Evaluating Primary Endpoints for COVID-19 Therapeutic Trials to Assess Recovery

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Abstract

Rationale: Uncertainty regarding the natural history of coronavirus disease 2019 (COVID-19) led to difficulty in efficacy endpoint selection for therapeutic trials. Capturing outcomes that occur after hospital discharge may improve assessment of clinical recovery among hospitalized COVID-19 patients.

Objectives: Evaluate 90-day clinical course of patients hospitalized with COVID-19 comparing three distinct definitions of recovery.

Methods: We used pooled data from three clinical trials of neutralizing monoclonal antibodies to compare: 1) the hospital discharge approach 2) the Therapeutics for Inpatients with COVID-19 (TICO) trials "sustained recovery" approach, and 3) a comprehensive approach. At the time of enrollment, all patients were hospitalized in a non-intensive care unit setting without organ failure or major extrapulmonary manifestations of COVID-19. We defined discordance as a difference between time to recovery.

Measurements and Main Results: Discordance between the hospital discharge and comprehensive approaches occurred in 170 (20%) of 850 enrolled participants, including 126 hospital readmissions and 24 deaths after initial hospital discharge. Discordant participants were older (median age 68 vs. 59 years; $p<0.001$) and more had a comorbidity (84% vs. 70%; $p<0.001$). Of 170 discordant participants, 106 (62%) had post-discharge events captured by the TICO approach.

Conclusions: Among patients hospitalized with COVID-19, 20% had clinically significant post-discharge events within 90 days after randomization, in patients that would be considered "recovered" using the hospital discharge approach. Employing the TICO approach balances length of follow-up with practical limitations. However, clinical trials of COVID-19 therapeutics should employ follow-up times up to 90 days to assess clinical recovery more accurately.

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INTRODUCTION

Uncertainty regarding the natural history of a novel disease such as COVID-19 led to difficulty in efficacy endpoint selection for therapeutic trial designs. Many inpatient COVID-19 trial platforms, including RECOVERY(1), ACTT(2), SOLIDARITY(3), REMAP-CAP(4), and ACTIV-4a(5, 6) collect data for 28 days or until hospital discharge (whichever occurs first), and assess survival to hospital discharge or to day 28 after randomization as the primary endpoint. Such designs enable rapid throughput of trials, rapid dissemination of results, require less follow-up and are less expensive to complete. Important events occurring late in the hospitalization (after day 28) or post-discharge, such as hospital readmission or death, are not routinely included. However, many COVID-19 patients experience events after hospital discharge, and their omission may lead to an underestimation of disease burden(5, 7, 8). Indeed, the United States Food and Drug Administration (FDA) guidelines recognized the importance of *sustained recovery,* defined as the absence of key COVID-19 related symptoms over a clinically meaningful time period(9). However, "clinically meaningful time" is not clearly defined by the FDA.

Intermittent surges in coronavirus disease 2019 (COVID-19) worldwide underscore the ongoing importance of assessing novel therapies for hospitalized patients with COVID-19. During a pandemic, when hospital capacities are strained(10), early patient discharges may be necessary in order to preserve hospital capacity. Such external pressure can lead to premature discharges as patients are released "quicker and sicker"(11) and prior to full convalescence, emphasizing the importance of patient follow-up after hospital discharge to assess sustained clinical recovery(12).

We sought to assess post-hospital discharge outcomes for COVID-19 patients and better evaluate sustained recovery for hospitalized patients. In the Therapeutics for Inpatients with COVID-19 (TICO) trials(13), we followed patients for 90 days after randomization and captured comprehensive information including level of care/residence, hospital readmission, and deaths occurring after discharge from the index hospitalization. Longer follow-up duration allows for a previously unreported comparison of three commonly used efficacy endpoints. The primary objective of our analysis was to compare three

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definitions of recovery for patients hospitalized with COVID-19 in order to inform future trial endpoint selection.

METHODS

Data Source

We utilized pooled data collected from three multinational, blinded, randomized, placebo-controlled trials of neutralizing monoclonal antibodies in hospitalized patients with COVID-19, conducted within the framework of the Therapeutics for Inpatients with COVID-19 (TICO/ACTIV-3) trial platform within the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) program. The rationale and design of TICO has been previously described(13). In brief, TICO facilitated the simultaneous testing of multiple agents using a common placebo group, designed as FDA registration trials under Investigational New Drug applications. Data used for the present analysis were from participants enrolled in the three trials evaluating bamlanivimab (Eli Lilly and Company)(14, 15), sotrovimab (Vir Biotechnology and GlaxoSmithKline) (15), and BRII-196/198 (Brii Biosciences) (16, 17).

Study Population

The TICO trials enrolled hospitalized patients with laboratory-confirmed SARS-CoV-2 infection and COVID-19 symptoms for ≤12 days. At the time of enrolment, patients in all three trials were hospitalized and without organ failure or major extrapulmonary manifestations of COVID-19. Patients receiving no oxygen therapy or standard oxygen therapy via nasal cannula were eligible for enrollment in all three trials. Patients receiving high-flow nasal oxygen or non-invasive ventilation at the time of assessment were excluded from the sotrovimab and BRII 196/198 studies but were included throughout the bamlanivimab study. Patients requiring invasive mechanical ventilation were excluded from all three trials. Between August 5, 2020 and March 1, 2021, 850 participants were enrolled and infused from 52 sites in the United States, Denmark, Switzerland, Poland, and Singapore. The protocol was approved by a

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governing institutional review board for each enrolling site. Written informed consent for trial participation was obtained from each participant or a legally authorized representative as applicable.

Evaluation of Post-Discharge Events and Recovery Time

In the present study, we evaluated the 90-day post-randomization clinical course of TICO trial participants hospitalized with COVID-19. We applied and compared three distinct definitions of recovery: 1) the Hospital Discharge approach, defined as discharged from the index hospitalization alive; 2) the TICO approach to "sustained recovery", defined as alive and home for 14 consecutive days within 90 days of randomization; and 3) a Comprehensive approach, which captured all non-recovered states through day 90, specifically post-discharge deaths, hospital readmissions, or discharge to a level of care higher than prior home location. Therefore, the Comprehensive approach defined recovery as the day the participant returned to their home location and stayed there, alive, through day 90.

Definition of Discharge Locations

Home was defined as the participant's level of care/residence prior to COVID-19 or a location that provided similar or less intensive medical care. Residence and facility groupings used to define home were: 1) Independent or community-dwelling with or without help, including house, apartment, undomiciled/homeless, shelter, or hotel; 2) Residential care facility (e.g., assisted living facility, group home, other non-medical institutional setting); 3) Other healthcare facility (e.g., skilled nursing facility, acute rehab facility; 4) Long-term acute care hospital (hospital aimed at providing intensive longer-term acute care services, often for more than 28 days). These definitions expanded on the acute respiratory distress syndrome (ARDS) Network SAILS trial definition(18), which considered discharge to long-term acute care hospitals or other healthcare facilities as not recovered.

Hospital Discharge Approach

The hospital discharge approach considers participants recovered when discharged alive from the index hospitalization with the time to recovery being the number of days from randomization to discharge. Participants still hospitalized at day 90 were classified as "not recovered" and given a censoring time of 90 days.

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TICO Approach

The primary outcome of the TICO trial was time from randomization to sustained clinical recovery through day 90, defined as being at home for at least 14 consecutive days. Importantly, participants who remained home for at least 14 consecutive days after index hospital discharge were classified as "recovered" for the purpose of evaluating treatment efficacy, regardless of oxygen use, and regardless of subsequent death or re-hospitalization. Thus, time to sustained recovery was the time from randomization to the end of the first 14-day period at home after the index hospitalization; re-hospitalization within 14 days would restart the clock. In the current study, we counted the time to the beginning of the 14-day period after the return to home as "time to recovery" in order to present the TICO approach on the same time scale as the other two recovery definitions.

Comprehensive Approach

For the comprehensive approach, only participants who were alive and at home at Day 90 were considered recovered, and the date of recovery was defined as the last date of discharge to home prior to Day 90. Participants who were initially discharged to a non-home location, required hospital readmission, or required an upgrade of care facility, could still be considered recovered by day 90 if they eventually returned home and stayed home through day 90. This approach requires completion of the full 90-day follow-up period to ascertain the recovery endpoint status, as a participant must return home and stay home until day 90 to be considered recovered. Participants not at home at day 90 were classified as "not recovered" and given a censoring time of 90 days.

Comparison Between Recovery Definitions

We assessed each participant for the three recovery definitions defined above. Two types of recovery were considered discordant if they resulted in different times of recovery for a given participant. Baseline demographics and clinical factors were compared between concordant and discordant participants. Time to event analyses, e.g., time from hospital discharge to a subsequent event that resulted in discordance of the recovery definitions (e.g., time from discharge to death), were used to assess the magnitude of the differences in time to recovery between the methods.

