For clinicaltrials.gov submission:

Full Title:

At-Home Inf**u**sion using Bamla**n**ivimab in Part**i**cipants with Mild **t**o Moderat**e** COVI**D**-19 symptoms Project **UNITED**

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PROTOCOL FACESHEET

Protocol Number	2020-0081
Principal Investigator	Daniel Griffin, MD, PHD
Title (Please include Initiative# as prefix)	At-Home Inf**u**sion using Bamla**n**ivimab in Part**i**cipants with Mild **t**o Moderat**e** COVI**D**-19 symptoms Project **UNITED**
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UHG Research Sites	Select Optum Infusion Sites – Sites dictate at-home locations for infusion of Bamlanivimab (LY3819253)
External Sites (if applicable)	None
Sub-Investigators	Ken Cohen, MD Ethan Berke, MD Deneen Vojta, MD
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1 RESEARCH OVERVIEW / ABSTRACT

This is an open-label, pragmatic, single-arm observational study using matched, real-world, external controls in participants with mild to moderate COVID-19. Potential participants will track for symptom development while at home and upon reporting of symptoms will be tested for COVID-19. If positive for COVID-19, a one-time at-home infusion of Bamlanivimab

(LY3819253) will be provided by Optum Infusion. Participants will then be tracked for 28 days to assess for any additional medical care needed or if hospitalization was required.

2. STUDY PURPOSE & OBJECTIVES

The purpose of this study is to: Assess the safety of at-home infusion of Bamlanivimab and to determine whether symptomatic high risk COVID-19 participants will have a reduction in hospitalizations compared to a real-world external control population when provided with a combination of symptom tracking and single dose administration of Bamlanivimab (LY3819253) via an at-home infusion visit.

The primary objectives are:

Safety

- To describe the incidence of infusion reactions during receipt of infusion and during the defined infusion follow-up period
- To describe the incidence of patient reported adverse event outcomes through Day 28

Efficacy

- To determine the incidence of COVID-related hospitalization at Day 28 among Bamlanivimab-treated participants (**long-term** – hospitalization rate via medical records/claims data and **short-term** via participant self-report during active study participation) relative to external controls.

The exploratory objective is:

- To determine the incidence of COVID-related mortality at Day 28 among Bamlanivimab-treated patients relative to external controls.

3. JUSTIFICATION & BACKGROUND

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in the pandemic spread of coronavirus disease 2019 (COVID-19), which in critical cases results in progressive pulmonary failure, complications with acute respiratory distress syndrome (ARDS), and in some cases death. There is an urgent need for effective therapeutics to modify disease outcomes. Bamlanivimab (LY3819253) is a neutralizing IgG1 monoclonal antibody (mAb) to the spike protein of SARS-CoV-2. It is designed to block viral attachment and entry into human cells, thus neutralizing the virus, potentially preventing and treating COVID-19.

4. STUDY DESIGN

4.1 Design

Open-label, single-arm, pragmatic, observational study using matched, real-world external controls (all enrolled participants receive 700 mg Bamlanivimab– there is no placebo arm)

4.2 Duration

For enrolled participants:

Overall duration → 6 months
Individual participant duration (symptom tracking only) → up to 6 months
Active participation after reporting symptoms → up to 38 days (28 days of active participation after receipt of infusion on Day 1 and up to 10 days from report of symptoms to receive infusion)

For matched controls:

Active insurance coverage after date of symptoms onset → up to 38 days. We require matched controls to remain enrolled under their UHC insurance plan to assure data availability. Similar to enrolled participants, matched controls may die after the synthetic date of treatment.

4.3 Data Description

This section describes the main sources of data to be utilized for study participants and matched controls in Table 1. Specific data elements to be utilized are listed in the next section 4.4.

Table 1. Main data sources of study participants and matched controls

Study population	*Data name*	*Data description*
Study participants	Optum infusion nurse data	Day 1 at-home infusion will collect vitals and other essential data pre, during and post-infusion using an established case report form (CRF) to collect any events experienced during and post-infusion related to Bamlanivimab (LY3819253)
	ProtectWell data	during symptom tracking – status of what was selected per daily check-in, first trigger point of noting experiencing symptoms, if COVID-19 positive and received infusion – Day 1-28 wellness tracking (in numeric 1-10 ratings)
	Patient reported data	from point of first report of symptoms through completion of participation on Day 28 (if COVID-19 positive after initial report of symptoms)
	UHC claims data	data including demographic characteristics (e.g. age, gender, race) and existing comorbidities (e.g. congestive heart failure, diabetes, chronic kidney disease)
	Blended Census Reporting Tool (BCRT) data	real-time inpatient admission data including ICD-10 diagnosis codes, discharge status, COVID test status reviewed by UHC's clinical team
	Clinical Data Services Management (CDSM) data	SARS-CoV-2 lab testing data from reporting health systems, clinics and third-party labs
Matched controls	OptumCare EMR data	primary source to confirm for presence of symptoms during COVID+ test of a matched individual (analogous to the symptoms collected as part of ProtectWell data for study participants)
	UHC claims data	data including demographic characteristics (e.g. age, gender, race) and existing comorbidities

	(e.g. congestive heart failure, diabetes, chronic kidney disease)
Blended Census Reporting Tool (BCRT) data	real-time inpatient admission data including ICD-10 diagnosis codes, discharge status, COVID test status reviewed by UHC's clinical team
Clinical Data Services Management (CDSM) data	SARS-CoV-2 lab testing data from reporting health systems, clinics and third-party labs

4.4 Metrics and Variables

The primary outcome of interest is COVID-related hospitalization rate in study participants and matched controls. We list all potential covariates in two phases. Phase I covers historical data and Phase II includes post COVID-19 diagnosis information. Phase I historical data will be collected for both study participants and matched controls. Phase II post-COVID 19 diagnosis data has two parts: data elements to be collected for both study participants and matched controls (Phase II.A), and data elements to be collected for only study participants (Phase II.B).

Phase I - Historical data: Study participants and matched controls:

1. **COVID-19-related information**:
   - Symptomatic or asymptomatic during COVID-19 test
   - Number of COVID-19 cases per 10,000 people in the county of residence during COVID-19 test (if available)
   - Number of COVID-19 deaths per 10,000 people in the county of residence during COVID-19 test (if available)
2. **Demographic:**
   - Age as of 2020
   - ZIP code of residence (may or may not be used for identifying matched controls)
   - Urbanization of residence in a zip code level (urban, suburban, rural)
   - Region/State of residence
   - Race
   - Gender
   - Flag determining whether a patient resides in a nursing facility (or has been staying in a nursing facility currently) – determining patient does not live at home
3. **Insurance:**
   - Line of business (should be mostly Medicare)
   - Dual-eligibility status
   - Continuous member enrollment in 2019
   - Continuous member enrollment in 2020
3. **Comorbidities in 2019:**
   - History of chronic kidney disease
   - History of diabetes
   - History of immunosuppressive disease
   - History of cardiovascular disease
   - History of hypertension
   - History of chronic obstructive pulmonary disease/other chronic respiratory disease

- Elixhauser score for readmission
- Historical flag for all other associated comorbidities used in computing Elixhauser score (i.e., 29 categories like kidney disease, cancer etc.)

