

Longitudinal Data Reviewer's Guide

**A Multicenter, Adaptive, Randomized Blinded Controlled Trial of
the Safety and Efficacy of Investigational Therapeutics for the
Treatment of COVID-19 in Hospitalized Adults
Adaptive COVID-19 Treatment Trial ACTT-2**

DMID Protocol: 20-0006

Version 2.0

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Table of Contents

1	Introduction	3
1.1	Purpose	3
1.2	Acronyms	3
1.3	Study Data Standards and Dictionary Inventory	3
1.4	Source Data Used for Analysis Dataset Creation.....	3
2	Protocol Description.....	3
2.1	Protocol Number and Title	3
2.2	Treatment Variables	3
2.3	Use of Visit Windowing, Unscheduled Visits, and Record Selection	4
2.4	Subject Issues that Require Special Analysis Rules.....	4
3	Analysis Dataset Descriptions.....	4
3.1	Overview	4
3.2	Analysis Datasets	4
3.2.1	actt2_longitudinal_addvars – Longitudinal Analysis Data Set	5

1 Introduction

1.1 Purpose

This document provides context for the data contained in the ACTT-2 longitudinal dataset.

1.2 Acronyms

Acronym	Translation
ACTT	Adaptive COVID-19 Treatment Trial
ACTT-2	Adaptive COVID-19 Treatment Trial Stage 2
ADaM	Analysis Data Model
COVID-19	Coronavirus Disease 2019
IG	Implementation Guide

1.3 Study Data Standards and Dictionary Inventory

No dictionaries were used for the data included in the transfer. See Section 3.2.1 for the definitions of the Ordinal Scale Scores.

1.4 Source Data Used for Analysis Dataset Creation

The source data for the Longitudinal Data was ACTT-2 Clinical Study Report ADaM datasets.

2 Protocol Description

2.1 Protocol Number and Title

Protocol Number: 20-0006

Protocol Title: Adaptive COVID-19 (Coronavirus Disease 2019) Treatment Trial (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

Protocol Version: Version: 6.0

2.2 Treatment Variables

ARM

- Planned/Randomized Treatment

ACTARM

- Actual Treatment

2.3 Use of Visit Windowing, Unscheduled Visits, and Record Selection

Was windowing used in one or more analysis datasets?

Yes. For Day 15, Day 22, and Day 29, if the subject died within the visit window then an ordinal score of 8 was used for the visit regardless of whether a lower ordinal score was recorded at the actual visit. The visit windows for Day 15 was +/- 2 days, Day 22 was +/- 3 days and Day 29 was +/- 3 days.

Were unscheduled visits used in any analyses?

Unscheduled visits were rare in this study as subjects were in the hospital at the start of the study and had daily visits until discharged. There were no clinical ordinal scores collected at unscheduled visits.

When were ordinal scores assessed?

Subjects were assessed for ordinal score every day while hospitalized and on Day 15, Day 22, Day 29 after discharge. The ordinal score recorded is the worst score on the previous day of the visit date. Assessment date is the date the ordinal score occurred.

2.4 Subject Issues that Require Special Analysis Rules

There were no special analysis rules identified.

3 Analysis Dataset Descriptions

3.1 Overview

- Do the analysis datasets support all protocol- and statistical analysis plan-specified objectives?

No. The longitudinal data set only contains a small subset of the protocol and statistical analysis plan objectives.

3.2 Analysis Datasets

<u>Dataset</u> Dataset Label	Efficacy	Safety	Baseline or other subject characteristics	Primary Objective	Structure
actt2_longitudinal_addarm Time-to-Event Dataset	X		X	X	One observation per subject per analysis visit

3.2.1 actt2_longitudinal_addvars – Longitudinal Analysis Data Set

actt2_longitudinal_addvars is an analysis dataset of the parameters for time to recovery, clinical ordinal score and mortality.

The table below provides a definition for each parameter.

