NCT04790786

UPMC OPTIMISE-C19 Trial, a COVID-19 Study (OPTIMISE-C19)

Document date: 5/2/2022

Supplementary Materials

The Comparative Effectiveness of COVID-19 Monoclonal Antibodies: A Learning Health System Randomized Clinical Trial

Table of Contents

Table S1: **U.S. Department of Health and Human Services - Food and Drug Administration Emergency Use Authorizations and UPMC Monoclonal Antibody Policy Changes Over Time**

Date	Change	Explanation
11-9-2021	*DHHS/FDA provides mAb EUAs and treatment for COVID-19 eligibility criteria*	Eligibility Criteria - High risk is defined as patients who meet at least one of the following criteria: • Have a body mass index (BMI) ≥35[a] • Have chronic kidney disease • Have diabetes • Have immunosuppressive disease[b] • Are currently receiving immunosuppressive treatment • Are ≥65 years of age • Are ≥55 years of age AND have cardiovascular disease, OR hypertension, OR chronic obstructive pulmonary disease/other chronic respiratory disease. • Are 12–17 years of age AND have BMI ≥85th percentile[a] for their age and gender based on CDC growth charts,[a] OR sickle cell disease, OR congenital or acquired heart disease, OR neurodevelopmental disorders, for example, cerebral palsy, OR a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR asthma, reactive airway or other chronic respiratory disease that requires daily medication for control. EUAs for • bamlanivimab • bamlanivimab and etesevimab (available 09-02-2021) • casirivimab and imdevimab
03-10-2021	UPMC – Opened study enrollment	Go-live date for trial with bamlanivimab, and casirivimab and imdevimab only and following COVID-19 Treatment Guidelines.
03-16-2021	UPMC - Incorporation of bamlanivimab-etesevimab into random allocation	Start incorporating bamlanivimab and etesevimab into most sites. There was a 1-week delay to use etesevimab at six sites due to low initial supply.
02-23-2021	UPMC - mAb treatment expanded to Emergency Departments	Based on published data from our health system demonstrating significant decrease in hospitalizations and deaths with bamlanivimab, the decision was made to invest resources in Emergency Department expansion to increase access to mAb treatment.
03-25-2021	*DHHS/FDA EUA for distribution of bamlanivimab alone was halted*	A memorandum on the Fact Sheet for bamlanivimab alone – Update was issued on 03/17/21. Pseudovirus neutralization data for SARS-CoV-2 variant substitutions with bamlanivimab alone was unsuccessful.
3-31-2021	UPMC – haulted bamlanivimab alone	Emerging data about lack of efficacy with SARS-COV-2 variants resulted in System COVID-19 Pharmacy & Therapeutics Committee's decision to remove bamlanivimab alone from formulary. All sites put on view to use bamlanivimab only with etesevimab.
04-16-2021	*DHHS/FDA EUA for bamlanivimab was revoked*	EUA revoked due to lack of efficacy with SARS-COV-2 variants.
04-25-2021	UPMC - Protocol Amendment 1 to remove use of bamlanivimab alone	Updated trial protocol to reflect clinical practice of no longer using bamlanivimab alone.
04-26-2021	UPMC – expanded study enrollment to observation status patients	Established process for treating observation status patients at UPMC hospitals.
05-06-2021	UPMC - Interim Analysis	Data supported it was safe to proceed.
05-14-2021	*DHHS/FDA EUA expands eligibility criteria*	Eligibility Criteria - The following medical conditions or other factors may place adults and pediatric patients (age 12–17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19: • Older age (for example age ≥65 years of age)

Date	Change	Explanation
		• Obesity or being overweight (for example, adults with BMI >25 kg/m2[a] or if age 12–17, have BMI ≥85th percentile[a] for their age and gender based on CDC growth charts • Pregnancy • Chronic kidney disease • Diabetes • Immunosuppressive disease[b] or immunosuppressive treatment • Cardiovascular disease (including congenital heart disease) or hypertension • Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension) • Sickle cell disease • Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies) • Having a medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID-19])
05-26-2021	*DHHS/FDA provides an EUA for sotrovimab*	Sotrovimab is a new mAb treatment.
06-03-2021	*DHHS/FDA EUA revised to decrease dose for casirivimab and imdevimab*	Casirivimab 600mg and imdevimab 600 mg
06-15-2021	UPMC - decreased dose for casirivimab and imdevimab	Casirivimab and imdevimab dose decreased from 2400 mg to 1200 mg.
06-25-2021	*DHHS/FDA EUA for distribution of bamlanivimab and etesevimab was paused*	FDA recommends not to use bamlanivimab and etesevimab together.
06-25-2021	UPMC - paused bamlanivimab and etesevimab	UPMC removes bamlanivimab and etesevimab from inventory.
06-25-2021	UPMC - Protocol Amendment 2: remove bamlanivimab and etesevimab, add sotrovimab, and update EUA expanded eligibility criteria	Updated trial protocol to reflect clinical practice of pausing use of bamlanivimab and etesevimab, add use of sotrovimab, and expanded eligibility criteria.

Abbreviations: mAb, monoclonal antibodies; DHHS/FDA, Department of Health and Human Services/Food and Drug Administration; EUA, emergency use authorization; BMI, body mass index.

[a]Calculated as weight in kilograms divided by height in meters squared.

[b]Immunosuppressive disease or treatment was defined as a history of HIV, cancer, transplant (solid organ, stem cell, bone marrow), chemotherapy treatment, lupus, rheumatoid arthritis, or liver disease.

Table S2: Comparison of 28-Day Hospitalization Rates by Treatment and Site Location

All Patients				Risk		Exceeds Upper Limit of 95% C.I.			
Treatment	N	No. (%)	95% C.I.	Difference	95% C.I.	3%	4%	5%	6%
B + E	885	130 (14.7%)	(12.4% to 17.4%)	0.4%	(-2.9% to 3.6%)	Yes	No	No	No
C + I	922	132 (14.3%)	(12.1% to 16.8%)	Reference		Reference			
ED Patients									
B + E	422	100 (23.7%)	(19.7% to 28.1%)	2.0%	(-3.6% to 7.5%)	Yes	Yes	Yes	Yes
C + I	460	100 (21.7%)	(18.0% to 25.8%)	Reference		Reference			
IC Patients									
B + E	463	30 (6.5%)	(4.4% to 9.1%)	-0.5%	(-3.7% to 2.8%)	No	No	No	No
C + I	462	32 (6.9%)	(4.8% to 9.6%)	Reference		Reference			

Abbreviations: B + E, bamlanivimab and etesevimab; C + I, casirivimab and imdevimab; C.I., confidence interval; ED, emergency department; IC, infusion center.

Table S3: Adverse Events in Patients Receiving Monoclonal Antibody Treatment

Patient ID	mAb Received	Mild Reaction	Severe Reaction	Reaction Description
1	Bamlanivimab and Etesevimab	Yes	..	Hypoglycemic, hypotension: infusion stopped treated with diphenhydramine and fluid, patient discharged stable to home.
2	Bamlanivimab and Etesevimab	Yes	..	Patient developed tightness in head/sinus area, and tightness in chest. Infusion not finished. Discharged home.
3	Bamlanivimab and Etesevimab	Yes	..	Patient reported chest tightness, became lightheaded and dizzy. Infusion not finished. Discharged home.
4	Bamlanivimab and Etesevimab	Yes	..	Patient developed hypotension; responded to 500 mL Lactated Ringers, discharged home normotensive.
5	Bamlanivimab and Etesevimab	Yes	..	Headache, responded to acetaminophen.
6	Bamlanivimab and Etesevimab	Yes	..	Flushed, chest pain. Stopped infusion.
7	Bamlanivimab and Etesevimab	Yes	..	Low back pain, radiating. Decreased infusion rate in half. Patient stated pain alleviated and denied any complaints.
8	Bamlanivimab and Etesevimab	Yes	..	Patient reported nausea, hot flash, severe lower back pain 1 minute into infusion.
9	Bamlanivimab and Etesevimab	..	Yes	Patient stated flushed/throat "closing". Stopped infusion. Sent to emergency department for evaluation.
10	Bamlanivimab and Etesevimab	Yes	..	Flushing and shortness of breath.
11	Bamlanivimab and Etesevimab	Yes	..	Mild itchiness and redness at infusion site.
12	Bamlanivimab and Etesevimab	Yes	..	Became itchy, developed hives, received diphenhydramine.
13	Casirivimab and Imdevimab	Yes	..	Headache.
14	Casirivimab and Imdevimab	..	Yes	Sudden onset nausea, vomiting, and weakness after 1 hour observation period; checked into emergency department and admitted post infusion.
15	Casirivimab and Imdevimab	Yes	..	Patient developed dizziness and chills which resolved prior to discharge.
16	Casirivimab and Imdevimab	Yes	..	Right before discharge patient mentioned dizziness and lower blood pressure. Discharged to home.
17	Casirivimab and Imdevimab	..	Yes	Hypertension and headache post-infusion, transferred to emergency department.
18	Casirivimab and Imdevimab	..	Yes	Patient became hot, red face, reported chest pain 9/10. Oxygen saturation went from 95% to 85% to 73%. Sent to emergency department.
19	Casirivimab and Imdevimab	Yes	..	Chills, flushing, chest tightness, headache. Infusion stopped.
20	Casirivimab and Imdevimab	..	Yes	Chest pain, shortness of breath, and back pain 2 minutes into infusion. Paramedics called.
21	Casirivimab and Imdevimab	Yes	..	Shortness of breath, chest tightness 3 minutes into infusion. Medication stopped and symptoms resolved.

