infusion, begin an IV infusion of 0.9% sodium chloride and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further BMS-986253 will be administered at that visit.

- For future infusions, the following prophylactic pre-medications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg should be administered at least 30 minutes before study treatment infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms (severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]; Grade 4: Life-threatening; pressor or ventilatory support indicated):

- Immediately discontinue infusion of study treatment. Begin an IV infusion of 0.9% sodium chloride and treat the participant as follows: recommend bronchodilators, epinephrine 0.2 mg to 1 mg of a 1: 1,000 solution for subcutaneous administration or 0.1 mg to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Study treatment will be permanently discontinued except for a Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

7.3 General Concomitant Medication and Supportive Care Guidelines

7.3.1 Concomitant Therapy

The following medications are prohibited during the study if the subject is randomized to the investigational therapy arm (unless utilized to treat a drug related AE):

- anti-IL-6, anti-IL-6R antagonists or Janus kinase inhibitor (JAKi)

7.3.2 Other Restrictions and Precautions

Patients being treated with anti-cancer immunotherapy are permitted.

7.4 Treatment Compliance

Treatment compliance with all study-related medications should be emphasized to the subject by the site personnel. Compliance with BMS-986253 will be documented in the medical record and monitored by the principal investigator of its designee.

7.5 Randomization and Blinding

Patients will be randomized 2:1 (anti-IL8: standard of care) in “real-time”. If the subject’s eligibility status is confirmed, the statistician will send the randomization assignment based on the pre-generated randomization scheme.

This is an open-label study.

7.6 Duration of Therapy

In the absence of treatment discontinuation due to adverse events, treatment may continue for up to 4 weeks or until one of the following criteria applies:

- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient has been discharged from the hospital

At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study and such extension is approved by Bristol Myers Squibb Company. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

7.7 Duration of Follow Up

Following completion of therapy, patient will have follow up by phone every 30 days for the first 100 days following the last dose of therapy. Patients will then have follow up by phone every 90 days (+/- 30 days) for up to 1 year. In addition, patients will be assessed 28 days (+/- 2 days) following start of treatment whether they are discharged or in the hospital. Participants who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with **Section 4.1** until death or the conclusion of the study.

7.8 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 8.6 applies. The reason for study removal and the date the patient was removed will be documented in the Case Report Form.

DOSING DELAYS/ DOSE MODIFICATIONS

7.9 Criteria and Procedures for Dose Modifications and Interruptions

Dose escalation/reduction is not permitted in this study in order to allow better evaluation of the safety and efficacy. However, if toxicities occur, subsequent doses of BMS-986253 should following the below guidelines:

Toxicity	Grade	Hold Treatment (Y/N)	Timing of Treatment Restart	Dose Schedule for Treatment Restart	Discontinue Subject
	1, 2	No	N/A	N/A	N/A

Hematologic Toxicity	3, 4	Yes	Toxicity resolves to ≤ Grade 1 or baseline	Restart at same dose. However, for all Grade 4 hematologic toxicities, treatment may not be restarted.	Toxicity does not resolve to ≤ Grade 1 or baseline by the time of next treatment dose. Permanent discontinuation should be considered for any severe or life-threatening event.
Non-Hematologic Toxicity Note: Exception to be treated similar to Grade 1 toxicity: - Grade 2 fatigue - Grade 3 rash in patients who have not experienced a grade 3 drug-related skin AE	1	No	N/A	N/A	N/A
	2	Consider holding for persistent symptoms	Toxicity resolves to ≤ Grade 1 or baseline	Restart at same dose	Toxicity does not resolve to ≤ Grade 1 or baseline by the time of next treatment dose. Permanent discontinuation should be considered for any severe or life-threatening event
	3	Yes	Toxicity resolves to ≤ Grade 1 or baseline	Restart at same dose	Toxicity does not resolve to ≤ Grade 1 or baseline by the time of next treatment dose. Permanent discontinuation should be considered for any severe or life-threatening event
	4	Yes	Discontinue treatment	Treatment may not be restarted	Yes.

Criteria to resume treatment:

Subsequent dosing with study therapy may resume once AEs resolve to Grade 1 or baseline.

Participants experiencing AEs not meeting criteria for permanent discontinuation as outlined in **Section 5.5** may resume treatment with study medication under the following criteria:

- Participants may resume treatment with study treatment when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:
  - Participants may resume treatment in the presence of Grade 2 fatigue.
  - Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
  - Participants with Grade 2 uveitis, episcleritis, iritis, eye pain, or blurred vision (except for patients that do not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment).
- For participants with Grade 2 AST, ALT, or total bilirubin elevations, dosing may resume when laboratory values return to baseline and management with corticosteroids (if needed) is complete.
- Participants with combined Grade 2 AST/ALT and total bilirubin values with symptomatic liver inflammation (eg, right upper quadrant tenderness, jaundice) should have treatment permanently discontinued.

Exceptions to permanent discontinuation criteria:

The following exceptions to permanent discontinuation will apply:

- Grade 3 diarrhea, nausea, vomiting, or abdominal pain that returns to Grade 1 or baseline within 3 days with medical intervention.

- Grade 3 pruritus or rash that returns to Grade 1 or baseline within 7 days with medical intervention.
- Isolated Grade 3 or 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 3 days of their onset.
- Grade 4 neutropenia < 7 days in duration.
- Grade 4 lymphopenia or leukopenia.
- Grade 3 or 4 increase in amylase or lipase that is not associated with clinical or radiographic evidence of pancreatitis.
- Grade 3 infusion reactions that return to Grade 1 in < 6 hours.
- Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical, or laboratory evidence of impaired end-organ perfusion).
- Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor).
- Grade 3 fatigue.
- Grade 3 or 4 drug-related endocrinopathy AEs, such as adrenal insufficiency, adrenocorticotropic hormone, hyper- or hypothyroidism, or glucose intolerance, which resolve or adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Sponsor-Investigator.
- Any AE, laboratory abnormality, or concurrent illness, which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued study treatment dosing.

Even if the criteria to resume treatment are met, the consideration to re-initiate study therapy under the following exception will be made on a case by case basis after considering the overall benefit/risk profile, and in consultation between the investigator and the Sponsor. Any AE with clinical risk will be assessed on a case by case basis with the investigator and the BMS Medical Monitor, to determine the risks and benefits of continuing on therapy following resolution versus discontinuing therapy permanently.

All participants who discontinue IP should comply with protocol specified follow-up procedures as outlined in **Section 5.5**. The only exception to this requirement is when a participant withdraws consent for all study procedures including post treatment study follow-up or loses the ability to consent freely (e.g., imprisonment, involuntarily incarceration for the treatment of either a psychiatric or physical illness). If study treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate case report form (CRF) page.

8. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

8.1 Adverse events

See Investigator's brochure for BMS-986253 and **Section 11** for details.

8.2 Definitions

Adverse Event:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

Serious Adverse Event:

A **S*erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

Non-serious Adverse Event:

- Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [eg, IND US trial] as part of an annual reporting requirement.

A ***non-serious adverse event*** is an AE not classified as serious.

