16 March 2021
EMA/177113/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 5(3) of Regulation (EC) No 726/2004

Eli Lilly and Company Limited use of bamlanivimab and etesevimab for the treatment of COVID-19

INN/active substance(s): bamlanivimab and etesevimab

Procedure number: EMEA/H/A-5(3)/1502

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. Information on the procedure

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus is the causative agent of coronavirus disease 2019 (COVID-19). Early treatment of patients with confirmed COVID-19 presenting only mild symptoms can reduce the number of patients that progress to more severe disease and require hospitalisation or admittance to ICU.

The European Medicines Agency (EMA) is aware of several therapeutic candidates with putative antiviral action which are currently in development for the treatment of these patients.

Amongst those treatments, LY-CoV555 or bamlanivimab, a neutralizing monoclonal antibody, has been associated with a decrease in viral load and the frequency of hospitalisations or emergency department visits among outpatients with COVID-19. Bamlanivimab was evaluated against placebo in a phase 2 trial[1], for quantitative virologic end points and clinical outcomes on outpatients with recently diagnosed COVID-19 without need of supplemental oxygen.

In addition, in more recent results[2] the effects of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate Covid-19 were presented. The treatment with a combination of bamlanivimab and etesevimab significantly decreased SARS-CoV-2 viral load at day 11 compared with placebo (between-group difference, −0.57 [95% CI, −1.00 to −0.14], $P = 0.01$). Moreover, in latest information[3], bamlanivimab 2800 mg and etesevimab 2800 mg together reduced COVID-19-related hospitalisations and deaths in high-risk patients recently diagnosed with Covid-19 (primary endpoint of Phase 3 BLAZE-1 trial). Across 1,035 patients, there were 11 events (2.1 %) in patients taking therapy and 36 events (7.0 %) in patients taking placebo, representing a 70 percent risk reduction (p= 0.0004).

These results are of great relevance and their application in the clinical setting before a formal authorisation is considered important in view of the current pandemic situation. In that respect, currently available information on bamlanivimab and etesevimab are of significant interest with a view to supporting national decisions on their potential conditions of use.

On 8 February the Executive Director of the Agency triggered a procedure under Article 5(3) of Regulation (EC) No 726/2004, and requested the CHMP to give a scientific opinion on the currently available quality, preclinical and clinical data on the potential use of bamlanivimab and etesevimab for the treatment of confirmed COVID-19 in patients that do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19.

2. Scientific discussion

2.1. Introduction

Bamlanivimab is a neutralizing immunoglobulin (IgG)-1 monoclonal antibody (mAb) to the Spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that is being evaluated for treatment and prophylaxis for COVID-19. Viral entry into host cells involves the S protein attachment through the receptor binding domain (RBD) to the human angiotensin-converting enzyme 2 (ACE2) receptor, enabling sufficient proximity for the virus to fuse with the target cell membrane. Bamlanivimab blocks binding of the RBD domain to the ACE2 receptor and thus inhibits infection.

[1] https://www.nejm.org/doi/pdf/10.1056/NEJMoa2029849?articleTools=true
[2] https://jamanetwork.com/journals/jama/fullarticle/2775647
[3] https://investor.lilly.com/news-releases/news-release-details/new-data-show-treatment-lillys-neutralizing-antibodies

Like bamlanivimab, etesevimab is a fully human IgG1 antibody that shows potent neutralization of live virus *in vitro*, high binding affinity to the viral S protein, and will be manufactured employing a similar Chemistry, Manufacturing, and Control (CMC) strategy to bamlanivimab. Etesevimab has abrogated fraction crystallizable (Fc) effector function due to the engineered LALA (L234A, L235A) mutation.

Bamlanivimab and etesevimab bind different but overlapping epitopes in the RBD region of the S protein. Thus, they have the potential to be combined with each other. Studies with other antiviral mAbs have shown that both monotherapies and combination therapies can be effective in neutralizing viral pathogens (Johnson et al. 1997[4]; Pelegrin et al. 2015[5]; Mulangu et al. 2019[6]). Lilly is examining monotherapy (for bamlanivimab) and combination therapies *in vitro* and *in vivo* to determine their efficacy in neutralizing the virus and emergence of resistant variants.

Bamlanivimab, a neutralizing monoclonal antibody, has been associated with a decrease in viral load and the frequency of hospitalisations or emergency department visits among outpatients with COVID-19. LY-CoV555 was evaluated against placebo in a phase 2 trial, for quantitative virologic end points and clinical outcomes on outpatients with recently diagnosed COVID-19 without need of supplemental oxygen.

In addition, in more recent results the effects of bamlanivimab (LY-CoV555) as monotherapy or in combination with etesevimab (LY-CoV016) on viral load in patients with mild to moderate Covid-19 were presented. The treatment with a combination of bamlanivimab and etesevimab decreased SARS-CoV-2 viral load at day 11 compared with placebo (between-group difference, −0.57 [95% CI, −1.00 to −0.14], $P = 0.01$). Moreover, in latest information, bamlanivimab (LY-CoV555) 2800 mg and etesevimab (LY-CoV016) 2800 mg together reduced COVID-19-related hospitalisations and deaths in high-risk patients recently diagnosed with Covid-19 (primary endpoint of Phase 3 BLAZE-1 trial). Across 1,035 patients, there were 11 events (2.1 %) in patients taking therapy and 36 events (7.0 %) in patients taking placebo, representing a 70 percent risk reduction (p= 0.0004).

2.2. Clinical aspects

The currently proposed indication *"treatment of confirmed COVID-19 in patients 12 years old and over that do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19"* is supported by data from Study PYAB (BLAZE-1), both for the monotherapy and combination therapy.

Table 1 – Overview of key efficacy data submitted

Study id and design / reference	**Key objectives / endpoints**	**Population**	**Inclusion/ exclusion criteria**	**Treatment**	**Main efficacy results**
Therapeutic indication: "treatment of confirmed COVID-19 in patients 12 years old and over that do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19"					
BLAZE-1/PYAB	Primary endpoint:	N= 577	female and male patients,	LY Mono: Single dose,	primary endpoint:

[4] Johnson, J. E., Schnell, M. J., Buonocore, L., and Rose, J. K. (1997). Specific targeting to CD41 cells of recombinant vesicular stomatitis viruses encoding human immunodeficiency virus envelope proteins. J. Virol. 71 (7), 5060–5068.
[5] Pelegrin M, Naranjo-Gomez M, Piechaczyk M. Antiviral Monoclonal Antibodies: Can They Be More Than Simple Neutralizing Agents? Trends Microbiol. 2015 Oct;23(10):653-665. doi: 10.1016/j.tim.2015.07.005. PMID: 26433697; PMCID: PMC7127033.
[6] Mulangu S, Dodd LE, Davey RT Jr, Tshiani Mbaya O, Proschan M, Mukadi D, Lusakibanza Manzo M, Nzolo D, Tshomba Oloma A, Ibanda A, Ali R, Coulibaly S, Levine AC, Grais R, Diaz J, Lane HC, Muyembe-Tamfum JJ; PALM Writing Group, Sivahera B, Camara M, Kojan R, Walker R, Dighero-Kemp B, Cao H, Mukumbayi P, Mbala-Kingebeni P, Ahuka S, Albert S, Bonnett T, Crozier I, Duvenhage M, Proffitt C, Teitelbaum M, Moench T, Aboulhab J, Barrett K, Cahill K, Cone K, Eckes R, Hensley L, Herpin B, Higgs E, Ledgerwood J, Pierson J, Smolskis M, Sow Y, Tierney J, Sivapalasingam S, Holman W, Gettinger N, Vallée D, Nordwall J; PALM Consortium Study Team. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. N Engl J Med. 2019 Dec 12;381(24):2293-2303. doi: 10.1056/NEJMoa1910993. Epub 2019 Nov 27. PMID: 31774950.

Phase-2 portion of the trial / Randomized, Double-blind, Placebo-Controlled (data base lock: 06 October 2020)	change from baseline to Day 11 (+/- 4 days) in SARS-COV-2 viral load <u>Key secondary endpoints:</u> 1. proportion of subjects with COVID-19 related hospitalization emergency room visit 2. symptom resolution (Day1 to Day 11)		aged ≥ 18 years, *Non*-hospitalised, mild-moderate COVID-19,	I.V. Treatment arms: Arm1: Placebo (n=156) Arm 2: 7000 mg (n=101) Arm:3 2800 mg (n=100) Arm:4 700mg (n=101) <u>LY Combo</u>: Arm 6: etesevimab 2800 mg + bamlanivimab 2800 mg (N=112), single dose i.v.	change from baseline to Day 11 in log10 viral load **was not met** for monotherapy but for combination therapy <u>secondary endpoint</u> 1. COVID-19 related hospitalization or ER: 5.8 % Placebo vs 1.6 % LY Mono vs 0.9% LY combo 2. lower time-weighted average symptom score from Day 1 to Day 11 for all LY Mono arms and LY combo arm compared to placebo
BLAZE-1/PYAB **Phase-3** portion of the trial / Randomized, Double-blind, Placebo-Controlled (data base lock: 20 January 2021)	<u>Primary endpoint:</u> Proportion of participants who experience COVID-19 related hospitalisation or death from any cause by day 29 <u>Key secondary endpoints:</u> 1. Viral load change from baseline to Day 7 2. Persistently High Viral Load (Day 7 viral load ≥ 5.27)	N=1035	Non-hospitalised, mild-moderate COVID-19, ≥12 years, at least 1 risk factor for developing severe COVID-19 disease	etesevimab 2800 mg + bamlanivimab 2800 mg, single dose, i.v.	<u>Primary endpoint:</u> 36 events on PBO vs. 11 on LY combo (p=0.0004) <u>Key secondary endpoints:</u> 1. LY combo improved viral load change from baseline to Day 7 compared to PBO (p<0.0001)

	3. COVID-19 related hospitalization, ER visits, or deaths by any cause 4. Time to sustained symptom resolution – 2 consecutive assessments				2. 34.0% of subjects under PBO vs 10.6% of subjects under LY combo (p<0.0001). 3. 37 events on PBO vs. 12 on LY combo (p=0.0005) 4. 9 days for PBO vs 8 days for LY combo (p=0.007)

2.2.1. Efficacy

2.2.1.1. Clinical Study

PYAB (BLAZE-1) is a randomized, double-blind, placebo-controlled, phase 2/3 study conducted to evaluate the efficacy and safety of bamlanivimab and etesevimab in participants with mild to moderate COVID-19 illness (J2W-MC-PYAB, also termed PYAB or BLAZE-1).

PYAB was initially planned as a Phase 2, placebo-controlled, double-blind, randomized single-dose study in participants with mild to moderate COVID-19 illness and later repeatedly amended to include further arms with different objectives.

The initial study protocol contained the single treatment arms and placebo. Combination arms (arms 6 & 7) were introduced with Protocol Amendment B. The initial statistical analysis plan was amended to reflect combination treatment arms in line with the protocol.

Amendment C introduced to study the combination therapy in a population with risk factors for severe COVID-19 illness (Arms 7 (combi) and 8 (corresponding placebo)). The new study arms were planned as phase 2 study with PHVL (persistent high viral load) on Day 7 as primary endpoint and a small sample size of 125 participants per treatment arm. Amendment D widened the inclusion criteria for the "high risk" population in treatment Arms 7 (combi) and 8 (corresponding placebo). With Amendment E, the study was changed to support a potential marketing authorisation. This includes changes to the sample size, objectives and endpoints. Proportion of participants who experience COVID-19 related hospitalization (≥24 hours of acute care) or death by Day 22 was added as primary endpoint. Amendment F was based on FDA feedback. Adolescent participants with high risk for severe COVID-19 were included in treatment Arms 7 (combi) and 8 (corresponding placebo). Clinical endpoints were reverted to Day 29. With Amendment G, new Arms 9 – 11 were introduced. Treatment arm 9 will explore a lower dose level of the combination of LY3819253 and LY3832479 (700 mg + 1400 mg). Treatment arm 10 will provide a bridge to the existing placebo arms. Treatment arm 11 is an open-label sub-study comprised of two cohorts to evaluate a faster IV infusion rate of the combination of LY3819253 and LY3832479. These arms are not part of the received data package. Only with Amendment I the study was relabelled from Phase 2 to Phase 2/3 study. This amendment addresses changes in response to discussions with the FDA to enable independent confirmation of the safety and efficacy of LY3819253 in combination with LY3832479 for the treatment of COVID-19. The decision

was made to remove treatment arms 10 and 11, and change the primary objective, statistical methods and sample size for treatment arms 7-9. PHVL was downgraded to a secondary endpoint. The sample size was increased to 450 participants per arm. The primary analysis was changed to a (frequentist) logistic regression model. With Amendment J, Arms 13 and 14 were added to study a lower dose of combination therapy (not part of the received data package). The sample size for arms 7-9 was increased to 500 participants per arm. Viral load (change from baseline to Day 7), PHVL, overall clinical status (primary endpoint + ER visits) and time to sustained symptom resolution were added as key secondary endpoints. By update of inclusion/exclusion criteria, pregnant females became eligible in the study.

An overview of the study design is provided below.

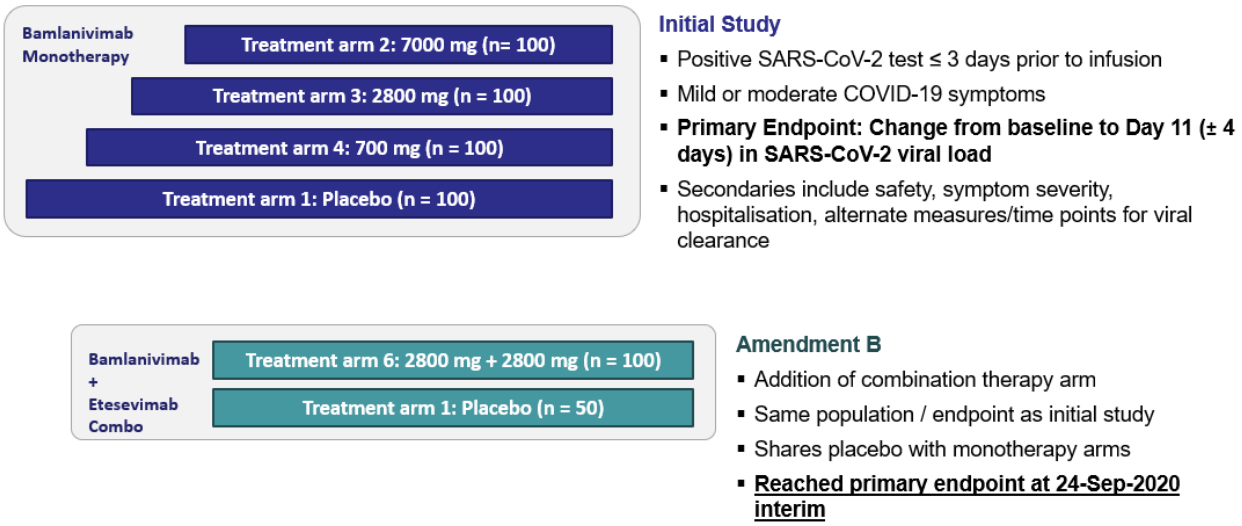


Figure 1 – Schematic of treatment arms 1 through 4 and 6 of Study PYAB

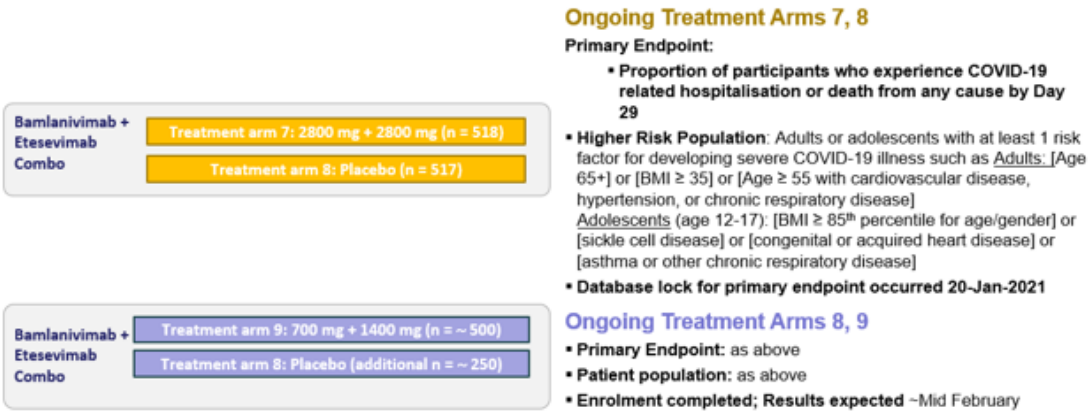


Figure 2 - Schematic of treatment arms 7 through 9 of study PYAB

Primary and secondary endpoints

Phase-2 portion of the study (Treatment Arms 1 through 4 and 6 of Study PYAB)

Primary endpoint:

- Change from baseline to day 11 (±4 days) in SARS-CoV-2 viral load

Secondary endpoints:

- Safety assessments such as AEs and SAEs
- Change from baseline to day 11 (±4 days) in SARS-CoV-2 viral load among participants enrolled with ≤ 8 days of symptoms prior to randomization
- Time to symptom resolution
- Proportion of participants demonstrating symptom resolution via the symptom questionnaire on days 7, 11, 15 and 22
- Change in symptom score (total of ratings) from baseline to Days 7, 11, 15 and 22
- Time to symptom improvement
- Proportion of participants demonstrating symptom improvement via the symptom questionnaire on days 7, 11, 15 and 22
- Proportion of participants that achieve SARS-CoV2 clearance (days 7, 11, 15 and 22)
- Time to SARS-CoV-2 clearance
- SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 29
- Proportion (percentage) of participants who experience these events by Days 29, 60 and 85
    - COVID-19 related hospitalization (defined as ≥24 hours of acute care)
    - a COVID-19 related emergency room visit, or
    - death

The adequacy of choosing viral load reduction as the primary clinical endpoint for a phase-2 confirmatory study (treatment Arm 1 through 4) is still debatable, however, the secondary endpoints provided were considered appropriate for a phase-2 biomarker/safety study.

The primary endpoint for Treatment Arms 6 (LY combo) and 1 (placebo) was considered adequate for a phase-2 biomarker/safety study and supportive of the results on viral load seen in phase-3 part (key secondary endpoint).

<u>Phase-3 portion of the study (Treatment Arm 7 (bamlanivimab 2800 mg + etesevimab 2800 mg) through 9 (placebo)) of study PYAB</u>

Primary endpoint:

- COVID-19 related hospitalisation or death from any cause by day 29

Key secondary endpoints:

1) Viral load change from baseline to Day 7 (±2 days)
2) Persistently High Viral Load (Day 7 ± 2 days; viral load ≥5.27)
3) COVID-19 related hospitalization, ER visits, or deaths by any cause
4) Time to sustained symptom resolution – 2 consecutive assessments

CHMP considered that the chosen primary endpoint for the Phase-3 portion (Treatment Arm 7 (bamlanivimab 2800 mg + etesevimab 2800 mg), 8 (placebo)) and 9 (bamlanivimab 700 mg + etesevimab 1400 mg)) of study PYAB is an appropriate clinically relevant endpoint for a confirmatory study. Key secondary endpoints provided were also considered appropriate.