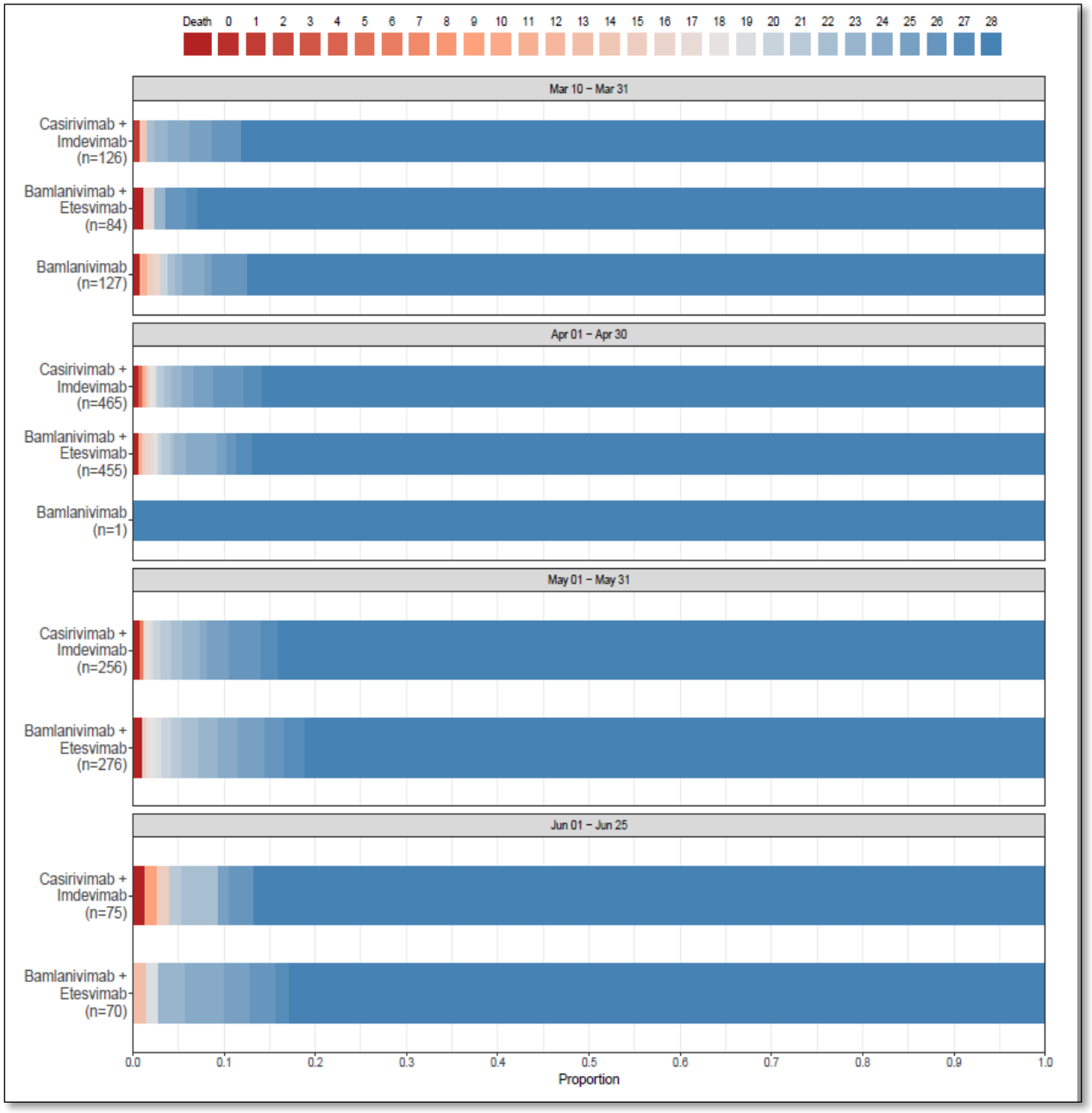
Abbreviations: mAb, monoclonal antibody.

Table S4: Baseline Characteristics of Patients Who Received a Randomized Monoclonal Antibody Allocation by Infusion Status (March 10–June 25, 2021)

	Randomized, infused (n=1,935)		Randomized, not infused/analyzed (n=443)	
Variable	**No.**	**Mean, (SD)**	**No.**	**Mean, (SD)**
Age in years	1935	55.5 (16.0)	443	53.1 (18.6)
Body mass index[a]	1302	34.8 (8.5)	306	34.8 (8.5)
Charlson Comorbidity Index[b]	1166	1.1 (1.5)	299	0.8 (1.1)
..	**No.**	**No. (%)**	**No.**	**No. (%)**
Age in years (categories)	1935	..	443	..
0 to 30	..	157 (8.1)	..	59 (13.3)
31 to 50	..	511 (26.4)	..	132 (29.8)
51 to 60	..	484 (25.0)	..	84 (19.0)
61 to 70	..	474 (24.5)	..	92 (20.8)
71 to 80	..	218 (11.3)	..	44 (9.9)
81 and older	..	91 (4.7)	..	32 (7.2)
Female sex[c]	1935	1041 (53.8)	443	274 (61.9)
Race[d]	1884	..	428	..
White	..	1498 (79.5)	..	345 (80.6)
Black	..	335 (17.8)	..	79 (18.5)
Other[e]	..	51 (2.7)	..	4 (0.9)
Body mass index (categories)[a]	1302	..	306	..
Less than 18.5	..	7 (0.5)	..	7 (2.3)
18.5 to less than 25.0	..	119 (9.1)	..	27 (8.8)
25.0 to less than 30.0	..	273 (21.0)	..	51 (16.7)
30.0 to less than 35.0	..	309 (23.7)	..	75 (24.5)
35.0 to less than 40.0	..	296 (22.7)	..	68 (22.2)
40.0 or higher	..	298 (22.9)	..	78 (25.5)
History of hypertension	1414	782 (55.3)	352	152 (43.2)
History of obstructive sleep apnea	1414	370 (26.2)	352	81 (23.0)
History of allergic rhinitis	1414	189 (13.4)	352	49 (13.9)
History of diabetes	1414	383 (27.1)	352	63 (17.9)
History of coronary artery disease	1414	172 (12.2)	352	35 (9.9)
History of congestive heart failure	1414	117 (8.3)	352	32 (9.1)
History of atrial fibrillation	1414	102 (7.2)	352	20 (5.7)
History of valvular heart disease	1414	97 (6.9)	352	26 (7.4)
History of stroke	1414	84 (5.9)	352	22 (6.2)
History of dyspnea	1414	105 (7.4)	352	20 (5.7)
History of asthma	1414	517 (36.6)	352	136 (38.6)
History of chronic obstructive pulmonary disease	1414	278 (19.7)	352	78 (22.2)
History of chronic kidney disease	1414	112 (7.9)	352	27 (7.7)
History of fatty liver disease	1414	83 (5.9)	352	14 (4.0)
History of viral hepatitis	1414	40 (2.8)	352	6 (1.7)
History of cancer	1414	186 (13.2)	352	32 (9.1)

