CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 20-0006
Study Title:
A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults (ACTT-3)

NCT04492475

ACTT-3 Version 2.0

DATE: 19 January 2021

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 20-0006 (ACTT-3)**
Development Phase:	Phase 3
Products:	Interferon beta-1a + Remdesivir Placebo + Remdesivir
Form/Route:	IV (Remdesivir) and SQ (Interferon beta-1a/Placebo)
Indication Studied:	COVID-19
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	August 5, 2020
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Version Number:	2.0

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

ACTT	A Multicenter, Adaptive Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults (Adaptative COVID-19 Treatment Trial)
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BEEC	Blinded Endpoint Evaluation Committee
CI	Confidence Interval
CoV / COV	Coronavirus
CRF / eCRF	Case Report Form / Electronic Case Report Form
CRP	C-reactive protein
CSR	Clinical Study Report
DAIDS	Division of AIDS
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data and Safety Monitoring Board
ECMO	Extracorporeal Membrane Oxygenation
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified Intention-to-Treat
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NEWS	National Early Warning Score
NIH	National Institutes of Health
OP	Oropharyngeal
OS	Ordinal Score
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PT	Preferred Term / Prothrombin Time

RCD	Reverse Cumulative Distribution
RDV	Remdesivir
RMST	Restricted Mean Survival Time
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SOC	System Organ Class
SQ	Subcutaneous
US	United States
WBC	White Blood Cell
WHO	World Health Organization

1. PREFACE

The Statistical Analysis Plan (SAP) for "A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults" (DMID Protocol 20-0006) describes and expands upon the statistical information presented in the protocol. This protocol is an adaptive protocol with different stages. Each stage will have a separate SAP. This SAP is for the study's 3rd stage "ACTT-3": Interferon beta-1a + Remdesivir vs. Remdesivir.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the final analyses. Regarding the final analyses and Clinical Study Report (CSR), this SAP follows the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

This document contains: a review of the study design, general statistical considerations, comprehensive statistical analysis methods for efficacy and safety outcomes, and a list of proposed tables, figures and listings. Within the table, figure, and listing mock-ups (Appendix 1, Appendix 2, Appendix 3), references to CSR sections are included. Any deviation from this SAP will be described and justified in protocol amendments and/or in the CSR, as appropriate. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

2. INTRODUCTION

Data from ACTT-1 showed that hospitalized adults with COVID-19 who were randomized to receive remdesivir had a shorter time to clinical recovery than those who received placebo (10 vs. 15 days, recovery rate ratio 1.29 (95% CI 1.12 to 1.49, p<0.001)). The odds of improvement were higher in the group that received remdesivir than in the placebo group (odds ratio 1.50; 95% CI 1.2 to 1.9, $p \leq 0.001$). After the release of these preliminary findings, the U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to permit the use of remdesivir for treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease. Remdesivir has also received, full or conditional approval in several other countries. On August 28, 2020, the FDA expanded the scope of the EUA to include hospitalized patients with suspected or laboratory-confirmed mild or moderate COVID-19 based on final data from ACTT-1 and two other clinical studies (add references).

While remdesivir is emerging as the standard of care for COVID-19, significant morbidity and mortality still occur despite its use. In ACTT-3, we will evaluate if we can improve clinical outcomes among hospitalized COVID-19 adult patients by administering remdesivir in combination with subcutaneous interferon beta-1a. Subcutaneous interferon beta-1a was selected because of its in vitro potency against SARS-CoV-2, known safety profile, and worldwide availability as a licensed drug.

Interferon-β has antiviral and anti-inflammatory properties. In response to infection with a single-stranded RNA virus, type I interferons including interferon beta are initially expressed after recognition of double-stranded RNA, the replicative intermediate of the virus, by cellular pattern-recognition receptors, such as melanoma differentiation-associated gene 5 (MDA-5; also known as Ifih1) and toll-like receptors (TLR), leading to activation of interferon regulatory factor (IRF) 3 and induction of interferon-β expression. Secreted interferon-β then functions in either an autocrine or paracrine manner to activate the Janus kinase–signal transducer and activator of transcription (STAT) pathway, inducing a wave of de novo transcription of antiviral genes, as well as expression of more type I interferon. For these reasons, interferon has been suggested as a putative therapeutic for SARS-CoV-2.

Interferon may be a good candidate for the treatment of COVID-19 because in vitro studies suggest weak induction of interferon following SARS-CoV-2 infection. Preliminary data from a cohort of hospitalized patients with COVID-19 indicate that there may be a subset of patients who lack a prominent interferon signature despite high viral titers and this phenotype may be associated with worse clinical outcomes [and unpublished data, from NIAID's Immune Phenotyping in a COVID-19 Cohort study (IMPACC)]. Type 1 interferon can inhibit SARS-CoV, MERS-CoV, and SARS-CoV-2 in vitro and recent data suggests that SARS-CoV-2 may be more sensitive than SARS-CoV to inhibition by interferon.

Recent clinical data suggest that SARS-CoV-2 infection may decrease interferon response, and two small RCTs in COVID-19 are suggestive of possible benefit from treatment with interferon beta.

2.1. Purpose of the Analyses

This SAP encompasses all interim analyses and the final analysis of primary and secondary outcome measures. These analyses will assess the efficacy and safety of interferon beta-1a +

remdesivir in comparison with remdesivir and will be included in the Clinical Study Report. This protocol is an adaptive design and, if the design is modified, the SAP will be amended accordingly. The protocol for DMID 20-0006 calls for a planned interim efficacy analysis once roughly 50% of the targeted number of ACTT-3 recoveries have been observed, and ongoing safety analyses. Safety interim analyses occur more frequently to review safety data in the event that the experimental agent inflicts harm. The goal of the efficacy interim analyses is to review endpoint data in order to recommend whether the current study arm should proceed or to stop early for benefit or futility.

This SAP describes the planned analysis to be conducted by the Investigational New Drug (IND) sponsor NIAID. Additional analyses, if any, performed by the product manufacturer will be pre-specified and described in an addendum to this SAP. Protocol-defined exploratory analyses will be included in a separate analysis plan.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Primary Objective

To evaluate the clinical efficacy, as assessed by time to recovery, of interferon beta-1a + remdesivir as compared to the placebo + remdesivir for patients with baseline ordinal score 4, 5, and 6.

Secondary Objectives

The key secondary objectives are

- To evaluate the clinical efficacy of interferon beta-1a + remdesivir relative to placebo + remdesivir in adults hospitalized with COVID-19 according to clinical status (8-point ordinal clinical scale) at Day 15 for patients with baseline ordinal score 4 and 5.
- To evaluate the clinical efficacy of interferon beta-1a + remdesivir compared to placebo + remdesivir, as assessed by time to recovery for patients with a baseline ordinal score of 4 and 5.

The other secondary objectives (by baseline severity [4 or 5] vs 6) are to:

1. Evaluate clinical efficacy of interferon beta-1a + remdesivir as compared placebo + remdesivir as assessed by:
    - Clinical Severity
        - 8-Point Clinical Status Ordinal scale:
            - Time to an improvement of one category and two categories from Day 1 (baseline) on the clinical status 8-point ordinal scale.
            - Subject clinical status using 8-point ordinal scale at Days 3, 5, 8, 11, 15, 22, and 29.
            - Mean change in the clinical status 8-point ordinal scale from Day 1 to Days 3, 5, 8, 11, 15, 22, and 29.
        - National Early Warning Score (NEWS):
            - Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
            - Change from Day 1 to Days 3, 5, 8, 11, 15, and 29 in NEWS.
        - Oxygenation:
            - Oxygenation use up to Day 29.
            - Incidence and duration of new oxygen use through Day 29.
        - Non-invasive ventilation/high flow oxygen:
            - Non-invasive ventilation/high flow oxygen use up to Day 29.

        - Incidence and duration of new non-invasive ventilation or high flow oxygen use through Day 29.
    - Invasive Mechanical Ventilation / extracorporeal membrane oxygenation (ECMO):
        - Ventilator/ECMO use up to Day 29.
        - Incidence and duration of new mechanical ventilation or ECMO use through Day 29.
- Hospitalization
    - Duration of hospitalization (in days) through Day 29.
- Mortality
    - 14-day mortality.
    - 28-day mortality.
- Laboratory Efficacy:
    - d-dimer, and C-reactive protein (CRP) over time

2. Evaluate the safety of interferon beta-1a + remdesivir through 28 days of follow-up as compared to the placebo + remdesivir as assessed overall, and by baseline ordinal scale category (4 or 5 vs. 6) by:
    - Cumulative incidence of SAEs through Day 29
    - Cumulative incidence of Grade 3 and 4 clinical and/or laboratory AEs through Day 29.
    - Discontinuation or temporary suspension of study product administrations (for any reason).
    - Changes in white cell count (WBC) with differential, hemoglobin, platelets, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and INR over time (analysis of lab values in addition to AEs noted above).

Exploratory Objective

1. The exploratory objective is to evaluate the virologic efficacy of interferon beta-1a + remdesivir as compared to placebo + remdesivir as assessed by:
    - Percentage of subjects with SARS-CoV-2 detectable in oropharyngeal (OP) sample at Day 3, 5, 8, 11, 15, and 29.
    - Quantitative SARS-CoV-2 virus in OP sample at Day 3, 5, 8, 11, 15, and 29.
    - Development of resistance of SARS-CoV-2 in OP sample at Day 3, 5, 8, 11, 15, and 29.
    - Quantitative SARS-CoV-2 virus in blood at Day 3, 5, 8, and 11.
2. To define immunophenotype of subjects most likely to benefit from interferon beta-1a by analyzing markers of inflammation, transcriptomics, epigenetics and cell populations.

3.2. Endpoints

Primary Endpoint

Time to recovery, where recovery is defined as clinical status in states 1, 2, or 3 of the 8-point ordinal scale, through Day 29 (+6).

- Clinical status of a subject (8-point ordinal scale) is defined below:

  8. Death;

  7. Hospitalized, on invasive mechanical ventilation or ECMO;

  6. Hospitalized, on non-invasive ventilation or high flow oxygen devices;

  5. Hospitalized, requiring supplemental oxygen;

  4. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);

  3. Hospitalized, not requiring supplemental oxygen - no longer requiring ongoing medical care;

  2. Not hospitalized, but new or increased limitation on activities and/or requiring new or increased home oxygen;

  1. Not hospitalized, no limitations on activities

Secondary Endpoints

The key secondary endpoints are:

- Clinical status (8-point ordinal scale) on Day 15.
- Time to recovery, where recovery is defined as clinical status in states 1, 2, or 3 of the 8-point ordinal scale, through Day 29 (+6).

The other secondary endpoints are:

- Ordinal outcome assessed while hospitalized (Days 3, 5, 8, 11) and on Days 15, 22, and 29.
- NEWS assessed daily while hospitalized (Days 3, 5, 8, 11) and on Days 15 and 29.
- Days of supplemental oxygen (if applicable).
- Days of non-invasive ventilation/high-flow oxygen (if applicable).
- Days of invasive mechanical ventilation/ECMO (if applicable).
- Days of hospitalization.
- Date and cause of death (if applicable).
- D-dimer and CRP on Day 1, while hospitalized (Days 3, 5, 8, 11), and on Days 15 and 29.
- SAEs.
- Grade 3 and 4 adverse events

- WBC with differentials, hemoglobin, platelets, creatinine, total bilirubin, ALT, AST, INR, d-dimer, and CRP on Day 1; Days 3, 5, 8, and 11 (while hospitalized); and Days 15 and 29 (if attends in-person visit or still hospitalized).

Exploratory Endpoints (not described in this SAP)

- Qualitative and quantitative polymerase chain reaction PCR for SARS-CoV-2 in OP swab on Day 1; Days 3, 5, 8, and 11 (while hospitalized); and Days 15 and 29 (if attends in-person visit or still hospitalized).
- Deep sequencing of the SARS-CoV-2 virus for those subjects with sustained vial shedding
- Qualitative and quantitative PCR for SARS-CoV-2 in blood on Day 1; Days 3, 5, 8, and 11 (while hospitalized).
    - Protein levels of cytokines, markers of inflammation, and other circulating proteins in plasma on Day 1; Days 3, 5, 8, and 11 (while hospitalized) and Day 29
    - Additionally, in a subset of subjects:
        - Transcriptome-wide gene expression levels based on transcriptomic analysis of RNA in whole blood and individual immune cells on Days 1, 3, 8 and 29
        - Interferon-stimulated-gene (ISG) expression levels based on transcriptomic analysis of RNA in whole blood and/or individual immune cells on Days 1, 3, 8 and 29
        - Assessment of T-cell and innate immune cells subpopulations in PBMCs on Days 1, 3, 8 and 29
        - Epigenetic modifications based on analysis of DNA extracted from PBMCs on Days 1 and 29

3.3. Study Definitions and Derived Variables

3.3.1. Baseline Value

For efficacy assessments, the baseline value will be defined as the last value obtained prior to randomization. For safety assessments, the baseline value will be defined as the last value obtained prior to the first on-trial dose of any study product (interferon beta-1a, remdesivir, or placebo). If the exact time of the assessment or the first dose is not available, but collected on the same date, the assessment will be assumed to have occurred prior to receipt of study product.

3.3.2. Recovery and Time to Recovery

The primary efficacy and one of the key secondary outcome measures is the time to recovery assessed through Day 29 + 6 days. Recovery will be defined as having a value of 1, 2, or 3 on the clinical status 8-point ordinal scale. The time to recovery will be defined as the elapsed time (in days) from randomization to the earliest day at which a subject reaches recovery. Note that since clinical status assessments are recorded as defined in Section 4.3, the day that is being assessed (not necessarily the day the response is collected) will be used to determine the timing of events. For example, a subject with a score of 5 recorded on Days 1-3 and a score of 3 recorded on

Day 4 will have a time to recovery equal to 3 days. It is also possible that a subject has a clinical status score > 3 reported for a particular day but was subsequently discharged on the same day. Such cases and other special cases will be reviewed by the Endpoint Review Committee or the NIAID Medical Officer, or her designee(s), to make the determination of whether the subject should be considered recovered in analyses. Subject data to be reviewed as part of this determination will include the reported clinical status scores while hospitalized, where the subject was discharged to (e.g. private residence, rehabilitation facility, long-term care/nursing home, comfort and care), and any information regarding readmittance. Subjects discharged to hospice or other end-of-life care will not be considered recovered. Additional information may be solicited to assess recovery.

Any subjects that are lost to follow-up or terminated early prior to an observed recovery will be censored at the day of their last observed assessment. Subjects who complete follow-up but do not experience recovery will be censored at the day of their Day 29 visit. All deaths that occur on or before Day 29 (and prior to any observed recovery) will be considered censored at 28 days. Note that we do not expect many subjects to worsen after discharge. However, we will evaluate whether any discharged subjects subsequently experience a worse clinical status and sensitivity analyses will be conducted accordingly. For these analyses, subjects who recover but are later re-admitted for COVID-19 will not be considered a recovery but will instead be censored at 28 days.

3.3.3. Clinical Status at Specific Timepoints

The key secondary analyses include evaluation of the clinical status score at Day 15. For this outcome, Study Visit Day 15 is the timepoint of interest, not necessarily the actual study day. The score collected at the study visit corresponding to Day 15 will be used for this outcome. For analyses of this outcome, imputation of the clinical score may be performed following the rules described in Section 6.5.

Additional analyses are clinical status at Days 3, 5, 8, 11, 15, 22, and 29. As the with above, the scores that will be used are those collected at the study visits corresponding to those days.

3.3.4. Time to Clinical Status Improvement

Additional analyses will evaluate the time to improvement of at least one point on the clinical status 8-point ordinal scale. That is, improvement will be defined as a decrease of at least one point on the 8-point scale compared to the baseline value (e.g. from 5 to 4; from 5 to 3) and the time to improvement will be defined as the elapsed time (in days) from randomization to the earliest day of observed improvement. Note that since clinical status assessments are recorded as defined in Section 4.3, the day that is being assessed (not necessarily the day the response is collected) will be used to determine the timing of events.

For analyses of this outcome, imputation of the clinical score may be performed following the rules described in Section 6.5.

Any subjects that are lost to follow-up or terminated early prior to an observed improvement will be censored at the day of their last observed assessment. Subjects who complete follow-up but do not experience improvement will be censored at the day of their Day 29 visit. All deaths that occur on or before Day 29 (and prior to any observed improvement) will be considered censored at 28 days.

An alternative definition of improvement will also be used where improvement will be defined as a decrease of at least two points on the 8-point scale compared to the baseline value (e.g. from 5 to 3; from 5 to 2). The timing and censoring definitions will follow similarly to the above.

3.3.5. Time to Discharge or NEWS of ≤ 2

The time to discharge or NEWS of ≤ 2 will be defined as the elapsed time (in days) from baseline to the earliest day at which either of the following occur:

- Discharge from hospital, unless discharged to hospital or end-of-life care.
- Reported NEWS of ≤ 2 which is maintained for 24 hours

For the latter bullet, to meet this criterion, scores of ≤ 2 must be reported on consecutive study visits. The timing of the event will be set to the day of the second assessment. Subjects who enroll with a baseline NEWS of ≤ 2 must be discharged from the hospital to meet this endpoint.

All deaths or discharge to hospice or other end-of-life care that occur before discharge or before an observed NEWS of ≤ 2 will be considered censored at 28 days.

3.3.6. Days of Non-invasive ventilation/high-flow oxygen

Non-invasive ventilation/high flow-oxygen days will be defined as the number of days where the clinical status score is equal to 6. The Post-Discharge Supplemental Oxygen CRF questions regarding days of non-invasive ventilation or high-flow oxygen will be used for any time period the subject is not hospitalized at the study hospital. The total number of days will be the sum of all reported days, regardless of whether the days occur consecutively or in disjoint intervals. See Section 6.5 for the plan for handling subjects who do not have data through Day 29 or die prior to Day 29.

3.3.7. Days of Invasive Mechanical Ventilation/ECMO

Invasive Mechanical Ventilator / ECMO days will be defined as the number of days where the clinical status score is equal to 7. The Post-Discharge Supplemental Oxygen CRF questions regarding days of ECMO or invasive ventilation will be used for any time period the subject is not hospitalized at the study hospital. The total number of days will be the sum of all reported days, regardless of whether the days occur consecutively or in disjoint intervals. See Section 6.5 for the plan for handling subjects who do not have data through Day 29 or die prior to Day 29.

3.3.8. Days of Oxygen

Oxygen days will be defined as the number of days where the clinical status score is equal to 5, 6, or 7. The Post-Discharge Supplemental Oxygen CRF question regarding days of oxygenation (including ECMO, invasive ventilation, non-invasive ventilation, high-flow oxygen devices, and all other oxygen delivery devices) will be used for any time period the subject is not hospitalized at the study hospital. The total number of days will be the sum of all reported days, regardless of whether the days occur consecutively or in disjoint intervals. See Section 6.5 for the plan for handling subjects who do not have data through Day 29 or die prior to Day 29.

3.3.9. Days of Hospitalization

Duration (in days) of hospitalization will be defined as the number of days subject is hospitalized for COVID-19-related reasons starting from the date of randomization. It will be calculated as the total number of days hospitalized, including readmissions for COVID-19-related reasons. See Section 6.5 for the plan for handling subjects who do not have data through Day 29 or die prior to Day 29.

3.3.10. Time to Death

For analysis of time to death, the time to death will be defined as the elapsed time (in days) from randomization to death. For the safety analysis, this will be elapsed time (in days) from the first dose of study treatment (interferon beta-1a, remdesivir, or placebo).

Any subjects that are lost to follow-up or terminated early prior to death will be censored at the day of their last observed assessment or last captured event (e.g. the end date of an adverse event). Subjects who complete follow-up will be censored at the earliest of their Day 29 visit and (actual) Day 29. Deaths that occur after Day 29 will be censored at Day 29.

Similar censoring methods will be used for the 14-day mortality analyses in that deaths that occur after Day 15 will be censored at Day 15 and subjects who are confirmed alive through Day 15 will be censored at Day 15. Subjects whose last observed assessment or last capture event (e.g. the end date of an adverse event) is prior to Day 15 will be censored at that last observed assessment/event.

3.3.11. Composite Endpoint of Death, SAEs, Severe AEs

A safety composite endpoint will be defined as the occurrence of at least one of the following through Day 29:

1. Death
2. SAE
3. Grade 3 or 4 AE

The time to this composite endpoint will be defined as the elapsed time (in days) from the day of the first dose of study treatment (interferon, remdesivir, or placebo) to the earliest date of any of the events. Any subjects that are lost to follow-up or terminated early prior to experiencing any of the events will be censored at the day of their last observed assessment. Subjects who complete follow-up but do not experience any of the events will be censored at the Day 29 visit.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

ACTT-3 will evaluate the combination of interferon beta-1a and remdesivir compared to remdesivir alone. Subjects will be assessed daily while hospitalized. If the subjects are discharged from the hospital, they will have a study visit at Days 15, 22, and 29. For discharged subjects, it is preferred that the Day 15 and 29 visits are in person to obtain safety laboratory tests and OP swab and blood samples for secondary research as well as clinical outcome data. However, infection control or other restrictions may limit the ability of the subject to return to the clinic. In this case, post-discharge visits may be conducted by phone call, home visit or remote telehealth procedure as per institutional standards. If the Day 15 and 29 visits are conducted by phone or remotely, only clinical data will be obtained (i.e., no specimens collected). The Day 22 visit does not have laboratory tests or collection of samples and is conducted by phone or remote telehealth procedure unless the subject is still hospitalized at Day 22 and then the visit is conducted in person.

4.2. Selection of Study Population

Male and non-pregnant female adults ≥18 years of age or older with COVID-19 and who meet all eligibility criteria will be enrolled at up to approximately 100 clinical trial sites globally. The target population should reflect the community at large.

See Section 5.1 and 5.2 of Appendix C of the study protocol for the full list of inclusion and exclusion criteria.

4.2.1. Treatments Administered

All subjects will receive remdesivir as a 200 mg intravenous (IV) loading dose on Day 1, followed by a 100 mg once-daily IV maintenance dose for the duration of the hospitalization. Enrollment may proceed for subjects who received one or two doses of remdesivir under EUA or similar mechanism prior to randomization. If subjects already received the loading dose, then the Day 1 dose will be 100 mg. Any doses of remdesivir under an EUA (or similar mechanism) within 1 week of enrollment will be counted, so the maximum number of remdesivir doses given to a subject is 10 (i.e., EUA doses + doses on this trial). See protocol Appendix C Section 6.1.2.

For the subcutaneous interferon beta-1a / placebo component, subjects will receive either active product or placebo as follows:

- Interferon beta-1a will be administered every other day as a 44-microgram subcutaneous dose for a total of 4 doses while hospitalized
- A saline placebo will be administered every other day as a subcutaneous injection for a total of 4 doses while hospitalized

4.2.2. Identity of Investigational Product(s)

See Section 6.1.1 of Appendix C of the study protocol.

4.2.3. Method of Assigning Subjects to Treatment Groups (Randomization)

Randomization will be stratified by:

- Site
- Severity of illness at randomization (by ordinal scale)
  - Hospitalized, on non-invasive ventilation or high flow oxygen devices.
  - Hospitalized, requiring supplemental oxygen, or
  - Hospitalized, not requiring supplemental oxygen.

Note: Category 7 (hospitalized, on invasive mechanical ventilation/ECMO) and Category 6 (hospitalized, on non-invasive ventilation or high flow oxygen devices) are not eligible for enrollment in protocol version 8.0. See description of recommendations made by the DSMB on September 4, 2020 below.

There was the hypothetical concern that interferon may worsen the pro-inflammatory state seen in COVID-19 late in the clinical course of the disease. For this reason, enrollment was staged based on severity of disease.

- For the first 2 weeks of the study, enrollment was limited to non-intubated, hospitalized COVID-19 patients who meet all eligibility criteria (i.e., patients with baseline ordinal scale score of 4, 5 or 6).
- On September 4, 2020, the DSMB met for an interim safety review of the ACTT-3 data. After their review, they notified NIAID that their recommendation was to close further enrollment to patients with a baseline ordinal score of 6. The DSMB noted there was no increase in mortality in this group, but that the risk/benefit in this group did not warrant further enrollment. Specifically, it was recommended by the DSMB:
  - No further enrollment of subjects with ordinal score of 6 at time of randomization.
  - Do not enroll subjects with ordinal score of 7 at time of randomization
  - Continue to enroll patients with a baseline ordinal score of 4 and 5.
- Furthermore, the DSMB recommended:
  - Subjects currently enrolled who have an ordinal score of 6, should not be given any more study injections (interferon/placebo) for the remainder of the study.
  - Subjects enrolled as a baseline ordinal 4 or 5 and remain as ordinal 4 or 5, should continue to receive study injections (interferon/placebo) and remdesivir per protocol.
  - If a subject enrolled as a baseline ordinal 4 or 5 and progresses to ordinal 6 or 7, the study injections (interferon/placebo) should be discontinued for the remainder of the study. In this case, the remdesivir infusions would continue per protocol. Importantly, all subjects should remain in the study and followed through day 29 in accordance with the protocol.

4.2.4. Selection of Doses in the Study

The dose of remdesivir used in this study will be the same dose that has been used in the human Ebola clinical trials and as in ACTT-1 and ACTT-2 studies.

The subcutaneous 44 mcg dose of Rebif is the dose that has been used in other COVID-19 clinical trials including the World Health Organization's Solidarity Trial.

4.2.5. Selection and Timing of Dose for Each Subject

See Sections 6.1.2 through 6.1.5 of Appendix C of the study protocol.

4.2.6. Blinding

As both arms are receiving remdesivir, the remdesivir product is not blinded and study infusions are labeled accordingly.

The subcutaneous interferon beta-1a/matching placebo component is blinded. Interferon beta-1a and placebo will be identical in appearance.

Unblinding of the study will occur after all subjects randomized have reached the end of study, and these visits are monitored and data is cleaned, or if the DSMB recommends unblinding. Treatment group-level unblinded analyses of subjects randomized in ordinal score category 6 may be conducted and published prior to the end of the trial to communicate the safety signal observed in this group by the DSMB during a safety review. If this analysis is conducted, only members of the unblinded analysis team will have access to subject-level treatment data while the study is ongoing; all other members of the study group will remain blinded to individual subject treatments as originally planned.

If AEs occur and investigators are concerned about the treatment allocation, the treatment can be discontinued. If a Serious Adverse Event occurs, that is thought to be related to the study drug, and the treating clinician believes that knowledge of the treatment arm may change the therapy provided to the patient, the individual subject can be unblinded. The procedure for unblinding will be further detailed in the Manual of Procedures (MOP).

4.2.7. Prior and Concomitant Therapy

See Section 6.5.1 of Appendix C of the study protocol for permitted concomitant therapy and procedures. See Section 6.5.2 of Appendix C of the study protocol for prohibited concomitant therapies.

4.2.8. Treatment Compliance

See Section 6.1.4 of Appendix C of the study protocol for details on dose modifications.

Each dose of study product will be administered by a member of the clinical research team who is qualified and licensed to administer the study product. Administration date and time will be entered into the case report form (CRF).

4.3. Efficacy and Safety Variables

For each study day while the patient is hospitalized, the clinical status will be recorded on an 8-point ordinal scale as follows:

- Day 1 – The clinical assessment at the time of randomization.
- Day 2 + - The most severe assessment occurring from midnight to midnight (00:00 to 23:59) of the prior day (e.g., the value recorded on Day 3 will be the most severe outcome that occurred on Day 2).

where the clinical status scale is defined as follows:

8. Death;

7. Hospitalized, on invasive mechanical ventilation or ECMO;

6. Hospitalized, on non-invasive ventilation or high flow oxygen devices;

5. Hospitalized, requiring supplemental oxygen;

4. Hospitalized, not requiring supplemental oxygen- requiring ongoing medical care (COVID-19 related or otherwise);

3. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;

2. Not hospitalized, but new or increased limitation on activities and/or requiring new or increased home oxygen;

1. Not hospitalized, no limitations on activities

A modified version of the ordinal scale will be used in sensitivity analyses of the primary and secondary outcomes. The modified scale will be as follows:

8. Death;

7. Hospitalized, on invasive mechanical ventilation or ECMO;

6. Hospitalized, on non-invasive ventilation or high flow oxygen devices;

5. Hospitalized, requiring supplemental oxygen;

4. Hospitalized, not requiring supplemental oxygen- requiring ongoing medical care (COVID-19 related or otherwise;

3. Not hospitalized, but new or increased limitation on activities and/or requiring new or increased home oxygen;

2. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; or Not hospitalized, no limitations on activities.

That is, category 1 and 3 of the original scale will be combined into the lowest category. This scale will be denoted as the "Modified Recovery" ordinal scale.

In review of study data and site data queries for ACTT-3 subjects who received study product after reaching ordinal score 6, the study team identified that there was ambiguity in the high-flow oxygen categorization. The language in the MOP allowed for different interpretation of high-flow oxygen use, where some clinical sites interpreted and entered any high-flow device use as Ordinal Score 6 while other sites used less than 15L on a high-flow device and entered this as Ordinal Score 5.