Patient population

The study included female and male patients, aged ≥ 18 years, who tested positive for SARS-COV-2 infection, were not hospitalized at the time of enrollment, had 1 or more mild or moderate COVID-19 symptoms and had samples collection for the first positive SARS-CoV-2 viral infection determination ≤3 days prior to the start of the infusion. Mild to moderate COVID-19 was defined per US Food and Drug Administration guidance and included symptoms such as fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, and shortness of breath with exertion. Investigators reviewed symptoms, risk factors, and other noninvasive inclusion and exclusion criteria prior to enrollment. Patient-reported race and ethnicity categories were collected as part of the demographic characteristics.

According to the latest protocol version (Amendment L), the following inclusion criteria were used in order to characterize the higher risk population that was included in the phase 3 portion of the study PYAB (treatment arms 7 and 8).

Participants were eligible to be included in the study only if the following criteria applied:

Are ≥ 18 years of age and satisfy at least one of the following at the time of screening

- Are pregnant
- Are ≥ 65 years of age
- Have a BMI ≥ 35
- Have chronic kidney disease
- Have type 1 or type 2 diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment, or
- Are ≥ 55 years of age AND have
    - cardiovascular disease, OR
    - hypertension, OR
    - chronic obstructive pulmonary disease or other chronic respiratory disease

Are 12-17 years of age (inclusive) AND satisfy at least one of the following at the time of screening

- Are pregnant
- Have a BMI ≥ 85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm
- Have sickle cell disease
- Have congenital or acquired heart disease

- Have neurodevelopmental disorders, for example, cerebral palsy
- Have a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)
- Have asthma or reactive airway or other chronic respiratory disease that requires daily medication for control
- Have type 1 or type 2 diabetes
- Have chronic kidney disease
- Have immunosuppressive disease, or
- Are currently receiving immunosuppressive treatment

Participants in Treatment Arms 7 and 8 represented a higher risk population and included solely adults and adolescents with at least 1 risk factor for developing severe COVID-19 disease. The inclusion criteria chosen to represent a population on higher risk for progression to severe COVID were considered appropriate by CHMP.

Treatment

Each patient received a single intravenous infusion of bamlanivimab or placebo monotherapy over approximately 1 hour. Bamlanivimab was administered to these patients in doses of 700 mg (101 patients), 2800 mg (107 patients), or 7000 mg (101 patients). Dose levels were fixed, and either bamlanivimab or placebo was administered within 3 days after positive results on SARS-CoV-2 testing.

No additional information on application of combination therapy (e.g. application in parallel vs one by one, duration of infusion, volume of infusion) was available based on the protocols submitted.

Randomization

Participants were to be stratified by duration since symptom onset to randomization (≤8 days versus >8 days). All eligible participants were to be randomized, initially following an equal allocation to treatment arms. Given the staggered start of the treatment arms, periodic adjustments to the allocation ratio, informed by planned interim analyses, were to be made in an effort to achieve an equal allocation across the treatment arms at the end of enrolment. As additional placebo participants were to be enrolled in both the Phase 2 part and the Phase 3 part, then the allocation ratio was changed accordingly.

CHMP considers the adaptation of randomization ratios over time critical as it might affect the comparability of arms. The Applicants rationale for the staggered entry in a Phase 2 dose finding study is endorsed. However, it is considered problematic for a confirmatory proof of efficacy. In both study parts (Phase 2 and Phase 3) additional arms which were to be compared to the same Placebo group were opened late. The size and direction of a potential bias due to non-concurrent controls is unknown and not fully quantifiable.

Blinding

The study was double-blind.

Sample Size

Arms 1-4 (monotherapy) and Arm 6 (combination therapy, Phase 2)

The initial planned sample size was to be approximately 400 participants equally allocated across four treatment arms. With Protocol Amendment b, which added a combination treatment arm (arm 6), the sample size was increased to 500 patients and additional placebo participants could be enrolled to ensure up to 50 concurrent placebo controls for each treatment arm 5-7.

A viral dynamic model was used to simulate viral loads over time for participants treated with bamlanivimab and placebo. This simulated population and Monte Carlo methods were used to estimate statistical power associated with the comparison of change from baseline to Day 11 (±4 days) in SARS-CoV-2 viral load between bamlanivimab and placebo. The mean log change from baseline to Day 11 for bamlanivimab and placebo in the simulated population were approximately -4.38 and -3.48 (standard deviation 1.9), respectively, representing an average of 87% viral load reduction. Given these assumptions, an assumed sample size of 100 participants per arm provides approximately 91% power to test superiority of bamlanivimab vs placebo in effect on viral load, as measured by change from baseline to Day 11 (± 4 days), at the two-sided 0.05 alpha level.

Arms 7-9 (combination therapy, Phase 3)

Participants in treatment arms 7-9 were to be adults and adolescents with at least 1 risk factor for developing severe COVID-19 illness (see age specific inclusion criteria). There is no set sample size for the adolescent participants. The planned sample size for the primary comparison of treatment arms 7 and 8 was planned as approximately 1000 participants equally randomized to placebo or the combination of Bamlanivimab and Etesevimab.

The planned sample size for treatment arm 9 is approximately 500 participants. Since treatment arm 9 started enrolment after treatment arm 7, additional participants were to be enrolled in treatment arm 8 to ensure at least a 33% increase in placebo participants and adequate placebo control for the primary comparison of treatment arms 8 and 9.

Sample size justification was based on the endpoint of proportion of participants experiencing COVID-related hospitalization or death from any cause. A sample size of approximately 500 adult participants per treatment arm was to provide ≥ 90% power to demonstrate that Bamlanivimab in combination with Etesevimab is statistically significantly better than placebo, defined as odds ratio <1 in the proportion of participants experiencing a COVID-related hospitalization or death from any cause. This sample size calculation assumed a placebo event rate of 8.7% and a relative reduction of 60% for Bamlanivimab in combination with Etesevimab, which were informed from available data on hospitalization or death events.

Overall, the provided sample size considerations were considered acceptable by CHMP.

Statistical Methods

Four analysis sets were pre-specified: The "entered" set (all participants who sign the informed consent form), the "efficacy" set (all randomized participants who received study intervention and provided at least one post-baseline measure for the relevant endpoint; analysed according to randomized treatment), the "safety" set (all randomized participants who received study intervention; analysed according to treatment received), and the "PK" set (all randomized participants who received study intervention and have evaluable PK samples; analysed according to treatment received). The primary analysis set for efficacy and PD analyses was to be the efficacy set.

Unless otherwise specified, variables were to be analysed in the original scale on which they were measured. SARS-CoV-2 viral load data was to be evaluated on a $\log_{10}$ scale.

Primary Endpoint

Arms 1-4 and 6

The primary endpoint was change from baseline to Day 11 (± 4 days) in SARS-CoV-2 viral load. Statistical hypothesis testing for the primary endpoint was to be conducted using a mixed model for repeated measures (MMRM) with treatment group, baseline value, visit and treatment by visit interaction as fixed effects. An unstructured covariance matrix for within-patient errors was assumed with pre-specified fallback options in case of none-convergence. Least-squares (LS) means were to be used for the statistical comparison and 95% confidence intervals (CI) were to be reported.

This model was to be applied for all repeated measures variables. For all variables other than the primary endpoint the randomisation stratification factor was to be included. The symptom onset stratification factor was not to be included for the primary endpoint (log10 viral load) to avoid the collinearity with the baseline viral load.

Depending on the reasons for missing observations, this approach might not be reasonable. A justification for the MAR assumption and supplementary analyses were not provided. Robustness of results hence could not be assessed by CHMP.

Arms 7-9

The primary endpoint was to be the overall participant clinical status, measured by the proportion (percentage) of participants who experience COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death from any cause by Day 29. The primary analysis method was to be a logistic regression with a primary success criterion of one-sided alpha level 0.025.

Sufficient details for the primary analysis for Arms 7-9 were lacking. It was merely stated that a logistic regression model was to be used. Not all details could hence be assessed by CHMP.

Multiplicity control

According to the protocol, all hypothesis tests were to be 2-sided at an alpha level of 0.05 and no adjustment for multiplicity was to be performed in this study.

CHMP considers a type 1 error control per arm in principle acceptable for a phase 2 dose-finding, safety and/or proof-of-concept study but considers the lack of study-wise type 1 error control (i.e. error control over all treatment arms) very critical for a formal proof of efficacy. For the Phase 2 trial (with four treatment arms to be compared to one placebo arm) the *two-sided* study-wise type 1 error rate might be as high as 18.5% (ignoring the correlation between the treatment arms)

Multiplicity control (Arms 7-9)

A hierarchical multiple comparisons procedure was to be implemented, to control type I error in the primary endpoint analysis. All primary and key secondary endpoints within a dose were to be tested in the following sequential manner at a 1-sided 0.025 significance level:

1) proportion of participants who experience COVID-19 related hospitalization or death from any cause by Day 29
2) change from baseline to Day 7 (±2 days) in viral load
3) proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 (±2 days)

4) proportion of participants who experience COVID-19 related hospitalization, COVID-19 related emergency room visit, or Death from any cause

5) time to sustained symptom resolution

The hierarchical approach per treatment arm is endorsed by CHMP. However, no multiplicity control was foreseen over the two treatment arms in the Phase 3 part. This is not endorsed by CHMP for a confirmatory study and increases the *one-sided* study-wise type 1 error up to 4.9% (ignoring the correlation between the treatment arms).

Interim analyses

In the protocol it was planned that the ongoing study might be modified based on planned interim analyses. Based on the observed data at the time of the interim analyses, the study might

- suspend enrolment to a bamlanivimab treatment arm (or arms) demonstrating lack of efficacy, and/or
- initiate/expand enrolment to an additional/existing bamlanivimab treatment arm (or arms).

Monitoring of unblinded safety data (including AEs, SAEs, and selected laboratory measurements) was to occur throughout the study and was to be conducted by Assessment Committee (AC) members. Details of the unblinded safety reviews, including the frequency and approximate timing, were to be specified in the AC charter.

Periodic adjustments to the allocation ratio were to be made to achieve an equal allocation treatment arms at the conclusion of enrolment. Only the AC was authorized to evaluate unblinded interim analyses and safety analyses.

The AC was to initially review summary unblinded data after approximately 25% (100) participants have had an opportunity to reach Day 11. It was anticipated that subsequent interim analyses were to occur after approximately 50%, 75%, and all participants have had an opportunity to reach Day 11. Safety was to be evaluated at each of these interim analyses and benefit/risk of LY3819253 was to be assessed if needed.

An interim analysis was planned when approximately 40% participants in the 7000 mg arm have had an opportunity to reach Day 11. However, this analysis was to be combined with the approximately 50% interim analysis if possible. The pre-planned interim analysis at 40% of participants in the 7000 mg arm completing 11 days was planned to inform a potential modification to the PYAB study. Based on a Bayesian model either the 700 mg arm might have been dropped (in the case that the 700 mg Arm was not substantially better than Placebo or the 7000 mg Arm was substantially better than the 700 mg Arm, each with a high posterior probability) or additional 100 patients might have been enrolled to an existing or new arm (in the case that the 700 mg was substantially better than Placebo with a high posterior probability).

According to AC charter provided, the AC was primarily tasked in reviewing safety data with the following exception. Efficacy data was to be supplied at the single pre-specified IA time point mentioned above (when approximately 40% participants in the 7000 mg arm have had an opportunity to reach Day 11). Other IA were to contain only safety data. However, the AC could request efficacy data at any time to assess benefit/risk if necessary.

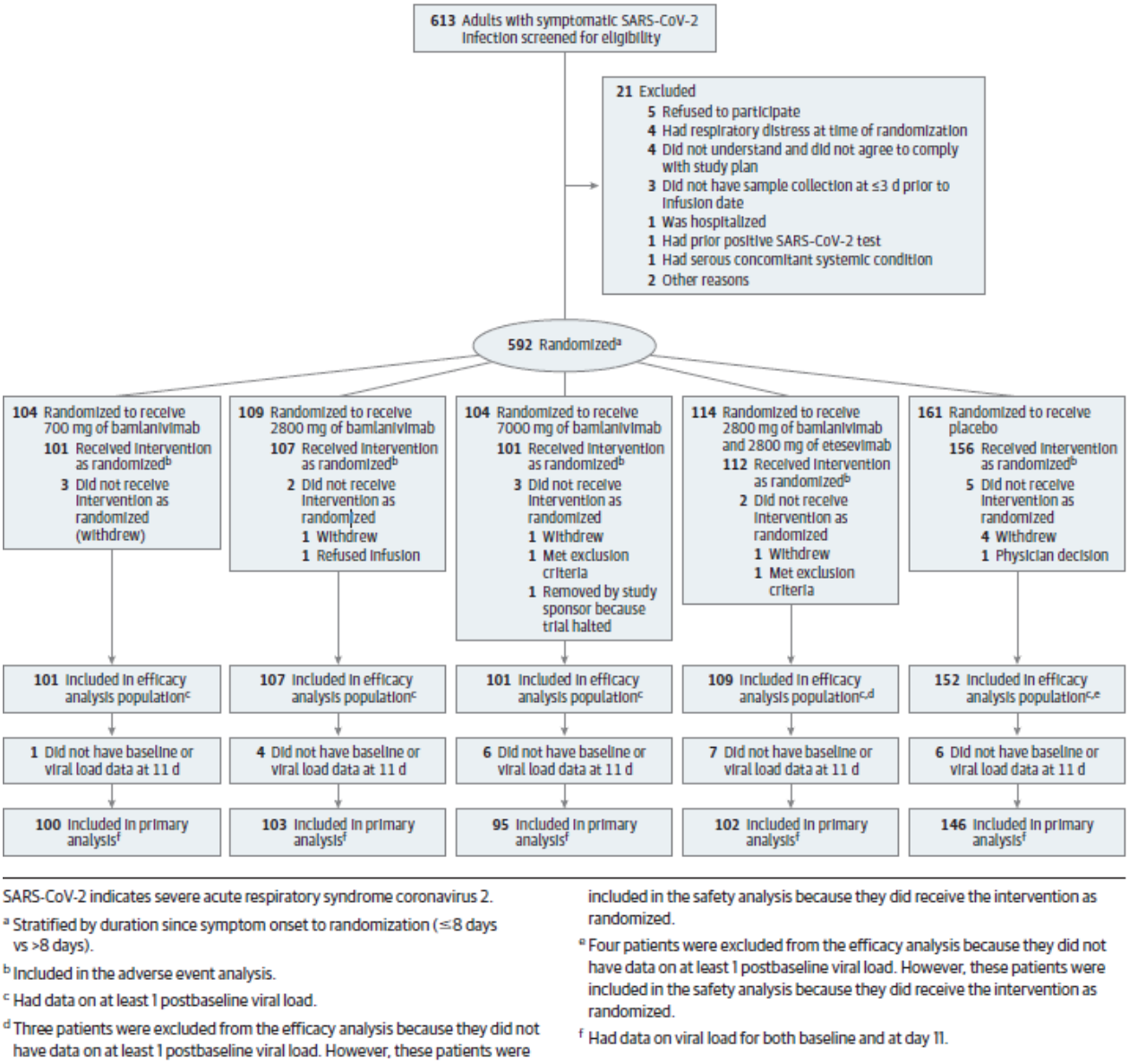
The interim analyses to evaluate the combination therapy were to occur after approximately 75, 150, and all participants have had an opportunity to reach Day 11. The last interim analysis with approximately all participants was to be conducted only if the optional Treatment Arm 7 was added per the sponsor decision.

Unblinded assessments of efficacy will be done separately for treatment arms 7 and 8, 8 and 9. For treatment arms 7 and 8, assessments were to begin when all participants for treatment arm 7 and concurrently enrolled treatment arm 8 completed the Day 29 visit. For treatment arms 8 and 9, assessments were to begin when all additional participants from treatment arm 8 and participants from treatment arm 9 completed the Day 29 visit.

Conduct of the study

The study protocol for the relevant study parts was amended 10 times. The provided protocols show a substantial number of extensive and critical changes in this complex study.

Patients' flow for the phase 2 portion of study PYAB



SARS-CoV-2 indicates severe acute respiratory syndrome coronavirus 2.

[a] Stratified by duration since symptom onset to randomization (≤8 days vs >8 days).

[b] Included in the adverse event analysis.

[c] Had data on at least 1 postbaseline viral load.

[d] Three patients were excluded from the efficacy analysis because they did not have data on at least 1 postbaseline viral load. However, these patients were included in the safety analysis because they did receive the intervention as randomized.

[e] Four patients were excluded from the efficacy analysis because they did not have data on at least 1 postbaseline viral load. However, these patients were included in the safety analysis because they did receive the intervention as randomized.

[f] Had data on viral load for both baseline and at day 11.

Figure 3 - Patients' flow (based on Gottlieb et al. 2021[7])

Baseline Demographics and Disease Characteristics

Baseline Demographics and Disease Characteristics from phase-2 portion of the study PYAB

Table 2 below summarizes key baseline demographics and disease characteristics from phase-2 portion of the study PYAB, treatment arms 1-4, and 6 (database lock 06 October 2020).

Table 2 - Baseline Demographics and Disease Characteristics for Treatment Arms 1-4, and 6 (Safety Population)

	PBO (N = 156)	700 mg LY (N = 101)	2800 mg LY (N = 107)	7000 mg LY (N = 101)	LY Mono[a] (N = 309)	LY Combo[b] (N = 112)
Female	85 (54.5)	63 (62.4)	51 (47.7)	58 (57.4)	172 (55.7)	58 (51.8)

[7] Gottlieb RL, Nirula A, Chen P, et al. Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. *JAMA.* 2021;325(7):632–644. doi:10.1001/jama.2021.0202

	PBO (N = 156)	700 mg LY (N = 101)	2800 mg LY (N = 107)	7000 mg LY (N = 101)	LY Mono[a] (N = 309)	LY Combo[b] (N = 112)
Hispanic or Latino	68 (43.6)	49 (48.5)	47 (43.9)	39 (38.6)	135 (43.7)	42 (37.5)
Black or African American	7 (4.6)	7 (6.9)	7 (6.7)	8 (8.0)	22 (7.2)	4 (3.6)
Age (median)	46.0	39.0	45.0	46.0	45.0	43.5
Age ≥65	23 (14.7)	11 (10.9)	8 (7.5)	14 (13.9)	33 (10.7)	13 (11.6)
BMI (mean)	30.1	30.5	30.3	29.4	30.1	28.8
40> BMI ≥30	63 (41.4)	34 (34.0)	50 (47.2)	28 (28.9)	112 (37.0)	33 (30.3)
BMI ≥40	9 (5.9)	11 (11.0)	6 (5.7)	7 (7.2)	24 (7.9)	7 (6.4)
High-Risk Status[c] for Severe COVID-19 Illness	105 (67.3)	74 (73.3)	78 (72.9)	63 (62.4)	215 (69.6)	67 (59.8)
Mild COVID-19	125 (80.1)	83 (82.2)	79 (73.8)	70 (69.3)	232 (75.1)	92 (82.1)
Moderate COVID-19	31 (19.9)	18 (17.8)	28 (26.2)	31 (30.7)	77 (24.9)	20 (17.9)
Duration of Symptoms (days, mean)	4.65	4.80	4.75	4.66	4.74	4.27
Duration of Symptoms ≤10 days	149 (95.5)	96 (95.0)	103 (96.3)	97 (96.0)	296 (95.8)	111 (99.1)
Viral Load (mean, CT value)[d]	23.8	23.8	24.5	23.4	23.9	22.7

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease 2019; CT = cycle threshold; LY = bamlanivimab; N = number of patients in the analysis population; PBO = placebo.

a LY Mono is pooled data from 700 mg bamlanivimab (Treatment Arm 2), 2800 mg bamlanivimab (Treatment Arm 3), and 7000 mg bamlanivimab (Treatment Arm 4).

b LY Combo is data from the 2800-mg bamlanivimab/2800-mg etesevimab group (Treatment Arm 6).

c Age ≥55 or BMI ≥30 or medical history event of interest.

d Efficacy Population.