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Statistical Analysis

All 850 TICO trial participants were included in the primary analysis. Missing recovery times were imputed for the comprehensive approach and the TICO approach for participants who were lost to follow-up before day 90 but were last known to be at home; these participants were considered recovered at the time they most recently returned home. Participants who were last known to be at a non-home location were censored with status "not recovered" with respect to the TICO and comprehensive approach at the time they were lost to follow-up. Participants who were censored while at home for less than 14 consecutive days were considered recovered at the time they last returned home in order to facilitate comparison with the comprehensive approach. Due to this standardization between the TICO and comprehensive approaches, participants who were not recovered according to the comprehensive approach were also not recovered according to the TICO approach. Since the TICO definition of sustained recovery requires a participant to remain home for 14 consecutive days before being considered recovered, we standardized these times by subtracting 14 days from the recovery time of those who recovered. As a sensitivity analysis, we also conducted a complete case analysis excluding participants who were lost to follow-up prior to day 90

Continuous variables were summarized by medians with interquartile ranges and compared across groups using Wilcoxon rank-sum tests. Categorical variables were summarized by counts with percentages and compared across groups using Fisher's exact tests. The association between baseline demographic and clinical factors and the odds of discordance between time to hospital discharge and time to recovery according to the comprehensive and TICO approaches was assessed using multivariable logistic regressions. Aalen-Johansen estimates of the cumulative incidence of recovery according to the three approaches were used to compare time to recovery across definitions(19), while accounting for the competing risk of death. Cumulative incidence curves depicting the time to post-discharge death, to the composite of post-discharge death or hospital readmission, or to any post-discharge event (death, readmission, discharge to a non-home location, or upgrade in level of care) were used to investigate when these events occurred relative to randomization and hospital discharge. Out-of-hospital mortality was

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treated as a competing risk for readmission and in-hospital mortality was treated as a competing risk for any discordance event when analyzing time from randomization. Aalen-Johansen estimates of the cumulative incidence were used in the presence of competing risks; otherwise, Kaplan-Meier estimates were used. The percent recovered, alive but not recovered, and dead at days 28, 60 and 90 were estimated using the Aalen-Johansen method. None of the three trials detected a difference between treatment groups for time to recovery, justifying pooling of the trials into a single cohort. Such a comparison would be difficult to interpret in the context of the present study. Therefore, we opted not to report the treatment difference estimated using the different approaches. Finally, histograms were used to show the distribution of differences in time to sustained recovery among participants with discordance between recovery approaches, and who recovered according to the more conservative definition.

All statistical tests were two-sided and p-values less than 0.05 were considered statistically significant. R, version 3.6.0 (R Foundation for Statistical Computing) was used for all analyses; the "prodlim" package was used for the Aalen-Johansen and Kaplan-Meier estimates. No adjustment was made for multiple comparisons.

RESULTS

Participants

A total of 850 participants were enrolled in the bamlanivimab, sotrovimab, and BRII-196/198 trials at 52 sites in the US, Denmark, Switzerland, Poland, and Singapore. Two participants were still hospitalized at day 90, and 42 (4.9%) died in the hospital, resulting in 806 participants being discharged alive from the initial hospitalization (**Figure 1**). Of the 806 participants discharged alive, 704 (87%) were discharged prior to day 28 , and 750 patients were discharged home by day 90. Only one patient was discharged to a non-home location and 13 patients who were discharged home died without being readmitted to a hospital (**Figure 1**). Of the 750 patients discharged home, 636 remained home through day 90. Of the 24 deaths that occurred post-hospital discharge, 14 were deemed related to COVID-29 by the blinded local site investigator.

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Comprehensive Approach vs. Hospital Discharge Approach

Using the comprehensive approach, 170 (20%) of 850 participants had a post-discharge event (death, readmission prior to day 90, or discharged/upgraded to a non-home location), which was not accounted for by the hospital discharge approach (**Table 1**). Participants with discordance between approaches were discharged to a non-home location (n=56, 33%), readmitted to a hospital by day 90 (n=126, 74%), upgraded to a higher level of care (n=1, 0.6%), or died after initial hospital discharge but by day 90 (n=24, 14%). Some participants experienced more than one of these events (**Figure 1**). Of the 750 participants who were initially discharged home, 100 (13%) were re-hospitalized by day 90, and 13 (1.7%) died without hospital readmission. One additional participant was discharged home and then upgraded to a higher level of care but not readmitted to a hospital by day 90 (**Figure 1**). Of the 56 participants who were initially discharged to a non-home location, 26 (46%) required rehospitalization by day 90, and 1 (1.8%) died without being readmitted to a hospital. Discordant participants were older, more likely had a comorbidity, had a shorter symptom duration prior to randomization, and were more likely to be seronegative for SARS-CoV-2 antibodies at baseline (**Table 1**). There was no difference in pulmonary ordinal scale at randomization or in receipt of at least one dose of SARS-CoV-2 vaccine on univariate analysis. However, after adjusting for relevant covariates, receiving greater levels of oxygenation support on the pulmonary ordinal scale was associated with discordance (**Supplemental Table 1**).

TICO Approach vs. Hospital Discharge Approach

Compared to the hospital discharge approach, the TICO approach was discordant for 105 (12%) of 850 participants (**Table 2**). Discordant participants were older, more had comorbidities, and required higher levels of respiratory support at randomization. After adjusting for relevant covariates, no individual comorbidity was associated with discordance (**Supplemental Table 2**). Of the 170 participants with discordance between the comprehensive approach and the hospital discharge approach, 105 (62%) were captured by the TICO approach, which focused on early events occurring before 14 consecutive days at home. Nine patients had additional post-discharge events occur after 14 days, therefore 96 (56%) were

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concordant between the TICO approach and the comprehensive approach. Comparison of the TICO approach vs the comprehensive approach is displayed in **Supplemental Table 3**.

Time to Discordance/Post-Discharge Events

By definition, the hospital discharge approach classifies participants as recovered earlier than either the TICO approach or the comprehensive approach (**Table 3**). Most post-discharge events that resulted in discordance between different recovery approaches, including hospital readmission and death, occurred in the first 2-3 weeks after hospital discharge (**Figure 2 and Supplemental Figure 1**). Most "recovery" events also occurred within this time frame (**Supplemental Figure 2**). In addition, post-discharge mortality attributable to COVID-19, as determined by the local site investigator, mainly occurred early after hospital discharge (**Supplemental Figure 3**).

Complete vs. Imputed Cohort Comparisons

Eighty-five (10%) of the 850 participants had incomplete 90-day follow-up data. For these patients, sustained recovery time for the comprehensive approach had been imputed in the primary analysis as the time they most recently arrived home if their last known location was at home, or follow-up was censored as not recovered at the time they were lost to follow-up if they were last known to be at a non-home location. Therefore, the 765 participants who completed follow-up to day 90 were included in a sensitivity analysis. No material difference was noted between the primary imputed cohort and the cohort which completed 90-day follow-up in this sensitivity analysis (**Supplemental Tables 4-6**).

DISCUSSION

Among COVID-19 patients in the first three TICO trials, 20% were known to have important medical events (death, readmission in the first 90 days, or discharge/upgrade to a non-home location) after discharge and were discordant in time to recovery when employing the hospital discharge approach compared to a comprehensive approach through 90 days after randomization. The TICO approach, requiring 14 days at home to define recovery, captured 62% of discordant patients. Many COVID-19 research platforms employ the hospital discharge approach, and accordingly do not report clinically

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important post-discharge events, at least in the primary endpoint. Such an approach may be particularly problematic during the COVID-19 pandemic, which, as we illustrate, has substantial rates of rehospitalization and death after discharge. Inclusion of post-discharge events more fully embraces the FDA definition of sustained recovery after hospitalization with COVID-19(9), and are both, clinically relevant and patient-centered. Of course, an evolving understanding of the clinical trajectory of COVID-19 may produce different efficacy endpoints in the future. At minimum, these events are important to describe the clinical trajectory of hospitalized COVID-19 patients enrolled in therapeutic trials. Additionally, if the post-discharge events, especially deaths, occur at different rates in the intervention versus control groups, there is potential to alter the primary results of these clinical trials and decisions about clinical efficacy.

A National Institutes of Health workshop identified the need for clinical researchers in ARDS to move "beyond mortality" by including functional, cost, and quality of life outcomes in future research endeavors(20, 21). Defining the recovery endpoint via the comprehensive approach discussed here certainly moves in this direction but is also more time- and resource-intensive to employ, especially during a global pandemic. Endpoints with longer follow-up also introduce a greater risk for incomplete data. In addition, differences between treatment groups, especially in later post-discharge events, may be less likely related to the intervention or initial acute COVID-19 illness. The TICO approach, on the other hand, focuses on early post-discharge events, which are more likely to be influenced by the acute illness and clinical interventions during the index hospitalization, balancing the pragmatism of required follow-up time and clinical relevance.

