Approvals

ACTIV-2/ACTG A5401

Statistical Analysis Plan

Exploratory Analysis of PASC Outcomes at Week 36

Randomized Comparison of BRII-196 + BRII-198 versus Placebo

Version 1.0

Adaptive Platform Treatment Trial for Outpatients with COVID-19

(Adapt Out COVID)

July 11, 2022

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Version History

Version	Changes Made	Date Finalized
1.0	Original Version	July 11, 2022

Glossary of Terms

AE	Adverse Event
BMI	Body Mass Index
COVID-19	Coronavirus Disease 2019
LTFU	Loss to Follow Up
PASC	Post-Acute Sequelae of SARS-CoV-2 infection
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SOC	System Organ Class
SOE	Schedule of Evaluations

1 Introduction

1.1 Purpose

This Statistical Analysis Plan (SAP) describes the general framework for the randomized comparisons of Post-Acute Sequelae of SARS-CoV-2 infection (PASC) for Amubarvimab/Romlusevimab (BRII-196+BRII-198) versus placebo at Week 36 in ACTIV-2/A5401. This analysis is restricted to Week 36 due to data availability at the anticipated time of conducting this analysis as questionnaires were introduced after the study was underway (affecting availability at Weeks 12 and 24) and participants were in follow-up (and so some have not reached Weeks 48 or 72). Other outcomes will also be evaluated, including quality of life measures from the EQ-5D-5L questionnaire, and safety.

Because scoring of quality of life measures from the SF-36 questionnaire will be undertaken at a later date, the team determined this analysis should proceed and focus on the long-term symptom diary (PASC outcomes) and EQ-5D-5L responses for presentation and publications in the interest of informing the field concerning treatment effects on PASC outcomes. Details on outcomes and analysis approaches of responses from the SF-36 will be included in future SAPs.

This SAP outlines the general statistical approaches that will be used in the analysis of the study and has been developed to facilitate discussion of the statistical analysis components among the study team, industry collaborators, and study sponsor; and to provide agreement between the study team and statisticians regarding the statistical analyses to be performed and presented.

1.2 Version History of this SAP

N/A

2 Study Overview

2.1 Study Design

ACTIV-2/A5401 is a master protocol to evaluate the safety and efficacy of investigational agents for the treatment of symptomatic non-hospitalized adults with COVID-19. The study is designed to evaluate both infused and non-infused investigational agents.

The trial has a randomized controlled adaptive platform study design that allows agents to be added or dropped during the course of the study for efficient phase II and phase III testing of new agents within the same trial infrastructure.

Enrollment to the phase II placebo-controlled evaluation of BRII-196+BRII-198 briefly coincided with the enrollment of other phase II agents. Thus, the placebo control group for BRII-196+BRII-198 includes one participant who received placebo for another agent. Enrollment to the phase III placebo-controlled evaluation of BRII-196+BRII-198 did not coincide with enrollment of any other agents in phase III, and so there is no sharing of the placebo control group for phase III.

Participants had intensive follow-up through day 28, followed by limited follow up through week 72 in phase II and phase III.

The study population consists of adults (≥ 18 years of age) with documented positive SARS-CoV-2 molecular test results collected within 240 hours (10 days) prior to study entry with no more than 10 days of symptoms of COVID-19 prior to study entry (shortened to 7 days during the course of the study), and with presence of select symptoms within 24 hours of study entry.

Enrollment to BRII-196+BRII-198 was restricted to individuals at higher risk for progression to severe COVID-19. Randomization in both study phases was stratified by time from symptom onset (≤5 days vs >5 days).

2.2 Analysis Objectives

Enrollment to BRII-196+BRII-198 was initiated under Protocol Version 2.0 and the following exploratory objectives were added in Protocol Version 6.0:

1) Phases II and III: To explore the prevalence, severity, and type of persistent symptoms and clinical sequelae in participants through end of study follow-up. [Protocol Objective 1.3.11].

2) Phase II and III: To explore measures of psychological health, functional health, and health-related quality of life in participants through end of study follow-up. [Protocol Objective 1.3.12].

3 Outcome Measures

3.1 Primary PASC Outcome Measure and Associated Supportive Outcome Measures

1) [Primary Outcome Measure] Presence of participant-reported PASC at study week 36, or death due to any cause or hospitalization due to any cause at or prior to week 36.