Table 3 – Serostatus at baseline for Treatment Arms 1-4, and 6 (Safety Population)

	PBO (N = 156)	700 mg LY (N = 101)	2800 mg LY (N = 107)	7000 mg LY (N = 101)	LY Mono[a] (N = 309)	LY Combo[b] (N = 112)
Seropositive, n (%)	12 (7.7)	10 (9.9)	15 (14.0)	14 (13.9)	39 (12.6)	12 (10.7)
Seronegative, n (%)	142 (91.0)	90 (89.1)	91 (85.0)	86 (85.1)	267 (86.4)	96 (85.7)

Abbreviations: LY = bamlanivimab; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo.

a LY Mono is pooled data from 700 mg bamlanivimab (Treatment Arm 2), 2800 mg bamlanivimab (Treatment Arm 3), and 7000 mg bamlanivimab (Treatment Arm 4).

b LY Combo is data from the 2800-mg bamlanivimab/2800-mg etesevimab group (Treatment Arm 6).

Note: Serostatus at baseline is not available for all patients.

No adolescents were randomised in the Phase-2 portion of the trial.

Baseline Demographics and Disease Characteristics from phase-3 portion of the study PYAB

Figure 4 below summarises key baseline demographics and disease characteristics from phase-3 portion of the study PYAB, treatment arms 7 (LY combo) and 8 (placebo) (database lock 20 January 2021).

Figure 4 - Baseline Demographics and Disease Characteristics (Safety Population) for Treatment Arms 7 (LY combo) and 8 (placebo)

	Safety Population	
	Placebo (N=517)	**LY Combo** (N=518)
Female	259 (50.1%)	279 (53.9%)
Hispanic or Latino	155 (30.0%)	149 (28.8%)
Black or African American	39 (7.6%)	44 (8.6%)
Age (median)	56.0	57.0
Age ≥ 65	155 (30.0%)	168 (32.4%)
BMI (mean)	33.4	33.9
Mild COVID-19	403 (77.9%)	397 (76.6%)
Moderate COVID-19	114 (22.1%)	121 (23.4%)
Duration of symptoms (days, mean)	4.20	4.13
Viral load (mean, CT value, efficacy population)	23.97	23.98

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease 2019; CT = cycle threshold; LY Combo = 2800 mg bamlanivimab and 2800 mg etesevimab administered together; N = number of participants in the analysis population.

There were 11 adolescents randomised to Arms 7 and 8 of the trial (7 to placebo and 4 to bamlanivimab and etesevimab administered together). These patients ranged between 12 and 17 years of age.

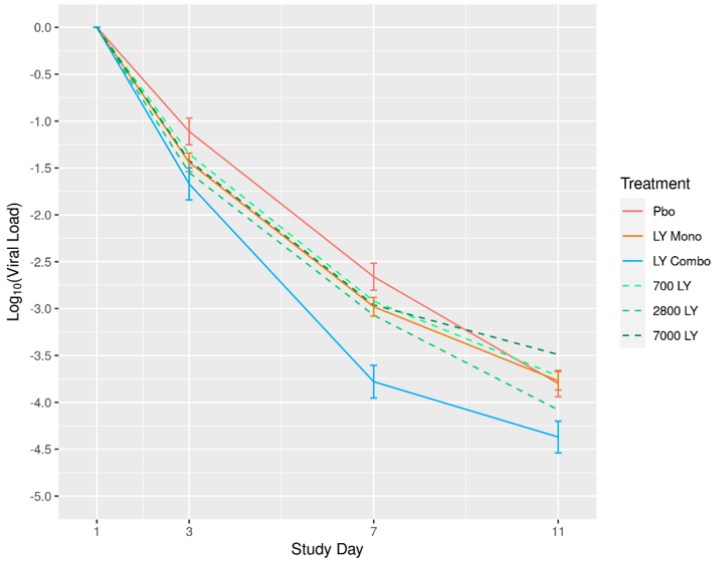
Efficacy of Bamlanivimab Monotherapy for the Treatment of COVID-19

Effect of bamlanivimab treatment on SARS-COV-2 viral load change from baseline to Day 11

The prespecified primary endpoint of change from baseline to Day 11 in $\log_{10}$ viral load was not met by bamlanivimab monotherapy at a dose of 700 mg (Figure 5).

- bamlanivimab 700 mg versus concurrent placebo: $\Delta=-0.01$
- bamlanivimab 2800 mg versus concurrent placebo: $\Delta=-0.37$
- bamlanivimab 7000 mg versus concurrent placebo: $\Delta=0.22$

This could possibly be explained by the fact that most participants receiving placebo had also effectively cleared the virus by Day 11 with an average RT PCR cycle threshold value of 37.0.



Legend
Pbo = placebo (Treatment Arm 1)
LY Mono = pooled data from

- 700 mg bamlanivimab (Treatment Arm 2)
- 2800 mg bamlanivimab (Treatment Arm 3), and
- 7000 mg bamlanivimab (Treatment Arm 4).

700 LY = bamlanivimab 700 mg (Treatment Arm 2)
2800 LY = bamlanivimab 2800 mg (Treatment Arm 3)
7000 LY = bamlanivimab 7000 mg (Treatment Arm 4)

Figure 5 - SARS-COV-2 viral load change from baseline by visit (with standard error).

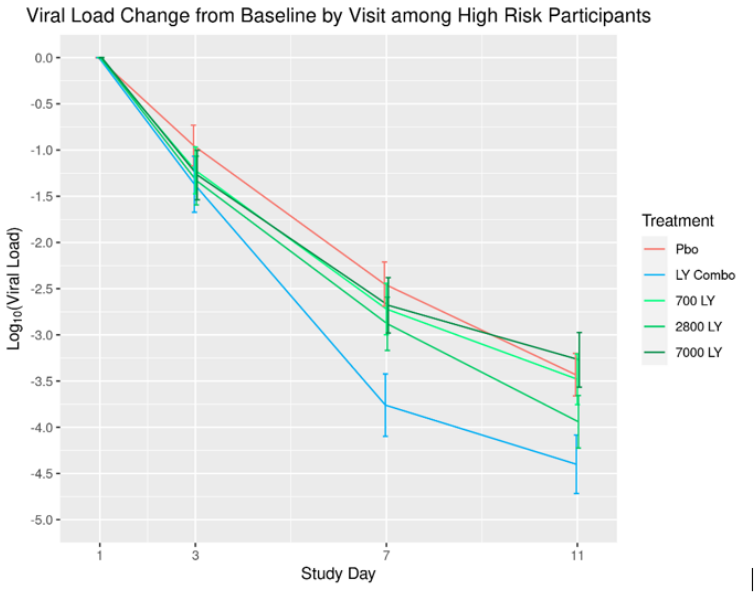
Because most participants receiving placebo effectively cleared virus by Day 11 with an average cycle threshold value of 37.0, the difference in viral load at Day 11, or lack thereof, is unlikely to be clinically relevant.

For the secondary endpoint of change from baseline in viral load at Day 7, the results are as follows:

- bamlanivimab 700 mg versus concurrent placebo: $\Delta=-0.16$
- bamlanivimab 2800 mg versus concurrent placebo: $\Delta=-0.31$
- bamlanivimab 7000 mg versus concurrent placebo: $\Delta=-0.20$

Only a pooled analysis for all LY mono arms shows non-overlapping CIs at day 3 and 7. This somehow makes the clinical relevance of effects questionable. The effect of the middle dose (2800 mg bamlanivimab) might at least be indicative of a benefit according to the pre-planned Bayesian decision rules where an effect of -0.3 was considered as the threshold.

Effect of bamlanivimab on the SARS-COV-2 viral load among high-risk participants
Additionally, a comparison of viral loads for participants who have at least 1 risk factor for progression to severe disease and/or hospitalization over the various time points that viral load was provided and assessed (figure 6).



Legend
Pbo = placebo (Treatment Arm 1)
LY Combo = 2800 mg bamlanivimab/2800 mg etesevimab (Treatment Arm 6)
700 LY = bamlanivimab 700 mg (Treatment Arm 2)
2800 LY = bamlanivimab 2800 mg (Treatment Arm 3)
7000 LY = bamlanivimab 7000 mg (Treatment Arm 4).

Figure 6 - Viral load change from baseline by visit among high risk participants, efficacy population, J2W-MC-PYAB.

Effect of bamlanivimab treatment on reducing high viral load

Table 4 - Percentage of Participants with SARS-CoV-2 Viral Load ≥5.27 (CT ≤27.5) at Day 7

	PBO (N = 145)	700 mg LY (N = 99)	2800 mg LY (N = 101)	7000 mg LY (N = 99)	LY Mono[a] (N = 299)
Response, n (%)	30 (20.7)	12 (12.1)	9 (8.9)	10 (10.1)	31 (10.4)

Abbreviations: CT = cycle threshold; LY = bamlanivimab; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; vs. = versus.

a LY Mono is pooled data from 700 mg bamlanivimab (Treatment Arm 2), 2800 mg bamlanivimab (Treatment Arm 3), and 7000 mg bamlanivimab (Treatment Arm 4).

Table 5 - Percentage of High-Risk Participants with SARS-CoV-2 Viral Load ≥5.27 (CT ≤27.5) at Day 7

	PBO (N = 66)	700 mg LY (N = 46)	2800 mg LY (N = 45)	7000 mg LY (N = 44)	LY Mono[a] (N = 135)
Response, n (%)	14 (22.6)	9 (19.6)	6 (14.3)	4 (9.5)	19 (14.6)

Abbreviations: CT = cycle threshold; LY = bamlanivimab; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a LY Mono is pooled data from 700 mg bamlanivimab (Treatment Arm 2), 2800 mg bamlanivimab (Treatment Arm 3), and 7000 mg bamlanivimab (Treatment Arm 4).

For a discussion on PHVL see sections "Correlation between viral load and COVID-19-related hospitalizations or emergency room visits" and "Use of PHVL as a surrogate for clinical outcomes" further below.

Effect of Bamlanivimab on Clinical Endpoints

COVID-19-Related Deaths

As of 04 November 2020, there have been no deaths caused by COVID-19 in Treatment Arms 1 through 4.

COVID-19-related hospitalizations and emergency room visits

Compared with placebo-treated participants, a smaller percentage of bamlanivimab monotherapy-treated participants progressed to COVID-19-related hospitalizations or emergency room visits. Additionally, a smaller percentage of bamlanivimab-treated participants who were at a higher risk of hospitalization (i.e. ≥65 years or BMI ≥35) progressed to COVID 19-related hospitalizations or emergency room visits compared with placebo.

Table 6 - Events of COVID-19-Related Hospitalizations or Emergency Room Visits within 28 Days after Treatment

•	PBO (N = 156)	700 mg LY (N = 101)	2800 mg LY (N = 107)	7000 mg LY (N = 101)	LY Mono[a] (N = 309)
• Events, n (%)	9 (5.8)	1 (1.0)	2 (1.9)	2 (2.0)	5 (1.6)

Abbreviations: COVID-19 = coronavirus disease 2019; LY = bamlanivimab; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; vs. = versus.

[a] LY Mono is pooled data from 700 mg bamlanivimab (Treatment Arm 2), 2800 mg bamlanivimab (Treatment Arm 3), and 7000 mg bamlanivimab (Treatment Arm 4).

Table 7 below presents data for rates of COVID-19-related hospitalizations or emergency room visits within 28 days of study drug by treatment group in Study PYAB for each epoch in which the arms eligible for randomization were updated for the participants receiving bamlanivimab monotherapy and the concurrently enrolled participants receiving placebo.

Table 7 – Covid-19-related hospitalization, emergency room visit, or death safety population, monotherapy patients - study JW2-MC-PYAB

•	PBO[a] (N = 100)	700 mg LY (N = 101)	2800 mg LY (N = 107)	7000 mg LY (N = 101)
• Events, n (%)	5 (5.0)	1 (1.0)	2 (1.9)	2 (2.0)

Abbreviations: COVID-19 = coronavirus disease 2019; LY = bamlanivimab; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo.

[a] Placebo includes all data from Treatment Arm 1.

Table 8 below presents a summary that compares rates of COVID-19-related hospitalizations and emergency room visits in the high-risk population for each dose, and combined monotherapy compared with placebo.

Table 8 - COVID-19-Related Deterioration at Any Time for High-Risk Patients

	PBO (N = 68)	700 mg LY (N = 46)	2800 mg LY (N = 45)	7000 mg LY (N = 44)	LY Mono[a] (N = 135)
Response, n (%)	7 (10.3)	1 (2.2)	1 (2.2)	2 (4.5)	4 (3.0)

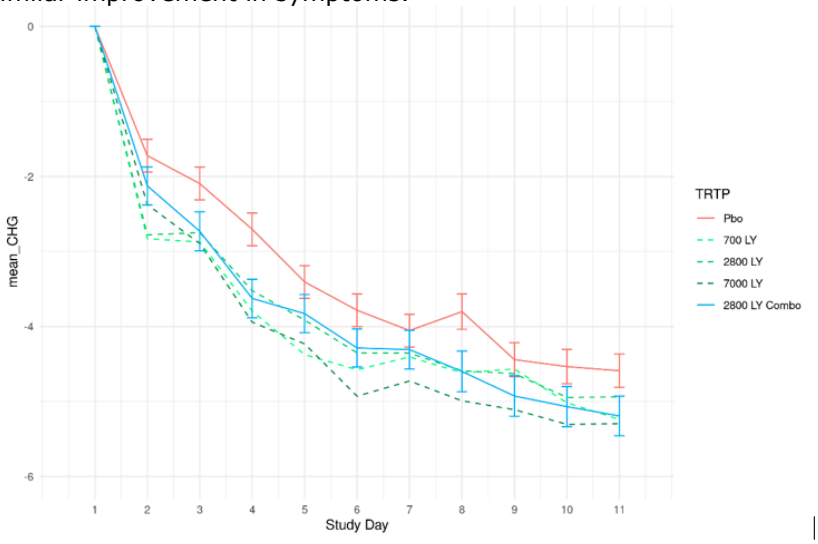
Abbreviations: COVID-19 = coronavirus disease 2019; LY = bamlanivimab; N = number of patients in the analysis population; n = number of patients in the specified category; vs = versus.

a LY Mono is pooled data from 700 mg bamlanivimab (Treatment Arm 2), 2800 mg bamlanivimab (Treatment Arm 3), and 7000 mg bamlanivimab (Treatment Arm 4).

Data presented for the secondary endpoint, COVID-19-Related Hospitalization, Emergency Room Visit, or Death could support that there might be a clinical effect. Although, hospitalisation was defined as at least 24 hours of acute care, no consistent, clear criteria were defined for the determination of whether a hospitalisation event or ER visit was related to COVID-19. This decision was on the discretion of the blinded investigator and was evaluated case-by-case. This reduces the validity of that endpoint. Furthermore, this remains non-conclusive due to missing error control. Thus, the clinical relevance is unclear.

Effect of bamlanivimab treatment on time to sustained symptom resolution

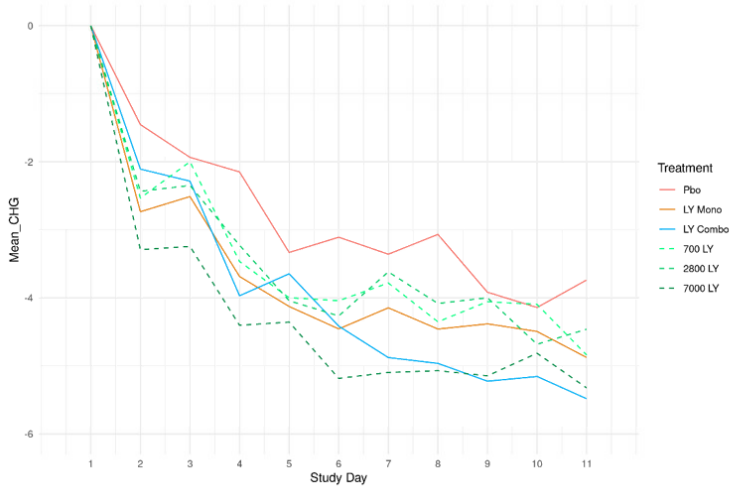
To assess the effect of treatment on Covid-19 symptoms, the change from baseline in symptom scores between the bamlanivimab group and the placebo group was compared. Regardless of dose, bamlanivimab monotherapy-treated participants had a lower time-weighted average symptom score from Day 1 to Day 11, compared with placebo-treated participants. The 3 bamlanivimab doses showed similar improvement in symptoms.



Legend
Pbo = placebo (Treatment Arm 1)
700 LY = bamlanivimab 700 mg (Treatment Arm 2)
2800 LY = bamlanivimab 2800 mg (Treatment Arm 3)
7000 LY = bamlanivimab 7000 mg (Treatment Arm 4)
2800 LY Combo = 2800 mg bamlanivimab/2800 mg etesevimab (Treatment Arm 6)
Note: Symptom improvement is defined as (1) all symptoms on the symptom questionnaire scored as moderate or severe at baseline are subsequently scored as mild or absent, AND (2) all symptoms on the symptom questionnaire scored as mild or absent at baseline are subsequently scored as absent versus otherwise.

Figure 7 - Symptom score change from baseline by visit (individual treatment arms).

The figure above presents the graphical representation of change in symptom score over time for participants who have at least 1 risk factor for progression to severe disease and/or hospitalization for each dose, and combined monotherapy compared with placebo.



Legend

Pbo = placebo (Treatment Arm 1)

LY Mono = pooled data from

- 700 mg bamlanivimab (Treatment Arm 2)
- 2800 mg bamlanivimab (Treatment Arm 3), and
- 7000 mg bamlanivimab (Treatment Arm 4).