While in-hospital mortality and length of stay are two of the most common outcomes reported by inpatient trials, hospital readmissions, discharges to non-home locations, and deaths that occur after hospital discharge were the primary sources of discordance observed in the present study. Since participants classified by an in-hospital method are not assessed following hospital discharge, assessment of sustained recovery, as defined by the FDA, cannot be achieved. In (non-COVID-19) ARDS survivors, readmission within 30 days of hospital discharge occur in 2.5% to 12% of patients(22, 23). At 12 months

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after discharge, this number increases to 40%(24). Readmission rates are similar for patients admitted for other pulmonary diseases such as COPD(25), asthma(26), and influenza(27). These numbers align well with our study, where 20% of patients experienced a significant post-discharge event. Most participants who were discharged by day 90 (97%) in the TICO trials were discharged by day 28 following randomization. Therefore, a material difference between approaches which considered recovery at hospital discharge compared to approaches which followed patients for 28 days after randomization is unlikely. A key tradeoff is that the hospital discharge approach achieves complete outcome assessment, whereas in the TICO trials, we had to censor 11% of participants at last known follow-up prior to day 90.

In the present study, participants who were discordant from the hospital discharge approach were older, more chronically ill, and more likely to be seronegative for SARS-CoV-2 antibodies at baseline. Such differences are not surprising given that discordance in the recovery outcomes signifies a higher risk for morbidity and mortality. The 24 discordant participants who were discharged alive from the hospital but died within 90 days (2.8% of the entire cohort, compared with the 90-day in-hospital mortality of 4.9%) represent the most clinically important discrepancy between the comprehensive approach and the hospital discharge approach. Advantages and disadvantages between the three approaches are presented in **Supplemental Table 7**.

The TICO approach requires more participant follow-up than the hospital discharge approach and captured 62% of discordance events. Likely these early post-discharge events, within 14 days, are more closely related to clinical interventions administered during the index hospitalization. Importantly, if a participant remained home for at least 14 consecutive days, they were classified as "recovered" even if the participant required rehospitalization or died after recovery but before day 90. Later events were captured as secondary endpoints and are considered less likely to be influenced by randomized/in-hospital treatments. For example, most of the post-discharge mortality events attributable to COVID-19 occurred in the first 14 days after index hospital discharge (**Supplemental Figure 1**). The TICO approach may, therefore, sufficiently capture the relevant signals for estimating the differential effect of the investigational treatment.

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Multiple recent studies have attempted to identify an optimal endpoint in COVID-19 clinical trials without reaching a consensus(7, 28-30). Both mortality and readmission must be examined in parallel to sustained recovery and time to discharge, as both consider mortality as a competing risk and do not account for deaths after recovery. Further, even well-intentioned discharge planning may not decrease rates of readmission in high-risk patients(31). In the present study, patients who were discharged to a non-home location were significantly more likely to require hospital readmission or die within 90 days. The clinical indication for readmission may differ in importance to different patients depending on individual value-based perspective. However, indications for readmission were not available for this study.

Many clinical trialists seek pragmatic, cost-efficient outcome measures while balancing many real-world factors. We demonstrate the TICO approach may strike this balance by capturing most early post-discharge events that are clinically relevant and patient centered. Notably, the TICO approach may not be optimal for studies focused on critically ill COVID-19 patients, including those receiving invasive mechanical ventilation. Critically ill patients with pulmonary disease and ARDS are more likely to experience significant events more than 14-days after hospital discharge(24). The TICO approach may not adequately capture these events. Decisions regarding the optimal efficacy endpoint may also be influenced by time and resources available, setting (including ability to follow participants successfully after hospital discharge), and the anticipated in-hospital mortality of the cohort with the hospital discharge approach being more pertinent when in-hospital mortality is high. Our study has several limitations. We chose not to report the treatment difference estimated using the different approaches since none of the three trials reported an efficacy signal and such a comparison would therefore be difficult to interpret in the context of the present study. Hospital outcomes may capture the maximal differential treatment effect and thus have a role as a primary outcome though our data suggest such outcomes are an incomplete measure of COVID-19 disease burden, including mortality, and would not capture later differential treatment effects. Critically ill patients requiring invasive mechanical ventilation or ECMO were not enrolled in any of the TICO trials. Inclusion of these patients would likely have increased both in-hospital mortality and the proportion of participants discordant after discharge. The indications for hospitalization

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among patients who were readmitted are not available from our database. Readmission indication may serve to better stratify the "weight" of discordance events at an individual level. Further, defining recovery strictly by returning home may not adequately capture recovery. Return to activities of daily living, employment, mood, home supplemental oxygen use, and prior activity levels remain important components of recovery, which were not addressed in this study. Alternative or more nuanced approaches may be more appropriate depending on the cohort, including those that focus on critically ill patients (e.g., NCT04843761). When comparing participants with concordant vs discordant outcomes, we did not adjust for multiple comparisons; some differences in comparing characteristics across groups may occur by chance alone.

In conclusion, among patients hospitalized with COVID-19, one in five TICO trial participants had post-hospital discharge events and thus were discordant from hospital discharge as to their time of recovery. Employing a comprehensive approach may represent an aspirational but not pragmatic assessment of sustained recovery. The TICO approach represents a reasonable alternative – balancing length of follow up with practical limitations. In studies of similar populations, researchers should consider assessing for 14 consecutive days at the patient's prior home location to capture the majority of clinically relevant adverse events and satisfy the need for rapid dissemination of results.

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TABLES

Table 1. Discordance Between the Hospital Discharge Approach and the Comprehensive Approach

Characteristic	Not Discordant	Discordant	p-value
Number of Participants (n)	680	170	
Age (years) (median[IQR])	59 [49, 70]	68 [56, 76]	<0.001
Gender – Female (%)	281 (41.3)	84 (49.4)	0.07
Race/Ethnicity (%)			0.01
Non-Hispanic White	330 (48.5)	97 (57.1)	
Non-Hispanic Black	140 (20.6)	41 (24.1)	
Hispanic	149 (21.9)	21 (12.4)	
Asian	37 (5.4)	4 (2.4)	
Other	24 (3.5)	7 (4.1)	
BMI (%)			0.006
Not Obese (< 30 kg/m^2)	305 (44.9)	89 (52.4)	
Obese (30 kg/m^2 ≤ BMI < 40 kg/m^2)	282 (41.5)	49 (28.8)	
Morbidly Obese (≥ 40 kg/m^2)	92 (13.5)	32 (18.8)	
Any Co-existing Chronic Illness (%)	478 (70.3)	142 (83.5)	<0.001
Hypertension	353 (51.9)	109 (64.1)	0.004
Diabetes Mellitus	206 (30.3)	76 (44.7)	0.001
Renal Impairment	64 (9.4)	28 (16.5)	0.01
Immunocompromised	62 (9.1)	23 (13.5)	0.09
Chronic Supplemental O_2 prior to COVID-19 (%)	9 (1.3)	8 (4.7)	0.01
≥ 1 Dose of SARS-CoV-2 Vaccine (%)	30 (4.5)	11 (6.5)	0.32
Symptom Duration (Days) (median [IQR])	8 [5, 9]	7 [5, 9]	<0.001
TICO Study Arm (%)			0.76
Bamlanivimab	135 (19.9)	28 (16.5)	
BRII-196/198	138 (20.3)	38 (22.4)	
Sotrovimab	144 (21.2)	38 (22.4)	
Placebo	263 (38.7)	67 (38.8)	
Baseline Pulmonary Ordinal Scale Category (%)†			0.25
No Supplemental O2	212 (31.2)	52 (30.6)	
Supplemental O2 < 4 L/min	285 (41.9)	60 (35.3)	
Supplemental O2 ≥ 4 L/min	147 (21.6)	46 (27.1)	
HFNC/Non-Invasive Ventilation*	36 (5.3)	12 (7.1)	
SARS-CoV-2 Antibodies – Positive (%)^	305 (46.6)	59 (36.2)	0.02
SARS-CoV-2 Antigen (pg/mL) (median [IQR])^	1260 [233, 3723]	1110 [169, 4315]	0.70
Prior Living Status (%)			<0.001
Independent, no professional medical help	632 (92.9)	136 (80.0)	
Other‡	48 (7.1)	34 (20.0)	

BMI: body mass index; COVID-19: coronavirus disease 2019, IQR: interquartile range; kg: kilogram; L: liters; m: meter; min: minute; n: number; O_2: oxygen; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; HFNC: High Flow Nasal Cannula

*Participants on HFNC/non-invasive ventilation only eligible for participation in bamlanivimab study; participants on invasive mechanical ventilation not eligible for any of the three agents

† For participants on chronic supplemental oxygen therapy prior to COVID-19, categorization on the pulmonary ordinal scale was based on oxygen flow rates above the pre-COVID oxygen flow rate. For example, a participant who chronically used supplemental oxygen at 2 liters/minute prior to COVID-19

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would be categorized as category 2 if using 2 liters/minute at randomization, category 3 if using >2 liters per minute and <6 liters/minute, and category 4 if using ≥6 liters/minute of supplemental oxygen.