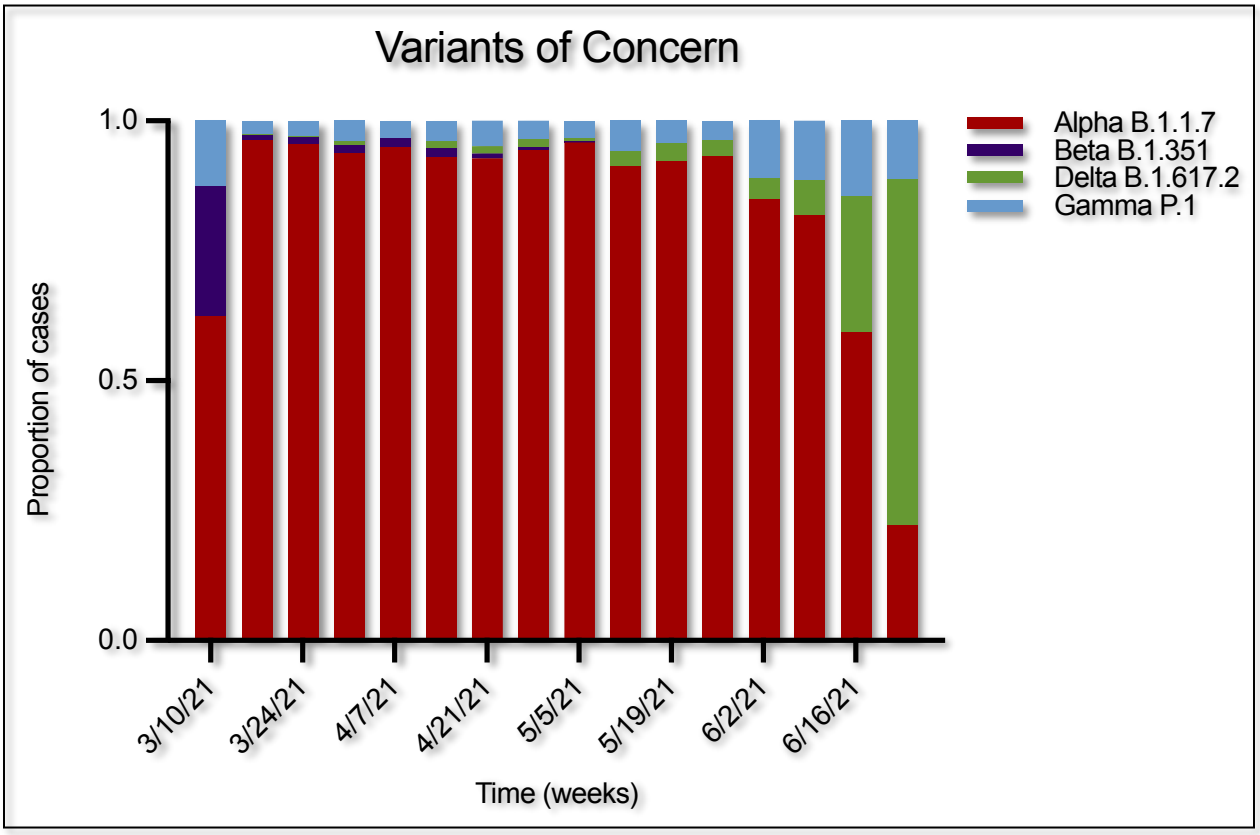
[a]Calculated as weight in kilograms divided by height in meters squared.
[b]Charlson Comorbidity Index is calculated as S – result from point addition; CCI ten year survival=0.983^{A} where A=$e^{(S \times 0.9)}$.
[c]Sex was reported by the patients.
[d]Race was reported by the patients.
[e]Other includes Chinese, Filipino, Hawaiian, American Indian/Alaskan Native, Asian, Hawaiian/other Pacific Islander, Middle Eastern, Native American, or Pacific Islander.

Figure S1: Treatment Heterogeneity Across Variant Date Prevalence Epochs



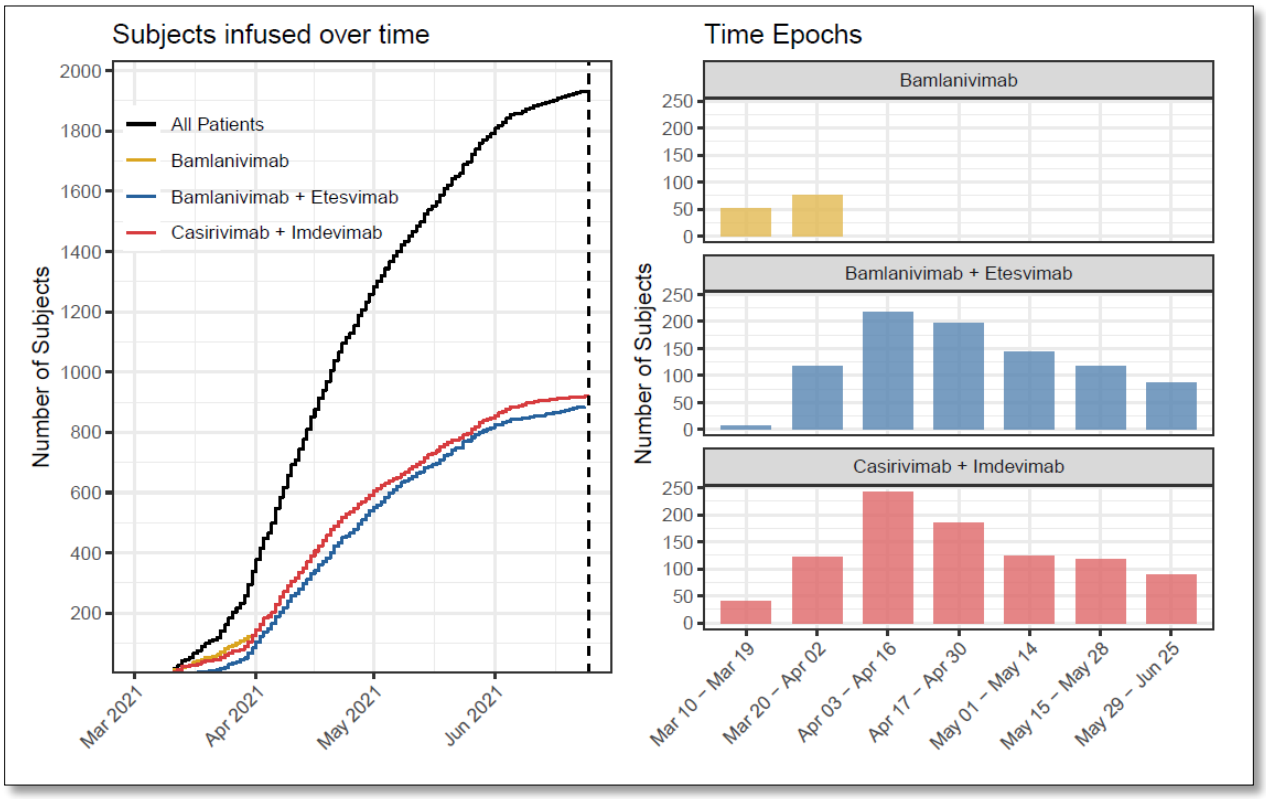
Red represents worse outcomes and blue represents better outcomes.

Figure S2: SARS-CoV-2 Variants of Concern Proportion in Pennsylvania During the Study (March 10–June 25, 2021)



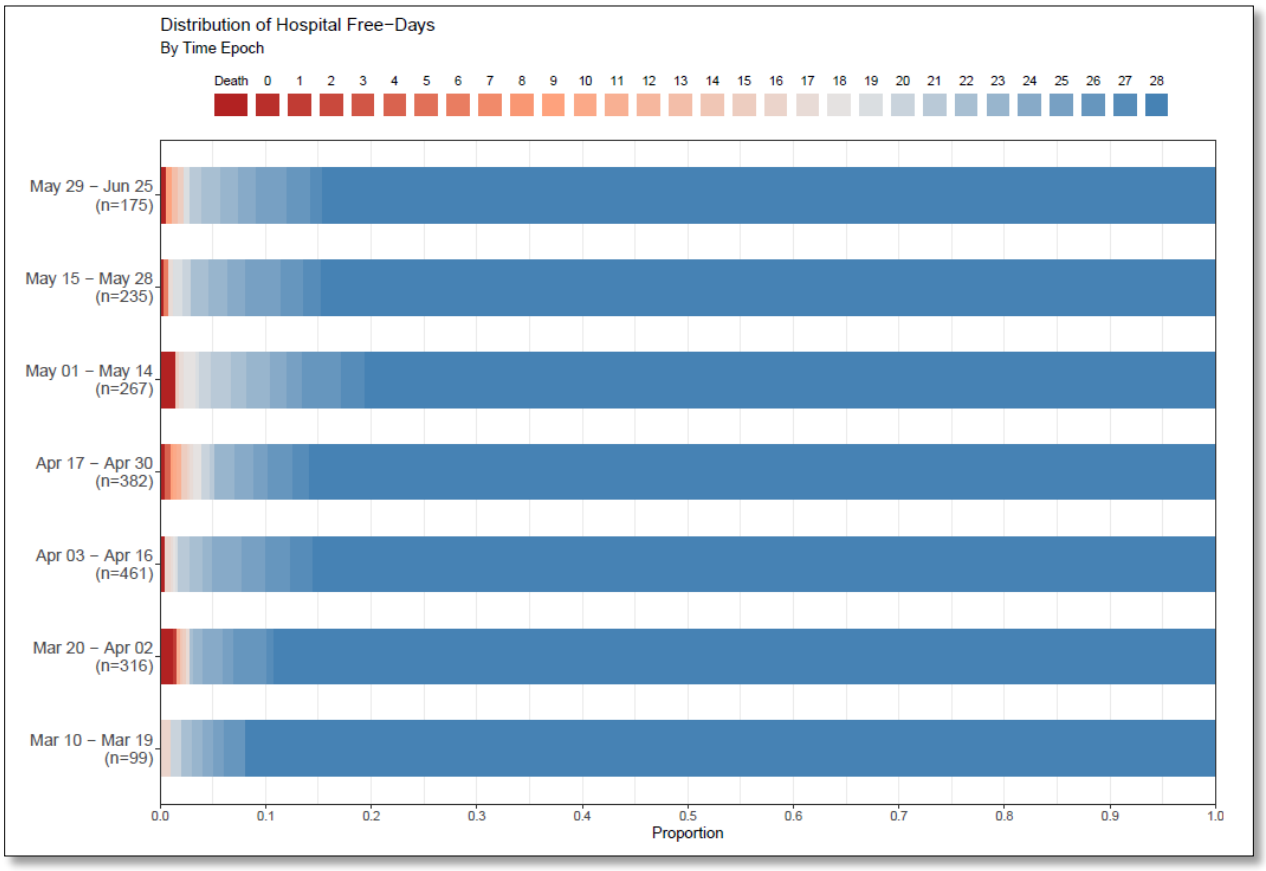
Red represents Alpha B.1.1.7, purple is Beta B.1.351, green is Delta B.1.617.2, and blue is Gamma P.1.

