Efficacy and Safety of LY3127804, an Anti-Angiopoietin-2 Antibody, in a Randomized, Double-Blind, Placebo-Controlled Clinical Trial in Patients Hospitalized with Pneumonia and Presumed or Confirmed COVID-19

Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine
Volume 16: 1–7

DOI: 10.1177/11795484221119316
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ABSTRACT

BACKGROUND: Severe cases of coronavirus disease 2019 (COVID-19) are characterized by progressive respiratory failure and the development of acute respiratory distress syndrome (ARDS), with high mortality rates for patients requiring mechanical ventilation. Levels of the vascular growth factor Angiopoietin 2 (Ang2) in plasma have been strongly correlated with increased ARDS risk in patients with pneumonia or sepsis. The intent of this study was to determine whether LY3127804, an anti-Ang2 monoclonal antibody, could reduce the need for mechanical ventilation among patients admitted to the hospital with pneumonia and presumed or confirmed COVID-19.

METHODS: Patients admitted to hospital with confirmed pneumonia, presumed or confirmed COVID-19, and infiltrates on chest imaging and/or oxygen saturation of ≤ 95% on room air were stratified by age group (< 65 years and ≥ 65 years), sex, and site and randomly assigned 1:1 within each stratum to receive either LY3127804 (20 mg/kg) or placebo on Day 1 and possibly on Day 15. The primary end point for this study was number of days in which a patient did not require a ventilator over the 28-day study period.

RESULTS: Interim analysis assessed study futility after 95 randomized patients had 28-day data available and showed no benefit of LY3127804 in reducing the number of ventilator days over placebo. The study was subsequently terminated.

CONCLUSION: LY3127804 treatment did not decrease the need for ventilator usage in patients hospitalized with pneumonia and presumed or confirmed COVID-19.

CLINICALTRIALS.GOV IDENTIFIER: NCT04342897

KEYWORDS: Acute respiratory distress syndrome, Angiopoietin 2, COVID-19, pneumonia, SARS-CoV-2.

RECEIVED: April 30, 2021. **ACCEPTED:** July 20, 2022.

TYPE: Original Research Article

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Eli Lilly and Company.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Rosie S. Jones, Patricia S. Smith, Paul H. Berg, Amparo de la Peña, and Yu Hu are employees and minor shareholders of Eli Lilly and Company. Robert Schott is a minor shareholder of Eli Lilly and Company. Paul P. Cook, Imad Shawa, and Kathleen M. Kioussopoulos have no competing interests to declare.

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Introduction

Infection with the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) in many instances results in coronavirus disease 2019 (COVID-19). Typical symptoms at onset include fever, fatigue, cough, and myalgia. Approximately 15% of COVID-19 cases are classified as severe, requiring hospitalization.[1] Severe cases are characterized by progressive respiratory failure and the development of acute respiratory distress syndrome (ARDS), with high mortality rates for patients requiring mechanical ventilation.[1-3]

ARDS is characterized by loss of integrity of capillary endothelium (endothelial tight junctions) with extravasation of protein-rich fluid and white blood cells into the alveolar interstitium. This is associated with inflammation, activation of tissue-resident macrophages, and immune activation, with patchy alveolar infiltrates evident on x-ray and pulmonary edema, and death from progressive respiratory failure.[4] It is conservatively estimated that 25% of patients hospitalized with COVID-19 will develop ARDS, with a case fatality rate of 50% in the first 30 days.[2,3,5] ARDS is known to be a heterogeneous disease, and case reports indicate that ARDS associated with COVID-19 may have a different phenotypic presentation than typical ARDS.[6-8] However, it is recommended that COVID-19-associated ARDS is managed using the traditional treatment guidelines.[9]

As of April 13 2021, there have been over 136 million cases of COVID-19 confirmed worldwide, with a case fatality rate of > 2%.[10] COVID-19 is characterized by widespread endothelial

inflammation with the formation of microthrombi, which in the lungs can lead to shunting and progressive hypoxia.[11] Currently, only the anti-viral agent remdesivir has Federal Drug Administration (FDA) approval for the treatment of patients 12 years of age or older who require hospitalization for COVID-19. Emergency use authorization (EUA) has been granted to monoclonal antibodies, such as bamlanivimab together with etesevimab and a coadministration of casirivimab and imdevimab for the treatment of mild-to-moderate COVID-19 in patients 12 years of age and older who are at high risk for progressing to severe COVID-19 and/or hospitalization.[12-14] Baricitinib in combination with remdesivir has EUA in hospitalized patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation.[15] Corticosteroids, such as dexamethasone, and anti-inflammatory agents, such as tocilizumab, have shown promising evidence of efficacy in reducing mortality and progression of COVID-19 pneumonia, respectively.[16,17]