^SARS-CoV-2 antibodies refer to GenScript Antibody interpretation and SARS-CoV-2 Antigen refers to Quanterix Antigen

‡ "Other" prior living status includes 1) long-term acute care facility, 2) Other health care facility, 3) residential care facility, 4) community-dwelling, 5) independent dwelling with professional medical help

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Table 2. Discordance Between the Hospital Discharge Approach and the TICO Approach

Characteristic	Not Discordant	Discordant	p-value
Number of Participants (n)	745	105	
Age (years) (median[IQR])	59 [49, 70]	68 [58, 76]	<0.001
Gender – Female (%)	313 (42.0)	52 (49.5)	0.17
Race/Ethnicity (%)			0.14
Non-Hispanic White	368 (49.4)	59 (56.2)	
Non-Hispanic Black	154 (20.7)	27 (25.7)	
Hispanic	158 (21.2)	12 (11.4)	
Asian	37 (5.0)	4 (3.8)	
Other	28 (3.8)	3 (2.9)	
BMI (%)			0.15
Not Obese (< 30 kg/m^2)	336 (45.2)	58 (55.2)	
Obese (30 $kg/m^2 \leq$ BMI < 40 kg/m^2)	298 (40.1)	33 (31.4)	
Morbidly Obese (≥ 40 kg/m^2)	110 (14.8)	14 (13.3)	
Any Co-existing Chronic Illness (%)	530 (71.1)	90 (85.7)	0.001
Hypertension	394 (52.9)	68 (64.8)	0.03
Diabetes Mellitus	239 (32.1)	43 (41.0)	0.08
Renal Impairment	73 (9.8)	19 (18.1)	0.02
Immunocompromised	70 (9.4)	15 (14.3)	0.12
Chronic Supplemental O_2 prior to COVID-19 (%)	11 (1.5)	6 (5.7)	0.01
≥ 1 Dose of SARS-CoV-2 Vaccine (%)	35 (4.8)	6 (5.7)	0.63
Symptom Duration (Days) (median [IQR])	8 [5, 9]	6 [4, 9]	0.01
TICO Study Arm (%)			0.68
Bamlanivimab	146 (19.6)	17 (16.2)	
BRII-196/198	157 (21.1)	19 (18.1)	
Sotrovimab	158 (21.2)	24 (22.9)	
Placebo	284 (38.1)	45 (42.9)	
Baseline Pulmonary Ordinal Scale Category (%)†			0.03
No Supplemental O2	236 (31.7)	28 (26.7)	
Supplemental O2 < 4 L/min	311 (41.7)	34 (32.4)	
Supplemental O2 ≥ 4 L/min	159 (21.3)	34 (32.4)	
HFNC/Non-Invasive Ventilation*	39 (5.2)	9 (8.6)	
SARS-CoV-2 Antibodies – Positive (%)^	330 (46.0)	34 (33.7)	0.02
SARS-CoV-2 Antigen (pg/mL) (median [IQR])^	1220 [230, 3660]	1260 [114, 5430]	0.72
Prior Living Status (%)			0.004
Independent, no professional medical help	682 (91.5)	86 (81.9)	
Other‡	63 (8.5)	19 (18.1)	

BMI: body mass index; COVID-19: coronavirus disease 2019, IQR: interquartile range; kg: kilogram; L: liters; m: meter; min: minute; n: number; O_2: oxygen; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; HFNC: High Flow Nasal Cannula

*Participants on HFNC/non-invasive ventilation only eligible for participation in bamlanivimab study; participants on invasive mechanical ventilation not eligible for any of the three agents

† For participants on chronic supplemental oxygen therapy prior to COVID-19, categorization on the pulmonary ordinal scale was based on oxygen flow rates above the pre-COVID oxygen flow rate. For example, a participant who chronically used supplemental oxygen at 2 liters/minute prior to COVID-19 would be categorized as category 2 if using 2 liters/minute at randomization, category 3 if using >2 liters

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per minute and <6 liters/minute, and category 4 if using ≥6 liters/minute of supplemental oxygen.

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‡ "Other" prior living status includes 1) long-term acute care facility, 2) Other health care facility, 3) residential care facility, 4) community-dwelling, 5) independent dwelling with professional medical help

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Table 3. Comparison of recovery/mortality status at three follow-up times according to the three approaches

Category, n(%)	Hospital Discharge Approach**	TICO Approach***	Comprehensive (90-Day) Approach
Day 28			
Recovered	782	737	671
Alive but Not Recovered	40	75	139
Dead	28	37	39
Status not ascertained*	0	1	1
Day 60			
Recovered	803	760	707
Alive but Not Recovered	7	37	82
Dead	40	52	60
Status not ascertained *	0	1	1
Day 90			
Recovered	806	766	744
Alive but Not Recovered	2	23	34
Dead	42	55	66
Status not ascertained *	0	6	6

* Status cannot be assigned even after implementation of the described simple imputation rules
** Hospital Discharge Approach implies that data are only collected up to the date of initial discharge, hence deaths occurring after discharge are not accounted for and not included under “dead”.
*** TICO Approach implies that data are only collected until the participant has been at home for 14 days, hence deaths occurring after this time are not accounted for and not included under “dead”.

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FIGURE LEGENDS

Figure 1. Flow diagram of patient outcomes, hospital discharge approach versus the comprehensive approach. Blue boxes indicate non-discordant participants. Red boxes indicate discordant participants. Home was defined as the level of residence or facility where the participant was residing prior to index hospital admission leading to enrollment. Residence and facility groupings used to define home were: 1) Independent community-dwelling with or without help, including house, apartment, undomiciled/homeless, shelter, or hotel; 2) Residential care facility (e.g., assisted living facility, group home, other non-medical institutional setting); 3) Other healthcare facility (e.g., skilled nursing facility, acute rehab facility; 4) Long-term acute care hospital (hospital aimed at providing intensive longer-term acute care services, often for more than 28 days).

Figure 2. Cumulative percentage of participants with discordance events in the days following a) randomization, and b) hospital discharge. The cumulative total of any discordance events is summarized in the black curves. Readmissions are displayed in the red curves, and mortality is displayed in the blue curves.

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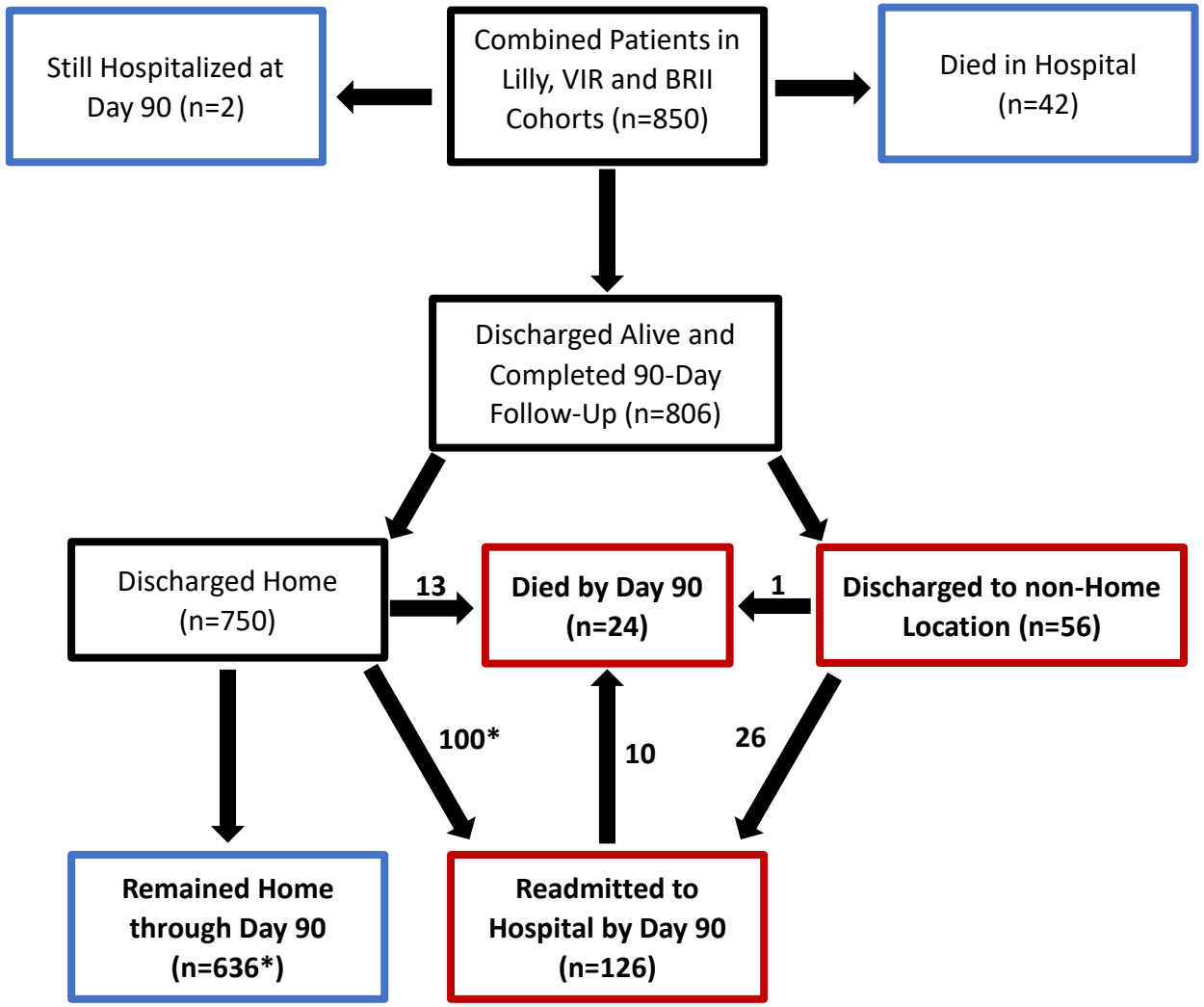