Figure S3: Number of Infused Patients Over Time and Distribution of Patients Within Each of the Time Buckets Used to Estimate Time Trends in the Analysis Model (Primary Analysis)



The time buckets are derived so that the first bucket is the most recent 4 weeks going backwards in time from the most recently infused patient in the dataset that has a complete hospital-free days outcome. Thereafter, each bucket is defined as the next 2-week interval backwards in time. The vertical dashed line indicates the infusion date for the last patient who has passed 28 days and has a known outcome on the primary endpoint at the time of this analysis.

Figure S4: Stacked Proportion of Hospital Free Days for Each Time Epoch (Primary Analysis; As-infused Population)



Red represents worse outcomes and blue represents better outcomes.

Study Protocol
Final Version 1.3, June 30, 2021

UPMC OPTIMISE-C19 (**OP**timizing **T**reatment and **I**mpact of **M**onoclonal ant**I**bodie**S** through **E**valuation for COVID-19)

A Pragmatic Evaluation of Monoclonal Antibody Treatments in Participants with COVID-19 Illness (ClinicalTrials.gov, NCT04790786)

Summary of Protocol Changes for Amendment on April 25, 2021

Page #	Protocol Section	Reason for Change
1	Protocol Title Page	Title changed to reflect new abbreviation being used for study
2-3	Summary Table	Summary table updated to reflect protocol changes
10	4.1	Clarification added to section 4.1 to reflect changing landscape of FDA EUA and revocation
12	5	Clarification added to section 5 to reflect changing landscape of FDA EUA and revocation
12	5.1	Removed section 5.1 bamlanivimab due to EUA revoked
17	8.1	Updated to provide more detail on the monitoring of data by UPMC clinical leadership
18	9	EUA for bamlanivimab removed

Summary of Protocol Changes for Amendment on June 30, 2021

Page #	Protocol Section	Reason for Change
NA	NA	Minor administrative changes throughout the document to reflect Amendment #2 documentation
2-3	Summary table	Summary table updated to reflect protocol changes
7	2.1.	Information regarding new monoclonal antibody sotrovimab
7	2.1.	Information added regarding the revocation of EUA approved of bamlanivimab and etesvimab
8	2.2.	Information added to reflect current COVID trends
10-11	4.1.1.	Updated Inclusion Criteria as per EUA requirements
12	5	Information added regarding the revocation of EUA approved of Bamlanivimab
12	5.1.	Removal of section 5.1. – bamlanivimab and etesvimab
12-13	5.2.	Addition of newly approved monoclonal antibody – sotrovimab
15	6.3.	Information added to reflect UPMC will utilize a pharmacy manual if provided by the drug manufacturer
19	9.0.	Exhibits added and removed to reflect current EUA approved monoclonal antibodies

Protocol Summary

Background	• FDA Emergency Use Authorization (EUA) exists for multiple monoclonal antibodies (mAb) to treat COVID-19; the EUAs stipulate eligibility criteria, patient-physician communication, and clinical monitoring. • UPMC provides mAbs as routine care; physicians order a mAb infusion and pharmacies assign whichever mAb is available under a therapeutic interchange approach. If scarcity exists, a lottery system is used. • Physicians review with patients the EUA Fact Sheet for each mAb and explain they could be assigned any of the EUA-governed mAbs.
Approach	• Structure the therapeutic interchange policy and lottery system using a UPMC pharmacy embedded assignment system that allows a comparative effectiveness evaluation of the multiple mAbs. • Collect data from clinically performed UPMC processes and EUA requirements for routine care.
Treatments	• Monoclonal antibodies (mAb) for COVID-19
Inclusion Criteria	These criteria are as per the FDA EUAs for COVID-19 mAbs as of June 2021. • Adult ($\geq$ 18 years old) • Children $\geq$ 12 years old weighing at least 40 kg • With a positive SARS-CoV-2 antigen or PCR test and within 10 days of symptom onset • High risk of disease progression High risk is defined as patients who meet at least one of the following criteria: • Are $\geq$ 65 years old • A Body Mass Index (BMI)>25, or if age 12–17, BMI $\geq$ 85th percentile • Pregnancy • Have chronic kidney disease • Have diabetes • Have immunosuppressive disease • Are currently receiving immunosuppressive treatment • Cardiovascular disease (including congenital heart disease) or hypertension • Chronic lung disease • sickle cell disease • neurodevelopmental disorders (e.g., cerebral palsy) or other conditions that confer medical complexity (e.g., genetic, or metabolic syndromes and severe congenital anomalies) • a medical-related technological dependence, for example, tracheostomy or gastrostomy) The EUAs note that other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression and authorization of mAb treatment under the EUA is not limited to the medical conditions or factors listed above.
Exclusion Criteria	These criteria are as per the FDA EUAs for COVID-19 mAbs as of April 2021. • Are hospitalized for the treatment of COVID-19 • Require oxygen therapy for the treatment of COVID-19 • Require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity • Have a known hypersensitivity to any antibody ingredient
Primary evaluation metric	Total hospital free days at 28 days

1. ABBREVIATIONS

AE	Adverse Events
BMI	Body Mass Index
C + I	casirivimab + imdevimab
CDC	Centers for Disease Control and Prevention
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus disease 2019
CVD	Cardiovascular Disease
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
HHS	Health and Human Services
HFD	Hospital Free Days
HTN	Hypertension
kDa	Kilodaltons
IgG1	Immunoglobulin G1
KG	Kilograms
OPTIMISE-C19	**OP**timizing **T**reatment and **I**mpact of **M**onoclonal ant**I**bodie**S** through **E**valuation
mAb	Monoclonal Antibodies
PCR	Polymerase Chain Reaction
SAEs	Serious Adverse Events
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
UATRC	UPMC Antibody Treatment and Evaluation Center
Vir-7831	sotrovimab

2. BACKGROUND and RATIONALE

3. BACKGROUND

While COVID-19 vaccination will reduce COVID-19-related morbidity and mortality, the learned immune response may vary between individuals. This means interventions such as monoclonal antibodies (mAb) will still be needed to prevent progression of COVID-19 illness. Monoclonal antibodies seek to mimic or enhance the natural immune system response against a pathogen and are often used in the care of patients with cancer or infection.
For viral infections, mAbs are created by exposing a white blood cell to a particular viral protein, which is then cloned to mass produce antibodies to target that virus. For SARS-CoV-2, the virus that causes COVID-19, IgG1 mAbs target the spike protein of SARS-CoV-2 and block viral attachment and entry into cells.

The SARS-CoV-2 mAbs bamlanivimab and etesevimab, and the REGN-COV2 combination (casirivimab + imdevimab) reduce nasopharyngeal viral burden plus clinical outcomes including future emergency department visits and hospitalizations (Weinreich 33332778, NEJM, Gottlieb 33475701). Each received FDA Emergency Use Authorization (EUA) for use in selected populations (**Exhibit**); in April 2021 FDA revoked the EUA for bamlanivimab monotherapy, and in June 2021 FDA recommended bamlanivimab and etesevimab not be used. Additional trials of pre-exposure prophylaxis (NCT04497987) and other applications are underway, and additional mAbs are in development.

In May 2021, it was announced that sotrovimab demonstrated clinical efficacy (85%) in reducing hospitalizations for more than 24 hours or death in those that received sotrovimab as compared to placebo (NCT04545060). Subsequently, it received EUA approval in select populations. Additional trials are underway.

The trials demonstrated the greatest impact of the REGN-COV2 dual therapy among patients who lacked neutralizing antibodies against SARS-CoV-2 at baseline and in those with high nasopharyngeal viral loads. Additionally, few patients in the bamlanivimab/etesevimab trial developed treatment-emergent SARS-CoV-2 resistance. This latter phenomenon may further enhance the need for therapies given the recent emergence of SARS-CoV-2 variants that may escape vaccination. However, the relative effectiveness of each mAb compared to the other is unknown, as is their effectiveness for emerging virus variants.

This Appendix to the UPMC Pilot Core (PittPro 20040210) describes the approach of the UPMC OPTIMISE-C19 evaluation. We will conduct a pragmatic evaluation of monoclonal antibody treatments in participants with COVID-19 illness, starting with the patient population approved under the current FDA mAb EUAs.

4. RATIONALE

As of June 2021, there are over 10,000 new cases of COVID-19 diagnosed daily in the US https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases, with over 1500 daily COVID-19 related hospital admissions Microsoft Power BI (powerbigov.us). Although case volumes are currently declining, COVID-19 remains a significant public health threat.