The vascular growth factor Angiopoietin 2 (Ang2), which is stored in the Weibel–Palade bodies of endothelial cells, is released as a result of endothelial stress and is a predictor of progression to ARDS in patients with sepsis.[18] Antagonism of Ang2 mitigates neovascular leakage in macular degeneration[19] and also plays a role in tumor angiogenesis by uncoupling the tight junctions in the vascular endothelium and releasing pericytes.[20] Ang2 levels in plasma are strongly correlated with increased ARDS risk in several human studies.[21-24] Importantly, Parikh et al showed that stimulation with Ang2 alone in murine models replicated 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.[22] In addition, RNAi Knockdown or anti-Ang2 antibody treatment improved survival and pulmonary function in experimental models of ARDS.[18,25]

LY3127804 (zansecimab) 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 indicate 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 was to determine whether LY3127804 could reduce the high proportion of patients who progress to pulmonary insufficiency, as assessed by ventilator free days (VFDs), after being admitted to the hospital with pneumonia and presumed or confirmed COVID-19.

Methods

Study design and participants

I7W-MC-UDAA was a multicenter, randomized, double-blind, parallel arm, placebo-controlled Phase 2 study in patients who were hospitalized with pneumonia and presumed or confirmed COVID-19 (see Supplemental Figure 1 for study design). The trial was conducted at 10 sites in the United States. Patients were enrolled from April 20th to August 13th, 2020.

Inclusion criteria consisted of admission to the hospital with confirmed pneumonia and presence of signs and symptoms of respiratory disease and infiltrates on chest imaging and/or oxygen saturation (SpO2) of $\leq$ 95% on room air; presumed or confirmed COVID-19; and aged 18 years or older.

Exclusion criteria included a diagnosis of ARDS and/or requirement of immediate intermittent mandatory ventilation (IMV); in the opinion of the investigator, was moribund irrespective of the provision of treatments; any concurrent serious medical condition; received treatment with a drug predominantly targeting Ang2 activity; or a known sensitivity to mAbs or other therapeutic proteins. For a full list of inclusion and exclusion criteria see Supplementary Appendix.

This study was compliant with the International Conference on Harmonization Guideline on Good Clinical Practice. All informed consent forms and protocols were approved by appropriate ethical review boards prior to initiation of the study. All patients or legally authorized representatives gave written informed consent prior to receiving study drug.

Randomization and masking

Patients who met all criteria for enrollment were stratified by age group (< 65 years and $\geq$ 65 years), sex, and site and randomly assigned on Day 1 using a 1:1 ratio within each stratum to receive either LY3127804 or placebo. Treatment assignment was determined by a computer-generated randomization sequence using an interactive web response system and the sites were responsible for administering study drug to the patients.

Patients, investigators, sponsor personnel, and site personnel performing trial-related activities or with the ability to influence study outcomes were blinded with respect to LY3127804 and placebo treatment. A study site pharmacist or other trained person was unblinded at the site for investigational product preparation. These individuals were segregated from the investigators involved in the oversight and conduct of the study. Individuals or designees from Eli Lilly Global Patient Safety remained unblinded to manage individual serious adverse events (SAE) and safety reporting. An independent Data Monitoring Committee (DMC) reviewed unblinded safety data and conducted an unblinded futility assessment.

Procedures and outcomes

This 28-day study was designed to establish the efficacy and safety of LY3127804 20 mg/kg administered intravenously (IV) once every two weeks compared to placebo, with the second dose of LY3127804 withheld if not supported by a benefit/risk assessment by the investigator. Study drug was

administered as a slow IV infusion over at least 90 (±15) minutes, with a maximum possible dose of 3000 mg. Dose selection was based on PK simulations data from a previous study in patients with advanced cancer, and their relationship to published median Ang2 concentrations observed in patients with pneumonia and ARDS.[21,26] Median plasma concentrations of LY3127804 after two 20 mg/kg doses were expected to exceed median circulating Ang2 concentrations by > 15-fold in patients with pneumonia.

The primary objective for this study was to evaluate VFDs during treatment with LY3127804. The endpoint for this objective was the number of days (from Day 1 to Day 28) in which a patient breathed without the assistance of a ventilator, if the period of unassisted breathing lasted at least 24 consecutive hours and the patient did not die within 28 days from the first dose of study drug.