4. Immunosuppressive treatment

- History of receiving immunosuppressive treatment (6 months prior to date of COVID diagnosis)

Phase II.A: Post COVID-19 diagnosis data: Study participants and Matched controls

- Date of COVID-19 diagnosis test
- Type of COVID-19 diagnosis test (e.g., PCR, Antigen)
- Hospital admission date (if patient is hospitalized)
- Type of hospital admission (measuring level of trauma) (if available)
    - Through ER (if any)
    - With ICU transfer (if any)
    - With ventilation (if any)
- Diagnosis and procedures associated with hospital admission
- Death date (if applicable)
- Discharge date (if applicable)

Phase II.B: Post COVID-19 diagnosis data: Study participants only

- Infusion date (i.e., date at which drug is administered)
- History of adverse effects (if any)
- Details of adverse effects (if any)
- Types of adverse effects (Based on Optum Infusion nurse data/ProtectWell assessment score of 1-10)
- Date of experiencing adverse effect(s) (if applicable)
- Drop-out date (If available)
- Drop-out reason (if applicable)

4.5 Materials/Devices/Technology

Primary materials that will be used in this study include:

- COVID-19 at-home test kits (Let's Get Checked, Everly Well)
- ProtectWell App - initial tracking for symptoms and for tracking wellness from Day 1-28 after receipt of Bamlanivimab (LY3819253)
- Optum Infusion Kits
- United in Research – Citizen Scientist Project Profile – to provide interim notifications and other check-in points as needed during the participation experience

5. STUDY POPULATIONS

5.1 Target (Source) Population

There are two study populations – study participants and matched controls. For study participants, we plan to enroll those who are 65 and older, and who are deemed high risk if contracting COVID-19. For matched controls, we primarily plan to utilize UHC members who have OptumCare EMR data to confirm presence of symptoms during COVID test as well as

having access to their claims and prospective hospitalization and death data. If applicable, non-UHC members may be used as members of the control population based on EMR review and matching to enrolled participants.

5.2 Number of Subjects

Number targeted for tracking for symptoms: 500,000

Number targeted for evaluable data (COVID-19 positive who receive Bamlanivimab (LY3819253)): 7500 (with an interim safety report to the FDA during the infusion of approximately 50 to 100 participants for safety concurrence and study progression)

Number of matched controls: 7500, same as number targeted for evaluable data

5.3 Eligibility

Both study participants and matched controls will meet the inclusion and exclusion criteria below.

Inclusion Criteria:

- Age 65+, confirmed SARS-CoV-2 positive, located in an area where Bamlanivimab (LY3819253) is available for infusion,
- Have mild or moderate COVID-19 symptoms (after stage 1 of symptom tracking)
- Control only: seek care at an OptumCare facility for confirmed symptomatic COVID-19

Exclusion Criteria:

- Current (from first symptom report) hospitalization for COVID-19
- Prior administration of Bamlanivimab

5.4 Potentially Vulnerable Populations (Please select all that apply to this research)

☒ UnitedHealth Group Employees
☒ Intellectually/ Cognitively / Developmentally Disabled Persons
☒ Economically Disadvantaged Persons
☐ Children
☐ Prisoners
☐ Pregnant Women

5.5 Subject Identification & Accrual Plan

Those who meet initial qualifying criteria (65+, located in an area with Bamlanivimab (LY3819253) is currently available or may become available) will be invited to participate.

5.6 Recruitment Plan and Materials

Email/mail invitations to consider participation will be sent to those who qualify to consider joining to track for symptoms (located in an area where Bamlanivimab (LY3819253) is currently available).

5.7 Enrollment / Consent Plan and Materials

Enrollment will occur in the online platform United in Research.

- https://www.unitedinresearch.com/volunteers-for-covid-19-experimental-treatment-studies

Enrollment plan:

- If registered through United in Research as a Citizen Scientist – in an area where Bamlanivimab (LY3819253) at-home infusion is currently available – enrollment experience is agreeing to: daily tracking for symptoms via ProtectWell, to being tested for COVID-19 upon reporting symptoms, to receiving the one-time at-home infusion of Bamlanivimab (LY3819253) if positive for COVID-19 and to provide wellness checks from Day 1-28 after receipt of Bamlanivimab (LY3819253).

Note: No participants will be able to begin tracking for symptoms via ProtectWell if they have not reviewed and signed the complete consent experience through receipt of Bamlanivimab (LY3819253) and ongoing wellness checks post-infusion. This is will keep participants informed about what the overall experience will entail should they contract COVID-19 and avoid making any less informed decisions during the period of reporting symptoms and awaiting COVID-19 results. Participants are free to withdraw at any time and will be reminded of this throughout their experience. This balances the request for consent up-front for a product they may never require if they do not contact COVID-19.

5.7 Compensation / Remuneration / Reimbursement

No compensation will be provided for participation. There are no potential costs to reimburse since all study related activity costs are covered. If additional COVID-19 care is required, this will be covered via usual insurance.

6. STUDY PROCEDURES

6.1 Procedures

Optum Infusion:

Optum Infusion Pharmacy is a home infusion provider that will manage the shipment and administration of the study drug to the participants per the study protocol. Upon testing positive for COVID-19, Optum Infusion Pharmacy will be notified by the sponsor. The study drug will be shipped from a licensed pharmacy in validated cold chain containers and administered as soon as possible by registered nurses at the participant's home within 10 days of symptom onset.

Receipt of Bamlanivimab:

One-time dose of Bamlanivimab, delivered via infusion through the vein, lasting around 30 minutes

Active Participation Period (up to Day 28):

After the Optum Infusion Nurse visit has concluded (any adverse event information during and immediately post-infusion will be collected by the Nurse and will be filed for safety assessment), participant will begin ProtectWell tracking on a daily basis from Day 1 (how do you feel starting on Day 1 – this is the baseline) through Day 28 with the following approach: Day 1 rating (1-10 with 1 being the worst they can feel and 10 being the best they can feel) and then rating on a daily basis Day 2-28 (if rating remains in a 1-3 range, this will trigger clinical follow-up as the participant is not getting better).

Note: if traditional ProtectWell tracking cannot be utilized, the participant will be provided with contact information to report any issues that they are experiencing or to report that they are not feeling well.

End of Study:

Given the virtual nature of participation after the initial in-person infusion visit, participants will receive a notification on Day 28 thanking them for their participation and asking if they are willing to complete a brief survey on their study experience.

6.2 Subject Participation

Enrolled in COVID-19 Readiness Cohort

- If located in an area where at-home infusion of Bamlanivimab is available, screened for detailed eligibility and begin symptom tracking upon determining eligible
- If symptoms begin to develop, receive COVID-19 test at home
- If COVID-19 positive, home infusion visit is scheduled/confirmed for enrolled participant

Please see Appendix 1 & 2 for additional detail.

6.3 Participant Engagement & Results

All those who participate will have the opportunity to review findings/results and what actions were taken in response to those results either via clinicaltrials.gov or on United in Research (findings of United in Research projects are shared on the site for all to review – regardless of participation – and those who participated would also receive a specific notification that findings/results have been posted).

6.4 Data Collection

Tracked data collection begins from first report of symptoms via ProtectWell (those who track but never experience symptoms will be accounted for in the final analysis but do not have a robust data collection process since they never proceed to the step of requiring a COVID-19 test).