The original (as-classified by the site) ordinal scores will be used as the primary scoring method for analyses. The following modified ordinal scale will be used in sensitivity analysis of select outcomes:

8. Death;

7. Hospitalized, on invasive mechanical ventilation or ECMO;

6. Hospitalized, on non-invasive ventilation or high flow oxygen devices at oxygen flow rate greater than 15L/min;

5. Hospitalized, requiring supplemental oxygen or high flow oxygen devices at oxygen flow rate less than or equal to 15L/min;

4. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);

3. Hospitalized, not requiring supplemental oxygen - no longer requiring ongoing medical care;

2. Not hospitalized, but new or increased limitation on activities and/or requiring new or increased home oxygen;

1. Not hospitalized, no limitations on activities.

This scale will be denoted as the "Modified Oxygen Use" ordinal scale.

NEWS has demonstrated an ability to discriminate subjects at risk of poor outcomes. This score is based on 7 clinical parameters (see Section 8.1.2.3 in Appendix C of the study protocol). This should be evaluated at the first assessment of a given study day and prior to administration of study product. The 7 parameters can be obtained from the hospital chart using the last measurement prior to the time of assessment and a numeric score given for each parameter (e.g., a RR of 9 is one point, oxygen saturation of 92 is two points). This is recorded for the day obtained. i.e., on Day N, the Day N score is obtained and recorded as the Day N score.

Oxygenation, Non-invasive ventilation/high flow oxygen, Invasive Mechanical Ventilation / extracorporeal membrane oxygenation (ECMO), hospitalization and mortality will be assessed using results of the 8-point ordinal scale and post discharge eCRF questions.

Safety will be assessed by the following:

- Cumulative incidence of serious adverse events (SAEs) through 28 days of follow-up.
- Cumulative incidence of Grade 3 and 4 AEs.
- Discontinuation or temporary suspension of study product administration (for any reason).
- Changes in white cell count, hemoglobin, platelets, creatinine, total bilirubin, ALT, AST, and INR, d-dimer, C-reactive protein over time. Note D-dimer and CRP are not graded.

Clinical labs will be drawn on Days 1, 3, 5, 8, 11 and on Day 15 and 29 if the subject is able to return to the clinic or is still hospitalized. The Ochsner Medical Center Kenner site used both a standard and high-sensitivity assay for measuring CRP. As results from these assays are not

comparable, CRP values from the high-sensitivity assay will be excluded from all CRP summaries and any analyses that use CRP values.

Virologic efficacy is an exploratory endpoint and will be assessed by the following:

- Qualitative and quantitative PCR for SARS-CoV-2 in OP swab on Days 1, 3, 5, 8, 11 (while hospitalized); and Day 15 and 29 (if able to return to clinic or still hospitalized).
- Qualitative and quantitative PCR for SARS-CoV-2 in blood on Days 1, 3, 5, 8, 11 (while hospitalized).

The schedule of study procedures is provided in Section 1.2 of Appendix C of the study protocol.

5. SAMPLE SIZE CONSIDERATIONS

Sample Size for Primary Analysis

The log-rank test will be used to compare treatment arms with respect to time to recovery. For the log-rank test, the two key determinants of power are the total number of events (i.e., recoveries) *E* and the treatment-to-control ratio of the rate of recovery. The number of events required for power $1-\beta$ to detect a recovery rate ratio of θ using a two-tailed test at alpha=0.05 is approximately

$$E = \frac{4\left(1.96 + z_{\beta}\right)^2}{\{\ln(\theta)\}^2},$$

where z_{β} is the $100(1-\beta)$th percentile of the standard normal distribution.

The force of recovery (sometimes loosely referred to as the "recovery ratio") is the analogue of the hazard ratio and the term "recovery rate ratio" is the analogue of the hazard ratio in this setting. A recovery rate ratio of 1.31 was reported in Cao, Wang, Wen et al. (2020) for a lopinavir/ritonavir trial that used time to improvement by 2 categories as primary endpoint. A preliminary review of data from ACTT-1 demonstrated a recovery rate ratio 1.312. It is unlikely the second component of treatment will have a similar effect size. Therefore, a recovery ratio of 1.25 is assumed for this trial. A total of 723 recoveries are needed for a recovery ratio of 1.25 with 85% power in those in ordinal score 4-6 at baseline.

The study will enroll participants until 831 recoveries. This total sample size was based on the above calculations for 723 recoveries for ordinal score 4-6 at baseline but with an increase to 831 recoveries due to anticipated lower efficacy in ordinal score 7. With the DSMB recommendation to continue enrollment only in those with baseline ordinal scores of 4 and 5, the total number of recoveries will remain 831. We anticipate that approximately 90% of subjects will recover within 28 days, and therefore the total sample size will be approximately 923. The date of study closure will be estimated based on enrollment rate and recovery/enrollment percentages.

See Section 9.2 of Appendix C of the study protocol for discussions on the sample size calculations for the key secondary outcome.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

This is a double-blind, placebo controlled randomized trial with a two-sided type I error rate of 0.05. Secondary hypotheses have been ordered according to relative importance. These will be described according to the appropriate summary statistics, e.g.:

- Percentages/proportions/odds ratios for categorical data. For tabular summaries of percentages/proportions, the denominator (e.g. number of subjects with non-missing data) will be displayed.
- Means, median, and range for continuous data, median for time-to-event data.

Confidence intervals will be generated; for the primary analysis, the confidence level will take into account the group-sequential design of the trial (see Section 6.6 and Section 8.1) whereas 95% confidence intervals will be generated for secondary and exploratory outcomes. For hazard ratio and odds ratio estimates, Wald confidence intervals will be used. For other efficacy outcomes (e.g. proportions), Wilson or Score confidence intervals will be used. For safety outcomes, exact (e.g., Clopper-Pearson) confidence intervals will be used.

When calculating treatment effects (e.g., differences, hazard ratios, odds ratios) and when using treatment arm as a covariate in regression modeling, the placebo + remdesivir arm will be used as the reference group. For regression modeling that uses strata variables defined in Section 6.4, the first stratum listed for each variable in that section will be used as the reference group.

For the final time-to-event analyses, the following SAS pseudocode will be used to perform stratified analyses to generate stratum-specific median time to event estimates and confidence intervals, stratum-specific Kaplan-Meier curves, and to perform the log-rank test. For any unstratified analyses, code can be used after the removal of the `strata … ;` line.

```
proc lifetest data=dataset plots=(s);
   time TimeVariable * CensorVariable(1);
   strata StrataVariable;
   test TreatmentVariable;
run;
```

Note that the interim efficacy analyses will be performed using R. For all interim and final analyses, the software used will calculate the log rank statistic using the formula in Section 8.1.1.

To perform a stratified Cox proportional hazards model for the final analysis and generate the treatment arm hazard ratio along with its confidence interval, the following pseudocode will be used. For any unstratified analyses, code can be used after the removal of the `strata … ;` line and strata variable in the `class` statement.

```
proc phreg data=dataset;
   class StrataVariable(ref=StrataLabel)
TreatmentVariable(ref=RemdesivirLabel);
   model TimeVariable * CensorVariable(1) = TreatmentVariable;
   strata StrataVariable;
   hazardratio TreatmentVariable / diff=ref cl=Wald;
   ods output HazardRatios = HRest;
run;
```

The following SAS pseudocode will be used to perform the final proportional odds model with treatment arm and disease severity as covariates and to generate the treatment odds ratio, p-value, and predicted probabilities of the ordinal scale levels by treatment arm and disease severity:

```
proc logistic data=dataset
      plots(only)=effect(x=ResponseVariable
      sliceby=DiseaseSeverityVariable*TreatmentVariable individual connect);
   class DiseaseSeverityVariable(param=ref ref=ModerateLabel)
         TreatmentVariable(param=ref ref=RemdesivirLabel);
   model ResponseVariable = TreatmentVariable StrataVariable;
   oddsratio TreatmentVariable;
   ods output OddsRatiosWald = ORest;
run;
```

6.2. Timing of Analyses

6.2.1. Interim analyses

A DSMB will monitor ongoing results to ensure patient well-being and safety as well as study integrity. The DSMB will be asked to recommend early termination or modification only when there is clear and substantial evidence of a treatment difference. More details about the interim analyses are described in Section 6.6.1 and Section 6.6.3 below. The summaries to be generated for the interim analysis are provided in the separate DSMB shell report.

6.2.2. Final Analyses

The final analyses of all outcomes and planned summaries/listings will be performed on the final full locked database and provided in the final report.

6.3. Analysis Populations

Summaries and analysis of safety data will be presented for the As Treated Population. Summaries and analysis of efficacy data will be presented for the modified intent-to-treat (mITT) population and As Treated population.

6.3.1. Intention-to-Treat (ITT) Population

The intention-to-treat (ITT) population includes all subjects who were randomized. ITT subjects will be classified by their randomized treatment assignment and randomized disease severity stratum (i.e. the stratum to which the subject randomized at enrollment, which is not necessarily equivalent to their baseline ordinal score if the subject was mis-stratified).

6.3.2. Modified Intention-to-Treat (mITT) and As Treated Populations

The modified intention-to-treat (mITT) population includes all subjects who were randomized. mITT subjects will be classified by their randomized treatment assignment and their baseline ordinal score, which is not necessarily equivalent to the disease severity stratum to which the subject randomized at enrollment.

The As Treated population includes all randomized subjects who received the interferon beta-1a/placebo study product, even if only one dose was administered.

For As Treated analyses of efficacy outcomes, subjects will be classified by their actual treatment assignment and their baseline ordinal score, unless otherwise specified in the table or figure shell. Note that if no subjects are administered the incorrect treatment and all subjects receive at least one dose of interferon beta-1a/placebo, the As Treated efficacy analysis will not be performed as they will be identical to the mITT analyses.

For As Treated analyses of safety outcomes, concomitant medications, and medical history, subjects will be classified by their actual treatment assignment and baseline ordinal score.

6.4. Covariates and Subgroups

As noted in Section 3.1, the main analysis of the key secondary efficacy outcomes will exclude subjects enrolled with a baseline ordinal score or 6. The main analyses of the remaining secondary efficacy outcomes will be performed in subgroups based on the baseline ordinal score. Analyses will be performed for the 4 or 5 (combined) subgroup separately from the 6 subgroup.

As a secondary analysis, the primary efficacy outcome will be summarized within each of the baseline ordinal score subgroups (4, 5, and 6 separately).

For subjects enrolled with a baseline ordinal score of 4 or 5, further subgroup analyses for the primary and key secondary efficacy outcomes will evaluate the treatment effect within the following subgroups:

- Geographic region:
  - US sites; Non-US sites
  - North American sites; Asian sites; European sites
- Duration of symptoms prior to randomization
  - Quartiles
  - <= 10 days; > 10 days
  - <= Median; > Median
- Race (White; Black/African American; Asian; Other)
- Comorbidities
  - None; Any
  - None, One, Two or more
  - Obese; Non-Obese
- Age (<40; 40-64; 65 and older),
- Sex (Female; Male),
- Severity of disease
  - Randomization stratification: 4 or 5 (separately) on ordinal scale.

  Note: separate analyses for randomized severity will only be performed if at least one subject is erroneously randomized into the incorrect disease severity stratum.

Additionally, analyses of all remaining secondary efficacy outcomes and the time to death by Day 15/29 outcomes will evaluate the treatment effect within the following subgroups (among subjects enrolled with baseline ordinal score of 4 or 5 only):

- Duration of symptoms prior to randomization (<= Median; > Median)
- Severity of disease
  - Randomization stratification: 4 or 5 (separately) on ordinal scale.
  - Baseline ordinal score: 4 or 5 (separately) on ordinal scale.

  Note: separate analyses for randomized stratum/baseline ordinal score will only be performed if at least one subject is erroneously randomized into the incorrect disease severity stratum.

There will also be a sensitivity analysis of the primary, key secondary, and mortality outcomes to evaluate the effect of concomitant therapy including experimental treatment and off-label use of marketed medications that are intended as treatment for COVID-19 and are given to patient prior to and during the study. A blinded review of the concomitant medication data will be performed by the medical monitor to identify medications that fall into any of the following categories of "Medications of Interest":

- Antivirals
  - Protease inhibitors
  - Polymerase inhibitors
- Potential Treatments for COVID-19
  - Hydroxychloroquine/Chloroquine
  - Other
- Corticosteroids
- RAS Inhibitors
- Other anti-inflammatory drugs
  - Monoclonal Antibodies Targeting Cytokines
  - Other Biologic Therapies

Summaries of subjects who report use of the categories and subcategories of therapies/treatments will be provided. Note that after the blinded review of the medications, additional categories/sub-categories may be defined and/or categories/sub-categories may be combined.

In addition, the sensitivity analyses will consider the following categories (individually):

- Any Medication of Interest
- Hydroxychloroquine/Chloroquine
- Corticosteroids
- RAS Inhibitors

- Other Anti-Inflammatory Drugs

For the recovery analyses, subjects will be censored at the time of medication/therapy initiation. If a subject recovered prior to use of any of the medications/therapies, then the subject will still be counted as a recovery in the sensitivity analysis. For the analysis of the key secondary outcome, if a subject reports use of any of the medications/therapies prior to their Day 15 assessment, then the subject's last clinical status score prior to medication/therapy use will be used as their Day 15 outcome. For the mortality analyses, subjects will be censored at the time of medication/therapy initiation. All medication of interest sensitivity analyses will exclude subjects with a baseline ordinal score of 6.

In addition, time to recovery will be explored within the following concomitant medication use subgroups:

- Pre Enrollment Corticosteroid Use (Yes/No)
- Post Enrollment Corticosteroid Use (Yes/No)
- Post Enrollment Dexamethasone Use (Yes/No)

The effect of on-study treatment on select efficacy outcomes will also be explored among subjects who reported use of statins, angiotensin receptor blockers (ARBs), or angiotensin converting enzyme inhibitors (ACEIs) via subgroup analyses. These additional concomitant medication analyses will also exclude subjects with a baseline ordinal score of 6.

Lastly, the effect of treatment on the primary and key secondary efficacy outcomes will be explored via regression modeling controlling for age, duration of symptoms prior to randomization, baseline d-dimer, and baseline CRP values as continuous covariates. As with the above, this will exclude subjects with a baseline ordinal score of 6.

6.5. Missing Data

All attempts will be made to collect all data per protocol. Any data point that appears to be erroneous or inexplicable based on clinical judgment will be investigated as a possible outlier. If data points are identified as outliers, sensitivity analyses may be performed to examine the impact of including or excluding the outliers. Any substantive differences in these analyses will be reported.

For time to event outcomes, subjects who are lost to follow-up or terminate the study prior to Day 29 and prior to observing/experiencing the event will be censored at the time of their last observed assessment. Subjects who die prior to observing/experiencing the event will be censored at Day 29.

For the analysis of the key secondary outcome, subjects who are discharged but are subsequently re-admitted prior to Day 15 without a reported clinical score, their clinical score will be imputed at 7, which is the highest value for a hospitalized subject.

For the analyses of the secondary outcomes that involve clinical score (i.e. the key secondary outcome and time to improvement), if a subject is discharged from the hospital (but not to hospice or other end-of-life care) without a previously or concurrently reported clinical score of 1 or 2, then their clinical score at the time of discharge will be imputed as 2, which is the highest value for a non-hospitalized subject. If a subject terminates early from the study while they are

hospitalized or completes the study while still hospitalized, the last observed clinical score assessment will be used as their final assessment.

For the modified version of the ordinal score described in Section 4.3, if a subject is discharged from the hospital without a previously or concurrently reported clinical score of 2 or 3, then their clinical score at the time of discharge will be imputed as 3, which is the highest value for a non-hospitalized subject.

For the analyses of the secondary outcomes described in Section 3.3, the following imputation rules will be used for subjects who are lost to follow-up, terminate early from the study, or do not have further outcome data available after discharge for any reason:

- NEWS Total score (any missing study day)
  - If the subject dies or is discharged to hospice or other end-of-life care prior to the missing study day, the worst NEWS score (20) will be imputed
  - If the subject is discharged (not to hospice or other end-of-life care) prior to the missing study day, a NEWS score of 2 will be imputed.
  - If the subject is neither dead nor discharged, use the previous NEWS total score, or missing component-carried forward for all subsequent visits.
- Days of Non-invasive ventilation/high-flow oxygen:
  - If the subject's clinical status scale is 6 at the last observed assessment, then the subject will be considered to be on non-invasive ventilation/high-flow oxygen through Day 29. The endpoint will be total days when assessments are available plus all imputed days following the last observed assessment.
  - If the subject is not on non-invasive ventilation/high-flow oxygen at the last observed assessment, then the subject will be considered to not be on non- invasive ventilation/high-flow oxygen for the remainder of follow-up. Thus, no additional imputed days will be added to the number of days recorded on available assessments.
- Days of ventilation/ECMO:
  - If the subject's clinical status scale is 7 at the last observed assessment, then the subject will be considered to be on ventilation/ECMO through Day 29. The endpoint will be total days when assessments are available plus all imputed days following the last observed assessment.
  - If the subject is not on ventilation/ECMO at the last observed assessment, then the subject will be considered to not be on ventilation/ECMO through Day 29. Thus, no additional imputed days will be added to the number of days recorded on available assessments.
- Days of Oxygen:
  - If the subject's clinical status score is 5, 6, or 7 at the last observed assessment, then the subject will be considered to be on oxygen through Day 29. The endpoint will be total days when assessments are available plus all imputed days following the last observed assessment.

- If the subject is not on oxygen at the last observed assessment, then the subject will be considered to not be on oxygen through Day 29. Thus, no additional imputed days will be added to the number of days recorded on available assessments.

- Days of Hospitalization
  - If the subject is discharged and no further hospitalization data are available, then the subject will be assumed to not have been readmitted. Thus, no additional imputed days will be added to the number of days recorded on available assessments. If a subject dies while hospitalized, the number of days of hospitalization will be imputed as 28 days.

- Lab Efficacy (d-dimer and CRP)
  - If results are not available for any visit day (s), but are available for visits before or after that visit, the average of the two nearest visits will be imputed for all missing visits between them. If a subject dies or is otherwise lost to follow-up, their last available observation will be carried forward. If baseline is missing, another pre-treatment dose will be used, or the earliest post-treatment dose will be used.

6.6. Interim Analyses and Data Monitoring

6.6.1. Planned Interim and Early Analyses

A DSMB will monitor ongoing results to ensure subject well-being and safety as well as study integrity. The DSMB will be asked to recommend early termination or modification only when there is clear and substantial evidence of a treatment difference.

On September 4, 2020, the DSMB met for an interim safety review of ACTT-3 data, and they recommended that DMID close further enrollment to patients with a baseline ordinal score of 6. Given that there are multiple clinical trials evaluating interferon beta for the treatment of COVID-19 worldwide, a public announcement describing the change in enrollment was made to inform the scientific community.

6.6.2. Interim Safety Review

Safety analyses will evaluate Grade 3 and 4 AE and SAEs by treatment arm. Safety monitoring will be ongoing with the DSMB reviewing safety data approximately every one to two weeks during the study. The unblinded statistical team will prepare these reports for review by the DSMB.

6.6.3. Interim Efficacy Review

An interim efficacy analysis will be conducted after approximately 50% of total information has been reached. The information fraction at an interim analysis will be computed as $t = r/723$ where r is the number of recoveries by the time of the data freeze date for the interim analysis. The Lan-DeMets spending function analog of the O'Brien-Fleming boundary will be used to monitor the primary endpoint using an overall two-sided type-I error rate of 0.05. Specifically, two one sided boundaries are constructed at level 0.025 using the spending function

$$\alpha^*(t) = 2[1 - \Phi\{2.241/t^{\frac{1}{2}}\}],$$

where Φ is the standard normal distribution function. Lan-DeMets software from the University of Wisconsin, now available in the R package `ldbounds', will be used to calculate boundaries.

Conditional power will be presented as an additional guide to the DSMB. Conditional power allows computation of the probability of obtaining a statistically significant result by the end of the trial given the data accumulated thus far, incorporating and assuming a hypothesized treatment effect (e.g., the treatment effect assumed for sample size determination) thereafter. If conditional power is less than 20% under the original trial assumptions, consideration should be given to stopping the trial.

The unblinded statistical team will prepare these closed session reports for DSMB review and recommendations. Analyses will be presented with blinded codes for treatment arms to protect against the possibility that the DSMB report may fall into the wrong hands. A DSMB Charter will further describe procedures and membership.

6.7. Multicenter Studies

Data will be pooled across all clinical sites. Secondary analyses of the primary outcome will account for site via stratification by geographic region as noted in Section 6.4.

A sensitivity analysis of the primary outcome will be performed to assess the impact of individual sites on the observed treatment effect. Letting *M* be the total number of sites, the primary analysis will be repeated by excluding a single clinical site and performing the analyses on the remaining *M-1* sites. This process will be repeated so that estimates are generated for each of the *M-1* subset datasets. Presentations from these analyses are described in Section 8.1.2.

6.8. Multiple Comparisons/Multiplicity

There is only one primary outcome measure. The study utilizes a group-sequential design to control the overall type I error rate while allowing for formal interim analyses of the primary outcome measure (as described in Section 6.6 and Section 8.1). For the primary analysis of time to recovery, the stratified log-rank test will be performed in the efficacy analysis populations including all three severity strata and the p-value will be reported. If the resulting p-value is significant, then the analysis that excludes subjects in the severity = 6 strata will include the stratified log-rank test and the p-value will be reported. If the p-value from the primary analysis (including all three strata) is not significant, then the stratified log-rank test will not be performed for the analysis that excludes the severity = 6 strata and no p-value will be reported.

Likewise, the p-value for the analyses of the following will only be reported if the p-value from the primary analysis of time to recovery (including all three strata) is significant:

- The proportional odds model for the key secondary endpoint of clinical status score at Study Visit Day 15;
- Time to death through Day 15 (baseline ordinal score 4 or 5);
- Time to death through Day 29 (baseline ordinal score 4 or 5).

There is no planned adjustment for multiple comparisons in any secondary or exploratory analyses.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

A summary of the reasons that subjects were screened but not randomized will be tabulated (Table 1).

The composition of analysis populations, including reasons for subject exclusion will be summarized by treatment group and disease severity (Table 2). A subject listing of subjects excluded from the As Treated Population will be generated (Listing 1).

The disposition of subjects will be tabulated by treatment group and randomized disease severity (Table 3). Study milestones included in the table will include, but not limited to: the total number of subjects that were randomized, completed expected blood draws, completed Study Day 15 visit, completed Study Day 22 visit, and completed Study Day 29 visit. For the calculation of percentages, subjects who die will not be included in the denominators for visits/assessments beyond their death. Subject status at study termination will be summarized by treatment group and baseline ordinal score (Table 4).

Treatment exposure will be summarized by treatment group (Table 5 and Table 6). Summaries of prior remdesivir treatment by treatment group and baseline ordinal score will also be provided (Table 7).

A flowchart showing the disposition of study subjects, adapted from the Consort Statement [4] will be generated (Figure 1). This figure will present the number of subjects screened, randomized, lost to follow-up, and analyzed, by treatment group and baseline disease severity (ordinal scale 4, 5, or 6). The number of subjects that terminated early by hospitalization status at the time of the last ordinal score collection will be summarized graphically (Figure 2).

A listing of subjects who discontinued dosing or terminated study follow-up and the reason will be generated (Listing 2).

7.2. Protocol Deviations

Subject-specific protocol deviations will be summarized by the reason for the deviation, the deviation category, treatment group, and disease severity (Table 8). A summary of major deviations will also be generated (Table 9). All subject-specific protocol deviations and non-subject specific protocol deviations will be included in listings (Listing 3 and Listing 4).

8. EFFICACY EVALUATION

8.1. Primary Efficacy Analysis

8.1.1. Primary Analysis of Time to Recovery

The primary analysis uses the stratified log rank test to compare treatment to control through Day 29 with respect to time to recovery, as defined in Section 3.3. Stratification is based on ordinal scale at baseline (4, 5, or 6). As noted in Section 3.3, all deaths within 29 days will be considered censored at Day 29 with respect to time to recovery. Conceptually, a death corresponds to an infinite time to recovery, but censoring at any time greater than or equal to Day 29 gives the same answer as censoring at Day 29; both correspond to giving deaths the worst rank.

As noted in Section 6.6.3, to maintain an overall two-sided type-I error rate of 0.05, the Lan-DeMets spending function analog of the O'Brien-Fleming boundary will be used to derive the cumulative error spending and boundaries for the interim analysis.

For the final analysis, the log rank test will be performed using the pseudocode provided in Section 6.1. The following pseudocode can be used to compute the bounds for the final analyses and compare to the calculated log-rank statistic. The Boundaries dataset will contain the updated boundaries calculated from the interim analyses using the actual information levels observed at the interim analysis.

```
data Parms_LogR;
   set logrankp(rename=(Statistic=Estimate));
   if Variable='TreatmentVariable';
   _Scale_='Score';
   _Stage_= AnalysisNumber;
   keep Variable _Scale_ _Stage_ StdErr Estimate;
run;

proc seqtest Boundary=Boundaries
             Parms(Testvar=TreatmentVariable)=Parms_LogR
             infoadj=prop
             boundaryscale=score
             ;
   ods output Test=FinalResults ParameterEstimates = LogHRest;
run;
```

If the trial is stopped at the interim analysis, then to derive the p-value, hazard ratio estimate, and confidence interval for the early and final analysis sets, stage-wise ordering of the sample space will be used [5]. The resulting p-value, median unbiased estimate, and confidence interval will be presented in the final report. If the trial is not stopped early, then the fixed sample estimates of the statistics using an alpha level of 5% will be computed and reported for the final analysis. The SAS pseudocode above provides estimates for the log hazard ratio and so the estimates will be exponentiated and reported.

The primary analysis will be performed in the mITT analysis population. The treatment hazard ratio estimate and confidence interval and p-value from the stratified log rank test will be presented (Table 10). The median time to event and 95% confidence interval will be summarized

by treatment arm and disease severity. In addition, stratum-specific estimates of the treatment hazard ratio from Cox models run within each of the disease severity strata will be presented. Kaplan-Meier curves for each treatment arm will be presented, supplemented with the hazard ratio estimate, p-value, and the number of subjects at risk in each arm and severity stratum at Days 1, 3, 5, 8, 11, 15, 22, and 29 (Figure 3).

Subject listings of the ordinal scale results by day will be generated (Listing 5).

8.1.2. Key Secondary, Supplemental, and Sensitivity Analyses of Time to Recovery

For all supplemental and sensitivity analyses of the primary outcome, p-values may or may not be reported, and 95% confidence levels will be used for confidence interval estimates.

The primary analysis will be repeated in the As Treated analysis population where subjects who are not treated will be censored at randomization. The tabular and graphical summaries described in the previous section will be replicated for this As Treated analysis. For the key secondary outcome measure, the analysis will follow as described in Section 8.1.1, excluding subjects with a baseline ordinal score of 6. The primary analysis will also be repeated using the Modified Oxygen Use ordinal scale described in Section 4.3 (Table 11).

Sensitivity analyses will be performed using Cox proportional hazards models to estimate the hazard ratio (Table 12). First, an mITT analysis will be performed in which subjects who die prior to recovering are treated as experiencing a competing risk in the Fine-Gray proportional hazards regression model. Second, a Cox model will be fit with binary indicators for treatment group and baseline ordinal score (4, 5, or 6 and separately 4+5 vs. 6) as well as a treatment * baseline ordinal score (as a continuous variable) interaction terms. The models will be fit to the mITT analysis population. The treatment group hazard ratios and CIs will be reported for both sets of models and the interaction term p-value will be reported for the interaction models. The tabular summary will also include results from an analysis of time to recovery controlling for age and duration of symptoms as continuous covariates and baseline d-dimer and CRP values as continuous covariates.

The primary analysis will also be repeated using the other subgroups defined in Section 6.4 in place of disease severity. Each subgroup will be considered separately and the tabular and graphical summaries described in the previous section will be replicated for each subgroup. A forest plot will be generated to display the overall treatment hazard ratio estimate and CI from each of the within-subgroup analyses (Table 13).

As noted in Section 6.4, analyses that take into account concomitant medication will be performed (Table 14). An additional sensitivity analysis will evaluate the effect of recoveries that were not sustained as indicated in Section 3.3.2 (Table 15).

A restricted mean survival time analysis will be performed as an exploratory analysis. The restricted mean recovery time estimates will be provided for each treatment group and baseline disease severity stratum as well as the difference in restricted mean recovery time between treatment groups within each of the severity strata (Table 16).

In addition, a forest plot will be generated for the “leave one out” sensitivity analyses described in Section 6.7 (Figure 10); hazard ratio estimates and CIs will be provided for each subgroup that leaves a single site out.

Two corroborative summaries will also be generated. A summary of the number and percentage of subjects in each treatment group who recovered (and are alive), did not recover (and are alive), and died by Day 29 will be summarized. The summary will also include the numbers and percentages, grouping deaths and non-recoveries together (Table 17). The summaries will also be provided by the Modified Oxygen Use ordinal scale and the duration of symptoms categorizations specified in Section 6.4.

Other censoring techniques and additional analyses of the primary outcome may be performed.

8.2. Secondary Efficacy Analyses

This section describes the planned analyses for the secondary efficacy outcome measures. Where applicable, refer to Section 6.1 for SAS pseudocode. Analyses of mortality will be described in Section 9.4.