Non-serious Adverse Event Collection and Reporting

The collection of serious and non-serious AE information should begin at initiation of study drug. All serious non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported to BMS as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

Potential Drug Induced Liver Injury (DILI)

All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs. Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Pregnancy

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

WOMEN IN THE FOLLOWING CATEGORIES ARE NOT CONSIDERED WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level

> 40 mIU/mL to confirm menopause.

Note: Women treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout periods indicated below are suggested guidelines, and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration
and until the end of relevant systemic exposure, which is defined as 105 days after completion of study treatment for monotherapy treatment and 155 days after completion of combination therapy treatment.

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine device[c] • Intrauterine hormone-releasing system[c] • Bilateral tubal occlusion

- Vasectomized partner

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of >1% per year when used consistently and correctly.

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action

Unacceptable Methods of Contraception

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus).
- Spermicide only
- Lactation amenorrhea method
-

Any pregnancy that occurs in a female or female partner of a male study participant should be reported to BMS. All pregnancy cases should be reported, within 5 months after the last exposure to BMS-986253. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

Contraception Guidance for Male Participants with Partner(s) of Child Bearing Potential

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until the end of relevant systemic exposure defined as 7 months Relevant Exposure after the end of treatment in the male participant.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months Relevant Exposure after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months Relevant Exposure after the end of treatment.
- Refrain from donating sperm for the duration of the study treatment and for 7 months after the end of treatment.

Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these

procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

Adverse Events of Special Interest:

An AESI is an event of scientific and medical interest or concern to the Sponsor's product or program, for which ongoing monitoring and rapid communication to the Sponsor could be appropriate. It may be a serious or non-serious AE, which may require further investigation in order to characterize and understand it.

AESI will include the following:

- Grade 3 or greater infusion reaction including CRS; and,
- Immune related AE of Grade 3 or greater suggestive of an autoimmune process, including, but not limited to, glomerulonephritis.

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious events should be regarded as non-serious adverse events.

Unanticipated Problem:

An unanticipated problem is any incident, experience or outcome involving risks to subjects or others in any human subjects research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document, and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in such research (e.g., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures (e.g., after the first dose of study treatment) to the end of the study treatment (e.g., last dose of study treatment) and/or follow-up. For this study, the study treatment follow-up is defined as 100 days following the last administration of study treatment.

Baseline/Preexisting Condition

A baseline/preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or if the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management (e.g., change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.).

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization for >24 hours or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.

- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.3 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.4 Reporting of Serious Adverse Events

8.4.1 IRB Notification by Sponsor-Investigator

Reports of all events (including follow-up information) that meet the definition of an unanticipated problem posing risk to subjects or others must be submitted to the IRB within one week (5 business days) following the occurrence of the unanticipated problem or the principal investigator's acquiring knowledge of the unanticipated problem in accordance with IRB policy. Additionally, the sponsor-investigator will submit a summary of all Unanticipated problems that occurred since the beginning of the study at the time of continuing review. Copies of each report and documentation of IRB notification and receipt will be kept in the Regulatory binder.

8.4.2 FDA Notification by Sponsor-Investigator

The Columbia University Medical Center Sponsor-Investigator, as holder of the IND, will be responsible for all communication with the FDA. Columbia University Medical Center Principal Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and there is evidence to suggest a causal relationship between the drug and the adverse event. These must be reported to the FDA and any affiliate sites as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting. The Sponsor-Investigator will also submit an IND annual report to the FDA in accordance with 21.CFR 312.33.

The Columbia University Medical Center Sponsor Investigator must report to the FDA and any affiliate site investigators as follows:

- Any unexpected fatal or life-threatening event must be reported as soon as possible, but no later than 7 calendar days after the sponsor investigator initial receipt of the information

- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible but no later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting
- Any findings from animal or in vitro testing whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible but no later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting
- Any clinically important increase in the rate of a serious suspected adverse reactions over that listed in the protocol or Investigator Brochure
- Expected SAEs and AEs will be included in the IND Annual Reports.

Follow-up information to a safety report should be submitted as soon as the relevant information is available. However, if the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable are so reportable, the sponsor investigator must report such experience as soon as possible, but no later than 15 calendar days after the determination is made.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

8.4.3 DSMC Reporting by the Sponsor Investigator

Serious adverse events not constituting unanticipated problems are to be reported to the HICCC DSMC. Reporting should occur within 24 hours of knowledge of the SAE occurring at our institution or affiliate sites.

8.4.4 Reporting to Drug Manufacturers by Sponsor-Investigator

The Sponsor-Investigator will report to investigational agent manufacturers any serious adverse events that meet the reporting criteria to the Institutional Review Board as described in section 10.4 and/or to the FDA as described in section 10.4 within 3 days of becoming aware of it, so that these reports can be evaluated and included in the Investigator's Brochure and for IND safety submissions per regulations. Reporting will occur by sending the reporting form along with any additional documentation sent to the regulatory authorities.

At the time of IRB renewal or at the request of the manufacturer, the Sponsor- Investigator will submit a summary of all Serious Adverse Events that have occurred inclusive of all sites to manufacturer.

All Serious Adverse Events (SAEs) that occur following the subject's treatment start date to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety and to Ferring Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

Following the subject's treatment start date, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.

- An SAE report should be completed for any event where doubt exists regarding its seriousness;
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

An appropriate SAE form (e.g. ex-US = CIOMS form or USA = Medwatch form)/ or equivalent (HICCC DSMC SAE Form) should be used to report SAEs to BMS. Note: Please include the BMS Protocol number on the SAE form or on the cover sheet with the SAE form transmission.

  - The CIOMS form is available at: http://www.cioms.ch/index.php/cioms-form-i
  - The MedWatch form is available at: MedWatch 3500 Form

-
- **SAE reporting to BMS:**
  - *The* Sponsor will reconcile the clinical database AE cases (**case level only**) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com).
    - The Investigator will request from BMS GPV&E, aepbusinessprocess@bms.com the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary
    - GPV&E will send the investigator the report to verify and confirm all SAEs have been transmitted to BMS GPV&E.
    - The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS (Worldwide.Safety@bms.com).

    In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected

Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of a SUSAR Report.

- Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
- In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

SAEs, whether related or not related to study drug, and pregnancies, must be reported to BMS within 24 hours of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved site SAE form.

- Pregnancies must be reported and submitted to BMS on any of the following form(s):
- 1. MedWatch or, CIOMS or
- 2. BMS Pregnancy Surveillance Form or,
- 3. Approved site SAE form

  SAE Email Address: Worldwide.Safety@BMS.com

  SAE Facsimile Number: +1 609-818-3804

- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
- If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours (excluding holidays and weekends) to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

Adverse Event Reporting to BMS

Adverse Events that are routinely collected according to GCP shall be submitted to BMS every three (3) months by the last working day of the third month.

The Adverse Event information required to be sent to BMS is noted in an 'Bristol-Myers Squibb Early Asset Investigator Sponsored Research (ISR) Import Plan' which describes the method of collection and submission to BMS via the mailbox:

MG-RD-GPVE-PHARMACOVIGILANCE@bms.com

When the file is submitted to BMS, it must be noted that the file contains all Non Serious Adverse Events (only adverse events not previously submitted to BMS within the 3 months).

The HICCC CPDM Multicenter Trials Core will submit on behalf of CUMC and all affiliate sites.