Secondary objectives included clinical status using the National Institute of Allergy and Infectious Diseases (NIAID) Ordinal Assessment as an endpoint, assessed daily and defined as the lowest score achieved for that day; survival without the need for mechanical ventilation (IMV/extracorporeal membrane oxygenation (ECMO)), defined as the proportion of patients who were alive at Day 28 and never required mechanical ventilatory support; mortality rate evaluated as death within 28 days of first LY3127804 dose; reduction in hospital stay based on length of hospitalization; and safety as measured by the incidence of adverse events and SAE.

The NIAID Ordinal Assessment is an 8-point scale determining clinical status: 1 = death; 2 = hospitalized, on invasive mechanical ventilation or ECMO; 3 = hospitalized, on noninvasive ventilation or high flow oxygen devices; 4 = hospitalized, requiring supplemental oxygen; 5 = hospitalized, not requiring supplemental oxygen but 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.

Study-specific clinical outcomes of progressive pulmonary failure in hospitalized patients with presumed or confirmed COVID-19 were exempt from all SAE reporting unless the investigator deemed the event to be related to the administration of study drug. Monitoring by the DMC included continuous assessment of a potential imbalance in aggregate events between the treatment and control groups. The following events were 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 PaO_2/FiO_2, 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); and secondary infections. An SAE was defined as any adverse event from this study that resulted in one of the following outcomes and was not classified as a clinical outcome of COVID-19: death that was not related to COVID-19 or a sequela of COVID-19 or death that was 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; and 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.

Statistical analysis

Enrollment was planned for approximately 210 patients 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 would have 81% power, demonstrated via simulations, 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 was based on an assumption of an IMV rate of 25% and mortality rate of 12.5% in the placebo group and a 50% improvement in IMV rate and mortality rate for the LY3127804 group relative to placebo, with a mean difference (LY3127804 minus placebo) of 3.0 VFDs. For the primary endpoint, if the patient died within 28 days of receiving the first dose of study drug, the value for VFD was set equal to −1. For details on the statistical methodology for the VFD measure, see Finkelstein and Schoenfeld.[27]

The efficacy analysis set includes all randomized patients and, as all these patients received at least one dose of the study treatment to which they were assigned, the efficacy population was identical to the safety population.

Descriptive statistics included the number of patients, mean, standard deviation, median, minimum and maximum for continuous measures, and frequency counts and percentages for categorical measures. Number of VFDs and NIAID Ordinal Assessment were analyzed using the Wilcoxon rank-sum test using the van Elteren test to adjust for the randomization stratification factors. Non-responder imputation was used when the response status for VFD could not be determined. Patients whose survival status could not be determined at Day 28 were treated as deaths.

Enrollment was paused after 95 patients were randomized, and an analysis was conducted to assess study futility. An unblinded snapshot of the electronic case report form database was used for this interim analysis. In addition to the safety data regularly provided to the DMC for their review, efficacy data consisting of ventilation status, hospital discharge, and mortality during Days 1–28, as well as the calculation of VFD, were provided for evaluation.

Table 1. Patient demographics and clinical characteristics.

Mean (SD) unless otherwise noted	Placebo IV N = 48	LY3127804 IV 20 mg/kg N = 47
Age, years	55.5 (14.4)	54.3 (14.1)
Weight, kg	97.5 (25.2)	96.3 (26.1)
BMI, kg/m^2	33.7 (7.7)	33.7 (7.0)
Sex, male (%)	64.6	61.7
Race, n (%)		
Black	7 (14.6)	8 (17.0)
Caucasian	38 (79.2)	36 (76.6)
Asian or Pacific Islander	3 (6.3)	2 (4.3)
Other[a]	0	1 (2.1)
Hispanic, n (%)	20 (41.7)	23 (48.9)
Diabetes mellitus, n (%)	23 (47.9)	12 (25.5)
Hypertension, n (%)	29 (60.4)	20 (42.6)
Confirmed COVID-19, n (%)	48 (100)	46 (97.9)
Respiration rate (breath/min)	23.9 (6.5)	23.2 (5.6)
C-reactive protein (mg/L)	236.2 (559.2)	134.9 (83.5)
IL-6 (ng/L)	54.8 (75.6)	60.1 (116.5)
D-Dimer (mg/L FEU)	2.8 (6.1)	1.1 (1.4)
NIAID Ordinal Assessment, n (%)		
2	1 (2.1)	0
3	20 (41.7)	13 (27.7)
4	24 (50.0)	29 (61.7)
5	3 (6.3)	5 (10.6)
Concomitant medications, n (%)		
Remdesivir	32 (66.7)	36 (76.6)
COVID-19 Convalescent plasma	12 (25.0)	7 (14.9)
Anti-coagulants (Heparin)[b]	48 (100.0)	46 (97.9)
Anti-coagulants (Other)[c]	10 (21.3)	13 (27.1)
Dexamethasone	28 (58.3)	19 (40.4)

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; FEU, fibrinogen-equivalent units; IV, intravenous therapy; N, number of patients; n, number of patients in a subgroup; NIAID, National Institute of Allergy and Infectious Diseases; SD, standard deviation.
[a]Other: Multiple.
[b]Anti-coagulants (Heparin): Enoxaparin, Heparin.
[c]Anti-coagulants (Other): Acetylsalicylic acid, Clopidogrel.

The conditional power for the primary efficacy analysis was calculated by the DMC statistician using the data collected as of the interim analysis to predict the data to be collected after the interim analysis. The pre-specified futility threshold was conditional power < 10% when approximately half the study was enrolled. The Bayesian predictive power was 1% with 95 of the planned 200 patients enrolled, therefore the DMC recommended stopping the study for futility. No new patients were to be randomized and no new doses of study drug would be given, and ongoing patients would be allowed to complete other protocol procedures and followed to collect their full data.

Table 2. Outcomes at day 28.

	Placebo IV N = 48	LY3127804 IV 20 mg/mL N = 47
Ventilator free days[a], n (%)		
−1	4 (8.3)	7 (14.9)
4	1 (2.1)	0
10	1 (2.1)	0
12	0	1 (2.1)
13	0	1 (2.1)
18	0	1 (2.1)
28	42 (87.5)	37 (78.7)
NIAID Ordinal Assessment[b], n (%)		
1	4 (8.3)	7 (14.9)
2	2 (4.2)	3 (6.4)
3	21 (43.8)	12 (25.5)
4	19 (39.6)	24 (51.1)
5	2 (4.2)	1 (2.1)
Respiratory failure-free survival, n (%)	42 (87.5)	37 (78.7)
All-cause mortality rate, n (%)	4 (8.3)	7 (14.9)
Length of hospital stay[c], days, median (min, max)	6.0 (2, 29)	6.0 (1, 29)

Abbreviations: IV, intravenous therapy; N, number of patients; n, number of patients in a subgroup; NIAID, National Institute of Allergy and Infectious Diseases.
[a]For patients who survive through Day 28, the value is the number of days free of mechanical ventilation; for patients who do not survive through Day 28, the value is set to −1.
[b]Lowest NIAID from Day 1 through Day 28.
[c]Length of hospitalization was computed during Day 1 through Day 28. For subjects who died during this period, the length was imputed as 29 days.

Results

Patients

A total of 95 patients hospitalized with pneumonia and presumed or confirmed COVID-19 were randomized in this study before termination, 47 received LY3127804 and 48 received placebo. Patient demographics and baseline clinical characteristics were generally well-balanced between treatment groups and are shown in Table 1. All 48 patients in the placebo

group, and 46 of 47 patients in the LY3127804 group, had positive SARS-CoV-2 test results as specified by local testing procedures, typically PCR. Biomarkers for inflammation were elevated at baseline (eg, C-reactive protein and IL-6), with evidence of activation of coagulation systems (elevated D-dimer). Although there is an apparent difference in the mean values of CRP and D-dimer between treatment groups, this is due to outliers in the placebo group. Wilcoxon two-sample rank analyses show no difference between the two treatment groups for either measure.

The 8-point NIAID Ordinal Assessment used in this study follows the original version used in the Adaptive COVID-19 Treatment Trial where death = 1. This scale was later updated to follow the direction of the World Health Organization Ordinal Scale for Clinical Improvement (where death = 8).[28,29]

Primary and secondary objectives

The primary objective of the study was to assess the number of VFD during treatment with LY3127804. The majority of patients in both treatment arms did not require IMV and achieved 28 VFD (Table 2). Only 4 patients (8.3%) in the placebo group and 8 patients (17.0%) in the LY3127804 group required IMV. Therefore, there was no benefit of LY3127804 over placebo (*P*-value .932), and the primary endpoint of the study was not met.

There was also no evident benefit of LY3127804 over placebo for any of the secondary outcomes of NIAID Ordinal Assessment, respiratory failure-free survival, all-cause mortality, or length of hospital stay (Table 2). The NIAID Ordinal Assessment over time was broken down into categories of death (NIAID score = 1), invasive mechanical ventilation/ECMO (NIAID score = 2), requiring O_2 or medical care (NIAID scores = 3-5), and not requiring O_2 nor medical care (NIAID scores = 6-8). There were no differences in the proportion of study participants in each of these categories between the LY3127804 treatment group and placebo group over the 28-day study period (Figure 1).

Safety

There were no safety findings that contributed to the termination of the study. An overview of the adverse event data is given in Table 3. There was only one study discontinuation due to an adverse event, which occurred in the placebo group. The most common treatment emergent adverse events (TEAE) were (in order of decreasing frequency) constipation, anxiety, respiratory failure, hypokalaemia, and insomnia. Although the rates of TEAE in the two treatment groups were similar, there were more SAE reported in the LY3127804 group (12.8% vs 4.2% in placebo group; Table 3). Included among the SAE experienced by patients in the LY3127804 treatment group were atrial fibrillation (4.3%) and cardiac arrest (2.1%), as well as sepsis (2.1%), pneumothorax (2.1%), and bacterial pneumonia (2.1%).

Discussion

The purpose of this study was to determine whether LY3127804 could prevent the progression of pulmonary symptoms in patients after hospital admission with pneumonia and presumed or confirmed COVID-19, measured as the number of VFDs.

These patients were severely ill with COVID-19 pneumonia, as evidenced by markedly elevated C-reactive protein and IL-6 levels at baseline. Although there was improvement in these inflammation biomarkers prior to discharge on Day 28, they remained above normal. Levels of D-dimer, a biomarker of coagulation activation, were elevated at baseline and remained elevated throughout the study, consistent with ongoing risk of venous thrombosis, a known complication of COVID-19 pneumonia. While more patients were diabetic and hypertensive in the placebo-treated group, this did not lead to worse outcomes for that group compared with the LY3127804-treated patients.

Following an interim analysis to assess study futility, it was determined that LY3127804 provided no benefit to the primary outcome compared with placebo and the study was terminated early. This outcome also would have been achieved if the primary end point had been based on NIAID Ordinal Assessment or length of hospitalization rather than VFD, as was the case in other studies with similar patient populations.[12,16,17] Although there were differences in the use rates of potentially therapeutic concomitant medications between treatment groups, no conclusion about their effects can be made because they were administered at the discretion of the investigators, not randomly assigned.

There were no safety findings that contributed to the termination of the study. The only study discontinuation due to an adverse event occurred in the placebo group. However, there were a numerically greater number of SAEs observed in the LY3127804 group.

This study was initiated during the early weeks of the COVID-19 pandemic in the US and so was designed with ease of implementation for sites in mind. Additional undue burden on site personnel was avoided (for example, by limiting sampling from patients and not requiring a positive SARS-CoV-2 test at baseline), and electronic consent was used to accommodate for the constraints of personal protection equipment and access to patients in an intensive care unit. The design was also updated following feedback from clinical sites and the FDA. Information from investigators about the baseline oxygen saturation of admitted patients resulted in an increased SpO_2 rate in the inclusion criteria from 93% to 95%, and many exclusion criteria were removed, and additional concomitant therapies permitted, to allow patients with the greatest need to be enrolled in the study.