*One patient who was initially discharged home, was subsequently upgraded to a higher level of care, but was not readmitted to the hospital. This patient returned home before day 90.

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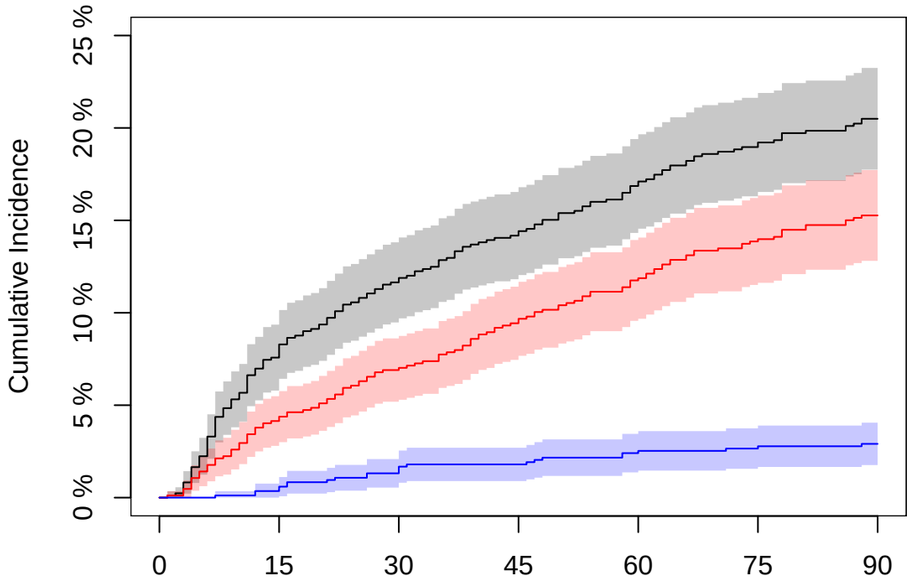
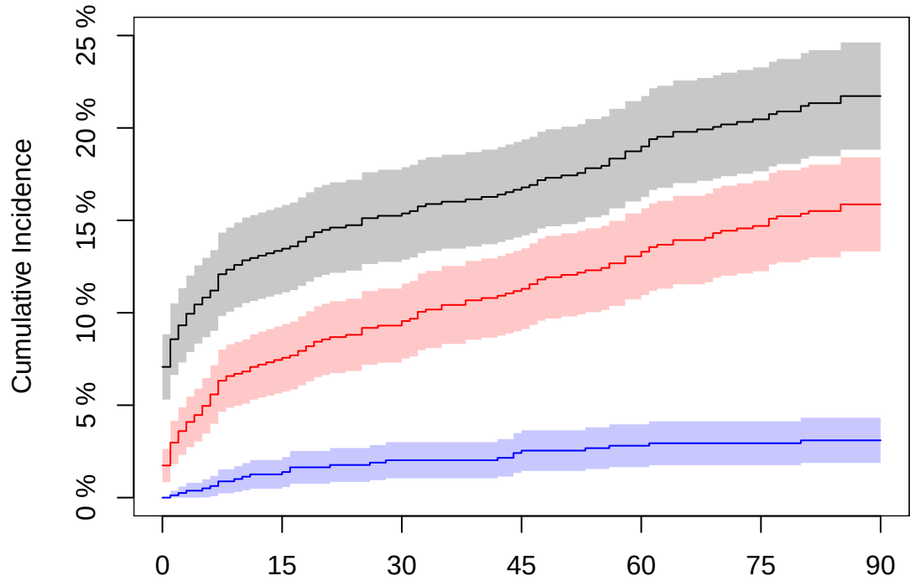
a)



Number at Risk:							
Any Discordance Event:	850	764	701	669	641	612	572
Readmission:	850	790	733	699	672	641	598
Death after Hospital Discharge:	850	823	786	770	759	742	705

b)



Number at Risk:							
Any Discordance Event:	806	684	665	644	618	569	14
Readmission:	806	738	721	700	680	646	14
Death after Hospital Discharge:	806	777	764	747	723	675	15

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Online Data Supplement

Evaluating Primary Endpoints for COVID-19 Therapeutic Trials to Assess Recovery

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SUPPLEMENTAL TABLES

Supplemental Table 1. Association between baseline demographic and clinical characteristics and the odds of discordance between time to hospital discharge and time to sustained recovery as determined by the comprehensive approach based on multivariable logistic regression.

Characteristic	OR [1]	95% CI[1]	p-value
Age (Years)	1.03	1.01, 1.04	<0.001
Gender			
Male	—	—	
Female	1.34	0.93, 1.99	0.12
Race/Ethnicity			
Non-Hispanic White	—	—	
Asian	0.48	0.13, 1.34	0.20
Non-Hispanic Black	0.79	0.48, 1.28	0.34
Hispanic	0.61	0.34, 1.08	0.10
Other	1.82	0.66, 4.59	0.22
BMI			
Not Obese (< 30 kg/m^2)	—	—	
Obese (≥30 & < 40 kg/m^2)	0.66	0.42, 1.02	0.06
Severely Obese (≥40 kg/m^2)	1.54	0.86, 2.71	0.14
Hypertension	0.90	0.59, 1.39	0.65
Diabetes Mellitus	1.80	1.20, 2.70	0.005
Renal Impairment	1.75	0.98, 3.08	0.05
Immunocompromised	1.48	0.83, 2.58	0.18
Chronic Supplemental O2 Prior to COVID-19	1.39	0.46, 4.16	0.55
≥1 Dose of SARS-CoV-2 Vaccine	0.81	0.34, 1.81	0.62
Symptom Duration (Days)	0.94	0.87, 1.00	0.06
TICO Study Arm			
Placebo	—	—	
Bamlanivimab	0.80	0.46, 1.38	0.44
BRII-196/198	1.23	0.74, 2.03	0.43
Sotrovimab	0.93	0.55, 1.55	0.77
Baseline Pulmonary Ordinal Scale Category			
No Supplemental O2	—	—	
Supplemental O2 < 4 L/min	1.13	0.70, 1.82	0.62
Supplemental O2 ≥ 4 L/min	1.85	1.10, 3.14	0.02
HFNC/Non-invasive Ventilation	2.77	1.13, 6.56	0.02
SARS-CoV-2 Antibody Status^			
Negative	—	—	
Positive	0.55	0.35, 0.87	0.01
SARS-CoV-2 Antigen (pg/mL)^	0.92	0.86, 0.98	0.01
Prior Living Status			

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Independent dwelling w/o professional medical help	—	—	
Other	2.37	1.35, 4.10	0.002

[1]CI: confidence interval; HFNC: high-flow nasal canula; OR: odds ratio

^SARS-CoV-2 antibodies refer to GenScript Antibody interpretation and SARS-CoV-2 Antigen refers to Quanterix Antigen. Antigen is presented on a log base 2 scale.

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Supplemental Table 2. Association between baseline demographic and clinical characteristics and the odds of discordance between time to hospital discharge and time to sustained recovery as determined by the TICO approach based on multivariable logistic regression.

