

Protocol: I7W-MC-UDAA(c)

A Randomized, Double-blind, Placebo-controlled, Clinical Trial of LY3127804 in Patients who are Hospitalized with Pneumonia and Presumed or Confirmed COVID-19

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LY3127804

Eli Lilly and Company
Indianapolis, Indiana USA 46285

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1. Synopsis

Title of Study:

A randomized, double-blind, placebo-controlled, clinical trial of LY3127804 in patients who are hospitalized with pneumonia and presumed or confirmed COVID-19.

Rationale:

The SARS-CoV 2 virus (Severe Acute Respiratory Syndrome Corona Virus) has resulted in the pandemic spread of coronavirus disease 2019 (COVID-19), which in severe cases results in progressive pulmonary failure with a high prevalence of acute respiratory distress syndrome (ARDS). In the early experience, approximately 15% of COVID-19 cases are classified as severe with pulmonary symptomology and require hospitalization. Reports on the prevalence of progression to ARDS vary, but conservatively estimates suggest that 25% of hospitalized patients will develop ARDS with a case fatality rate (CFR) of 50% in the first 30 days for those who develop ARDS. ([Wang et al 2020](#), [Liu et al 2019](#), [Guan et al 2020](#), [Huang et al 2020](#)). Although a number of therapies have been explored in severe COVID-19 patients, none to date have been shown to improve survival (including antivirals, glucocorticoids, and immunoglobulins; [Liu et al 2019](#)).

ARDS is characterized by loss of integrity of capillary endothelium (endothelial tight junctions) with extravasation of protein rich fluid and white blood cells (WBC) into the alveolar interstitium. This is associated with inflammation, activation of resident tissue macrophages and immune activation with patchy alveolar infiltrates evident on x-ray and with pulmonary edema and death from progressive respiratory failure ([Thompson et al. 2017](#)). Angiopoietin 2 (Ang2) levels in plasma are strongly correlated with increased ARDS risk in several human studies ([Gutbier et al. 2018](#), [Qi et al 2016](#), [van der Heijden et al 2008](#), [Parikh et al 2006](#)). Importantly, [Parikh et al.](#) showed that Ang2 alone is able to replicate the pathological features of progressive lung failure observed in patients, namely the loss of tight junctions in the pulmonary epithelium, vascular hyperpermeability, and pulmonary congestion. In addition, RNAi Knockdown or anti-Ang2 antibody treatment improves survival and pulmonary function in experimental models of ARDS ([Lomas-Neira et al. 2016](#), [Steihl et al. 2014](#)).

LY3127804 is an anti-Ang2 monoclonal antibody (mAb) that has been evaluated in both monotherapy and combined with ramucirumab in a Phase 1 clinical study of patients with advanced solid tumors ([NCT02597036](#)). The study results indicated LY3127804 has an acceptable safety profile with dose linear PK and evidence of target engagement (Ang 2) both as a single agent and in combination across the range of doses (4 mg/kg to 27 mg/kg). Study Protocol I7W-MC-UDAA (UDAA) will test whether LY3127804 can reduce the high proportion of patients who progress with pulmonary insufficiency, as assessed by ventilator free days, after being admitted to the hospital with a pneumonia and presumed or confirmed COVID-19 patient.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To evaluate ventilator free days during treatment with LY3127804 	<ul style="list-style-type: none"> Number of days from Day 1 to Day 28 on which a patient breathes without assistance, if the period of unassisted breathing lasted at least 24 consecutive hours and the patient did not die within 28 days from first dose of study drug
Secondary	
<ul style="list-style-type: none"> To evaluate clinical status of patients during treatment with LY3127804 	<ul style="list-style-type: none"> NIAID ordinal assessment (see Section 9.1.2.1 for definition)
<ul style="list-style-type: none"> To evaluate survival without the need for IMV/ECMO in patients treated with LY3127804 	<ul style="list-style-type: none"> Proportion of patients who are alive and respiratory failure free (i.e. never having required mechanical ventilatory support) by Day 28
<ul style="list-style-type: none"> To evaluate mortality rate during treatment with LY3127804 	<ul style="list-style-type: none"> Death within 28 days from first dose of study drug
<ul style="list-style-type: none"> To evaluate reduction in hospital stay during treatment with LY3127804 	<ul style="list-style-type: none"> Length of hospitalization
<ul style="list-style-type: none"> To evaluate safety of LY3127804 	<ul style="list-style-type: none"> AEs and SAEs

Abbreviations: AE = adverse event; ECMO = extracorporeal membrane oxygenation; IMV= intermittent mandatory ventilation; NIAID = National Institute of Allergy and Infectious Diseases; SAE = serious adverse event; SpO₂ = oxygen saturation

Summary of Study Design:

Study I7W-MC-UDAA (UDAA) is a multicenter, randomized, double-blind, parallel, placebo-controlled study in patients who are hospitalized for pneumonia and presumed or confirmed COVID-19.

Treatment Arms and Duration:

LY3127804 20 mg/kg or placebo administered intravenously (IV) on Days 1 and 15. If patients are discharged from the hospital prior to day 15, they will not receive a second dose and will undergo Completion or Hospital Discharge visit procedures.

Number of Patients:

Approximately 210 patients will be enrolled so that 200 patients complete the study, for an estimated total of 100 evaluable patients per treatment group. A sample size of 100 in each group will have 81% power to detect a difference between the placebo group and the LY3127804 group using a Wilcoxon rank-sum test with a 0.05 one-sided significance level.

Statistical Analysis:

The Wilcoxon rank-sum analysis of the primary endpoint, days free of mechanical ventilation within 28 days among survivors, will use a scoring scheme where a higher score is a better patient outcome. We will assign a score of -1 to patients who die before 28 days. For those patients who survive to Day 28 the score will be equal to the number of ventilator free days (VFDs) calculated according to the above definition. The statistical method for this endpoint will be based on the van Elteren test adjusting for the randomization stratification factors.

Randomization will be stratified by age group (<65 years and \geq 65 years), sex and site.

Secondary efficacy analyses will assess secondary endpoints as well as analyses of relevant subgroups.

Safety analyses will include assessments of adverse events, vital signs, electrocardiograms and laboratory parameters.

An independent Data Monitoring Committee will be used to monitor unblinded safety data.

2. Schedule of Activities

Table 2-1. Schedule of Activities

Study Day	S ^a	Treatment						Completion or Hospital Discharge or ED ^{b,c}	Follow-Up Phone Visit 1 ^d	Follow-Up Phone Visit 2 ^d
	≤1	1	2	7	15	16	21	28 (or the day discharged from hospital or ED)	42 ^d	60
Window Period (days)		-	-	±2	-	-	±2	±1	±2	±2
Eligibility review	X									
Informed consent	X									
Demographics	X									
Medical history ^e	X									
Height	X									
Weight	X							X		
Physical examination (directed unless otherwise noted)	X (complete)	X		X	X		X	X (complete)		
Vital signs ^f	X	← Every day from Day 1 to 27 → Predose and postdose on Days 1 and 15						X		
Hematology and clinical chemistry		X (pre-dose) ^g	X	X	X (pre-dose)	X	X	X		
COVID-19 panel ^h		X (pre-dose)	X	X		X	X	X		
Influenza/RSV/respiratory viral panel ⁱ		X								
Thyroid function test (TSH and FT4)		X (pre-dose)						X		
Pregnancy Test ^j	X (serum / urine)							X (urine)		
12-Lead ECG ^k		X (pre-and post-dose) ^l			X (pre-and post-dose)			X		

	S ^a	Treatment						Completion or Hospital Discharge or ED ^{b,c}	Follow-Up Phone Visit 1 ^d	Follow-Up Phone Visit 2 ^d
Study Day	≤1	1	2	7	15	16	21	28 (or the day discharged from hospital or ED)	42 ^d	60
Window Period (days)		-	-	±2	-	-	±2	±1	±2	±2
Randomization ^m		Within 24 hours of screening								
Study drug administration ⁿ		Within 8 hours of randomization			X					
SpO ₂ , O ₂ flow rate ^o	X	← Every day from Day 1 to 27 →						X		
NIAID ordinal assessment ^p	X	← Every day from Day 1 to 27 →						X	X	X
Adverse event monitoring ^q		← Every day from Day 1 to 27 →						X	X	X
Supportive pulmonary care ^r		← Every day from Day 1 to 27 →						X		
Concomitant medications ^s		← Every day from Day 1 to 27 →						X		

Abbreviations: ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; ED = early discontinuation; fT4 = free thyroxine; FU = follow-up; h = hours; ICF = informed consent form; IMV = intermittent mandatory ventilation; NIAID = National Institute of Allergy and Infectious Diseases; PK = pharmacokinetic; S = Screening; SO₂ = oxygen saturation; TSH = thyroid stimulating hormone.