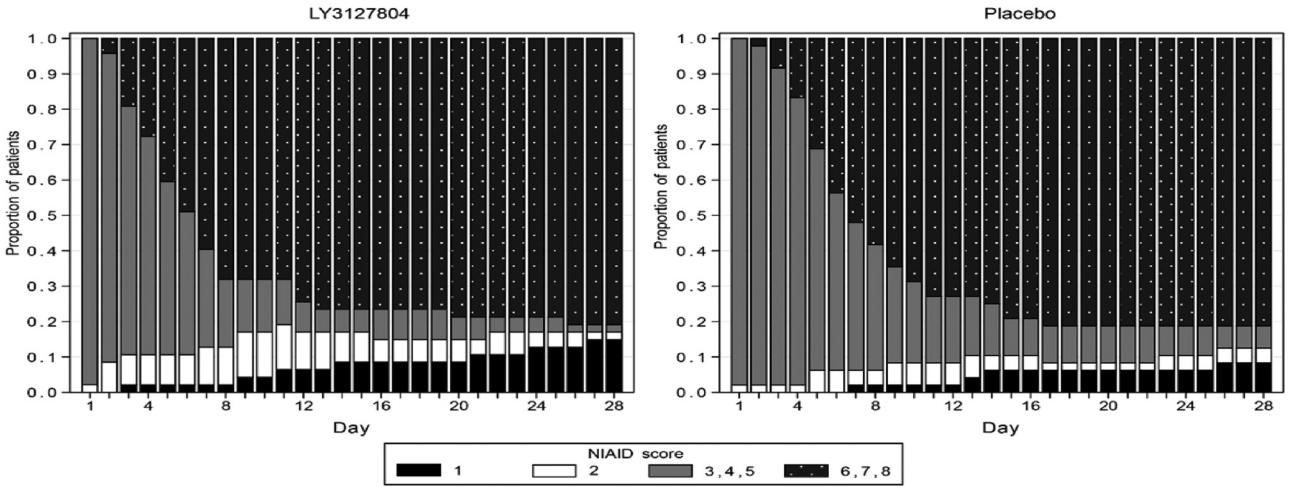

Figure 1. NIAID Ordinal Assessment Category over time by treatment group. Death (NIAID score = 1), invasive mechanical ventilation/ECMO (NIAID score = 2), requiring O_2 or medical care (NIAID scores = 3, 4, 5), and not requiring O_2 nor medical care (NIAID scores = 6, 7, 8).
Abbreviation: NIAID, National Institute of Allergy and Infectious Diseases.

Table 3. Safety.

	Placebo IV N = 48	LY3127804 IV 20 mg/mL N = 47
TEAE, n (%)[a]	31 (64.6)	33 (70.2)
SAE, n (%)	2 (4.2)	6 (12.8)
Discontinuations due to AE, n (%)	1 (2.1)	0
Most common TEAEs, n (%) (decreasing frequency[b])		
Constipation	7 (14.6)	6 (12.8)
Anxiety	6 (12.5)	4 (8.5)
Respiratory failure	5 (10.4)	4 (8.5)
Hypokalaemia	3 (6.3)	6 (12.8)
Insomnia	3 (6.3)	5 (10.6)

Abbreviations: AE, adverse event; IV, intravenous therapy; N, number of patients; SAE, serious adverse event; TEAE, treatment emergent adverse event.
[a]n (%) is the number (percentage) of subjects with at least one AE of the particular category.
[b]Most common TEAEs: as percentage of total population.

When this study was designed, it was assumed that progression of COVID-19 resulted in ARDS. It is now understood that COVID-19-associated ARDS may differ from the typical presentation.[6-8] This may be the reason why IMV rates in study participants were much lower than anticipated (which may have affected the analysis of LY3127804 efficacy as the primary outcome measure was VFD) as the majority of patients achieved 28 VFD. The fact that the study participants experienced a lower rate of IMV than expected could have contributed to the failure of the study.

Although all but one patient tested positive for SARS-CoV-2, due to the timing and availability of testing relative to the onset of symptoms no data on viral load at the time of study drug administration was available. In order to prevent undue burden on site personnel, only thyroid function and COVID-19 panel were assessed over and above standard testing; no biomarker data relating to Ang2 or LY3127804 were collected. Therefore, this study was unable to answer key scientific questions, such as whether Ang2 levels were elevated in patients with COVID-19 or whether the dose of LY3127804 was sufficient for target saturation.

In conclusion, interim analysis showed that LY3127804 did not increase the number of VFD compared to placebo in patients hospitalized with pneumonia and presumed or confirmed COVID-19, and the study was terminated after 95 patients were randomized.

Acknowledgements

The authors thank the participants, caregivers, and investigators. The authors would like to acknowledge Dr Sudhakar Chintharlapalli, who was the Ang2 teams' Biology scientific leader while at Eli Lilly and Company and who provided the biological rationale and physiological context for the use of Ang2 as a potential therapy for COVID-related pneumonia. The authors would like to thank Dr Zach Neeb for his contributions to the initial conceptual discussion and clinical approach to evaluating the use of Ang2 as a potential therapy for COVID-related pneumonia, including the choice of clinical status scale. We also acknowledge Catherine Lynch of Eli Lilly and Company for assistance with manuscript preparation and process support.

Author contribution(s)

Rosie S. Jones: Data curation; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing.

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Amparo de la Peña: Conceptualization; Investigation; Methodology; Writing – review & editing.
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Robert J. Schott: Conceptualization; Investigation; Methodology; Writing – review & editing.

Data Sharing Statement

Lilly provides access to all individual participant data collected during the trial, after anonymization. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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Supplemental Material

Supplemental material for this article is available online.

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