   Participant-reported PASC is defined as having either ‘mild’, ‘moderate’ or ‘severe’ symptoms present in the past 4 weeks as recorded in the first global assessment question on the Long-Term Follow-Up Participant Study Diary. PASC is not present if a participant reported ‘no symptoms’.

2) [Supportive] Severity of participant-reported PASC at study week 36

   Severity of participant-reported PASC scored from 0 to 3, with 0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe symptoms present, and with 4 = death/hospitalization at or prior to week 36.

3.2 Secondary PASC Outcome Measures

3) Worst severity of symptoms present at week 36

   Across all the 27 possible symptoms, the worst severity reported ranging from severe, moderate, mild, and none.

4) Total symptom score at study week 36.

   Total symptom score defined as the sum of severity scores for the 27 symptoms, each ranging from 0 (none) to 3 (severe). Thus, total symptom score range is from 0 to 81.

5) General physical health status (positive or negative) at study week 36

   General physical health status is determined based on the second global assessment question on the Long-Term Follow-up Participant Study Diary. Positive health status is defined as participant-reported health status over the past 4 weeks as ‘excellent’, ‘very good’ or ‘good’. Negative health status is defined as self-reported health status over the past 4 weeks as ‘fair’ or ‘poor’.

6) Return to usual (pre-COVID) health status at study week 36

   Return to usual (pre-COVID) health status is determined based on the third global assessment question on the Long-Term Follow-up Participant Study Diary. Participants are considered to have returned to their usual (pre-COVID) health if they answer ‘yes’ and are not considered to have returned to their usual (pre-COVID) health if they answer ‘no’.

7) Number of symptoms present at week 36

   The number of symptoms present is defined as the total number of symptoms present among the 27 possible symptoms. A symptom is considered present if the participant reports the symptom as ‘mild’, ‘moderate’, or ‘severe’. Symptom severity, over the past 4 weeks, is recorded as ‘absent’, ‘mild’, ‘moderate’, or ‘severe’ for each of 27 symptoms in question 4 in the Long-Term Follow-Up Participant Study Diary.

8) Presence of four or more symptoms at week 36

   Defined as having four of more, of the 27 symptoms, reported as ‘mild’, ‘moderate’, or ‘severe’.

9) Presence of Upper Respiratory symptoms at week 36

   Upper respiratory symptoms include ‘sore throat‘, ‘nasal obstruction or congestion (stuffy nose)‘, and ‘nasal discharge (runny nose)‘. Upper respiratory symptoms are considered present if any of the symptoms are reported as ‘mild’, ‘moderate’, or ‘severe’.

10) Presence of Cardiopulmonary/Cardiothoracic symptoms at week 36

    Cardiopulmonary/cardiothoracic symptoms include ‘cough‘, ‘shortness of breath or difficulty breathing‘, ‘palpitations or fast heartbeat‘, and ‘chest pain‘. Cardiopulmonary/cardiothoracic symptoms are considered present if any of the symptoms are reported as ‘mild’, ‘moderate’, or ‘severe’.

11) Presence of Constitutional symptoms at week 36

    Constitutional symptoms include ‘feeling feverish‘, ‘chills‘, ‘fatigue (low energy) ‘, and ‘decreased appetite‘. Constitutional symptoms are considered present if any of the symptoms are reported as ‘mild’, ‘moderate’, or ‘severe’.

12) Presence of Musculoskeletal symptoms at week 36

    Musculoskeletal symptoms include ‘body pain or muscle pain or aches‘, ‘muscle weakness‘, and ‘joint pain‘. Musculoskeletal symptoms are considered present if any of the symptoms are reported as ‘mild’, ‘moderate’, or ‘severe’.

13) Presence of Gastrointestinal symptoms at week 36

    Gastrointestinal symptoms include ‘diarrhea‘, ‘nausea‘, and ‘vomiting‘. Gastrointestinal symptoms are considered present if any of the symptoms are reported as ‘mild’, ‘moderate’, or ‘severe’.