Data collection timepoints:

1. First report of symptoms
2. COVID-19 test result (positive – moves forward; negative – resets the experience)
3. Date of receipt of Bamlanivimab (LY3819253) via infusion (Day 1)
4. Day 1 infusion (pre, during, post) collection of CRF data (participant vitals/health information and any events experienced)
5. Day 1 post-infusion baseline wellness check through Day 28 final wellness check
6. Any point during Day 1 post-infusion baseline through Day 28 where wellness check indicates participant is feeling worse
7. Point from participant marking feeling worse through action taken (live daily check-in via clinical support, recommendation to seek medical care and/or requiring hospitalization)

6.5 Data Analysis

There are four research objectives: one primary efficacy objective, one exploratory efficacy objective, and two secondary safety objectives. A control group will be needed to address the study objectives on efficacy of treatment. The following sections describe the creation of a real-world external control group, methods for matching study participants to controls, and analysis for the study objectives.

Figure 1 illustrates the timeline for study participants and controls to ensure alignment on an index date for symptoms onset and the follow-up period. Since the control group will not have an infusion date associated with them, we will randomly select a number from the distribution of number of days after date of symptoms onset in study participants to identify an index date with which to define 28 days post infusion where we will monitor claims and EMR data for hospitalizations and mortality.

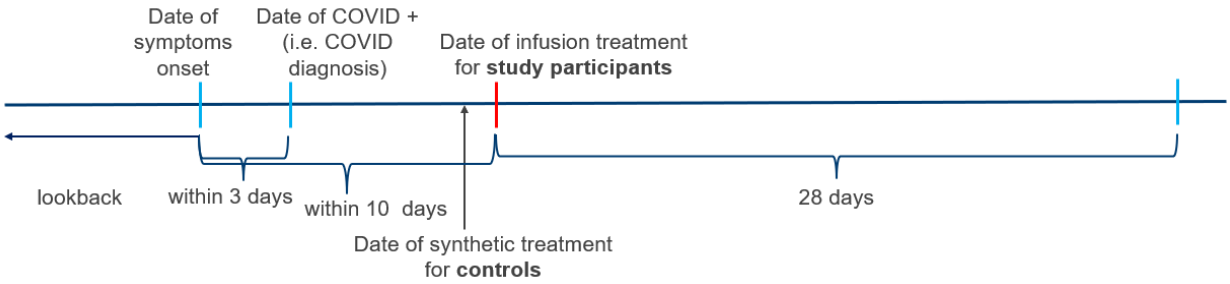


Figure 1. Illustration of the timeline for study participants and controls

6.5.1 Methodology for creating a matched cohort for the study participants

Research Questions:	Data Variables:	Data Source:
Can we build a control group for the study participants? Do we observe any differences in demographics and comorbidities between study participants and potential controls before matching?	• Flag of infusion treatment • Demographics • Elixhauser conditions • Symptoms	• Optum infusion nurse data • UHC claims data • CDSM • BCRT • OptumCare EMR data

We consider three types of matching methods to identify a control cohort: propensity score matching (PSM) as the primary method and prognostic score matching (PrSM) as the alternative method. Each matching method has its strengths and weaknesses. Propensity score matching is the most used method for matching, but it is usually challenging to justify all confounders are considered and available. In general, inference based on propensity method works well if the PSM model consists of statistically significant covariates that vary considerably between treatment and control. Alternative methods are proposed and to be used to ensure robustness of inference.

6.5.1.1 Pre-matching identification of risk factors as matching covariates

Before matching, we will identify the risk factors that are associated with COVID hospitalization. The result of this will be a parsimonious list of variables on which treatment and control group will be matched.

Consider a binary response taking a value of 1 if a patient is hospitalized due to COVID-19, and 0 if a patient is tested positive for SARS-CoV2 but does not have a record of subsequent COVID-related hospitalization (hospitalization within 38 days of a positive test). We include risk factors such as demographic (e.g., gender, age, race, geographical area such as state or

county), comorbidities (Elixhauser scores related comorbidities such as diabetes, metastatic cancer, heart diseases, obesity, coagulopathy, and so on), and other potential clinical attributes as available in the identification of the appropriate matched-cohort. These risk factors will also include all clinically identified variables by Eli Lilly to define moderate and high-risk groups. We will run this step three times with three datasets; specifically, we consider:

a. *Iteration 1:* This is based on retrospective data available in-house consisting of Medicare Advantage (MA) members, aged greater than or equal to 65, and COVID diagnosed. We will exploit BCRT and CDSM, UHC Claims. The study cohort here is a broader population than the study participants.
b. *Iteration 2:* This is solely based on data associated with study participants. We will exploit risk factors from UHC Claims. and study enrollment information from Optum infusion nurse data.
c. *Iteration 3:* This is based on information of both the general MA population and study participants –retrospective and prospective data in Iteration 1 and Iteration 2, respectively. We will exploit COVID labs and hospitalizations from BCRT and CDSM, risk factors from UHC Claims data, and study enrollment information from Optum infusion nurse data.

We will identify the covariates that are consistent across all three iterations and select the final set based on data, literature, and clinician decision. The main objective of this initial iteration step is to reduce dimension, exclude noise variables, include clinically meaningful variables, and lay out the foundation for the subsequent analyses. We will develop a generalized linear (mixed) model (Nelder, 1972) (McCulloch, 2014) with appropriately chosen link functions to quantify the association and make inferences about the parameter estimates based on the retrospective data. The appropriateness of using random effects will be evaluated by the likelihood ratio test (LRT) and summary information criteria (e.g., conditional or marginal Akaike information criteria (AIC)). We will select influential risk factors in the light of both clinical relevance and statistical significance. In this pursuit, we will use GL(M)M with a Least Absolute Shrinkage Penalty (LASSO) (Tibshirani, 1996) to develop a parsimonious model; here, the optimum parameters will be selected by *k*-fold cross-validation with the 1-standard-error rule. We will also check the statistical significance of any association based on Wald test statistic between each covariate and response based on univariate and multivariate GL(M)M; a pre-determined threshold of, say 0.10 (level of significance), will be used to select covariates. This sequential inferential approach (i.e., Wald) is supplementary to the regularization step (i.e., GLMM-LASSO), and the final set of covariates will be determined by exploiting both/either approaches and will be combined with clinical relevance (i.e., factors used in determining high, moderate, low risk groups by Lilly).

6.5.1.2 Primary method – propensity score matching

The main objective of propensity score matching is to ensure balance between the treatment and control group on the selected covariates. Propensity score matching will be conducted after the completion of treatment enrollment (28-day study period) and upon the availability of information of study participants. Data sources of information for calculating the propensity scores for study participants will be Optum infusion nurse data, UHC claims data, and CDSM data. Note for the matched controls we will select them from OptumCare EMR+claims dataset, we will include only members who are COVID diagnosed, have documented symptoms of COVID-19, meet the inclusion/exclusion criteria for the study, and have historical information about selected risk factors (either through claims or EMR).

In this pursuit, we will apply propensity score matching techniques described in (Guo, 2014). We will fit a GLM assuming a known functional form (e.g., main effects) with response being the log odds of receiving treatment, and estimate balancing (i.e., propensity) scores which are next to be used in finding the matched pair between treatment and control group. We will use nearest neighbor matching with a caliper which its size will be determined empirically. Note this matching model is different from 6.5.1.1.1 in terms of response (hospitalization flag vs receiving treatment). We will evaluate balance in covariates between study participants and matched controls by absolute standardized difference in mean (Austin, 2009) and variance ratio of propensity score and covariates since it is more robust in terms of sample size and covariate distribution requirements in comparison to other balance diagnostics (Ali, 2016). We will also conduct a hypothesis test to examine if a significant difference in matching covariates exists between treatment and control groups, such as Wilcoxon rank-sum (Mann-Whitney) test, *t*-test, or other bivariate analysis. We will use these tests to evaluate covariate balances before and after matching and repeat the processes if covariate imbalances remain.