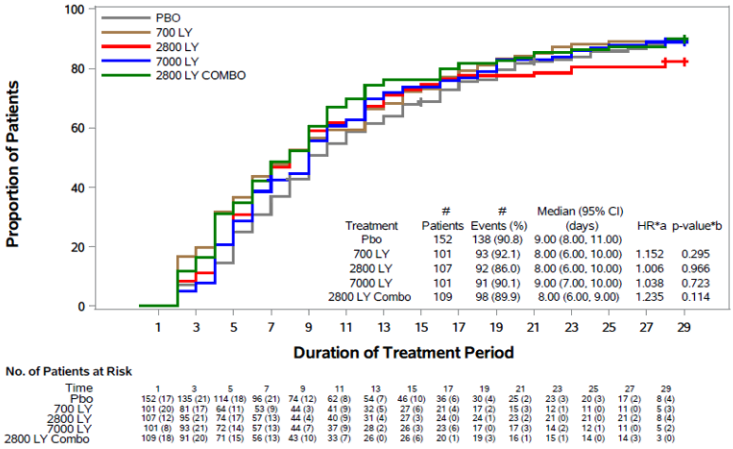
LY Combo = 2800 mg bamlanivimab/2800 mg etesevimab (Treatment Arm 6)

700 LY = bamlanivimab 700 mg (Treatment Arm 2)

2800 LY = bamlanivimab 2800 mg (Treatment Arm 3)

7000 LY = bamlanivimab 7000 mg (Treatment Arm 4)

Figure 8 - Change in symptom score over time for subjects who have at least 1 risk factor for progression to severe disease and/or hospitalization for each dose, and combined monotherapy compared with placebo.



Abbreviations: CI = confidence interval; HR = hazard ratio.
Note: Patients at risk displayed under Day x are calculated based on patients whose time to event or censoring >Day x date. Number of events displayed under Day x are calculated based on events that occurred during the time interval from Day x (excluding Day x date) to the day of next reported Day y (including Day y date).
*a HR – stratified by duration since symptom onset to randomization.
*b Stratified log-rank for comparison with placebo.
Legend
Pbo = placebo (Treatment Arm 1).
700 LY = bamlanivimab 700 mg (Treatment Arm 2)
2800 LY = bamlanivimab 2800 mg (Treatment Arm 3).
7000 LY = bamlanivimab 7000 mg (Treatment Arm 4).
2800 LY Combo = 2800 mg bamlanivimab/2800 mg etesevimab (Treatment Arm 6).

Figure 9 - Time to first symptomatic resolution, Kaplan–Meier product limit curve, efficacy population, J2W-MC-PYAB.

Efficacy of Bamlanivimab in Combination with Etesevimab for the Treatment of COVID-19

Results on primary endpoint of phase-3 portion of the study PYAB (Treatment Arm 7 (LY combo) and 8 (placebo))

Primary Endpoint: COVID-19 related hospitalization* or death by any cause by Day 29

- ***p*=0.0004 (70% reduction** – 36 events on PBO vs. 11 on LY)
- **defined as "≥24 hours of acute care"*

Abbreviations: COVID-19 = coronavirus disease 2019; ER = emergency room; LY = 2800 mg bamlanivimab and 2800 mg etesevimab administered together; PBO = placebo.

Table 9 - All Deaths, Regardless of Cause in Treatment Arms 7 (LY combo) and 8 (placebo).

Patient	Treatment	Age	BMI	Sex	Symptom onset	Day of death	COVID-19 related death?
1	Placebo	39	49	M	1 day	Day 20	Yes
2	Placebo	73	29	M	4 days	Day 13	Yes
3	Placebo	54	40	F	4 days	Day 36	Yes
4	Placebo	77	34	F	3 days	Day 16	Yes

5	Placebo	75	22	M	7 days	Day 24	Yes
6	Placebo	62	32	M	2 days	Day 24	Yes
7	Placebo	62	23	M	4 days	Day 25	Yes
8	Placebo	65	40	M	4 days	Day 36	Yes
9	Placebo	59	61	M	7 days	Day 3	No
10	Placebo	62	39	M	3 days	Day 19	Yes

Abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus 2019; CVD = cardiovascular disease

Results on key secondary endpoints of phase-3 portion of the study + supportive data from phase-2 portion of the study PYAB

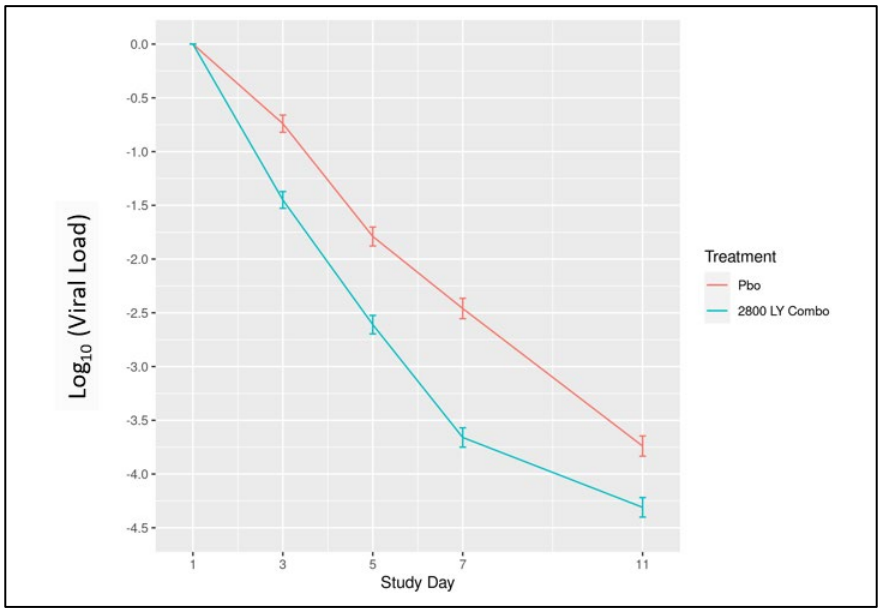
Key Secondary Endpoints:

1. Viral load change from baseline to Day 7:
   $p < 0.001$
2. Persistently high viral load (Day 7 viral load > 5.27)
   $p < 0.001$ (34% on placebo vs. 16.0% on LY)
3. COVID-19 related hospitalisations, ER visit, or death by any cause
   $p < 0.005$ (37 events on PBO vs. 12 on LY)
4. Time to sustained symptom resolution – 2 consecutive assessments
   $p < 0.007$ (median: 9 days for PBO vs. 8 days for LY)

Results on key secondary endpoints from the phase-3 portion of the study PYAB (Treatment Arm 7 (LY combo) and 8 (placebo)) are presented below, followed by supportive data from phase-2 portion (Treatment Arms 6 (LY combo) and 1 (placebo).

Effect of etesevimab and bamlanivimab treatment on viral load change from baseline to Day 7

The figure below shows mean viral load change from baseline from phase-3 portion of the study PYAB (treatment arms 7 (LY combo) and 8 (placebo)).



Abbreviations: 2800 LY Combo = 2800 mg bamlanivimab and 2800 mg etesevimab administered together; PBO = placebo.

Figure 10 - Mean viral load change from baseline (with standard error) for Treatment Arms 7 (LY combo) and 8 (placebo).

For supportive data from phase-2 portion of the study PYAB, see Figure for mean viral load change from baseline as well as Figure for mean viral load change from baseline among high-risk participants PYAB.

Effect of etesevimab and bamlanivimab treatment on reducing high viral load

In phase-3 portion of the trial, there were 10.6% of subjects with persistent high viral load (≥5.27) at Day 7 in Ly combo group and 34.0% of subjects in the placebo group (p<0.001).

Additionally, in the phase-2 portion of the trial treatment with etesevimab and bamlanivimab combination therapy reduced the percentage of participants with persistent high viral load (see table 10 and table 11 below; (supportive data)).

Table 10 - Percentage of Participants with SARS-CoV-2 Viral Load ≥5.27 (CT ≤27.5) at Day 7 in Treatment Arms 6 (LY combo) and 1 (placebo)

	PBO (N = 145)	LY Combo[a] (N = 100)
Response, n (%)	30 (20.7)	3 (3.0)

Abbreviations: CT = cycle threshold; LY = bamlanivimab; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; vs. = versus.

a LY Combo is data from the 2800-mg bamlanivimab/2800-mg etesevimab group (Treatment Arm 6).

As discussed above, the predictive value of the biomarker PHVL is considered of limited magnitude (PPV ~ 11%-12%; NPV ~ 98%-99%) and the clinical relevance is considered questionable. PHVL was not established as a surrogate endpoint.

Table 11 - Percentage of High-Risk Participants with SARS-CoV-2 Viral Load ≥5.27 (CT ≤27.5) at Day 7 in Treatment Arms 6 (LY combo) and 1 (placebo)

	PBO (N = 66)	LY Combo[a] (N = 36)
Response, n (%)	14 (22.6)	1 (3.2)

Abbreviations: CT = cycle threshold; LY = bamlanivimab; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a LY Combo is data from the 2800-mg bamlanivimab/2800-mg etesevimab group (Treatment Arm 6).

Effect of etesevimab and bamlanivimab treatment on COVID-19-Related Deaths, Hospitalizations, and Emergency Room Visits

In the phase-3 portion of the trial there were 12 events of COVID-19 related hospitalisation, ER visits, or death from any cause in patients taking Ly combo therapy and 37 events in patients taking placebo (p= 0.0005).

Compared with placebo-treated participants, a smaller percentage of etesevimab and bamlanivimab combination therapy-treated participants progressed to COVID-19-related hospitalizations or emergency room visits in the phase-2 part of the study PYAB (see table 12 below (supportive data)).

Table 12 - Events of COVID-19-Related Hospitalizations or Emergency Room Visits within 28 Days after Treatment in Treatment Arms 6 (LY combo) and 1 (placebo)

	PBO (N = 156)	LY Combo[a] (N = 112)
Events, n (%)	9 (5.8)	1 (0.9)

Abbreviations: COVID-19 = coronavirus disease 2019; LY = bamlanivimab; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; vs. = versus.

[a] LY Combo is data from the 2800-mg bamlanivimab/2800-mg etesevimab group (Treatment Arm 6).

The table below presents a summary that compares rates of COVID-19-related hospitalizations and emergency room visits in the high-risk population for bamlanivimab/etesevimab combination compared with placebo.

Table 13 - COVID-19-Related Deterioration at Any Time for High-Risk Patients in Treatment Arms 6 (LY combo) and 1 (placebo)

	PBO (N = 68)	LY Combo[a] (N = 38)
Response, n (%)	7 (10.3)	1 (2.6)

Abbreviations: COVID-19 = coronavirus disease 2019; LY = bamlanivimab; N = number of patients in the analysis population; n = number of patients in the specified category; vs = versus.

[a] LY Combo is data from the 2800-mg bamlanivimab/2800-mg etesevimab group (Treatment Arm 6).

The table below provides further information on the patient experiencing emergency room visit in the LY combo treatment group (treatment arm 6):

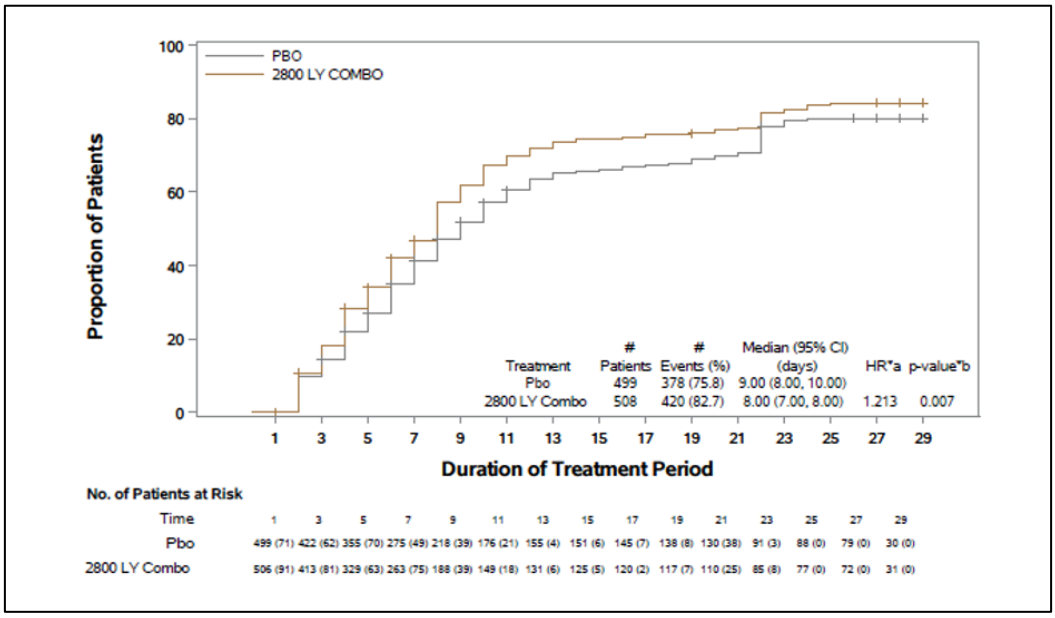
Table 14 - Further information on the patient experiencing emergency room visit in the LY combo treatment group (Treatment Arm 6)

Patient ID	Treatment	Age	BMI	Sex	Rand. Date	Event Start Date	Type of Event	Reason
153-10627	Combo	20	18	F	03-Sep-20	05-Sep-20	ER[a]	COVID-19, dehydration

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease 2019; ER = emergency room visit; EUA = Emergency Use Authorization; F = female; Hosp. = hospitalization; ICU = intensive care unit; M = male; Rand. = randomization.

Effect of etesevimab and bamlanivimab treatment on time to sustained symptom resolution

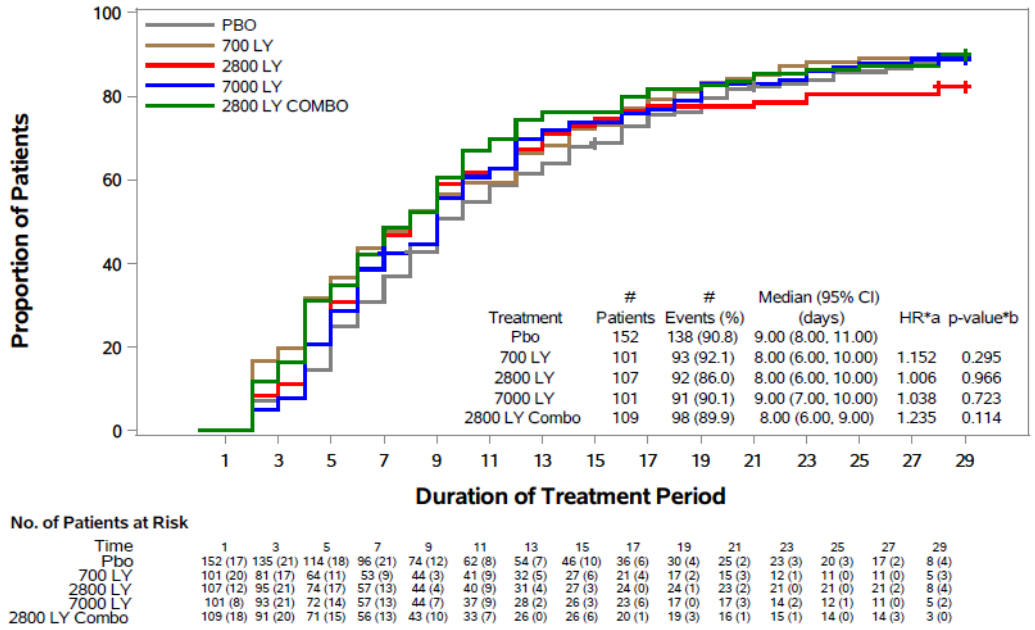
The figure below shows time to sustained symptom resolution in the phase-3 portion of the study PYAB (treatment arms 7 (LY combo) and 8 (placebo)).



Abbreviations: 2800 LY Combo = 2800 mg bamlanivimab and 2800 mg etesevimab administered together; CI = confidence interval; HR = hazard ratio; PBO = placebo.

Figure 11 - Time to sustained symptom resolution for Treatment Arms 7 (LY combo) and 8 (placebo).

The figure below shows time to sustained symptom resolution from phase-2 portion of the study PYAB (treatment arms 6 (LY combo) and 1 (placebo), supportive data).



Abbreviations: CI = confidence interval; HR = hazard ratio.

Note: Patients at risk displayed under Day x are calculated based on patients whose time to event or censoring >Day x date. Number of events displayed under Day x are calculated based on events that occurred during the time interval from Day x (excluding Day x date) to the day of next reported Day y (including Day y date).

*a HR – stratified by duration since symptom onset to randomization.

*b Stratified log-rank for comparison with placebo.

Legend

Pbo = placebo (Treatment Arm 1).

700 LY = bamlanivimab 700 mg (Treatment Arm 2)

2800 LY = bamlanivimab 2800 mg (Treatment Arm 3).

7000 LY = bamlanivimab 7000 mg (Treatment Arm 4).

2800 LY Combo = 2800 mg bamlanivimab/2800 mg etesevimab (Treatment Arm 6).

Figure 12 - Time to first symptomatic resolution, Kaplan–Meier product limit curve, efficacy population including treatment arm 6 (Ly combo) and 1 (placebo)

Correlation between viral load and clinical endpoints

Correlation between viral load and COVID-19-related hospitalizations or emergency room visits

Analysis using data pooled across all treatment arms revealed a strong correlation between persistent high viral load on Day 7 (as defined by cycle threshold value of 27.5 or less) and COVID-19-related hospitalizations or emergency room visits (Figure 13). Participants who did not effectively lower viral load by Day 7 were observed to progress to COVID-19-related hospitalizations or emergency visits at 13 times the rate of the other participants.

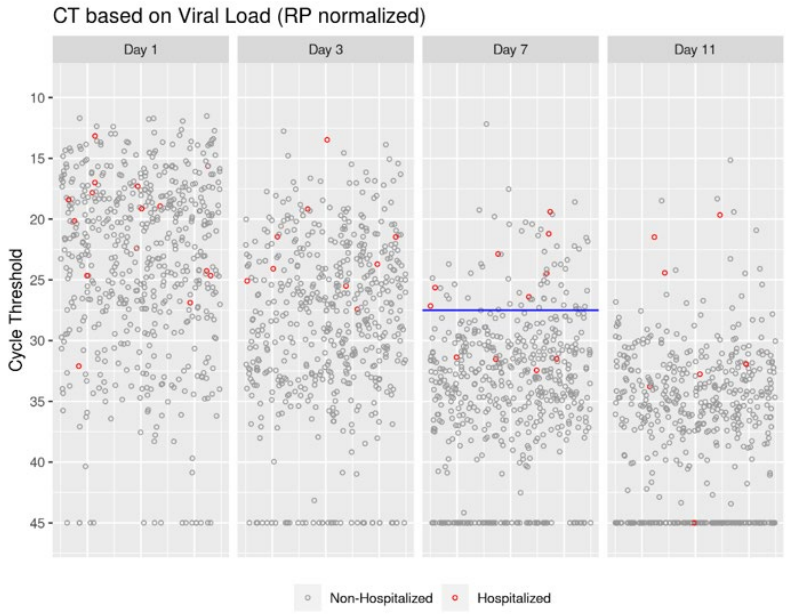


Figure 13 - Participants with COVID-19-related hospitalizations or emergency visits had persistent high viral loads. Abbreviations: CT= cycle threshold; RP= Ribonucleases P

Use of PHVL as a surrogate for clinical outcomes

Further details on the derivation of the biomarker persistent high viral load on Day 7 (PHVL) were provided.

Analysis of Phase 2 data from Study PYAB showed a potential correlation between PHVL at Day 7 and hospitalisation. Regardless of treatment, patients with PHVL at Day 7 were more likely to be hospitalised by Day 29, but fewer bamlanivimab-treated patients were hospitalised than placebo.