- a Any procedure done as a standard of care 1 calendar day prior to ICF may be used as the screening procedure. Screening and Day 1 may occur on the same day.
- b Patients who are discharged from the hospital will complete the Completion or Hospital Discharge visit procedures
- c Patients who discontinue the study prior to study completion will complete the ED visit procedures.
- d Follow-up phone visit 1 should be conducted at 14 days after completion or hospital discharge or early discontinuation, or 28 days after the first dose of study drug, whichever occurs later. Follow-up phone visit 2 should be conducted at 60 days after first dose of study drug.
- e Ensure the onset of illness symptoms are captured, examples include fever, coughing, extreme fatigue, headache, myalgia.
- f Includes respiration rate, heart rate, temperature, and blood pressure. Vital signs need to be recorded once at approximately the same time each day. Post dose vital signs on Days 1 and 15 should be collected at the end of infusion and at approximately 1 hr after end of infusion.
- g If procedures were performed within 1 calendar day prior to infusion as part of standard of care and prior to ICF, that may be used as the sample collection on Day 1.
- h Data should be collected from local COVID19 panel laboratory pre-dose within 1 calendar day ≤Day 1, between 24 and 48 hr postdose on Day 2, and Day 16; and at any time on Days 7, 21, and 28 (or discharge or ED). Collection on Days 16 and 21 to be performed only if a Day 15 dose of study treatment was administered ([Appendix 2](#)).

- i Viral testing is only performed for patients who have undetermined or negative COVID-19 test(s). Viral testing is per the institution's testing guidelines.
- j For pregnancy test, only for women of child-bearing potential.
- k Single 12-lead ECGs will be obtained in the supine position at all indicated timepoints. On Days 1 and 15, ECGs will be collected pre-dose and at the end of infusion.
- l Pre-dose ECG to be collected within 1 calendar day of study drug administration. Post-dose ECG to be collected within 1 hour of study drug administration.
- m The time from screening to randomization is provided as a guidance and may be modified based on clinical needs.
- n The exact start and end time study drug infusion will be recorded. The time from randomization to study drug administration is provided as a guidance and may be modified based on clinical needs.
- o Range of the average lowest value of the SpO₂ and highest value of O₂ flow rate administered and method of delivery should be recorded.
- p NIAID ordinal scale is provided in Section 9.1.2.1. If IMV/ECMO is initiated or withdrawn, the date and reason for initiation and withdrawal of care (clinical deterioration, lack of clinical response, resource limitation, or other medical decision) should be captured.
- q Any secondary infection in addition to Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV-2) is an Adverse Event of Special Interest (See Section 9.2.4) and the site of infection, the culture source, and the pathogen(s) identified should be captured. Anti-infective therapy initiated (including anti-bacterial and anti-fungal agents) should be captured under Concomitant Medications.
- r Supportive pulmonary care provided should be recorded as specified in the data capture documents. Specifically, proning should be recorded for any treatment day on which the time of maintaining a patient in a prone position is at least 8 hours.
- s Concomitant medications captured should include unapproved ("off-label") medication (for example, chloroquine, hydroxychloroquine, and IL-6 antagonists).

3. Introduction

3.1. Study Rationale

The SARS-CoV 2 virus (Severe Acute Respiratory Syndrome Corona Virus) has resulted in the pandemic spread of coronavirus disease 2019 (COVID-19), which in severe cases results in progressive pulmonary failure with a high prevalence of acute respiratory distress syndrome (ARDS). In the early experience, approximately 15% of COVID-19 cases are classified as severe with pulmonary symptomology and require hospitalization. Reports on the prevalence of progression to ARDS vary, but it is conservatively estimated that 25% of hospitalized patients will develop ARDS with a case fatality rate (CFR) of 50% in the first 30 days for those who develop ARDS ([Wang et al 2020](#), [Liu et al 2019](#), [Guan et al 2020](#), [Huang et al 2020](#)). Although a number of therapies have been explored in severe COVID-19, none to date have been shown to improve survival (including antivirals, glucocorticoids, and immunoglobulins; [Liu et al 2019](#)).

3.2. Background

ARDS is characterized by loss of integrity of capillary endothelium (endothelial tight junctions) with extravasation of protein rich fluid and white blood cells (WBC) into the alveolar interstitium. This is associated with inflammation, activation of resident tissue macrophages and immune activation with patchy alveolar infiltrates evident on x-ray and with pulmonary edema and death from progressive respiratory failure ([Thompson et al. 2017](#)). Angiopoietin 2 (Ang2) levels in plasma are strongly correlated with increased ARDS risk in several human studies ([Gutbier et al. 2018](#), [Qi et al 2016](#), [van der Heijden et al 2008](#), [Parikh et al 2006](#)). Importantly, [Parikh et al.](#) showed that Ang2 alone is able to replicate the pathological features of progressive lung failure observed in patients, namely the loss of tight junctions in the pulmonary epithelium, vascular hyperpermeability, and pulmonary congestion. In addition, RNAi Knockdown or anti-Ang2 antibody treatment improves survival and pulmonary function in experimental models of ARDS ([Lomas-Neira et al. 2016](#), [Steihl et al. 2014](#)).

LY3127804 is an anti-Ang2 monoclonal antibody (mAb) that has been evaluated in both monotherapy and combined with ramucirumab in a Phase 1 clinical study of patients with advanced solid tumors ([NCT02597036](#)). The study results indicated LY3127804 has an acceptable safety profile with dose linear pharmacokinetics (PK) and evidence of target engagement (Ang2) both as a single agent and in combination across the range of doses (4 mg/kg to 27 mg/kg).

The intent of this study is to test whether LY3127804 can reduce the high proportion of patients who progress with pulmonary insufficiency, as assessed by ventilator free days (VFDs), after being admitted to the hospital with a pneumonia and presumed or confirmed COVID-19.

3.3. Benefit/Risk Assessment

The potential benefit of LY3127804 has been described in Section 3.2. Based on the nonclinical safety data and clinical data reported so far, LY3127804 initial clinical data have shown it to have an acceptable safety profile at the dose selected for this study. Given the lack of any available therapy that has shown to be effective in preventing progressive pulmonary failure and

progression to ARDS in patients with viral induced pneumonia, there currently exists an acute need for such treatment to address the immense unmet medical need resulting from large numbers of patients presenting with COVID-19, some of which will progress to ARDS with unacceptably high mortality. Given the acceptable safety profile of LY3127804 and the dire prognosis for patients progressing to ARDS secondary to SARS-CoV-2 infection, the potential benefit of LY3127804 outweighs the potential risk.