14) Presence of Neurocognitive symptoms at week 36

    Neurocognitive symptoms include ‘dizziness/balance issues‘, ‘headache‘, ‘insomnia‘, ‘difficulty with concentration and thinking‘, ‘difficulty with reasoning and solving problems‘, and ‘memory loss (short or long term)‘. Neurocognitive symptoms are considered present if any of the symptoms are reported as ‘mild’, ‘moderate’, or ‘severe’.

15) Presence of Sensory symptoms at week 36

    Sensory symptoms include ‘smell disorder‘ and ‘taste disorder‘. Sensory symptoms are considered present if any of the symptoms are reported as ‘mild’, ‘moderate’, or ‘severe’.

16) Presence of Dermatologic symptoms at week 36

    Dermatologic symptoms include ‘hair loss‘ and ‘skin rash‘. Dermatologic symptoms are considered present if any of the symptoms are reported as ‘mild’, ‘moderate’, or ‘severe’.

3.3 Secondary Quality of Life Outcome Measures (as assessed in the EQ-5D-5L questionnaire)

17) Presence of mobility problems at study week 36

    Mobility problems is defined as self-reporting slight, moderate, or severe problems walking about, or reporting being unable to walk about to the ‘mobility’ question on the EQ-5D-5L questionnaire.

18) Presence of self-care problems at study week 36

    Self-care problems is defined as self-reporting slight, moderate, or severe problems washing or dressing myself, or reporting being unable to wash or dress myself to the ‘self-care’ question on the EQ-5D-5L questionnaire.

19) Presence of problems doing my usual activities at study week 36

    Problems doing my usual activities is defined as self-reporting slight, moderate, or severe problems doing my usual activities, or reporting being unable to do my usual activities to the ‘usual activities’ question on the EQ-5D-5L questionnaire.

20) Presence of pain or discomfort at study week 36

    Pain or discomfort is defined as self-reporting slight, moderate, severe, or extreme pain or discomfort to the ‘pain/discomfort’ question on the EQ-5D-5L questionnaire.

21) Presence of anxiety or depression at study week 36

    Anxiety or depression is defined as self-reporting being slightly, moderately, severely, or extremely anxious or depressed to the ‘anxiety/depression question on the EQ-5D-5L questionnaire.

22) Current health score at study week 36

    Current health score is self-reported by the participant ranging from 0 (the worst health you can imagine) to 100 (the best health you can imagine) on the EQ-5D-5L questionnaire.

3.4 Other Supportive Outcome Measures

23) Death due to any cause or hospitalization due to any cause during the 36-week period from and including the day of the first dose of investigational agent or placebo.

    Hospitalization is defined as ≥24 hours of acute care, in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic.

24) New Grade 3 or higher AE through week 36.

    New Grade 3 or higher AE is defined as: Grade 3 or higher event that was new in onset or aggravated in severity or frequency from the baseline condition (i.e., Grade 1 or 2 at baseline escalates to Grade 3 or higher, or Grade 3 at baseline escalates to Grade 4 or higher), following the start of study treatment.

4 Statistical Principles

4.1 General Considerations

The analysis population consists of all participants who were randomized to, and received, BRII-196+BRII-198 or its shared placebo, with the addition of any exclusions/modifications implemented for the primary day 28 analysis of the BRII-196+BRII-198.

Study visit windows for reporting are based on the Schedule of Evaluations (SOE) defined in the protocol (in person visits shown in the below table) and in the Primary SAP. To maximize the amount of data captured after Day 28, the analysis windows have been expanded to six weeks, as compared to four weeks in the Primary SAP.

Key study visits include Day 0, Day 28, and Week 36. Day 0 is the date the first dose of BRII-196+BRII-198 or placebo occurred. Day 28 is the last day the acute COVID-19 symptom diary was completed.

SOE Visit	Protocol Range (Days)	Analysis Range (Days)	Analysis Window (Days)
Day 0*	0	-1, 0	-1, 0
Day 28	28, 32	22, 38	-6, +10
Week 12	77, 91	42, 126	+/- 42
Week 24	161, 175	127, 210	-41, +42
Week 36	245, 266	211, 294	-41, +42
Week 48	329, 350	295, 378	-41, +42
Week 72	497, 518	462, 546	+/- 42

*The Day 0 analysis window is designed to capture data in scenarios where randomization occurs on the day prior to treatment initiation.