Data from the bamlanivimab and etesevimab development programs show a strong relationship between PHVL and hospitalisations ($p<0.001$).

Evaluation of data from the Phase 2 and Phase 3 portions of Study PYAB (see table below) showed that PHVL as a biomarker for hospitalisation or ER visits was both sensitive (69% to 70% of the time) and specific (76% to 87% of the time).

This shows that sensitivity and specificity were in an acceptable range, but not very promising. The more relevant predictive values were not reported. Based on CHMP's own calculations using the numbers provided in Table 15, the positive predictive value for the derived biomarker was as low as 11% and 12% in the Phase 2 and 3 study, respectively. This means that only around 11% to 12% of patients with PHVL at Day 7 would be hospitalized in the latter course of disease. Hence, the use of PHVL as a surrogate endpoint for clinical outcome and biomarker should be considered with great caution.

Table 15 - COVID-19-Related Hospitalisation by Day 29

	Arms 1 - 4 and 6 (Phase 2)		Arms 7 and 8 (Phase 3)	
	No Hospitalization	**Hospitalization**	**No Hospitalization**	**Hospitalization**
Non-PHVL	490	4	751	14
PHVL	74	9	234	32

Abbreviations: COVID-19 = coronavirus disease 2019; PHVL = persistently high viral load (Day 7 viral load >5.27).

Clinical resistance

Mutations that can cause resistance have also been monitored in patients treated in two clinical trials, namely the Phase 1 Study J2W-MC-PYAA (PYAA) "A Randomized, Placebo-Controlled, Double-Blind, Sponsor Unblinded, Single-Ascending Dose, Phase 1, First-in-Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Intravenous LY3819253 in Participants Hospitalized for COVID-19" and the Phase 2 Study J2W-MC-PYAB (PYAB) A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of LY3819253 and LY3832479 in Participants with Mild to Moderate COVID-19 Illness".

The results of the study PYAA are shown in the table below.

Table 16 - SARS-CoV-2 Spike Gene Sequencing Results Summary

Spike Protein Position	Protein Change	LY3819253 In Vitro Resistance	GISAID Frequency (N)[a]	Domain	Variants Identified at Baseline		Treatment-Emergent Variants	
					Frequency (N)	Participant Identifier	Frequency (N)	Participant Identifier
256	S:S256L		0.013% (7)	S1:NTD	7.1% (1/14)	206		
494	S:S494P	B+, PV+, MARM+	0.013% (7)	S1:RBD			9.1% (1/11)	206
522	S:A522V		0.027% (14)	S1:RBD	7.1% (1/14)	207		
614	S:D614G		78.449% (40970)	S1	100% (14/14)	100 101 103 200 202 203 204 206 207 208 210 211 213 604	18.2% (2/11)	205[b] 700[b]
625	S:H625R		0.01% (5)	S1	7.1% (1/14)	604		

Abbreviations: A = alanine; B = Binding Affinity Loss; D = aspartate; G = glycine; GISAID = Global Initiative on Sharing All Influenza Data; H = histidine; L = leucine; MARM = (previous identification as an in vitro) monoclonal antibody-resistant mutant; N = number of samples from participants that had positive PCR and passed next generation sequencing quality control criteria; NTD = spike protein 1 N-terminal domain; P = proline; PCR = polymerase chain reaction; PV = Pseudovirus Susceptibility Loss; R = arginine; RBD = receptor-binding domain; S = serine; S1 = spike protein gene; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; V = valine.

a Frequency determined from 52,225 total number of spike sequences as of 11 August 2020.

b No baseline sequence was obtained; sequence compared to reference sequence for treatment-emergent designation.

Variants S256L, A522V, and H625R were identified in 1 participant each, whereas all samples contained the D614G variation, which has become the prevalent circulating strain in the United States. Of note, one participant was administered placebo. While the S494P variant was previously identified as a resistance-associated mutation in the in vitro studies described above. S494P was identified in 1 of the 11 participants with post-baseline sample sequence. This participant was administered 2800 mg of LY3819253 (bamlanivimab). The participant was discharged 2 days after the infusion. In total, the participant had 4 nasal samples collected over the course of the study. All nasal samples were positive for viral RNA and have associated sequence data. The S494P mutation was first observed in the sample collected on Day 7 and was again observed in the Day 11 sample. Although the participant was doing well clinically, he did not attend follow-up visits after Day 11 and subsequently withdrew from the study.

Study PYAB

Fifty percent or greater allelic frequency

The majority of variations identified at positions of known resistance were E484A, E484K, E484Q, and S494P; with the E484K and E484Q exhibiting most frequent detection. With this analysis, participants had total variations detected at frequencies of

- Placebo: 3.4%
- 700 mg LY3819253: 6.1%
- 2800 mg LY3819253: 6.9%
- 7000 mg LY3819253: 11.3% and
- 2800 mg LY3819253 + 2800 mg LY3832479: 0%.

Of note, combination therapy arm participants had no variations that were detected at positions of known resistance.

Fifteen percent or greater allelic frequency

When analysis was broadened to include minor variations (≥15% allelic frequency), additional amino acid variations were observed at positions of known LY3819253 or LY3832479-resistance including D420N, N460T, E484A/D/K/Q/V, F490L/S/V and S494L/P. Of these, only the D420N, E484K/Q, F490S, and S494P have been assessed phenotypically to date. E484K and E484Q were the most frequently detected variants across all treatment groups.

The overall frequency of variations in the combination arm was lower than that of the placebo or monotherapy arms.

- Placebo: 6.2%
- 700 mg LY3819253: 9.2%
- 2800 mg LY3819253: 12.7%
- 7000 mg LY3819253: 15.5%, and
- 2800 mg LY3819253 + 2800 mg LY3832479: 2.9%.

Of particular interest are the variations not present at baseline but that appeared after treatment. These variations were monitored among all trial participants as well as in the high-risk group and high viral load group of patients, as shown in the four tables below.

Table 17 - Spike Variations at Positions of Known LY3819253 or LY382479-Resistance Not Present at Baseline, but Emerged Posttreatment at an Allelic Frequency of ≥50% Study J2W-MC-PYAB

Spike Protein Position	Protein Change	GISAID Frequency (N)[a]	Domain	Confirmed Resistant Phenotype		Frequency (N)				
				LY3819253	LY3832479	Placebo	LY3819253 700 mg	LY3819253 2800 mg	LY3819253 7000 mg	LY3819253 + LY3832479
484	E484A	0.003% (4)	S1:RBD	-	-	0% (0/145)	1.0% (1/98)	0% (0/102)	2.1% (2/97)	0% (0/102)
484	E484K	0.013% (18)	S1:RBD	Yes	No	2.1% (3/145)	2.0% (2/98)	2.9% (3/102)	6.2% (6/97)	0% (0/102)

484	E484Q	0.009% (12)	S1:RBD	Yes	No	0.7% (1/145)	3.1% (3/98)	4.9% (5/102)	2.1% (2/97)	0% (0/102)
494	S494P	0.048% (66)	S1:RBD	Yes	No	0.7% (1/145)	1.0% (1/98)	1.0% (1/102)	1.0% (1/97)	0% (0/102)
All	NA	NA	NA	NA	NA	3.4% (5/145)	6.1% (6/98)	6.9% (7/102)	11.3% (11/97)	0% (0/102)

Table 18 - Spike Variations at Positions of Known LY3819253 or LY3832479-Resistance Not Present at Baseline, but Emerged Posttreatment at an Allelic Frequency of ≥15% Study J2W-MC-PYAB

Spike Protein Position	Protein Change	GISAID Frequency (N)[a]	Domain	Confirmed Resistant Phenotype		Frequency (N)				
				LY3819253	LY3832479	Placebo	LY3819253 700 mg	LY3819253 2800 mg	LY3819253 7000 mg	LY3819253 and LY3832479
420	D420N	0% (0)	S1:RBD	No	Yes	0% (0/145)	0% (0/98)	1.0% (1/102)	0% (0/97)	0% (0/102)
460	N460T	0.001% (1)	S1:RBD	-	-	0% (0/145)	0% (0/98)	0% (0/102)	0% (0/97)	1.0% (1/102)
484	E484A	0.003% (4)	S1:RBD	-	-	0% (0/145)	1.0% (1/98)	0% (0/102)	2.1% (2/97)	0% (0/102)
484	E484D	0.002% (3)	S1:RBD	-	-	0% (0/145)	1.0% (1/98)	0% (0/102)	0% (0/97)	0% (0/102)
484	E484K	0.013% (18)	S1:RBD	Yes	No	2.8% (4/145)	2.0% (2/98)	5.9% (6/102)	8.2% (8/97)	0% (0/102)
484	E484Q	0.009% (12)	S1:RBD	Yes	No	1.4% (2/145)	3.1% (3/98)	5.9% (6/102)	2.1% (2/97)	0% (0/102)
484	E484V	0% (0)	S1:RBD	-	-	0% (0/145)	0% (0/98)	1.0% (1/102)	0% (0/97)	0% (0/102)
490	F490L	0.004% (5)	S1:RBD	-	-	0.7% (1/145)	0% (0/98)	1.0% (1/102)	0% (0/97)	1.0% (1/102)
490	F490S	0.005% (7)	S1:RBD	Yes	No	0% (0/145)	0% (0/98)	2.0% (2/102)	0% (0/97)	0% (0/102)
490	F490V	0% (0)	S1:RBD	-	-	0.7% (1/145)	0% (0/98)	0% (0/102)	0% (0/97)	0% (0/102)
494	S494L	0.002% (3)	S1:RBD	-	-	0% (0/145)	1.0% (1/98)	1.0% (1/102)	2.1% (2/97)	0% (0/102)

494	S494P	0.048% (66)	S1:RBD	Yes	No	0.7% (1/145)	2.0% (2/98)	1.0% (1/102)	2.1% (2/97)	**1.0% (1/102)**
All	NA	NA	NA	NA	NA	6.2% (9/145)	9.2% (9/98)	12.7% (13/102)	15.5% (15/97)	2.9% (3/102)

Table 19 - Spike Variations at Positions of Known LY3819253 or LY3832479-Resistance Not Present at Baseline, but Emerged Posttreatment at an Allelic Frequency of ≥50% in High Risk Population Study J2W-MC-PYAB

Spike Protein Position	Protein Change	GISAID Frequency (N)[a]	Domain	Confirmed Resistant Phenotype		Frequency (N)				
				LY3819253	LY3832479	Placebo	LY3819253 700 mg	LY3819253 2800 mg	LY3819253 7000 mg	LY3819253 + LY3832479
484	E484A	0.003% (4)	S1:RBD	-	-	0% (0/65)	2.3% (1/43)	0% (0/42)	0% (0/44)	0% (0/33)
484	E484K	0.013% (18)	S1:RBD	Yes	No	0% (0/65)	0% (2/43)	7.1% (3/42)	11.4% (5/44)	0% (0/33)
484	E484Q	0.009% (12)	S1:RBD	Yes	No	0% (0/65)	2.3% (1/43)	9.5% (4/42)	4.5% (2/44)	0% (0/33)
494	S494P	0.048% (66)	S1:RBD	Yes	No	1.5% (1/65)	2.3% (1/43)	2.4% (1/42)	2.3% (1/44)	0% (0/33)
All	NA	NA	NA	NA	NA	1.5% (1/65)	9.3% (4/43)	14.3% (6/42)	18.2% (8/44)	0% (0/33)

Table 20 - Spike Variations at Positions of Known LY3819253 or LY3832479-Resistance Not Present at Baseline, but Emerged Posttreatment at an Allelic Frequency of ≥15% in High Risk Population Study J2W-MC-PYAB

Spike Protein Position	Protein Change	GISAID Frequency (N)[a]	Domain	Confirmed Resistant Phenotype		Frequency (N)				
				LY3819253	LY3832479	Placebo	LY3819253 700 mg	LY3819253 2800 mg	LY3819253 7000 mg	LY3819253 and LY3832479
484	E484A	0.003% (4)	S1:RBD	-	-	0% (0/65)	2.3% (1/43)	0% (0/42)	0% (0/44)	0% (0/33)
484	E484D	0.002% (3)	S1:RBD	-	-	0% (0/65)	2.3% (1/43)	0% (0/42)	0% (0/44)	0% (0/33)
484	E484K	0.013% (18)	S1:RBD	Yes	No	0% (0/65)	4.7% (2/43)	14.3% (6/42)	15.9% (7/44)	0% (0/33)
484	E484Q	0.009% (12)	S1:RBD	Yes	No	0% (0/65)	2.3% (1/43)	11.9% (5/42)	4.5% (2/44)	0% (0/33)
484	E484V	0% (0)	S1:RBD	-	-	0% (0/65)	0% (0/43)	2.4% (1/42)	0% (0/44)	0% (0/33)
490	F490L	0.004% (5)	S1:RBD	-	-	1.5% (1/65)	0% (0/43)	0% (0/42)	0% (0/44)	0% (0/33)
490	F490S	0.005% (7)	S1:RBD	Yes	No	0% (0/65)	0% (0/43)	4.8% (2/42)	0% (0/44)	0% (0/33)

494	S494L	0.002% (3)	S1:RBD	-	-	0% (0/65)	2.3% (1/43)	2.4% (1/42)	0% (0/44)	0% (0/33)
494	S494P	0.048% (66)	S1:RBD	Yes	No	1.5% (1/65)	2.3% (1/43)	2.4% (1/42)	4.5% (2/44)	0% (0/33)
All	NA	NA	NA	NA	NA	3.1% (2/65)	14.0% (6/43)	23.8% (10/42)	22.7% (10/44)	0% (0/33)

Table 21 - Variations in Spike Present at <1% Baseline, but Emerged at a Frequency of ≥15% in 2 or More LY3819253-Treated Patients Who Meet the Persistently High Viral Load Definition Study J2W-MC-PYAB

Spike Protein Position	Protein Change	GISAID Frequency (N)[a]	Domain	Confirmed Resistant Phenotype		Frequency (N)				
				LY3819253	~~LY3819253~~ 3832479	Placebo	LY3819253 700 mg	LY3819253 2800 mg	LY3819253 7000 mg	LY3819253 + LY3832479
37	Y37F	0% (0)	S1:NTD	-	-	0% (0/30)	8.3% (1/12)	11.1% (1/9)	0% (0/10)	0% (0/3)
124	T124del	0% (0)	S1:NTD	-	-	6.7% (2/30)	8.3% (1/12)	0% (0/9)	0% (0/10)	33.3% (1/3)
484	E484A	0.003% (4)	S1:RBD	-	-	0% (0/30)	8.3% (1/12)	0% (0/9)	10% (1/10)	0% (0/3)
484	E484K	0.013% (18)	S1:RBD	Yes	No	3.3% (1/30)	16.7% (2/12)	33.3% (3/9)	40% (4/10)	0% (0/3)
484	E484Q	0.009% (12)	S1:RBD	Yes	No	0% (0/30)	16.7% (2/12)	33.3% (3/9)	0% (0/10)	0% (0/3)
494	S494P	0.048% (66)	S1:RBD	Yes	No	0% (0/30)	8.3% (1/12)	11.1% (1/9)	0% (0/10)	0% (0/3)

Overall, the same variants were detected among the different group of patients, in particular among the mutations affecting bamlanivimab activity. Of note, these latter mutations emerged also (and sometimes even more frequently) in the high-dose arm. However, only seldomly they were found in the combination therapy arm (only the mutation S494P in one patient).

Preliminary serologic assessment of Study J2W-MC-PYAB (Arms 1 to 4, and 6)

Furthermore, analysis were performed to determine anti-virus antibody after infection, to identify those patients that would benefit more from the treatment (seronegative patients). The majority of study participants (79.4%) displayed seroconversion, i.e., had a negative baseline sample with at least 1 or more positive post-baseline samples, whereas only a few participants (9.2%) were persistently seronegative. Of the participants with viral samples containing variations at positions D420, N460, E484, F490, and S494, 48 had samples that passed quality control to be included in the analysis. This subgroup showed very similar rates as the overall study with 77.1% seroconversion, and 10.4% persistent seronegative.

Anti-SARS-CoV-2 Luminex serology assessment

When comparing reactivities to the different spike RBD proteins, similar seroconversion rates as well as overall geometric mean fold changes over time were observed, suggesting that the polyclonal immune response to SARS-CoV-2 can efficiently recognize the LY3819253-resistant variant (E484Q) and the LY3832479-resistant variant (N460K).

Clinical outcome analysis

The clinical outcomes as of 06 October 2020 of all individuals who were found to have viral sequences that had phenotypically confirmed LY3819253 and LY3832479-resistance-associated variants at ≥15% allele frequency are provided in the table below.

Of note, the symptom score (based on symptom questionnaire, where 8 symptoms are scored 0 to 3, and the maximum score is 24) on Day 10 is given for patients whose symptom score on Day 11 is not available.

Table 22 - Clinical Outcomes in Study J2W-MC-PYAB Participants with Emergent Putative LY3819253-Resistance Variants (D420N; E484K; E484Q; F490S and S494P) ≥15% Allele Frequency

Treatment	Clinical Outcome
LY 2800 mg	Not hospitalized. Day 11 symptom score 7.
LY 2800 mg	Not hospitalized. Day 11 symptom score 0.
LY 7000 mg	Not hospitalized. Day 11 symptom score 12.
LY 2800 mg	Not hospitalized. Day 11 symptom score 1.
LY 2800 mg	Not hospitalized. Day 11 symptom score 0.
LY 7000 mg	COVID-19-related hospitalization 10 days after dosing for pneumonia. 39-year-old female, BMI 35, with history of ADD and insomnia.
LY 2800 mg	Not hospitalized. Day 11 symptom score 2.
LY 700 mg	Not hospitalized. Day 11 symptom score 2.
LY 7000 mg	COVID-19-related hospitalization 1 day after dosing for pneumonia. 74-year-old female, BMI 31, with history of anxiety, depression, hyperlipidemia, and gastrectomy.
LY 700 mg	Not hospitalized. Day 11 symptom score 0.
PBO	Not hospitalized. Day 11 symptom score 0.
PBO	Not hospitalized. Day 10 symptom score 0.
LY 2800 mg	Not hospitalized. Day 11 symptom score 3.
LY 7000 mg	Not hospitalized. Day 11 symptom score 0.
LY 2800 mg	Not hospitalized. Day 11 symptom score 0.
LY 7000 mg	Not hospitalized. Day 11 symptom score 1.
LY 700 mg	Not hospitalized. Day 11 symptom score 0.
LY 7000 mg	Not hospitalized. Day 11 symptom score 0.
LY 700 mg	Not hospitalized. Day 11 symptom score 4.
PBO	Not hospitalized. Day 11 symptom score 1.
LY 2800 mg	Not hospitalized. Day 11 symptom score 3.
LY 7000 mg	Not hospitalized. Day 11 symptom score 2.
PBO	Not hospitalized. Day 11 symptom score 0.
LY 700 mg	Not hospitalized. Day 11 symptom score 0.
LY 700 mg	Not hospitalized. Day 11 symptom score 0.
LY 2800 mg	Not hospitalized. Day 10 symptom score 0.
PBO	Not hospitalized. Day 11 symptom score 2.
LY 7000 mg	Not hospitalized. Day 11 symptom score 0.
LY 2800 mg	COVID-19-related hospitalization 21 days after dosing, for weakness and shortness of breath. 79-year-old male, BMI 27, with history of diabetes mellitus, blood cholesterol increased, and hypertension.
LY 2800 mg	Not hospitalized. Day 11 symptom score 0.
PBO	Not hospitalized. Day 11 symptom score 0.
LY 7000 mg	Not hospitalized. Day 11 symptom score 1.
LY 700 mg	Not hospitalized. Day 11 symptom score 4.
LY 7000 mg	Not hospitalized. Day 11 symptom score 2.
LY 7000 mg	Not hospitalized. Day 11 symptom score 0.