As noted in Section 3.1, the main analysis of the key secondary efficacy outcomes will exclude subjects enrolled with a baseline ordinal score or 6. The main analyses of the remaining secondary efficacy outcomes will be performed in subgroups based on the baseline ordinal score. Analyses will be performed for the 4 or 5 (combined) subgroup separately from the 6 subgroup.

Analyses of the key secondary outcome measure will be explored in the specified subgroups described in Section 6.4. Analyses of the other secondary outcome measures will be performed by treatment arm only and repeated for specified subgroups described in Section 6.4 and Section 6.7 via stratified analyses. As with the analyses described in Section 8.1.2, tabular summaries will follow the structure of the main tabular summaries planned for each outcome with the modification that stratified estimates will be provided in separate rows. Forest plots will display confidence intervals of outcomes/estimates across subgroups, where applicable.

All secondary efficacy analyses will be performed in the mITT population. As Treated analyses may be explored to investigate consistency of results compared to the mITT analyses.

8.2.1. Ordinal Scale Outcomes (Key Secondary Outcome Measure)

For the analysis of the first key secondary outcome measure, the distribution of the 8-point ordinal clinical status scale with 8 categories at Study Visit Day 15 (not necessarily actual study day 15), the outcome will be analyzed using a proportional odds model with treatment arm and disease severity as covariates. The treatment odds ratio estimated from the model will be presented along with the p-value (Table 18 and Table 19). The analysis will be repeated using the modified oxygen use scale. The Study Visit Day 15 clinical status score will be depicted graphically using shifted bar plots; the outcomes will be presented by baseline ordinal score and treatment group (Figure 11). In addition to the subgroup analyses, the main analysis will be repeated including a treatment * baseline ordinal score interaction term, where the interaction term p-value will be reported for the interaction model.

Multiple supplemental analysis of this key secondary outcome will be performed. Time to improvement by at least one category in the clinical status 8-point scale (see Section 3.3). The log rank test will be performed using a Cox proportional hazards model to test whether the curves differ between treatment arms. The median time to event and CI in each treatment group will be summarized along with the treatment hazard ratio estimate and log rank p-value (Table 20). Differences in time-to-event endpoints by treatment arm will be summarized with

Kaplan-Meier curves (Figure 12). Number at risk, hazard ratio and log rank p-values will be presented on the figures. The analyses (and tabular and graphical summaries) will be repeated using the outcome of time to improvement in two categories of the ordinal scale defined in Section 3.3.

The above analyses will be repeated with the Modified Recovery ordinal scale described in Section 4.3 (Table 21). The only subgroup analysis that will be performed for time to improvement will be an analysis that classifies subjects by the duration of symptoms at baseline subgroups (above/below the median) (Table 22).

The number and proportion of subjects along with 95% confidence intervals by category of clinical status will be presented by treatment arm at Study Visit (not necessarily actual) Days 1, 3, 5, 8, 11, 15 and 29 (Table 23). These summaries will be replicated using the Modified Oxygen Use ordinal scale described in Section 4.3. Change from baseline (using the as-reported ordinal scores) will also be summarized at Days 3, 5, 8, 11, 15, 22, and 29 (Table 27).

8.2.2. NEWS

The median time to discharge or to a NEWS of ≤ 2 and CI will be summarized by treatment group (Table 29). The hazard ratio and log rank p-values will be provided with the summaries. Differences in time-to-event endpoints by treatment arm will be summarized with Kaplan-Meier curves. Number at risk, hazard ratio and log rank p-values will be included on the figures (Figure 16).

The mean, confidence interval, median, minimum, and maximum NEWS at Baseline and Study Visit (not necessarily actual) Days 3, 5, 8, 11, 15 and 29 will be presented by treatment arm as well as change from baseline at each post-Day 1 visit (Table 31). A figure with mean and confidence interval over time will also be presented by treatment arm (Figure 18).

Subject listings of NEWS responses (overall and individual components) by day will be generated (Listing 6).

8.2.3. Days of Oxygenation

Duration of oxygenation use will be summarized in a table using medians and quartiles by treatment arm (Table 33). Analyses will be performed in the mITT and As Treated populations. Bee swarm plots of oxygen days by treatment arm will be generated, where subjects whose days are imputed to the maximum of 28 days due to death are grouped separately from subjects who do not die (Figure 20).

8.2.4. Incidence of New Oxygen use

The incidence and duration of new oxygen use will be analyzed by treatment arm. This will only include subjects in category 4 at randomization. New use will be identified by a post-randomization score of at least 5; the number of subjects reporting new use and the incidence rate (and CI) will be reported.

8.2.5. Days of Non-Invasive Ventilation/High-Flow Oxygen

Duration of non-invasive ventilation/high flow oxygen use will be summarized in a table using medians and quartiles by treatment arm. Analyses will be performed in the mITT and As Treated

populations. Bee swarm plots of non-invasive ventilation/high flow oxygen days by treatment arm will be generated, where subjects whose days are imputed to the maximum of 28 days due to death are grouped separately from subjects who do not die.

8.2.6. Incidence of New Non-Invasive Ventilation/High-Flow Oxygen

The incidence and duration of new Non-Invasive Ventilation/High-Flow Oxygen use will be analyzed by treatment arm. This will only include subjects in category 4 or 5 at randomization. New use will be identified by a post-randomization score of 6. The number of subjects reporting new use and the incidence rate (and CI) will be reported.

8.2.7. Days of Invasive Mechanical Ventilation/ECMO

Duration of Invasive Mechanical Ventilation/ECMO use will be summarized in a table using medians and quartiles by treatment arm. Analyses will be performed in the mITT and As Treated populations. Bee swarm plots of Invasive Mechanical Ventilation/ECMO days by treatment arm will be generated, where subjects whose days are imputed to the maximum of 28 days due to death are grouped separately from subjects who do not die.

8.2.8. Incidence of New Invasive Mechanical Ventilation/ECMO

The incidence and duration of new Invasive Mechanical Ventilation/ECMO use will be analyzed by treatment arm. New use will be identified by a post-randomization score of 7. The number of subjects reporting new use and the incidence rate (and CI) will be reported.

8.2.9. Days of Hospitalization

Duration of hospitalization will be summarized in a table using medians and quartiles by treatment arm. Incidence of readmittance will also be summarized (Table 42). Analyses will be performed in the mITT and As Treated population. Bee swarm plots of days hospitalized by treatment arm will be generated, where subjects whose days are imputed to the maximum of 28 days due to death are grouped separately from subjects who do not die.

8.3. Exploratory Efficacy Analyses

Analyses of exploratory outcome measures are not covered in this SAP.

9. SAFETY EVALUATION

9.1. Demographic and Other Baseline Characteristics

Summaries of age, sex, height, weight, BMI, ethnicity, and race will be presented by treatment group as well as geographic region, comorbidities, duration of symptoms prior to randomization, and disease severity (Table 47 and Table 48). Ethnicity will be categorized as Hispanic or Latino, or not Hispanic and not Latino. In accordance with NIH reporting policy, subjects may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as "No" to each racial option.

Individual subject listings will be presented for all demographics and baseline characteristics (Listing 7).

9.1.1. Prior and Concurrent Medical Conditions

Focused medical history is obtained at the screening visit that includes the following:

- History of chronic medical conditions related to inclusion and exclusion criteria
- Review medications and therapies for this current illness.

Medical history is limited to the following conditions: asthma, cancer, cardiac valvular disease, chronic kidney disease, chronic liver disease, chronic oxygen requirement, chronic respiratory disease, coagulopathy, congestive heart failure, coronary artery disease, current nicotine consumption, diabetes I and II, hypertension, immune deficiency, and obesity. All current illnesses and past pre-existing medical conditions will be MedDRA® coded using MedDRA dictionary version 23.0 or higher. Summaries of subjects' pre-existing medical conditions will be presented by treatment group (Table 49).

Individual subject listings will be presented for all medical conditions (Listing 8).

9.1.2. Prior and Concomitant Medications

Medication history (concomitant medications) includes a review of all current medications and medications taken within 7 days prior to enrollment through approximately Day 15 or early termination (if Day 15), whichever occurs first.

Summaries of medications that were started prior to dosing and continued at the time of dosing or started after dosing while on study will be presented by WHO Drug Level 1 and 2 Codes, disease severity, and treatment group (Table 50). Summaries of overall use of medications/therapies of interest listed in Section 6.4 that were started prior to dosing and continued at the time of dosing or started after dosing while on study as well as use by select study days will also be generated (Table 51 and Table 52).

Individual subject listings will be presented for all concomitant medications (Listing 9), corticosteroid use (Listing 10), and medications of interest (Listing 11).

9.2. Measurements of Treatment Compliance

Section 7 provides the descriptions of summaries of key treatment compliance milestones/variables. Individual subject listings will be presented for all subjects who discontinued dosing (Listing 2). Individual subject listings will be presented for all subjects who missed, halted or slowed any dose (Listing 12).

9.3. Adverse Events

For the calculation of incidence of adverse events (i.e., on a per subject basis), each subject will only be counted once and any repetitions of adverse events within a subject will be ignored; the denominator will be the number of subjects in the Treated population. All adverse events reported and treatment emergent will be reported in tables and listings; treatment emerge events are adverse events anytime following the initiation of administration with any study product (interferon beta-1a, remdesivir, or placebo). Select adverse event summaries will be replicated using the modified oxygen use scale.

An overall summary by treatment arm and disease severity of adverse events is presented that includes, but not limited to: subjects with at least one event, at least one related event, at least one SAE, at least one related SAE and at least one AE leading to early termination (Table 53, Table 54, Table 55).

Adverse events occurring in 5% of subjects (by MedDRA preferred term) in any treatment group will be presented (Table 61, Table 62, Table 63).

The proportion of subjects reporting at least one adverse event will be summarized by MedDRA system organ class and preferred term for each treatment arm, disease severity and overall. Denominators for percentages are the number of subjects in the Treated population.

The following summaries for adverse events will be presented by MedDRA system organ class, preferred term, disease severity and treatment group:

- Renal adverse events by preferred term (Table 65, Table 66);
- Hepatic adverse events by preferred term (Table 67, Table 68)
- Related adverse events by MedDRA system organ class and preferred term (Table 69, Table 70);
- Subject listing of non-serious adverse events (Listing 13) and listing of related adverse events (Listing 14);
- Bar chart of non-serious related adverse events by severity and MedDRA system organ class (Figure 28, Figure 29);
- Bar chart of non-serious related adverse events by maximum severity and MedDRA system organ class (Figure 30, Figure 31).

9.4. Deaths, Serious Adverse Events and other Significant Adverse Events

Serious adverse events will be summarized by MedDRA system organ class and preferring term (Table 57, Table 58, Table 59). Listings of death and other serious adverse events will be

presented, including Subject ID, treatment group, Adverse Event Description, Number of Days Post Dose (Duration), Number of Days Post Dose the Event Became Serious, Reason Reported as an SAE, Severity, Relationship to Treatment, Alternate Etiology if not Related, Action Taken with Study Treatment, Subject Discontinuation, Outcome, MedDRA SOC, and MedDRA PT (Listing 15 and Listing 16).

The number of subjects who die by Day 15 and Day 29 will be presented by treatment arm. The 14- and 28-day mortality rate, which will use Kaplan-Meier estimator, will be presented (Table 71, Table 72, Table 73, Table 74). Summaries will be provided for both the as-reported baseline ordinal score and the Modified Oxygen Use ordinal score described in Section 4.3.

Mortality through Day 15 and 29 will also be analyzed as a time to event endpoint (see Section 3.3). A table will present median time to event along with 95% confidence intervals overall for each treatment arm along with the hazard ratio estimate and log rank p-values (Table 75). Differences in time-to-event endpoints by treatment will be summarized with Kaplan-Meier curves (Figure 32). Analyses of mortality will be performed in the mITT and the Treated analysis populations and will be replicated using the Modified Oxygen Use ordinal score described in Section 4.3. As a supplemental analysis, a Cox model will be fit with binary indicators for treatment group and disease severity as well as a treatment * disease severity interaction term. The model will be fit in the mITT and As Treated analysis populations. The treatment group hazard ratios and CIs and the interaction term p-value will be reported. Finally, the results of the subgroup and sensitivity time-to event analyses described in Section 6.4 will be presented in a table. A restricted mean survival time analysis of mortality will be performed as an exploratory analysis. The restricted mean mortality time estimates will be provided for each treatment group and randomized disease severity stratum as well as the difference in restricted mean recovery time between treatment groups within each of the severity strata (Table 82).

Analyses of the time to death or progression to invasive ventilation through Day 28 will be performed. Stratified (by baseline ordinal score) and subgroup (by baseline ordinal score) analyses will be performed (Table 83, Table 84). The analysis will be repeated using the modified oxygen use scale. The analyses will also be replicated to explore time to death or progression to ventilation (non-invasive or invasive) through Day 28 (Table 87, Table 88, Table 89). These analyses will mirror those performed for the time to death outcome with the addition that the analyses will explore the outcome in the statin/ARB/AECI use subgroups.

Rates of Grade 3 and 4 AE occurrence will be summarized by treatment arm (Table 90). Rates of SAE occurrence will also be compared between treatment arms using Barnard's exact test and presented. Further, the composite endpoint of the occurrence of death, SAE, or Grade 3 or 4 AE described in Section 3.3 will be analyzed as a time to event outcome. A table will present median time to event along with 95% confidence intervals overall for each treatment arm along with the hazard ratio estimate and log rank p-values (Table 91). Differences in time-to-event endpoints by treatment will be summarized with Kaplan-Meier curves.

9.5. Pregnancies

For any subjects in the Treated population who become pregnant during the study, every attempt will be made to follow these subjects to completion of pregnancy to document the outcome, including information regarding any complications with pregnancy and/or delivery. Note that the CSR will not be delayed to wait for outcomes of any pregnancies; an addendum to the CSR

would be provided in such a scenario. A set of listings of pregnancies and outcomes will be presented (Listing 17, Listing 18, Listing 19, Listing 20, and Listing 21).

9.6. Clinical Laboratory Evaluations

Clinical safety laboratory adverse events are collected Day 1, 3, 5, 8, 11 and Day 15 and 29 if able to return to clinic or still hospitalized. Parameters evaluated include white blood cell count, absolute neutrophil count, eGFR, platelet count, hemoglobin concentration, creatinine, glucose, total bilirubin, ALT, AST, INR, d-dimer, and CRP. Laboratory safety parameters will be graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017). For sites that do not report an upper (lower) limit for the value of a laboratory parameter, the median of the reported upper (lower) limits across the other sites will be used.

The distribution of Grade 3 and 4 chemistry and hematology laboratory results by maximum severity, time point, disease severity and treatment group will be presented (Table 92). Treatment-emergent laboratory abnormalities will be summarized by parameter and grade (Table 94).

Descriptive statistics including mean, median, standard deviation, maximum, and minimum values and change from baseline by time point, for all and each chemistry and hematology laboratory parameter will be summarized by disease severity and treatment arm (Table 96). Changes in chemistry and hematology laboratory values will be presented in line graphs over time with median, Q1 and Q3 plotted by disease severity and treatment arm (Figure 49).

Listings will provide a complete listing of individual chemistry and hematology laboratory results with applicable reference ranges (Listing 22).

9.7. Vital Signs and Physical Evaluations

Vital sign measurements include pulse, systolic blood pressure, respiratory rate, SpO_2 and oral temperature. Vital signs were assessed as part of the NEW score (assessed daily while hospitalized and on Day 15) and will be listed in Listing 6.

Targeted Physical examinations are performed at Day 1 and are performed post-baseline only when needed to evaluate possible adverse events. At the screening visit, the targeted physical examination is focused on lung auscultation. Physical exam findings per subject will be detailed in a listing (Listing 23).

9.8. Concomitant Medications

Concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary. The use of prior and concomitant medications taken during the study will be recorded on the CRFs. Concomitant medication and corticosteroid use will be presented in subject listings (Listing 9 and Listing 10). The use of concomitant medications during the study (regardless of whether the medications were started prior to enrollment or after enrollment) will be summarized by ATC1, ATC2 code, disease severity and treatment group for the As Treated population (Table 50).

9.9. Other Safety Measures

No additional safety analyses are planned.

10. PHARMACOKINETICS

Not applicable.

11. IMMUNOGENICITY

Not applicable.

12. OTHER ANALYSES

Not applicable.

13. REPORTING CONVENTIONS

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; p-values less than 0.0005 will be reported as "<0.001" and p-values greater than 0.9995 will be reported as ">0.999".

The mean, confidence intervals, median, IQR, and other statistics will be reported to 1 decimal place greater than the original data. The minimum and maximum will use the same number of decimal places as the original data.

Proportions will be presented as 2 decimal places; values greater than zero but <0.005 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values greater than zero but < 0.5% will be presented as "<1"; values greater than 99.5% but less than 100% will be reported as >99.

For all other estimators, the NEJM statistical reporting guidelines will be followed: results will be presented with no more precision than is of scientific value and is meaningful. For example, measures of association, such as odds ratios, will be reported to two or three significant digits. Results derived from models will be limited to the appropriate number of significant digits.

14. TECHNICAL DETAILS

SAS version 9.4 or above, or R language and environment for statistical computing 3.6.1 or above, will be used to generate all tables, figures and listings.

15. SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Summary of changes from version 1.0 of the SAP:

1. Throughout document: typos and errors were fixed and clarifications were added. Updates were made to the text as well as table, listing, and figure titles, row/column headers, footnotes, and implementation notes.
2. Throughout document: The use of "actual disease severity" was replaced by "baseline ordinal score" for clarity.
3. Throughout document: Multiple tables and figures that provided non-essential, supplemental summaries were removed for brevity.
4. Throughout document: in review of study data and site data queries for ACTT-3 subjects who received study product after reaching ordinal score 6, the study team identified that there was ambiguity in the high-flow oxygen categorization. The language in the MOP allowed for different interpretation of high-flow oxygen use, where some clinical sites interpreted and entered any high-flow device use as Ordinal Score 6 while other sites used less than 15L on a high-flow device and entered this as Ordinal Score 5. A Modified Oxygen Use ordinal scale was added and select summaries will be replicated using this scale as sensitivity analyses.
5. Efficacy Analyses: a sensitivity analyses of the primary outcome using the ITT population was added.

16. REFERENCES

1. Schoenfeld, D. 1981. The asymptotic properties of nonparametric tests for comparing survival distributions. Biometrika. 68 (1): 316–319.
2. Cao, Wang, Wen et al. 2020. A trial of lopinavir–ritonavir in adults hospitalized with severe covid-19. New DOI: 10.1056/NEJMoa2001282.
3. Whitehead, J. 1993. Sample size calculations for ordered categorical data. Statistics in Medicine 12, 2257-2271.
4. Drummond R. CONSORT Revised: Improving the Reporting of Randomized Clinical Trials. JAMA. 2001; 285(15):2006-2007.
5. Jennison C., Turnbull B.W. 2000. Group sequential methods with applications to clinical trials. Chapman & Hall, Boca Raton.

17. LISTING OF TABLES, FIGURES, AND LISTINGS

Table, figure, and listing shells are presented in Appendices 1, 2, and 3.

The formatting of the final version of a table, figure, or listing may differ from what is presented in the shell or the presentation of the results may be changed, however the key content will remain unchanged. Additional summaries/data points may be included in the final version of a table, figure, or listing, as well. Additional tables, figures, and listings may be generated to supplement the planned output.

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

Table 1: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
All Subjects	**Total number of subjects failing any eligibility criterion or were eligible but not randomized**	**X**	**100**
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	X	xx
Inclusion	Any inclusion criterion	X	xx
	[inclusion criterion 1]	X	xx
	[inclusion criterion 2]	X	xx
	[inclusion criterion 3]	X	xx
Exclusion	Any exclusion criterion	X	xx
	[exclusion criterion 1]	X	xx
	[exclusion criterion 2]	X	xx
	[exclusion criterion 3]	X	xx
Eligible but Not Randomized		X	xx

[a] More than one criterion may be marked per subject.
[b] Denominator for percentages is the total number of screen failures.

Programming Note: Subjects who are eligible but not randomized will be counted in the denominator.

Table 2: Analysis Population Eligibilities by Treatment Group and Baseline Ordinal Score

		Interferon Beta-1a + RDV			Placebo + RDV		
Analysis Population	**Inclusion / Reason for Exclusion**	**Baseline OS 4**	**Baseline OS 5**	**Baseline OS 6**	**Baseline OS 4**	**Baseline OS 5**	**Baseline OS 6**
		n	**n**	**n**	**n**	**n**	**n**
Intent-to-Treat Population (Randomized Baseline Score)	Included in Population	x	x	x	x	x	x
Modified Intent-to-Treat Population (Actual Baseline Score)	Included in Population[a]	x	x	x	x	x	x
As Treated Population (Actual Baseline Score)	Included in Population[b]	x	x	x	x	x	x
	Excluded from Population[a]	x	x	x	x	x	x
	Did Not Receive Dose of Interferon/Placebo[a]	x	x	x	x	x	x

[a] Counts are the numbers of subjects randomized to the specified treatment group with the specified baseline ordinal score.
[b] Counts are the numbers of subjects who received the specified treatment with the specified baseline ordinal score.

Programming Notes:

If at least one subject received the incorrect treatment, then a footnote will be added which reads "XX subject[s] [was/were] randomized to [insert randomized treatment] but was administered [insert actual treatment]. In addition, a row under "Included in Population" and "Excluded from Population" will be added for the As Treated Population section with the label "Randomized to [insert randomized treatment] but administered [insert actual treatment]."

Table 3: Subject Disposition by Treatment Group and Baseline Ordinal Score – mITT Population

Subject Disposition	Interferon beta-1a + RDV (N=X)						Placebo + RDV (N=X)						All Subjects (N = X)					
	Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Randomized	x/x	100	x/x	100	x/x	100	x/x	100	x/x	100	x/x	100	x/x	100	x/x	100	x/x	100
Terminated Early from Study	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Discharged from Hospital	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Died During Follow-up	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Completed Follow-up (Study Day 1) – Hospitalized Subjects in Study	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Ordinal Scale Data Available	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
NEWS Data Scale Data Available	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Safety Laboratory Blood Draw	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
OP Swab Collection	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
PCR Assays Blood Draw	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Secondary Research Blood Draw	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Repeat for Days 3, 5, 8, 11																		
Completed Follow-up (Study Day 15) – All Subjects in Study	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Ordinal Scale Data Available	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
NEWS Data Scale Data Available	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Safety Laboratory Blood Draw	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
OP Swab Collection	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Secondary Research Blood Draw	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Completed Follow-up (Study Day 22) – All Subjects in Study	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Ordinal Scale Data Available	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx

Subject Disposition	Interferon beta-1a + RDV (N=X)						Placebo + RDV (N=X)						All Subjects (N = X)					
	Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
NEWS Data Scale Data Available (Inpatient Subjects Only)	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Completed Follow-up (Study Day 29) – All Subjects in Study	x/x	xx	x/x	Xx	x/x	xx	x/x	Xx	x/x	xx	x/x	Xx	x/x	Xx	x/x	xx	x/x	Xx
Ordinal Scale Data Available	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
NEWS Data Scale Data Available	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Safety Laboratory Blood Draw	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
OP Swab Collection	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Secondary Research Blood Draw	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx

N = Number of subjects randomized and in study for visits 1, 15, 22 and 29 and the number of subjects hospitalized and in study for visits 3, 5, 8 and 11. Subjects that died or terminated from the study on or prior to the study visit are not included in the denominators.

Table 4: Subject Status at Study Termination by Treatment Group and Baseline Ordinal Score – mITT Population

Baseline Ordinal Score	Category	Status at Termination	Interferon Beta-1a + RDV			Placebo + RDV		
			N	n	%	N	n	%
All Subjects	Any Status	All Subjects	x	x	x	x	x	x
	Recovery	Recovered	x	x	x	x	x	x
		Not Recovered	x	x	x	x	x	x
	Hospitalization	Hospitalized	x	x	x	x	x	x
		Not Hospitalized	x	x	x	x	x	x
	Relative to Day 15	Prior to Day 15	x	x	x	x	x	x
		On or After Day 15	x	x	x	x	x	x
Continue for Ordinal Score 4, 5, 6	…	…	…	…	…	…	…	…
N = Number of subjects in the mITT Population with the baseline ordinal score. Status at termination based on the time of the last ordinal score collection.								

Table 5: Interferon beta-1a/Placebo Exposure by Treatment Group and Baseline Ordinal Score – mITT Population

	Interferon Beta-1a + RDV (N = X)			**Placebo + RDV (N = X)**		
	Baseline OS 4 (N=X)	**Baseline OS 5 (N=X)**	**Baseline OS 6 (N=X)**	**Baseline OS 4 (N=X)**	**Baseline OS 5 (N=X)**	**Baseline OS 6 (N=X)**
Number of Injections Received						
N	x	x	x	x	x	x
Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Median	x	x	x	x	x	x
Q1, Q3	x, x	x, x	x, x	x, x	x, x	x, x
Min, Max	x, x	x, x	x, x	x, x	x, x	x, x
Number of Subjects by Injections Received						
1 Dose	x	x	x	x	x	x
2 Doses	x	x	x	x	x	x
3 Doses	x	x	x	x	x	x
4 Doses	x	x	x	x	x	x
Number of Subjects Discontinuing Treatment	x	x	x	x	x	x
Number of Subjects by Reason for Discontinuation	x	x	x	x	x	x
[Reason 1]	x	x	x	x	x	x
[Reason 2]	x	x	x	x	x	x
Etc…	x	x	x	x	x	x

Table 6: Remdesivir Exposure by Treatment Group and Baseline Ordinal Score – mITT Population

	Interferon Beta-1a + RDV (N = X)			**Placebo + RDV (N = X)**		
	Baseline OS 4 (N=X)	**Baseline OS 5 (N=X)**	**Baseline OS 6 (N=X)**	**Baseline OS 4 (N=X)**	**Baseline OS 5 (N=X)**	**Baseline OS 6 (N=X)**
Number of Doses Received						
N	x	x	x	x	x	x
Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Median	x	x	x	x	x	x
Q1, Q3	x, x	x, x	x, x	x, x	x, x	x, x
Min, Max	x, x	x, x	x, x	x, x	x, x	x, x
Number of Subjects who Received RDV Prior to Enrollment	x	x	x	x	x	x
Number of Subjects by Doses Received						
1 Dose	x	x	x	x	x	x
2 Doses	x	x	x	x	x	x
3 Doses	x	x	x	x	x	x
4 Doses	x	x	x	x	x	x
5 Doses	x	x	x	x	x	x
6 Doses	x	x	x	x	x	x
7 Doses	x	x	x	x	x	x
8 Doses	x	x	x	x	x	x
9 Doses	x	x	x	x	x	x
10 Doses	x	x	x	x	x	x
Number of Subjects Discontinuing Treatment	x	x	x	x	x	x
Number of Subjects by Reason for Discontinuation	x	x	x	x	x	x
[Reason 1]	x	x	x	x	x	x
[Reason 2]	x	x	x	x	x	x
Etc…	x	x	x	x	x	x

Table 7: Subjects Reporting Prior Remdesivir Treatment by Baseline Ordinal Score and Treatment Group – mITT Population

Prior RDV Treatment Summary	Interferon beta-1a + RDV (N=X)			Placebo + RDV (N=X)		
	Baseline OS 4 (N=X)	Baseline OS 5 (N=X)	Baseline OS 6 (N=X)	Baseline OS 4 (N=X)	Baseline OS 5 (N=X)	Baseline OS 6 (N=X)
Received RDV Treatment Prior to Enrollment – n (%)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Number of Doses of RDV Received Prior to Enrollment						
Number of Subjects with Data	x	x	x	x	x	x
Mean (STD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Median	x.x	x.x	x.x	x.x	x.x	x.x
IQR	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
Range (Min, Max)	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
N = Number of subjects in the mITT Population.						