Characteristic	OR [1]	95% CI[1]	p-value
Age (Years)	1.03	1.01, 1.05	<0.001
Gender			
Male	—	—	
Female	1.38	0.88, 2.19	0.16
Race/Ethnicity			
Non-Hispanic White	—	—	
Asian	0.91	0.25, 2.65	0.88
Non-Hispanic Black	0.99	0.55, 1.73	0.96
Hispanic	0.59	0.27, 1.19	0.16
Other	1.18	0.26, 3.80	0.80
BMI			
Not Obese (< 30 kg/m^2)	—	—	
Obese (≥30 & < 40 kg/m^2)	0.74	0.43, 1.26	0.27
Severely Obese (≥40 kg/m^2)	1.02	0.48, 2.06	0.97
Hypertension	0.82	0.49, 1.38	0.46
Diabetes Mellitus	1.30	0.79, 2.11	0.30
Renal Impairment	1.91	0.98, 3.64	0.05
Immunocompromised	1.45	0.72, 2.75	0.28
Chronic Supplemental O2 Prior to COVID-19	1.85	0.55, 5.72	0.30
≥ 1 Dose of SARS-CoV-2 Vaccine	0.76	0.26, 1.93	0.58
Symptom Duration (Days)	0.94	0.86, 1.02	0.12
TICO Study Arm			
Placebo	—	—	
Bamlanivimab	0.66	0.33, 1.26	0.22
BRII-196/198	0.85	0.45, 1.57	0.61
Sotrovimab	0.86	0.46, 1.55	0.62
Baseline Pulmonary Ordinal Scale Category			
No Supplemental O2	—	—	
Supplemental O2 < 4 L/min	1.52	0.84, 2.78	0.17
Supplemental O2 ≥ 4 L/min	3.09	1.65, 5.88	<0.001
HFNC/Non-invasive Ventilation	4.96	1.79, 13.3	0.002
SARS-CoV-2 Antibody Status^			
Negative	—	—	
Positive	0.50	0.28, 0.86	0.01
SARS-CoV-2 Antigen (pg/mL)^	0.92	0.85, 0.99	0.02
Prior Living Status			
Independent dwelling w/o professional medical help	—	—	
Other	1.43	0.73, 2.72	0.28

[1]CI: confidence interval; HFNC: high-flow nasal cannula; OR: odds ratio

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^SARS-CoV-2 antibodies refer to GenScript Antibody interpretation and SARS-CoV-2 Antigen refers to Quanterix Antigen. Antigen is presented on a log base 2 scale.

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Supplemental Table 3. Discordance Between the TICO Approach and the Comprehensive Approach

Characteristic	Not Discordant	Discordant	p-value
Number of Participants (n)	776	74	
Age (years) (median[IQR])	60 [49, 71]	65 [53, 75]	0.03
Gender – Female (%)	327 (42.1)	38 (51.4)	0.14
Race/Ethnicity (%)			0.04
Non-Hispanic White	383 (49.4)	44 (59.5)	
Non-Hispanic Black	164 (21.1)	17 (23.0)	
Hispanic	161 (20.7)	9 (12.2)	
Asian	41 (5.3)	0 (0.0)	
Other	27 (3.5)	4 (5.4)	
BMI (%)			0.001
Not Obese (< 30 kg/m^2)	361 (46.6)	33 (44.6)	
Obese (30 $kg/m^2 \leq$ BMI < 40 kg/m^2)	312 (40.3)	19 (25.7)	
Morbidly Obese (≥ 40 kg/m^2)	102 (13.2)	22 (29.7)	
Any Co-existing Chronic Illness (%)	560 (72.2)	60 (81.1)	0.10
Hypertension	416 (53.6)	46 (62.2)	0.18
Diabetes Mellitus	244 (31.4)	38 (51.4)	0.001
Renal Impairment	80 (10.3)	12 (16.2)	0.12
Immunocompromised	75 (9.7)	10 (13.5)	0.31
Chronic Supplemental O_2 prior to COVID-19 (%)	13 (1.7)	4 (5.4)	0.05
≥ 1 Dose of SARS-CoV-2 Vaccine (%)	33 (4.3)	8 (10.8)	0.02
Symptom Duration (Days) (median [IQR])	8 [5, 9]	7 [5, 8]	0.03
TICO Study Arm (%)			0.40
Bamlanivimab	152 (19.6)	11 (14.9)	
BRII-196/198	157 (20.2)	19 (25.7)	
Sotrovimab	163 (21.0)	19 (25.7)	
Placebo	304 (39.2)	25 (33.8)	
Baseline Pulmonary Ordinal Scale Category (%)†			0.91
No Supplemental O2	240 (30.9)	24 (32.4)	
Supplemental O2 < 4 L/min	313 (40.3)	32 (43.2)	
Supplemental O2 ≥ 4 L/min	178 (22.9)	15 (20.3)	
HFNC/Non-Invasive Ventilation*	45 (5.8)	3 (4.1)	
SARS-CoV-2 Antibodies – Positive (%)^	336 (45.0)	28 (39.4)	0.39
SARS-CoV-2 Antigen (pg/mL) (median [IQR])^	1260 [217, 3962]	1030 [228, 2490]	0.25
Prior Living Status (%)			<0.001
Independent, no professional medical help	712 (91.8)	56 (75.7)	
Other‡	64 (8.2)	18 (24.3)	

BMI: body mass index; COVID-19: coronavirus disease 2019, IQR: interquartile range; kg: kilogram; L: liters; m: meter; min: minute; n: number; O_2: oxygen; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; HFNC: High Flow Nasal Cannula

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*Participants on HFNC/non-invasive ventilation only eligible for participation in bamlanivimab study; participants on invasive mechanical ventilation not eligible for any of the three agents

† For participants on chronic supplemental oxygen therapy prior to COVID-19, categorization on the pulmonary ordinal scale was based on oxygen flow rates above the pre-COVID oxygen flow rate. For example, a participant who chronically used supplemental oxygen at 2 liters/minute prior to COVID-19 would be categorized as category 2 if using 2 liters/minute at randomization, category 3 if using >2 liters per minute and <6 liters/minute, and category 4 if using ≥6 liters/minute of supplemental oxygen.

^SARS-CoV-2 antibodies refer to GenScript Antibody interpretation and SARS-CoV-2 Antigen refers to Quanterix Antigen

‡ "Other" prior living status includes 1) long-term acute care facility, 2) Other health care facility, 3) residential care facility, 4) community-dwelling, 5) independent dwelling with professional medical help

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Supplemental Table 4. Discordance Between the Hospital Discharge Approach and the Comprehensive Approach, excluding patients without complete 90-day follow up.

Characteristic	Not Discordant	Discordant	p-value
Number of Participants (n)	614	151	
Age (years) (median[IQR])	59 [49, 70]	69 [56, 78]	<0.001
Gender – Female (%)	256 (41.7)	75 (49.7)	0.08
Race/Ethnicity (%)			0.03
Non-Hispanic White	310 (50.5)	89 (58.9)	
Non-Hispanic Black	125 (20.4)	35 (23.2)	
Hispanic	127 (20.7)	16 (10.6)	
Asian	29 (4.7)	4 (2.6)	
Other	23 (3.7)	7 (4.6)	
BMI (%)			0.002
Not Obese (< 30 kg/m^2)	281 (45.8)	79 (52.3)	
Obese (30 $kg/m^2 \leq$ BMI < 40 kg/m^2)	256 (41.8)	42 (27.8)	
Morbidly Obese (≥ 40 kg/m^2)	76 (12.4)	30 (19.9)	
Any Co-existing Chronic Illness (%)	431 (70.2)	128 (84.8)	<0.001
Hypertension	323 (52.6)	96 (63.6)	0.02
Diabetes Mellitus	180 (29.3)	66 (43.7)	0.001
Renal Impairment	58 (9.4)	26 (17.2)	0.009
Immunocompromised	56 (9.1)	22 (14.6)	0.05
Chronic Supplemental O_2 prior to COVID-19 (%)	8 (1.3)	8 (5.3)	0.006
≥ 1 Dose of SARS-CoV-2 Vaccine (%)	27 (4.5)	8 (5.3)	0.67
Symptom Duration (Days) (median [IQR])	8 [5, 10]	7 [4, 9]	0.001
TICO Study Arm (%)			0.82
Bamlanivimab	126 (20.5)	26 (17.2)	
BRII-196/198	123 (20.0)	33 (21.9)	
Sotrovimab	129 (21.0)	33 (21.9)	
Placebo	236 (38.4)	59 (39.1)	
Baseline Pulmonary Ordinal Scale Category (%)†			0.37
No Supplemental O2	191 (31.1)	47 (31.1)	
Supplemental O2 < 4 L/min	255 (41.5)	53 (35.1)	
Supplemental O2 ≥ 4 L/min	134 (21.8)	41 (27.2)	
HFNC/Non-Invasive Ventilation*	34 (5.5)	10 (6.6)	
SARS-CoV-2 Antibodies – Positive (%)^	282 (47.6)	52 (35.9)	0.01
SARS-CoV-2 Antigen (pg/mL) (median [IQR])^	1225 [222, 3720]	1125 [204, 4100]	0.78
Prior Living Status (%)			<0.001
Independent, no professional medical help	568 (92.5)	121 (80.1)	
Other‡	46 (7.5)	30 (19.9)	