8.5 Reporting Process

Adverse events may be submitted on FDA Form 3500A, the HICCC DSMC Serious Adverse Event Reporting Form, or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 10.

9. PHARMACEUTICAL INFORMATION

STUDY DRUGS

9.1 BMS-986253

9.1.1 Dispensing of BMS-986253

The investigator or designee will calculate the number of BMS-986253 vials needed, pull the appropriate number of vials to prepare the infusion solution, and enter the vials used into the eCRF and drug accountability log. The Principal Investigator must keep accurate and up-to-date dispensation records. Any discrepancies between the amounts of Study drug dispensed and returned must also be explained in writing. All such records of drug accountability must be entered on the corresponding Subject CRFs.

9.1.2 Packaging and Formulation

Product Description / Class and Dosage Form	**Potency**	**IP/Non -IMP**	**Blinded or Open Label**	**Packaging / Appearance**	**Storage Conditions (per label)**

BMS-986253 for injection	1000mg/vial (100mg/mL)	IP	Open Label	Vial	Refer to the label on container

For additional details refer to the Investigator's Brochure.

9.1.3 Storage

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.1.4 Administration

Administer intravenously over 120 minutes. Do not co-administer other drugs through the same infusion line. See **Section 8.1** for details on BMS-986253 administration.

9.1.5 Disposal

The investigator is responsible for keeping accurate records of the clinical supplies received from BMS or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

9.1.6 Drug Interactions and Concomitant Therapy

The expected in vivo degradation of mAbs is via biochemical pathways that are independent of typical small molecule drug metabolizing enzymes. Consequently, typical mAbs, such as BMS-986253 or HuMax-Inflam, are not expected to have interactions with molecules that are metabolized by these enzymes.

No formal pharmacokinetic drug interaction studies have been conducted with BMS-986253.

9.1.7 Adverse Events

Potential adverse events are summarized in the Investigator's Brochure.

Study HuMax-Inflam-001: Safety in Participants with PPP

Within the dose range up to 8 mg/kg as a single-dose administration, the MTD of HuMaxInflam was not reached. Administration of HuMax-Inflam in a single dose of up to 8 mg/kg and up to 4 mg/kg in 4 weekly doses was safe and well tolerated by participants with PPP. Approximately 50% of reported AEs (45 of 85) were judged attributable to the study drug. The most frequent AEs were nausea, nasopharyngitis, and headache. There was no increase in the frequency of AEs with increasing dose. Administration of HuMax-Inflam did not lead to formation of antibodies against HuMax-Inflam.

Study CA027-001: Safety with BMS-986253 Monotherapy in Participants with Cancer

Multiple ascending doses of BMS-986253 were well tolerated across the dose range of 4 to 32 mg/kg Q2W in 15 adults with advanced tumors treated in Study CA027-001. AEs leading to discontinuation were reported in 3 (20.0%) participants, and all were considered not related to BMS-986253. AEs leading to discontinuation included Grade 3 increased blood alkaline phosphatase (ALP), Grade 2 increased blood creatinine, Grade 3 hypertension, Grade 3 fall, and Grade 3 back pain. There were no deaths due to AEs in this study. The MTD was not reached, and no DLTs were observed. There was 1 death due to disease progression within 48 days of the last dose of BMS-986253.

Five of the 15 participants were considered by the Investigator to have experienced AEs related toBMS-986253 monotherapy. All TRAEs were Grade 1 or Grade 2 in severity. The most common TRAEs were nausea (N = 2) and fatigue (N = 2). 1 patient treated at 16mg/kg with grade 1 "reduced white blood cells" related to study drug.

Study CA027-002: BMS-986253 plus Nivolumab in Advanced Cancers

In the ongoing Study CA027-002 (data cut-off date of 16-Jan-2020), 92 participants have been treated with varying doses of BMS-986253 in combination with a flat dose of 480-mg nivolumab Q4W: 600 mg Q4W (N = 16), 1,200 mg Q4W (N = 15), 2,400 mg Q4W (N = 18), 1,200 mg Q2W (N = 12), and 2,400 mg Q2W (N = 31). Of these 92 participants, 9 received treatment as part of a safety lead-in: 5 received 2,400-mg BMS-986253 Q4W and 480-mg nivolumab Q4W, and 4 received 2,400-mg BMS-986253 Q2W and 480-mg nivolumab Q4W. All 9 participants dosed cleared a 28-day DLT period, with no DLTs observed. Overall, based on the available data as of 16-Jan-2020, no significant safety trends were identified.

Thirty of 92 (32.6%) participants experienced AEs related to the study drug combination. The most common TRAEs (N > 2) were Grade 1/2 fatigue (N = 9), Grade 1/2 nausea (N = 7), Grade 1 rash (N = 3), and Grade 1/2 decreased appetite (N = 3). Most TRAEs were Grade 1/2, and based on the available data, no dose-dependent TRAEs were identified. Of

note, 1 participant treated with Q2W BMS-986253 2,400mg experienced Grade 3 neutropenia on Cycle 2 Day 1; this participant was asymptomatic without evidence of infection, and the episode resolved without intervention in < 2 weeks. 2 patients experienced infusion reactions (1 patient grade 2 reaction and 1 patient with grade 4 infusion reaction).

9.2 Subject Compliance Monitoring

Study treatments will be administered by healthcare professionals under the supervision of the Investigators. Records of study treatment dose calculation, administration, and dosing regimen will be accurately maintained by site staff. The monitor will review dose calculation, administration and regimen as well as medication accountability during investigational site visits and at the completion of the study.

10. STUDY CALENDAR

Every effort should be made to keep visits, tests, and procedures on schedule. Acceptable deviations are listed below.

	Screening Evaluation [a]	During Hospitalization (daily unless indicated)	Day 29 and Follow-up (after discharge)[f]
Informed consent	X		
Medical history (including baseline ECOG)	X		X
Review of medications	X	X	X
Physical assessment[k]	X	X	
Vital signs (including Sp02/FIO2 if on supplemental oxygen)	X	(3 times per day)[i]	
Height and weight	X		
Laboratory studies[b]	X	X	
Inflammatory markers[j]	X	Every 2 days	
NLR and absolute lymphocyte count	X	X	
Serum[c]	X	Every 7 days (+/- 2 days)[c]	
NEWS2 score [d]	X	X	
7-point ordinal scale[l]	X	X	
Chest imaging (optional) [e]	X	Every 7 days (+/- 2 days) [e]	
BMS-986253 dose		Every 2 weeks for 1-3 doses[g]	
Toxicity assessment		X	X[h]