Table 8: Distribution of Subject Specific Protocol Deviations by Category, Type, Treatment Group, and Baseline Ordinal Score - mITT Population

Category	Deviation Type	Interferon beta-1a + RDV (N=X)						Placebo + RDV (N=X)						All Subjects (N=X)					
		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)	
		# of Subj	# of Dev	# of Subj	# of Dev	# of Subj	# of Dev	# of Subj	# of Dev	# of Subj	# of Dev	# of Subj	# of Dev	# of Subj	# of Dev	# of Subj	# of Dev	# of Subj	# of Dev
Eligibility/ randomization	Any type	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Did not meet inclusion criterion	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Met exclusion criterion	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	ICF not signed prior to study procedures	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Treatment administration schedule	Any type	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Out of window visit	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Missed visit/visit not conducted	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Missed treatment administration	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Delayed treatment administration	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Follow-up visit schedule	Any type	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Out of window visit	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Missed visit/visit not conducted	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Protocol procedure/ assessment	Any type	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Incorrect version of ICF signed	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Category	Deviation Type	Interferon beta-1a + RDV (N=X)						Placebo + RDV (N=X)						All Subjects (N=X)					
		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)	
		# of Subj	# of Dev	# of Subj	# of Dev	# of Subj	# of Dev	# of Subj	# of Dev	# of Subj	# of Dev	# of Subj	# of Dev	# of Subj	# of Dev	# of Subj	# of Dev	# of Subj	# of Dev
	Blood not collected	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Oropharyngeal swab not collected	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Other specimen not collected	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Specimen result not obtained	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Required procedure not conducted	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Required procedure done incorrectly	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Study product temperature excursion	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Specimen temperature excursion	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Stratification error	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Treatment administration	Any type	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Required procedure done incorrectly	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Study product temperature excursion	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Blinding policy/procedure	Any type	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Treatment unblinded	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
N = number of subjects randomized																			

Table with similar format:

Table 9: Distribution of Major Subject Specific Protocol Deviations by Category, Type, Treatment Group, and Baseline Ordinal Score – mITT Population

Table 10: Time to Recovery by Treatment Group and Baseline Ordinal Score

Analysis Population	Treatment Group	Baseline Ordinal Score	n	First Quartile Time to Recovery (Days)		Median Time to Recovery (Days)		Third Quartile Time to Recovery (Days)		HR		P-value
				Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	
mITT Population	**Interferon beta-1a + RDV (N=X)**	**4**	x	x.x	x.x, x.x	x.x	x.x, x.x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo + RDV (N=X)		x	x.x	x.x, x.x	x.x	x.x, x.x	x.x	x.x, x.x			
	Interferon beta-1a + RDV (N=X)	**5**	x	x.x	x.x, x.x	x.x	x.x, x.x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo + RDV (N=X)		x	x.x	x.x, x.x	x.x	x.x, x.x	x.x	x.x, x.x			
	Interferon beta-1a + RDV (N=X)	**6**	x	x.x	x.x, x.x	x.x	x.x, x.x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo + RDV (N=X)		x	x.x	x.x, x.x	x.x	x.x, x.x	x.x	x.x, x.x			
	Interferon beta-1a + RDV (N=X)	**Any Baseline Ordinal Score**	x	x.x	x.x, x.x	x.x	x.x, x.x	x.x	x.x, x.x	x.xx	x.xx, x.xx	0.xxx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x	x.x	x.x, x.x	x.x	x.x, x.x			
	Interferon beta-1a + RDV (N=X)	**Any Baseline Ordinal Score (4 or 5)**	x	x.x	x.x, x.x	x.x	x.x, x.x	x.x	x.x, x.x	x.xx	x.xx, x.xx	0.xxx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x	x.x	x.x, x.x	x.x	x.x, x.x			
Repeat for the As Treated Population and ITT Population.												

N= Number of subjects in the specified treatment group, baseline ordinal score, and analysis population.
n = Number of recovered subjects.
HR is the ratio of the hazard of recovery in each treatment group estimated from the Cox model. The ratio is Interferon beta-1a + RDV to Placebo + RDV.
HR for the 'Any Baseline Ordinal Score' group is the hazard ratio from the stratified Cox Model.
P-value calculated using the stratified log-rank test

Programming Notes:

The p-value for the stratified log-rank test in the (4 or 5) subgroup will only be reported if the p-value for the "Any Severity" analysis is significant (see Section 6.8).

Table with similar format:

Table 11: Time to Recovery by Treatment Group and Baseline Modified Oxygen Use Ordinal Score

Programming Note:

The table will include the footnote: This analysis used a modified version of the ordinal scale where the definitions of categories 5 and 6 are, respectively, “Hospitalized, requiring supplemental oxygen or high flow oxygen devices at oxygen flow rate less than or equal to 15L/min” and “Hospitalized, on non-invasive ventilation or high flow oxygen devices at oxygen flow rate greater than 15L/min”.

Table 12: Time to Recovery by Treatment Group and Baseline Ordinal Score: Sensitivity and Exploratory Analyses – mITT Population

Model	Treatment Group	Baseline Ordinal Score	HR		Interaction P-value[a]
			Estimate	95% CI	
Fine-Gray	**Interferon beta-1a + RDV (N=X)**	**4**	x.xx	x.xx, x.xx	--
	Placebo + RDV (N=X)				
	Interferon beta-1a + RDV (N=X)	**5**	x.xx	x.xx, x.xx	--
	Placebo + RDV (N=X)				
	Interferon beta-1a + RDV (N=X)	**Any Baseline Ordinal Score (4 or 5)**	x.xx	x.xx, x.xx	--
	Placebo + RDV (N=X)				
Covariate-Adjusted	**Interferon beta-1a + RDV (N=X)**	**Any Baseline Ordinal Score (4 or 5)**	x.xx	x.xx, x.xx	0.xxx
	Placebo + RDV (N=X)		x.xx	x.xx, x.xx	
Treatment Arm-Baseline Ordinal Score Interaction	**Interferon beta-1a + RDV (N=X)**	**4 or 5**	x.xx	x.xx, x.xx	0.xxx
	Placebo + RDV (N=X)				
	Interferon beta-1a + RDV (N=X)	**6**	x.xx	x.xx, x.xx	
	Placebo + RDV (N=X)				
Treatment Arm-Continuous Baseline Ordinal Score Interaction	**Interferon beta-1a + RDV (N=X)**	**4**	x.xx	x.xx, x.xx	0.xxx
	Placebo + RDV (N=X)				
	Interferon beta-1a + RDV (N=X)	**5**	x.xx	x.xx, x.xx	
	Placebo + RDV (N=X)				
	Interferon beta-1a + RDV (N=X)	**6**	x.xx	x.xx, x.xx	
	Placebo + RDV (N=X)				
Treatment Arm-Categorical Baseline Ordinal Score Interaction	**Interferon beta-1a + RDV (N=X)**	**4**	x.xx	x.xx, x.xx	0.xxx
	Placebo + RDV (N=X)				
	Interferon beta-1a + RDV (N=X)	**5**	x.xx	x.xx, x.xx	
	Placebo + RDV (N=X)				
	Interferon beta-1a + RDV (N=X)	**6**	x.xx	x.xx, x.xx	
	Placebo + RDV (N=X)				

HR is the ratio of the hazard of recovery in each treatment group estimated from the indicated model. The ratio is Interferon beta-1a + RDV to Placebo + RDV.
HR for the 'Any Baseline Ordinal Score' group is the hazard ratio from the stratified Cox Model.
For the Fine-Gray model, subjects who die prior to any observed recovery as coded as experiencing a competing risk.
Covariate adjustment is by age, duration of symptoms prior to randomization, baseline d-dimer, and baseline CRP values as continuous covariates. This analysis is restricted to subjects with a baseline ordinal score of 4 or 5. High-sensitivity CRP values are excluded from this analysis.
Estimates are HR and CIs from Fine-Gray or interaction Cox models. For the interaction models, HRs are calculated at the level of each individual OS category.
a: P-values are from the likelihood ratio test.

Programming Notes:

For the “Treatment Arm-Baseline Ordinal Score Interaction”, the severity covariate will be treated as a categorical variable.

Tables with similar format as Table 12:

Table 13: Time to Recovery by Treatment Group within Subgroups – mITT Population, Baseline Ordinal Score of 4 or 5

Table 14: Time to Recovery by Treatment Group and Baseline Ordinal Score: Readmittance Sensitivity Analysis – mITT Population, Baseline Ordinal Score of 4 or 5

Table 15: Time to Recovery by Treatment Group and Baseline Ordinal Score: Medications of Interest Sensitivity Analysis – mITT Population, Baseline Ordinal Score of 4 or 5

Programming Notes for Table 13:

This table is restricted to subjects with a baseline ordinal score of 4 or 5. The "Disease Severity" and "Analysis Population" columns will be removed. A "Subgroup" column will be inserted to the left of the "Treatment Group" column. This table will not display the "Any…" rows. The elements for the "n" and "Median Time to Recovery" columns will display "-". This table will include the statin/ARB/AECI use, corticosteroid use, and dexamethasone use (see Section 6.4) subgroups. P-values will not be included in this table. Disease severity subgroups will not be included in this table.

Programming Notes for Table 14 and Table 15:

These tables are restricted to subjects with a baseline ordinal score of 4 or 5. P-values will not be included in these tables.

Table 14 will include a column to the left of the "n" column titled "m". The corresponding footnote will read "m = Number of subjects readmitted for COVID-19." Table will include the following footnote: "In this analysis, subjects that recover and are subsequently readmitted for COVID-19 are censored at 28 days".

Table 15 will include a column to the left of the "n" column titled "m". The corresponding footnote will read "m = Number of subjects reporting use of a medication of interest." The "Analysis Population" column will be replaced by a column labeled "Medication of Interest". Separate models will be fit for the following categories of medications (see Section 6.4):

- Any Medication of Interest
- Hydroxychloroquine/Chloroquine
- Corticosteroids
- Anti-Inflammatory Drugs

Include a footnote for "Any Medication of Interest" noting that this excludes statins, ARBs, and AECIs. The table will include the following footnote: "In this analysis, subjects that reported use of the specified medications of interest are censored at time of medication receipt."

Table 16: Time to Recovery by Treatment Group and Baseline Ordinal Score: Restricted Mean Survival Time Analysis

Analysis Population	Treatment Group	Baseline Ordinal Score	n	Restricted Mean Recovery Time		Difference	
				Estimate	95% CI	Estimate	95% CI
mITT Population	**Interferon beta-1a + RDV (N=X)**	**4**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x		
	Interferon beta-1a + RDV (N=X)	**5**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x		
	Interferon beta-1a + RDV (N=X)	**6**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x		
	Interferon beta-1a + RDV (N=X)	**Any Baseline Ordinal Score**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x		
	Interferon beta-1a + RDV (N=X)	**Any Baseline Ordinal Score (4 or 5)**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x		
Repeat for the As Treated Population.							

N= Number of subjects in the specified treatment group, baseline ordinal score, and analysis population.
n = Number of recovered subjects.
Difference is the difference in the restricted mean recovery time between Interferon beta-1a + RDV and Placebo + RDV.

Programming Notes:

Within an OS stratum:

```
proc lifetest data=enrevent plots=(rmst) method=breslow rmst(cl);
by stratum;
time evntday * Censor(1);
strata trtcode /diff=all;
ods output  rmst=rmst;
run;
```

Stratified by Baseline Ordinal Score (“Any Baseline Ordinal Score” row).

```
proc lifetest data=enrevent plots=(rmst) method=breslow rmst(cl);
time evntday * Censor(1);
strata trtcode CRSEVERE /diff=all;
ods output  rmst=rmst;
run;
```

Table 17: Summary of Recoveries and Deaths by Day 29 – mITT Population

Grouping Variable	Baseline Ordinal Score	Treatment Group	Recovered		Did Not Recover		Deaths		Not Recovered or Died	
			n	%	n	%	n	%	n	%
Baseline Ordinal Score	4	Interferon beta-1a + RDV (N=X)	x	x	x	x	x	x	x	x
		Placebo + RDV (N=X)	x	x	x	x	x	x	x	x
	5	Interferon beta-1a + RDV (N=X)	x	x	x	x	x	x	x	x
		Placebo + RDV (N=X)	x	x	x	x	x	x	x	x
	6	Interferon beta-1a + RDV (N=X)	x	x	x	x	x	x	x	x
		Placebo + RDV (N=X)	x	x	x	x	x	x	x	x
	Any Baseline Ordinal Score	Interferon beta-1a + RDV (N=X)	x	x	x	x	x	x	x	x
		Placebo + RDV (N=X)	x	x	x	x	x	x	x	x
	Any Baseline Ordinal Score (4 or 5)	Interferon beta-1a + RDV (N=X)	x	x	x	x	x	x	x	x
		Placebo + RDV (N=X)	x	x	x	x	x	x	x	x
Repeat for Modified Oxygen Use ordinal scale (Section 4.3) and duration of symptoms categories in Section 6.4										
N= Number of subjects in the mITT Population.										

Programming Note: For the categories of "Recovered", "Did Not Recover" and "Deaths", subjects who recover but subsequently die will be classified under "Recovered" and "Deaths". If there are cases of this, a footnote will be added that states "Counts of recoveries and deaths include X subjects who recovered but subsequently died."

Table 18: Odds Ratio for Better (Lower) Clinical Status Score at Study Visit Day 15 by Treatment Using a Proportional Odds Model, Interferon beta-1a + RDV Relative to Placebo + RDV – mITT Population

Analysis/Subgroup	Treatment Group	Odds Ratio		P-value
		Estimate	95% CI	
Main Analysis of Key Secondary Endpoint				
Analysis of Key Secondary Endpoint[a]	Interferon beta-1a + RDV (N=X)			
	Placebo + RDV (N=X)	x.xx	x.xx, x.xx	0.xxx
Analysis of Key Secondary Endpoint using Modified Oxygen Use Scale				
Analysis of Key Secondary Endpoint[b]	Interferon beta-1a + RDV (N=X)			
	Placebo + RDV (N=X)	x.xx	x.xx, x.xx	--
Subgroup Analyses of Key Secondary Endpoint[c]				
[Repeat for each Section 6.4 subgroups]	Interferon beta-1a + RDV (N=X)			
	Placebo + RDV (N=X)	x.xx	x.xx, x.xx	--
Medications of Interest Subgroup Analyses[c]				
Any Medication of Interest[d]	Interferon beta-1a + RDV (N=X)			
	Placebo + RDV (N=X)	x.xx	x.xx, x.xx	--
Hydroxychloroquine/Chloroquine	Interferon beta-1a + RDV (N=X)			
	Placebo + RDV (N=X)	x.xx	x.xx, x.xx	--
Corticosteroids	Interferon beta-1a + RDV (N=X)			
	Placebo + RDV (N=X)	x.xx	x.xx, x.xx	--
Anti-Inflammatory Drugs	Interferon beta-1a + RDV (N=X)			
	Placebo + RDV (N=X)	x.xx	x.xx, x.xx	--
Covariate-Adjusted Model[c]				
Covariate-Adjusted	Interferon beta-1a + RDV (N=X)			
	Placebo + RDV (N=X)	x.xx	x.xx, x.xx	--
Interaction Models				
Treatment-Baseline Ordinal Score Interaction (4 or 5 vs. 6)	Interferon beta-1a + RDV (N=X)			
	Placebo + RDV (N=X)	x.xx	x.xx, x.xx	--
Treatment-Continuous Baseline Ordinal Score (4 or 5) Interaction	Interferon beta-1a + RDV (N=X)	x.xx	x.xx, x.xx	
	Placebo + RDV (N=X)	x.xx	x.xx, x.xx	--
Treatment-Categorical Baseline Ordinal Score (4 or 5) Interaction	Interferon beta-1a + RDV (N=X)	x.xx	x.xx, x.xx	
	Placebo + RDV (N=X)	x.xx	x.xx, x.xx	--

[a]Analysis of key secondary endpoint using those subjects in the mITT Population with baseline ordinal score (actual score) of 4 or 5 with disease severity as a model covariate.
[b]This analysis used a modified version of the ordinal scale where the definitions of categories 5 and 6 are, respectively, "Hospitalized, requiring supplemental oxygen or high flow oxygen devices at oxygen flow rate less than or equal to 15L/min" and "Hospitalized, on non-invasive ventilation or high flow oxygen devices at oxygen flow rate greater than 15L/min".
[c]Restricted to subjects with baseline ordinal score of 4 or 5.
[d]Excluding statins, ARBs, and AECIs.
Odds ratios for interaction models are calculated at the level of each individual OS category.

Programming Notes:

For the Main Analysis, the p-value will only be reported if the p-value from the primary analysis of time to recovery (including all three OS strata) is significant. If the p-value will not be reported, then the columns will be removed.

Apart from the "Treatment-Baseline Ordinal Score Interaction (4 or 5 vs. 6)" model, all analyses will be restricted to subjects with a baseline ordinal score of 4 or 5.

P-value of treatment comparison will only be displayed for the main analysis. For the interaction models, the p-value for the interaction term will be provided in a footnote reading "The p-value for the treatment by baseline ordinal score interaction term was 0.xxx." or "The p-value for the treatment by [continuous/categorical] baseline ordinal score interaction term was 0.xxx.".

For the covariate-adjusted model, the model will be run with age, duration of symptoms prior to randomization, baseline d-dimer, and baseline CRP values included as continuous covariates. High sensitivity CRP values are excluded from this analysis (denote this in a footnote).

Table with similar format:

Table 19: Odds Ratio for Better (Lower) Clinical Status Score at Study Visit Day 15 by Treatment Using a Proportional Odds Model, Interferon beta-1a + RDV Relative to Placebo + RDV – As Treated Population

Programming Note: P-value of treatment comparison will only be displayed for the main analysis. For the interaction models, the p-value for the interaction term will be provided in a footnote reading "The p-value for the treatment by baseline ordinal score interaction term was 0.xxx." or "The p-value for the treatment by [continuous/categorical] baseline ordinal score interaction term was 0.xxx.".

Table 20: Time to Improvement on the 8-Point Ordinal Scale by Treatment Group

Analysis Population	Baseline Ordinal Score	Treatment Group		Median Time		HR	
			n	Estimate	95% CI	Estimate	95% CI
Improvement by at least One Category							
mITT Population	**4 or 5**	**Interferon beta-1a + RDV (N=X)**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
		Placebo + RDV (N=X)	x	x.x	x.x, x.x		
As Treated Population	**4 or 5**	**Interferon beta-1a + RDV (N=X)**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
		Placebo + RDV (N=X)	x	x.x	x.x, x.x		
mITT Population	**6**	**Interferon beta-1a + RDV (N=X)**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
		Placebo + RDV (N=X)	x	x.x	x.x, x.x		
As Treated Population	**6**	**Interferon beta-1a + RDV (N=X)**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
		Placebo + RDV (N=X)	x	x.x	x.x, x.x		
Improvement by at least Two Categories							
mITT Population	**4 or 5**	**Interferon beta-1a + RDV (N=X)**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
		Placebo + RDV (N=X)	x	x.x	x.x, x.x		
As Treated Population	**4 or 5**	**Interferon beta-1a + RDV (N=X)**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
		Placebo + RDV (N=X)	x	x.x	x.x, x.x		
mITT Population	**6**	**Interferon beta-1a + RDV (N=X)**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
		Placebo + RDV (N=X)	x	x.x	x.x, x.x		
As Treated Population	**6**	**Interferon beta-1a + RDV (N=X)**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
		Placebo + RDV (N=X)	x	x.x	x.x, x.x		

N = Number of subjects in the specified treatment group, analysis population, and baseline ordinal score group.
n = Number of subjects with improvement.
HR is the ratio of the hazard of improvement in each treatment group estimated from the Cox model. The ratio is Interferon beta-1a + RDV to Placebo + RDV.

Tables with similar format:

Table 21: Time to Improvement on the 8-Point Ordinal Scale by Treatment Group: Modified Recovery Ordinal Scale

Table 22: Time to Improvement on the 8-Point Ordinal Scale by Treatment Group and Duration of Symptoms at Baseline – mITT Population

Programming notes for Table 21:

The table will include the footnote: This analysis used a modified version of the ordinal scale where the categories “Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care” and “Not hospitalized, no limitations on activities” were classified together and given a score of 2 while the category “Not hospitalized, but new or increased limitation on activities and/or requiring new or increased home oxygen” was given the score 3.”

Programming notes for Table 22:

The "Analysis Population" column will be re-labeled "Duration of Symptoms at Baseline". The "Baseline Ordinal Score" column will be removed. Rows will be generated for each subgroup defined by duration above/below the median. Only subjects with baseline ordinal score 4 or 5 will be included in the table. The footnote for "N" will read "N = Number of subjects in the specified treatment group and analysis population with a baseline ordinal score of 4 or 5."

Table 23: Clinical Status Scores by Treatment Group and Study Visit – mITT Population, Baseline Ordinal Score of 4 or 5

Study Visit	Ordinal Scale Measure	Interferon beta-1a + RDV (N=X)			Placebo + RDV (N=X)			Risk Difference	
		n	%	95% CI	n	%	95% CI	%	95% CI
Day 1	Death at or before Study Visit (8)	x	x	x.x, x.x	x	x	x.x, x.x	x.x	x.x, x.x
	Hospitalized, on invasive mechanical ventilation or ECMO (7)	x	x	x.x, x.x	x	x	x.x, x.x	x.x	x.x, x.x
	Hospitalized, on non-invasive ventilation or high flow oxygen devices (6)	x	x	x.x, x.x	x	x	x.x, x.x	x.x	x.x, x.x
	Hospitalized, requiring supplemental oxygen (5)	x	x	x.x, x.x	x	x	x.x, x.x	x.x	x.x, x.x
	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise) (4)	x	x	x.x, x.x	x	x	x.x, x.x	x.x	x.x, x.x
	Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (3)	x	x	x.x, x.x	x	x	x.x, x.x	x.x	x.x, x.x
	Not hospitalized, but new or increased limitation on activities and/or requiring new or increased home oxygen (2)	x	x	x.x, x.x	x	x	x.x, x.x	x.x	x.x, x.x
	Not hospitalized, no limitations on activities (1)	x	x	x.x, x.x	x	x	x.x, x.x	x.x	x.x, x.x
[Repeat for Study Visit Days 3, 5, 8, 11, 15, 22, and 29]									

N = Number of Subject in the mITT Population.
n = Number of subjects who reported the respective score
95% CI calculated using Wilson CIs

Tables with similar format:

Table 24: Clinical Status Scores by Treatment Group and Study Visit – mITT Population, Baseline Ordinal Score of 6

Table 25: Clinical Status Scores by Treatment Group and Study Visit – mITT Population, Baseline Modified Oxygen Use Ordinal Score of 4 or 5

Table 26: Clinical Status Scores by Treatment Group and Study Visit – mITT Population, Baseline Modified Oxygen Use Ordinal Score of 6

Programming notes for Table 25 and Table 26:

The tables will include the footnote: This analysis used a modified version of the ordinal scale where the definitions of categories 5 and 6 are, respectively, “Hospitalized, requiring supplemental oxygen or high flow oxygen devices at oxygen flow rate less than or equal to 15L/min” and “Hospitalized, on non-invasive ventilation or high flow oxygen devices at oxygen flow rate greater than 15L/min”.

Table 27: Summary of Clinical Status Score by Treatment Group and Study Visit – mITT Population, Baseline Ordinal Score of 4 or 5

Study Visit	Statistic	Interferon beta-1a + RDV (N=X)	Placebo + RDV (N=X)	Difference
Baseline	Number of reported clinical scores	x	x	--
	Mean (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)	x.x (x.x, x.x)
	Median	x.x	x.x	x.x (x.x, x.x)
	Range (Min, Max)	x, x	x, x	--
Day 3	Number of reported clinical scores	x	x	--
	Mean (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)	x.x (x.x, x.x)
	Median	x.x	x.x	x.x (x.x, x.x)
	Range (Min, Max)	x, x	x, x	--
	Change from Baseline Mean (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)	--
Continue for Days 5, 8, 11, 15, 22, 29				

N = Number of subjects in the mITT Population.
Missing values were imputed using Last Observation Carried Forward. Clinical scores of 8 were carried forward from the date of death for subjects who died.

Table with similar format:

Table 28: Summary of Clinical Status Score by Treatment Group and Study Visit – mITT Population, Baseline Ordinal Score of 6

Table 29: Time to Discharge or to a NEWS of ≤ 2 by Treatment Group – Baseline Ordinal Score of 4 or 5

Analysis Population	Treatment Group	m	n	First Quartile Time (Days)		Median Time (Days)		Third Quartile Time (Days)		HR	
				Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
mITT Population	**Interferon beta-1a + RDV (N=X)**	x	x	x.x	x.x, x.x	x.x	x.x, x.x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)	x	x	x.x	x.x, x.x	x.x	x.x, x.x	x.x	x.x, x.x		
As Treated Population	**Interferon beta-1a + RDV (N=X)**	x	x	x.x	x.x, x.x	x.x	x.x, x.x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)	x	x	x.x	x.x, x.x	x.x	x.x, x.x	x.x	x.x, x.x		

N= Number of subjects in the specified treatment group and analysis population.
m = Number of subjects had a NEWS of ≤ 2 at baseline.
n = Number of subjects who discharged or had a NEWS of ≤ 2 prior to Day 29.
HR is the ratio of the hazard of discharge or NEWS of ≤ 2 in each treatment group estimated from the Cox model. The ratio is Interferon beta-1a + RDV to Placebo + RDV.

Table with similar format:

Table 30: Time to Discharge or to a NEWS of ≤ 2 by Treatment Group – Baseline Ordinal Score of 6

Table 31: Summary of NEWS by Treatment Group and Study Visit – mITT Population, Baseline Ordinal Score of 4 or 5

Study Visit	Statistic	Interferon beta-1a + RDV (N=X)	Placebo + RDV (N=X)	Difference
Baseline	n	x	x	--
	Mean (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)	x.x (x.x, x.x)
	Median	x.x	x.x	x.x (x.x, x.x)
	Range (Min, Max)	x, x	x, x	--
Day 3	n	x	x	--
	Mean (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)	x.x (x.x, x.x)
	Median	x.x	x.x	x.x (x.x, x.x)
	Range (Min, Max)	x, x	x, x	--
	n[a]	x	x	--
	Change from Baseline Mean (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)	x.x (x.x, x.x)
[Repeat for Study Visit Days 5, 8, 11, 15, 22, 29 and Change from Baseline at each]				

n = Number of subjects with an assessment at both baseline and the time point being summarized.
n[a] = Number of subjects with an assessment at both baseline and the time point being summarized.

Programming Notes:

Use imputed NEWS scores as defined in Section 6.5.

Table with similar format:

Table 32: Summary of NEWS by Treatment Group and Study Visit – mITT Population, Baseline Ordinal Score of 6

Table 33: Oxygen Use by Treatment Group – Baseline Ordinal Score of 4 or 5

Analysis Population	Oxygen Use	Statistic	Treatment Group	
			Interferon beta-1a + RDV	Placebo + RDV
mITT Population	**On Oxygen at Baseline (N = x)**			
	Days on Oxygen (Including imputations for subjects who died)[a]	N	x	x
		Q1	x.x	x.x
		Median	x.x	x.x
		Q3	x.x	x.x
		Difference in Medians (95% CI)	x.x (x.x, x.x)	
	Days of Oxygen (Among subjects who did not die)	N	x	x
		Q1	x.x	x.x
		Median	x.x	x.x
		Q3	x.x	x.x
		Difference in Medians (95% CI)	x.x (x.x, x.x)	
	Not on Oxygen at Baseline (N = x)			
	New Oxygen Use	N	x	x
		n	x	x
		Incidence Rate	x.x	x.x
		Incidence Rate 95% CI	x.x, x.x	x.x, x.x
		Difference in Rates (95% CI)	x.x (x.x, x.x)	
	Days on Oxygen (Including imputations for subjects who died)[a]	N	x	x
		Q1	x.x	x.x
		Median	x.x	x.x
		Q3	x.x	x.x
		Difference in Medians (95% CI)	x.x (x.x, x.x)	
	Days of Oxygen (Among subjects who did not die)	N	x	x
		Q1	x.x	x.x
		Median	x.x	x.x
		Q3	x.x	x.x
		Difference in Medians (95% CI)	x.x (x.x, x.x)	
Repeat for As Treated Population.				

N = Number of subjects in the specified analysis population and oxygen use category.
Q1 and Q3 are the first and third quartiles, respectively.
Refer to Section 11.4.2.2 of the Clinical Study Report for details regarding imputations.
[a]Subjects who died were imputed as 28 days.

Programming Note: For the "Days on Oxygen" statistics within the "Not on Oxygen at Baseline" subgroup, only summarize days for subjects who reported new use.

Tables with similar format:

Table 34: Oxygen Use by Treatment Group – Baseline Ordinal Score of 6

Table 35: Oxygen Use by Treatment Group and Duration of Symptoms at Baseline – Baseline Ordinal Score of 4 or 5

Table 36: Non-invasive Ventilation/High-Flow Oxygen Use by Treatment Group – Baseline Ordinal Score of 4 or 5

Table 37: Non-invasive Ventilation/High-Flow Oxygen Use by Treatment Group – Baseline Ordinal Score of 6

Table 38: Non-invasive Ventilation/High-Flow Oxygen Use by Treatment Group and Duration of Symptoms at Baseline – Baseline Ordinal Score of 4 or 5

Table 39: Ventilation/ECMO Use by Treatment Group – Baseline Ordinal Score of 4 or 5

Table 40: Ventilation/ECMO Use by Treatment Group – Baseline Ordinal Score of 6

Table 41: Ventilation/ECMO Use by Treatment Group and Duration of Symptoms at Baseline – Baseline Ordinal Score of 4 or 5

Programming notes for Table 35, Table 38, and Table 41:

"Analysis Population" will be replaced by "Duration of Symptoms at Baseline" column. The tables will consider the duration above/below median subgroup. Summaries will only be generated for mITT population.

Programming notes for Table 39, Table 40, Table 41:

The "On Ventilation/ECMO at Baseline" section of the table will not be generated.

Programming notes for Table 34 and Table 37:

The "New Use" section of the table will not be generated.

Programming notes for Table 38:

The "On Non-Invasive Ventilation/High-Flow Oxygen at Baseline" section of the table will not be generated.

Table 42: Hospitalization by Treatment Group – Baseline Ordinal Score of 4 or 5

Analysis Population	Summary	Statistic	Treatment Group	
			Interferon beta-1a + RDV	Placebo + RDV
mITT Population	Days of Hospitalization (including imputation for subjects who died)[a]	N	x	x
		Q1	x.x	x.x
		Median	x.x	x.x
		Q3	x.x	x.x
		Difference in Medians (95% CI)	x.x (x.x, x.x)	
	Days of Hospitalization (among subjects who did not die)	N	x	x
		Q1	x	x
		Median	x	x
		Q3	x.x, x.x	x.x, x.x
		Difference in Medians (95% CI)	x.x (x.x, x.x)	
	Readmittance	N	x	x
		n	x	x
		Percentage	x	x
		Percentage 95% CI	x.x, x.x	x.x, x.x
		Difference in Rates (95% CI)	x.x (x.x, x.x)	
Continue for As Treated Population….				

N = Number of subjects in the specified analysis population.
Q1 and Q3 are the first and third quartiles, respectively.
Denominator of readmittance percentages is the number of subjects in the specific analysis population.
[a]Subjects who died were imputed as 28 days.

Tables with similar format:

Table 43: Hospitalization by Treatment Group – Baseline Ordinal Score of 6

Table 44: Hospitalization by Treatment Group and Duration of Symptoms at Baseline – Baseline Ordinal Score of 4 or 5

Programming Note for Table 41: "Analysis Population" will be replaced by "Duration of Symptoms at Baseline" column. The table will consider the duration above/below median subgroup. Summaries will only be generated for mITT population

Table 45: Summary Statistics of Laboratory Efficacy Results by Study Visit Day, and Treatment Group – mITT Population, Baseline Ordinal Score of 4 or 5

Laboratory Parameter	Study Visit Day	Treatment Group	Absolute					Change from Baseline				
			N	Mean	95% CI	Median	Min, Max	N	Mean	95% CI	Median	Min, Max
d-dimer	Baseline	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	---	---	---	---	---
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	---	---	---	---	---
	Day 3	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
	Day 5	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
	Day 8	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
	Day 11	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
	Day 15	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
	Day 29	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x

Laboratory Parameter	Study Visit Day	Treatment Group	Absolute					Change from Baseline				
			N	Mean	95% CI	Median	Min, Max	N	Mean	95% CI	Median	Min, Max
CRP	Baseline	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	---	---	---	---	---
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	---	---	---	---	---
	Day 3	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
	Day 5	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
	Day 8	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
	Day 11	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
	Day 15	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
	Day 29	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
Continue for all parameters…												

N = Number of subjects in the As Treated Population with laboratory data available for the parameter at the specified study visit.
High-sensitivity CRP values are excluded from the summaries.

Table with similar format:

Table 46: Summary Statistics of Laboratory Efficacy Results by Parameter, Study Visit Day, and Treatment Group – mITT Population, Baseline Ordinal Score of 6

Programming notes for Table 45 and Table 46:

Use imputed results for missing data, see Section 6.5.

Table 47: Categorical Demographic and Baseline Characteristics by Baseline Ordinal Score and Treatment Group – mITT Population

Demographic Category	Characteristic	Interferon beta-1a + RDV								Placebo + RDV								All Subjects							
		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		All Subjects (N=X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		All Subjects (N=X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sex	Male	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Female	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ethnicity	Not Hispanic or Latino	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Hispanic or Latino	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Not Reported	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Race	American Indian or Alaska Native	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Asian	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Native Hawaiian or Other Pacific Islander	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Black or African American	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	White	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Multi-Racial	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Geographic Region	Region 1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	…Continue for all region categorizations	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Country	Country 1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	…Continue for all countries	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Age	< 40	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	40-64	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	>=65	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood Type	A+	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Demographic Category	Characteristic	Interferon beta-1a + RDV								Placebo + RDV								All Subjects							
		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		All Subjects (N=X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		All Subjects (N=X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	A-	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	…Continue for all blood types	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Duration of Symptoms prior to randomization	Categorization 1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	…Continue for all symptom categorizations	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Comorbidities	Comorbidity 1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Comorbidity 2	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	…Continue for all comorbidities	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Comorbidities Group X	…Continue for all comorbidity categorizations	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Chronic Pulmonary Disease	Yes	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	No	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pre-COVID-19 Use of Supplemental Oxygen	Yes	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	No	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 48: Continuous Demographic and Baseline Characteristics by Baseline Ordinal Score and Treatment Group – mITT Population

Variable	Statistic	Interferon beta-1a + RDV				Placebo + RDV				All Subjects			
		Baseline OS 4 (N=X)	Baseline OS 5 (N=X)	Baseline OS 6 (N=X)	All Subjects (N=X)	Baseline OS 4 (N=X)	Baseline OS 5 (N=X)	Baseline OS 6 (N=X)	All Subjects (N=X)	Baseline OS 4 (N=X)	Baseline OS 5 (N=X)	Baseline OS 6 (N=X)	All Subjects (N=X)
Age (years)	Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	IQR	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x	x	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x	x	x	x	x	x
Height (cm)	Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	IQR	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x	x	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x	x	x	x	x	x
Weight (Kg)	Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	IQR	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x	x	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x	x	x	x	x	x
BMI	Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	IQR	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x	x	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x	x	x	x	x	x

Variable	Statistic	Interferon beta-1a + RDV				Placebo + RDV				All Subjects			
		Baseline OS 4 (N=X)	**Baseline OS 5 (N=X)**	**Baseline OS 6 (N=X)**	**All Subjects (N=X)**	**Baseline OS 4 (N=X)**	**Baseline OS 5 (N=X)**	**Baseline OS 6 (N=X)**	**All Subjects (N=X)**	**Baseline OS 4 (N=X)**	**Baseline OS 5 (N=X)**	**Baseline OS 6 (N=X)**	**All Subjects (N=X)**
Duration of Symptoms prior to Randomization (Days)	Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	IQR	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x	x	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x	x	x	x	x	x

Table 49: Summary of Subjects with Pre-Existing Medical Conditions Treatment Group - As Treated Population

Condition	Interferon beta-1a + RDV (N=X)								Placebo + RDV (N=X)								All Subjects (N=X)							
	Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		All Subjects (N = X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		All Subjects (N = X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		All Subjects (N = X)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Any Condition	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Diabetes I	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Diabetes II	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
…continue for all solicited conditions…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…

N = Number of subjects in the As Treated Population;

n = Number of subjects reporting the condition. Subjects who report 'unknown' for a condition are assumed to not have the condition.

Programming Note: "None" and "Any Condition" will be the first two rows. The remainder of the rows will be sorted in order of prevalence, with the condition most reported among All Subjects being displayed first.

Table 50: Number and Percentage of Subjects with Prior and Concurrent Medications by WHO Drug Classification, Baseline Ordinal Score, and Treatment Group – As Treated Population

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	Interferon beta-1a + RDV (N=X)								Placebo + RDV (N=X)								All Subjects (N=X)							
		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		All Subjects (N = X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		All Subjects (N = X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		All Subjects (N = X)	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
[ATC Level 1 - 1]	Any [ATC 1 – 1]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[ATC 2 - 1]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[ATC 2 - 2]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[ATC 2 - 3]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
[ATC Level 1 – 2]	[ATC 2 - 1]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[ATC 2 - 2]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[ATC 2 - 3]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx

N = Number of subjects in the As Treated Population.
N = Number of subjects reporting taking at least one medication in the specified WHO Drug Class.

Programming Note: Only include medications with missing end dates (i.e., ongoing) or end dates on or after the enrollment date.

Table 51: Number and Percentage of Subjects Reporting On-Study Use of Statins/ARBs/AECIs and Medications of Interest by Baseline Ordinal Score, and Treatment Group – As Treated Population

Medication/Therapies	Interferon beta-1a + RDV (N=X)								Placebo + RDV (N=X)								All Subjects (N=X)							
	Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		All Subjects (N=X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		All Subjects (N=X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Statins/ARBs/AECIs	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Protease inhibitors	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Polymerase inhibitors	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Potential Treatments for COVID-19	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Chloroquine/Hydroxychloroquine	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Other	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Corticosteroids	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Other anti-inflammatory drugs	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Monoclonal Antibodies Targeting Cytokines	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Other Biologic Therapies	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx

N = Number of subjects in the As Treated Population.

n=Number of subjects reporting taking at least one medication in the specified category.

Programming Note: only include medications where the end date is missing (i.e., ongoing) or end date is on or after enrollment date

Table 52: On-Study Use of Statins/ARBs/AECIs and Medications of Interest by Study Day, Baseline Ordinal Score, and Treatment Group – As Treated Population

Study Day	Interferon beta-1a + RDV (N=X)								Placebo + RDV (N=X)								All Subjects (N=X)							
	Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		All Subjects (N=X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		All Subjects (N=X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Statins/ARBs/AECIs																								
Day 1	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Day 3	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Day 5	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Day 8	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Day 11	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
…Repeat for all categories and sub-categories of the medications in Section 6.4																								
N = Number of subjects in the As Treated Population. n=Number of subjects reporting taking at least one prohibited medication by the specified study day.																								

Programming Note: If the start date of the prohibited medication is on or before the specified (actual) study day, then the subject will be denoted as taking the med for that Study Day.

Table 53: Overall Summary of Adverse Events – As Treated Population

Subjects[a] with	Interferon beta-1a + RDV (N=X)						Placebo + RDV (N=X)					
	Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)	
	n	%	n	%	n	%	n	%	n	%	n	%
At least one adverse event (serious or non-serious)	x	x	x	x	x	x	x	x	x	x	x	x
At least one Severe or Life-threatening (Grade 3 or 4) adverse event (serious or non-serious)	x	x	x	x	x	x	x	x	x	x	x	x
At least one related adverse event (serious or non-serious)	x	x	x	x	x	x	x	x	x	x	x	x
Moderate (Grade 2)	x	x	x	x	x	x	x	x	x	x	x	x
Severe (Grade 3)	x	x	x	x	x	x	x	x	x	x	x	x
Life-threatening (Grade 4)	x	x	x	x	x	x	x	x	x	x	x	x
Severe or Life-Threatening (Grade 3 or 4)	x	x	x	x	x	x	x	x	x	x	x	x
Death (Grade 5)	x	x	x	x	x	x	x	x	x	x	x	x
At least one not related adverse event (serious or non-serious)	x	x	x	x	x	x	x	x	x	x	x	x
Moderate (Grade 2)	x	x	x	x	x	x	x	x	x	x	x	x
Severe (Grade 3)	x	x	x	x	x	x	x	x	x	x	x	x
Life-threatening (Grade 4)	x	x	x	x	x	x	x	x	x	x	x	x
Death (Grade 5)	x	x	x	x	x	x	x	x	x	x	x	x
At least one serious adverse event	x	x	x	x	x	x	x	x	x	x	x	x
At least one serious adverse event with fatal outcome	x	x	x	x	x	x	x	x	x	x	x	x
At least one related serious adverse event	x	x	x	x	x	x	x	x	x	x	x	x
At least one related serious adverse event with fatal outcome	x	x	x	x	x	x	x	x	x	x	x	x

Subjects[a] with	Interferon beta-1a + RDV (N=X)						Placebo + RDV (N=X)					
	Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)		Baseline OS 4 (N=X)		Baseline OS 5 (N=X)		Baseline OS 6 (N=X)	
	n	%	n	%	n	%	n	%	n	%	n	%
At least one adverse event (serious or non-serious) leading to study drug discontinuation	x	x	x	x	x	x	x	x	x	x	x	x
At least one related adverse event (serious or non-serious) leading to study drug discontinuation	x	x	x	x	x	x	x	x	x	x	x	x
At least one adverse event (serious or non-serious) leading to early termination[b]	x	x	x	x	x	x	x	x	x	x	x	x
At least one unanticipated problem	x	x	x	x	x	x	x	x	x	x	x	x

N = Number of subjects in the baseline ordinal score stratum and As Treated Population

N = Number of subjects with a treatment emergent AE or any fatal AE.

[a]Subjects are counted once for each category regardless of the number of events.

[b]The number of subjects with adverse events leading to discontinuation of treatment or early termination from the study are based on the data collected on the Adverse Event eCRF.

All Grade 3 and 4 AEs are captured as AEs. In addition, any Grade 2 or higher suspected drug-related hypersensitivity reaction is reported as an AE.

Table 54: Subject-Level Rates of Adverse Events and Differences between Treatment Groups – As Treated Population, Baseline Ordinal Score of 4 or 5

Subjects[a] with at least one:	Interferon beta-1a + RDV (N=X)		Placebo + RDV (N=X)		Risk Difference (95% CI)
	n	%	n	%	
Adverse event (serious or non-serious)	x	x	x	x	x.x (x.x, x.x)
Related adverse event (serious or non-serious)	x	x	x	x	x.x (x.x, x.x)
Grade 3-4 adverse event (serious or non-serious)	x	x	x	x	x.x (x.x, x.x)
Grade 3-4 Related adverse event (serious or non-serious)	x	x	x	x	x.x (x.x, x.x)
Serious adverse event	x	x	x	x	x.x (x.x, x.x)
Related serious adverse event	x	x	x	x	x.x (x.x, x.x)
Serious adverse event with fatal outcome	x	x	x	x	x.x (x.x, x.x)
Related serious adverse event with fatal outcome	x	x	x	x	x.x (x.x, x.x)
Adverse event (serious or non-serious) leading to discontinuation of study drug	x	x	x	x	x.x (x.x, x.x)
Related adverse event (serious or non-serious) leading to discontinuation of study drug	x	x	x	x	x.x (x.x, x.x)

N = Number of subjects in the As Treated Population (number of subjects at risk).
N = Number of subjects with a treatment emergent AE or any fatal AE.
[a]Subjects are counted once for each category regardless of the number of events.

Tables with similar format:

Table 55: Subject-Level Rates of Adverse Events and Differences between Treatment Groups – As Treated Population, Baseline Ordinal Score of 6

Table 56: Subject-Level Rates of Adverse Events and Differences between Treatment Groups – As Treated Population, Baseline Modified Oxygen Use Ordinal Score of 6

Programming Note for Table 56:

The table will include the footnote: This analysis used a modified version of the ordinal scale where the definitions of categories 5 and 6 are, respectively, “Hospitalized, requiring supplemental oxygen or high flow oxygen devices at oxygen flow rate less than or equal to 15L/min” and “Hospitalized, on non-invasive ventilation or high flow oxygen devices at oxygen flow rate greater than 15L/min”.

Table 57: Serious Adverse Events by MedDRA System Organ Class and Preferred Term, and Treatment Group - As Treated Population

MedDRA System Organ Class	Preferred Term	Interferon beta-1a + RDV (N=X)			Placebo + RDV (N=X)			Risk Difference	
		n	%	Events	n	%	Events	%	95% CI
SOC1	PT1	x	x	x	x	x	x	x.x	x.x, x.x
Etc.	Etc.	x	x	x	x	x	x	x.x	x.x, x.x

N = Number of subjects in the As Treated Population (number of subjects at risk).
n = Number of subjects reporting event.
Events = total frequency of events reported.

Tables with similar format:

Table 58: Serious Adverse Events by MedDRA System Organ Class and Preferred Term, and Treatment Group – As Treated Population, Baseline Ordinal Score of 4 or 5

Table 59: Serious Adverse Events by MedDRA System Organ Class and Preferred Term, and Treatment Group – As Treated Population, Baseline Ordinal Score of 6

Table 60: Serious Adverse Events by MedDRA System Organ Class and Preferred Term, and Treatment Group – As Treated Population, Baseline Modified Oxygen Use Ordinal Score of 6

Programming Note for Table 60:

The table will include the footnote: This analysis used a modified version of the ordinal scale where the definitions of categories 5 and 6 are, respectively, “Hospitalized, requiring supplemental oxygen or high flow oxygen devices at oxygen flow rate less than or equal to 15L/min” and “Hospitalized, on non-invasive ventilation or high flow oxygen devices at oxygen flow rate greater than 15L/min”.

Table 61: Non-Serious Adverse Events Occurring in 5% of Subjects in Any Treatment Group by MedDRA System Organ Class and Preferred Term, and Treatment Group - As Treated Population

Preferred Term	MedDRA System Organ Class	Interferon beta-1a + RDV (N=X)			Placebo + RDV (N=X)			Risk Difference	
		n	%	Events	n	%	Events	%	95% CI
PT1	SOC1	x	x	x	x	x	x	x.x	x.x, x.x
Etc.	Etc.	x	x	x	x	x	x	x.x	x.x, x.x

N = Number of subjects in the As Treated Population (number of subjects at risk).
n = Number of subjects reporting event.
Events = total frequency of events reported.

Programming Note: Select all preferred terms/system organ classes among non-serious AEs where the % for any treatment group or overall is >= 5%. For both sections, sort preferred terms by descending order of frequency (overall frequency, then by Interferon beta-1a + RDV, then by Placebo + RDV).

Tables with similar format:

Table 62: Non-Serious Adverse Events Occurring in 5% of Subjects in Any Treatment Group by MedDRA System Organ Class and Preferred Term, and Treatment Group – As Treated Population, Baseline Ordinal Score of 4 or 5

Table 63: Non-Serious Adverse Events Occurring in 5% of Subjects in Any Treatment Group by MedDRA System Organ Class and Preferred Term, and Treatment Group – As Treated Population, Baseline Ordinal Score of 6

Table 64: Non-Serious Adverse Events Occurring in 5% of Subjects in Any Treatment Group by MedDRA System Organ Class and Preferred Term, and Treatment Group – As Treated Population, Baseline Modified Oxygen Use Ordinal Score of 6

Programming Note for Table 64:

The table will include the footnote: This analysis used a modified version of the ordinal scale where the definitions of categories 5 and 6 are, respectively, “Hospitalized, requiring supplemental oxygen or high flow oxygen devices at oxygen flow rate less than or equal to 15L/min” and “Hospitalized, on non-invasive ventilation or high flow oxygen devices at oxygen flow rate greater than 15L/min”.

Table 65: Renal Adverse Events by Preferred Term and Treatment Group – As Treated Population, Baseline Ordinal Score of 4 or 5

Preferred Term	Interferon beta-1a + RDV (N=X)			Placebo + RDV (N=X)			Risk Difference	
	n	%	Events	n	%	Events	%	95% CI
Any hepatic adverse event	**x**	**x**	**x**	**x**	**x**	**x**	**x.x**	**x.x, x.x**
Glomerular filtration rate decreased	x	x	x	x	x	x	x.x	x.x, x.x
Blood creatinine increased	x	x	x	x	x	x	x.x	x.x, x.x
Acute kidney injury	x	x	x	x	x	x	x.x	x.x, x.x
Creatinine renal clearance decreased	x	x	x	x	x	x	x.x	x.x, x.x
Renal failure	x	x	x	x	x	x	x.x	x.x, x.x
Renal impairment	x	x	x	x	x	x	x.x	x.x, x.x
Proteinuria	x	x	x	x	x	x	x.x	x.x, x.x
Renal tubular necrosis	x	x	x	x	x	x	x.x	x.x, x.x
Blood creatinine abnormal	x	x	x	x	x	x	x.x	x.x, x.x
Continuous haemodiafiltration	x	x	x	x	x	x	x.x	x.x, x.x
Glomerular filtration rate abnormal	x	x	x	x	x	x	x.x	x.x, x.x

N = Number of subjects in the As Treated Population (number of subjects at risk).
n = Number of subjects reporting event.
Events = Total frequency of events reported.

Tables with similar format:

Table 66: Renal Adverse Events by Preferred Term and Treatment Group – As Treated Population, Baseline Ordinal Score of 6

Table 67: Hepatic Adverse Events by Preferred Term and Treatment Group – As Treated Population, Baseline Ordinal Score of 4 or 5

Table 68: Hepatic Adverse Events by Preferred Term and Treatment Group – As Treated Population, Baseline Ordinal Score of 6

Table 69: Related Adverse Events by MedDRA System Organ Class and Preferred Term, and Treatment Group - As Treated Population, Baseline Ordinal Score of 4 or 5

MedDRA System Organ Class	Preferred Term	Interferon beta-1a + RDV (N=X)			Placebo + RDV (N=X)			Risk Difference	
		n	%	Events	n	%	Events	%	95% CI
Any SOC	Any PT	x	x	x	x	x	x	x.x	x.x, x.x
SOC1	Any PT	x	x	x	x	x	x	x.x	x.x, x.x
Etc.	Etc.	…	…	…	…	…	…	…	…

N = Number of subjects in the As Treated Population (number of subjects at risk).
n = Number of subjects reporting event.
Events = total frequency of events reported.

Table with similar format:

Table 70: Related Adverse Events by MedDRA System Organ Class and Preferred Term, and Treatment Group - As Treated Population, Baseline Ordinal Score of 6

Table 71: Deaths by Day 15 or Day 29 by Treatment Group and Baseline Ordinal Score – mITT Population

Study Day	Baseline Ordinal Score	Interferon beta-1a + RDV (N=X)			Placebo + RDV (N=X)		
		n	Mortality Rate[a]	Rate 95% CI	n	Mortality Rate[a]	Rate 95% CI
Day 15	6	X	x.x	x.x, x.x	x	x.x	x.x, x.x
	5	X	x.x	x.x, x.x	x	x.x	x.x, x.x
	4	X	x.x	x.x, x.x	x	x.x	x.x, x.x
	Any Baseline Ordinal Score	X	x.x	x.x, x.x	x	x.x	x.x, x.x
	Any Baseline Ordinal Score (4 or 5)	X	x.x	x.x, x.x	x	x.x	x.x, x.x
Day 29	6	X	x.x	x.x, x.x	x	x.x	x.x, x.x
	5	X	x.x	x.x, x.x	x	x.x	x.x, x.x
	4	X	x.x	x.x, x.x	x	x.x	x.x, x.x
	Any Baseline Ordinal Score	X	x.x	x.x, x.x	x	x.x	x.x, x.x
	Any Baseline Ordinal Score (4 or 5)	X	x.x	x.x, x.x	x	x.x	x.x, x.x

N = Number of subjects in the specified treatment group and analysis population.
n = Number of subjects in a given treatment group who died by the given timepoint
[a] Mortality Rate is the Kaplan-Meier estimate.

Tables with similar format:

Table 72: Deaths by Day 15 or Day 29 by Treatment Group and Baseline Ordinal Score – As Treated Population

Table 73: Deaths by Day 15 or Day 29 by Treatment Group and Baseline Modified Oxygen Use Ordinal Score – mITT Population

Table 74: Deaths by Day 15 or Day 29 by Treatment Group and Baseline Modified Oxygen Use Ordinal Score – As Treated Population

Programming notes for Table 73 and Table 74:

The table will include the footnote: This analysis used a modified version of the ordinal scale where the definitions of categories 5 and 6 are, respectively, “Hospitalized, requiring supplemental oxygen or high flow oxygen devices at oxygen flow rate less than or equal to 15L/min” and “Hospitalized, on non-invasive ventilation or high flow oxygen devices at oxygen flow rate greater than 15L/min”.

Table 75: Time to Death through Day 15 and 29 by Treatment Group and Baseline Ordinal Score – mITT Population

Study Day	Treatment Group	Baseline Ordinal Score	n	HR		P-value
				Estimate	95% CI	
Day 15	**Interferon beta-1a + RDV (N=X)**	**4**	x	x.xx	x.xx, x.xx	--
	Placebo + RDV (N=X)		x			
	Interferon beta-1a + RDV (N=X)	**5**	x	x.xx	x.xx, x.xx	--
	Placebo + RDV (N=X)		x			
	Interferon beta-1a + RDV (N=X)	**6**	x	x.xx	x.xx, x.xx	--
	Placebo + RDV (N=X)		x			
	Interferon beta-1a + RDV (N=X)	**Any Baseline Ordinal Score**	x	x.xx	x.xx, x.xx	x.xxx
	Placebo + RDV (N=X)		x			
	Interferon beta-1a + RDV (N=X)	**Any Baseline Ordinal Score (4 or 5)**	x	x.xx	x.xx, x.xx	x.xxx
	Placebo + RDV (N=X)		x			
Day 29	**Interferon beta-1a + RDV (N=X)**	**4**	x	x.xx	x.xx, x.xx	--
	Placebo + RDV (N=X)		x			
	Interferon beta-1a + RDV (N=X)	**5**	x	x.xx	x.xx, x.xx	--
	Placebo + RDV (N=X)		x			
	Interferon beta-1a + RDV (N=X)	**6**	x	x.xx	x.xx, x.xx	--
	Placebo + RDV (N=X)		x			
	Interferon beta-1a + RDV (N=X)	**Any Baseline Ordinal Score**	x	x.xx	x.xx, x.xx	x.xxx
	Placebo + RDV (N=X)		x			
	Interferon beta-1a + RDV (N=X)	**Any Baseline Ordinal Score (4 or 5)**	x	x.xx	x.xx, x.xx	x.xxx
	Placebo + RDV (N=X)		x			

NE = Not Estimated.
N= Number of subjects in the specified treatment group and analysis population.
n = Number of subjects who died by the specified study day.
HR is the ratio of the hazard of Death in each treatment group estimated from the Cox model. The ratio is Interferon beta-1a + RDV to Placebo + RDV.
HR for the 'Any Baseline Ordinal Score' and 'Any Baseline Ordinal Score (4 or 5)' group is the hazard ratio from the stratified Cox Model.
P-value calculated using the stratified Log-rank test.

Programming Notes:

The p-value for the stratified log-rank test in the (4 or 5) subgroup will only be reported if the p-value from the primary analysis of time to recovery (including all three OS strata). Otherwise the p-value from the analysis including the 6 subgroup will be reported.

Tables with similar format:

Table 76: Time to Death through Day 15 and 29 by Treatment Group and Baseline Ordinal Score – As Treated Population

Table 77: Time to Death through Day 15 and 29 by Treatment Group and Baseline Modified Oxygen Use Ordinal Score – mITT Population

Table 78: Time to Death through Day 15 and 29 by Treatment Group and Baseline Modified Oxygen Use Ordinal Score – As Treated Population

Table 79: Time to Death through Day 15 and 29 by Treatment Group within Subgroups – mITT Population

Table 80: Time to Death through Day 15 and 29 by Treatment Group: Medications of Interest Sensitivity Analysis – mITT Population

Table 81: Time to Death through Day 15 and 29 by Treatment Group: Interaction Modeling – mITT Population

Programming notes for Table 77 and Table 78:

The table will include the footnote: This analysis used a modified version of the ordinal scale where the definitions of categories 5 and 6 are, respectively, “Hospitalized, requiring supplemental oxygen or high flow oxygen devices at oxygen flow rate less than or equal to 15L/min” and “Hospitalized, on non-invasive ventilation or high flow oxygen devices at oxygen flow rate greater than 15L/min”.

Programming notes for Table 79:

Log-rank p-values will not be included in this table so the column will be removed. The Baseline Ordinal Score column will be removed and to the left of the Study Day column, a column titled “Analysis/Subgroup” will be inserted. Rows will be generated for each subgroup. This table will include the statin/ARB/AECI use subgroups. Baseline Ordinal Score will be excluded from this table; only subjects with baseline ordinal score of 4 or 5 will be included.

Programming notes for Table 80:

Log-rank p-values will not be included in this table so the column will be removed. The table will include a column to the left of the “n” column titled “m”. The corresponding footnote will read “m = Number of subjects reporting use of the medication of interest.” The Baseline Ordinal Score column will be removed and a “Medication of Interest” column will be inserted to the left of Study Day. Separate models will be fit for the following categories of medications (see Section 6.4):

- Any Medication of Interest

- Hydroxychloroquine/Chloroquine
- Corticosteroids
- Anti-Inflammatory Drugs

Include a footnote for "Any Medication of Interest" noting that this excludes statins, ARBs, and AECIs. The table will include the following footnote: "In this analysis, subjects that reported use of the specified medications of interest (Section 6.4) are censored at time of medication receipt." Only subjects with baseline ordinal score of 4 or 5 will be included

Programming notes for Table 81:

This table will only include the Treatment Group and HR columns only as well as a column to the left of Treatment Group titled "Interaction". The following models will be run:

- "Treatment – Baseline Ordinal Score (4 or 5 vs. 6)" will include a treatment*Baseline Ordinal Score interaction term.
- "Treatment – Continuous Actual Baseline Ordinal Score" will include a treatment*baseline ordinal score interaction term.
- "Treatment – Categorical Actual Baseline Ordinal Score" will include a treatment*baseline ordinal score interaction term.

Only run the actual severity models if at least one subject was randomized to the incorrect stratum. For each interaction model, the p-value for the interaction term will be provided in a footnote reading "The p-value for the treatment by [Baseline ordinal score / continuous/categorical baseline ordinal score] interaction term was 0.xxxx.".

Table 82: Time to Death through Day 15 and 29 by Treatment Group: Restricted Mean Survival Time Analysis – mITT Population

Study Day	Treatment Group	Baseline Ordinal Score	n	Restricted Mean Recovery Time		Difference	
				Estimate	95% CI	Estimate	95% CI
Day 15	**Interferon beta-1a + RDV (N=X)**	**4**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x		
	Interferon beta-1a + RDV (N=X)	**5**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x		
	Interferon beta-1a + RDV (N=X)	**6**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x		
	Interferon beta-1a + RDV (N=X)	**Any Baseline Ordinal Score**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x		
	Interferon beta-1a + RDV (N=X)	**Any Baseline Ordinal Score (4 or 5)**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x		
Repeat for Day 29							

N= Number of subjects in the specified treatment group, baseline ordinal score, and analysis population.
n = Number of recovered subjects.
Difference is the difference in the restricted mean recovery time between Interferon beta-1a + RDV and Placebo + RDV.

Table 83: Time to Death or Progression to Invasive Ventilation through Day 28 by Treatment Group and Baseline Ordinal Score – mITT Population

Treatment Group	Baseline Ordinal Score	n	HR	
			Estimate	95% CI
Interferon beta-1a + RDV (N=X)	**4**	x	x.xx	x.xx, x.xx
Placebo + RDV (N=X)		x		
Interferon beta-1a + RDV (N=X)	**5**	x	x.xx	x.xx, x.xx
Placebo + RDV (N=X)		x		
Interferon beta-1a + RDV (N=X)	**6**	x	x.xx	x.xx, x.xx
Placebo + RDV (N=X)		x		
Interferon beta-1a + RDV (N=X)	**Any Baseline Ordinal Score**	x	x.xx	x.xx, x.xx
Placebo + RDV (N=X)		x		
Interferon beta-1a + RDV (N=X)	**Any Baseline Ordinal Score (4 or 5)**	x	x.xx	x.xx, x.xx
Placebo + RDV (N=X)		x		

NE = Not Estimated.
N= Number of subjects in the specified treatment group, baseline ordinal score, and analysis population.
n = Number of subjects who died or progressed to invasive ventilation by Day 28.
HR is the ratio of the hazard of death or progression to invasive ventilation in each treatment group estimated from the Cox model. The ratio is Interferon beta-1a + RDV to Placebo + RDV.
HR for the 'Any Baseline Ordinal Score' and 'Any Baseline Ordinal Score (4 or 5)' group is the hazard ratio from the stratified Cox Model.

Tables with similar format:

Table 84: Time to Death Progression to Invasive Ventilation through Day 28 by Treatment Group and Baseline Ordinal Score – As Treated Population

Table 85: Time to Death Progression to Invasive Ventilation through Day 28 by Treatment Group and Baseline Modified Oxygen Use Ordinal Score – As Treated Population

Table 86: Time to Death or Progression to Non-Invasive or Invasive Ventilation through Day 28 by Treatment Group and Baseline Modified Oxygen Use Ordinal Score – mITT Population

Table 87: Time to Death or Progression to Non-Invasive or Invasive Ventilation through Day 28 by Treatment Group and Baseline Ordinal Score – mITT Population

Table 88: Time to Death or Progression to Non-Invasive or Invasive Ventilation through Day 28 by Treatment Group and Baseline Ordinal Score – As Treated Population

Table 89: Time to Death or Progression to Non-Invasive or Invasive Ventilation through Day 28 by Treatment Group, Baseline Ordinal Score, and Statin/ARB/AECI Use – mITT Population

Programming Notes for Table 85 and Table 86:

The table will include the footnote: This analysis used a modified version of the ordinal scale where the definitions of categories 5 and 6 are, respectively, “Hospitalized, requiring supplemental oxygen or high flow oxygen devices at oxygen flow rate less than or equal to 15L/min” and “Hospitalized, on non-invasive ventilation or high flow oxygen devices at oxygen flow rate greater than 15L/min”.

Programming notes for Table 89:

Use the Statins use subgroups described in Section 6.4. The Baseline Ordinal Score column will be replaced by a “Statins Use” column. Only subjects with a baseline score of 4 or 5 will be included.

Table 90: Subjects Experiencing Grade 3 or 4 AEs and SAEs through Day 29 by Treatment Group and Baseline Ordinal Score – As Treated Population

Safety Event Outcome	Interferon beta-1a + RDV			Placebo + RDV		
	n	%	95% CI	n	%	95% CI
Any Baseline Ordinal Score (N = X)						
Grade 3 or 4 AE	x	x	x.x, x.x	x	x	x.x, x.x
SAE	x	x	x.x, x.x	x	x	x.x, x.x
Any Baseline Ordinal Score (4 or 5) (N = X)						
Grade 3 or 4 AE	x	x	x.x, x.x	x	x	x.x, x.x
SAE	x	x	x.x, x.x	x	x	x.x, x.x
Baseline Ordinal Score 4 (N = X)						
Grade 3 or 4 AE	x	x	x.x, x.x	x	x	x.x, x.x
SAE	x	x	x.x, x.x	x	x	x.x, x.x
Baseline Ordinal Score 5 (N = X)						
Grade 3 or 4 AE	x	x	x.x, x.x	x	x	x.x, x.x
SAE	x	x	x.x, x.x	x	x	x.x, x.x
Baseline Ordinal Score 6 (N = X)						
Grade 3 or 4 AE	x	x	x.x, x.x	x	x	x.x, x.x
SAE	x	x	x.x, x.x	x	x	x.x, x.x

N = Number of Subject in the As Treated Population and specified baseline ordinal score stratum.
n = Number of subjects in a given treatment group who experienced the specified safety event outcome.
95% CI calculated using C-P/Blaker method.

Table 91: Analysis of Time to Death, SAEs, or Grade 3 or 4 AEs by Treatment Group – As Treated Population

Baseline Ordinal Score	Treatment Group	n	HR	
			Estimate	95% CI
Any Baseline Ordinal Score (N=X)	**Interferon beta-1a + RDV (N=X)**	X		
	Placebo + RDV (N=X)	X	x.xx	x.xx, x.xx
Any Baseline Ordinal Score (4 or 5) (N=X)	**Interferon beta-1a + RDV (N=X)**	X		
	Placebo + RDV (N=X)	X	x.xx	x.xx, x.xx
Baseline Ordinal Score 4 (N=X)	**Interferon beta-1a + RDV (N=X)**	X		
	Placebo + RDV (N=X)	X	x.xx	x.xx, x.xx
Baseline Ordinal Score 5 (N=X)	**Interferon beta-1a + RDV (N=X)**	X		
	Placebo + RDV (N=X)	X	x.xx	x.xx, x.xx
Baseline Ordinal Score 6 (N=X)	**Interferon beta-1a + RDV (N=X)**	X		
	Placebo + RDV (N=X)	X	x.xx	x.xx, x.xx

N= Number of subjects in the As Treated Population and specified baseline ordinal score stratum.
n = Number of subjects who died or experienced SAEs or Grade 3 or 4 AEs.
HR is the ratio of the hazard of Death/SAE/AE of Grade 3 or 4 in each treatment group estimated from the Cox model. The ratio is Interferon beta-1a + RDV to Placebo + RDV.
HR for the 'Any Baseline Ordinal Score' and 'Any Baseline Ordinal Score (4 or 5)' group is the hazard ratio from the stratified Cox Model.

Table 92: Abnormal Laboratory Results of Grade 3 or 4 by Parameter, Maximum Severity, Time Point, and Treatment Group – As Treated Population, Baseline Ordinal Score of 4 or 5

Laboratory Parameter	Time Point	Treatment Group	N	Severe/ Grade 3		Life Threatening/ Grade 4		Severe/Grade 3 or Life Threatening/Grade 4	
				n	%	n	%	n	%
Any Parameter	Baseline	Interferon + RDV	x	x	x	x	x	x	x
		Placebo + RDV	x	x	X	x	x	x	x
	Day 3	Interferon + RDV	x	x	X	x	x	x	x
		Placebo + RDV	x	x	X	x	x	x	x
	Day 5	Interferon + RDV	x	x	X	x	x	x	x
		Placebo + RDV	x	x	X	x	x	x	x
	Day 8	Interferon + RDV	x	x	X	x	x	x	x
		Placebo + RDV	x	x	X	x	x	x	x
	Day 11	Interferon + RDV	x	x	X	x	x	x	x
		Placebo + RDV	x	x	X	x	x	x	x
	Day 15	Interferon + RDV	x	x	X	x	x	x	x
		Placebo + RDV	x	x	X	x	x	x	x
	Day 29	Interferon + RDV	x	x	X	x	x	x	x
		Placebo + RDV	x	x	X	x	x	x	x
	Maximum Severity Post Baseline	Interferon + RDV	x	x	X	x	x	x	x
		Placebo + RDV	x	x	X	x	x	x	x
Each parameter will be summarized individually similar to the above…									
The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments and assessments beyond Day 29. N = Number of subjects in the As Treated Population									

Programming Note: D-dimer and CRP results are not included in this table. Include all lab parameters that are being graded in this table.

Table with similar format:

Table 93: Abnormal Laboratory Results of Grade 3 or 4 by Parameter, Maximum Severity, Time Point, and Treatment Group – As Treated Population, Baseline Ordinal Score of 6

Table 94: Treatment-Emergent Laboratory Abnormalities - As Treated Population, Baseline Ordinal Score of 4 or 5

Laboratory Parameter	Grade	Interferon beta-1a + RDV (N=X)			Placebo + RDV (N=X)		
		N	n	%	N	n	%
Any Parameter	1	x	x	x	x	x	x
	2	x	x	X	x	x	x
	3	x	x	X	x	x	x
	4	x	x	X	x	x	x
	Any Grade	x	x	X	x	x	x
Continue for all graded parameters							

N = Number of subjects in the As Treated Population with any post-baseline data available for the specified Lab Parameter.
n = Number of subjects in the As Treated Population with treatment emergent abnormalities for the specified Lab Parameter.
A treatment emergent laboratory abnormality is defined as a post-baseline abnormal value with a severity grade greater than at baseline.

Table with similar format:

Table 95: Treatment-Emergent Laboratory Abnormalities - As Treated Population, Baseline Ordinal Score of 6

Table 96: Summary Statistics of Laboratory Results by Parameter, Study Visit Day, and Treatment Group – As Treated Population, Baseline Ordinal Score of 4 or 5

Laboratory Parameter	Study Visit Day	Treatment Group	Absolute					Change from Baseline				
			N	Mean	95% CI	Median	Min, Max	N	Mean	95% CI	Median	Min, Max
Parameter 1	Baseline	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	---	---	---	---	---
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	---	---	---	---	---
	Day 3	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
	Day 5	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
	Day 8	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
	Day 11	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
	Day 15	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
	Day 29	Interferon + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x, xx.x	xx.x	xx.x, xx.x
Continue for all parameters…												
N = Number of subjects in the As Treated Population with laboratory data available for the parameter at the specified study visit.												

Programming Note: Include all lab parameters in this table except d-dimer and CRP.

Table with similar format:

Table 97: Summary Statistics of Laboratory Results by Parameter, Study Visit Day, and Treatment Group – As Treated Population, Baseline Ordinal Score of 6

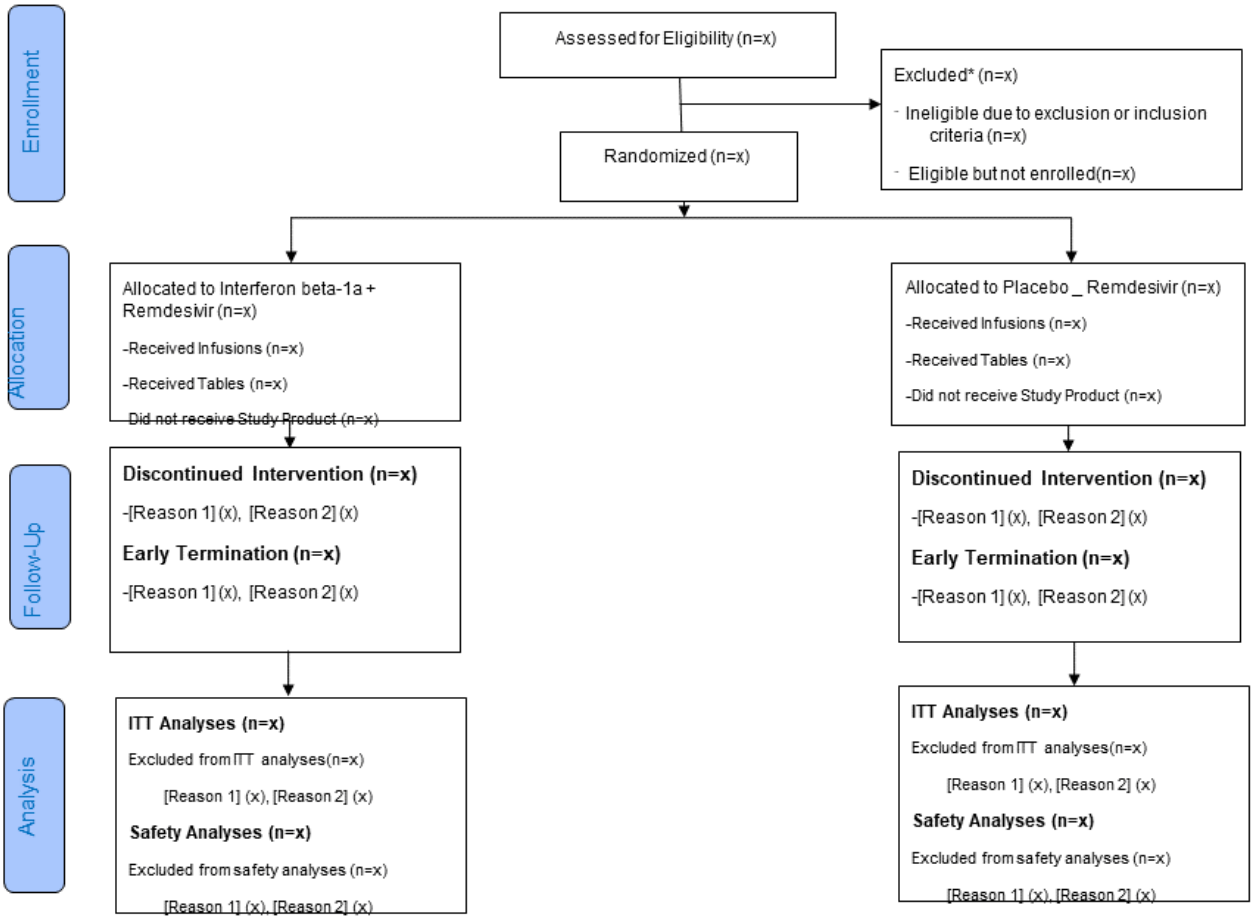
APPENDIX 2. FIGURE MOCK-UPS

General Programming Notes for figures:

- Treatment group labeling will be the following:
  - Interferon Beta-1a + RDV
  - Placebo + RDV
- If the treatment group labels need to be abbreviated to improve fit, the following abbreviations will be used:
  - Ib + R
  - P + R
- Use the same color for a treatment on the different graphs (SAS standard colors):
  - Interferon Beta-1a + RDV = Blue
  - Placebo + RDV = Red
- For severity graphs (SAS standard colors):
  - Mild = yellow
  - Moderate = orange
  - Severe = red
  - Life-threatening = brown
  - Death = black

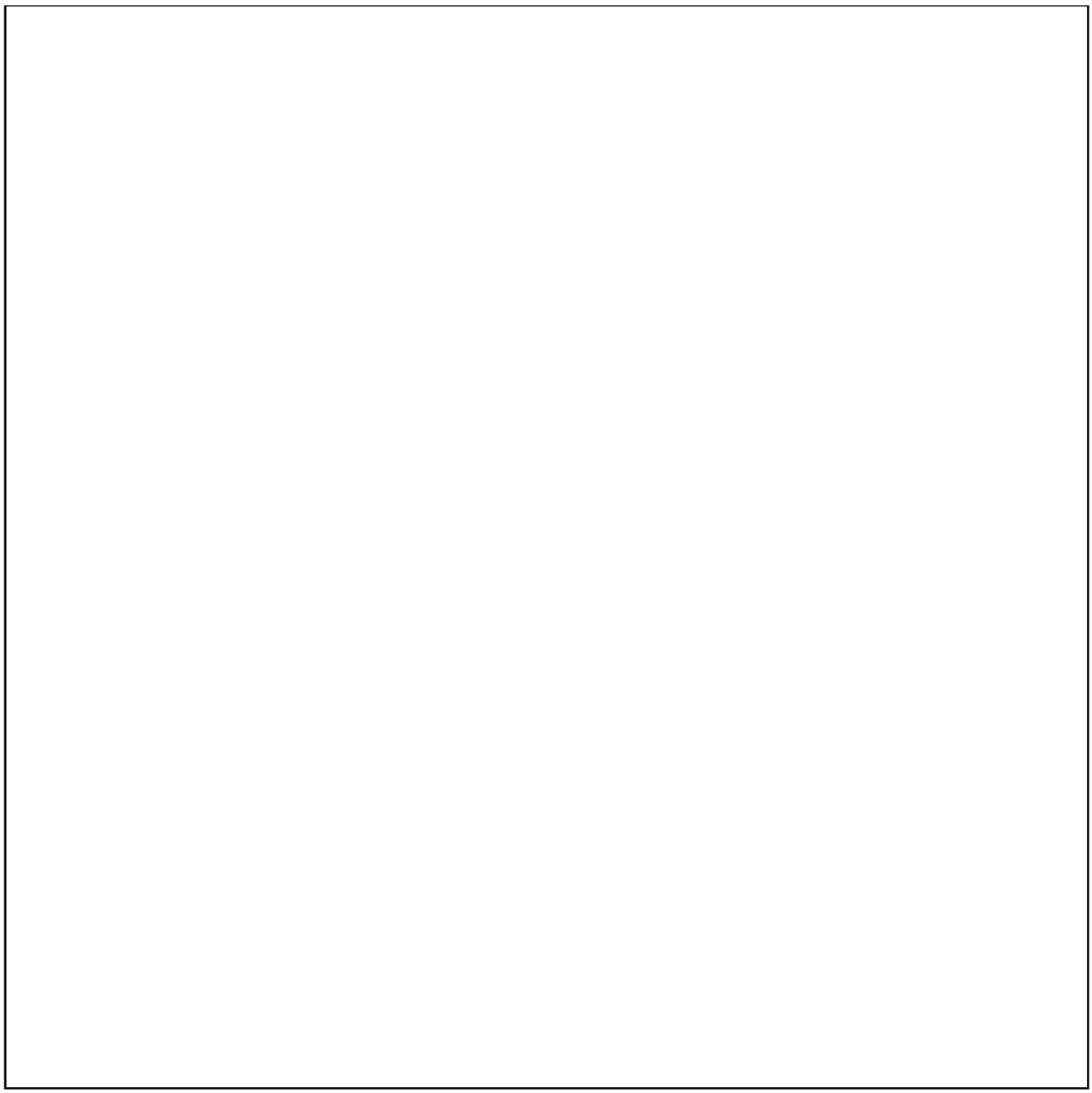
LIST OF FIGURES

Figure 1: CONSORT Flow Diagram



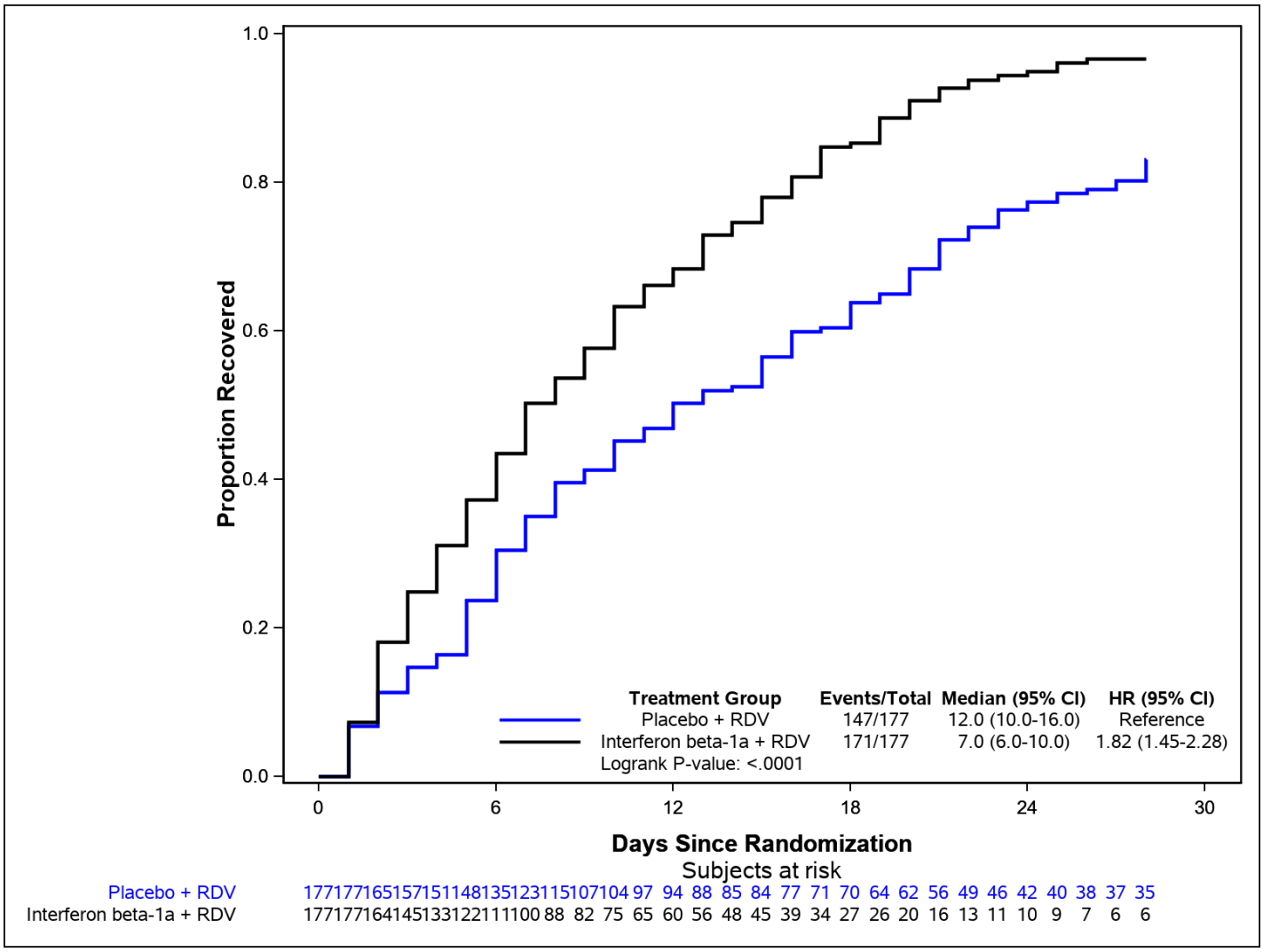
Programming Note: Diagram will collapse across baseline ordinal score strata. Content of individual boxes may be altered from the shell.

Figure 2: Number of Subjects that Terminated by Study Day, Baseline Ordinal Score, and Hospitalization Status at the Time of Last Ordinal Score Collection – mITT Population



Programming Notes: The shell above is a generic shell. For the panels, the rows will be, going top to bottom, "All Subjects", "Interferon beta-1a + RDV" and "Placebo + RDV". The columns will be, going left to right, "Ordinal Score 4", "Ordinal Score 5", and "Ordinal Score 6". Within each panel, the x-axis will be labeled "Study Day of Last Ordinal Score" and will have a tick at each Study Day. The blue bars will be "Hospitalized" and the red bars will be "Not Hospitalized".

Figure 3: Kaplan-Meier Curves of Time to Recovery by Treatment Group – mITT Population



Programming Note: For Subjects at risk counts, only display Days 1, 3, 5, 8, 11, 15, 22, 29. Report p-value to 3 decimal places as noted in Section 13.

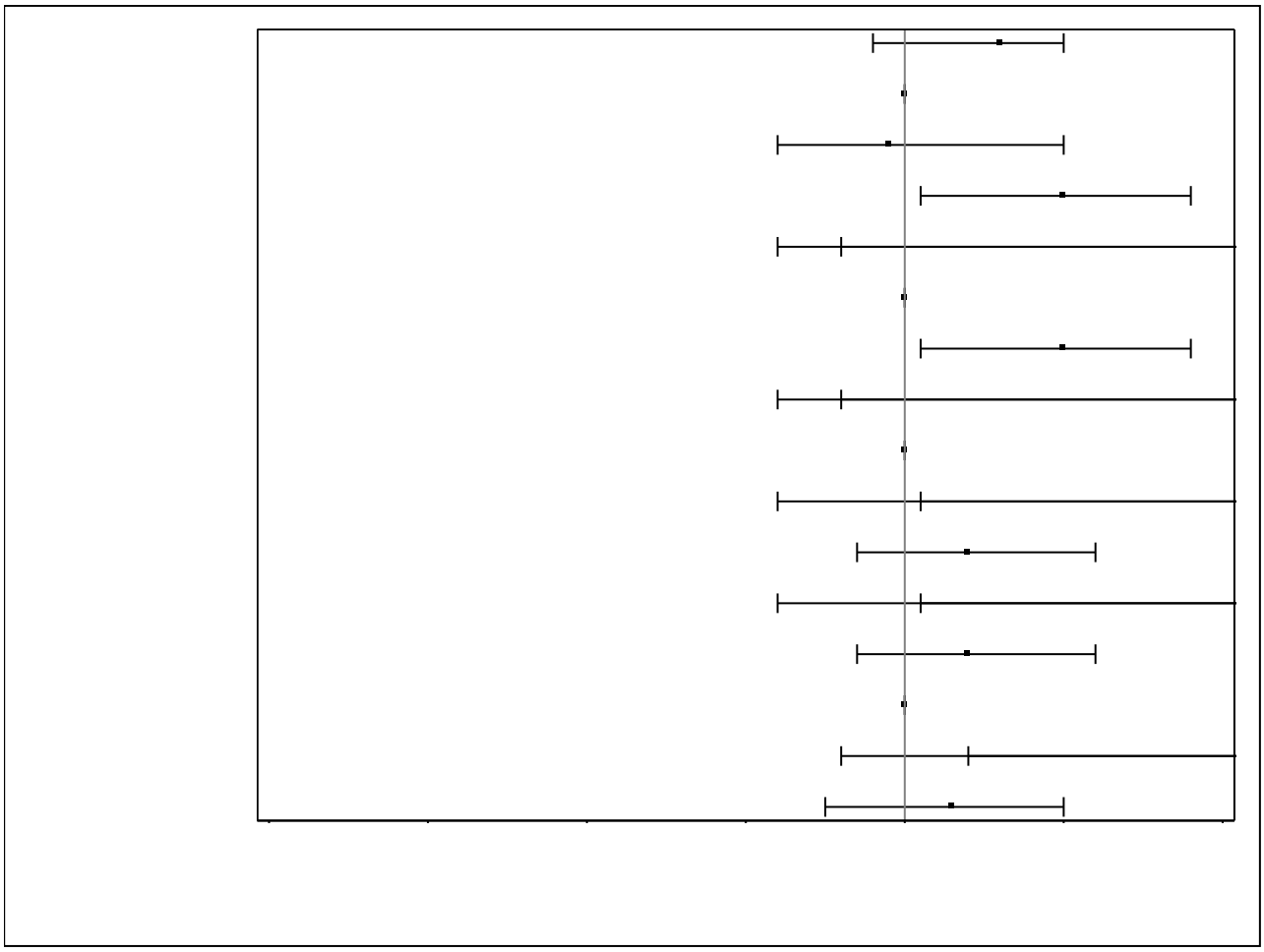
Figures with similar format:

Figure 4: Kaplan-Meier Curve of Time to Recovery by Treatment Group – mITT Population, Baseline Ordinal Score of 4

Figure 5: Kaplan-Meier Curve of Time to Recovery by Treatment Group – mITT Population, Baseline Ordinal Score of 5

Figure 6: Kaplan-Meier Curve of Time to Recovery by Treatment Group – mITT Population, Baseline Ordinal Score of 6

Figure 7: Forest Plot of Hazard Ratios of Time to Recovery by Subgroup - mITT Population



Figures with similar format:

Figure 8: Forest Plot of Hazard Ratios of Time to Recovery by Subgroup - mITT Population, Baseline Ordinal Score of 4 or 5

Figure 9: Forest Plot of Hazard Ratios of Time to Recovery by Comorbidity - mITT Population

Figure 10: Forest Plot of Hazard Ratios of Time to Recovery: Leave One Site Out Sensitivity Analysis - mITT Population

Figure 11: Study Visit Day 15 Clinical Status Score by Baseline Ordinal Score and Treatment Group – mITT Population

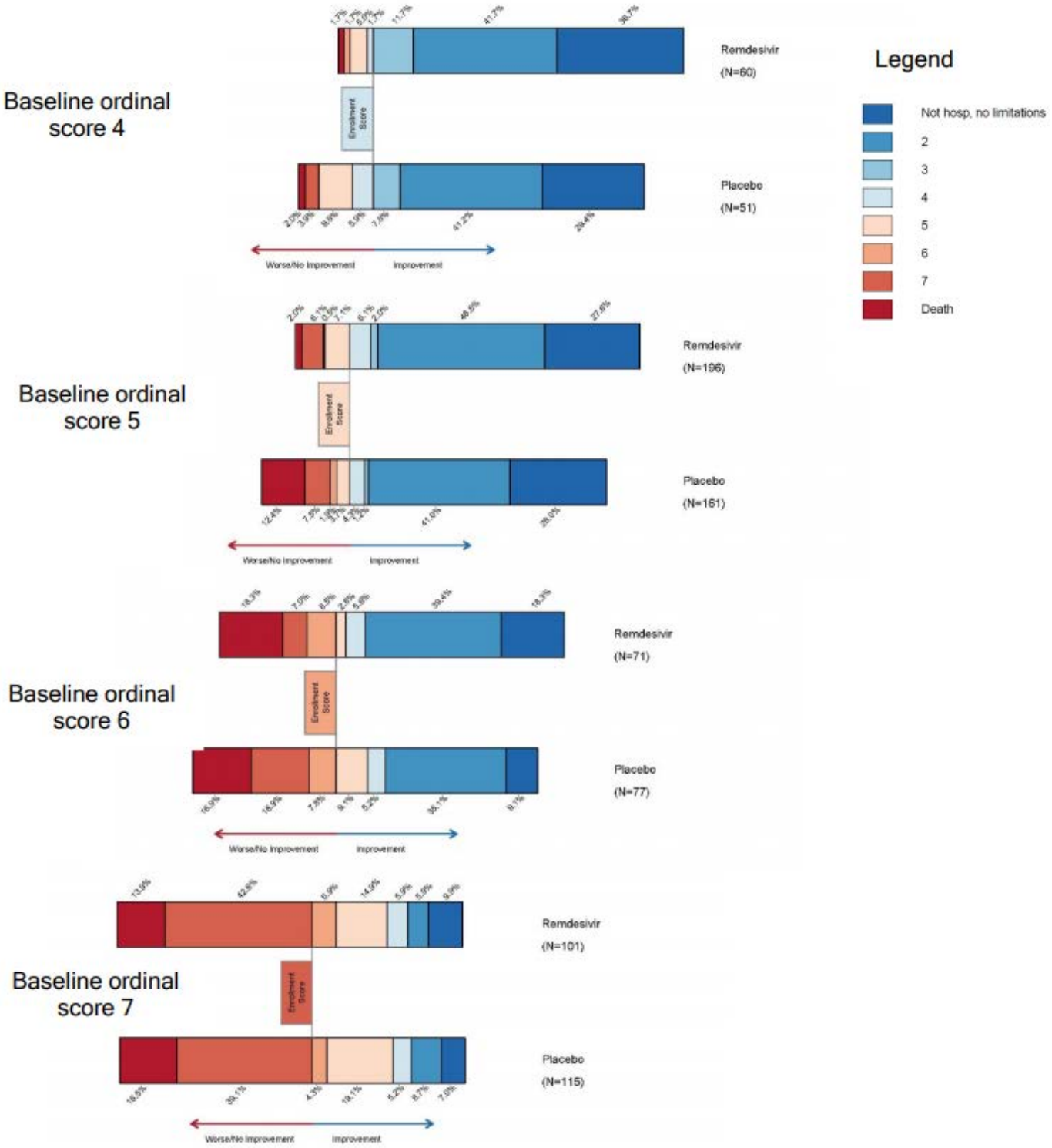
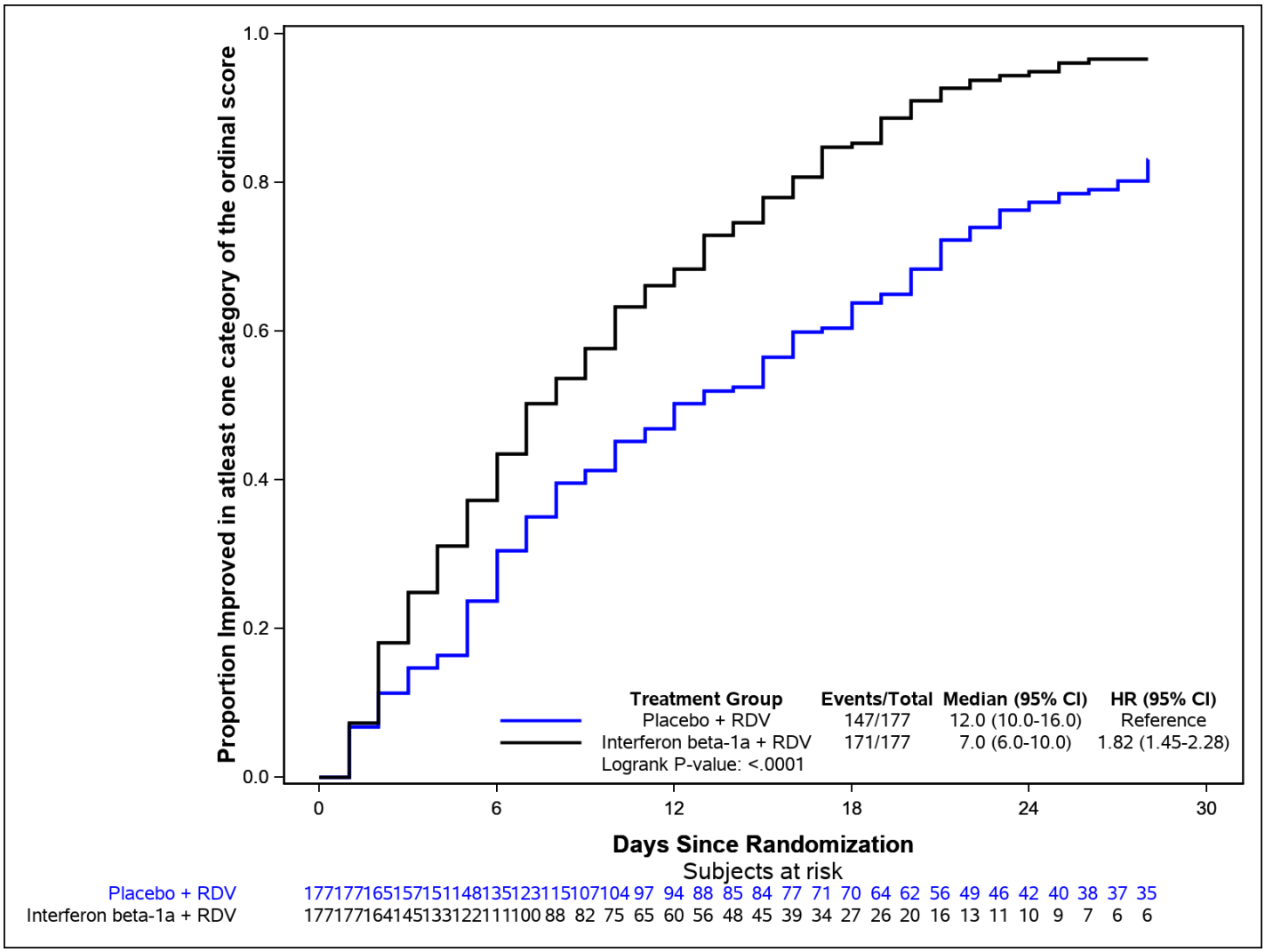


Figure 12: Kaplan-Meier Curves of Time to Improvement by at least One Category of Clinical Status Score by Treatment Group – mITT Population, Baseline Ordinal Score of 4 or 5



Figures with similar format:

Figure 13: Kaplan-Meier Curves of Time to Improvement by at least Two Categories of Clinical Status Score by Treatment Group – mITT Population, Baseline Ordinal Score of 4 or 5

Figure 14: Kaplan-Meier Curves of Time to Improvement by at least One Category of Clinical Status Score by Treatment Group – mITT Population, Baseline Ordinal Score of 6

Figure 15: Kaplan-Meier Curves of Time to Improvement by at least Two Categories of Clinical Status Score by Treatment Group – mITT Population, , Baseline Ordinal Score of 6

Figure 16: Kaplan-Meier Curves of Time to Discharge or NEWS ≤ 2 by Treatment Group – mITT Population, Baseline Ordinal Score of 4 or 5

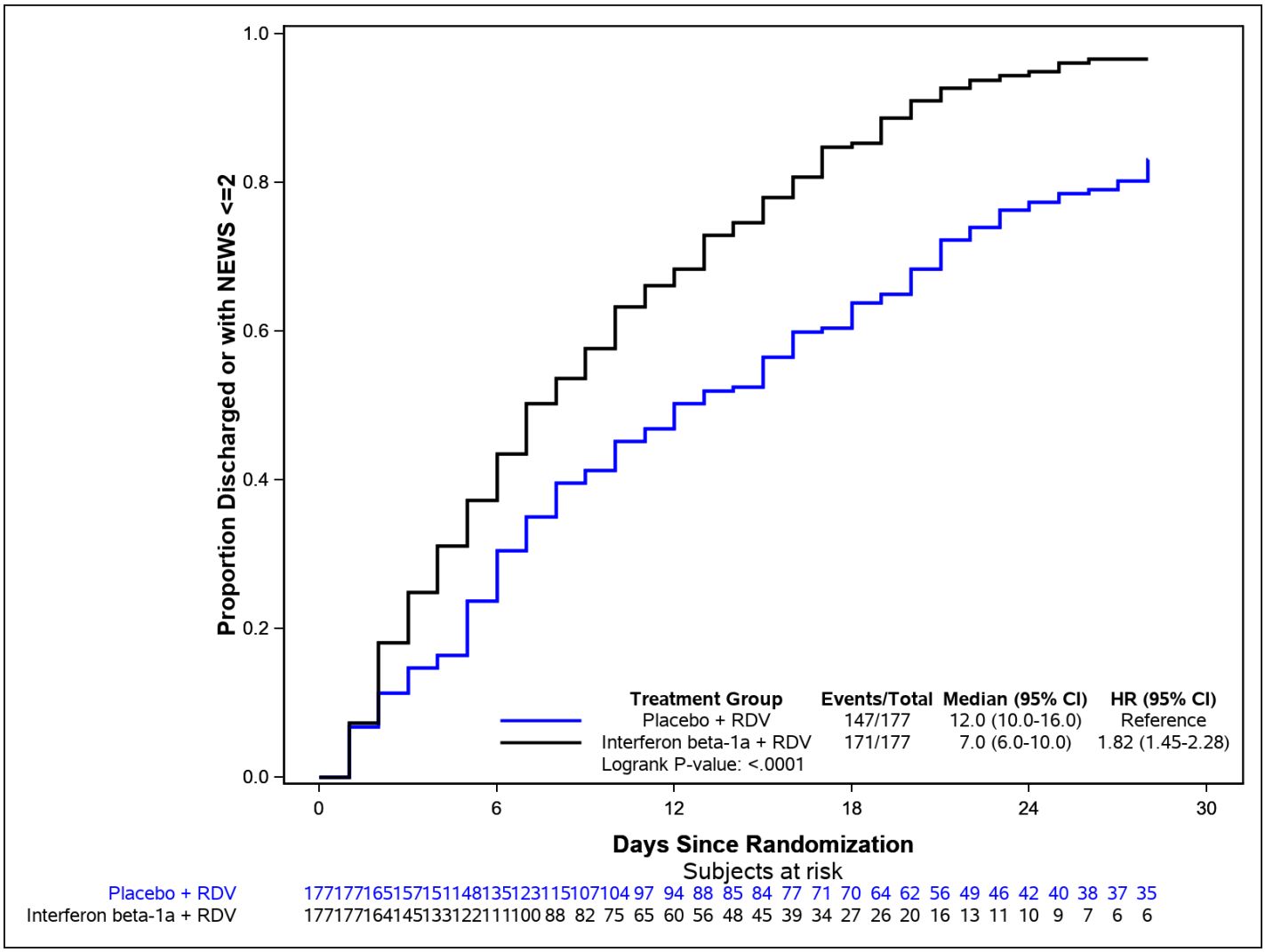
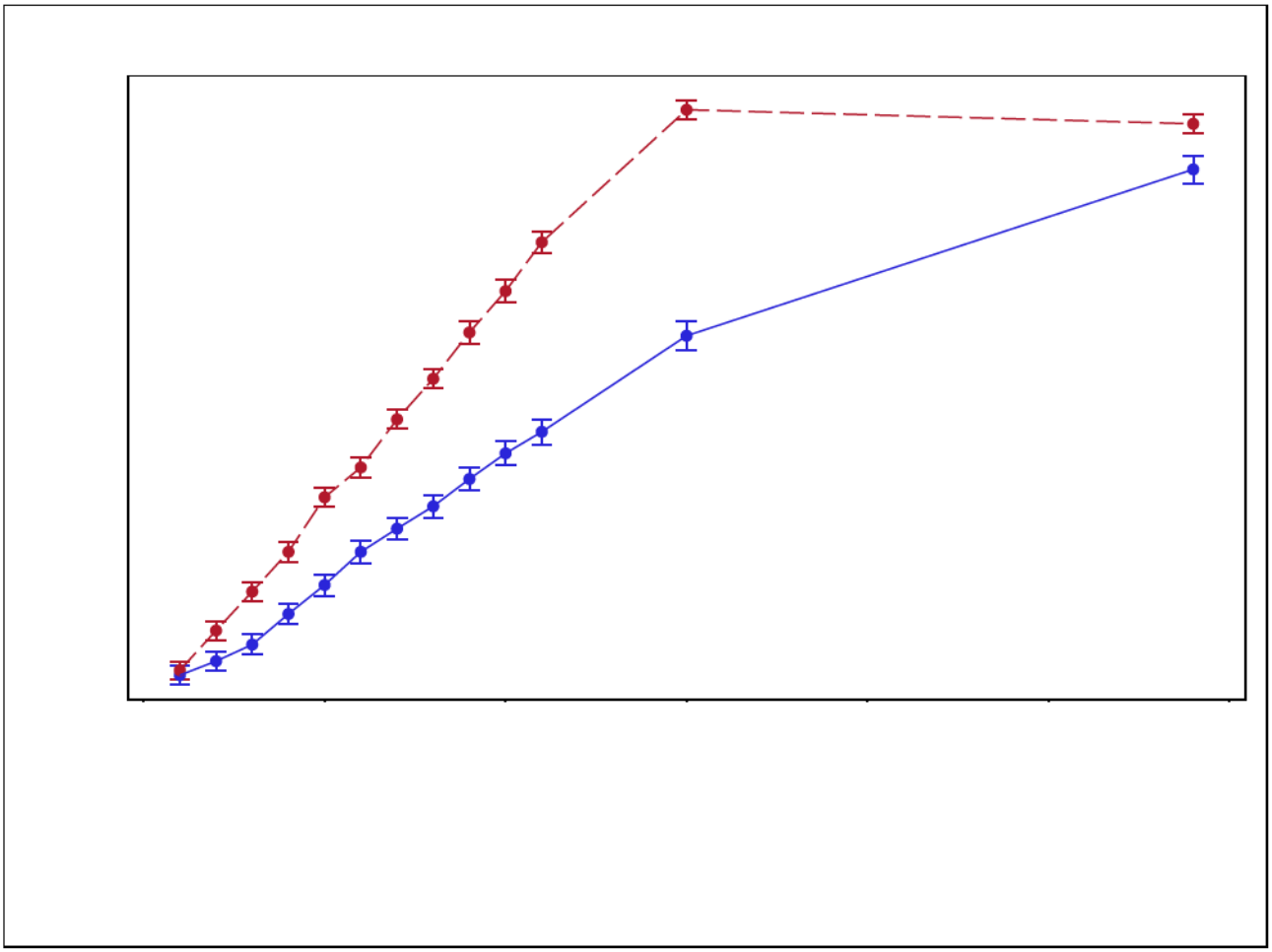


Figure with similar format:

Figure 17: Kaplan-Meier Curves of Time to Discharge or NEWS ≤ 2 by Treatment Group – mITT Population, Baseline Ordinal Score of 6

Figure 18: Mean NEWS by Day and Treatment Group – mITT Population, Baseline Ordinal Score of 4 or 5

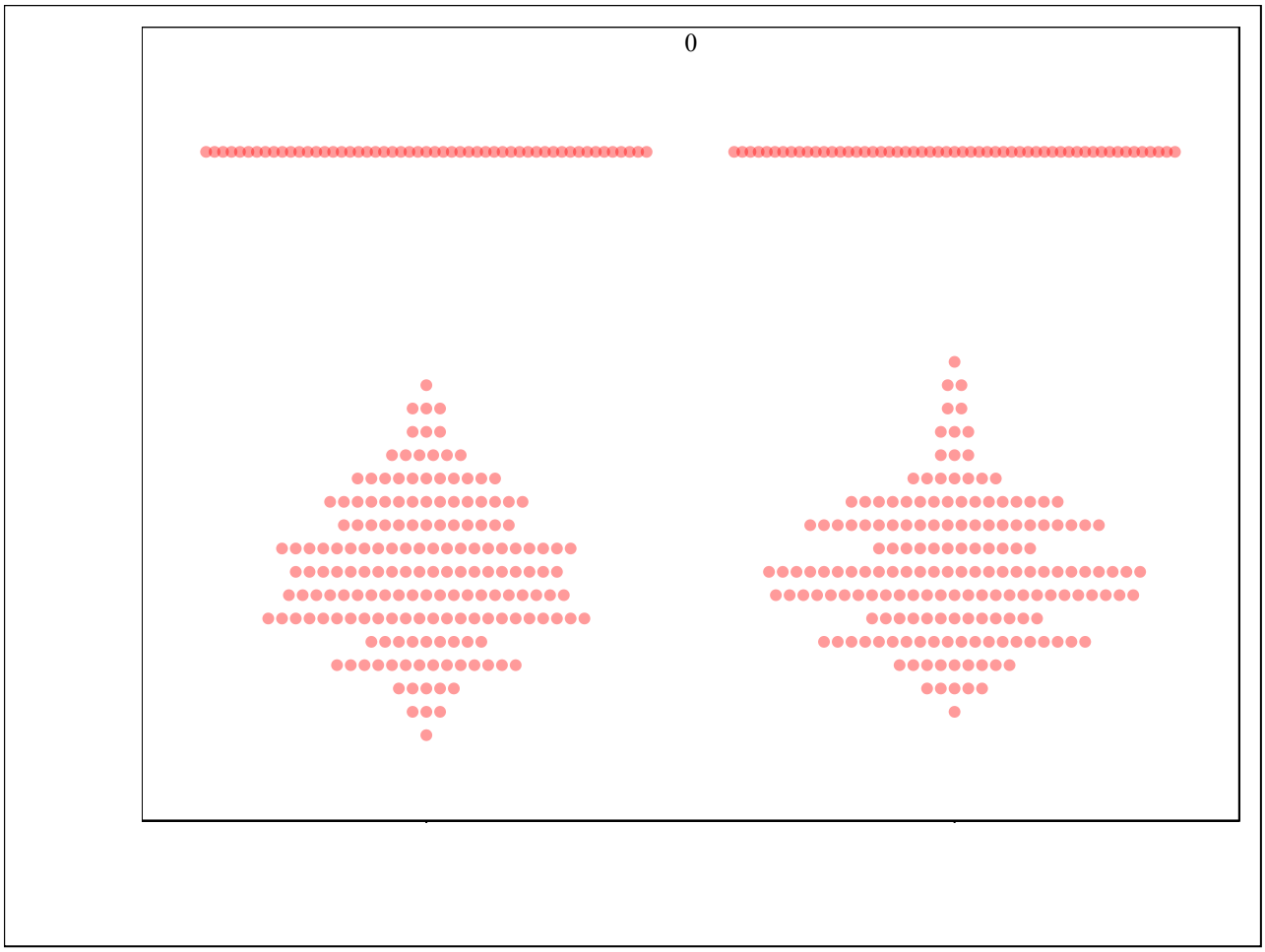


Programming Note: Bars reflect the CIs. Use imputed NEWS scores as defined in Section 6.5 .

Figure with similar format:

Figure 19: Mean NEWS by Day and Treatment Group – mITT Population, Baseline Ordinal Score of 6

Figure 20: Bee Swarm Plot of Oxygen Days by Treatment Group – mITT Population, Baseline Ordinal Score of 4 or 5



Programming Note: Use the format used for ACTT-1 which incorporated summary statistics.

Figures with similar format:

Figure 21: Bee Swarm Plot of Oxygen Days by Treatment Group – mITT Population, Baseline Ordinal Score of 6

Figure 22: Bee Swarm Plot of Non-invasive Ventilation/High-Flow Oxygen Days by Treatment Group – mITT Population, Baseline Ordinal Score of 4 or 5

Figure 23: Bee Swarm Plot of Non-invasive Ventilation/High-Flow Oxygen Days by Treatment Group – mITT Population, Baseline Ordinal Score of 6

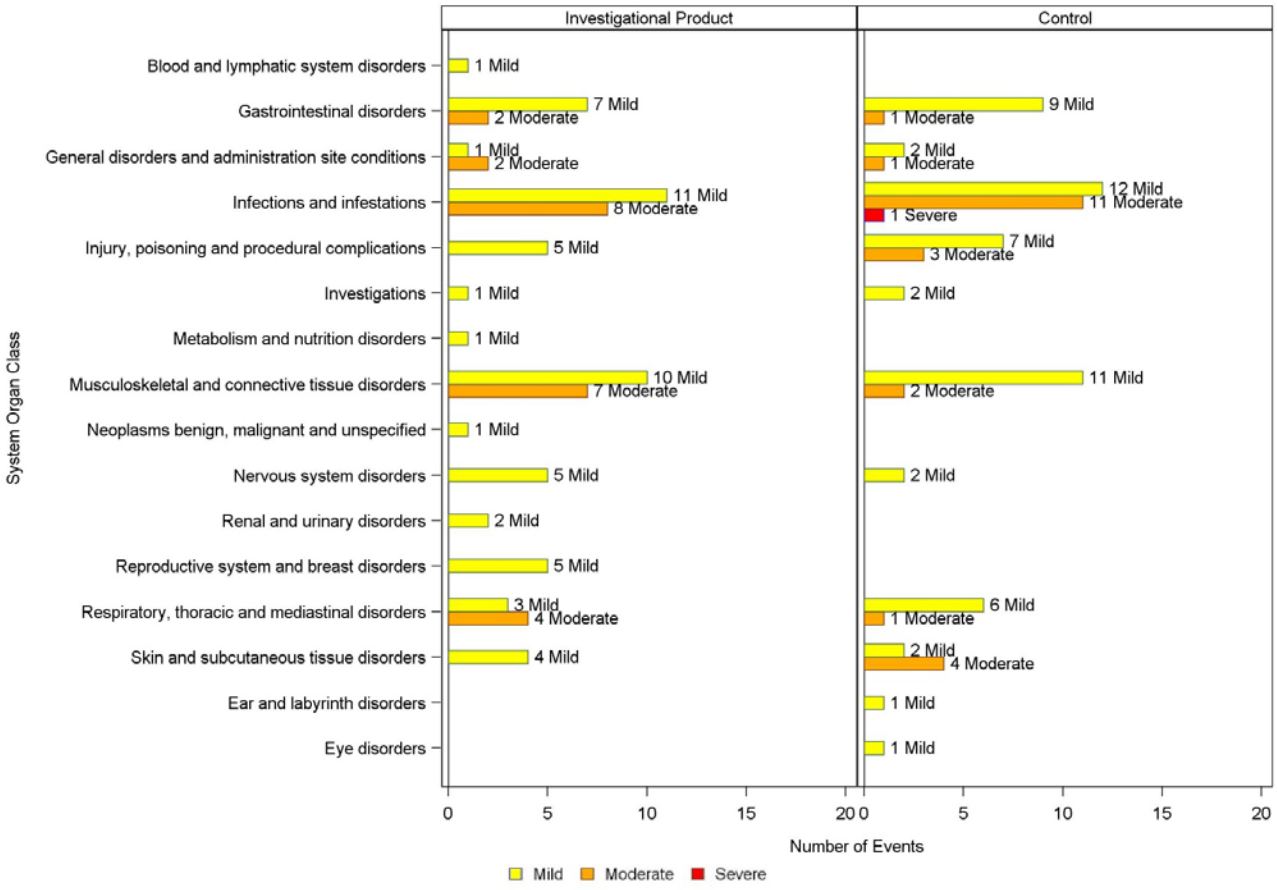
Figure 24: Bee Swarm Plot of Invasive Mechanical Ventilation/ECMO Days by Treatment Group – mITT Population, Baseline Ordinal Score of 4 or 5

Figure 25: Bee Swarm Plot of Invasive Mechanical Ventilation/ECMO Days by Treatment Group – mITT Population, Baseline Ordinal Score of 6

Figure 26: Bee Swarm Plot of Hospitalization Days by Treatment Group – mITT Population, Baseline Ordinal Score of 4 or 5

Figure 27: Bee Swarm Plot of Hospitalization Days by Treatment Group – mITT Population, Baseline Ordinal Score of 6

Figure 28: Frequency of Non-Serious Related Adverse Events by MedDRA System Organ Class, Severity, and Treatment Group - As Treated Population, Baseline Ordinal Score of 4 or 5

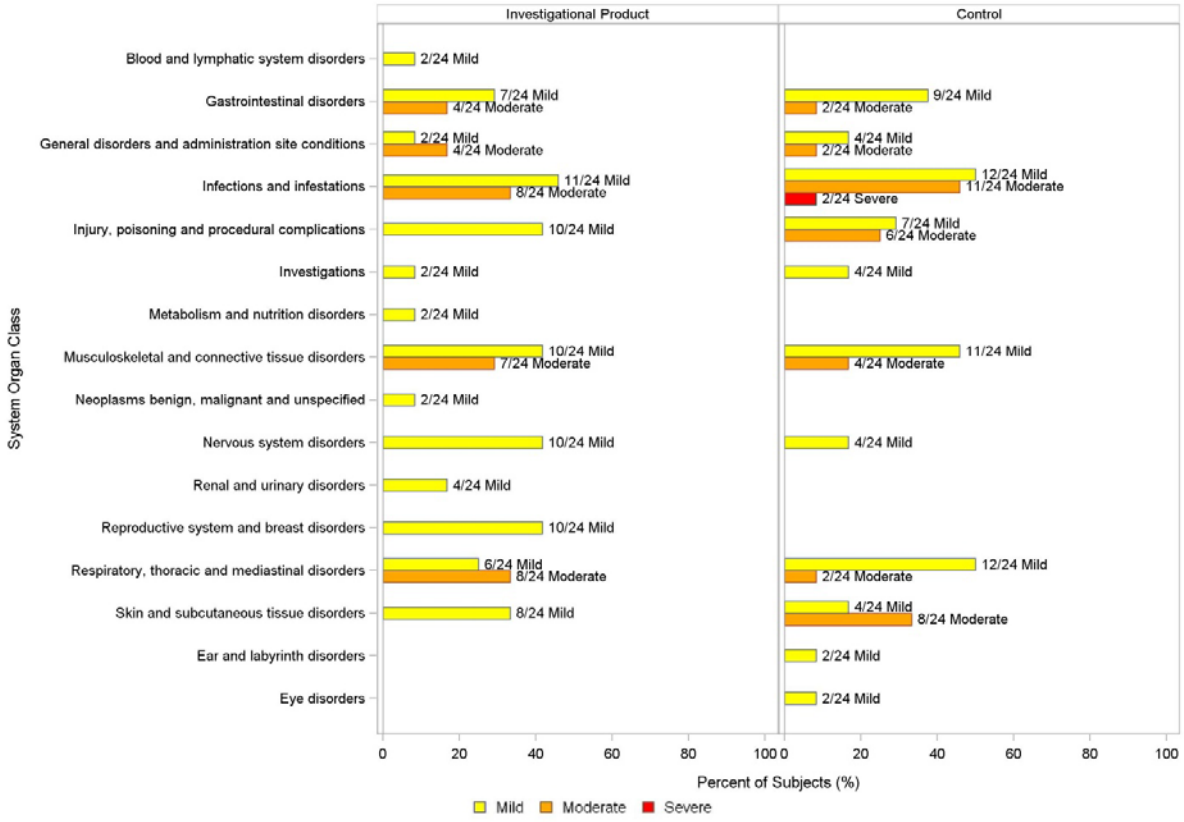


Programming Note: Two separate sub-figures will be generated for each disease severity. Baseline Ordinal Score will be used for each figure.