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of LY3127804 are to be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To evaluate ventilator free days during treatment with LY3127804 	<ul style="list-style-type: none"> Number of days from Day 1 to Day 28 on which a patient breathes without assistance, if the period of unassisted breathing lasted at least 24 consecutive hours and the patient did not die within 28 days from first dose of study drug
Secondary	
<ul style="list-style-type: none"> To evaluate clinical status of patients during treatment with LY3127804 	<ul style="list-style-type: none"> NIAID ordinal assessment (see Section 9.1.2.1 for definition)
<ul style="list-style-type: none"> To evaluate survival without the need for IMV/ECMO in patients treated with LY3127804 	<ul style="list-style-type: none"> Proportion of patients who are alive and respiratory failure free (i.e. never having required mechanical ventilatory support) by Day 28
<ul style="list-style-type: none"> To evaluate mortality rate during treatment with LY3127804 	<ul style="list-style-type: none"> Death within 28 days from first dose of study drug
<ul style="list-style-type: none"> To evaluate reduction in hospital stay during treatment with LY3127804 	<ul style="list-style-type: none"> Length of hospitalization
<ul style="list-style-type: none"> To evaluate safety of LY3127804 	<ul style="list-style-type: none"> AEs and SAEs
Exploratory	
<ul style="list-style-type: none"> To evaluate pulmonary function of patients during treatment with LY3127804 	<ul style="list-style-type: none"> SpO₂, O₂ flow rate

Abbreviations: AE = adverse event; ECMO = extracorporeal membrane oxygenation; IMV= intermittent mandatory ventilation; NIAID = National Institute of Allergy and Infectious Diseases; SAE = serious adverse event; SpO₂ = oxygen saturation

5. Study Design

5.1. Overall Design

Study I7W-MC-UDAA is a multicenter, randomized, double-blind, parallel, placebo-controlled Phase 2 study in patients who are hospitalized with pneumonia and presumed or confirmed COVID-19.

Study governance considerations are described in detail in [Appendix 3](#).

[Figure 5-1](#) illustrates the study design.

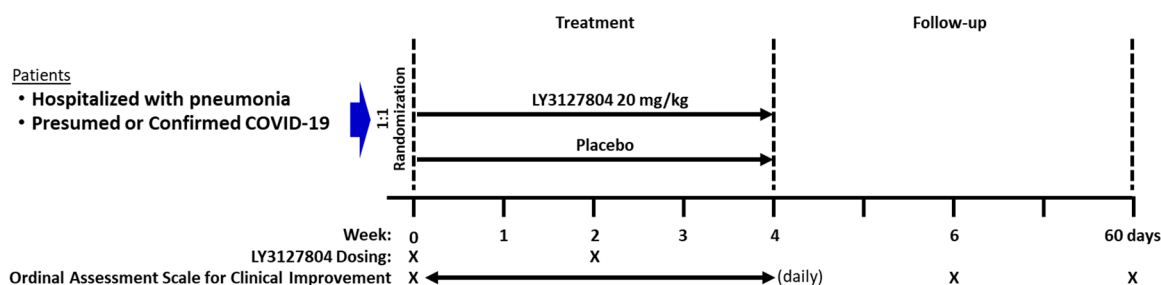


Figure 5-1. Illustration of study design for Clinical Protocol I7W-MC-UDAA.

5.2. Number of Patients

Approximately 210 patients will be enrolled so that 200 patients complete the study, for an estimated total of 100 evaluable patients per treatment group.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patients.

5.4. Scientific Rationale for Study Design

Approximately 25% of patients who are hospitalized with COVID-19 are admitted to the intensive care unit (ICU) and develop ARDS; half of patients with COVID-19-associated ARDS die within 30 days ([Liu et al 2019](#)). ARDS is characterized by loss of capillary endothelial integrity with increased permeability across endothelial tight junctions, permitting extravasation of protein rich fluid and WBCs into the alveolar interstitium, which (along with activation of resident macrophages) results in immune activation with inflammation, pulmonary edema and ultimately death from progressive pulmonary failure ([Yadav et al. 2017](#)). Many previous clinical trials have failed to improve outcomes when treatment was initiated after ARDS onset ([Fuller et al. 2015](#), [Matthay et al. 2011](#), [Rice et al. 2011](#), [Unknown Authors 2002](#), [Abraham et al. 1999](#), [Bernard et al. 1997](#), [Zeiber et al. 2004](#), [Liu et al. 2008](#), [Unknown Authors 2000](#), [Davidson et al. 2006](#), [McAuley et al. 2014](#)); resulting in the National Heart, Lung, and Blood Institute (NHLBI) to recommend that future therapies target prevention of ARDS ([Spragg et al. 2010](#)). Ang2 acts directly on endothelial cells to promote permeability across the microvascular barrier, vascular leakage, and WBC infiltration ([Augustin et al. 2009](#), [Zeiber et al. 2013](#), [Fiedler and Augustin](#)

2006, Fiedler et al. 2006, David et al. 2012), which all occur in the early stages of ARDS development. The present Study UDAA is designed to evaluate LY3127804 for the prevention of progression of respiratory distress to ARDS in hospitalized patients with confirmed or suspected COVID-19, that are presenting with pneumonia.

Patients who are discharged from the hospital will complete study procedures for a Completion or Hospital Discharge visit (see Section 2). Those patients will not return to the site for evaluation, study procedures, or additional study drug administration. However, patients will be contacted for vital status, including the NIAID ordinal assessment; first phone visit at 14 days after completion or hospital discharge or early discontinuation, or 28 days after the first dose of study drug, whichever occurs later; second phone visit at 60 days after the first dose of study drug. This strategy was chosen to remove the burden of return visits for the hospital and clinical trial staff reflecting limited medical resources in the COVID-19 pandemic and to minimize exposure risk to patients and their caregivers.

5.5. Justification for Dose

In a previous study conducted in advanced cancer patients (I7W-MC-JQBA; JQBA), the maximum tolerated dose of LY3127804 was not reached at doses up to 27 mg/kg given IV once every 14 days (Q2W) and the recommended Phase 2 dose was 20 mg/kg IV Q2W. In JQBA, LY3127804 had an acceptable safety profile. The PK of LY3127804 was linear in the 4-27 mg/kg Q2W dose range. However, due to significantly reduced Ang2 clearance associated with binding to LY3127804, pharmacodynamic (PD; total Ang2 in plasma) did not show a dose-dependency, and a PK/PD model could not be derived to explain the relationship of LY3127804 dose or concentrations to Ang2 plasma concentrations. Therefore, the LY3127804 concentration at which the target would be optimally saturated could not be estimated.

In lieu of a PK/PD model, PK simulations were performed to evaluate the potential benefit of using different doses and compared to median Ang2 concentrations observed in patients with pneumonia/ARDS in the literature (Gutbier et al. 2018, Calfee et al. 2015).

Figure 5-2 shows simulations for several LY3127804 doses compared to the median Ang2 levels in patients with pneumonia reported in Gutbier et al. 2018.

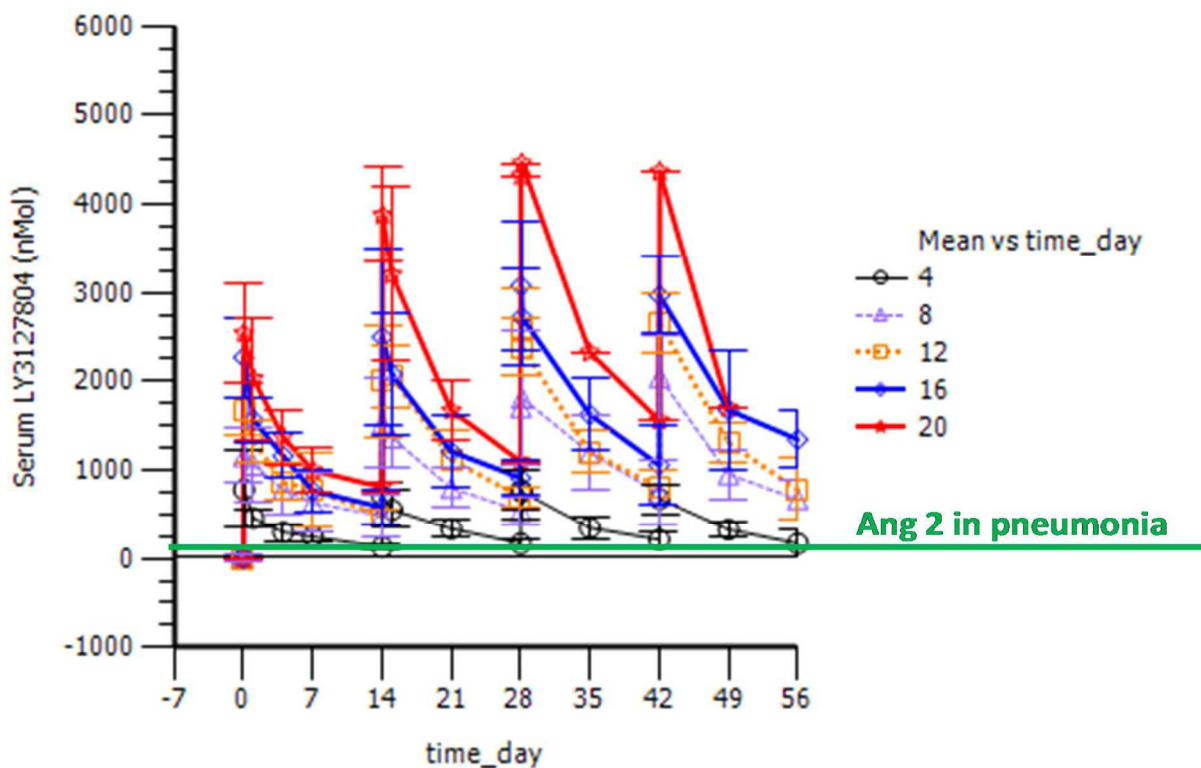


Figure 5-2. Simulations for several dose levels (in mg/kg, given IV Q2W) compared to the median Ang2 levels reported in patients with pneumonia.

Based on Study JQBA data and PK simulations based on the JQBA data, median LY3127804 plasma concentrations after two 20 mg/kg doses (~1200 – 2200 nM) are expected to exceed median circulating Ang2 concentrations on a molar basis by >15-fold in patients with pneumonia. In addition, each LY3127804 molecule can bind to two Ang2 molecules, effectively doubling the effective LY3127804 exposure available for target binding.

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at screening, unless specified otherwise:

1. Must be admitted to the hospital
2. Confirmed pneumonia with:
 - a. Presence of signs and symptoms of respiratory disease (ie, cough, tachypnea, and/or shortness of breath)
and at least one of the following
 - b. Infiltrates on chest imaging
 - c. oxygen saturation (SpO₂) of $\leq 95\%$ on room air
3. With presumed or confirmed COVID-19
4. Are at least 18 years of age at the time of randomization.
5. Are able and willing to give signed informed consent (legally authorized representative can provide informed consent if needed).

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening, until specified otherwise:

1. Have ARDS and/or require immediate intermittent mandatory ventilation (IMV).
2. In the opinion of the investigator, is moribund irrespective of the provision of treatments.
3. Any concurrent serious medical condition (e.g. patients with estimated glomerular filtration rate [eGFR] < 15 mL/min/1.73m² or on dialysis, preexisting lung disease requiring O₂ at rest, a body mass index [BMI] that precludes techniques such as proning) or concomitant medication that in the opinion of the investigator that would preclude participation in the study.
4. Have received treatment with a drug predominantly targeting Ang2 activity (e.g., tyrosine kinase inhibitors and/or antibody treatment) within the past month or 5 half-lives, whichever is longer.
5. Have a known sensitivity to mAbs or other therapeutic proteins, to agents of similar biologic composition as LY3127804, or to any products used in the formulation of LY3127804 (refer to the IB for LY3127804 for details) or are incompatible with the treatment of LY3127804.

6. Have a known history or show evidence of human immunodeficiency virus (HIV) and/or hepatitis A, B or C
7. Exclusion Criterion [7] has been deleted.
8. Have a significant bleeding disorder or active vasculitis or had a Grade ≥ 3 bleeding episode within 12 weeks prior to receiving treatment
9. Have experienced any arterial thromboembolic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months prior to receiving treatment
10. Have experienced any Grade 3 or 4 venous thromboembolic event that is considered by the investigator to be life-threatening or that is symptomatic and not adequately treated by anticoagulation therapy within 6 months prior to receiving treatment. Patients with chronic portal vein thrombosis who are asymptomatic and not considered to need anticoagulation therapy are eligible.
11. Have chronic congestive heart failure (New York Heart Association class ≥ 3) or uncontrolled cardiac dysrhythmia
12. Have a serious nonhealing: (a) wound, (b) peptic ulcer, or (c) bone fracture, within 28 days prior to receiving first dose of study drug
13. Have undergone major surgery within 28 days prior to randomization or central venous access device placement for another pre-existing condition within 7 days prior to receiving first dose of study drug
14. Have liver cirrhosis with a Child-Pugh class B or worse or cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis.
15. Have a history of hypertensive crisis or hypertensive encephalopathy or current poorly controlled hypertension (systolic BP ≥ 160 mm Hg and/or diastolic BP ≥ 95 mm Hg) despite standard medical management.
16. Are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.
17. Female patients who are pregnant and/or lactating.
18. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
19. Are Lilly employees or are employees of any third-party involved in the study who require exclusion of their employees.

6.3. Lifestyle Restrictions

Study patients must be instructed not to donate blood or blood products during the study and for 8 weeks following the last dose of study drug.

The following patients must agree to use medically approved contraceptive methods during the study and for 90 days post the last dose of study drug:

- Male patients with female partners of child-bearing potential
- Female patients of childbearing potential who have a fertile male sexual partner

Medically approved contraceptives include the following:

- Hormonal contraceptives (oral, transdermal patches, vaginal or injectable),
- Intrauterine device with or without hormones,
- Condom ('barrier' method),
- Diaphragm or cervical cap ('barrier' method),
- Sexual abstinence

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of LY3127804 20 mg/kg administered intravenously once every two weeks to placebo. The investigator may withhold the second dose (refer to Section 8.1). Table 7-1 shows the treatment regimens.

Table 7-1. Treatment Regimens

Regimen	Dose Day 1	Dose Day 15
LY3127804	20 mg/kg	20 mg/kg
Placebo	Matching placebo	Matching placebo

Note: Patients weighing 150 kg and above will receive a maximum LY3127804 dose of 3000 mg. Please see the Pharmacy Manual for further instructions.

LY3127804 will be administered as a slow IV infusion over at least 90 (± 15) minutes. Infusion duration may be increased or stopped as deemed necessary based on the institutional standard of care. If an infusion reaction is observed, the patient should be treated according to instructions in Section 9.2.2. Resuscitation equipment and emergency drugs must be available at all times when the patient is being infused. Patients should be observed for at least 60 minutes after completion of the infusion. The actual start and stop time of infusion will be recorded.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the investigational agent(s) to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of investigational product infusion and collection
- at the end of the study returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law.

7.1.1. Packaging and Labelling

The drug product will be manufactured, tested, packaged, and labeled in accordance with all applicable Good Manufacturing Practice (GMP) requirements and country's regulatory requirements. A certificate of analysis confirming the materials are released for human use in clinical trials will be supplied. LY3127804 drug products are for investigational use only and are to be used only within the context of this study.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be stratified by age group (<65 years and ≥ 65 years), sex, and site, and then, on Day 1, randomly assigned in a 1:1 ratio within each stratum to receive either LY3127804 or placebo. Treatment assignment will be determined by a computer generated randomization sequence using an interactive web response system (IWRS).

7.2.1. Selection and Timing of Doses

The doses will be administered at approximately the same times on each day. The actual time of all dose administrations will be recorded in the patient's electronic case report form (eCRF).

7.3. Blinding

This is a double-blind study; patients, investigator, and site personnel performing trial related activities or with the ability to influence study outcomes will be blinded with respect to LY3127804 and placebo treatment. To preserve the blinding, all sponsor personnel involved in study conduct will remain blinded to treatment while the study is ongoing, except for individuals (or designee) from Global Patient Safety (GPS) to manage individual serious adverse events and safety reporting. This individual from the GPS team is not involved in day-to-day activities of study conduct. Site staff who are responsible for drug preparation will not be blinded; laboratory personnel will also not be blinded.

After the reporting database is locked for statistical analysis of the double-blind treatment phase, a limited number of sponsor personnel will be unblinded to complete the study report. However, any sponsor personnel continuing with the management and oversight of the study will remain blinded to patients' treatment assignments.

Emergency unblinding may be performed through the IWRS. This option may be used only if the patient's well-being requires knowledge of the patient's treatment assignment. All unblinding events will be recorded and reported by the IWRS.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. The patient's safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, it is the responsibility of the Investigator to promptly document the decision and rationale and notify sponsor as soon as possible.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a sponsor medical representative for the patient to continue in the study. During the study, emergency unblinding should occur only by accessing the IWRS.

This is a double-blind study.

Upon completion of the study, all codes must be returned to the sponsor or its designee.

7.4. Dosage Modification

Not applicable.

7.5. Preparation/Handling/Storage/Accountability

The investigator or his/her designee is responsible for the following:

- confirming appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- ensuring that only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- the investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation and final disposition records).

Detailed instructions for the preparation and handling of LY3127804 and placebo will be provided to the unblinded site pharmacy personnel by the Sponsor.

LY3127804 for Injection vials are to be stored in refrigerated condition (2°C to 8°C).

7.6. Treatment Compliance

All study drug doses will be administered at study site.

7.7. Concomitant Therapy

All concomitant therapies that are part of routine care are allowed and can be used during the study. If indicated, anticoagulation therapies, including full-dose anticoagulation therapies, are allowed.

All concomitant therapies must be recorded in the eCRF.

Concomitant medications captured should include unapproved (“off-label”) medication, such as, for example, convalescent antibodies, remdesivir, chloroquine, hydroxychloroquine, and IL-6 antagonists.

7.8. Treatment after the End of the Study

Study drug will not be made available after conclusion of the study to patients.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of study drug:

- Patient Decision
 - the patient requests to discontinue study drug.
- Investigator Decision
 - The investigator may discontinue treatment after the first dose, if in the judgement of the investigator the benefit/risk assessment for LY3127804 does not support administration of a second dose.
- Grade 3 or higher infusion-related reaction per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) 5.0 (refer to Section 9.2.2)
- Grade 2 and greater bleeding events associated with study treatment.

Patients discontinuing from the study drug prematurely for any reason should complete adverse event and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- patient consent withdrawal

Patients discontinuing from the study prematurely for any reason should complete adverse event and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients for the follow-up phone visit.

Site personnel, or an independent third party, will attempt to collect the vital status of the patient within legal and ethical boundaries for all patients randomized, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined, this will be documented and the patient will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect vital status information.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

Appendix 2 lists the laboratory tests that will be performed for this study.

Appendix 4 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed per local site procedures.

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessments

Ventilator free days will be defined as the number of days from Day 1 to Day 28 on which a patient does not require a ventilator (IMV), if the period of breathing without a ventilator (IMV) lasted at least 24 consecutive hours and the patient did not die within 28 days from first dose of study drug; if the patient died within 28 days, then this end point will be set equal to -1.

9.1.2. Secondary Efficacy Assessments

9.1.2.1. NIAID Ordinal Assessment

The NIAID will be assessed daily and defined as the lowest score achieved for that day [[NCT04280705](#)].

- 1- Death
- 2- Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
- 3- Hospitalized, on non-invasive ventilation or high flow oxygen devices
- 4- Hospitalized, requiring supplemental oxygen
- 5- Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)
- 6- Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
- 7- Not hospitalized, limitation on activities and/or requiring home oxygen
- 8- Not hospitalized, no limitations on activities.

9.1.2.2. Survival Without the Need for Mechanical Ventilation

Proportion of patients who are alive and respiratory failure free (i.e., never having required mechanical ventilatory support; i.e. IMV/ECMO) will be calculated at Day 28.

9.1.2.3. 28-day Mortality

Mortality will be defined as 28-day all-cause mortality, defined as 672 hours from the time of randomization. All patients will be classified as either “alive at Study Day 28” or, if dead, “dead at Study Day 28.”

9.1.2.4. Length of hospital stay

Length of hospital stay will be defined as the number of days hospitalized for at least 1 hour duration.

9.1.3. Exploratory Efficacy Analysis**9.1.3.1. Pulmonary Function**

Pulmonary function will be assessed daily as the range of the average lowest value for SpO₂ and the highest value of O₂ flow rate for that day.

9.1.4. Appropriateness of Assessments

All assessments are widely used and generally regarded as reliable, accurate, and relevant.

9.2. Adverse Events

A clinical trial AE is any untoward medical event associated with the use of a drug or drug delivery system in humans, whether or not it is considered related to that drug or drug delivery system.

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting the sponsor or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

Investigators must document their review of each laboratory safety report and electrocardiogram (ECG).

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the study drug before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the informed consent form (ICF) is signed, study site personnel will record via electronic data capture (EDC) the occurrence and nature of each patient’s pre-existing conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record via eCRF any change in the condition(s) and any new conditions as

AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure or investigational product via EDC.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment, and pathologies.

A “reasonable possibility” means that there potentially is a cause and effect relationship between the investigational product, study device, and/or study procedure and the AE.

The investigator will use AE follow-up forms to record additional details regarding AEs related to injection sites and hypersensitivity events.

If a patient’s study drug is discontinued as a result of an AE, study site personnel must report this to the sponsor or its designee via EDC, clarifying if possible the circumstances leading to discontinuation of treatment.

9.2.1. Serious Adverse Events

Study-specific clinical outcomes of progressive pulmonary failure in hospitalized patients with presumed or confirmed COVID-19 are exempt from all serious adverse event reporting unless the investigator deems the event to be related to the administration of study drug. Monitoring by the DMC will include continuous assessment of a potential imbalance in aggregate events between the treatment and control groups (please refer to Section 9.4.5).

The following events will be considered clinical outcomes and not reported as SAEs:

- Death related to progressive pulmonary failure and/or ARDS, that is, related to severe ARDS or a sequela of ARDS based on the interpretation of the investigator.
- Cardiovascular events: cardiac failure.
- Respiratory events: pneumonia, hemoptysis, decreased PaO₂/FiO₂, mechanical ventilation/ECMO, hypoxia, hypoxemia, ARDS, acute lung injury, or respiratory failure.
- Systemic inflammatory response syndrome related criteria: tachypnea, hypopnea, leukocytosis, leukopenia, hypothermia, hyperthermia, tachycardia, or bradycardia.
- Secondary infections

An SAE is any AE from this study that results in one of the following outcomes and is not classified as a clinical outcome of COVID-19 using the definitions shown in Section 9.2.:

- death that is not related to COVID-19 or a sequela of COVID-19 or death that is considered by the investigator to be related to study drug
- prolonged inpatient hospitalization or re-hospitalization life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect

- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

The study site personnel must alert the sponsor, or its designee, of any SAE as soon as practically possible but no later than 24 hours.

Additionally, study site personnel must alert the sponsor, or its designee, of any SAE within 24 hours of Investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Although all AEs are recorded in the case report form or EDC after signing informed consent, SAE reporting to the Sponsor begins after the patient has signed informed consent and has received the study drug. However, if an SAE occurs after signing informed consent, but prior to receiving the study drug, AND is considered Reasonably Possibly Related to a study procedure then it MUST be reported.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued from and/or completed the study (the patient disposition EDC has been completed). However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the Investigator must promptly notify Lilly.

Pregnancy (maternal or paternal exposure to the study drug) does not meet the definition of an adverse event. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

The designated medical monitor of the Sponsor will monitor safety data throughout the course of the study. The Sponsor and/or its designee will review SAEs within appropriate timeframes to meet reporting obligations imposed by regulatory authorities. All serious and unexpected AEs for this study will be reported to regulatory authorities in accordance with local laws, directives, and regulations.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Infusion-Related Reactions

As with other mAbs, infusion-related reactions may occur during or following LY3127804 administration. Infusion-related reactions will be defined according to the NCI-CTCAE 5.0 definition of infusion-related reactions (refer to “General disorders and administration site conditions” in NCI-CTCAE 5.0), as detailed below.

Symptoms occurring during or after infusion of study drug(s) may also be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome (refer to “Immune System Disorders” in NCI-CTCAE 5.0). If symptoms occur during or after infusion of LY3127804, investigators are encouraged to use the AE term “infusion-related reaction” and any additional terms (including those not listed here) that best describe the event. Those described above should be graded as shown in [Table 9-1](#).

Table 9-1. NCI-CTCAE 5.0 Infusion-Related Reactions

Adverse Event	Grade				
	1	2	3	4	5
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hr	Prolonged (e.g., not rapidly responsive to medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse reaction to the infusion of pharmacologic or biologic substances.					
Allergic reaction	Systemic intervention not indicated	Systemic intervention not indicated	Systemic intervention not indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	—	—	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death.					
Cytokine-	Fever with or	Fever with or without	Fever with or without	Fever with or	Death

Adverse Event	Grade				
	1	2	3	4	5
release	without	constitutional	constitutional	without	
syndrome	constitutional symptoms	symptoms	symptoms	constitutional symptoms	

Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokine.

Abbreviations: hr = hours; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug.

Consistent with usual medical practice, selected parenteral medications may be used for Grade 2 allergic/hypersensitivity reaction as detailed below. The Lilly CRP/study team must be contacted immediately.

The following are treatment guidelines for infusion-related reactions:

Grade 1

- Slow the infusion rate by 50% (by doubling the infusion time).
- Monitor the patient for worsening of condition.
- For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent); additional premedication may be administered at the investigator's discretion.

Grade 2

- Stop the infusion.
- Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), acetaminophen 650 mg orally for fever, and oxygen.
- Resume the infusion at 50% of the prior rate (by doubling the infusion time) once the infusion-related reaction has resolved or decreased to Grade 1; the infusion duration should not exceed 4 hours.
- Monitor for worsening of condition.
- For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent); additional premedication may be administered at the investigator's discretion.

For a second Grade 1 or 2 infusion-related reaction, administer dexamethasone 8 to 10 mg IV (or equivalent).

Grade 3

- Stop the infusion and disconnect the infusion tubing from the patient.
- Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), dexamethasone 8 to 10 mg IV (or equivalent), bronchodilators for bronchospasm, and other medications/treatment as medically indicated.

Patients who have a Grade 3 infusion-related reaction will not receive further treatment with LY3127804 but will continue to be followed per protocol.

Grade 4

- Stop the infusion and disconnect the infusion tubing from the patient.
- Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), dexamethasone 8 to 10 mg IV (or equivalent), and other medications/treatment as medically indicated.
- Give epinephrine or bronchodilators as indicated.

Patients who have a Grade 4 infusion-related reaction will not receive further treatment with LY3127804 but will continue to be followed in the study.

9.2.3. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study patients, monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the study drug so that the situation can be assessed.

9.2.4. Adverse Events of Special Interest – Secondary Infections

Adverse events of special interest for this study including infections in addition to SARS-CoV-2, inclusive of all sites and pathogens. Site of infection, source of culture (e.g. BAL, tracheal aspirate, sputum, blood, urine) and pathogen(s) identified (including fungal and bacterial pathogens) should be recorded.

9.3. Treatment of Overdose

There is no antidote to LY3127804. In case of overdose, use supportive measures.

9.4. Safety**9.4.1. Electrocardiograms**

For each patient, ECGs should be collected according to the Schedule of Activities (Section 2).

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational treatment should be reported to Lilly or its designee as an AE via EDC.

9.4.2. Vital Signs

For each patient, vital sign measurements should be conducted according to the Schedule of Activities (Section 2).

The sponsor recognizes that vital sign assessments will be performed more frequently than indicated in the Schedule of Events, with continuous monitoring in the ICU and every 2 to 4 hours in non-ICU settings. The time points specified in the protocol are collection times used for data analysis purposes only. The vital sign schedule in the protocol is not intended to interfere with standard of care practices in a given hospital unit. In all cases, institutional standard of care with respect to monitoring of patients is allowed and encouraged.

Any clinically significant findings from vital sign measurements that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via EDC.

9.4.3. Laboratory Tests

For each patient, laboratory tests detailed in ([Appendix 2](#)) should be conducted according to the Schedule of Activities (Section 2).

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of investigational product should be reported to Lilly or its designee as an AE via EDC.

9.4.4. Immunogenicity Assessments

Results from Clinical Study JQBA are consistent with a low risk for the development of significant levels of anti-drug antibodies. The proposed treatment will include one or two doses of LY3127804, making the mounting of a significant specific immune response to LY3127804 unlikely. Additionally, the collection of multiple blood draws presents significant challenges and an additional risk of infection to site personnel and is deemed unfeasible. There will be no assessment of immunogenicity as part of Study UDAA.

9.4.5. Safety Monitoring

The study will have a Data Monitoring Committee (DMC) consisting of at least 2 physicians and one statistician, all experienced clinical trialists and external to the sponsor. The role of the DMC is to advise the sponsor regarding conduct of the study. Only the DMC is authorized to evaluate unblinded data. Study sites will receive unblinded results ONLY if they need to know for the safety of their patients. Unblinding details are specified in the unblinding plan section of the statistical analysis plan (SAP) or a separate unblinding plan document.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the DMC can conduct additional analyses of the safety data.

All deaths and SAE reports will be reviewed in a blinded manner by Lilly during the clinical trial. These reports will be reviewed to assure completeness and accuracy but will not be unblinded to Lilly during the clinical trial. If a death or clinical AE is deemed serious, unexpected, and possibly related to investigational product, one individual (or designee) in Lilly Global Patient Safety will be unblinded for regulatory reporting and safety monitoring purposes. These measures will preserve the integrity of the data collected during this trial and minimize any potential for bias while providing for appropriate safety monitoring.

9.5. Pharmacokinetics

Samples for pharmacokinetic analysis will not be collected in this study.

9.6. Pharmacodynamics

Samples for pharmacodynamic analysis will not be collected in this study.

9.7. Pharmacogenomics/Genetics

Samples for pharmacogenomics or genetics will not be collected in this study.

9.8. Health Economics

Not applicable.

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 210 patients may be enrolled in a 1:1 ratio to LY3127804 or placebo (105 per treatment group) in order that 200 patients complete the study. A sample size of 100 in each group will have 81% power to detect a difference between the placebo group and the LY3127804 group using a Wilcoxon rank-sum test with a 0.05 one-sided significance level. This powering is based on the following assumptions: IMV rate of 25% and mortality rate of 12.5% in the placebo group, 50% improvement in IMV rate and mortality rate for the LY3127804 group relative to placebo, and a mean difference (LY3127804 minus placebo) of 3.0 ventilator-free days where patients who die are assigned a value of -1.

Randomization will be stratified by age group (<65 years and ≥65 years), sex, and site.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled Set	All patients who sign informed consent
Efficacy Analysis Set	All randomized patients who take at least 1 dose of double-blind study treatment. Patients will be included in the treatment group they were randomized.
Safety Analysis Set	All randomized patients who take at least 1 dose of double-blind study treatment. Patients will be analyzed according to the treatment they actually received.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. A detailed statistical analysis plan (SAP) describing the statistical methodologies will be developed.

Efficacy analyses will be conducted on the Efficacy Analysis Set; safety analyses will be conducted on the Safety Analysis Set.

Descriptive statistics will include the number of patients, mean, standard deviation, median, minimum, and maximum for continuous measures, and frequency counts and percentages for categorical measures.

Investigators with fewer than 2 randomized patients per treatment group will be pooled for statistical analysis purposes. Sensitivity analyses accounting for missing data will be described in the SAP.

Unless otherwise noted, treatment comparisons of discrete variables will be made using logistic regression analysis with treatment and randomization stratification variables in the model. The percentages, difference in percentages, and 95% confidence interval (CI) of the difference in percentages will be reported.

Unless otherwise noted, treatment comparisons of continuous variables will be made using a restricted maximum likelihood-based mixed-effects model of repeated measures (MMRM). The model will include treatment, age group, and site, and, if applicable, study day and treatment-by-study day interaction as fixed categorical effects. Additional details on the MMRM analyses will be described in the SAP.

All tests of treatment effects will be conducted at a 1-sided alpha level of 0.05, unless otherwise stated.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.2. Patient Comparability

10.3.2.1. Patient Disposition

A detailed description of patient disposition will be provided at the end of the study. Reasons for discontinuation will be summarized by treatment group.

10.3.2.2. Patient Characteristics

Demographic and baseline characteristics will be described. No statistical comparisons between treatment groups will be made.

10.3.2.3. Concomitant Therapy

Concomitant medications will be summarized for patients who enter each treatment period and will be presented by anatomical therapeutic chemical drug classes using the latest version of the WHO drug dictionary.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The Wilcoxon rank-sum analysis of the primary endpoint, death at day 28 and days free of mechanical ventilation within 28 days among survivors (VFDsurv), will use a scoring scheme with patients from the Efficacy Analysis Set who do better getting a higher score. We will assign a VFDsurv score of -1 to patients who die before 28 days. For those patients who survive to day 28 the VFDsurv score will be equal to the number of VFDs calculated according to the above definition. If a patient is discharged from the hospital before day 28, and if the patient is still alive at day 28, they will be credited with ventilator free days from the time of discharge until day 28. The statistical method for this endpoint will be based on the van Elteren test adjusting for the randomization stratification factors (age group, sex, and site).

10.3.3.2. Secondary Analyses

Secondary end points will be described and compared between treatment groups. The NIAID ordinal scale and length of hospitalization will be analyzed with the Wilcoxon rank-sum test.

Mortality, survival without respiratory failure, and categorical changes on the NIAID ordinal scale will be analyzed as discrete variables.

10.3.3.3. Exploratory Analyses

Pulmonary function will be analyzed via MMRM analysis.

10.3.4. Safety Analyses

Safety will be assessed by evaluating all reported AEs and changes in laboratory analytes, ECGs, and vital signs (including body weight) in the Safety Analysis Set and summarized by treatment group.

Duration of exposure to therapy will be calculated for each patient.

AEs will be coded according to the Medical Dictionary for Regulatory Activities and summarized by system organ class, preferred term, severity, and relationship to investigational product. A TEAE is defined as an event that first occurred or worsened in severity after baseline. In the analysis of TEAEs, all preexisting conditions recorded before the first dose of study drug will be used as baseline. For each event classification term, the number of patients experiencing a TEAE with that classification term will be tabulated. Treatment-related TEAEs are defined as events that are indicated by the investigator on the eCRF to be related to treatment. If a patient reports the occurrence of a particular event more than once, the most severe of those events will be included in the summary tables of TEAEs, and the most severe of the most related of those events will be included in the summary tables of treatment-related events.

Additional safety parameters include laboratory test results, ECGs, and vital-sign measurements. The baseline for computing the change in safety data is the last value collected before the first dose of study drug. The parameters will be listed and summarized with standard descriptive statistics. Change from baseline will also be summarized.

10.3.5. Other Analyses

10.3.5.1. Subgroup Analyses

Subgroup analyses of the primary analysis will be conducted on relevant subgroups, including patients who are confirmed SARS-CoV-2 positive, age group, and sex.

10.3.6. Interim Analyses

An interim analysis may be conducted to assess efficacy results. The interim efficacy results may be used for internal decision-making to trigger planning activities associated with the investigational product and/or to assess futility. No adjustment of Type I error will be performed as the study will not be stopped for efficacy, and no modification of Study UDAA is expected based on these interim results, other than possibly stopping the study for futility. The assessment would be conducted by a sponsor assessment committee with a limited number of preidentified team members who do not have direct site contact or data entry/validation responsibilities. Unblinding details will be specified in the unblinding plan section of the SAP or in a separate

unblinding plan document. Information that may unblind the study during the analyses will not be reported to study sites or to the blinded study team until the study has been unblinded.

An independent DMC will review unblinded safety data on an ongoing basis (Section [9.4.5](#)). Details are specified in the DMC Charter.

Ongoing monitoring of safety data (including AEs, SAEs, and selected laboratory measurements) will continue throughout the study by the sponsor using blinded data.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
Ang2	angiopoietin 2
ARDS	Acute respiratory distress syndrome
AST	aspartate aminotransferase
Blinding	A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CFR	case fatality rate
COVID-19	coronavirus disease
CI	confidence interval
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
DMC	data monitoring committee
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
ED	early discontinuation
EDC	electronic data capture

enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
FT4	free thyroxine
FU	follow-up
GCP	good clinical practice
GPS	Global Patient Safety
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IMV	intermittent mandatory ventilation
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
IV	intravenous
IWRS	interactive web-response system
mAb	monoclonal antibody
MMRM	mixed-effects model of repeated measures
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIAID	National Institute of Allergy and Infectious Diseases
PK/PD	pharmacokinetics/pharmacodynamics
QTc	corrected QT interval
Q2W	every two weeks
SAE	serious adverse event
SAP	statistical analysis plan

Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SpO₂	oxygen saturation
SUSARs	suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TSH	thyroid stimulating hormone
VFD	ventilator free days
VFDsurv	ventilator free days among survivors
WBC	white blood cell

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology

Hemoglobin
 Hematocrit
 Erythrocyte count (RBC)
 Mean cell volume
 Mean cell hemoglobin concentration
 Leukocytes (WBC)
 Neutrophils, segmented
 Lymphocytes
 Monocytes
 Eosinophils
 Basophils
 Platelets

COVID-19 Panel

D-dimer
 Cardiac troponin (I or T)
 LDH
 C-reactive protein
 Procalcitonin
 Ferritin
 IL-6
 BNP

Clinical Chemistry**Serum Concentrations of:**

Sodium
 Potassium
 Total bilirubin
 Direct bilirubin
 Alkaline phosphatase
 Alanine aminotransferase (ALT)
 Aspartate aminotransferase (AST)^a
 Blood urea nitrogen (BUN)
 Creatinine
 Uric acid
 Calcium
 Glucose (random)
 Albumin
 Creatine kinase (CK)
 Total protein

Pregnancy Test (females only)**Thyroid Function Test**

Free thyroxine (fT4)
 Thyroid stimulating hormone (TSH)

Influenza/RSV/Respiratory Viral Panel^b

Abbreviations: BNP = brain natriuretic peptide; IL-6 = interleukin 6; LDH = lactate dehydrogenase; RBC = red blood cells; RSV = respiratory syncytial virus; WBC = white blood cells.

- a For purposes of this study, if AST is not routinely reported when ALT is normal, then AST is not required.
 b Viral testing is only performed for patients who have undetermined or negative COVID-19 test(s). Viral testing is per the institution's testing guidelines.

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.
- ensuring that a copy of the ICF is provided to the patient or the patient's legal representative and is kept on file.
- ensuring that the medical record includes a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Appendix 3.1.2. Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes.

Investigator(s) will be responsible for patient recruitment through local requirements or processes.

Appendix 3.1.3. Ethical Review

The investigator or an appropriate local representative must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

The study site's ERB(s) should be provided with the following:

- the protocol and related amendments and addenda, current Investigator Brochure (IB) and updates during the course of the study
- informed consent form
- other relevant documents (for example, curricula vitae, advertisements)

Appendix 3.1.4. Regulatory Considerations

This study will be conducted in accordance with the protocol and with the:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third party.

Appendix 3.1.5. Investigator Information

Physicians with a specialty in pulmonology and/or intensive care and/or other identified critical care staff will participate as investigators in this clinical trial.