In the absence of a reported date for the SF-36 and EQ-5D-5L questionnaires, the available visit label will be used to identify the analysis time point.

Analyses of primary and secondary outcomes will not adjust for multiple comparisons.

Continuous variables will be summarized using mean, standard deviation, median, interquartile range (Q1 and Q3), 10^{th} and 90^{th} percentile, and min and max; categorical variables will be summarized using frequency and percentage.

5 Analysis Approaches

5.1 Descriptive Analyses

The following descriptive analyses will be provided:

5.1.1 CONSORT Summary/Data Completeness

- Number of participants who started active or placebo treatment
- Number with available Long-Term Diary (complete or partial)
- Number with available EQ-5D-5L Questionnaires (complete or partial)
- Number missing Long-Term Diary and EQ-5D-5L (separately by questionnaire)
    - LTFU by Week 36
    - Died by Week 36
    - Hospitalized at Week 36
    - Missed visit
    - Visit but no diary
    - Other

5.1.2 Baseline Characteristics

- Demographics (age, sex, gender, race, ethnicity, country)
- BMI
- Smoking Status
- Number of high risk comorbidities
- Duration of symptoms prior to study entry
- Vaccination Status
- Symptoms from Acute Diary

5.1.3 Week 36 Characteristics

Presented by treatment arm as well as by PASC diary availability at week 36:

- Vaccination Status through Week 36
- Symptom presence between Day 22 and 28 on the acute diary (i.e. persistent acute symptoms)
- Hospitalizations through Week 36
- Deaths through Week 36
- New Grade 3 or higher AE through Week 36
    - By MedDRA System Organ Class (SOC), Preferred Term, and grade.

See **Supportive Analyses** below for randomized comparisons of hospitalizations, deaths and AEs between randomized arms.

5.1.4 Outcome Measures

- Descriptive summaries (frequency and percent) of each outcome

5.2 Primary Analysis

The follow table outlines the primary objective and corresponding estimand, with additional details that follow. A supplementary analysis of the primary objective is included in the next section.

<table>
<tr><td colspan="2">Primary Objective: To explore the prevalence, severity, and type of persistent symptoms and clinical sequelae in participants through end of study follow-up.</td></tr>
<tr><td>Estimand</td><td>Ratio (BRII-196+BRII-198 divided by placebo) of the proportion with participant-reported PASC at week 36, or death due to any cause or hospitalization due to any cause at or prior to week 36, among adults with documented positive SARS-CoV-2 molecular test results collected within 240 hours (10 days) prior to study entry with no more than 10 days of symptoms of COVID-19 prior to study entry, and with presence of select symptoms within 24 hours of study entry</td></tr>
<tr><td>Treatment</td><td>BRII-196+BRII-198 or placebo</td></tr>
<tr><td>Target population</td><td>Analysis set</td></tr>
<tr><td>Adults (≥ 18 years of age) with documented positive SARS-CoV-2 molecular test results collected within 240 hours (10 days) prior to study entry with no more than 10 days of symptoms of COVID-19 prior to study entry, and with presence of select symptoms within 24 hours of study entry</td><td>All participants who were randomized to, and received, BRII-196+BRII-198 or its shared placebo</td></tr>
<tr><td>Variable(s)</td><td>Outcome measure(s)</td></tr>
<tr><td>PASC at week 36 or death at/prior to week 36 or hospitalization at/prior to week 36 (coded as 1 if the participant had PASC or died or was hospitalized, and 0 otherwise)</td><td>Presence of participant-reported PASC at study week 36, or death due to any cause or hospitalization due to any cause at or prior to week 36</td></tr>
<tr><td>Handling of intercurrent events</td><td>Handling of missing data</td></tr>
<tr><td>A composite strategy will be implemented to handle intercurrent deaths and hospitalizations. Deaths due to any cause or hospitalizations due to any cause at or prior to week 36 will be included in the variable</td><td>Missing data will be ignored in the primary analysis, as they are considered non-informative.