Figure with similar format:

Figure 29: Frequency of Non-Serious Related Adverse Events by MedDRA System Organ Class, Severity, and Treatment Group – As Treated Population, Baseline Ordinal Score of 6

Figure 30: Incidence of Non-Serious Related Adverse Events by MedDRA System Organ Class, Severity, and Treatment Group - As Treated Population, Baseline Ordinal Score of 4 or 5

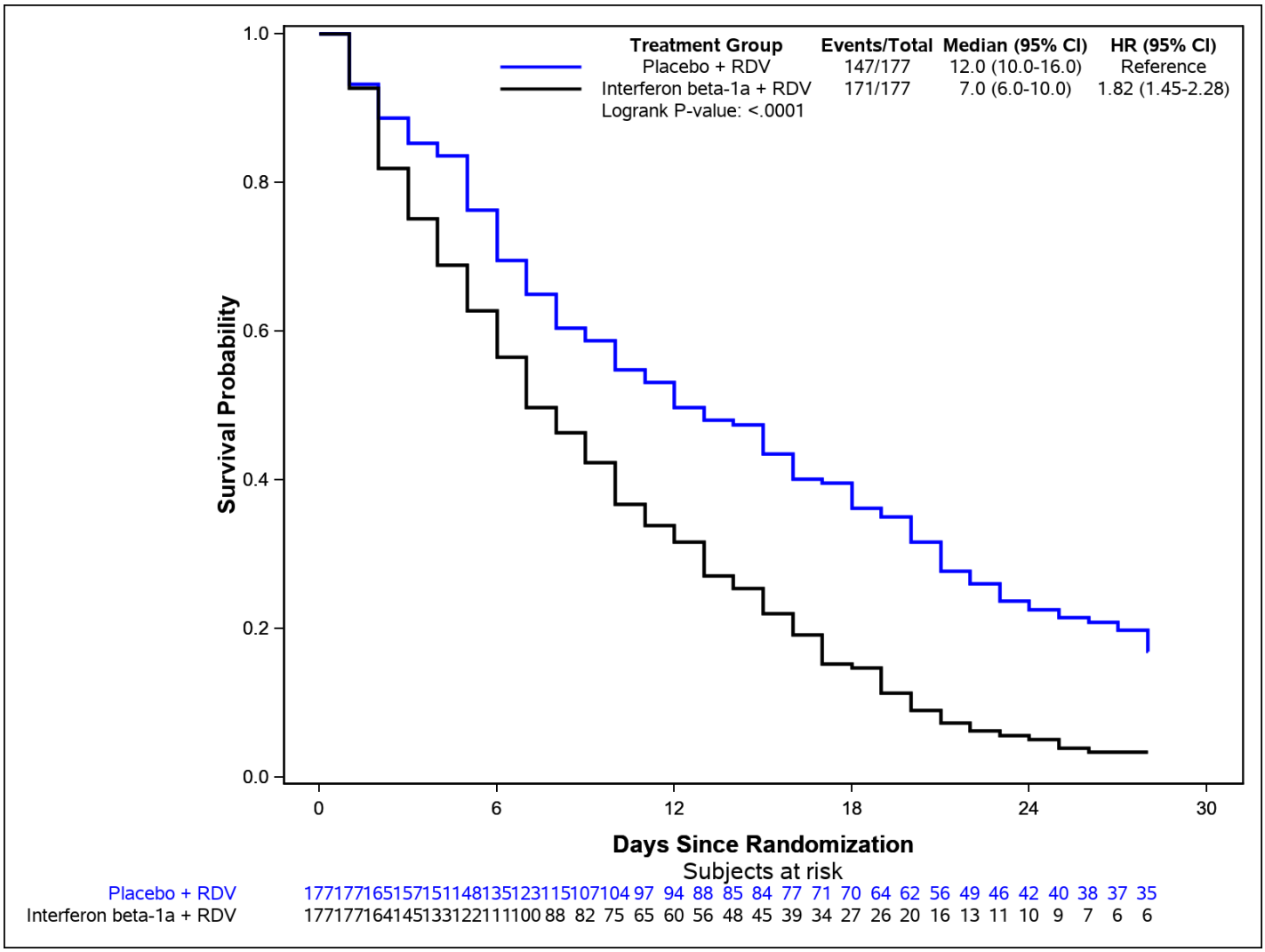


Programming Note: Two separate sub-figures will be generated for each disease severity. Baseline Ordinal Score will be used for each figure.

Figure with similar format:

Figure 31: Incidence of Non-Serious Related Adverse Events by MedDRA System Organ Class, Severity, and Treatment Group – As Treated Population, Baseline Ordinal Score of 6

Figure 32: Kaplan-Meier Curve of Time to Death through Day 29 by Treatment Group – mITT Population



Figures with similar format:

Figure 33: Kaplan-Meier Curve of Time to Death through Day 29 by Treatment Group – As Treated Population

Figure 34: Kaplan-Meier Curve of Time to Death through Day 29 by Treatment Group – mITT Population, Baseline Ordinal Score of 4

Figure 35: Kaplan-Meier Curve of Time to Death through Day 29 by Treatment Group – mITT Population, Baseline Ordinal Score of 5

Figure 36: Kaplan-Meier Curve of Time to Death through Day 29 by Treatment Group – mITT Population, Baseline Ordinal Score of 6

Figure 37: Kaplan-Meier Curve of Time to Death or Progression to Invasive Ventilation through Day 28 by Treatment Group – mITT Population

Figure 38: Kaplan-Meier Curve of Time to Death or Progression to Invasive Ventilation through Day 28 by Treatment Group – As Treated Population

Figure 39: Kaplan-Meier Curve of Time to Death or Progression to Invasive Ventilation through Day 28 by Treatment Group – mITT Population, Baseline Ordinal Score of 4

Figure 40: Kaplan-Meier Curve of Time to Death or Progression to Invasive Ventilation through Day 28 by Treatment Group – mITT Population, Baseline Ordinal Score of 5

Figure 41: Kaplan-Meier Curve of Time to Death or Progression to Invasive Ventilation through Day 28 by Treatment Group – mITT Population, Baseline Ordinal Score of 6

Figure 42: Kaplan-Meier Curve of Time to Death or Progression to Ventilation through Day 28 by Treatment Group – mITT Population

Figure 43: Kaplan-Meier Curve of Time to Death or Progression to Ventilation through Day 28 by Treatment Group – As Treated Population

Figure 44: Kaplan-Meier Curve of Time to Death or Progression to Ventilation through Day 28 by Treatment Group – mITT Population, Baseline Ordinal Score of 4

Figure 45: Kaplan-Meier Curve of Time to Death or Progression to Ventilation through Day 28 by Treatment Group – mITT Population, Baseline Ordinal Score of 5

Figure 46: Kaplan-Meier Curve of Time to Death or Progression to Ventilation through Day 28 by Treatment Group – mITT Population, Baseline Ordinal Score of 6

Figure 47: Kaplan-Meier Curve of Time to Death, SAE, or Grade 3 or 4 AE through Day 29 by Treatment Group – As Treated Population, Baseline Ordinal Score of 4 or 5

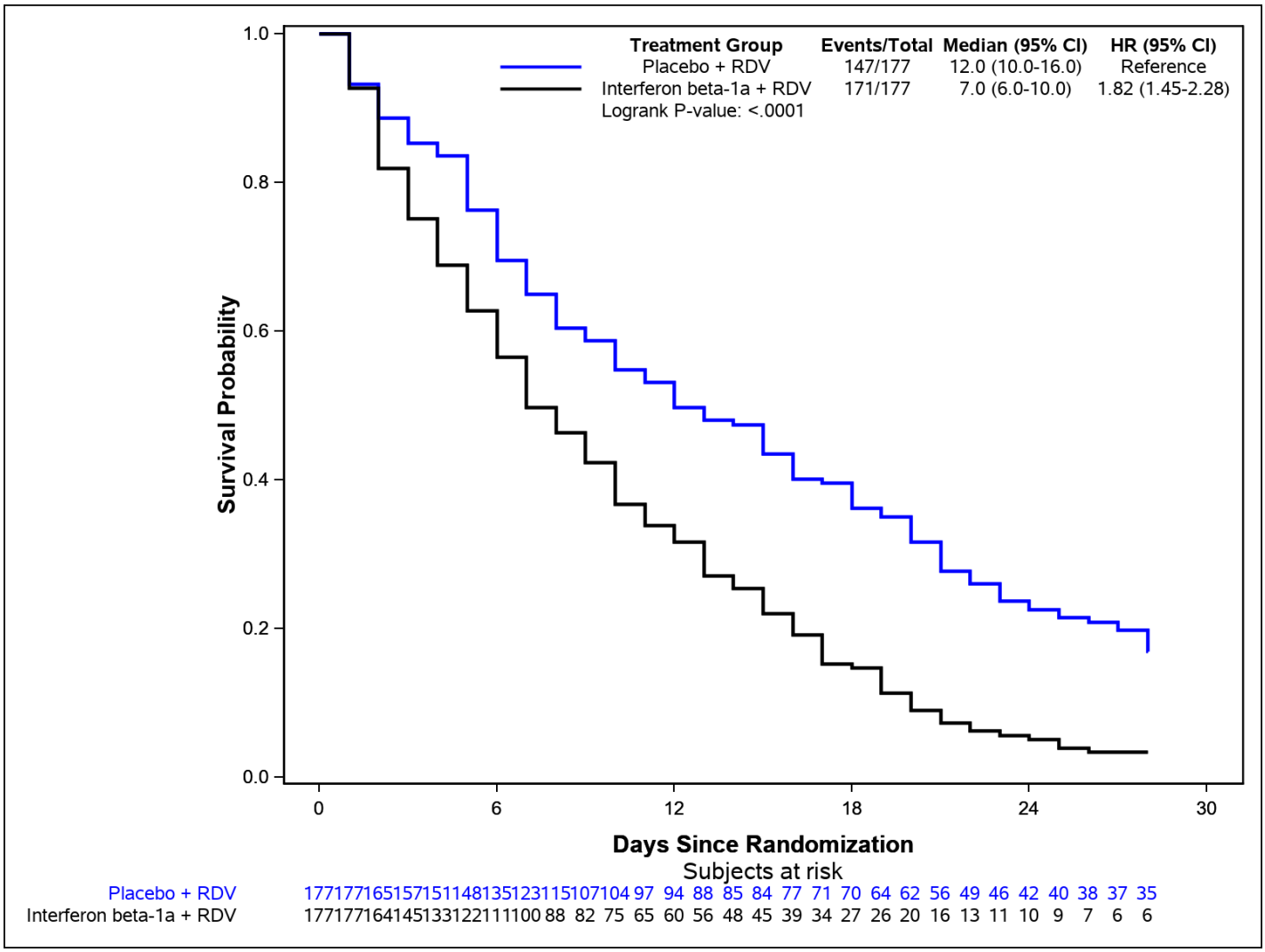
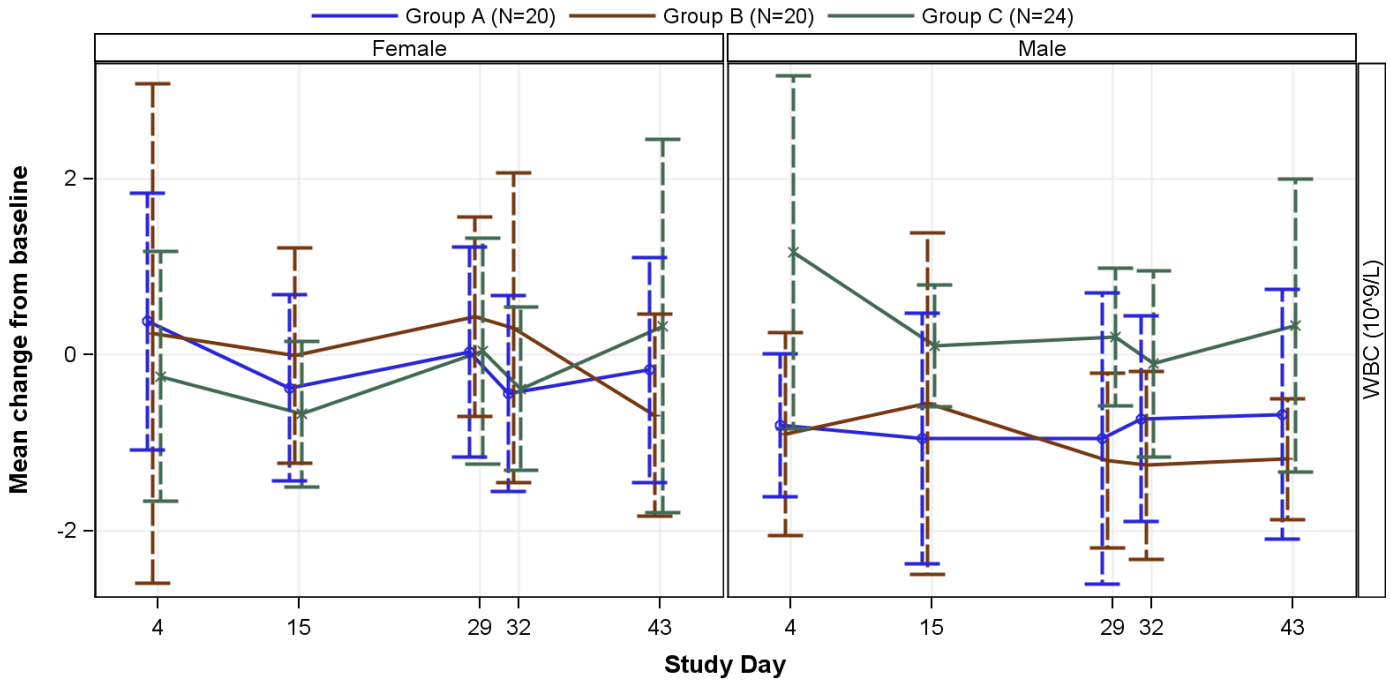


Figure with similar format:

Figure 48: Kaplan-Meier Curve of Time to Death, SAE, Discontinuation of Study Infusions or Grade 3 or 4 AE through Day 29 by Treatment Group – As Treated Population, Baseline Ordinal Score of 6

Figure 49: [Parameter X] Results by Scheduled Visits: Change from Baseline by Treatment Group – As Treated Population



Programming Note: The shell provided is a generic figure. The Groups within a panel will be treatment groups and the panels will be Baseline Ordinal Score (4, 5, or 6). The points will be the median change from baseline and the bars will represent the Q1 and Q3 quartiles of the change from baseline at each time point. Panels for each laboratory parameter will be generated.

APPENDIX 3. LISTINGS MOCK-UPS

TABLE OF LISTINGS

Listing 1: Exclusions from the As Treated Population

Planned Treatment Group	Baseline Ordinal Score	Subject ID
Interferon beta-1a + RDV/ Placebo + RDV	6/5/4	XXXXX

Programming Notes: Include randomized subjects only. Sort Order = Treatment Group, Baseline Ordinal Score (descending order, i.e. 6, then 5 then 4), USUBJID.

Listing 2: Subjects who Early Terminated or Discontinued Treatment

Actual Treatment Group	Baseline Ordinal Score	Subject ID	Category	Treatment Discontinued	Reason for Early Termination or Treatment Discontinuation	Study Day
Interferon beta-1a + RDV/ Placebo + RDV	6/5/4	XXXXX	Early Termination/Treatment Discontinuation	NA/Infusions/Injections/Infusions + Injections	Xxxxxx	xxxx

Programming Notes: Sort Order = Actual Treatment Group, Baseline Ordinal Score (descending order, i.e. 6, then 5 then 4), USUBJID, category where Treatment discontinuation is sorted prior to Early termination. If there are multiple treatment discontinuations (i.e. distinct dates for each product type) the order will be sorted by Study day. If both treatments were discontinued at the same time "Infusions + Injections" will be displayed in the Treatment Discontinued column. If subjects were randomized and not dosed are categorized as "Not Treated" and sorted after Placebo + RDV if applicable.

Listing 3: Subject-Specific Protocol Deviations

Actual Treatment Group	Baseline Ordinal Score	Subject ID	DV Number	Deviation	Deviation Classification	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Comments
Interferon beta-1a + RDV/ Placebo + RDV	6/5/4	Xxxxx	xx	xxx	Major/Minor	xxx	x	xxxx	Yes/No	Yes/No	Yes/No	xxxx

Programming Notes: Sort Order = Actual Treatment Group, Baseline Ordinal Score (descending order, i.e. 6, then 5 then 4), USUBJID, Deviation Number. Concatenate all the specify fields as appropriate. If the columns do not fit within the eCTD specified margins, then Actual Treatment Group, Baseline Ordinal Score, Subject ID will be placed in a header row as in the AE listings.

Listing 4: Non-Subject-Specific Protocol Deviations

Site	Start Date	End Date	Deviation	Deviation Classification	Reason for Deviation	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Category	Comments
xxxx	xxxx	xxxx	xxxx	Major/Minor	xxxx	Yes/No	Yes/No	xxxx	Xxxxx

Programming Notes: Sort Order = Site (use site name and not the 5 alphanumeric site code), start date, deviation. Concatenate all the specify fields as appropriate

Listing 5: Individual Efficacy Response Data: Clinical Status Score Data

Actual Treatment Group	Baseline Ordinal Score	Subject ID	Study Visit Day of Assessment	Actual Study Day of Assessment	Clinical Status Score	Clinical Status
Interferon beta-1a + RDV/ Placebo + RDV	6/5/4	xxxxx	xx	xx	xx	xxxxx

Programming Notes: Sort Order = Actual Treatment Group, Baseline Ordinal Score (descending order, i.e. 6, then 5 then 4), USUBJID, Study Day. Clinical status should match the wording of the scale definitions in Section 4.3.

Listing 6: Individual Efficacy Response Data: NEWS

Study Visit Day	Actual Study Day	Respiratory Rate		O_2 Saturation		Any Supplemental O_2		Temperature		Systolic BP		Heart Rate		Level of Consciousness		Total Score
		bpm	Score	%	Score	Yes/No	Score	°C	Score	mmHg	Score	bpm	Score	A/V/P/U	Score	
Actual Treatment Group: , Baseline Ordinal Score: , Subject ID:																
xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
If the subject was on ECMO, heart rate and respiratory rate is denoted with a "-" and score of 3. If the subject is ventilated, the respiratory rate is denoted with a "-" and a score of 3.																

Programming Notes: Sort Order = Actual Treatment Group, Baseline Ordinal Score (descending order, i.e. 6, then 5 then 4), USUBJID, Study Visit Day.

Listing 7: Demographic Data

Actual Treatment Group	Baseline Ordinal Score	Subject ID	Geographic Region	Sex	Age at Randomization (years)	Ethnicity	Race	Duration of Symptoms prior to Randomization (Days)	Weight (Kg)	Height (Cm)	BMI
Interferon beta-1a + RDV/ Placebo + RDV	6/5/4	xxxxx	xxx	xxx	Xx	xxx	xxx	xxx	xx	Xx	Xxx

Programming Notes: Sort Order = Actual Treatment Group, Baseline Ordinal Score (descending order, i.e. 6, then 5 then 4), USUBJID.

Listing 8: Pre-Existing and Concurrent Medical Conditions

Actual Treatment Group	Baseline Ordinal Score	Subject ID	History of DVT or PE	Major Surgery, Significant Trauma, Long Hospitalization within one month of screening	Prolonged Immobility within one month of screening	Medical History Number	Medical History Term	MedDRA System Organ Class	MedDRA Preferred Term
Interferon beta-1a + RDV/ Placebo + RDV	6/5/4	Xxx001	Yes/No/Unknown	Yes/No/Unknown	Yes/No/Unknown	01	xxxxx	Xxxx	xxxx
						02	xxxxx	Xxxx	xxxx

Programming Note: Sort Order = Actual Treatment Group, Baseline Ordinal Score (descending order, i.e. 6, then 5 then 4), USUBJID, MH Number. Each subject will have one row per medical condition reported on the Medical History CRF. If the subject reported "no" they do not have that pre-existing condition, the condition is not present in the line listing. If there is not enough space to fit all columns within the eCTD specified margins, then Actual Treatment Group, Baseline Ordinal Score, and Subject ID can be displayed in a header row as in the AE listings.

Listing 9: Concomitant Medications

Actual Treatment Group	Baseline Ordinal Score	Subject ID	Medication Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Description; Number)	Taken for a condition on Medical History? (MH Description; Number)	ATC Level 1 (ATC Level 2)
Interferon beta-1a + RDV/ Placebo + RDV	6/5/4	xxx	xx	xxxx	x	x	xxxx	Yes/No	Yes/No	xxxx / xxxx

Programming Notes: Sort Order = Actual Treatment Group, Baseline Ordinal Score (descending order, i.e. 6, then 5 then 4), USUBJID, CM number

Note: If medication started prior to enrollment and there is no date, then Medication Start Day = Prior to Enrollment

If medication is ongoing at end of study, the Medication End Day = Ongoing

Listing 10: Corticosteroid Use

Actual Treatment Group	Baseline Ordinal Score	Subject ID	Medication Number	Medication	Medication Start Day	Medication End Day	Dose / Route	Frequency	Indication	Taken for an AE? (AE Description; Number)
Interferon beta-1a + RDV/ Placebo + RDV	6/5/4	xxx	xx	xxxx	x	x	xx / xx	xx	xxxx	Yes/No

Programming Notes: Sort Order = Actual Treatment Group, baseline OS (descending order, i.e. 6, then 5 then 4), USUBJID, CM number. If medication started prior to enrollment and there is no date, then Medication Start Day = Prior to Enrollment. If medication is ongoing at end of study, the Medication End Day = Ongoing

Listing 11: Medications of Interest

Actual Treatment Group	Baseline Ordinal Score	Subject ID	Medication Number	Medication	Medication Start Day	Medication End Day	Indication	Medication of Interest Category	Medication of Interest Subcategory	ATC Level 1 (ATC Level 2)
Interferon beta-1a + RDV/ Placebo + RDV	6/5/4	xxx	xx	xxxx	x	x	xxxx	xxxx	xxxx	xxxx / xxxx

Programming Notes: Sort Order = Actual Treatment Group, Baseline Ordinal Score (descending order, i.e. 6, then 5 then 4), USUBJID, CM number

Note: If medication started prior to enrollment and there is no date, then Medication Start Day = Prior to Enrollment

If medication is ongoing at end of study, the Medication End Day = Ongoing

If the medication does not have an applicable subcategory, then display 'N/A'

This listing will include statins/ARBs/AECIs under the category "Statins/ARBs/AECIs".

Listing 12: Compliance Data

Dose Number	Infusions				Injections		Reason for Missed Dose	Comments
	Infusion Administered?	Infusion Slowed or Stopped?	Reason(s) for Slowed/Stopped Infusion	Volume Administered if Stopped/Slowed (mL)	Number of Injections Administered	Injection Administered Successfully?		
Actual Treatment Group: , Baseline Ordinal Score: , Subject ID: , Study Day of Discharge: , Study Day of Death:								
1	Yes/No	No/Yes (Slowed)/Yes (Stopped)	Xxxxx / NA	Xxx	4/3/2/1	Yes/No	Xxx/NA	
2	Yes/No	No/Yes (Slowed)/Yes (Stopped)	Xxxxx / NA	Xxx	4/3/2/1	Yes/No	Xxx/NA	
…		…	…	…	…	…	…	…

Programming Notes: Sort Order = Actual Treatment Group, Baseline Ordinal Score (descending order, i.e. 6, then 5 then 4), USUBJID.

Listing 13: Listing of Non-Serious Adverse Events

Adverse Event	Study Day	Duration (Days)	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Unanticipated Problem	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Actual Treatment Group: Baseline Ordinal Score: , Subject ID: , AE Number:											
xxx	xx	x	xxx	Related/Not Related	xxxx	Yes/No	xxx	Yes/No	xxxx	xxxx	xxxx
Comments: xxxx											

Programming Note: Sort order will be Actual Treatment Group, Baseline Ordinal Score (descending order, i.e. 6, then 5 then 4), USUBJID, AE Number.

Listing 14: Listing of Related Adverse Events

Adverse Event	Study Day	Duration (Days)	Severity	Unanticipated Problem	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Actual Treatment Group: Baseline Ordinal Score: , Subject ID: , AE Number:									
xxx	xx	x	xxx	Yes/No	xxx	Yes/No	xxxx	xxxx	xxxx
Comments: xxx									

Programming Note: Sort order will be Actual Treatment Group, Baseline Ordinal Score (descending order, i.e. 6, then 5 then 4), USUBJID, AE Number.

Listing 15: Listing of Non-Fatal Serious Adverse Events

Adverse Event	Study Day	Duration (Days)	No. of Days Post First Dose the Event Became Serious	Reason Reported as an SAE	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Unanticipated Problem	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Actual Treatment Group: , Baseline Ordinal Score: , Subject ID: , AE Number:													
xxxx	x	x	x	xxxxx	xxx	Related/Not Related	xxxx	Yes/No	xxxx	Yes/No	xxxxx	xxxxx	xxxxx
Comments: xxxx													

Programming Note: Sort order will be Actual Treatment Group, Baseline Ordinal Score (descending order, i.e. 6, then 5 then 4), USUBJID, AE Number.

Listing 16: Listing of Deaths

Adverse Event	Study Day	Duration (Days)	No. of Days Post First Dose the Event Became Serious	Reason Reported as an SAE	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Unanticipated Problem	Action Taken with Study Treatment	Subject Discontinued Due to AE	MedDRA System Organ Class	MedDRA Preferred Term
Actual Treatment Group: , Baseline Ordinal Score: , Subject ID: , AE Number:												
xxxx	x	x	x	xxxxx	xxx	Related/Not Related	xxxx	Yes/No	xxxx	Yes/No	xxxxx	xxxxx
Comments: xxxx												

Programming Note: Sort by Actual Treatment Group, Baseline Ordinal Score (descending order, i.e. 6, then 5 then 4), USUBJID.

Listing 17: Pregnancy Reports – Maternal Information

Actual Treatment Group	Subject ID	Pregnancy Number	Study Day Corresponding to Estimated Date of Conception	Source of Maternal Information	Pregnancy Status	Mother's Pre-Pregnancy BMI	Mother's Weight Gain During Pregnancy	Tobacco, Alcohol, or Drug Use During Pregnancy?	Medications During Pregnancy?	Maternal Complications During Pregnancy?	Maternal Complications During Labor, Delivery, or Post-Partum?
Maternal Complications are included in the Adverse Event listing. Medications taken during pregnancy are included in the Concomitant Medications Listing.											

Listing 18: Pregnancy Reports – Gravida and Para

			Live Births													
Actual Treatment Group	**Subject ID**	**Pregnancy Number**	**Gravida**	**Extremely PB[a]**	**Very Early PB[a]**	**Early PB[a]**	**Late PB[a]**	**Early TB[b]**	**Full TB[b]**	**Late TB[b]**	**Post TB[b]**	**Still Births**	**Spontaneous Abortion/ Miscarriage**	**Elective Abortions**	**Therapeutic Abortions**	**Major Congenital Anomaly with Previous Pregnancy?**
Interferon beta-1a + RDV/ Placebo + RDV																
Gravida includes the current pregnancy, para events do not.																

[a] Preterm Birth
[b] Term Birth

Listing 19: Pregnancy Reports – Live Birth Outcomes

Actual Treatment Group	Subject ID	Pregnancy Number	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Live Birth	Size for Gestational Age	Apgar Score, 1 minute	Apgar Score, 5 minutes	Cord pH	Congenital Anomalies?	Illnesses/ Hospitalizations within 1 Month of Birth?
Interferon beta-1a + RDV/ Placebo + RDV													
Congenital Anomalies are included in the Adverse Event listing.													

Listing 20: Pregnancy Reports – Still Birth Outcomes

Actual Treatment Group	Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Still Birth	Size for Gestational Age	Cord pH	Congenital Anomalies?	Autopsy Performed?	If Autopsy, Etiology for Still Birth Identified?
Interferon beta-1a + RDV/ Placebo + RDV												

Listing 21: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

Actual Treatment Group	Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Gestational Age at Termination	Abnormality in Product of Conception?	Reason for Therapeutic Abortion
Interferon beta-1a + RDV/ Placebo + RDV							

Listing 22: Clinical Laboratory Results

Actual Treatment Group	Baseline Ordinal Score	Subject ID	Planned Time Point	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Toxicity Grade)	Change from Baseline	Reference Range Low	Reference Range High
Interferon beta-1a + RDV/ Placebo + RDV	6/5/4	xxx	xx	xx	Xx	x	xxx (xxx)	xxx (xxxx)	xxx	xxxx	xxxx

Programming Note: Sort order will be Actual Treatment Group, Baseline Ordinal Score (descending order, i.e. 6, then 5 then 4), USUBJID, planned time point, and lab parameter. If subjects were randomized and not dosed "Not Treated" will be used for the actual treatment category and will be sorted after Placebo+ RDV. All parameters will be included in the listing.

Listing 23: Physical Exam Findings

Actual Treatment Group	Baseline Ordinal Score	Subject ID	Planned Study Day	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)
Interferon beta-1a + RDV/ Placebo + RDV	6/5/4	xxx	xx	xx	xxxx	xxxxxx	Yes/No/NA

Programming Note: For respiratory findings denoted as 'Yes' on the Physical Exam CRF, denote the Body System as 'Respiratory Finding' and denote the Abnormal Finding as the symptom name; e.g. if Wheezing is reported, the Abnormal Finding will be 'Wheezing'. The Reported as an AE cell will be denoted as 'NA' for respiratory findings. Each reported respiratory finding will appear in its own row. If the finding was not reported as an AE as recorded on the CRF or the site did not report whether the finding was reported as an AE, the cell will display 'No'.

Sort order will be Actual Treatment Group, Baseline Ordinal Score (descending order, i.e. 6, then 5 then 4), USUBJID, planned time point, and body system.

Listing 24: Subjects who Received the Incorrect Treatment

Subject ID	Randomized Treatment Group	Number of Interferon/Placebo Doses Received	Number of RDV Doses Received	Number of Incorrect Doses Received
xxx	Interferon beta-1a + RDV/ Placebo + RDV	x	x	x

Listing 25: Subjects Randomized to the Incorrect Disease Severity Stratum

Subject ID	Actual Treatment Group	Randomized Disease Severity	Baseline Ordinal Score
xxx	Interferon beta-1a + RDV/ Placebo + RDV	6/5/4	6/5/4

Programming Note: Sort by USUBJID. If subjects were randomized and not dosed "Not Treated" will be used for the actual treatment category.