Label	Variable	Definition	Corresponding ACTT-2 Original Data Set Variable
Unique Subject ID	USUBJID	Unique Subject Identifier	USUBJID
Randomized Treatment	ARM	Treatment Randomized to Receive	TRTP
Actual Treatment	ACTARM	Treatment Received	Not contained in ACTT-2 Original Data Set
Baseline Severity – Actual Ordinal Scale	BCSOSN	Baseline Ordinal Scale Score at Time or Randomization	ORDSCG
Time to Death (days) ¹	D29DTHE0	Date of Death – Date of Randomization	TTDEATH where DTHCNSR=0 D29DTHE0 is missing for subjects where DTHCNSR=1 in the ACTT-2 Original Data Set
Time to Death Censor Time Point (days) ¹	D29 DTHE1	Date of Last Visit – Date of Randomization	TTDEATH where DTHCNSR=1 D29DTHE1 is missing for subjects where DTHCNSR=0 in the ACTT-2 Original Data Set
Time to Recovery (days) ^{1,2}	TTRECOV0	Date of Recovery – Date of Randomization	TTRECOV where RECCNSR=0 TTRECOV0 is missing for subjects with RECCNSR=1 in the ACTT-2 Original Data Set
Time to Recovery Censor Time Point (days) ¹	TTRECOV1	Date of Last Visit – Date of Randomization	TTRECOV where RECCNSR=1 TTRECOV1 is missing for subjects with RECCNSR=0 in the ACTT-2 Original Data Set

Label	Variable	Definition	Corresponding ACTT-2 Original Data Set Variable
Ordinal Scale Score Assessment Day ¹	ADYC	Baseline=Last Observed Ordinal Score prior to Randomization ADYC="1" is ordinal score between Randomization and midnight on day of Randomization. ADYC="2", "3" ... is Assessment Date – Randomization Date + 1	Not contained in ACTT-2 Original Data Set
Ordinal Scale Score ²	ORDSCOR	See table below. This column does not include any imputations for missing data, other than death. Death was carried forward for Assessment Days 15, 22 and 29, if the death occurred prior to the visit.	Ordinal score values for timepoints other than baseline and Day 15 are not contained in the ACTT-2 Original Data Set
Ordinal Scale Score Day 15	OR15SCOR	If a subject was missing Day 15 ordinal score, then the following imputations were used: <ul style="list-style-type: none"> • Subject was randomized but had no ordinal score data available for any timepoint (pre- or post-randomization): OR15SCOR="7". • Subject died on or prior to study day 15: OR15SCOR = "8" • Subject was discharged from the hospital not due to death or transfer to hospice/another hospital and did not return for the Day 15 visit: OR15SCOR = "2" • Subject was discharged from the hospital due to transfer to hospice: OR15SCOR = "7". • Subject was discharged from the hospital due to transfer to another hospital: OR15SCOR = last observed ORDSCOR. • Subject was terminated from the study while hospitalized (termination not due to death) prior to Day 15 assessment: OR15SCOR = last observed ORDSCOR. • Subject was discharged and 	ORDSCR15

Label	Variable	Definition	Corresponding ACTT-2 Original Data Set Variable
		readmitted 2 or more days later to the hospital prior to Day 15 assessment and was still hospitalized at study day 15: OR15SCOR = "7".	
Age (years)	AGEC	Age at Time of Randomization. Note: Age is a character field as all subjects > 89 years of age are included with an age of >89 to help maintain data anonymity.	AGE
Sex	SEX	M=Male F=Female	SEX
Duration of Symptoms (days)	BDURSYMP	Subject Reported Duration of Symptoms at Time of Randomization	BDURSYMP
Comorbidities	COMORB1	Any Comorbidities Reported at BaselineCategorized as: <ul style="list-style-type: none"> Any Comorbidities No Comorbidities Unknown The following comorbidities are included: <ul style="list-style-type: none"> Baseline Hypertension Baseline Coronary Artery Disease Baseline Congestive Heart Failure Baseline Chronic Respiratory Disease Baseline Chronic Oxygen Requirement Baseline Chronic Liver Disease Baseline Chronic Kidney Disease Baseline Diabetes I Baseline Diabetes II Baseline Obesity Baseline Cancer Baseline Immune Deficiency Baseline Asthma 	COMORB1