The following sensitivity analyses will be considered to evaluate the sensitivity of the missing data assumption:

1) Assume those with missing data have PASC at week 36
2) Assume those with missing data do not have PASC at week 36
3) Assume those with missing data in the BRII-196+BRII-198 arm have PASC and those in the placebo arm do not have PASC
4) Assume those with missing data in the BRII-196+BRII-198 arm do not have PASC and those in the placebo arm do have PASC</td></tr>
<tr><td>Population-level summary measure</td><td>Analysis approach</td></tr>
<tr><td>Ratio of proportion with PASC at week 36, or death due to any cause or hospitalization due to any cause at or prior to week 36</td><td>The following will be used for primary and sensitivity analyses:

Ratio of proportion with PASC at week 36 or death due to any cause or hospitalization due to any cause at or prior to week 36 obtained from Poisson regression with robust variance estimation and log-link.</td></tr>
</table>

Analysis Approach

The proportion of participants with participant-reported PASC symptoms present at week 36, or death due to any cause or hospitalization due to any cause at or prior to week 36 will be estimated and compared between randomized arms (BRII-196+BRII-198 versus shared placebo) using Poisson regression with robust variance and log-link. A 95% confidence interval for the risk ratio and a two-sided p-value from a Wald test of the null hypothesis that the risk ratio is one will also be provided.

Sensitivity Analyses

The following sensitivity analyses are included to evaluate impact of missing data. The primary analysis will be repeated making the following assumptions:

1) Those with missing data have PASC at week 36;

2) Those with missing data do not have PASC at week 36;

3) Those with missing data in the BRII-196+BRII-198 arm have PASC and those in the placebo arm do not have PASC;

4) Those with missing data in the BRII-196+BRII-198 arm do not have PASC and those in the placebo arm have PASC.

In addition, an analysis will be undertaken using observed data only (i.e. ignoring missing data and prior deaths and hospitalizations). In part, this is also to provide linkage with analyses of secondary outcome measures, which will focus on observed data only.

5.3 Supportive Analyses to the Primary Analysis

Severity of participant-reported PASC at week 36 (secondary outcome 2) is included as supplementary to the primary PASC outcome. In this analysis, those who die (due to any cause) or are hospitalized (due to any cause) at or before week 36 will be classified as having the worst severity. This outcome will be summarized descriptively by category of severity, ranging from no symptoms to hospitalized/died, and will be summarized by randomized arm with proportions and frequencies. Cumulative logistic regression, with an ordinal multinomial outcome of severity, will be used to generate a corresponding p-value.

5.4 Secondary Analyses: PASC Outcomes

Analyses of secondary outcome measures will be restricted to those who did not die before week 36 (principal stratum policy); all missing data among individuals alive at week 36 are considered non-informative and will be ignored in the analysis.

Worst severity of symptoms (secondary outcome 3) will be analyzed using the same methods at the PASC severity outcome. That is, it will be summarized descriptively by category of severity, ranging from no symptoms to severe, and will be summarized by randomized arm with proportions and frequencies. Cumulative logistic regression, with an ordinal multinomial outcome of severity, will be used to generate a corresponding p-value.

Distributions of the total symptom score (secondary outcome 4) and the number of symptoms present at week 36 (secondary outcome 7) will be compared between arms using a non-parametric Wilcoxon test; cumulative distribution function plot will also be provided. Dichotomous secondary outcomes (5, 6, 8-16) will be compared between randomized arms using Poisson regression with robust variance and log-link. A 95% confidence interval for the risk ratio and a two-sided p-value from a Wald test of the null hypothesis that the risk ratio is one will also be provided.

5.5 Secondary Analyses: Quality of Life (EQ-5D-5L)

Analyses of secondary outcome measures will be restricted to those who did not die before week 36 (principal stratum policy); all missing data among individuals alive at week 36 are considered non-informative and will be ignored in the analysis.

Secondary quality of life measures evaluating the presence of different conditions/symptoms, as measured by the EQ-5D-5L questionnaire, will be compared between arms using Poisson regression with robust variance and log-link. A 95% confidence interval for the risk ratio and a two-sided p-value from a Wald test of the null hypothesis that the risk ratio is one will also be provided. Distributions of current health score (secondary outcome 21) will be compared between arms using a non-parametric Wilcoxon test; cumulative distribution functions will also be provided.