Appendix 3.1.6. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Appendix 3.1.7. Final Report Signature

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 3.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- review study data remotely where possible

- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or electronic mail
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs. This may be virtual as current sites are not allowing monitors on site to reduce the risk of COVID-19 contamination.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 3.2.1. Data Capture System

An EDC system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Case report form data will be encoded and stored in a clinical trial database.

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.3.2. Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.4. Publication Policy

The publication policy for Study UDAA is described in clinical trial agreement.

Appendix 4. Sampling Summary

This table summarizes the approximate number of samples [venipunctures, blood draws from lines, urine] and volumes for all sampling [screening, standard of care laboratory,] and tests during the study. Fewer samples may actually be taken, but this will not require a protocol amendment.

Protocol I7W-MC-UDAA Sampling Summary

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples	Maximum Total Amount
Hematology and Chemistry (most are stand of care samples) ^a	Blood	3-6 mL	7	21-42 mL
Pregnancy Test (blood or urine)	Blood/ urine	3 mL blood or urine sample	2	6 mL blood or urine sample
Thyroid Function Test and Covid Panel (Appendix 2)	Blood	8.5 mL	3	25.5 mL

^a Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with Lilly-designated Medical Monitor.

Appendix 5. Protocol Amendment I7W-MC-UDAA(c) Summary

Protocol I7W-MC-UDAA has been amended; the new version is indicated as amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

Section	Changes made	Rationale for the change
6.1 Inclusion Criteria	Removed time frame for admission to the hospital and increased SpO ₂ to 95%	Feedback from sites regarding baseline SpO ₂ in admitted patients; to allow including moderately ill patients
6.2 Exclusion Criteria	Exclusion criteria revised to <ul style="list-style-type: none"> • remove ineligibility of patients with DNI orders • not exclude patients with active malignancies or patients with postorgan transplant • delete BMI criteria as long as proning is possible • remove ineligibility of patients anticipated to receive or receiving anticoagulants • clarify “active” vasculitis • replace “symptomatic” with “chronic” congestive heart failure and clarify wording 	Following evolving feedback from clinical sites and FDA to include patients who have the greatest need to be enrolled in the study.
7.1 Treatments Administered	Added a footnote to the table to reflect a maximum dose of 3000 mg	For consistency with existing instructions in the Pharmacy manual
7.7 Concomitant Therapy	Amended to include <ul style="list-style-type: none"> • anticoagulation therapies at any time during the study • convalescent antibodies, and • remdesivir 	Following evolving feedback from clinical sites and FDA
8.1 Discontinuation from Study Treatment	Added discontinuation for bleeding events	Per FDA feedback
10.3.6 Interim Analysis	Added the potential for a futility analysis	Per FDA feedback

Revised Protocol Sections

Note: Deletions have been identified by ~~strike-throughs~~ or grayed out for figures. Additions have been identified by the use of underscore.

6. Study Population

6.1 Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at screening, unless specified otherwise:

1. Must be admitted to the hospital ~~for less than 48 hours~~
2. Confirmed pneumonia with:
 - a. Presence of signs and symptoms of respiratory disease (ie, cough, tachypnea, and/or shortness of breath)
 - and at least one of the following**
 - b. Infiltrates on chest imaging
3. oxygen saturation (SpO₂) of ~~≤95%~~≤93% on room air

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening, until specified otherwise:

1. Have ARDS and/or require immediate intermittent mandatory ventilation (IMV) ~~or are ineligible for IMV due to a pre-existing medical condition, including those with DNI orders.~~
3. Any concurrent serious medical condition (e.g. ~~active malignancies on chemotherapy, post organ transplant,~~ patients with estimated glomerular filtration rate [eGFR] <15 mL/min/1.73m² or on dialysis, preexisting lung disease requiring O₂ at rest, body mass index [BMI] ≥40 kg/m² that precludes techniques such as proning) or concomitant medication that in the opinion of the investigator that would preclude participation in the study.
7. Exclusion Criterion [7] has been deleted. ~~At the time of study drug administration, anticipated to be requiring full-dose (therapeutic) anticoagulation with warfarin and/or other anticoagulants~~

~~Patients receiving prophylactic, low-dose anticoagulation therapy are eligible provided that they are on low-molecular-weight heparin or oral Factor Xa inhibitors or it is medically appropriate at the investigator's judgment that patients switch to low-molecular-weight heparin or oral Factor Xa inhibitors before initiation of study therapy~~

8. Have a significant bleeding disorder or active vasculitis or had a Grade ≥ 3 bleeding episode within 12 weeks prior to receiving treatment
11. Have ~~chronic~~symptomatic congestive heart failure (New York Heart Association class ≥ 3) or ~~symptomatic or poorly~~ uncontrolled cardiac dysarrhythmia

7.1. Treatments Administered

Table 7-1. Treatment Regimens

Regimen	Dose Day 1	Dose Day 15
LY3127804	20 mg/kg	20 mg/kg
Placebo	Matching placebo	Matching placebo

Note: Patients weighing 150 kg and above will receive a maximum LY3127804 dose of 3000 mg. Please see the Pharmacy Manual for further instructions.

7.7. Concomitant Therapy

All concomitant therapies that are part of routine care are allowed and can be used during the study. If indicated, ~~after completion of study drug administration,~~ anticoagulation therapies, including full-dose anticoagulation therapies, are allowed.

All concomitant therapies must be recorded in the eCRF.

Concomitant medications captured should include unapproved (“off-label”) medication, such as, for example, convalescent antibodies, remdesivir, chloroquine, hydroxychloroquine, and IL-6 antagonists.

8.1. Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of study drug:

- Patient Decision
 - the patient requests to discontinue study drug.
- Investigator Decision
 - The investigator may discontinue treatment after the first dose, if in the judgement of the investigator the benefit/risk assessment for LY3127804 does not support administration of a second dose.
- Grade 3 or higher infusion-related reaction per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) 5.0 (refer to Section 9.2.2).

- Grade 2 and greater bleeding events associated with study treatment.

10.3.6. Interim Analysis

An interim analysis may be conducted to assess efficacy results. The interim efficacy results may be used for internal decision-making to trigger planning activities associated with the investigational product and/or to assess futility. No adjustment of Type I error will be performed as the study will not be stopped for efficacy, and no modification of Study UDAA is expected~~will be~~ based on these interim results, other than possibly stopping the study for futility. The assessment would be conducted by a sponsor assessment committee with a limited number of preidentified team members who do not have direct site contact or data entry/validation responsibilities. Unblinding details will be specified in the unblinding plan section of the SAP or in a separate unblinding plan document. Information that may unblind the study during the analyses will not be reported to study sites or to the blinded study team until the study has been unblinded.

Document Approval Form

Document Information

Document Type	Protocol Amendment
Component ID	5cdb0673-4945-42f2-b8d0-18129ce3d83e
Document Title	UDAA 05 Protocol (c).pdf
Version Number	(c)
Storage Location	Leo Storage/Clinical/LY3127804/I7W-MC-UDAA/Clinical Protocol/LY3127804 I7W-MC-UDAA Clinical Protocol (c)/UDAA 05 Protocol (c).pdf

Compound and/or LY #	LY3127804
Study Identifier	N/A
Site Number	N/A
Investigator	N/A
Country	US

Comments

Complete this field to capture additional information.

Reviewer and Approver

REVIEWED BY: Only include the name(s) and the signature(s) of the individuals who are required to review the document by procedure. The signature(s) represents that the document and/or source has been reviewed for accuracy. Add or delete rows as necessary.

Name	Title	Signature	Date (dd-Mmm-yyyy)

APPROVED BY: Include the name(s) and signature(s) of the approver(s). The signature(s) represent(s) that the appropriate reviews have occurred and the document is appropriate for its intended use. THE LAST APPROVAL DATE IS USED AS THE APPROVAL DATE FOR THE DOCUMENT. Add or delete rows as necessary.

PPD