Treatment	Clinical Outcome
PBO	Not hospitalized. Day 11 symptom score 0.
LY Combo	Not hospitalized. Day 11 symptom score 0.

Of note 11 patients belonged to the 2800mg group, another 11 to the 7000mg group, 7 to the 700mg group and another 7 to the placebo group. Only one belonged to the combination group. The vast majority of the patients did not required hospitalisation and had a relative low symptoms score. Three patients (2 in the 7000mg and 1 in the 2800mg group) required hospitalisation.

Putative Resistance-Associated Variants in Clinical Studies

Non-clinical studies using serial passage of SARS-CoV-2 and directed evolution of the S protein were unable to select for resistant viral variants under the pressure of the combination of bamlanivimab and etesevimab.

Evaluation of susceptibility of variants identified through global surveillance in subjects treated with bamlanivimab and etesevimab is ongoing. Genotypic and phenotypic testing and analysis are ongoing to monitor for potential bamlanivimab- and etesevimab-resistance-associated spike variations in clinical trials. Detection of phenotypically confirmed bamlanivimab- or etesevimab-resistant variants in baseline samples have been rare; (0% 0/14) in the Phase 1 clinical study PYAA and 0.4% (2/523) in clinical study BLAZE-1 (Treatment Arms 1 through 4 and 6).

In the bamlanivimab monotherapy Phase 1 study, PYAA, one of the 11 participants had a treatment-emergent variation detected at S494P of the S protein. This variant was previously identified in the in vitro selection studies and had showed a bamlanivimab-resistant phenotype when tested in the vesicular stomatitis pseudovirus neutralization assay (>100-fold reduction). However, etesevimab retains full potency versus the S494P variant.

Viral sequencing and subsequent analysis is still in progress for the BLAZE-1 clinical study treatment arms 1 through 4 and 6. Preliminary analysis has focused on the presence of variations at sites of phenotypically confirmed bamlanivimab- or etesevimab-resistance-associated variations (bamlanivimab: E484, F490, Q493, S494; etesevimab: K417, D420 and N460).

Considering all variants detected at positions D420, N460, E484, F490, and S494, 6.1% (6/98) and 9.2% (9/98) of participants in the 700-mg bamlanivimab arm harbored such a variant post baseline at ≥50% and ≥15% allele fractions, respectively. Although overall less than 10%, this was more frequent than what was observed in the combination of etesevimab with bamlanivimab: 0% (0/102) and 3.9% (4/102) at ≥50% and ≥15% allele fractions, respectively. The majority of the variants were first observed on Day 7 following treatment initiation. Some of the variants were detected in individuals at more than one time point in the 700 mg bamlanivimab arm: 4/9 and 4/6 at ≥15% and ≥50% allele fractions, respectively; however, in the bamlanivimab and etesevimab arm there were no such observations (0/4 at ≥15% allele fraction). When the genotypic analysis was restricted to high-risk participants, no variations were detected in the etesevimab with bamlanivimab combination arm. In the 700-mg bamlanivimab arm, variants were detected at 9.3% (4/43) and 14.0% (6/43) variant frequency for the ≥50% and ≥15% allele fractions, respectively.

Change in viral load was analysed excluding all treated subjects that had a treatment-emergent detection of a phenotypically confirmed bamlanivimab-resistant variation in spike (table 23). Numerically greater reduction in viral load by the monotherapy can be observed on Study Days 3 and 7 when compared with the analysis of all patients. The clinical relevance of this observation is not known.

Table 23 - Bamlanivimab and Etesevimab Treatment-Emergent Resistance-Associated Variations at Positions K417, D420, N460, E484, F490, and S494

•	LY Combo	700 mg LY Mono	2800 mg LY Mono	7000 mg LY Mono	PBO
• All Participants • ≥50% VAF	0% (0/102)	6.1% (6/98)	6.9% (7/102)	11.3% (11/97)	3.4% (5/145)
• All Participants • ≥15% VAF	3.9% (4/102)	9.2% (9/98)	12.7% (13/102)	15.5% (15/97)	6.2% (9/145)
• Multiple Time Points Detection ≥50% VAF	0/0	4/6	6/7	7/11	0/5
• Multiple Time Points Detection ≥15% VAF	0/4	4/9	6/13	8/15	0/9
• High-Risk Participant ≥50% VAF	0% (0/33)	9.3% (4/43)	14.3% (6/42)	18.2% (8/44)	1.5% (1/65)
• High-Risk Participant ≥15% VAF	0% (0/33)	14.0% (6/43)	23.8% (10/42)	22.7% (10/44)	3.1% (2/65)

Abbreviations: VAF = variant allele frequency; LY mono = bamlanivimab; LY combo = bamlanivimab + etesevimab.

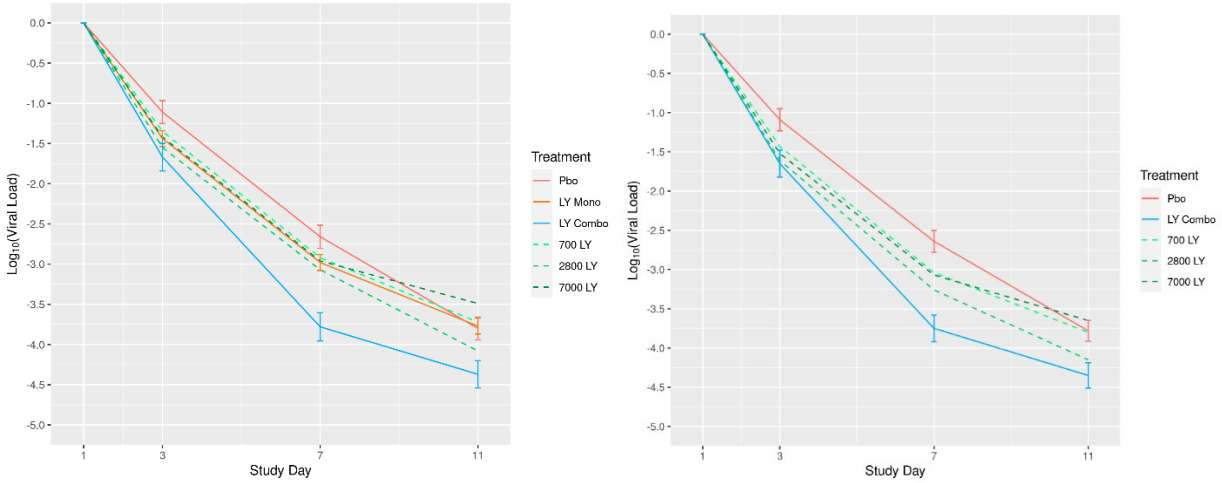


Figure 14 - ARS-CoV-2 viral load change from baseline by visit (with standard error). Left: All treated subjects; Right: Data with exclusion of subjects with phenotypically confirmed bamlanivimab-resistant variations.

Phenotypic data generated to date show that the bamlanivimab and etesevimab-resistant variants observed clinically are susceptible to neutralization in vitro by the other half of the combination, with no cross-resistance detected. In addition, the majority of participants harboring resistant associated viruses exhibited viral clearance, suggestive of participants developing an effective adaptive polyclonal immune response.

Overall, the data collected to date suggest that resistance-associated variations could potentially lead to treatment failure in a low proportion of treated subjects, however these genetic variants have not resulted in clinical safety concerns. Subjects having viruses with resistance-associated variations have shown similar Day 11 symptom scores and outcomes as those without. Although the detection of treatment-emergent variations was lower in the combination therapy arms, the frequency of detection with the 700 mg bamlanivimab monotherapy was still less than 10%, which is of minimal overall risk compared to the relative benefit of treatment. Thus, this data supports the use of bamlanivimab monotherapy in the setting of a pandemic.

2.2.2. Conclusions on Efficacy

Data to justify Bamlanivimab monotherapy was only based on a non-confirmatory Phase 2 study with 3 monotherapy arms (plus one additional combination therapy arm) and no error control for interim analyses or across arms. In this Phase 2 part of study PYAB, the change from baseline to Day 11 in SARS-CoV-2 viral load was assessed as the primary endpoint. No significant differences between bamlanivimab monotherapy, independent of the administered dose, compared to placebo could be demonstrated. However, it should be noted that also participants receiving placebo showed effective viral clearance by Day 11.

Results from the secondary endpoint of change from baseline in viral load at Day 7 suggest a potential treatment effect for bamlanivimab monotherapy, as differences in viral load compared to placebo were seen in all bamlanivimab dose groups.

The pooled analysis for all bamlanivimab arms also showed differences compared to placebo at days 3 and 7 with p-values below 5%. Nevertheless, there are limitations due to the pooled data and no subsequent confirmation of clinical efficacy in the intended patient population.

Subgroup analyses for Bamlanivimab monotherapy in patients who are at high risk for severe COVID-19 disease and patients with high baseline viral load were defined post hoc. Results in these subgroups need to be treated with great care.

Covid-19–related in-patient hospitalization, a visit to the emergency department, or death was a secondary endpoint in the phase-2 portion of the trial.

In total 14 of 465 participants, needed COVID-19-related hospitalizations and emergency room visits. A smaller percentage of bamlanivimab monotherapy-treated participants progressed to COVID-19-related hospitalizations or emergency room visits compared with placebo-treated participants. This also applied to the group of high-risk participants. The hospitalisation was defined in the protocol as at least 24 hours of acute care. However, no consistent, clear criteria were defined for the determination of whether a hospitalisation event or ER visit was related to COVID-19. This decision was on the discretion of the blinded investigator and was evaluated case-by-case. This reduces the validity of that endpoint. In addition, clinical endpoints were only secondary endpoints without error control and limited sample size. In conclusion, data presented for the secondary endpoints, COVID-19-Related Hospitalization, Emergency Room Visit, or Death might support a clinical effect.

In the phase-2 portion of the study for the Symptom score change from baseline by visit, bamlanivimab monotherapy treated participants showed a lower time-weighted average symptom score from Day 1 to Day 11, compared with placebo-treated participants. All three bamlanivimab doses showed a similar change from baseline in symptom score.

For subjects who have at least 1 risk factor for progression to severe disease and/or hospitalization, the best results in change in symptom score over time was shown in patients receiving the highest bamlanivimab dose at day 11 compared to placebo.

For the time to first symptom resolution (measured at a single time point), median time was reduced by 1 day under bamlanivimab treatment compared to placebo (8 days for bamlanivimab 700 mg and 2800 mg vs 9 days for placebo).

Regarding Bamlanivimab/Etesevimab combination therapy, the primary endpoint was met for the phase-3 part of the study. There were 11 events of COVID-19 related hospitalisation or death from any cause by day 29 in patients taking Ly combo therapy and 36 events in patients taking placebo, representing a 70 percent relative risk reduction (p= 0.004).

Based on the data available the absolute risk reduction is assumed to be 36/499 (PBO) - 11/508 (Ly Combo) = 0.072 – 0.022 = 0.05, i.e. 5%.

All 10 cases of death by any cause occurred in the placebo group. Narratives of deaths were provided for 7 subjects; for 3 subjects only few baseline characteristics and study dates of events were provided. The following causes of death were reported: fatal respiratory failure grade V/ worsening COVID-19 pneumonia; shortness of breath; hypertensive coronary heart disease/ chronic cellulitis of lower extremities/ hyperlipidaemia/ hypercholesterolemia/ atherosclerotic heart disease; elevated D-dimer/ low O2 level/ abnormal breath sounds; acute hypoxic respiratory failure; hypoxemia secondary to COVID-19; hyperglycaemia. Two (2) cases seem to be a result of deterioration of underlying chronic disease, whereas 5 cases were associated with respiratory symptoms.

In the phase 2 portion of the study, no deaths occurred under Ly combo therapy or the corresponding placebo treatment. One (1) event (0.9%) of COVID-19-Related Hospitalization occurred under Ly combo therapy, while 9 events (5.8%) occurred under placebo.

The secondary endpoint observing viral load was also met for the phase-3 part of the study - treatment with etesevimab and bamlanivimab combination therapy improved viral load change from baseline to Day 7 compared to placebo. This effect is also supported by phase-2 data (from treatment arm 6 (LY combo) and 1 (placebo), which showed comparable results for overall population as well as for high-risk population. Additionally, the pre-specified primary endpoint of phase-2 portion of the study, namely change from baseline to Day 11 in viral load, was met for the combination of bamlanivimab and etesevimab. The clinical relevance of these findings remains unclear.

Phase-2 data suggest that the effect of etesevimab and bamlanivimab treatment on reduction of viral load may be more pronounced in subjects with high baseline viral load. It is not clear if this translates to clinical endpoints such as hospitalization or death of any cause as subgroup analyses for this endpoint are not considered reasonable due to the very low number of overall events. Thus, based on currently available data, no clear conclusion can be drawn on whether or not patients with high viral load will especially benefit from treatment with etesevimab and bamlanivimab combination therapy.

In the phase-3 part of the study, treatment with etesevimab and bamlanivimab combination therapy reduced the percentage of participants with persistent high viral load (PHVL) compared to placebo. This effect is also supported by phase-2 data (from treatment arm 6 (LY combo) and 1 (placebo)), which showed comparable results for overall population as well as for high-risk population. The use of PHVL as surrogate endpoint for hospitalization or death remains questionable at present.

Median time to sustained symptom resolution (measured at 2 consecutive time points) was 1 day shorter under etesevimab and bamlanivimab treatment compared to placebo (median: 8 days for Ly combo vs 9 days for placebo). The magnitude of this treatment effect is of questionable clinical relevance.

A dose of 700 mg bamlanivimab administered alone has been proposed for the monotherapy. Administration of bamlanivimab is expected to occur within 10 days of symptom onset. Results from Study PYAB show that 96% of the participants were enrolled within 10 days of symptom onset. The

dose levels of bamlanivimab administered in Study PYAB were informed by pharmacokinetics/pharmacodynamics (PK/PD) modelling and observed data from Study J2W MC (PYAA) supporting safety, tolerability, and PK of bamlanivimab (please see non-clinical section). The starting dose of 700 mg bamlanivimab in Study PYAA was selected as the maximum therapeutic dose to reduce viral load based on viral dynamic PK/PD modelling and has a sustained concentration above the estimated IC90 of viral neutralisation for at least 28 days in 90% of the patient population. In addition, the exposure-multiple is greater than 55-fold supporting the toxicology margin of safety. The data from Study PYAB showed that all 3 doses of bamlanivimab (700, 2800, and 7000 mg), when compared to placebo, were effective at reducing viral load, decreasing the time to symptom improvement and resolution, as well as decreasing the frequency of COVID-19-related emergency room visits and hospitalisations. Given the similar response across the range of 700 mg to 7000 mg, it has been proposed to administer bamlanivimab 700 mg as an IV infusion.

The PK of bamlanivimab were not different between Study PYAA and Study PYAB, suggesting PK was not affected by disease severity or markers of inflammation. No dose adjustment is recommended in patients based on disease severity.

Dose justification for monotherapy in paediatric patients is based on PK and PK/PD modelling data only. Based on exposure-matching using an allometric PK model of bamlanivimab, the dose for paediatric patients weighing 40 kg or higher is the same as the adult dose of 700 mg.

It should be emphasized that the presented data package did not include any clinical data for the proposed posology of 700 mg bamlanivimab + 1400 mg etesevimab, but only results for 2800 mg bamlanivimab +2800 mg etesevimab. The Applicant used modeling approaches in order to support the lower doses.

Similarly, as for monotherapy, deterministic simulations were performed using the population parameter estimates to obtain a greater understanding of the treatment effect. The simulation results suggested that the treatment effect is expected to be greater for patients who are treated earlier during the course of the disease, as expected. Further, PK/PD modelling suggests a faster time to viral clearance by an average of 1.5 days (high risk) to 3 days (low risk) from placebo following the combination treatment. Slightly greater reduction is also reflected in model-based estimated IC90 values: The serum concentration IC90 (90% maximal inhibitory concentration) estimate from the viral dynamic model was 1.0 µg/mL (upper 95% CI) for bamlanivimab (< 2.3 µg/mL estimated for monotherapy). This value again compares well with the in vitro 95% CI of 0.029-0.265 µg/mL, after accounting for 6.5% lung penetration (0.446-4.1 µg/mL). Monte Carlo simulations were also performed to determine the probability of patients achieving the IC90 concentration 28 days after a single 700 mg IV dose of bamlanivimab and 1400 mg of etesevimab. Results indicate that the proposed target doses but also lower doses would result in exposure > IC90 28 days after dosing for over 90% of the simulated population. Thus, based on PK/PD analysis of all available data from Study PYAB revealing very flat relationships over different dose strength of both antibodies, and in vitro potency information, the viral load reduction for 2800 mg bamlanivimab and 2800 mg etesevimab administered together is expected to be equivalent to the effect of 700 mg and 1400 mg. This seems to be supported by data from Study PYAH (BLAZE-4) in terms of viral load change from baseline.

Overall, from PK/PD and symptom-viral dynamic modelling results, it is indicated that timing (time after symptom onset) of dosing seems to outweigh the effect of different dose strength for bamlanivimab monotherapy and in combination with etesevimab. Dose selection is supported by PK/PD modelling in terms of a) resulting in exposure for most patients exceeding the IC90 values calculated by PK/PD modelling (viral load data) and in vitro data and b) indicating a slightly greater reduction in viral load for combination. However, only high dose combination data (2800 mg/2800 mg) were used in PK/PD modelling, limiting modelling-based conclusions for lower dose combinations

(700 mg/1400 mg.). Furthermore, data and modelling show very flat PK/PD relationships that prevents definite conclusions on precise dose selection based on viral load data.

Dose justification in paediatric patients is based on PK and PK/PD modelling data only. In general, pediatric dosing of adolescent patients aged 12 years or older and weighing at least 40 kg based on exposure matching with adult exposure is endorsed. Exposure for adolescents weighing at least 40 kg can be robustly predicted and are expected to match the adult exposure following the adult target dose(s).

Viral sequencing and subsequent analysis for viral mutations is still in progress for the BLAZE-1 clinical study treatment arms 1 through 4 and 6. At present, there are insufficient clinical data to state unequivocally that bamlanivimab and etesevimab is effective against the viral variants. Some data suggest that resistance-associated variations could potentially lead to treatment failure in a low proportion of treated subjects. A combination of both, bamlanivimab and etesevimab could possibly minimize this risk of treatment failure by viral variants. More data are required to obtain and evaluate a significant effect against the viral variants.