BMI: body mass index; COVID-19: coronavirus disease 2019, IQR: interquartile range; kg: kilogram; L: liters; m: meter; min: minute; n: number; O_2: oxygen; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; HFNC: High Flow Nasal Cannula

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† For participants on chronic supplemental oxygen therapy prior to COVID-19, categorization on the pulmonary ordinal scale was based on oxygen flow rates above the pre-COVID oxygen flow rate. For example, a participant who chronically used supplemental oxygen at 2 liters/minute prior to COVID-19 would be categorized as category 2 if using 2 liters/minute at randomization, category 3 if using >2 liters per minute and <6 liters/minute, and category 4 if using ≥6 liters/minute of supplemental oxygen.

^SARS-CoV-2 antibodies refer to GenScript Antibody interpretation and SARS-CoV-2 Antigen refers to Quanterix Antigen

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Supplemental Table 5. Discordance Between the Hospital Discharge Approach and the TICO Approach, excluding patients without complete 90-day follow up.

Characteristic	Not Discordant	Discordant		p-value
Number of Participants (n)	673	92		
Age (years) (median[IQR])	60 [49, 71]	70 [62, 78]		<0.001
Gender – Female (%)	286 (42.5)	45 (48.9)		0.26
Race/Ethnicity (%)				0.17
Non-Hispanic White	346 (51.4)	53 (57.6)		
Non-Hispanic Black	137 (20.4)	23 (25.0)		
Hispanic	134 (19.9)	9 (9.8)		
Asian	29 (4.3)	4 (4.3)		
Other	27 (4.0)	3 (3.3)		
BMI (%)				0.09
Not Obese (< 30 kg/m^2)	307 (45.7)	53 (57.6)		
Obese (30 $kg/m^2 \leq$ BMI < 40 kg/m^2)	271 (40.3)	27 (29.3)		
Morbidly Obese (≥ 40 kg/m^2)	94 (14.0)	12 (13.0)		
Any Co-existing Chronic Illness (%)	477 (70.9)	82 (89.1)		<0.001
Hypertension	359 (53.3)	60 (65.2)		0.03
Diabetes Mellitus	207 (30.8)	39 (42.4)		0.03
Renal Impairment	67 (10.0)	17 (18.5)		0.02
Immunocompromised	64 (9.5)	14 (15.2)		0.10
Chronic Supplemental O_2 prior to COVID-19 (%)	10 (1.5)	6 (6.5)		0.008
≥ 1 Dose of SARS-CoV-2 Vaccine (%)	32 (4.9)	3 (3.3)		0.79
Symptom Duration (Days) (median [IQR])	8 [5, 9]	7 [4, 9]		0.02
TICO Study Arm (%)				0.63
Bamlanivimab	137 (20.4)	15 (16.3)		
BRII-196/198	139 (20.7)	17 (18.5)		
Sotrovimab	143 (21.2)	19 (20.7)		
Placebo	254 (37.7)	41 (44.6)		
Baseline Pulmonary Ordinal Scale Category (%)†				0.01
No Supplemental O2	214 (31.8)	24 (26.1)		
Supplemental O2 < 4 L/min	280 (41.6)	28 (30.4)		
Supplemental O2 ≥ 4 L/min	143 (21.2)	32 (34.8)		
HFNC/Non-Invasive Ventilation*	36 (5.3)	8 (8.7)		
SARS-CoV-2 Antibodies – Positive (%)^	304 (46.8)	30 (33.7)		0.02
SARS-CoV-2 Antigen (pg/mL) (median [IQR])^	1200 [225, 3515]	1500 [114, 5430]		0.53
Prior Living Status (%)				0.02
Independent, no professional medical help	613 (91.1)	76 (82.6)		
Other‡	60 (8.9)	16 (17.4)		

BMI: body mass index; COVID-19: coronavirus disease 2019, IQR: interquartile range; kg: kilogram; L: liters; m: meter; min: minute; n: number; O_2: oxygen; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; HFNC: High Flow Nasal Cannula

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† For participants on chronic supplemental oxygen therapy prior to COVID-19, categorization on the pulmonary ordinal scale was based on oxygen flow rates above the pre-COVID oxygen flow rate. For example, a participant who chronically used supplemental oxygen at 2 liters/minute prior to COVID-19 would be categorized as category 2 if using 2 liters/minute at randomization, category 3 if using >2 liters per minute and <6 liters/minute, and category 4 if using ≥6 liters/minute of supplemental oxygen.

^SARS-CoV-2 antibodies refer to GenScript Antibody interpretation and SARS-CoV-2 Antigen refers to Quanterix Antigen

‡ "Other" prior living status includes 1) long-term acute care facility, 2) Other health care facility, 3) residential care facility, 4) community-dwelling, 5) independent dwelling with professional medical help

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Supplemental Table 6. Discordance Between the TICO Approach and the Comprehensive Approach, excluding patients without complete 90-day follow up.

Characteristic	Not Discordant	Discordant	p-value
Number of Participants (n)	700	65	
Age (years) (median[IQR])	61 [50, 71]	66 [53, 75]	0.04
Gender – Female (%)	297 (42.4)	34 (52.3)	0.15
Race/Ethnicity (%)			0.09
Non-Hispanic White	360 (51.4)	39 (60.0)	
Non-Hispanic Black	145 (20.7)	15 (23.1)	
Hispanic	136 (19.4)	7 (10.8)	
Asian	33 (4.7)	0 (0.0)	
Other	26 (3.7)	4 (6.2)	
BMI (%)			<0.001
Not Obese (< 30 kg/m^2)	333 (47.6)	27 (41.5)	
Obese (30 kg/m^2 ≤ BMI < 40 kg/m^2)	281 (40.2)	17 (26.2)	
Morbidly Obese (≥ 40 kg/m^2)	85 (12.2)	21 (32.3)	
Any Co-existing Chronic Illness (%)	507 (72.4)	52 (80.0)	0.24
Hypertension	380 (54.3)	39 (60.0)	0.44
Diabetes Mellitus	215 (30.7)	31 (47.7)	0.008
Renal Impairment	73 (10.4)	11 (16.9)	0.14
Immunocompromised	68 (9.7)	10 (15.4)	0.19
Chronic Supplemental O_2 prior to COVID-19 (%)	12 (1.7)	4 (6.2)	0.04
≥ 1 Dose of SARS-CoV-2 Vaccine (%)	30 (4.4)	5 (7.7)	0.22
Symptom Duration (Days) (median [IQR])	8 [5, 9]	7 [5, 8]	0.09
TICO Study Arm (%)			0.47
Bamlanivimab	141 (20.1)	11 (16.9)	
BRII-196/198	140 (20.0)	16 (24.6)	
Sotrovimab	145 (20.7)	17 (26.2)	
Placebo	274 (39.1)	21 (32.3)	
Baseline Pulmonary Ordinal Scale Category (%)†			0.63
No Supplemental O2	215 (30.7)	23 (35.4)	
Supplemental O2 < 4 L/min	280 (40.0)	28 (43.1)	
Supplemental O2 ≥ 4 L/min	163 (23.3)	12 (18.5)	
HFNC/Non-Invasive Ventilation*	42 (6.0)	2 (3.1)	
SARS-CoV-2 Antibodies – Positive (%)^	310 (45.9)	24 (38.7)	0.29
SARS-CoV-2 Antigen (pg/mL) (median [IQR])^	1232 [198, 3902]	1045 [252, 2365]	0.36
Prior Living Status (%)			0.001
Independent, no professional medical help	639 (91.3)	50 (76.9)	
Other‡	61 (8.7)	15 (23.1)	

BMI: body mass index; COVID-19: coronavirus disease 2019, IQR: interquartile range; kg: kilogram; L: liters; m: meter; min: minute; n: number; O_2: oxygen; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; HFNC: High Flow Nasal Cannula

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Supplemental Table 7. Advantages and Disadvantages of TICO Approach Compared to Comprehensive Approach and Hospital Discharge Approach

	Hospital Discharge Approach	**TICO Approach**	**Comprehensive Approach**
Advantages	Minimal to no post-discharge follow-up; limited missing data Least costly Earliest dissemination of results Easiest to implement	Balance of data collection and follow-up resources May capture most clinically important post-discharge events attributable to in-hospital interventions Increases confidence in trial conclusions Appears more patient-centered	Accounts for clinically important adverse events to day 90 Highest confidence in trial conclusions
Disadvantages	May miss significant clinical events that occur after discharge May decrease validity of trial conclusions Less patient-centered	Moderate intensity of data collection and follow-up More expensive and time consuming than hospital discharge approach	Highest intensity of data collection and follow-up Most expensive, time-consuming and labor-intensive Highest risk of missing data

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SUPPLEMENTAL FIGURE LEGENDS

Supplemental Figure 1. Histogram of time to discordance events following hospital discharge. Day 0 is the day of hospital discharge. (a) hospital discharge versus comprehensive approach, (b) hospital discharge versus TICO approach, (c) TICO versus comprehensive approach

Supplemental Figure 2: Cumulative incidence of recovery for the three definitions of recovery: the hospital discharge approach (blue), the TICO approach of sustained recovery (red), and the comprehensive (90-day) approach (black). Day 0 is the day of randomization to study protocol.