We will consider multiple greedy matching algorithms (Smith, 2005) based on nearest neighbor matching, caliper matching, and nearest neighbor matching within a caliper, and obtain 1-to-1 match after the baseline matching and before accessing any outcome data. As an alternative approach, optimal matching technique may also be adopted, in the event that the covariate imbalances persist using the prior methods. In addition, greedy matching methods make decisions about inclusion a pair of treated-control participants as a matched set sequentially; here decisions are made one at a time without reconsidering early decisions as later ones are made. From this point of view, such mechanism is not optimal and therefore optimal matching based sensitivity analyses will be performed to assess the numerical performances. In addition, propensity score subclassification (Rosenbaum, 1984) in conjunction with trimming strategy (Crump, 2009) will be adopted. Such greedy matching methods require a sizable (e.g., 70%) common support region for logit between treated and control, known as “overlap assumption”. It is possible that greedy matching excludes participants because treated cases fall outside the lower end of the common support region (those who have low logit) and nontreated cases fall outside the upper end of the common support region (those who have high logit). This can be investigated once we fit PSM model, estimate the logits, and plot them side-by-side for treated and control. If we see significant nonoverlap then we may need to try alternative such as trimming method. Regarding unmeasured confounding, we will also consider sensitivity analyses such as the e-value (VanderWeele, 2017) or the method of Zhang et. al (2018).

6.5.2 Primary efficacy outcome analysis: COVID-related hospitalization rate at Day 28

Research Questions:	Data Variables:	Data Source:
Do we find a significant difference in rate of COVID-related hospitalization at Day 28 between study participants and matched controls?	• Flag of infusion treatment • Demographics • Elixhauser conditions	• Patient self-reported data • Optum infusion nurse data • UHC claims data • CDSM COVID labs data • BCRT COVID hospitalizations data • OptumCare EMR data

What characteristics do those hospitalized study participants and matched controls have?		

Understanding the COVID-related hospitalization rate at Day 28 between study participants and matched controls is the key primary objective. We consider the analysis in combinations of with/without time-related outcome and with/without covariate adjustment. A single model will be selected and documented prior to accessing outcome data with the focus of including covariates expected to be strongly related to outcome based on other studies.

First, consider the simplest scenario without covariates adjustment and time-related outcome; we will use nonparametric McNemar's test and Wilcoxon signed-rank test to compare the hospitalization rate at Day 28 between the treatment and control groups at the level 0.05. On the other hand, for those who are not admitted due to COVID at Day 28, we will treat their non-hospitalization as a censored response after Day 28, instead of assuming no COVID hospitalizations after Day 28. Without covariates adjustment, we will draw Kaplan-Meier curves and perform log-rank test to compare the hospitalization rate between the treatment and control groups.

Next, consider covariates adjustment, this will allow us to compare hospitalization rate between treatment and control groups given a subset of matching covariates or covariates not included in matching. We will construct a generalized linear model with fixed or mixed effects to examine if the hospitalization rate differs between study participants and matched controls after adjusting demographics and comorbidities. Considering the time component in the response, we will use Cox proportional hazard model, accelerated failure time model and other survival models. Method selection will depend on if model assumptions hold in our data.

In the short term, we will use patient-reported data and BCRT data to identify hospitalization among the treatment group; in the long term, we will use UHC claims data for inpatient records to examine if we obtain consistent results and receive additional information such as procedures and allowed amounts and for identification of hospitalizations for the control group.

6.5.3 Exploratory efficacy outcome analysis: COVID-related mortality rate at Day 28

Research Questions:	Data Variables:	Data Source:
Do we observe COVID-related mortality at Day 28 between study participants and matched controls? What characteristics do those deceased study participants and matched controls have if any?	• Flag of infusion treatment • Demographics • Elixhauser conditions • Symptoms	• Patient self-reported data • Optum infusion nurse data • UHC claims data • CDSM COVID labs data • BCRT COVID hospitalizations data • OptumCare EMR data

We will perform descriptive analysis and report summary statistics if there will be COVID deaths in study participants and matched controls.

To address the secondary (safety) objectives we will perform the following analyses.

6.5.4 Secondary safety outcome analysis: Incidence of infusion reactions

Research Questions:	Data Variables:	Data Source:
Do we find any infusion reactions during receipt of infusion and during the infusion follow-up period? Do infusion reactions vary from demographic characteristics or comorbidities?	• Date of infusion treatment • Date of infusion reactions of interest • Demographics • Elixhauser conditions	• Patient self-reported data • Optum infusion nurse data • UHC claims data

Clinicians will start with qualitative analysis on a case by case basis. We will report descriptive statistics according to the data we will obtain. If we have a sufficient size of study participants with particular infusion reactions, we can calculate descriptive statistics, run Chi-square independence test and Kruskal-Wallis test to examine if infusion reactions vary from demographics or comorbidities.

6.5.5 Secondary safety outcome analysis: Adverse events

Research Questions:	Data Variables:	Data Source:
Do we find any self-reported adverse events between receipt of infusion and day 28 from study participants? Do patient-reported adverse events vary from demographic characteristics or comorbidities?	• Date of infusion treatment • Date of infusion reactions of interest • Demographics • Elixhauser conditions	• Patient self-reported data • Optum infusion nurse data • UHC claims data

Once adverse events are defined or classified and adjudicated, we can perform the same methodology described in 6.5.4.

6.5.6 Subgroup Analysis

Research Questions:	Data Variables:	Data Source:
Is the time gap between a COVID positive test result and an infusion associated with COVID hospitalization? Do we find any patterns in a subgroup with certain demographic characteristics or comorbidities of interest?	• Flag of infusion treatment • Demographics • Elixhauser conditions • Symptoms	• Patient self-reported data • Optum infusion nurse data • UHC claims data • CDSM COVID labs data • ProtectWell data

There are two pre-specified subgroup analyses we will pursue aside from the primary and secondary objectives (efficacy and safety) above.

First, we want to understand if the timing of the infusion relative to a positive COVID test, impacts hospitalizations. We will compute the Cramer's V and phi coefficient as one-number summary of correlation between two categorical variables when we group time gap between date of COVID positive and date of home infusion. If considering this time gap as a continuous variable, we will run a simple logistic regression model to examine if time gap is associated with the hospitalization rate at Day 28. Then, we will apply the same methodology described above for categorical and continuous covariates and binary outcomes.

Second, we want to understand if the timing of the infusion relative to a symptom onset, impacts hospitalizations. We will compute the Cramer's V and phi coefficient as one-number summary of correlation between two categorical variables when we group time gap between date of COVID positive and date of home infusion. If considering this time gap as a continuous variable, we will run a simple logistic regression model to examine if time gap is associated with the hospitalization rate at Day 28. Then, we will apply the same methodology described above for categorical and continuous covariates and binary outcomes.