2.2.3. Safety

Safety of Bamlanivimab Monotherapy for the Treatment of COVID-19

The safety data presented within this section is from the 04 November 2020 database lock, at which point all participants in Treatments Arms 1 through 4 had reached Day 29.

Adverse Events

Summary of Adverse Events

Table 24 - Summary of Adverse Events

• n (%)	PBO[a] (N = 156)	700 mg LY (N = 101)	2800 mg LY (N = 107)	7000 mg LY (N = 101)	LY Mono[b] (N = 309)
• TEAEs	44 (28.2)	29 (28.7)	26 (24.3)	24 (23.8)	79 (25.6)
• TEAEs by severity					
• Mild	23 (14.7)	18 (17.8)	17 (15.9)	11 (10.9)	46 (14.9)
• Moderate	18 (11.5)	7 (6.9)	7 (6.5)	8 (7.9)	22 (7.1)
• Severe	3 (1.9)	3 (3.0)	2 (1.9)	5 (5.0)	10 (3.2)
• Deaths[d]	0	0	0	0	0
• SAEs	1 (0.6)	1 (1.0)	0	0	1 (0.3)
• DCs due to AEs	0	0	0	0	0

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; DC = discontinuation of study drug; LY = bamlanivimab; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

a Placebo is data from Treatment Arm 1.

b LY Mono is pooled data from 700 mg bamlanivimab (Treatment Arm 2), 2800 mg bamlanivimab (Treatment Arm 3), and 7000 mg bamlanivimab (Treatment Arm 4).

e Does not include SAEs and Deaths related to COVID 19, as they are captured as study outcomes.

Treatment-emergent adverse events (TEAEs)

Treatment-emergent adverse events (TEAEs) reported in ≥1% of all participants in Treatment Arms 1 through 4 of Study PYAB are summarized in table 25.

Table 25 - Treatment-Emergent Adverse Events by Preferred Term Occurring in ≥1% of All Patients in Study PYAB

• n (%)	PBO (N = 156)	700 mg LY (N = 101)	2800 mg LY (N = 107)	7000 mg LY (N = 101)	LY Mono[a] (N = 309)
• Nausea	6 (3.8)	3 (3.0)	4 (3.7)	4 (4.0)	11 (3.6)
• Pruritus	1 (0.6)	2 (2.0)	3 (2.8)	0	5 (1.6)
• Diarrhoea	7 (4.5)	1 (1.0)	1 (0.9)	5 (5.0)	7 (2.3)
• Dizziness	3 (1.9)	3 (3.0)	3 (2.8)	3 (3.0)	9 (2.9)
• Rash	1 (0.6)	1 (1.0)	0	1 (1.0)	2 (0.6)
• Vomiting	4 (2.6)	1 (1.0)	3 (2.8)	1 (1.0)	5 (1.6)
• Pyrexia	0	1 (1.0)	2 (1.9)	1 (1.0)	4 (1.3)
• Headache	3 (1.9)	3 (3.0)	2 (1.9)	1 (1.0)	6 (1.9)
• Chills	0	0	1 (0.9)	3 (3.0)	4 (1.3)
• Hypertension	1 (0.6)	1 (1.0)	0	3 (3.0)	4 (1.3)

• n (%)	PBO (N = 156)	700 mg LY (N = 101)	2800 mg LY (N = 107)	7000 mg LY (N = 101)	LY Mono[a] (N = 309)
• Blood pressure increased	0	3 (3.0)	0	0	3 (1.0)
• Chest discomfort	1 (0.6)	0	1 (0.9)	2 (2.0)	3 (1.0)
• Dyspnoea	0	1 (1.0)	1 (0.9)	1 (1.0)	3 (1.0)
• Fatigue	0	0	1 (0.9)	2 (2.0)	3 (1.0)
• Lipase increased	0	1 (1.0)	0	2 (2.0)	3 (1.0)
• Nasal congestion	1 (0.6)	2 (2.0)	1 (0.9)	0	3 (1.0)
• Thrombocytosis	0	1 (1.0)	2 (1.9)	0	3 (1.0)

Abbreviations: LY = bamlanivimab; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo.

[a] LY Mono is pooled data from 700 mg bamlanivimab (Treatment Arm 2), 2800 mg bamlanivimab (Treatment Arm 3), and 7000 mg bamlanivimab (Treatment Arm 4).

Deaths, Serious Adverse Events, and Discontinuations due to Adverse Events

Deaths

As of 04 November 2020, there have been no deaths in Treatment Arms 1-4.

Serious Adverse Events

Two Serious adverse events (SAEs) were reported: a severe case of upper abdominal pain in a patient who received placebo and a severe case of diabetic ketoacidosis in a patient who received bamlanivimab 700mg.

Discontinuations due to Adverse Events

As of 04 November 2020 (the database lock for this data), there have been no discontinuations due to AEs.

Hypersensitivity and Infusion-related Reactions

Immediate hypersensitivity events

No cases of Anaphylaxis were identified via the Anaphylactic Reaction SMQ algorithmic search. Additionally, no infusion-related reactions were reported.

The following preferred terms (PTs) (narrow terms) were reported within 24 hours of administration:

- 2 (0.6%) participants reported an event, including swelling face (1) and hypersensitivity (1) from the all bamlanivimab monotherapy group.
- No participants reported a narrow term from the placebo arm.

Broad terms reported within 24 hours of administration included

- pruritis (3), flushing (1), and chest discomfort (1) from the all bamlanivimab monotherapy group

- flushing (1) from the placebo arm.

The most common event reported within 24 hours was pruritis.

Non-immediate hypersensitivity events

The following PTs (narrow terms) were reported greater than 24 hours after study drug administration:

- 5 (1.6%) participants reported events, including rash (2), hypersensitivity (1), urticaria (1), and swelling face (1) from the bamlanivimab monotherapy arm
- 4 (2.6%) participants reported the events of rash (1), hypersensitivity (1), urticaria (1), and dermatitis contact (1) from the placebo arm.

Broad terms reported greater than 24 hours after study drug administration included:

- chest discomfort (2), cough (2), dyspnoea (3), pruritis (2), stomatitis (1), and oedema peripheral (1) from the bamlanivimab monotherapy arm, and
- asthma (1), chest discomfort (1), conjunctivitis (1), cough (1), and pruritis (1) from the placebo arm.

Overall, TEAEs were non-serious, predominantly mild to moderate in severity, and none led to interruption or discontinuation of study drug.

Other Adverse Events and Laboratory Abnormalities

For haematology parameters and serum creatinine, clinical significance was defined as

- CTCAE Grade 3 with associated clinical AEs reported, or
- CTCAE Grade 4.

For liver function tests (LFTs), clinical significance was defined as

- leading to additional testing, per protocol, with associated clinical AEs reported.

Absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and triggering LFT testing were the only clinically significant treatment-emergent changes in haematology or clinical chemistry parameters.

There were no treatment-emergent (TE)-decreases in ALC or LFT events that led to addition testing.

Anti-drug Antibodies

Samples for immunogenicity assessments have been collected and stored. The anti-drug antibody (ADA) assays for bamlanivimab (LY3819253) are currently being validated. PYAB immunogenicity samples will be analysed as soon as the assays are available. To date, no subjects with clear evidence of increased drug clearance or safety events that are indicative of clinically impactful ADA in any study have been observed. The risks to subjects from ADA is minimized by the single-dose treatment.

Pregnancy

One participant reported pregnancy at Day 11 in the bamlanivimab 2800-mg monotherapy treatment arm. A urine pregnancy test at the screening visit was negative. The patient decided to terminate the pregnancy at Day 53.

Post-Emergency Use Authorisation Spontaneous Data

Currently it is not possible to adequately estimate how many patients have been administrated bamlanivimab on a post-authorisation setting.

The Lilly Safety System data was searched cumulatively through 18 December 2020 for all spontaneously reported cases with adverse events where bamlanivimab was administered under the US emergency use authorisation. Two hundred sixty-six cases (794 events total) were identified from this search. Of the 266 cases, 181 (68%) were serious and 85 (32%) were non serious. Six out of the 266 cases included an event with a fatal outcome (Section 4.4.1.1.4.1). Where time to onset information was reported, 151 cases included an event that occurred within 24 hours of infusion.

Events that occurred within 24 hours of bamlanivimab infusion

The 266 spontaneously reported cases received cumulatively through 18 December 2020 were reviewed, including the potential for confusion or disorientation and clinical worsening or onset of symptoms associated with COVID-19 that occurred within 24 hours of bamlanivimab administration.

Upon review of these cases, 151 of 266 cases (57%) involved 1 or more event that occurred within 24 hours of infusion, and most of the events (58%) were during or within 2 hours of infusion. These 151 cases included 408 events. The event outcomes were reported as recovered (99), recovering (38), not recovered (37), fatal (1), and unknown (233).

One hundred and seven cases reported infusion-related events within 24 hours of bamlanivimab administration, of which 42% (45 of 107 patients) were hospitalised. Fifty-eight percent did not require further intervention, 27% were treated with steroids and/or antihistamines, 20% required oxygen due to decreased oxygen saturations, 8% required administration of cardiovascular medications due to dysrhythmias, and 3% were treated with epinephrine or norepinephrine.

Of the 107 cases involving infusion-related events, there were 10 cases describing confusion or disorientation. Where age was noted, 70% were ≥70 years of age. Four were experiencing fevers at the time of event, and 2 had past medical history that may have potentiated the event (i.e., sundowning or dementia). In the majority of these cases, the outcome of the events was unknown.

These cases were also reviewed for clinical worsening or onset of symptoms associated with COVID-19 within 24 hours of bamlanivimab administration; and while only a few cases reported the event of COVID-19 or COVID-19 pneumonia, 28 cases described symptoms consistent with COVID-19, and 21 of these required hospitalisation. Although the majority of patients were treated within days of a positive test, it is unclear how long these patients had symptoms prior to receiving bamlanivimab.

Clinical Worsening or Onset of Symptoms Associated with COVID-19

Of the 107 cases reporting infusion-related events within 24 hours of bamlanivimab administration, there were 28 cases involving events that appeared to be related to clinical worsening or onset of symptoms associated with COVID-19.

The clinical presentation of the cases (26% [28/107]) included hypoxia, shortness of breath, pyrexia, and decreased oxygen saturation. Of these 28 cases, 21 required hospitalisation. The outcomes included 5 recovered, 3 recovering, 1 not recovered, 1 fatal, and 18 outcome unknown.

Safety of Bamlanivimab in Combination with Etesevimab for the Treatment of COVID-19

The primary safety evaluation was based on data from the phase-3 portion of the study PYAB. Data from the phase-2 portion of the trial are considered as supportive for safety assessment.

Summary of adverse events

The table below shows an overview of Treatment-Emergent Adverse Events in the safety population of the phase-3 portion of the study PYAB (treatment arms 7 (LY combo) and 8 (placebo)).

Table 26 - Overview of Adverse Events (Safety Population) in Treatment Arms 7 (LY combo) and 8 (placebo)

Category	Pbo (N=517) n (%)	2800 LY Combo (N=518) n (%)	Total (N=1035) n (%)	p-values*b 2800 LY Combo vs. Pbo
Treatment-emergent adverse event (TEAE)	60 (11.6)	69 (13.3)	129 (12.5)	0.452
TEAE by severity *a				
Mild	35 (6.8)	37 (7.1)	72 (7.0)	
Moderate	20 (3.9)	24 (4.6)	44 (4.3)	
Severe	5 (1.0)	7 (1.4)	12 (1.2)	0.773
Missing	0	1 (0.2)	1 (0.1)	
Death	2 (0.4)	0	2 (0.2)	0.249
Serious adverse event	5 (1.0)	7 (1.4)	12 (1.2)	0.773
Discontinuation from study treatment due to adverse event (including death)	2 (0.4)	0	2 (0.2)	0.249

Abbreviations: 2800 LY Combo = 2800 mg bamlanivimab and 2800 mg etesevimab administered together; N = number of participants in the analysis population; n = number of participants in the specified category; Pbo = placebo; TEAE = treatment-emergent adverse event; vs = versus.
Note: After DBL, it was determined that there was only 1 non-COVID-19-related death. The tables will be updated during an upcoming data refresh.
*a Patients with multiple occurrences of the same event are counted under the highest severity.
*b p-value was computed using Fisher's test.

The table below presents an overview of TEAEs from the phase-2 portion of the study PYAB (excerpt for treatment arms 1 and 6, supportive data).

Table 27 - Summary of Adverse Events in Treatment Arms 6 (LY combo) and 1 (placebo)

n (%)	PBO[a] (N = 156)	LY Combo[b] (N = 112)
TEAEs	44 (28.2)	20 (17.9)
TEAEs by severity		
Mild	23 (14.7)	15 (13.4)
Moderate	18 (11.5)	4 (3.6)
Severe	3 (1.9)	1 (0.9)
Deaths[c]	0	0
SAEs	1 (0.6)	1 (0.9)
DCs due to AEs	0	0

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; DC = discontinuation of study drug; LY = bamlanivimab; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
a Placebo is data from Treatment Arm 1.
b LY Combo is data from the 2800-mg bamlanivimab/2800-mg etesevimab group (Treatment Arm 6).
c Does not include SAEs and Deaths related to COVID 19, as they are captured as study outcomes

Analysis of Adverse Events - TEAEs

The table below provides TEAEs by preferred terms occurring in ≥3 study subjects of the phase-3 portion of the study PYAB (treatment arms 7 (LY combo) and 8 (placebo)).

Table 28 - Treatment-Emergent Adverse Events Occurring in 3 or More Study Participants (Safety Population) in Treatment Arm 7 (Ly combo) and 8 (placebo)

Preferred Term	Pbo (N=517) n (%)	2800 LY Combo (N=518) n (%)	Total (N=1035) n (%)	p-values*b 2800 LY Combo vs. Pbo
Subjects with >= 1 TEAE	60 (11.6)	69 (13.3)	129 (12.5)	0.452
Nausea	4 (0.8)	5 (1.0)	9 (0.9)	>0.999
Rash	3 (0.6)	6 (1.2)	9 (0.9)	0.506
Dizziness	3 (0.6)	4 (0.8)	7 (0.7)	>0.999
Diarrhoea	2 (0.4)	2 (0.4)	4 (0.4)	>0.999
Hypertension	2 (0.4)	2 (0.4)	4 (0.4)	>0.999
Vaginal infection*a	1 (0.4)	1 (0.4)	2 (0.4)	>0.999
Gastrooesophageal reflux disease	0	3 (0.6)	3 (0.3)	0.249
Pruritus	0	3 (0.6)	3 (0.3)	0.249
Urinary tract infection	0	3 (0.6)	3 (0.3)	0.249
Urticaria	1 (0.2)	2 (0.4)	3 (0.3)	>0.999
Vomiting	1 (0.2)	2 (0.4)	3 (0.3)	>0.999

Abbreviations: 2800 LY Combo = 2800 mg bamlanivimab and 2800 mg etesevimab administered together; N = number of participants in the analysis population; n = number of participants in the specified category; Pbo = placebo; TEAE = treatment-emergent adverse event; vs = versus.

*a Denominator adjusted because gender-specific event for females: N = 259 (Pbo), N = 279 (2800 LY Combo).

*b p-values was computed using Fisher's exact test.

An excerpt for treatment arms 1 and 6 of TEAEs reported in ≥1% of all participants in the phase-2 portion of the study PYAB is presented in the table below (supportive data).

Table 29 - Treatment-Emergent Adverse Events by Preferred Term Occurring in ☐1% of All Patients in Phase-2 portion of Study PYAB, treatment arm 1 and 6

n (%)	PBO (N = 156)	LY Combo[a] (N = 112)
Nausea	6 (3.8)	4 (3.6)
Pruritus	1 (0.6)	2 (1.8)
Diarrhoea	7 (4.5)	1 (0.9)
Dizziness	3 (1.9)	1 (0.9)
Rash	1 (0.6)	1 (0.9)
Vomiting	4 (2.6)	1 (0.9)
Pyrexia	0	1 (0.9)
Headache	3 (1.9)	0
Chills	0	0
Hypertension	1 (0.6)	0
Blood pressure increased	0	0
Chest discomfort	1 (0.6)	0
Dyspnoea	0	0
Fatigue	0	0
Lipase increased	0	0
Nasal congestion	1 (0.6)	0
Thrombocytosis	0	0

Abbreviations: LY = bamlanivimab; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo.

[a] LY Combo is data from the 2800-mg bamlanivimab/2800-mg etesevimab group (Treatment Arm 6).

Deaths

No deaths have occurred so far.

Serious Adverse Events

The table below provides SAEs within SOC of the phase-3 portion of the study PYAB (treatment arms 7 (LY combo) and 8 (placebo)).

Table 30 - Serious Adverse Events within System Organ Class (Safety Population) in Treatment Arms 7 (LY combo) and 8 (placebo)

System Organ Class Preferred Term	Pbo (N=517) n (%)	2800 LY Combo (N=518) n (%)	Total (N=1035) n (%)	p-values*b 2800 LY Combo vs. Pbo
Subjects with >= 1 SAE	5 (1.0)	7 (1.4)	12 (1.2)	0.773
Cardiac disorders	0	4 (0.8)	4 (0.4)	0.124
Acute myocardial infarction	0	1 (0.2)	1 (0.1)	>0.999
Atrial fibrillation	0	1 (0.2)	1 (0.1)	>0.999
Atrial flutter	0	1 (0.2)	1 (0.1)	>0.999
Ventricular extrasystoles	0	1 (0.2)	1 (0.1)	>0.999
Metabolism and nutrition disorders	2 (0.4)	1 (0.2)	3 (0.3)	0.624
Hyperglycaemia	1 (0.2)	1 (0.2)	2 (0.2)	>0.999
Dehydration	1 (0.2)	0	1 (0.1)	0.500
Gastrointestinal disorders	1 (0.2)	0	1 (0.1)	0.500
Abdominal pain	1 (0.2)	0	1 (0.1)	0.500
General disorders and administration site conditions	1 (0.2)	0	1 (0.1)	0.500
Sudden death	1 (0.2)	0	1 (0.1)	0.500
Injury, poisoning and procedural complications	0	1 (0.2)	1 (0.1)	>0.999
Toxicity to various agents	0	1 (0.2)	1 (0.1)	>0.999
Investigations	0	1 (0.2)	1 (0.1)	>0.999
Catheterisation cardiac	0	1 (0.2)	1 (0.1)	>0.999
Nervous system disorders	1 (0.2)	0	1 (0.1)	0.500
Syncope	1 (0.2)	0	1 (0.1)	0.500
Renal and urinary disorders	0	1 (0.2)	1 (0.1)	>0.999
Acute kidney injury	0	1 (0.2)	1 (0.1)	>0.999
Reproductive system and breast disorders	0	1 (0.2)	1 (0.1)	>0.999
Menorrhagia*a	0	1 (0.4)	1 (0.2)	>0.999
Respiratory, thoracic and mediastinal disorders	0	1 (0.2)	1 (0.1)	>0.999
Hypoxia	0	1 (0.2)	1 (0.1)	>0.999

Abbreviations: 2800 LY Combo = 2800 mg bamlanivimab and 2800 mg etesevimab administered together; N = number of participants in the analysis population; n = number of participants in the specified category; Pbo = placebo; SAE = serious adverse event; vs = versus.