Supplemental Figure 3: Aalen-Johansen estimate of cumulative incidence for time from hospital discharge to death following hospital discharge stratified by cause. COVID-19 attributable causes were assessed by investigators at individual sites.

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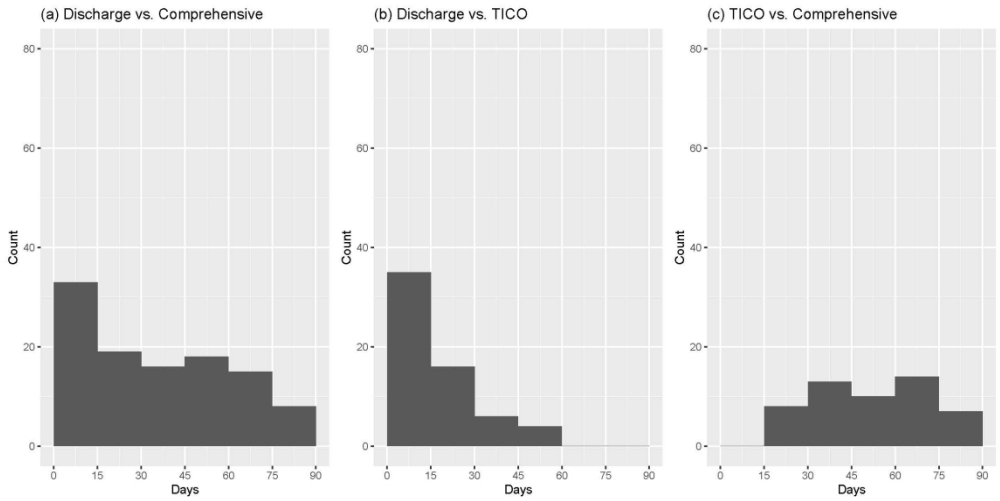

Supplemental Figure 1. Histogram of time to discordance events following hospital discharge. Day 0 is the day of hospital discharge. (a) hospital discharge versus comprehensive approach, (b) hospital discharge versus TICO approach, (c) TICO versus comprehensive approach

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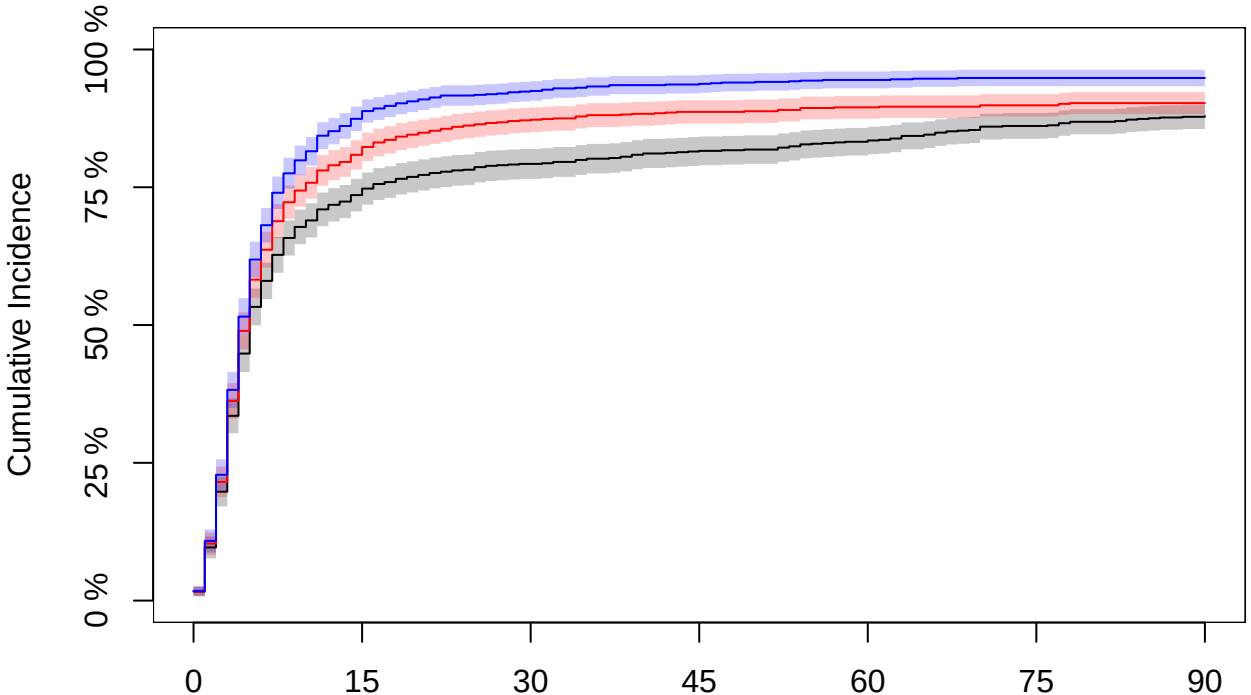

Number at Risk:							
Comprehensive:	850	208	132	103	82	53	34
TICO:	850	146	67	46	37	30	23
Hospital Discharge:	850	94	32	15	7	3	2

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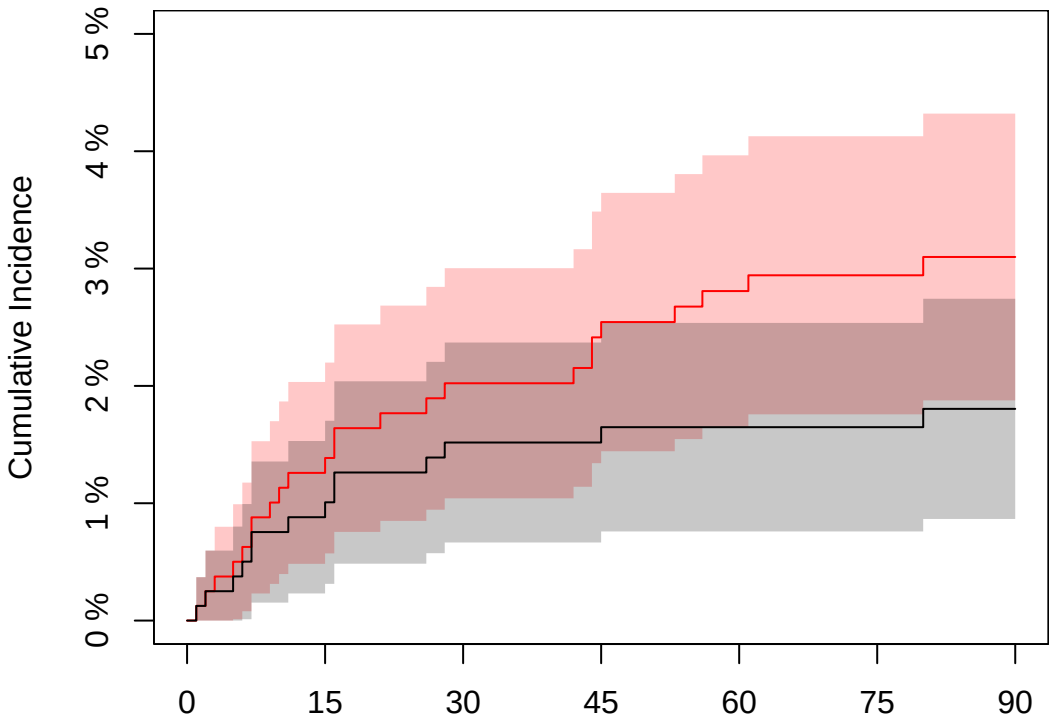

Number at Risk:							
All−Cause Mortality:	806	777	764	747	723	675	15
Mortality Attributed to COVID−19:	806	777	764	747	723	675	15

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