a: The screening (pre-treatment) evaluation should be conducted within 1 day prior to dose of BMS-986253. If screening done on same day as treatment then treatment day 1 assessments do not need to be repeat (screening assessments will suffice)
b: Laboratories should include hemoglobin, hematocrit, white blood cell count with differential (including absolute eosinophil count), platelets, sodium, potassium, chloride, bicarbonate, urea nitrogen, creatinine, glucose, calcium, albumin, total protein, bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase. Prothrombin time (PT/INR), activated partial thromboplastin time (APTT) will be drawn at baseline and then as clinically indicated.
c: Serum samples should be collected for cytokine and PK analysis at screening, day 8, 15, 22, 29, and EOT if possible (not required). Should be collected prior to the treatment dose of day 15 and 29. For patients ready for discharge prior to day 8, a serum sample should be collected, when feasible, prior to discharge.
d: NEWS2 score is calculated considering respiratory rate, oxygen saturation, systolic blood pressure, pulse rate, level of consciousness/confusion, temperature.
e: CT chest or CXR at baseline (within 2 days of enrollment) and after 7 days (+/- 2 days) if clinically indicated.
f: Can be done by phone: at day 29 (+/- 1 day) and every 1 month (+/- 1 week) (until 100 days following last dose of treatment), then every 3 months (+/- 1 month) from registration to up to 1 year follow up.
g: If randomized to anti-IL-8 therapy, BMS-986253 will be given every 2 weeks (+/- 2 days). 2nd dose will be given if patient is still hospitalized. 3rd dose is optional and will be given if patient still hospitalized with severe COVID-19. If randomized to control, patients will receive standard of care as determined by their treating physician.
h: Follow-up for toxicity will be done until 100 days following last dose of treatment
i: Vitals sings should include temperature, heart rate, blood pressure, respiratory rate and oxygen saturation and FI02 if on supplemental oxygen
j: Inflammatory markers will include: LDH, D-Dimer, CRP, sIL-6 (+/- 1 day).
k: Documented physical exam from primary treatment team will be sufficient with chart review by research team.
l: 7-point ordinal scale scored as follows: (1) death, (2) hospitalized on invasive mechanical ventilation or extracorporeal membrane oxygenation, (3) hospitalized, requiring non-invasive ventilation or high flow nasal cannula, (4) hospitalized, requiring supplemental oxygenation (5) hospitalized, not requiring supplemental oxygenation and requiring ongoing medical care (COVID-19 related or otherwise) (6) Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care, (7) not hospitalized.

10.1 Screening/Pretreatment Evaluation

Before initiating any screening activities, the scope of the study should be explained to each patient. Patients should be advised of any known risks inherent in the planned procedures, any alternative treatment options, their right to withdraw from the study at any time and for any reason, and their right to privacy. After this explanation, patients should be asked to sign and date an IRB-approved informed consent form that meets the requirements of the Code of Federal Regulations (Federal Register Vol. 46, No. 17, January 27, 1981, part 50).

The pretreatment/screening visit will determine patient eligibility according to the inclusion and exclusion criteria. All subjects must undergo a number of baseline evaluations as part of this screening visit, as detailed below. All of these evaluations should be conducted within 1 day of starting the protocol. This information is also summarized in the Study Calendar (Table 1).

- informed consent
- demographic information
- medical history, including review of systems and baseline ECOG score.
- physical assessment
- vital signs: temperature, pulse, blood pressure, respiratory rate, oxygen saturation and FIO2 and SpO2/FIO2
- height and weight
- current medication list, including drug allergies/adverse events
- hematological laboratories (hemoglobin, hematocrit, white blood cell count with differential [including absolute eosinophil count], platelets)
- coagulation profile (INR, aPTT)
- serum chemistry (sodium, potassium, chloride, bicarbonate, urea, creatinine, glucose, calcium, albumin, protein, bilirubin, ALT, AST, alkaline phosphatase)
- CRP, D-Dimer, LDH, sIL-6 level
- Neutrophil-to-lymphocyte ratio (NLR), absolute lymphocyte count
- NEWS2 score
- 7-point ordinal score
- CT or CXR of the chest (optional)
- Sera for biomarker and PK analysis.

After all relevant screening information is documented, registration should be finalized and appropriate documents (*i.e.*, signed informed consent, supporting source documentation for eligibility) should be faxed or emailed to CPDM Central Registration Office for review.

Information on patients who do not meet eligibility criteria to participate in this study (*i.e.*, screening failures) should also be captured.

10.2 During Hospitalization:

The following must be performed during hospitalization (if screening assessments done <1 day prior to first treatment dose, they do not need to be repeated on Day 1 of treatment).

- review of medication list daily
- review of toxicity/adverse events daily
- vital signs (pre- and post-infusion of BMS-986253) and three times per day including temperature, heart rate, blood pressure, respiratory rate, oxygen saturation and FIO2 and SpO2/FIO2 if on supplementation oxygen.
- physical exam daily
- hematological laboratories (hemoglobin, hematocrit, white blood cell count with differential [including absolute eosinophil count], platelets) daily
- coagulation profile (INR, aPTT) as clinically indicated.
- serum chemistry profile (sodium, potassium, chloride, bicarbonate, urea, creatinine, glucose, calcium, albumin, total protein, bilirubin, ALT, AST, alkaline phosphatase) daily
- CRP, D-Dimer, LDH, sIL-6 level every other day
- Neutrophil-to-lymphocyte ratio (NLR), absolute lymphocyte count daily
- NEWS2 score daily
- 7-point ordinal score daily
- CT or CXR of the chest weekly (+/- 2 days) (optional)
- Sera for biomarker and PK analysis day 8, 15, 22, 29, and EOT (+/- 2 days). Where possible, the Day 15 and 29 PK samples should be collected just prior to dosing. (optional). For patients ready for discharge prior to day 8, a serum sample should be collected, when feasible, prior to discharge.
- Patients randomized to anti-IL-8 therapy will receive BMS-986253 every 2 weeks (+/- 2 days) x 1-3 doses, with 2nd dose given if patient still hospitalized and then 3rd dose optional if patient still hospitalized with severe COVID-19. Patients randomized to control will receive standard of care.

10.3 Follow-Up After Discharge:

Following completion of therapy, patient will have follow up by phone every 30 days for the first 100 days following the last dose of therapy. Patients will then have follow up by phone every 90 days (+/- 30 days) for up to 1 year. In addition, patients will be assessed 28 days (+/- 2 days) following start of treatment whether they are discharged or in the hospital. These assessments will include:

- review of medication list
- review of toxicity/adverse events (for up to 100 days following last dose of treatment)
- Evaluation of Katz basic ADLs and Lawton IADLs (Appendix C and D)

- assessment for survival

Patients withdrawing from the study early because of adverse events should be followed until the adverse event has either resolved or stabilized. Reasons for premature withdrawal should be determined and documented.

11. MEASUREMENT OF EFFECT

11.1 Primary Endpoint

11.1.1 Time to improvement (2 points) in 7-point ordinal scale

The time to improvement (2 points) will be defined as the time (days) required from the start of treatment to the improvement of clinical status (2 points) assessment from baseline based on the 7-point ordinal scale. Patients for whom there was no event will be censored from this analysis. 7-point ordinal scale will be calculated as follows: (1) death, (2) hospitalized on invasive mechanical ventilation or extracorporeal membrane oxygenation, (3) hospitalized, requiring non-invasive ventilation or high flow nasal cannula, (4) hospitalized, requiring supplemental oxygenation (5) hospitalized, not requiring supplemental oxygenation and requiring ongoing medical care (COVID-19 related or otherwise) (6) Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care, (7) not hospitalized.

11.2 Secondary Endpoints

11.2.1 Time to death

The time to death will be defined as the time from onset from symptoms until death from any cause. Patients who are alive or lost to follow-up at the cut-off date will be censored from this analysis.