7. RISKS AND BENEFITS

7.1 Risks and Risk Mitigation

Bamlanivimab (LY3819253) is an investigational product for those who are at high-risk of experiencing more severe symptoms if they contract COVID-19. The receipt of Bamlanivimab (LY3819253) occurs under an Optum Infusion Nurse monitored procedure, with appropriate protections in place to address any expected infusion reactions (either from Bamlanivimab (LY3819253) or the process of infusion) as well as to address any unexpected events that occur either pre, during or post-infusion of Bamlanivimab (LY3819253). Nurses will remain for a period of up to two hours while preparing for, during and follow-up after infusion to confirm that the participant is stable and does not require any further medical oversight.

Participants will self-report a baseline on Day 1 after receipt of the infusion and this baseline will create the landscape for their wellness reports Day 2 through 28 after receipt of infusion. We will have additional contacts for participants external to the daily ProtectWell wellness check via the app, including using post-infusion Optum Infusion clinical support features as needed for anyone who is experiencing anything that requires more immediate attention.

The risk of loss of confidentiality given the number of partners engaging to execute the research is always a possibility. The risk is mitigated by using appropriate protected electronic files and to avoid exchanging information that contains protected health information (PHI) and no PHI will be released to the external partners, but personal identifying information (i.e. name, address) will be provided as needed.

7.2 Benefits

There is no guarantee of direct benefit from participating. The study will test the hypothesis that treatment with Bamlanivimab (LY3819253) will reduce the incidence of COVID-19 related hospitalization and mortality in mild or moderate COVID-19 patients who are at high risk of progressing to severe COVID-19 and/or hospitalization, relative to matched external controls. The study will further describe the incidence of infusion related reactions and patient reported adverse events in patients treated with Bamlanivimab (LY3819253).

Given the available data and the recent emergency use authorization of Bamlanivimab (LY3819253) in this patient population, the benefit-risk assessment for this study is favorable.

8. DATA HANDLING

8.1 Data Protection and Storage Plan

The Data Operations Team and study staff within UHG R&D are responsible for adhering to the following Best Practices for Data Management:
Data Operations follows the standards of HITRUST for data management and data governance

1. Data always remains encrypted in transit and at rest.
2. Managed access with expiration dates.
3. Minimum use regarding dataset usage.

Access to protected data is limited to the Data Operations Team within UHG R&D

1. Data Operations does not participate in research efforts.
2. Data Operations uses identifiable data to match across all data sources and issue surrogate keys.
3. Data Operations de-identifies and lands the matched data in the Data Factory for use by the organization in research efforts.

Restricted research project data can be isolated from other data sources

1. Data Operations uses the Master Data Management (MDM) asset which contains logic to identify sources and matched people that have restrictions for use.
2. The MDM de-identified surrogate key crosswalks are maintained in separate restricted datasets using the restricted flag as referenced in #1 above.
3. Data operations user groups allow access to be limited to only those users with permission to work with restricted data. The restricted data is managed by the Data Operations to ensure isolation from other data sources.
4. Data for use in operations businesses is also isolated at the project level in the Person ID Management (PIM) asset. Only users with project level access may view the identifiable data associated with these restricted records.

8.2 Power Analysis

In this section, we detail the methodology and results for power analysis. To evaluate treatment effects based on the discrete clinical endpoint (hospitalization rate at Day 28 post infusion), we compared the proportion of events (i.e., prevalence rate or COVID hospitalization rate) between treatment and matched-control group which is our primary objective of interest. Specifically, we are interested in testing the efficacy (superiority) of treatment effects, which can be written formally in one- or two-sided hypotheses. Assume the null hypothesis is two-sided. We performed the power analyses based on a 5% level of significance (Type-I error) for a set of values of power (i.e., 0.75, 0.80, 0.85, 0.90, 0.95). We obtained the minimally required sample size for multiple scenarios - (a) hospitalization rate (0.20, 0.25, 0.30, 0.35) based on BCRT and CDSM data (b) different possible efficacy rates (reduction rates in hospitalization after using treatment). We used multiple methods - (i) a two-sample proportion test in detecting a difference between two binomial probabilities (Casagrande, 1978) (Fleiss, 1980) and (ii) McNemar's test (Agresti, 2003).

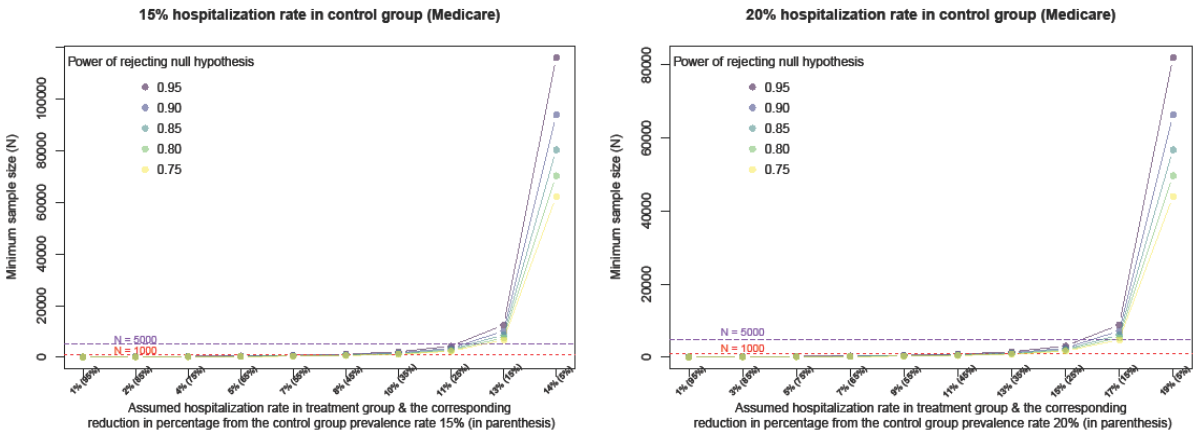
The former test statistic follows Gaussian distribution asymptotically exploiting large sample theory and the latter is designed to test categorical shift (or association) in responses (hospitalization rate in our example) between treatment and control group where the idea is to cast the data into a 2 x 2 contingency table. While both these methods provide competitive and

comparable results, reported below are the results based on the first method, a two-sample proportion test with continuity correction. The one-sided hypothesis requires a smaller sample size than that of a two-sided test.

Figure 2 illustrates the sample size required with a case and control ratio being 1:1 for different hypothetical scenarios. As expected, when the true prevalence rates between treatment and control groups are small, it requires a larger sample size to detect a statistically significant difference. As reported in the Lilly SARS-CoV-2 Neutralizing Antibody Program Update, the hospitalization rate for the treatment (i.e., LY-CoV555 Mono) group drops by 75% compared to that of the placebo group. Based on this relative change, we will need a total sample size less than 1,000; follow the power curves (i.e., corresponding to 0.10 Type-II error) in Figure 2 top-right panel with 75% (approximately) reduction rate. For example, using the COVID hospitalization rate of 25%, reported below in Table 2, are the minimum COVID diagnosed patients required to detect varying differences between the proportions at a 5% level of significance with 90% power of rejecting a two-sided null hypothesis.

Table 2: A case study for baseline hospitalization rate of 25%.