Label	Variable	Definition	Corresponding ACTT-2 Original Data Set Variable
Comorbidities	COMORB2	<p>Number of Comorbidities Reported at BaselineCategorized as:</p> <ul style="list-style-type: none"> • None • 1 Comorbidity • 2 or more Comorbidities <p>The following comorbidities are included:</p> <ul style="list-style-type: none"> • Baseline Hypertension • Baseline Coronary Artery Disease • Baseline Congestive Heart Failure • Baseline Chronic Respiratory Disease • Baseline Chronic Oxygen Requirement • Baseline Chronic Liver Disease • Baseline Chronic Kidney Disease • Baseline Diabetes I • Baseline Diabetes II • Baseline Obesity • Baseline Cancer • Baseline Immune Deficiency • Baseline Asthma 	COMORB2
Race	RACE	<p>Reported Race, including:</p> <ul style="list-style-type: none"> • American Indian or Alaska Native • Asian • Native Hawaiian or Other Pacific Islander • Black or African American • White • Multiple • Unknown 	RACE
Ethnicity	ETHNIC	<p>Reported Ethnicity, including:</p> <ul style="list-style-type: none"> • Not Hispanic or Latino • Hispanic or Latino • Not Reported • Unknown, 	ETHNIC
BMI (kg/m2)	BMI	Defined as: $\text{Weight} / (\text{Height} / 100)^2$	BMI

Label	Variable	Definition	Corresponding ACTT-2 Original Data Set Variable
Geographic Region 1	REGION1	<ul style="list-style-type: none"> • US Site • Non-US Site 	Not contained in ACTT-2 Original Data Set
Geographic Region 2	REGION2	<ul style="list-style-type: none"> • North America • Europe • Asia 	REGION
Randomized Disease Severity Stratum (N)	STRATAR	Disease Severity used for Randomization: <ul style="list-style-type: none"> • Severe Disease • Moderate Disease 	Not contained in ACTT-2 Original Data Set
Actual Disease Severity Stratum (N)	STRATAV	Actual Disease Severity at the Time of Randomization <ul style="list-style-type: none"> • Severe Disease • Moderate Disease 	STRATUM
Baseline Hypertension Flag	HYPFL	Y, N, or null; subject reported hypertension at time of screening	HYPFL
Baseline Coronary Artery Disease Flag	CADFL	Y, N, or null; subject reported coronary artery disease at time of screening	CADFL
Baseline Congestive Heart Failure Flag	CHFFL	Y, N, or null; subject reported congestive heart failure at time of screening	CHFFL
Baseline Chronic Resp Disease Flag	CRDFL	Y, N, or null; subject reported chronic respiratory disease at time of screening	CRDFL
Baseline Chronic Oxygen Requirement Flag	CORFL	Y, N, or null; subject reported chronic oxygen requirement at time of screening	CORFL

Label	Variable	Definition	Corresponding ACTT-2 Original Data Set Variable
Baseline Chronic Liver Disease Flag	CLDFL	Y, N, or null; subject reported chronic liver disease at time of screening	CLDFL
Baseline Chronic Kidney Disease Flag	CKDFL	Y, N, or null; subject reported chronic kidney disease at time of screening	CKDFL
Baseline Diabetes I Flag	DIAB1FL	Y, N, or null; subject reported Diabetes I at time of screening	DIAB1FL
Baseline Diabetes II Flag	DIAB2FL	Y, N, or null; subject reported Diabetes II at time of screening	DIAB2FL
Baseline Obesity Flag	OBESIFL	Y, N, or null; subject reported obesity at time of screening	OBESIFL
Baseline Cancer Flag	CANCERFL	Y, N, or null; subject reported cancer at time of screening	CANCERFL
Baseline Immune Deficiency Flag	IMMDFL	Y, N, or null; subject reported immune deficiency at time of screening	IMMDFL
Baseline Asthma Flag	ASTHMAFL	Y, N, or null; subject reported asthma at time of screening	ASTHMAFL

¹Time to death and time to recovery fields will be one day less than the Ordinal Scale Score Assessment Day. The Assessment Day is the Study Day while the time to death or recovery is the days from randomization. For example, subjects are randomized on Day 1 and if a subject died on Day 3, the time to death would be 2 days.

²Time to recovery does not align with the first observed ordinal score of a 1, 2 or 3 in many cases. This is due to subjects being discharged from the hospital and the site then collects the next ordinal scale score at their next visit on Days 15, 22 or 29. Since they are discharged, the subject meets the definition of a 1 or 2 ordinal scale score once discharged and their time to recovery is the time to discharge.

The table below provides the ordinal scale definitions.

Ordinal Scale	Ordinal Scale Score
Death	8
Hospitalized, on invasive mechanical ventilation or ECMO	7
Hospitalized, on non-invasive ventilation or high flow oxygen devices	6
Hospitalized, requiring supplemental oxygen	5
Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care	4
Hospitalized, not requiring supplemental oxygen, no longer requires ongoing medical care	3
Not hospitalized, limitation on activities and/or requiring home oxygen	2
Not hospitalized, no limitation on activities	1