11.2.2 Mortality at 1 month

1-month mortality is defined as the percentage of patients who have died 1 month from the time of start of treatment.

11.2.3 Time to intubation

The time to intubation will be defined as the time from symptom onset until time of intubation. Any patients already intubated at enrollment will be censored from this analysis.

11.2.4 Time to improvement in oxygenation

The time to improvement in gas exchange will be defined as the time from time of start of treatment until a ≥ 30% decrease in oxygen requirement compared to

baseline [or elimination of oxygen requirement] without a decrease in SpO2 sustained for at least 48hrs or until discharge.

11.2.4 Proportion of patients requiring ICU admission at 1 month.

The proportion of patients requiring ICU admission will be calculated as the number of patients requiring ICU admission over the course of their hospitalization over the number of evaluable patients.

11.2.5 Safety and Toxicity

All subjects receiving at least one dose of the study drug will be evaluated for safety by monitoring symptoms, physical examinations, and laboratory tests. Adverse events will be classified and graded according to the NCI Common Toxicity Criteria version 5.0 (see Appendix A). The absolute number and frequency of each adverse event will be reported, and subdivided according to toxicity grade. A description of adverse events by treatment arm will also be reported. A particular adverse event occurring more than once in the same subject will be counted only once and at its worse grade.

11.2.6 Duration of Hospitalization

Duration of hospital admission will be measured from the time of admission until the time of discharge.

11.2.7 7-point Ordinal Scale Score

The mean/medians of the 7-point ordinal raw scores at day 14 from the start of treatment will be computed and compared between the treatment and control groups.

Exploratory Endpoints.

11.2.8 Change in inflammatory markers from baseline

Changes in LDH, D-Dimer, CRP, ESR, NLR and absolute lymphocytes before and after treatment and over time with be measured every other day during hospitalization.

11.2.9 Change in circulating sIL-6 levels from baseline

Change in sIL-6 levels before and after treatment and over time will be measured every other day during hospitalization.

11.2.10 Radiographic response

Radiological response will be evaluated by comparing % of lung fields with infiltrates on chest imaging (CXR and CT) through independent radiology review between baseline and day 8) if available.

11.2.11 Proportion of patients with multiorgan failure at 1 month

The proportion of patients with multiorgan failure will be defined as the number of patients with multiorgan failure during their hospitalization measured at 1 month over the number of evaluable patients.

11.2.12 Time to improvement in NEWS2 score ≤ 2

Determine the time to improvement in NEWS score will be defined as time from start of treatment until NEWS score ≤ 2 and maintained for at least 24hrs. The NEWS 2 score is calculated based respiratory rate, oxygen saturation, systolic blood pressure, pulse rate, level of consciousness/confusion and temperature.

11.2.13 To measure time on ventilation

Measured from time of intubation to time of definitive extubation. Will censor for patients not requiring intubation.

11.2.12 Change in NEWS2 from baseline

Changes in NEWS2 score will be reported at days 3, 5, 8, 11, 15, and 29.

11.2.15 Change in IL-8 and downstream cytokines.

Circulating IL-8 and additional cytokines (IL1B, IL2, IL4, IL5, IL6, IL7, IL9, IL10, IFNgamma, TNFalpha and others) will be measured at baseline and at additional time points when possible (day 8, 15, 22, 29).

11.2.16 Change in humoral immune response

The humoral immune response will be assessed by protein microarray antibody profiling at baseline and at additional time points when possible (day 8, 15, 22, 29).

11.2.17 To characterize PK of BMS-986253

Will assess PK at screening, day 8, 15, 22, 29, and EOT by collection of serum at these time points when feasible. For patients ready for discharge prior to day 8, a serum sample should be collected, when feasible, prior to discharge.

Stopping Rules

The study may be discontinued by the data and safety monitoring committee (DSMC), the Food and Drug Administration (FDA), or other regulatory authorities. Any unforeseen deaths or serious adverse events may, after a discussion between the principal investigator, prompt an interruption to study accrual pending a full investigation into the circumstances surrounding the event.

Continuous Toxicity Monitoring

As this trial will be the first time an anti-IL-8 will be tested in patients with severe COVID-19, safety will be monitored on a continual basis. Sequential boundaries will be used to monitor dose-limiting toxicity rate.[16] The accrual will be halted if excessive numbers of dose-limiting toxicities are seen, that is, if the number of dose-limiting toxicities is equal to or exceeds b_n out of n patients with full follow-up (see Table 3). This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most 0.05 when the rate of dose-limiting toxicity is equal to the acceptable rate of 30%. For the purposes of this stopping rule, dose-limiting toxicities will be defined as any treated related grade 3 or 4 toxicity.

Table 3. Toxicity Monitoring

Number of Patients, n	1	2	3	4	5	6-7	8-9	10-11	12-14	15-16	17-18	19-21	22-23	24-25	26-28	29-30	31-33	34-36	37-38
Boundary, b_n*	**-**	**-**	**-**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Number of Patients, n	39-41	42-43	44-46	47-49	50-51	52-54	55-57	58-59	60-62	63-65	66-67	67-70	71-73	74-76	77-78	79-81	82-84	85-87	98-90
Boundary, bn*	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**
Number of Patients, n	91-92																		
Boundary, bn*	**39**																		

*This boundary is equivalent to testing the null hypothesis, after each patient, that the event rate is equal to 30%, using a one-sided level 0.009 test.

For example, based on the boundaries above, if 12 out of the first 20 patients enrolled in the anti-IL-8 arm experience dose-limiting toxicities, the trial will be stopped for safety. In this case, the 95% exact confidence interval will be (0.36, 0.81), with the lower confidence limit exceeding the event rate (30%).

12 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10.0 (Adverse Events: List and Reporting Requirements). The Data Safety Monitoring Plan is described in Section 14.3.

12.1 Data Collection

The Herbert Irving Comprehensive Cancer Center has an electronic clinical trials and data management system (CTMS) that will be used for data collection. CRFs for the study will be built into the CTMS for data entry. The system has full auditing capabilities which is web-based and housed on a server in a fully HIPAA compliant server room with restricted access and video

camera monitoring. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials. Users are only able to see study information if they are indicated as study personnel in our electronic IRB system. Users are limited to access based on the role assigned in their corresponding protocol. Subject data is entered directly into the system, which (in the case of Columbia subjects) confirms the correct identity of patients via an interface with the electronic medical patient index. Staff with the appropriate IRB defined roles can run reports within the system for reporting purposes.

12.2 Data Reporting

Case Report Forms will be completed for each subject enrolled into the clinical study through the CTMS. It is the investigator's responsibility for ensuring that all clinical and laboratory data entered on the corresponding CRFs are complete, accurate and authentic.

12.3 Data and Safety Monitoring Committee

The NCI-approved Data Safety and Monitoring Committee (DSMC) of the Herbert Irving Comprehensive Cancer Center (HICCC) will monitor every subject who receives treatment on this protocol for toxicity. This protocol will adhere to the policies of the currently approved HICCC Data and Safety Monitoring Plan (DSMP), which is in accordance with NCI and CUMC-IRB policy and guidelines. The committee is chair is appointed by the HICCC Director. The committee consists of HICCC faculty and staff with expertise in oncology, research pharmacy, research nursing, and data management. The DSMC convenes twice a month to review patient safety and the conduct of the trial. The PI will submit data and safety monitoring reports to the DSMC at a frequency to be determined by the DSMC based on risk to the subjects.