Absolute differences (assumed) between prevalence rates of treatment and control group (% reduction from baseline rate)	**Total sample size (treatment and control as 1:1)**
0.24 (95%)	97
0.21 (85%)	129
0.19 (75%)	175
0.16 (65%)	244
0.14 (55%)	355
0.11 (45%)	550
0.09 (35%)	940
0.06 (25%)	1,899
0.04 (15%)	5,416
0.01 (5%)	49,900



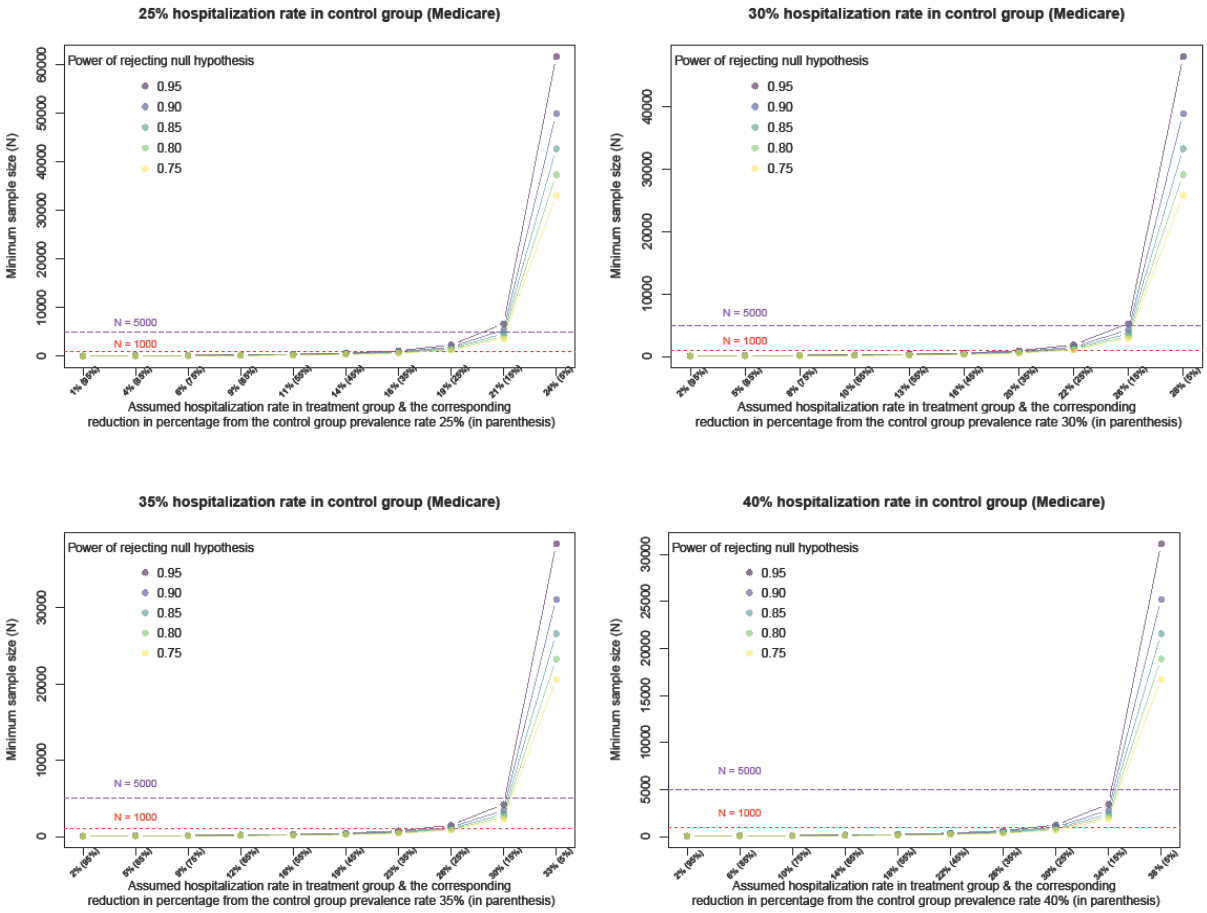


Figure 2: Power analyses at 5% level of significance for six scenarios with baseline COVID hospitalization rates of 15% (top-left), 20% (top-right), 25% (middle-left), 30% (middle-right), 35% (bottom-left), and 40% (bottom-right) based on CDSM and BCRT databases. Varying prevalence rates along with reduction (in parenthesis) in hospitalization from baseline (i.e., control group) for the treatment group are considered (X-axis) as 95% to 5%. Reference lines corresponding to 5,000 and 2,000 sample size are drawn for convenience of comparison.

8.3 Future Utilization

There are no samples being collected from the participants in this study and therefore, there will be no residual biospecimens. The data collected from this study, combined with appropriate health record and claims data, will be retained for additional analysis/utilization if determined appropriate (this will require a separate protocol submission or a modification to this existing study to outline the additional analysis occurring and the associated plan to retain confidentiality for the data being utilized).

8.4 Publication Plan

There is intention to publish the findings of the study in partnership with Eli Lilly and Company. Any data used for publication purposes will be presented in aggregate and will not identify individual participants.

1. QUALITY CONTROL, MONITORING AND REPORTING

9.1 Issues Management Plan

There are two potential sources of issues that may be experienced during participation in the study. We will limit monitoring and reporting to those participants who receive Bamlanivimab (LY3819253).

Participant Reported Issues:

Participants will track daily how they are feeling from Day 1 post-infusion (their baseline of how they are currently feeling) through Day 28 (end of active study). This tracking will be conducted via the ProtectWell application and will have two potential outcomes: 1) Participant indicates they are feeling the same or better (no further follow-up needed) or 2) Participant marks they are feeling worse and there will be a reminder notification via ProtectWell if they are experiencing severe/life-threatening symptoms to seek help and it will trigger a clinical follow-up with that participant (clinical follow-up will occur via phone outreach to result in a discussion with the participant). Based on the discussion, one of the following may occur:1) participant is OK to remain at-home and on study or 2) participant should seek medical care and are marked as meeting an end point (and we will track outcome of what they needed and if they required hospitalization).

In addition, when speaking to the participant, the clinical team will attempt to ascertain if the issue is: 1) related to worsening COVID-19 symptoms, 2) a potential side effect of Bamlanivimab (LY3819253) or 3) any other unanticipated event that might occur during active study participation. If the issue is potentially related to a side effect of Bamlanivimab (LY3819253), the clinical team will engage the UHG R&D clinical support team (internal R&D team with nurse management oversight for connection for clinical consult when needed) and that project support team will report the issue to Eli Lilly and Company if determined by the PI or delegate to be an unexpected and likely related to the study event (related to receiving Bamlanivimab (LY3819253) – not related to COVID-19 infection which is not due to participating in the study).

Optum Infusion Reported Issues:

Optum Infusion has three potential touch points with the participants in the study:

Pre-Infusion:

- Any issues that arise during the contact call to set up shipping the drug and scheduling the at-home infusion visit
- Any issues that arise during the period from scheduling the at-home visit through to infusion visit

Infusion Visit:

- Collection of pre, during and post-infusion information and any adverse reactions or other reported symptoms (this is formally documented on the case report form (CRF) and is compiled and reported to the UHG R&D project support team (and the project report team may determine that Eli Lilly and Company needs to be informed of information on the CRF and will follow-up on that accordingly – events that are likely to be related and/or unexpected in severity/frequency will be reported to Lilly).