5.6 Other Supportive Analyses

Summaries of deaths, hospitalizations, and adverse events through week 36 will be provided as supportive analyses. Analyses methods will follow those outlined in the study's primary SAP.

5.6.1 Death and Hospitalization

The analysis will compare the cumulative proportion of participants hospitalized or died (due to any cause), from day 0 through week 36, between randomized arms using a ratio of proportions; hospitalizations and deaths that occur at week 36 (252 days) will be included. The cumulative proportion will be estimated for each randomized arm using Kaplan-Meier methods to account for losses to follow up. For analysis purposes, the integer scale will be used as the time scale; if an event occurs on day 0 then event time will be set to 0.5 for analysis. Participants will have follow-up censored at the date they were last known to be alive and not hospitalized through week 36.

The absolute difference in the estimated log-cumulative proportion will be calculated between randomized arms; a 95% CI will be obtained for this difference in log-cumulative proportion calculated using a variance for this difference being the sum of the variances for each randomized arm obtained using Greenwood's formula. Results will be anti-logged to give the estimated ratio of cumulative proportions through week 36 (investigational agent vs placebo) and associated 95% CI. Two-sided 95% confidence intervals (CIs) and p-value (for the test of no difference between groups) will be obtained; a nominal 95% CI and p-value will also be provided.

5.6.2 Adverse Events

Occurrence of any new Grade 3 or higher AE through week 36 will be analyzed in the following manner. The proportion of participants who experienced a new Grade 3 or higher AE will be estimated and compared between randomized arms using log-binomial regression, with log link, in order to obtain a risk ratio estimate; the model will include a main effect for randomized arm. A 95% confidence interval for the risk ratio and a two-sided p-value from a Wald test of the null hypothesis that the risk ratio is one will also be provided. In the event the log-binomial regression model fails to converge or has questionable convergence, a Poisson regression model with robust variance and log-link will be used instead.

6 Appendix 1: SF-36

The following analysis details correspond to data collected as part of the SF-36 questionnaire, which were pending availability in the database at the time this SAP was finalized. Analyses of these data are anticipated to occur at a future time, but are included here to document the planned analytic approaches.

6.1 Outcome Measures

1) Physical Functioning (PF) transformed score at study week 36

   Physical Functioning (PF) transformed score is defined as the transformed score of the PF items from SF-36v2 questionnaire.

2) Physical Role (PR) transformed score at study week 36

   Physical Role (PR) transformed score is defined as the transformed score of the PR items from SF-36v2 questionnaire.

3) Bodily Pain (BP) transformed score at study week 36

   Bodily Pain (BP) transformed score is defined as the transformed score of the BP items from SF-36v2 questionnaire.

4) General Health (GH) transformed score at study week 36

   General Health (GH) transformed score is defined as the transformed score of the GH items from SF-36v2 questionnaire.

5) Vitality (VT) transformed score at study week 36

   Vitality (VT) transformed score is defined as the transformed score of the VT items from SF-36v2 questionnaire.

6) Social Function (SF) transformed score at study week 36

   Social Function (SF) transformed score is defined as the transformed score of the SF items from SF-36v2 questionnaire.

7) Emotional Role (ER) transformed score at study week 36

   Emotional Role (ER) transformed score is defined as the transformed score of the ER items from SF-36v2 questionnaire.

8) Mental Health (MH) transformed score at study week 36

   Mental Health (MH) transformed score is defined as the transformed score of the MH items from SF-36v2 questionnaire.

9) Physical Health Component Summary score at study week 36

   Physical Health Component Summary is a composite of Physical Function, Physical Role, Bodily Pain, and General Health as defined above.

10) Mental Health Component Summary score at study week 36

    Mental Health Component Summary is a composite of Vitality, Social Functioning, Emotional Role, and Mental Health as defined above.

6.2 Analysis Approaches

Analyses of secondary outcome measures will be restricted to those who did not die before week 36 (principal stratum policy); all missing data among individuals alive at week 36 are considered non-informative and will be ignored in the analysis.

Secondary quality of life measures, as measured by the SF-36 questionnaire, will be compared between arms using Poisson regression with robust variance and log-link. A 95% confidence interval for the risk ratio and a two-sided p-value from a Wald test of the null hypothesis that the risk ratio is one will also be provided.