At the time of renewal, the study team will submit the most recent DSMC approval letter for safety review to the CUMC IRB. Any modifications that are required by the DSMC to ensure patient safety will be submitted to the IRB. All protocol deviations, violations, and eligibility waivers will be submitted to and approved by the DSMC prior to being reported to the IRB. All study data reviewed and discussed during these meetings will be kept confidential.

12.4 Quality Control and Quality Assurance

Independent monitoring of the clinical study for protocol and GCP compliance will be conducted periodically by the CPDM Compliance Core on behalf of the HICCC DSMC. Additionally, the Compliance Oversight Committee of the IRB at Columbia University Medical Center may audit the study at any time per institutional policies and procedures. The investigator-sponsor and Columbia University Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

A risk-based approach will be used by the Compliance Core to determine the frequency, number of subject charts, and data elements to be monitored. The Compliance Coordinator will review the

study status and summarize enrollment, toxicities, SAEs/UPs, dose escalation, statistical endpoints (e.g., stopping rules), etc. for the full DSMC membership at the regularly scheduled meetings.

Internal On-site Monitoring:

- Initial, recurrent, and close-out on-site monitoring visits will also be conducted at remote clinical sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).

- The Compliance Coordinator will communicate with the site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.

- The assigned Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

12.5 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (e.g., that the subject is alive) at the end of their scheduled study period.

The subject binders will be maintained with in the CPDM offices, a secured floor within the Herbert Irving Pavilion and only the investigator and study staff will have access to the file.

12.6 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. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

12.7 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A".

12.8 Records Retention

Records relating to a specific research activity, including research records collected by investigators, must be maintained for at least three years after completion of the research (45 CFR 46.115(b); 21 CFR 56.115(b); 21 CFR 312.62). This minimum retention period applies whether or not any subjects were enrolled in the study. If the research is FDA regulated, records should be retained for at least two years after approval of the investigational agent by FDA; if it is not approved, records should be retained at least two years after the study is terminated and FDA is notified (note the additional requirement below for clinical research studies); Clinical records, including consent forms that document clinical intervention or clinical diagnostic procedure research-related procedures, must be retained in medical records by the institution for at least seven years, per CUMC and NYP policy which is based on state law.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design and Sample Size

This study is a single-center, randomized open-label phase 2 trial to evaluate the efficacy and safety of anti-IL-8 in hospitalized adults with severe or critical COVID-19. The primary endpoint is time to improvement in clinical status: the time (days) required from the start of treatment to the improvement of clinical status (2 points) assessment from baseline based on the 7-point ordinal scale. Patients for whom there was no event will be censored.

Patients will be randomized in a 2:1 allocation ratio to either anti-IL-8 or standard of care. Patients will be assessed daily while hospitalized. Discharged patients will be contacted by telephone on Day 29 and then monthly up to one-year to assess status. In addition to these specific assessment times, one interim analysis is planned at and the DSMC will actively monitor interim data to make recommendations about early signs of overwhelming efficacy and futility/study closure (see Section 13.4.)

With a sample size of 138 patients: N=92 patients randomized to the treatment arm and N=46 patients assigned to the standard of arm/control, the study will have 80% power to detect an increase in median time to improvement from 2 days (control) to 5 days (treatment arm) with one-sided alpha of 0.025. The sample size was estimated based on a hazard ratio (HR) of 0.40 assuming an exponential survival distribution with inflation to account for one interim look and 5% drop-out rate.

13.2 Study Endpoints and Analysis Plan

All subjects who receive at least one dose of study drug will be considered evaluable and included in the efficacy and safety analysis.

Analytic plan for primary objective:

The primary efficacy null hypothesis of the equality of time to improvement (2 points) in clinical status curves will be tested with the log-rank test. The overall type I error for the primary analysis will be considered one-sided alpha of 0.025. Kaplan-Meier estimates will be reported for each of the two arms with median time to improvement and 95% confidence intervals (CI). Cox regression will be employed to estimate the treatment effect (HR) and 95% CI.

Analytic plan for secondary and exploratory objective:

We will estimate the distributions of all time-to-event endpoints using the Kaplan-Meier method and if possible, provide medians (95% CI). Comparisons between survival curves will be assessed using log-rank tests and Cox regression models.

For each arm, we will estimate the 1-month mortality rate and incidence of adverse events graded by CTCAE v5.0 using the exact 95% confidence intervals. Comparisons between the two arms will assessed using chi-squared or Fisher's exact tests. The mean/medians of the 7-point ordinal scores at day 14 after the start of treatment will be computed and compared between the two groups using two-sample t-test or the equivalent non-parametric Wilcoxon Rank-Sum test if normality is not satisfied.

Changes in exploratory endpoints (before and after treatment) will be quantified using means (95% CI) and/or medians (inter-quartile ranges) for non-normal data. Comparisons between the two arms will be made using two-sample independent t-tests or the non-parametric equivalent, Wilcoxon Rank-Sum test. The associations between baseline levels and/or changes over time of IL-8 and other key cytokines (TNF, IL-1b, IL-6) with outcomes will be assessed using regression models.

13.3 Subgroup Analysis

A post-hoc, subgroup analysis will be employed to compare the primary and secondary endpoints for cancer vs non-cancer patients.

A post-hoc, subgroup analysis based on severity of respiratory symptoms is also planned to investigate the consistency or heterogeneity of the treatment effect across the following pre-specified groups:

1) Severe Respiratory Disease – defined as oxygen saturation ≤ 93% on room air, RR ≥ 24 or ≥50% lung involvement on imaging within 24 - 48hrs.

2) Critical Respiratory Disease – defined as respiratory failure requiring non-rebreather, high-flow nasal cannula, ICU admission, non-invasive ventilation, invasive ventilation.

13.4 Interim analyses

One interim analysis is planned after approximately 17 (40% of the total 41 events) have been observed using O'Brien and Fleming stopping boundary using the Lan-DeMets spending function at a nominal type I error of 0.025. The intent-to-treat (ITT) principle is applied to the analysis, and therefore, we inflated the sample size by 5% to safeguard against drop-outs.

An independent Data Safety Monitoring Committee (DSMC) will serve as the primary reviewer of the results of the interim analyses of the study and will make recommendations for discontinuation of the study or protocol modifications. Stopping rules for overwhelming efficacy and/or futility are provided in Table 4 below.