Despite the EUAs, the clinical use of mAbs is low due in part to lack of patient access, complexities in drug allocation, and lack of knowledge among providers are contributing factors. Further, the comparative effectiveness of different mAbs is unknown and not yet directly studied. The National Academies of Sciences, Engineering, and Medicine recently called for expanded access and clinical use of mAbs, noting it is "critical to collect data and evaluate whether they are working as predicted."

This evaluation seeks to expand access to mAbs at UPMC and determine their relative effects versus each other, starting with those governed by EUAs.

5. OBJECTIVES AND METRICS

6. OBJECTIVES

The primary objective is to evaluate the clinical and biological effect of multiple monoclonal antibodies (mAbs) in patients with COVID-19.

The primary hypothesis is clinical and biological effect will vary between mAbs, by SARS-CoV-2 variants, and patient characteristics.

7. METRICS

The primary evaluation metric is total hospital free days (HFD) at 28 days after mAb receipt calculated as 28 minus the number of days during the index stay minus the number of days readmitted during the 28 days after treatment. Death within 28 days is recorded as -1 HFD.

Secondary evaluation metrics include:

- All-cause and all-location mortality at 28 and 90 days
- Emergency department visits at 28 days
- Organ-support free days at day 28
- Where feasible:
    - SARS-CoV-2 nasopharyngeal and plasma viral loads among participants from baseline and longitudinally through day 28
    - SARS-CoV-2 antibody titers, antibody neutralization, and other immune responses at baseline and longitudinally through day 28
    - Detection of SARS-CoV-2 variants through next-generation sequencing at baseline and longitudinally through day 28
    - Determining the duration of SAR-CoV-2 infectivity and non-culture surrogates for SARS-CoV-2 infectivity among patients with persistent nasopharyngeal swab viral shedding

8. DESIGN

We will conduct a pragmatic evaluation of participants with COVID-19 illness under existing UPMC processes for the clinical care of COVID-19 positive patients, including EUA requirements for mAb administration. A patient who presents to a UPMC facility and tests positive for COVID-19 will, as per current common care, be offered monoclonal antibodies. Data that are already collected according to UPMC procedures and EUA requirements are used for analysis.

9. POPULATION

We will evaluate patients that present to UPMC Emergency Departments, urgent care sites, infusions centers and other facilities that can or do provide mAbs for COVID-19. As of June 30, 2021, there are 2 EUAs for COVID-19 mAbs, with common inclusion and exclusion criteria, and we will evaluate patients that meet these criteria. As FDA antibody decisions change (E.g., FDA revokes or grants EUAs, or changes eligibility criteria), eligibility criteria will change.

10. INCLUSION CRITERIA

As per the current EUA criteria (June 2021), the following patients are included:

- Adult ($\geq$ 18 years old)
- Children $\geq$ 12 years old weighing at least 40 kg
- With a positive SARS-CoV-2 antigen or PCR test and within 10 days of symptom onset
- High risk of disease progression

High risk is defined as patients who meet at least one of the following criteria:

- Are $\geq$ 65 years old
- A Body Mass Index (BMI)>25, or if age 12–17, BMI $\geq$ 85th percentile
- Pregnancy
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung disease
- sickle cell disease
- neurodevelopmental disorders (e.g., cerebral palsy) or other conditions that confer medical complexity (e.g., genetic, or metabolic syndromes and severe congenital anomalies)
- a medical-related technological dependence, for example, tracheostomy or gastrostomy)

The EUAs note that other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression and authorization of mAb treatment under the EUA is not limited to the medical conditions or factors listed above.

11. EXCLUSION CRITERIA

As per the current EUA criteria (June 2021), the following are excluded:

- Are hospitalized for the treatment of COVID-19
- Require oxygen therapy for the treatment of COVID-19
- Require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity
- Have a known hypersensitivity to any antibody ingredient

12. EVALUATED TREATMENTS

We will evaluate mAbs governed by FDA EUAs. Patients will receive COVID-19 mAbs governed by FDA EUAs, when their treating physician orders a mAb and they meet EUA criteria. As FDA antibody decisions change (e.g., FDA revokes or grants EUAs, provides full approval, or changes eligibility criteria), available evaluated treatments

will change. In April 2021, FDA revoked the EUA for bamlanivimab monotherapy and in June 2021 FDA recommended bamlanivimab and etesevimab not be used.
As of June 30, 2021, the EUA-approved mAbs are as listed below.

13. CASIRIVIMAB and IMDEVIMAB

Casirivimab, a human immunoglobulin G-1 (IgG1) monoclonal antibody (mAb), is covalent eterotetramer consisting of 2 heavy chains and 2 light chains produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture and has an approximate molecular weight of 145.23 kDa.
Imdevimab, a human IgG1 mAb, is a covalent heterotetramer consisting of 2 heavy chains and 2 light chains produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture and has an approximate molecular weight of 144.14 kDa.

14. SOTROVIMAB

Vir 7831 (sotrovimab) is a recombinant human IgG1k monoclonal antibody that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2. Sotrovimab does not compete with human ACE2 receptor binding.

15. CONCOMITANT THERAPY

All care and concomitant therapy are as per the treating providers.

16. CONDUCT

17. DATA COLLECTION

The EUAs require that healthcare facilities and providers report therapeutic information and utilization data through HHS Protect, Teletracking, or National Healthcare Safety Network as directed by the US Department of Health and Human Services.

We will collect data including baseline demographics and underlying conditions, results of SARS-COV-2 PCR or antibody testing, and initial care including mAb infusion completion. We will collect post-randomization healthcare encounters, including hospitalization, emergency department visits, ICU care, and other measures of healthcare utilization. We will use an electronic health record data collection process to augment existing UPMC data collection processes, as necessary.

All data will be handled and secured as per University of Pittsburgh and UPMC data guidelines.

There will be no research activities involving direct interaction with subjects performed as part of this evaluation.

In addition to the primary and secondary outcome data referenced in this submission, data collected will include the below areas. All data will be abstracted directly from the electronic health record and handled anonymously.

- mAb was administered, including date, time, and infusion completion as well as the location of the infusion
- Demographics (including age, sex, race, body weight, vaccination status)
- Healthcare encounters, including hospital and ICU admission status if applicable
- Medication usage and doses
- Hospital and ICU admission status, if applicable
- Administration of medications related to COVID-19, if applicable
- Remnant blood availability
- Laboratory and microbiology data, including COVID-19 testing done for clinical purposes

18. BIOSPECIMENS

Where feasible, we will collect discarded remnant blood samples and nasal/oropharyngeal swab samples to quantify the viral load and host response to the virus. As noted under data collection, we will record laboratory and microbiology data performed for clinical purposes.

19. ANTIBODY ADMINISTRATION

Antibodies will be administered as per the EUAs, UPMC Pharmacy and Therapeutics policies and the respective Pharmacy Manuals (as generated by the pharmaceutical companies), if applicable. Providers will explain mAb risks and benefits and provide the EUA Fact Sheets for Patients, Parents and Caregivers as per EUA requirements.

20. mAb assignment

The COVID-19 mAbs are currently routinely used at UPMC. Once any order for mAb infusion is approved by the UPMC system oversight group, the pharmacy provides whichever EUA-governed mAb is available under a therapeutic interchange approach. Ordering physicians review with the patient the EUA Fact Sheet for each mAb and explain that the patient could receive any of the mAbs governed by FDA EUAs.

If demand for mAb exceeds supply, UPMC has a lottery system to allot who receives the therapy once requested by a physician.

Our current proposal is a UPMC system quality improvement initiative, embracing and extending the current lottery system and therapeutic interchange policy for EUA-governed mAbs for COVID-19 as follows:

1. The Physician orders mAb.
    a. If scarcity present and lottery system allow provision, proceed.
2. The Pharmacy fills order with one of the EUA-governed COVID-19 mAbs using an embedded assignment system akin to current mAb provision. This system will allow a comparative effectiveness evaluation of the multiple mAbs by effectively ensuring random allocation.
3. The Physician can agree to the assigned mAb or can request a specific mAb.

It is the treating physician's choice to accept the assigned mAb or not, and therefore patient consent for the mAb assignment is not required. Patients will be told which mAb they are receiving, along with an EUA Fact Sheet, as per EUA requirements.

21. STATISTICAL CONSIDERATIONS

22. STRATA

Predefined strata will include patients discharged home after infusion, patients admitted to hospital after infusion, prior vaccination, and if known, presence of virus variants of concern at baseline and presence of neutralizing antibodies to SARS-CoV-2 at baseline.

23. NUMBER of PARTICIPANTS

Sample size is determined by case volume throughout the course of the pandemic.

24. STATISTICAL ANALYSIS

The primary evaluation metric is the number of days free from hospitalization to day 28. We will finalize a statistical analysis plan which will consider mAb assignment, heterogeneity of treatment effect by patient characteristics and virus variants, and interaction with other treatments. Due to uncertainty in sample size, we will use a Bayesian adaptive design to ensure ability to provide statistical inference despite variable sample size.

25. ETHICAL CONSIDERATIONS

26. DATA MONITORING

UPMC clinical leadership will regularly monitor monthly reports on enrollment, patient characteristics, and outcomes. Leadership will also receive regular interim analyses from the adaptive statistical model to inform UPMC clinical policy.

27. CONSENT

As per EUA requirements, physicians will discuss the risks and benefits of mAbs and patients will consent to receive a mAb as part of usual care, should they desire mAb treatment. As per UPMC policy, the ordering physician reviews with patients the EUA Fact Sheet for each mAb and explain that the patient could receive any of the mAbs governed by FDA EUAs.

28. ADVERSE EVENTS and SERIOUS ADVERSE EVENTS

The EUAs require providers and/or their designees report all medication errors and serious adverse events potentially related to the antibodies within seven calendar days from the onset of the event. Serious adverse events are defined as death, life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, substantial disruption of ability to conduct normal life functions, a congenital anomaly/birth defect, or an intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.
The EUAs require adverse event reports be submitted to FDA MedWatch via one of multiple methods. Copies of all FDA MedWatch forms are also to be sent to the antibody manufacturer.

Thus, there already exist reporting requirements for UPMC associated with mAb prescription. We will track and record these reported data and adverse events by mAb assignment.

29. SAFETY and RISK MITIGATION

The EUAs stipulate warnings including hypersensitivity, clinical worsening, and side effects. As per EUA requirements, warnings will be communicated by providers to patients, adverse events will be reported as above, and post-infusion clinical monitoring will be done. Administration of mAbs for patients with COVID-19 is routine care at UPMC, and their administration is not a research procedure.

30. MANAGEMENT of INFUSION REACTIONS

As per the EUAs, all participants should be monitored closely, as there is a risk of infusion reaction and hypersensitivity (including anaphylaxis) with any biological agent. Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and dizziness.

31. EXHIBITS

EUA fact sheets for health care providers:
https://www.fda.gov/media/149534/download (sotrovimab).
https://www.regeneron.com/downloads/treatment-covid19-eua-fact-sheet-for-hcp.pdf (casirivimab and imdevimab).

CONSORT Extension for Pragmatic Trials Checklist

Section	Item	Standard CONSORT Description	Pragmatic Trials Extension	Page
Title and abstract	1	How participants were allocated to interventions (e.g., "random allocation," "randomized," or "randomly assigned")		Title page 1 & Abstract page 4-5
Introduction				
Background	2	Scientific background and explanation of rationale	Describe the health or health service problem that the intervention is intended to address and other interventions that may commonly be aimed at this problem	6
Methods				
Participants	3	Eligibility criteria for participants; settings and locations where the data were collected	Eligibility criteria should be explicitly framed to show the degree to which they include typical participants and/or, where applicable, typical providers (e.g., nurses), institutions (e.g., hospitals), communities (or localities e.g., towns) and settings of care (e.g., different healthcare financing systems)	8
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered	Describe extra resources added to (or resources removed from) usual settings in order to implement intervention. Indicate if efforts were made to standardize the intervention or if the intervention and its delivery were allowed to vary between participants, practitioners, or study sites	8-10
			Describe the comparator in similar detail to the intervention	
Objectives	5	Specific objectives and hypotheses		6
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors)	Explain why the chosen outcomes and, when relevant, the length of follow-up is considered important to those who will use the results of the trial	9
Sample size	7	How sample size was determined; explanation of any interim analyses and stopping rules when applicable	If calculated using the smallest difference considered important by the target decision maker audience (the minimally important difference) then report where this difference was obtained	10-11
Randomization—sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (e.g., blocking, stratification)		7-9
Randomization—allocation concealment	9	Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned		7-9
Randomization—implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups		7-9
Blinding (masking)	11	Whether participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment	If blinding was not done, or was not possible, explain why	10-11

Section	Item	Standard CONSORT Description	Pragmatic Trials Extension	Page
Statistical methods	12	Statistical methods used to compare groups for primary outcomes; methods for additional analyses, such as subgroup analyses and adjusted analyses		10-12
Results				
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended)—specifically, for each group, report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome; describe deviations from planned study protocol, together with reasons	The number of participants or units approached to take part in the trial, the number which were eligible, and reasons for non-participation should be reported	11-12
Recruitment	14	Dates defining the periods of recruitment and follow-up		11-12
Baseline data	15	Baseline demographic and clinical characteristics of each group		13-14
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether analysis was by "intention-to-treat;" state the results in absolute numbers when feasible (e.g., 10/20, not 50%)		14
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (e.g., 95% CI)		17-20
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating which are prespecified and which are exploratory		17-20
Adverse events	19	All-important adverse events or side effects in each intervention group		20
Discussion				
Interpretation	20	Interpretation of the results, considering study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes		21-23
Generalizability	21	Generalizability (external validity) of the trial findings	Describe key aspects of the setting which determined the trial results. Discuss possible differences in other settings where clinical traditions, health service organization, staffing, or resources may vary from those of the trial	21-23
Overall evidence	22	General interpretation of the results in the context of current evidence		21-23

Statistical Analysis Plan Final Version 1.1, July 26, 2021
Design for UPMC Antibody Treatment and Evaluation Center
Berry Consultants

Summary of Statistical Analysis Plan Changes for Amendment 1 on July 26, 2021

Page #	Plan Section	Reason for Change
3	Model Convergence	Clarify handling of model convergence.
6	**Modeling Treatment Heterogeneity**	Additional use of Pennsylvania statewide variant data as a surrogate for patient-level variant data
6	Appendix Read-out	Provided details of the final analytical read-out.

Trial Design Introduction

This trial is a platform trial investigating the relative safety and efficacy of multiple monoclonal antibody (mAb) regimens for the treatment of COVID-19 illness. This document describes the statistical details for the trial investigating the relative efficacy of multiple mAb regimens for patients meeting the FDA emergency use authorization (EUA).

The trial randomly allocates which mAb regimen patients receive and will evaluate their comparative effectiveness. Adaptive randomization will be utilized where mAb arms that are performing better will be given higher randomization probabilities. Different mAb arms may be added during the course of the trial and different mAb strategies may be dropped for futility. For the primary analysis of patients within the FDA EUA, there will be no control arm and all arms will be directly compared to all other arms for relative efficacy.

Treatment Arms

The trial may investigate multiple mAb strategy arms. Let k the number of active mAb strategies at any time in the trial. We label these arms as $a=1,...,k$.

Primary Endpoint

The primary endpoint in the trial is hospital-free days (HFDs). The endpoint is a composite of death and number of days alive and free of the hospital. The worst outcome is that a patient dies within 28 days. This outcome is labeled as a –1 HFDs. For patients who do not die within 28 days the primary endpoint is the number of days alive and free of hospitalization. For patients alive at day 28 the endpoint is characterized as an integer value with the number of days free of hospital admission, with possible values 0, 1, 2, 3, …, 28. For statistical analyses the endpoint is modeled as an ordered categorical variable. If a patient has intervening days free of hospital and then has a re-hospitalization the patient will be given credit for the intervening days as "free" of the hospital.

Primary Analysis Population

The primary analysis population, used for all adaptive analyses is the "As-Infused" population. The intent-to-treat population includes all patients randomized to an mAb arm. The "as-infused" population includes those patients that show up and are infused for their mAb. Given that all arms are a mAb arm, there is no anticipated relationship between lack of infusion and the assigned arm. Hence all adaptive analyses and safety analyses will be based on the as-infused population (where patients are coded by the mAb arm they receive). Patients who receive a randomized mAb allocation and are not infused may be tracked as a real-world evidence arm of outcome for a non-mAb control (see secondary analyses).

Primary Analysis Model

The primary analysis model for the primary endpoint is a cumulative proportional odds model. Let the probability of an outcome of less than or equal to y be $\pi_y = Pr(Y \leq y)$. Let a be the indicator of treatment arm (a=1,…,k). The model adjusts for the following baseline variables:

1. ED or infusion center (0=infusion center, 1=ED)
2. Age (with categories of <30, 30-39, 40-49, 50-59, 60-69, 70-79, and ≥80; 60-69 will be used as the referent)
3. Sex (sex at birth, male is the referent)
4. COVID-19 variant (0=unknown/uncollected (referent), categorical endpoint for each known variant)
5. Time (two-week epochs of time are used for adjustments; the most current 4-week period is the referent)

The primary analysis model is based on a cumulative logistic regression, where $\pi_y = \Pr(Y \leq y)$, where

$$\log\left(\frac{\pi_y}{1-\pi_y}\right) = \alpha_y - \theta_a\delta_{[a]} - \sum_{v=1}^{4}\beta_{vj}\delta_{vj} - \lambda_{[time]};\ y = -1,0,1,2,\dots 27.$$

The additive covariate effects across all treatment arms for each patient are modeled through the β parameters. The δ parameters are indicator functions for the treatment arm and covariate values for the baseline covariates. The efficacy of the treatment arms is modeled with the θ parameters. The ordinal effect parameters (α_y) are modeled with a Dirichlet distribution with equal weight on each outcome and a sum of 1.

The baseline covariate effects are modeled with independent weak prior distributions:

$$\beta_{vj} \sim N(0,10^2), v = 1,\dots,4;\ j = 1,\dots,n_v.$$

The appropriate coefficients will be set to 0 within each covariate for identifiability (the goal will be the largest category set to 0).

The effects of time are adjusted within the model using two-week epochs and a smoothing model over time. The modeling of the time effects is set up with the most current period (2 epochs combined being the most recent month are set to 0):

$$\lambda_1 \equiv \lambda_2 \equiv 0$$

$$\lambda_2 - \lambda_1 \sim N(0, 0.15^2)$$

$$\lambda_T - 2\lambda_{T-1} + \lambda_{T-2} \sim N(0, \tau_\lambda^2); T \geq 3$$

$$\tau_\lambda^2 \sim IG(0.25, 0.00562)$$

The prior distributions for the mAb treatment effects are weak:

$$\theta_a \sim N(0,10), a = 1,\dots,k.$$

Arms

One of the treatment arms is selected as the referent arm for treatment effects and assigned a treatment effect of $\theta_a = 0$. The treatment arm at the first adaptive analysis with the largest sample size will be specified as the referent arm for the remainder of the trial.

Model Convergence

Given the complexity of the model, conventions may be taken by the analysis team if there are convergence issues or model stability issues. For example, there may be outcome categories in the 30 possible primary outcome values (e.g., k number of hospital-free days, patient death) that do not occur. If this happens at analysis, the cells will be

combined to achieve model convergence. For example, if the 4 hospital-free day outcome value does not occur it will be combined with 3, and so on, until every cell has occurred. Additional model stability conventions will be taken to preserve the model stability.

Missing and Partial Data

If there are missing covariates for a patient in the as-infused patient population, the following conventions will be used.

1. If the treatment arm is missing the patient will be ignored.
2. If a baseline covariate is missing the referent value for that covariate will be used

For all model analyses, only patients who have achieved 28-days of follow-up from the date of the index infusion will be used in the analysis. No use or imputation of patient data for patients with less than 28 days will be conducted.

Given the EHR-based data summaries there will be no missing outcome data. If there is deemed to be a corrupted outcome that patient will be ignored. Some patients may have 28 hospitalization-free days that at subsequent analyses are found to have out of system hospitalizations. The data will be updated at future analyses.

Trial Inferences

For the primary analysis, there is no "control" treatment and so all inferences are made comparing the individual treatment arms to each other. The main quantity of interest will be the relative odds ratio between any two treatments arms

$$OR_{ij} = \exp(\theta_i)/\exp\,(\theta_j).$$

The posterior probability that the odds ratio for arm *i* compared to arm *j* is greater than 1 (signifying that treatment *i* is superior to treatment *j*) is used as a comparison between arms. Additionally, the posterior mean and 95% confidence interval between arms will be used to summarize relative treatment effects.

Adaptive Design

The trial design is adaptive. A sequence of frequent interim analyses will be conducted as a function of enrollment rate. The expectation is to conduct monthly adaptive analyses. The following decision triggers will be addressed at each adaptive analysis:

Arm Inferiority: If one of the arms has a 99% chance of being inferior to any of the other available arms then the inferior arm will be declared inferior and may be removed from the trial. There may be conditions of the pandemic (e.g., variant frequency, new variants) or drug supply concerns that an arm is retained.

Equivalence: Any two arms in the trial may reach a declaration of equivalence. It is anticipated that no actions would take when equivalence is reached but a declaration and public disclosure may be made. There is a sliding scale of equivalence with different levels of equivalence bounds. A declaration of equivalence will be tied to the equivalence level. Equivalence with a bound of d is declared if the posterior probability of the odds ratio is with d is at least 95%:

$$\Pr\left(\frac{1}{1+\delta} \leq OR_{ij} \leq 1+\delta\right) \geq 0.95$$

The following levels are pre-defined:

1. The first level of equivalence occurs when there is 95% posterior probability that the odds-ratio is within a bound of d=0.25

2. The second level of equivalence occurs when there is a 95% posterior probability that the odds-ratio is within a bound of d=0.20
3. The third level of equivalence occurs when there is a 95% posterior probability that the odds-ratio is within a bound of d=0.15
4. The fourth level of equivalence occurs when there is a 95% posterior probability that the odds-ratio is within a bound of d=0.10
5. The fifth level of equivalence occurs when there is a 95% posterior probability that the odds-ratio is within a bound of d=0.05

Combination Futility: When combinations of mAb are used the combination therapy may be compared to individual components of the combination. If there is more than a 95% probability that the effect of the combination mAb is no better than a 20% improvement in the odds ratio compared to each individual component then the combination may be declared *not clinically relevantly superior (futile)* to the individual components and the combination will be stopped. The comparison between a combination and the individual components will be declared when the combination is included within the platform trial.

Trial Read-Outs: There may be periodic "unblinding" of the trial results. When an arm is removed for inferiority or futility, the results for the inferior and the superior or the combination and its components of the two arms in the trigger will be unblinded and publicly released. The trial will continue and will utilize all data for any new inferences in the trial. Additionally, there may be need for periodic disclosure of the current trial results, such as when FDA revokes authorization for a given mAb. These disclosures will be made and the trial will continue unchanged.

Response-Adaptive Randomization: Assuming R arms available in the trial, response adaptive randomization will be utilized. The response adaptive randomization is conducted based on the probability that each arm has the optimal treatment effect (largest θ). Let q_a be the posterior probability that arm a is the optimal arm among the R arms in the randomization arm space:

$$q_a = \Pr(\theta_a = \max\{\theta_1, \dots, \theta_R\})$$

The randomization probabilities are weighted toward being equal to maintain sufficient randomization to each arm and because the assignment is open-label, to prevent any obvious patterns of assignments. The allocation probability for each arm is

$$\text{Allocation probability} = \frac{q_a + 1/R}{1+1}.$$

If an arm joins the trial and has no data on the primary endpoint, then the value of q_a for that arm is assigned to be 1/R and the remaining arms probability of optimal summing to $1 - \frac{1}{R}$. This convention will create fixed randomization to a new arm in the trial until there is at least 1 observation of the primary endpoint for modeling.

Modeling Treatment Heterogeneity

During the course of the trial, and during a trial read-out, inferences of relative treatment effect by different subgroups may be utilized. In these cases, the treatment effect is modeled as a function of subgroup within the single larger model. Each level of the subgroup will be identified and added as a covariate in the model and then the treatment effect, θ_a, will be modeled separately within each subgroup, $s = 1, \dots, S$, as $\theta_{a1}, \theta_{a2}, \dots, \theta_{aS}$, with hierarchical prior distribution:

$$\theta_{as} \sim N(\mu_a, {\tau_a}^2), a = 1, \dots, k;\ s = 1, \dots, S.$$

$$\mu_a \sim N(0, 10^2); \tau_a^2 \sim IG(0.25, 0.1).$$

Assessment of COVID-19 Variants

The COVID-19 variant type is a predefined subgroup for analysis. The variant type for each patient is unknown at baseline, but samples will be collected and reported upon sequencing. The posterior median odds ratios and 95% credible intervals will be reported for each arm comparison within each variant subset. In addition, because a large percentage of mAb infused patients will not have variant sequencing data (at least in near real time), a second "surrogate" approach will be used to compare the relative efficacy of the mAb regimens in the full treated population over time and by variant type.
Using Pennsylvania statewide data, we will estimate the prevalence of a given variant type by time. Then, we can categorize patients into various time epochs relative to the variant prevalence. These categories will be provided based upon the changing distributions over time in our region.

To consider the internal validity of this "surrogate" approach, we will use data from the subset of patients with actual genotype sequencing, compare the proportion of patients with prevalence of the variant type of interest across levels of the surrogate classification (i.e., Cochran Mantel-Haenszel test of trend).

Adaptive Analyses Reporting

The primary analysis will read out with summaries of the potential arm triggers for each arm actively in the "regimen space." These summaries will include the probability each mAb is optimal in the active regimen space and the randomization probabilities.

A second analysis will be conducted with all arms (even those closed) in the regimen space, to report the probability each regimen is optimal among the larger regimen space.

As the EHR system contains the same covariate and baseline data for both mAb treated and untreated patients, we have continuously updated flags for each patient in the system as being "mAb eligible" (or not) based on EUA criteria on the date the patient became COVID-19 positive. With appropriate selection, this affords 2 untreated control groups for analysis that we will describe using mean (SD), median [IQR}, and proportions, as appropriate: mAb eligible patients who were never randomly assigned to a respective mAb regimen, and mAb eligible patients who were randomly assigned to a mAb regimen yet did not receive treatment.

Readout

Introduction

This document describes the detail of the analysis read-out from July 26, 2021. This document is an appendix to the Statistical Analysis Plan for the "UPMC Antibody Treatment and Evaluation Center" with the details for this analysis read-out.

- We will analyze and report three treatment arms (below) as the first two have been administratively closed to enrollment due to FDA decisions.

- Unblinded data from this and prior interim analyses can be shared with investigators after the last randomized allocations (June 25) to the two mAb treatment arms closed by FDA.

- This unblinding is appropriate as future analyses of patients randomized to the third arm (C+I) will not be compared to the first two arms, there are no "control" arms as all patients receive mAb treatment, and future comparisons will be of C+I vs newer mAbs.

- Enrollment continues in the currently available treatment arms (C+I and S). “S” refers to sotrovimab, produced by GSK and Vir.

Treatment Arms

There are three treatment arms that will be included in this analysis. The treatment arms are

1. B (Bamlanivimab)
2. B+E (Bamlaniviman/Etesevimab combination)
3. C+I (casirivimab/imdevimab combination)

Primary Endpoint

The primary endpoint for this read-out is hospital-free days.

Primary Analysis Population

The primary analysis population for this read-out is the “As-Infused” population. This analysis will include each patient randomized from March 10, 2021 until June 25, 2021. The date of the data set snapshot is on July 26, 2021.

Primary Analysis Model

The primary analysis model is as described in the trial SAP.

The primary analysis for the primary endpoint is a cumulative proportional odds model. Let the probability of an outcome of less than or equal to y be $\pi_y = Pr(Y \leq y)$. Let a be the indicator of treatment arm (a=1,…,k). The model adjusts for the following baseline variables:

- ED or infusion center (0=infusion center, 1=ED)
- Age (with categories of <30, 30-39, 40-49, 50-59, 60-69, 70-79, and ≥80; 60-69 will be used as the referent)
- Sex (sex at birth, male is the referent)
- Covid variant is not modeled in this primary analysis
- Time (two-week epochs of time are used for adjustments; the most current 4-week period is the referent)

The primary analysis model is based on a cumulative logistic regression, where $\pi_y = \Pr(Y \leq y)$, where

$$\log\left(\frac{\pi_y}{1-\pi_y}\right) = \alpha_y - \theta_a\delta_{[a]} - \sum_{v=1}^{4}\beta_{vj}\delta_{vj} - \lambda_{[time]};\ y = -1,0,1,2,\dots 27.$$

The additive covariate effects across all treatment arms for each patient are modeled through the β parameters. The δ parameters are indicator functions for the treatment arm and covariate values for the baseline covariates. The efficacy of the treatment arms is modeled with the θ parameters. The ordinal effect parameters (α_y) are modeled with a Dirichlet distribution with equal weight on each outcome and a sum of 1.

The baseline covariate effects are modeled with independent weak prior distributions:

$$\beta_{vj} \sim N(0,10^2), v = 1,\dots,4;\ j = 1,\dots,n_v.$$

The appropriate coefficients will be set to 0 within each covariate for identifiability (the goal will be the largest category set to 0).

The effects of time are adjusted within the model using two-week epochs and a smoothing model over time. The modeling of the time effects is set up with the most current period (2 epochs combined being the most recent month are set to 0):

$$\lambda_1 \equiv \lambda_2 \equiv 0$$

$$\lambda_2 - \lambda_1 \sim N(0, 0.15^2)$$
$$\lambda_T - 2\lambda_{T-1} + \lambda_{T-2} \sim N(0, \tau_\lambda^2); T \geq 3$$

$$\tau_\lambda^2 \sim IG(0.25, 0.00562)$$

The prior distributions for the mAb treatment effects are weak:

$$\theta_a \sim N(0,10), a = 1,2,3.$$

Arms

The treatment arms with the largest sample size should be selected as the referent arm (label a=1)_for treatment effects and assigned a treatment effect of $\boldsymbol{\theta_1 = 0}$.

Model Convergence

Given the complexity of the model, conventions may be taken by the analysis team if there are convergence issues or model stability issues. For example, there may be outcome categories in the 30 possible primary outcome values (e.g., k number of hospital-free days, patient death) that do not occur. If this happens at analysis, the cells will be combined to achieve model convergence. For example, if the 4 hospital-free day outcome value does not occur it will be combined with 3, and so on, until every cell has occurred. Additional model stability conventions will be taken to preserve the model stability.

Missing and Partial Data

If there are missing covariates for a patient in the as-infused patient population, the following conventions will be used.

- If the treatment arm is missing the patient will be ignored.
- If a baseline covariate is missing the referent value for that covariate will be used

For all model analyses, only patients who have achieved 28-days of follow-up from the date of the index infusion will be used in the analysis. No use or imputation of patient data for patients with less than 28 days will be conducted.

Given the HER-based data summaries there will be no missing outcome data. If there is deemed to be a corrupted outcome that patient will be ignored. Some patients may have 28 hospitalization-free days that at subsequent analyses are found to have out of system hospitalizations. The data will be updated at future analyses.

Trial Inferences

For the primary analysis, there is no "control" treatment and so all inferences are made comparing the individual treatment arms to each other. The main quantity of interest will be the relative odds ratio between any two treatments arms

$$OR_{ij} = \exp(\theta_i)/\exp(\theta_j).$$

The posterior probability that the odds ratio for arm *i* compared to arm *j* is greater than 1 (signifying that treatment *i* is superior to treatment *j*) is used as a comparison between arms. Additionally, the posterior mean and 95% confidence interval between arms will be used to summarize relative treatment effects.

Arm Inferiority: If one of the arms has a 99% chance of being inferior to any of the other available arms then the inferior arm will be declared inferior and may be removed from the trial. There may be conditions of the pandemic (variation frequency, new variations) or drug supply concerns that an arm is retained.

Equivalence: Any two arms in the trial may reach a declaration of equivalence. It is anticipated that no actions would take when equivalence is reached but a declaration and public disclosure may be made. There is a sliding scale of equivalence with different levels of equivalence bounds. A declaration of equivalence will be tied to the equivalence level. Equivalence with a bound of d is declared if the posterior probability of the odds ratio is with d is at least 95%:

$$\Pr\left(\frac{1}{1+\delta} \leq OR_{ij} \leq 1+\delta\right) \geq 0.95$$

The following levels are pre-defined:

- The first level of equivalence occurs when there is 95% posterior probability that the odds-ratio is within a bound of d=0.25
- The second level of equivalence occurs when there is a 95% posterior probability that the odds-ratio is within a bound of d=0.20
- The third level of equivalence occurs when there is a 95% posterior probability that the odds-ratio is within a bound of d=0.15
- The fourth level of equivalence occurs when there is a 95% posterior probability that the odds-ratio is within a bound of d=0.10
- The fifth level of equivalence occurs when there is a 95% posterior probability that the odds-ratio is within a bound of d=0.05

Combination Futility: For comparing B+E to B the combination (B+E) will be compared to the individual component arm (B). If there is more than a 95% probability that the effect of the combination B+E is no better than a 20% improvement in the odds ratio compared to B, then the combination will be declared *not clinically relevantly superior (combination futile)* to N.

Modeling Treatment Heterogeneity Across Variant Date Prevalence Epochs

For this read out, the following time epochs will be modeled with different treatment effects using the Treatment Heterogeneity analysis model.

The treatment effect, θ_a, will be modeled separately within each epoch, $s = 1, \ldots, S$, as $\theta_{a1}, \theta_{a2}, \ldots, \theta_{aS}$, with hierarchical prior distribution:

$$\theta_{as} \sim N(\mu_a, {\tau_a}^2), a = 1, \ldots, 3;\ s = 1, \ldots, S.$$

$$\mu_a \sim N(0, 10^2);\ \tau_a^2 \sim IG(0.25, 0.1).$$

The following time epochs are specified:

1. March 10 - March 31
2. April 1 – April 30
3. May 1 – May 31
4. June 1 – June 25

Specific Analyses

#	Status	Population	Endpoint	Other
1	Primary	As-Infused to B, B+I, or C+I on or before June 25, 2021	HFD	
2	Variant Secondary	As-Infused to B, B+I, or C+I on or before June 25, 2021	HFD	Differential efficacy by time epoch specified

The Primary Analysis

Quantity of Interest	Posterior Probability
B+E superior to B	
B+E combination futile to B	
C+I superior to B	
C+I superior to B+E	

Statistical Triggers Met for Equivalence with Delta Ranges of Equivalence

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 30				
Age 30 – 39				
Age 40 – 49				
Age 50 – 59				
Age 60 – 69	1			
Age 70 – 79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Referent Arm	1			
Arm #2				
Arm #3				
Arm #2/Arm #3				

Graphical summaries

1. Stacked bar plots and cumulative distributions of HFDs by treatment arm
2. Stacked bar plots and cumulative distributions of HFDs by time epochs
3. Stacked bar plots and cumulative distributions of HFDs by sex
4. Stacked bar plots and cumulative distributions of HFDs by treatment arm by time epoch

The Variant Secondary Analysis

Quantity of Interest	Posterior Probability
B+E superior to B	
B+E combination futile to B	
C+I superior to B	
C+I superior to B+E	

Statistical Triggers Met for Equivalence with Delta Ranges of Equivalence

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 30				
Age 30 – 39				
Age 40 – 49				
Age 50 – 59				
Age 60 – 69	1			
Age 70 – 79				
Age 80+				
Female				
Time Bucket 1				
…				

Time Bucket k-1				
Referent Arm	1			
For each time-epoch				
Arm #2				
Arm #3				
Arm #2/Arm #3				