Post-Infusion:

Optum Infusion will provide contact information for the participants at the infusion visit and the participant may opt to use this for outreach (they will also have ProtectWell and the outreach number provided on the consent document) and the Optum Infusion representative will discuss the issue with the participant and make a determination if they can give descriptive advice or if they need to loop in the UHG R&D project support team to engage either the UHG clinical team (if deemed appropriate) or
to inform Eli Lilly and Company of the issue and expected plan of action to address the issue.

- Any issues reported via either mechanism will be documented, assessed whether the event was related to study drug.
- For Serious Adverse Events (SAEs) – events resulting in hospitalization, substantial action being required (without hospitalization) or death – events must be reported/assessed and submitted to the IRB for consideration within 72 hours
    - For any serious adverse events that meet the following criteria and result in any of the outcomes listed – these will be reported to Lilly upon discovery within 24 hours:
        - Suspected adverse reaction
        - Serious
        - Unexpected

    And result in the following outcomes (i.e. serious adverse events):
        - Death
        - Life-threatening adverse drug experience (meaning determined related to bamlanivimab)
        - Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours)
        - Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
        - Congenital anomaly/birth defect (not likely to apply to this protocol)
        - Important Medical Event (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

- For Adverse Events (AEs) – events must be reported/assessed and submitted to the IRB for consideration within 10 business days
- For any events – if event is likely related to Bamlanivimab – event will be assessed by the PI and medical review team and findings will be reported to Lilly in alignment with the FDA EUA requirements

Interim Safety Analysis and FDA Reporting:

During the period of active at-home infusions (including post-infusion observation period), data will be compiled and assessed real time for any unanticipated problems or other serious adverse events that may require reporting to either Lilly and/or the FDA. In addition, after infusion of approximately 50 to 100 participants (up to 100 participants), an interim safety report will be compiled for Lilly and the FDA, per the FDA's request in the IND correspondence letter received on December 23, 2020. Given the design of the study and the fact that there is a 10-day from symptom onset window to infuse participants after confirmed COVID-19 diagnosis with a constant rolling list of eligible participants to have an at-home infusion of Bamlanivimab scheduled – the number of participants infused will be at least 50 and no more than 100 when this interim report is filed with Lilly and the FDA. Enrollment of new participants to enter the first stage of the trial (symptom screening) will pause while FDA review of the interim safety data occurs and enrollment will not recommence until FDA concurrence of enrollment expansion is received.

APPENDIX

1. Subject Participation Flow

Prospective/Potential Participant is informed about joining the COVID-19 Readiness Cohort and to visit United in Research to create a Citizen Scientist profile (or if they are already registered – they can log into their existing profile and review and choose to join the COVID-19 Readiness Cohort

↓

For those who are willing/interested, a Citizen Scientist profile is created (the profile collects the following information: name, age, best contact information including cell phone number, and whether the person has UHC insurance)

↓

After creating a profile, the Citizen Scientist is now eligible to pre-enroll into the COVID-19 Readiness Cohort to be placed on the waiting list for notification that their area was selected due to location to product supplier for the Lilly product and Optum Infusion Nurses

↓

During pre-enrollment, additional information is collected from the Citizen Scientist – specific to information needed to determine eligibility for the Lilly product study (this includes: confirming home address, height/weight, race/ethnicity, any potential exclusions such as pregnancy, cancer, transplants, transfusions, or COVID vaccines, confirmation that they are willing to use a smartphone app for symptom tracking (Protect Well), willingness to do COVID testing – either at home and mail it back, at a clinic or that either is fine and willingness to consent to the Lilly product trial)

After reviewing what they are agreeing to (the COVID-19 Readiness Cohort Consent) – if they choose to join, they are on the waiting list for location selection eligibility determination (along with individual eligibility determination from that point forward – but the first step is picking a location where they can reasonably receive the product and have it infused)

If their area is selected as a Lilly product eligible site – the pre-enrolled Citizen Scientists in the COVID-19 Readiness Cohort in that area will receive an automated email notification (to whatever preference email they have in United in Research or a text message if that was their preferred method of contact) that they are now eligible to enroll into symptom tracking via Protect Well and will provide instructions for how they should do that and begin tracking

If symptomology in the ProtectWell app indicates likely COVID-19 infection, a kit would be expedited (if they are not in Well At Home) to the house address for the participant to complete/return

If symptomology in the ProtectWell app indicates likely COVID-19 infection, the registered participant would receive notification of how to proceed with completing the test kit and sending in/processing for results

In either scenario, once the kits are completed/returned and COVID-19 infection is confirmed via the test, the participant becomes eligible to move forward into actively participating in the Lilly product trial and UHG R&D will flag them as ready to schedule the at-home infusion

At-home infusion appointment is scheduled – aligning with product preparation and considerations for site specific travel times and product shelf-life after preparation – and confirmed with those in the household receiving the infusion

At-home infusion occurs, and proper protocol is followed for infusion of the product and monitoring those who received it for any unexpected effects after receipt of the product

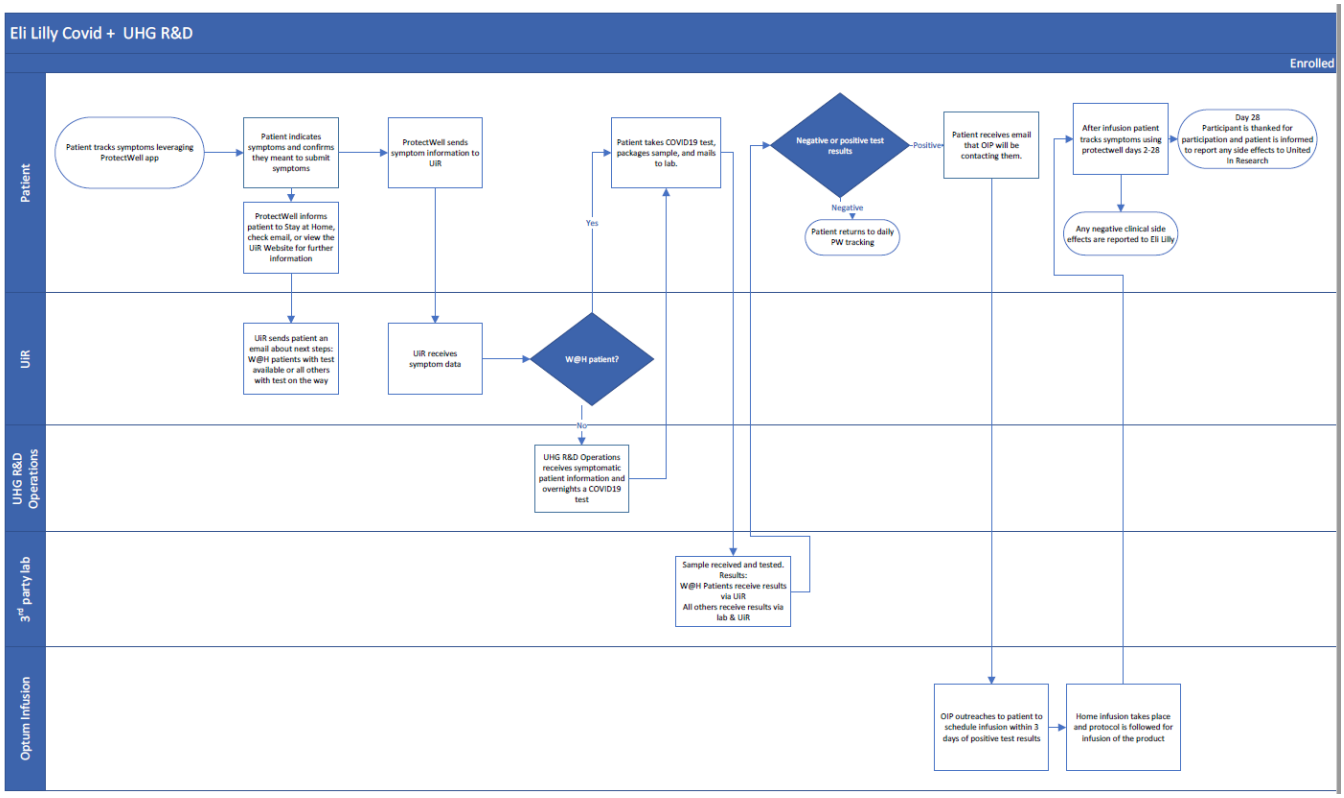
After at-home infusion, the household will be tracked via the ProtectWell app and any specific symptom/side effect tracking mechanisms in the United in Research platform will also occur to monitor how the participants are doing