Table 4. Efficacy and Boundaries and Properties for the Time to Improvement Analysis

Analysis*	**Value**	**Efficacy**	**Futility**
IA1: 40%	Nominal critical point Z-value	3.3569	0.0811
N: 138	p (1-sided)	0.0004	0.4677
Events: 17	~HR at bound	0.1720	0.9584
Month: 2.6	P(Cross) if HR=1	0.0004	0.5323
	P(Cross) if HR=0.4	0.0599	0.0427
IA2: 100%	Nominal critical point Z-value	1.9622	1.9622
N: 138	p (1-sided)	0.0249	0.0249
Events: 41	~HR at bound	0.5217	0.5217
Month: 7	P(Cross) if HR=1	0.0240	0.9760
	P(Cross) if HR=0.4	0.8000	0.2000

*This column displays the number of events and percentage (%) of needed time to improvement events, the expected sample size (N), and the estimated months (Month) after first participant is randomized for each analysis.
p (1-sided): the nominal α for testing.
~HR at bound: the approximate hazard ratio required to reach the bound for overwhelming efficacy or futility stop.
P (Cross if HR=1): the probability of crossing a bound at or before each analysis under the null hypothesis.
P (Cross if HR=0.40): the probability of crossing a bound at or before each analysis under the alternative hypothesis.
Abbreviations: HR = hazard ratio; IA = interim analysis.

13.5 Analysis Populations

13.5.1 Intention-to- treat and per protocol population

ITT population: The intention-to-treat (ITT) population includes all randomized patients who received at least one dose of the study drug. Analysis of the ITT population will be done according to the initial treatment assigned to the patient (as randomized). ITT population may be used for sensitivity analysis of the efficacy endpoints, as well as for analysis of data including (but not limited to) demographics and baseline characteristics.

PP population: The per protocol population set (PPS) includes all ITT patients who did not have any relevant major protocol deviations, e.g., patients who are randomized and treated, but do not have laboratory-confirmed SARS-CoV-2 infection will be excluded from PPS. Analysis of the PPS will be done according to the treatment the patient

actually received (as treated). The PPS will be used for sensitivity analysis of the primary efficacy endpoint.

13.5.2 Safety population

The safety population includes all randomized patients who received at least one dose of the study drug. Analysis of the Safety population will be done according to the treatment received (as treated).

13.6 Safety Analysis

All subjects receiving at least one dose of the study drug will be evaluated for safety by monitoring symptoms, physical examinations, and laboratory tests. Adverse events will be classified and graded according to the NCI Common Toxicity Criteria version 5.0 (see Appendix B). The absolute number and frequency of each adverse event will be reported, and subdivided according to toxicity grade. A description of adverse events by treatment arm will also be reported. A particular adverse event occurring more than once in the same subject will be counted only once and at its worse grade. At the end of study, the cumulative incidences of these events will be compared between the two treatment groups using Fisher's exact test.

13.4.1 Evaluation of adverse events

Treatment-emergent adverse events will be translated from investigator terms to MedDRA version 22.1 terminology and summarized (number and percentage of patients) for all patients who receive at least one dose of the study drug(s). Adverse event summaries will be organized by body system, frequency of occurrence, intensity (*i.e.*, severity grade), and causality or attribution. Patients who experience an adverse event more than once will be counted only once. The occurrence with the maximum severity will be used to calculate intensity.

13.4.2 Evaluation of serious adverse events and premature withdrawals

Adverse events deemed serious and those resulting in early treatment withdrawal or death will be summarized separately. Narrative paragraphs will be generated to describe the circumstances surrounding each SAE and each death.

13.4.3 Evaluation of laboratory parameters and assays

Abnormal laboratory parameters (*e.g.* electrolyte levels, liver function tests, renal function tests, complete blood counts) will be summarized, and clinically significant changes from baseline will be discussed.

14 PROTECTION OF HUMAN SUBJECTS

This study is to be conducted in accordance with applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be obtained before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, as outlined in the IRB approved protocol, and the investigator-designated research professional obtaining the consent.

The PI, co-investigators and research nurses will conduct a remote consent discussion with the subject. Eligible study participants will be given detailed information about the study purpose, procedures, and requirements. The research team will be available to answer all the patients' questions adequately before he/she decides to enroll in the study. It will be emphasized to patients that enrolling in the study may or may not directly benefit them, nor will choosing not to participate affect their treatment or care in any way. Patients will be informed that the information collected from their medical records, specimens, and blood samples will be kept confidential. Each patient will be assigned a study ID number to which all study information will be linked. Patients will be assured that the only document linking their personal identification information to this number will be kept in a locked secure location. We will enroll non-English speaking participants. Non-English speaking participants will be enrolled in accordance with the CUMC IRB enrollment of non-English speaking subjects' policy.

15. STUDY FINANCES

15.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the Columbia University Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved prior to participation in this study. All CUMC investigators will follow the University conflict of interest policy.

16 PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

17 REFERENCES

1. Arshad Ali S, Baloch M, Ahmed N, Arshad Ali A, Iqbal A. The outbreak of Coronavirus Disease 2019 (COVID-19)-An emerging global health threat. J Infect Public Health 2020.
2. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19): WHO; 2020.
3. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020.
4. Li LQ, Huang T, Wang YQ, et al. 2019 novel coronavirus patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol 2020.
5. Guan W-j, Ni Z-y, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. New England Journal of Medicine 2020.
6. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020;21:335-7.
7. Chang YJ, Liu CY, Chiang BL, Chao YC, Chen CC. Induction of IL-8 release in lung cells via activator protein-1 by recombinant baculovirus displaying severe acute respiratory syndrome-coronavirus spike proteins: identification of two functional regions. J Immunol 2004;173:7602-14.
8. Han S, Mallampalli RK. The acute respiratory distress syndrome: from mechanism to translation. J Immunol 2015;194:855-60.
9. Williams AE, Jose RJ, Mercer PF, et al. Evidence for chemokine synergy during neutrophil migration in ARDS. Thorax 2017;72:66-73.
10. Nieto-Torres JL, DeDiego ML, Verdia-Baguena C, et al. Severe acute respiratory syndrome coronavirus envelope protein ion channel activity promotes virus fitness and pathogenesis. PLoS Pathog 2014;10:e1004077.
11. Conti P, Ronconi G, Caraffa A, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents 2020;34.
12. Lau SKP, Lau CCY, Chan KH, et al. Delayed induction of proinflammatory cytokines and suppression of innate antiviral response by the novel Middle East respiratory syndrome coronavirus: implications for pathogenesis and treatment. J Gen Virol 2013;94:2679-90.
13. Chen IY, Moriyama M, Chang MF, Ichinohe T. Severe Acute Respiratory Syndrome Coronavirus Viroporin 3a Activates the NLRP3 Inflammasome. Front Microbiol 2019;10:50.
14. Alosaimi B, Hamed ME, Naeem A, et al. MERS-CoV infection is associated with downregulation of genes encoding Th1 and Th2 cytokines/chemokines and elevated inflammatory innate immune response in the lower respiratory tract. Cytokine 2020;126:154895.
15. Liu J, Liu Y, Xiang P, et al. Neutrophil-to-Lymphocyte Ratio Predicts Severe Illness Patients with 2019 Novel Coronavirus in the Early Stage. medRxiv 2020:2020.02.10.20021584.
16. Ivanova A, Qaqish BF, Schell MJ. Continuous toxicity monitoring in phase II trials in oncology. Biometrics 2005;61:540-5.

18 ATTACHMENTS

APPENDIX A: COMMON TOXICITY CRITERIA, VERSION 5.0

Adverse events will be described and graded using the NCI Common Toxicity Criteria (Version 5.0).A copy of this document can be downloaded from the CTEP website (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All treatment areas must have a copy of this document, or must be able to access a copy.

In general, the grading system can be summarized as follows:

Grade:	***Severity:***	***Description:***
Grade 1	Mild	Mild; asymptomatic or mild symptom; clinical or diagnostic observation only; intervention not indicated.
Grade 2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death	Death related to an adverse event.

APPENDIX B: NATIONAL EARLY WARNING SCORE 2 (NEWS2)

Chart 1: The NEWS scoring system

Physiological parameter	Score						
	3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

APPENDIX C: KATZ INDEX OF INDEPENDENCE IN ACTIVITIES OF DAILY LIVING

Patient Name:_____ Date:_____
Patient ID #_____

Katz Index of Independence in Activities of Daily Living

Activities Points (1 or 0)	**Independence** (1 Point) **NO** supervision, direction or personal assistance.	**Dependence** (0 Points) **WITH** supervision, direction, personal assistance or total care.
BATHING Points: _____	**(1 POINT)** Bathes self completely or needs help in bathing only a single part of the body such as the back, genital area or disabled extremity.	**(0 POINTS)** Need help with bathing more than one part of the body, getting in or out of the tub or shower. Requires total bathing
DRESSING Points: _____	**(1 POINT)** Get clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.	**(0 POINTS)** Needs help with dressing self or needs to be completely dressed.
TOILETING Points: _____	**(1 POINT)** Goes to toilet, gets on and off, arranges clothes, cleans genital area without help.	**(0 POINTS)** Needs help transferring to the toilet, cleaning self or uses bedpan or commode.
TRANSFERRING Points: _____	**(1 POINT)** Moves in and out of bed or chair unassisted. Mechanical transfer aids are acceptable	**(0 POINTS)** Needs help in moving from bed to chair or requires a complete transfer.
CONTINENCE Points: _____	**(1 POINT)** Exercises complete self control over urination and defecation.	**(0 POINTS)** Is partially or totally incontinent of bowel or bladder
FEEDING Points: _____	**(1 POINT)** Gets food from plate into mouth without help. Preparation of food may be done by another person.	**(0 POINTS)** Needs partial or total help with feeding or requires parenteral feeding.
TOTAL POINTS: _____	**SCORING:** 6 = High (*patient independent*) 0 = Low (*patient very dependent*	

APPENDIX D: LAWTON INSTRUMENTAL ACTIVITIES OF DAILY LIVING SCALE

THE LAWTON INSTRUMENTAL ACTIVITIES OF DAILY LIVING SCALE

Ability to Use Telephone

1. Operates telephone on own initiative; looks up and dials numbers 1
2. Dials a few well-known numbers 1
3. Answers telephone, but does not dial 1
4. Does not use telephone at al 0

Shopping

1. Takes care of all shopping needs independently 1
2. Shops independently for small purchases 0
3. Needs to be accompanied on any shopping trip 0
4. Completely unable to shop 0

Food Preparation

1. Plans, prepares, and serves adequate meals independently 1
2. Prepares adequate meals if supplied with ingredients 0
3. Heats and serves prepared meals or prepares meals but does not maintain adequate diet 0
4. Needs to have meals prepared and served 0

Housekeeping

1. Maintains house alone with occasion assistance (heavy work) 1
2. Performs light daily tasks such as dishwashing, bed making 1
3. Performs light daily tasks, but cannot maintain acceptable level of cleanliness 1
4. Needs help with all home maintenance tasks 1
5. Does not participate in any housekeeping tasks 0

Laundry

1. Does personal laundry completely 1
2. Launders small items, rinses socks, stockings, etc 1
3. All laundry must be done by others 0

Mode of Transportation

1. Travels independently on public transportation or drives own car 1
2. Arranges own travel via taxi, but does not otherwise use public transportation 1
3. Travels on public transportation when assisted or accompanied by another 1
4. Travel limited to taxi or automobile with assistance of another 0
5. Does not travel at all 0

Responsibility for Own Medications

1. Is responsible for taking medication in correct dosages at correct time 1
2. Takes responsibility if medication is prepared in advance in separate dosages 0
3. Is not capable of dispensing own medication 0

Ability to Handle Finances

1. Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank); collects and keeps track of income 1
2. Manages day-to-day purchases, but needs help with banking, major purchases, etc 1
3. Incapable of handling money 0

Scoring: For each category, circle the item description that most closely resembles the client's highest functional level (either 0 or 1).

APPENDIX E: CONSENT GUIDANCE

CONSENT GUIDANCE

In light of COVID-19, extra precautions are being taken to ensure the safety of patients and staff.

CONSENT PROCESS

- Consent process will begin with a patient being identified. After preliminary prescreening is performed and the patient appears potentially eligible, the consent form will be given to nurse or provider caring for the patient to give to them to read.
- Paper consent form will **NOT** be returned
- All consent discussions will be held **over the telephone.**

USE OF LEGALLY AUTHORIZED REPRESENTATIVE

If it appears to the study physician that a potential subject lacks cognitive capacity to understand the ICF, then a physician not associated with the study will be consulted.

If the independent consultant agrees, then an appropriate legally authorized representative (LAR) will be identified in accordance with CUMC IRB Informed Consent Policy (CUIRB Policy, Informed Consent, 26Oct2013, Section 4.F) and New York State Law. The LAR will sign the IRB-approved ICF and HIPAA authorization in lieu of the subject.

If the potential subject regains capacity during the study in the opinion of both the study physician and an independent consulting physician, then the study procedures performed to date will be discussed with the subject who will provide re-consent before continuing study related procedures per IRB policy.

METHODS OF CONSENT

AN EMAIL WITH DOCU SIGN USING #ENCRYPT PHI

1. A copy of the consent explaining the study will be emailed to the patient or LAR for review.
2. The patient or LAR will be contacted via phone by an authorized consentor and the consent will be explained in detail to the patient or LAR.
3. The patient or LAR will docu sign the consent which will be returned. Authorized consentor will sign and complete ICF checklist
4. The ICF document will be scanned into the subject's electronic medical record.
5. The consent process will be documented by the authorized consentor who will complete the CPDM IC Process Checklist.

AN EMAIL USING #ENCRYPT PHI

1. A copy of the consent explaining the study will be emailed to the patient or LAR for review.
2. The patient or LAR will be contacted via phone by an authorized consentor and the consent will be explained in detail to the patient or LAR.
3. The patient or LAR will sign the consent then take a picture and email the picture to the authorized consentor. Authorized consentor will print and sign.
4. The ICF document will be scanned into the subject's electronic medical record
5. The consent process will be documented by the authorized consentor who will complete the CPDM IC Process Checklist.

TELEPHONE WITH NO ABILITY TO SIGN

1. A copy of the consent will be provided to the patient for the patient to review explaining the study.
2. The patient or LAR will be contacted via phone by an authorized consenter and the consent will be explained in detail to the patient.
3. The patient or will provide verbal consent. This will be documented by the authorized consenter who will complete the CPDM IC Process Checklist. The following comments will be recorded:

- Method of consent
- Time of consent
- Translator identity if applicable

4. A signature from the patient or LAR will not be obtained. The authorized consentor will sign the consent form and note in the IC checklist that consent was obtained verbally. This document will be scanned into the subject's electronic medical record.
5. The consent process will be documented by the authorized consentor who will complete the CPDM IC Process Checklist.