STUDY PROTOCOL

Study Title:	A Multi-center, Multi-country Retrospective Cohort Study to Evaluate the Clinical Outcomes in Adults with Severe COVID-19
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	Not Applicable
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	Not Applicable
Indication:	COVID-19
Protocol ID:	GS-US-540-5807
Study Director:	PPD Senior Director Medical Affairs Telephone: PPD
Protocol Version/Date:	Original: 24 March 2020

CONFIDENTIALITY STATEMENT

STUDY PROTOCOL

Objectives:

Primary

The primary objectives of this study are to assess the clinical course and outcome of adults with severe COVID-19 assessed by:

1. a 7-point ordinal scale on Day 14;
2. all-cause mortality at day 28;

Secondary

The secondary objectives are to assess the clinical course and outcome of adults with severe COVID-19 with respect to the following:

1. time to SpO2 > 94% on room air;
2. time to first negative SARS-CoV-2 polymerase chain reaction (PCR)
3. duration of oxygen therapy (days)
4. proportion of the use of mechanical ventilation/ECMO (extracorporeal membrane oxygenation);
5. duration of hospitalization

Study Design:

This is a multi-center, multi-country retrospective cohort study. Up to 2000 severe COVID-19 cases across up to 50 participating study sites who meet all eligibility criteria will be included in the analysis. Deidentified data will be extracted from electronic medical record (EMR) databases, clinical registries, case series or additional sources from participating sites and countries, and then entered into a structured e-CRF system (or transferred electronically if feasible), then pooled into one database with standard data format. This real-world standard of care (SOC) cohort can be used to assess efficacy comparisons to potential future treatments. In addition, each site/country will be surveyed to determine the local standard of care therapy for COVID-19 infection.

Number of Sites and Subjects Planned

Up to 50 centers globally with 2000 severe cases

Target Population

Adults with severe COVID-19

Duration of Treatment

Duration of treatment with standard of care per local clinical practice

Diagnosis and Main Eligibility Criteria

Adult participants with COVID-19 confirmed by PCR who meet the following criteria:

1. Hospitalized
2. COVID-19 confirmed by PCR
3. SpO2 ≤94% on room air
4. Radiographic evidence of pulmonary infiltrates
5. Did not receive remdesivir (RDV) at any time during illness

Only real-world retrospective data will be used for this study. Retrospective data will be extracted at each clinical site from databases and pseudonymized. No personally identifiable data will be transmitted to Gilead. Data will be extracted from electronic medical record (EMR) databases, clinical registries, case series or additional sources from different sites and countries, and then pooled into one database with standard data format at Gilead Sciences. The data elements will be extracted from the databases according to the following schedule.

	Day1 (Hospital Admission)	**Day7 (+/- 1 day) and Day14 (+/- 2 days) / last observation**	**Day 28 (+/- 2 days)**
Medical History [a]	X		
Pregnancy test	X		
Vital Signs [b]	X	X	X [f]
Laboratory Testing [c]	X	X	
Oxygenation [d]	X	X	X
Ordinal Scale [e]	X	X	
Treatments for COVID 19	X	X	

a Focused medical history and also the following information (e.g. demographics, baseline characteristics)
b SpO2, body temperature, body weight and height on admission
c Includes white blood cell count, creatinine, total bilirubin, ALT, AST, radiographic findings at baseline and as available and SARS CoV 2 testing.
d Includes oxygen supplementation: room air, low flow O2 (L/min and %), high flow O2 (L/min and %), non invasive positive pressure ventilation (FiO2 or %), mechanical ventilation (FiO2 or %), ECMO (extracorporeal membrane oxygenation)
e The scale is as: 1. Death, 2. Hospitalized, on invasive mechanical ventilation or ECMO, 3. Hospitalized, on non invasive ventilation or high flow oxygen devices, 4. Hospitalized, requiring low flow supplemental oxygen, 5. Hospitalized, not requiring supplemental oxygen requiring ongoing medical care (COVID 19 related or otherwise), 6. Hospitalized, not requiring supplemental oxygen no longer requires ongoing medical care, 7. Not hospitalized
f Only death will be collected on day28

Criteria for Evaluation

Primary Endpoints

1. Clinical status assessed by a 7-point ordinal scale on Day 14, where the 7-point ordinal scale is defined as:
    1. Death

2. Hospitalized, on invasive mechanical ventilation or ECMO
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices
4. Hospitalized, requiring low flow supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
7. Not hospitalized

2. all-cause mortality at day 28

Secondary Endpoints

1. Time to SpO2 > 94% on room air
2. Time to first negative SARS-CoV-2 PCR
3. Duration of oxygen therapy (days)
4. Proportion of clinical improvement at Day 14, defined as a ≥ 2-point improvement from Day 1 on a 7-point ordinal scale
5. need for mechanical ventilation/ECMO
6. duration of hospitalization

Statistical Methods:

Retrospective Cohort Study (RCS) Data Analysis
Summary statistics will be generated for the cohort overall and by contributing site/country. For categorical variables, numbers and percentages of patients will be reported including the 95% confidence intervals. For continuous variables, mean, standard deviation (SD), minimum, first and third quartile (Q1, Q3), median, maximum and 95% confidence intervals will be calculated, together with the total number of observations and the number of missing values. Descriptive statistics will summarize demographics and baseline characteristics.

Analysis to compare SOC from RCS and agents potentially active against SARC CoV-2
Data from this retrospective cohort study may be used to compare the efficacy of potential investigational antiviral agents against this cohort which did not receive such agents. For example, the cohort data may be compared to uncontrolled Gilead study arms or datasets of RDV (i.e., subjects enrolled in GS-US-540-5773 and compassionate use datasets). Such analyses will use appropriate statistical methods for comparisons of non-randomized cohorts, such as weighted analysis and propensity score analysis. Full details of the analyses will be in the Statistical Analysis Plan (SAP).

Publication:
Data from the RCS will not be published independently by Gilead. Gilead publications will consist of comparative data analysis of the RCS with data from RDV clinical studies. All contributing PI

investigators will have the opportunity to participate in publication (abstracts and manuscripts) on the combined analyses.

This study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practice (GPP) and Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.