If any issues develop during the active follow-up period, the issues will be presented to Lilly (if they are medical/clinical in nature – not logistical or operational issues) for consideration of: 1) how to address for the particular participant (or whether any action is required) and 2) if the issues reported warrant informing the FDA

At completion of the active follow-up period data will be compiled and prepared and shared with Lily for review/analysis in order to produce interim findings (and any unexpected findings) during active conduct of the study

Once a participant has completed their active follow-up phase, we will either thank them for their participation and consider them as completed (informing them that we will circle back with results of the project) or if there is any advantage to keeping them tracking for long-term response or effects, we could develop a long-term follow-up mechanism (i.e. please do inform us via United in Research if you start developing symptoms again or if a member of the household gets sick)

2. Subject Participation Flow Visual



3. Wellness check plan and clinical connection

Instructing Patients for Using ProtectWell Wellness Check via the App Post-Infusion from Day 1 – Day 28

<u>Rating system:</u>

- Using a 1 – 10 system (1 = the worst you can feel and 10 = feeling great)
- Grouping:

    - 1-3 rating (potential flag for clinical outreach)
    - 4-7 rating (feeling OK – no action needed)
    - 8-10 (feeling good/great – no action needed)
- Day 1 rating dictates baseline for Days 2-28
    - Goal is for patients to either stay steady at Day 1 rating or to continue to see an increase as they progressively feel better
- Rating drops between Day 2 and Day 28
    - If rating drops back to a 4 or above from where the patient was (for example – registered a 6 and the next day registered a 4) – no clinical follow-up at that time but will get a note recognizing that they took a step back in their ratings
    - If rating drops back to 3 or below from where the patient was (for example – registered a 5 and the next day registered a 3) – this would trigger clinical outreach by the UHG Clinical Team
- Post-Infusion Day 1 – Baseline
    - It is fine to start at a 1-3 (and likely expected as these folks have COVID-19 and even though symptoms are mild to moderate – they are probably not feeling too well)
    - It is fine to stay in the 1-3 range for a few days if they are either:
        - Staying the same as baseline
        - Seeing minor increases (for example – going from a 1 to a 2 or a 2 to a 3)
    - If the patient continues to check the same rating but does not get above a 3 – this would be flagged for clinical follow-up – the clinical lead will assess what day of the experience the participant is in and either flag them for clinical follow-up connection or document permitting another wellness day check-in to see if the level of wellness improves
- Clinical Follow-up/Outreach During 28-day active period
    - UHG R&D internal clinical team (leadership role is a RN) will review the twice daily reports that have extracted any participants who have a 1-3 rating
    - This report will dictate who requires clinical follow-up/outreach or it will be documented as to the reason why clinical connection was not (see example above – closer to day 1 post-infusion)
    - Clinical follow-up will occur with consistency by using the "Symptoms List for Clinical Outreach and Action Plan"
    - Information collected during clinical follow-up will be consistently documented in the participant file and reports for symptoms and other issues being reported will be generated for assessment as needed (i.e. aggregate reports for assessing severity/frequency of events as needed)
    - Clinical action taken in response to reported symptoms/issues will also be documented
- Overall goal
    - Patients will progress from the lower numbers to the higher range numbers during the 28-day period (with hopefully a good jump from initial receipt of infusion)

4. Symptom checker and clinical action

Participant ID:

Assessment Date: (DD/MMM/YYYY)

High priority
Cough – requires immediate medical attention if *severe* symptoms reported

○ Yes
- ○ Mild
- ○ Moderate
- ○ Severe

○ No (Absent)

High priority
Shortness of breath – requires immediate medical attention if *moderate to severe* symptoms reported

○ Yes
- ○ Mild
- ○ Moderate
- ○ Severe

○ No (Absent)

High priority
Feeling feverish – requires immediate medical attention if *high fever* is reported. For *moderate* fever, clinical call required

○ Yes
- ○ Low grade (<100 degrees F)
- ○ Moderate – (100-102 degrees F)
- ○ High (anything above 102 degrees F)

○ No (Absent)

High priority
Chills/Shaking – requires immediate medical attention if *severe* symptoms reported (severe symptoms being "shaking chills" – i.e. teeth chattering, body shakes)

○ Yes
- ○ Mild
- ○ Moderate
- ○ Severe

○ No (Absent)

Body aches and pain – requires immediate medical attention if *severe* symptoms reported ○ Yes ○ Mild ○ Moderate ○ Severe ○ No (Absent)	**Headache** ○ Yes ○ Mild ○ Moderate ○ Severe ○ No (Absent)
Fatigue	**Loss of taste**

○ Yes

- ○ Mild
- ○ Moderate
- ○ Severe

○ No (Absent)

Sore throat

○ Yes

- ○ Mild
- ○ Moderate
- ○ Severe

○ No (Absent)

Loss of appetite

○ Yes

- ○ Mild
- ○ Moderate
- ○ Severe

○ No (Absent)

○ Yes

○ No

Loss of smell

○ Yes

○ No

Nausea

○ Yes

- ○ Mild
- ○ Moderate
- ○ Severe – how often _____

○ No (Absent)

Nausea

○ Yes

- ○ Mild
- ○ Moderate
- ○ Severe – how often _____

○ No (Absent)

Diarrhea

○ Yes

- ○ Mild
- ○ Moderate

	○ Severe – how often _____ ○ No (Absent)

Are you experiencing any additional symptoms/health issues beyond what was just asked above?

○ Yes

○ No

If yes – please explain:

Overall, how bad are your symptoms TODAY?

○ No symptoms

○ Mild

○ Moderate

○ Severe

○ Very severe

Overall, how is your general physical health TODAY?

○ Poor

○ Fair

○ Good

○ Very good

○ Excellent

For any issues reported or discovered that may meet the following criteria, please contact Tracy Ziolek immediately at 215-868-3114 or tracy_ziolek@uhg.com to report:

Event is **likely related to bamlanivimab** and is **both unexpected and serious** (see outcomes below for serious adverse events) →

Event outcomes resulted in:

1) Death

2) Life-threatening adverse drug experience (meaning determined related to bamlanivimab)

3) Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours) *already being checked for due to primary efficacy endpoint

4) Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

5) Congenital anomaly/birth defect

6) Important Medical Event (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition