Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2029849

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Supplementary Methods

RT-PCR for SARS-CoV-2

In brief, RT-PCR for detection of SARS-CoV-2 was performed on nasopharyngeal swabs collected in sterile viral transport media using the materials, extraction method, and RT-PCR protocol described in the "Lilly SARS-CoV-2 Assay EUA Summary" published on the US Food and Drug Administration website (https://www.fda.gov/media/140543/download). The SARS-CoV-2 specific primers "N1" and "N2" target different sequences of the SARS-CoV-2 nucleocapsid N gene, and are co-amplified with a human internal control target, RNase P, hereafter referred to as "RP," for 45 cycles of PCR. Primer and probe sequences are available in the "Lilly SARS-CoV-2 Assay EUA Summary" and were obtained from Integrated DNA Technologies (IDT, San Jose, CA).

RT-PCR results were interpreted as follows. A clinical sample was "positive" for detection of SARS-CoV-2 if either or both of the SARS-CoV-2 specific N1 and N2 targets showed clear and unambiguous amplification with a cycle threshold (Ct) determined. A clinical sample was "negative" for detection of SARS-CoV-2 if neither of the N1 or N2 targets showed amplification, while the internal human control RP target showed clear and unambiguous amplification. A clinical sample was "invalid" if all three targets showed no amplification. Viral presence or absence and any quantitative determination was not scored for "invalid" samples. All amplification curves were reviewed by a board certified pathologist (AS, GJO) who were blinded to treatment assignment.

Determination of Viral Clearance and Time To Viral Clearance

For qualitative endpoints in the trial (viral clearance yes/no, time to viral clearance) the qualitative determination of "positive"/"negative" was used, as described above. SARS-CoV-2 clearance is defined as 2 consecutive negative RT-PCR tests for the SARS-CoV-2 virus as previously described. The date of viral clearance was defined as the earliest date of the 2 consecutive negative tests.

Quantitation of RT-PCR Results

For quantitative endpoints in the trial what we refer to as "viral load" was derived using the Ct values for the N1 target. If a clinical sample was positive per the diagnostic criteria above with only N2, and no Ct determined for N1, the N2 Ct value was used instead. The (log base 10) viral load was calculated from the Ct value according to the following formula:

Log viral load = (45-Ct)/log210

For the purposes of this calculation, qualitatively negative RT-PCR results for SARS-CoV-2 were assigned a Ct value of 45 for N1.

Two Ct values will be provided on 2 different genes: N1 and N2. N1 will be used as the primary measure; N2 will only be used when the Ct value for N1 is not available.

For Figures 2a and 2b, for any sample with a positive CoV-2 test result, an additional normalization step was taken to reduce pre-analytical variability in the viral load measurements. The N1 Ct value for any positive sample in these treatment arms (or N2 Ct value if N1 was not available as previously described) was subtracted by the RP Ct value for that sample minus 26.17:

N1/N2 Ct value for that sample – [(corresponding RP Ct value for that sample) – 26.17)] = Normalized N1/N2 Ct value

The correction factor of 26.17 is a historical average value of RP Ct for this assay, and was used here to normalize N1/N2 “viral load” calculations to RP.

Following this correction, the RP-normalized log “viral load” was then calculated as follows:

Log viral load = (45 - Normalized N1/N2 Ct value)/ log210

LY-CoV555 Dose Justification

The doses of LY-CoV555 studied in BLAZE-1 were initially selected for the first-in-human dose-escalation study in hospitalized patients with COVID-19 illness. The starting dose of 700 mg was projected to be a maximally efficacious therapeutic dose to reduce viral load. In the pandemic mindset of "leaving no one behind" for this patient population, we included doses up to ten-fold higher than the projected maximally efficacious dose to explore a wide drug exposure-response range, to mitigate translational uncertainty in the model predicted pharmacokinetics (PK) and e pharmacodynamics (PD), and to establish the safety and tolerability profiles of LY-CoV555.

Specifically, LY-CoV555 dose was predicted using 2 different but complementary modeling approaches. The first approach employs an adaptation of a SARS-CoV-2 viral dynamic model of viral clearance and the second approach employs a physiologically-based PK (PBPK) model of monoclonal antibody that was able to predict drug concentration in the target tissue, i.e., in the lung interstitial space.

Pharmacodynamic model of viral clearance

A SARS-COV-2 viral dynamic model was developed based on published literature based on data from patients with COVID-19 during in the early stage of the pandemic[1]. The model assumes that the drug concentration in the lung tissue binds the free virus and prevents infection of target cells using a maximum effect model that incorporated an IC50 potency from in vitro live SARS-COV-2 virus neutralization assay. A wide range of doses was evaluated using the model and these in silico simulations demonstrated that an intravenous dose of 700 mg or greater would result in rapid maximum viral clearance.

Physiologically-based pharmacokinetic model of monoclonal antibody

A PBPK model was developed based on published literature that incorporated monoclonal antibody distribution kinetics in humans[2]. The criteria for dose selection was to maintain lung interstitial concentrations at or above the in vitro IC90 of viral neutralization in 90% of the patient population for up to 28 days post-dose administration.

Taking together, both methods predicted that a dose of 700 mg is expected to achieve maximum reduction in viral load in the shortest time from onset of symptoms and have a sustained concentration above in vitro IC90 of viral cell-entry neutralization in at least 90% of the patient population for at least 4

weeks. As LY-CoV555 is expected to have low risk of adverse events for this monoclonal antibody that does not bind to an endogenous target, the maximum dose of 7000 mg was selected to mitigate the risk of underdosing patients, considering the uncertainty in clinical translation of PK and viral dynamics in the early stage of drug development.

Symptom Questionnaire

Questionnaire obtained by: Lilly	Study ID J2W-MC-PYAB	Subject Number	Visit/Cycle Number	**Signature of Individual Completing Form**
	Investigator Number	Page 1 of 2		**Date Signed by Individual Completing Form**

1. Assessment Date: _____ (DD/MMM/YYYY)

2. Cough
○ Yes
○ Mild
○ Moderate
○ Severe
○ No (Absent)

3. Shortness of breath
○ Yes
○ Mild
○ Moderate
○ Severe
○ No (Absent)

4. Feeling feverish
○ Yes
○ Mild
○ Moderate
○ Severe
○ No (Absent)

5. Fatigue
○ Yes
○ Mild
○ Moderate
○ Severe
○ No (Absent)

6. Body aches and pain
○ Yes
○ Mild
○ Moderate
○ Severe
○ No (Absent)

7. Sore throat
○ Yes
○ Mild
○ Moderate
○ *Severe*

8. Chills
- ○ Yes
  - ○ Mild
  - ○ Moderate
  - ○ Severe
- ○ No (Absent)

9. Loss of appetite
- ○ Yes
  - ○ Mild
  - ○ Moderate
  - ○ Severe
- ○ No (Absent)

10. Headache
- ○ Yes
  - ○ Mild
  - ○ Moderate
  - ○ Severe
- ○ No (Absent)

11. Loss of taste
- ○ Yes
- ○ No

12. Loss of smell
- ○ Yes
- ○ No

13. Overall, how bad are your symptoms TODAY (check one)?
- ○ No symptoms
- ○ Mild
- ○ Moderate
- ○ Severe
- ○ Very severe

14. Overall, how is your general physical health TODAY (check one)?
- ○ Poor
- ○ Fair
- ○ Good
- ○ Very good
- ○ Excellent

15. Have you returned to your usual (pre-COVID) health today (check one)?
- ○ Yes
- ○ No

Supplementary Figures

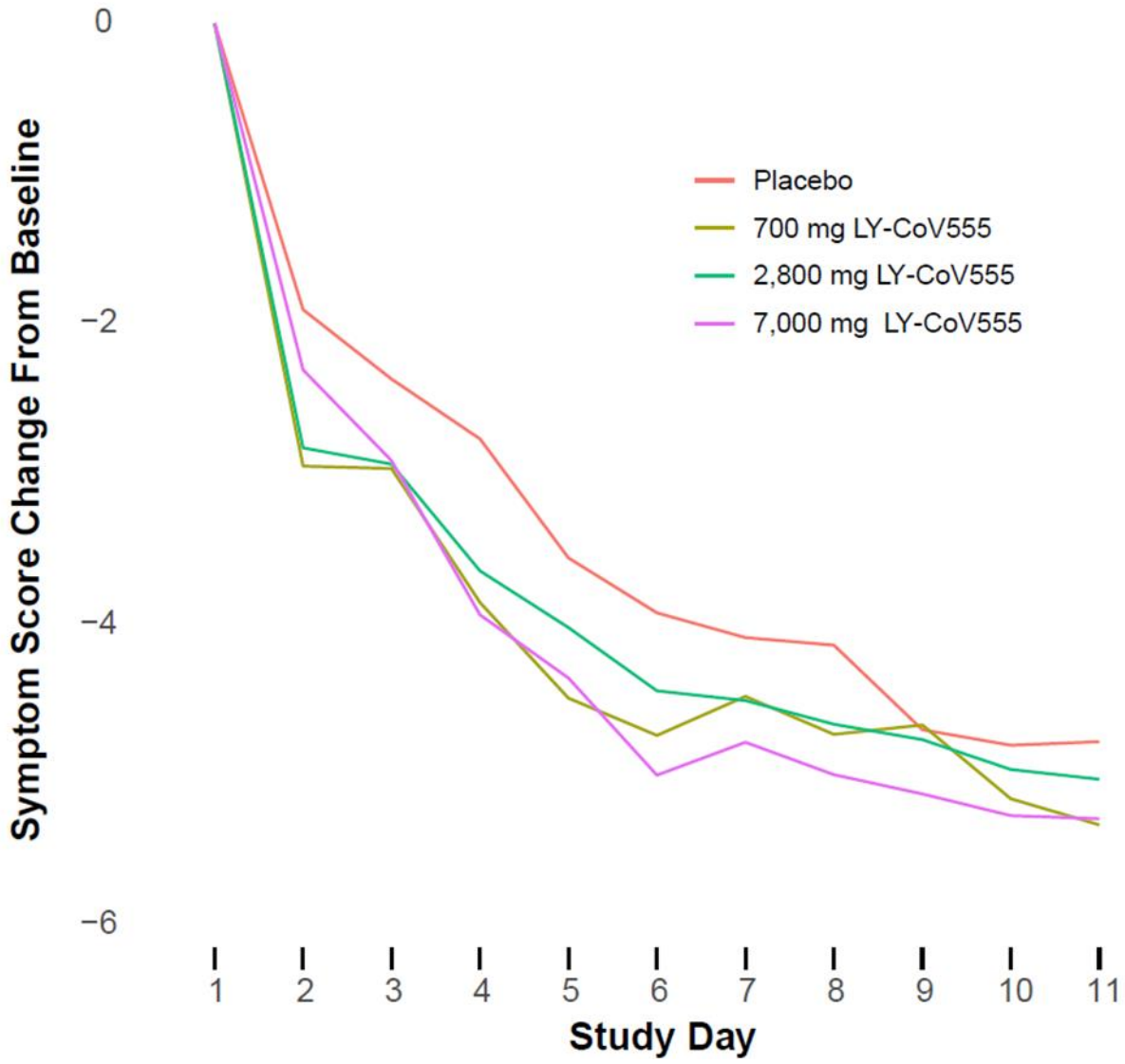

Figure S1: Symptom score (change from baseline) for placebo and each LY-CoV555 dose

References

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