*a Denominator adjusted because gender-specific event for females: N= 259 (Pbo), N = 279 (2800 LY Combo).

*b p-values was computed using Fisher's exact test.

Discontinuations due to adverse events

No Discontinuations due to Adverse Events occurred so far.

Hypersensitivity and Infusion-Related Reactions

Analysis of hypersensitivity, anaphylaxis and infusion-related reactions was performed for the phase-2 portion of the study only.

Immediate hypersensitivity events

No cases of Anaphylaxis were identified via the Anaphylactic Reaction SMQ algorithmic search. Additionally, no infusion-related reactions were reported.

No preferred terms (PTs) (narrow terms) were reported within 24 hours of administration of bamlanivimab/etesevimab combination or placebo

Broad terms reported within 24 hours of administration included

- pruritis (2) from the bamlanivimab/etesevimab combination group, and
- flushing (1) from the placebo arm.

Non-immediate hypersensitivity events

The following PTs (narrow terms) were reported greater than 24 hours after study drug administration:

- 1 (0.9%) participant reported a rash from the bamlanivimab/etesevimab combination arm, and
- 4 (2.6%) participants reported the events of rash (1), hypersensitivity (1), urticaria (1), and dermatitis contact (1) from the placebo arm.

Broad terms reported greater than 24 hours after study drug administration included:

- no event in the bamlanivimab/etesevimab combination arm
- asthma (1), chest discomfort (1), conjunctivitis (1), cough (1), and pruritis (1) from the placebo arm.

Overall, TEAEs were non-serious, predominantly mild to moderate in severity, and none led to interruption or discontinuation of study drug.

Laboratory Abnormalities

Analysis of clinically significant laboratory abnormalities was performed for the phase-2 portion of the study only, with no event detected under bamlanivimab/etesevimab combination treatment.

Immunological Events

The anti-drug antibody (ADA) assays for bamlanivimab and etesevimab are currently being validated. PYAB immunogenicity samples will be analysed as soon as the assays are available. To date, no subjects with clear evidence of increased drug clearance or safety events that are indicative of clinically impactful ADA in any study have been observed. The risks to subjects from ADA is minimized by the single-dose treatment.

Pregnancies

No pregnancies occurred so far under bamlanivimab/etesevimab combination treatment.

2.2.4. Conclusions on safety

Monotherapy

The primary evaluation of safety was based on data from the PYAB trial.

No clinically meaningful differences in the frequency of TEAEs by system organ class (SOC) were observed across treatment groups. The Gastrointestinal Disorders SOC, followed by the Nervous System Disorders SOC, had the highest frequency of participants with TEAEs. TEAEs were non-serious, predominantly mild to moderate in severity, and none led to interruption or discontinuation of study drug.

Only two Serious adverse events (SAEs) were reported: a severe case of upper abdominal pain in a patient who received placebo and a severe case of diabetic ketoacidosis in a patient who received bamlanivimab 700mg.

The most frequently reported hypersensitivity reaction within 24 hours after dose administration was pruritus. Regarding to the delayed reactions, the patients experienced few cases of rash and urticaria, which were non-serious and mild or moderate in intensity. These types of reactions are expected and

have been described as potential COVID-19 signs in the literature (Recalcati, 2020[8]; Young, 2020[9] and Marzano, 2020[10]).

There is a potential risk for hypersensitivity reactions and a definite risk of infusion reactions directly related to the administration of bamlanivimab. Appropriate precautions should be taken during infusion.

In total, three patients reported clinically significant decreases in ANC in BAM group (much higher doses than currently proposed) and one patient in placebo arm. But no detailed information for these cases was provided.

No anti-drug antibody (ADA) assay for bamlanivimab is validated, so far. Thus, no data of ADAs were reported. Although, ADA is minimized by the single-dose treatment and the risks to subjects from ADAs may be considered low, ADAs should be analysed and considered when administrating bamlanivimab. Based on the submitted data, no conclusions can be drawn as to whether ADAs have an impact on the treatment of patients or not and should be investigated to exclude any potential risk.

No clinical data about the potential risk of bamlanivimab treatment for pregnant and lactating women are available.

In conclusion, safety data from Study PYAB showed that bamlanivimab was well tolerated, similar across all dose groups, and seemingly comparable to placebo. Thus, there are no serious concerns about patient safety. Overall, based on the available data, the safety profile is considered to be acceptable by CHMP.

Combination

In the phase-3 portion of the study PYAB, the frequency of TEAEs was comparable in the LY combo treatment group and placebo group (13.3 vs 11.6%). TEAEs were mainly of mild (7.1 vs 6.8%) or moderate (4.6 vs 3.9%) intensity in both treatment groups. There were 7 SAEs in the LY combo treatment group (1.4%) vs. 5 SAEs in the placebo group (1.0%).

In the phase-2 portion of the study, the frequency of TEAEs was lower for LY combo compared to placebo group (17.9 vs 28.2%). Analysis of severity revealed that the frequency of mild TEAEs was comparable between both treatment groups (13.4 vs 14.7%), while the frequency of moderate and severe events was lower for LY combo compared to placebo (moderate: 3.6 vs 11.5%; severe: 0.9 vs 1.9%).

Bamlanivimab and etesevimab have no human target. Thus, no potential risks based on mechanism of action, are expected. Potential concerns associated with protein-based infusion therapies include anaphylaxis, hypersensitivity reactions, and infusion-related reactions. Antibody-dependent enhancement of disease should also be considered as a theoretical risk.

In the LY combo treatment group of the phase-3 part, the highest frequency AEs (reported in ≥3 patients) by PT were rash, nausea, dizziness, gastroesophageal reflux disease, pruritus, and urinary tract infection. Rash occurred twice as frequently as in the placebo group; gastroesophageal reflux disease, pruritus, and urinary tract infection occurred in 3 cases in the Ly combo group, respectively,

[8] Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. J Eur Acad Dermatol Venereol. 2020 May;34(5):e212-e213. doi: 10.1111/jdv.16387. PMID: 32215952.
[9] Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, Ng OT, Marimuthu K, Ang LW, Mak TM, Lau SK, Anderson DE, Chan KS, Tan TY, Ng TY, Cui L, Said Z, Kurupatham L, Chen MI, Chan M, Vasoo S, Wang LF, Tan BH, Lin RTP, Lee VJM, Leo YS, Lye DC; Singapore 2019 Novel Coronavirus Outbreak Research Team. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. JAMA. 2020 Apr 21;323(15):1488-1494. doi: 10.1001/jama.2020.3204. Erratum in: JAMA. 2020 Apr 21;323(15):1510. PMID: 32125362; PMCID: PMC7054855.
[10] Marzano AV, Cassano N, Genovese G, Moltrasio C, Vena GA. Cutaneous manifestations in patients with COVID-19: a preliminary review of an emerging issue. Br J Dermatol. 2020 Sep;183(3):431-442. doi: 10.1111/bjd.19264. Epub 2020 Jul 5. PMID: 32479680; PMCID: PMC7300648.

with no case in the placebo group. In the by study-phase comparisons (phase-3 and phase-2 portion of the study), the most common AEs by PT in the LY combo treatment groups and placebo treatment groups were generally similar.

Four events of cardiac disorders - atrial flutter, ventricular extrasystoles, myocardial infarction, and atrial fibrillation - were reported for bamlanivimab/etesevimab combination treatment (none for placebo. For two subjects, medical history revealed an underlying heart condition. The other two had pre-existing risk factors without cardiac impairment. There is also evidence that COVID-19 infection itself may cause cardiovascular toxicity (Khan, 2020[11]; Costa, 2020; Ragab, 2020[12]; Driggin, 2020[13]). As such, based on the currently available data, it is not possible to make a conclusive assessment of the impact of the of bamlanivimab/etesevimab combination therapy on cardiac risk.

One case of acute kidney injury was presented for the combination therapy that was considered to be associated with lithium toxicity. COVID-19 infection itself may also cause acute kidney injury (Darriverre, 2020[14]). Thus, based on currently available data there is no signal for increased risk of renal impairment under bamlanivimab/etesevimab combination treatment.

Three events of urinary tract infections (UTI) were reported for bamlanivimab/etesevimab combination treatment in the phase 3 portion of the study PYAB (zero for placebo). One of them was considered serious. Additionally, 1 SAE of UTE occurred under bamlanivimab/etesevimab combination treatment in the phase-2 portion of the trial. As such, based on the currently available data, it is not possible to make a conclusive assessment of the impact of the of bamlanivimab/etesevimab combination therapy on urinary tract infections.

One case of hypoxia under bamlanivimab/etesevimab combination treatment was reported as a symptom of asthma exacerbation. As no information regarding laboratory data and clinical course was provided for the time of the event, a deterioration of COVID-19 as possible cause of hypoxia cannot be fully assessed.

No analysis for hypersensitivity, anaphylaxis and infusion-related reactions for the phase-3 portion of the study were performed. Phase-2 portion of the study revealed no safety concerns regarding hypersensitivity, anaphylaxis or infusion-related reactions. Based on currently available data, the risk of hypersensitivity, anaphylaxis and infusion-related reactions under bamlanivimab/etesevimab combination treatment cannot be fully assessed.

No analysis for clinically significant laboratory abnormalities for the phase-3 portion of the study were performed. Phase-2 portion of the study revealed no safety concerns regarding clinically significant laboratory abnormalities. Based on currently available data, the risk of clinically significant laboratory abnormalities under bamlanivimab/etesevimab combination treatment cannot be fully assessed.

No data have been presented on immunological events. Based on the fact that both antibodies are fully human and a single infusion is envisaged, the theoretical risk to subjects from ADA may be considered low.

[11] Khan S, Liu J, Xue M. Transmission of SARS-CoV-2, Required Developments in Research and Associated Public Health Concerns. *Front Med (Lausanne)*. 2020;7:310. Published 2020 Jun 9. doi:10.3389/fmed.2020.00310

[12] Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 Cytokine Storm; What We Know So Far. Front Immunol. 2020 Jun 16;11:1446. doi: 10.3389/fimmu.2020.01446. PMID: 32612617; PMCID: PMC7308649.

[13] Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, Brown TS, Der Nigoghossian C, Zidar DA, Haythe J, Brodie D, Beckman JA, Kirtane AJ, Stone GW, Krumholz HM, Parikh SA. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic. J Am Coll Cardiol. 2020 May 12;75(18):2352-2371. doi: 10.1016/j.jacc.2020.03.031. Epub 2020 Mar 19. PMID: 32201335; PMCID: PMC7198856.

[14] Darriverre L, Fieux F, de la Jonquière C. COVID-19 et insuffisance rénale aiguë en réanimation [Acute renal failure during COVID-19 epidemic]. Prat Anesth Reanim. 2020 Sep;24(4):207-211. French. doi: 10.1016/j.pratan.2020.07.004. Epub 2020 Jul 10. Erratum in: Prat Anesth Reanim. 2020 Dec;24(6):338. PMID: 32837207; PMCID: PMC7351375.

In conclusion, safety data from Study PYAB showed that the combination of bamlanivimab/etesevimab did not reveal any serious concerns. Overall, based on the available data, the safety profile is considered to be acceptable by CHMP.

2.3. Non-clinical aspects

Overview of the non-clinical studies planned or already performed for Bamlanivimab, Etesevimab and the combination, as well as relevant summary of results, with focus on neutralisation activity against virus mutants and potential ADE were submitted.

2.3.1. Pharmacodynamics

Bamlanivimab

Surface plasmon resonance (SPR) experiments were performed in order to characterise the binding activity of bamlanivimab. Competitions with the binding to ACE2 was also investigated. The neutralization capacity of bamlanivimab was assessed *in vitro* using SARS-CoV2 material of different origins. Bamlanivimab has a similar IC50 for all the three isolates analysed (US, Italy, Netherlands), regarding the IC90, higher efficacy is shown against the US (WA1/2020) virus isolate. The Fc-dependent effector functions of Bamlanivimab were also evaluated. Of note, Bamlanivimab is a fully human unmodified IgG1. Bamlanivimab binding with human FcγRI, FcγRIIa, FcγRIIb, and FcγRIIIa receptor extracellular domains, and to the complement protein C1q was reported. However, while ADCC activity was detected, there was no signs of CDC activity.

In vitro selection and characterization of monoclonal antibody-resistant mutations were performed, as well as a study on the neutralisation activity against circulating virus variants of interest (please see discussion below).

Etesevimab

ELISA and SPR experiment to determine Etesevimab binding features were performed. Etesevimab is an IgG1 kappa mAb directed against a foreign target and with abrogated Fc effector function, given by the LALA mutation. The Applicant reports that Etesevimab possesses minimal or no binding affinity for FcγRI, FcγRIIA R167, or FcγRIIIA-V176. Consistently ADCC and CDC activities were not detected.

Etesevimab was also tested for its capacity to neutralise the SarsCoV2 virus. Of note, only two isolates were tested this time (US and Italy isolates). Results indicate a neutralising ability slightly lower than Bamlanivimab.

TCR studies were performed in human (adult and foetal) tissues as well as in cynomolgus monkey tissues. No staining was detected and cynomolgus monkey was selected as relevant species for the toxicology program. A GLP-compliant, 3-week repeat-dose toxicity and toxicokinetic study in cynomolgus monkeys was performed, which evidenced no treatment related adverse findings. As such, the NOAEL dose was considered to be the maximum dose (205mg/kg). The risk of Etesevimab in inducing ADE *in vitro* and *in vivo* was also evaluated. The risk of *in vivo* ADE for Etesevimab was also evaluated *in vivo* in the African green monkey model. No sign of ADE was reported, *in vitro* or *in vivo*.

Combination

The *in vitro* efficacy (viral neutralisation) was also assessed for the combination, with the US and Italy isolate. The neutralisation potency of the combination seems better than Etesevimab alone, and comparable to Bamlanivimab alone. Co-crystal structural analysis of Bamlanivimab and Etesevimab were

preformed, which indicated that the two mAbs bind to two different but overlapping epitopes of the Receptor Binding Site (RBD) of the SARS-CoV-2-S protein. As a consequence, they compete with one another for the binding of the Spike protein.

Analysis of resistance mutations

An *in vitro* selection and characterization of monoclonal antibody-resistant mutations was performed. Two methods were used to evaluate the development of viral resistance to Bamlanivimab, Etesevimab and the combination of Bamlanivimab + Etesevimab: serial passage of 3 authentic SARS-CoV-2 viruses in cell culture, and directed evolution using yeast display libraries of the S-RBD.

Additionally, a panel of variants of interest that were identified through surveillance of the GISAID sequence database were tested, in order to confirm activity of Bamlanivimab and Etesevimab against SARS-CoV-2 isolates in circulation (as of October 2020).

SARS-CoV-2 passaging studies

The potential for SARS-CoV-2 to escape neutralization under selective pressure by Bamlanivimab or Etesevimab, singly or in combination, was studied by *in vitro* serial passages of authentic virus in the presence of Bamlanivimab and/or Etesevimab at a concentration 20 times higher than the IC_{90} for the individual mAb. Cytopathic Effect (CPE) was evidenced at passage 1 or 2. The results are shown in the tables below (derived from the analysis performed with two different instruments).

Table 31 – Resistance of SARS-CoV-2 variants isolated under monoclonal antibody selective pressure

Selection mAb	Parental Isolate	Spike Variant	Neutralization Selection mAb		Cross Neutralization	
			IC_{50} µg/mL (95% CI)	Ratio (Variant/WT)	IC_{50} µg/mL (95% CI)	Ratio (Variant/WT)
LY3819253 (LY-CoV-555) Bamlanivimab	Italy	WT	0.056 (0.027, 0.119)		0.761 (0.341, 1.757)	
		S494P	>4 (no curve)	>71	0.565 (0.051, 7.03)	0.74
	Washington, US	WT	0.008 (0.005, 0.014)		0.025 (0.001, 0.032)	
		F490S	>4 (no curve)	>485	0.130 (0.032, 0.625)	5.2
	Netherlands	WT	0.044 (0.038, 0.051)		0.944 (0.789, 1.134)	
		S494P	>4 (no curve)	>91	0.497 (0.130, 2.064)	0.53
LY3832479 (LY-CoV-016) Etesevimab	Italy	WT	0.761 (0.341, 1.757)		0.056 (0.027, 0.119)	
		N460K	>40 (no curve)	>53	0.019 (0.002, 0.154)	0.34
	Washington, US	WT	0.025 (0.001, 0.032)		0.008 (0.005, 0.014)	
		D420N	>40 (no curve)	>1593	0.019 (0.001, 0.415)	2.4
	Netherlands	WT	0.310 (0.107, 1.071)		0.072 (0.068, 0.075)	
		N460K	>40 (no curve)	>129	0.013	0.18

					(0.001, 0.180)	

Table 32 - Amino Acid Substitutions in SARS-CoV-2 Spike Protein Isolated Under Monoclonal Antibody Selective Pressure

Selection mAb	Virus Isolate	Primary Amino Acid Variations in Spike Protein	Secondary Amino Acid Variations in Spike Protein
LY3819253 (LY-CoV-555) **Bamlanivimab**	Italy	S494P (99%)	None NSPRRARSVA679**del** (100%)
	Washington, US	F490S (99%)	None NSPRRARSVA679**del** (80%)
	Netherlands[a]	S494P (99%)	W64R (21%) W152R (11%) E484D (5%)
LY3832479 (LY-CoV-016) **Etesevimab**	Italy	N460K (66%)	K417N (28%) NSPRRARSVA679**del** (100%)
	Washington, US	D420N (85%)	N460T (15%) QTQTN675**del** (81%)
	Netherlands[a]	N460K (79%) D215H (78%)	N460Y (19%) A1174V (18%)

Abbreviations: A = alanine; D = aspartic acid; del = deletion; E = glutamic acid; F = phenylalanine; G = glycine; H = histidine; K = lysine; mAb = monoclonal antibody; N = asparagine; P = proline; Q = glutamine; R = arginine; S = serine; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; T = threonine; US = United States; V = valine; W = tryptophan; Y = tyrosine.

Note: Percent coverage in the sequence population is indicated in parentheses.

[a] D614G was present in the Netherlands isolate at baseline and after cell culture passages

The two analysis identified several escape mutations for both Bamlanivimab and Etesevimab, however there were no shared mutations between the two mAbs. As a consequence, the combination of the two mAbs was able to neutralize even the mutants. No escape mutants were identified using the combination of the two mAbs.

In vitro directed evolution

The RBD (residues 319 to 541) of SARS-CoV-2 spike protein (Genbank MN908947.3) was expressed on the surface of yeast cells and confirmed to be reactive with soluble hACE2 and both LY3819253 and LY3832479 using a flow cytometric assay. A library was constructed in which all amino acid residues were sampled at positions 403 to 409, 415 to 421, 455 to 460, and 467 to 505 of the spike glycoprotein containing the epitopes of LY3819253 and LY3832479. Another library using error-prone PCR to randomly sample a wider range of the RBD was also constructed (BTDR484 Report). Neutralization abilities were tested in comparison with the "original Wuhan variant". Results are shown in the table below.

Table 33 - Angiotensin-Converting Enzyme 2 Binding Inhibition of Monoclonal Antibody for Wuhan and Variant Receptor-Binding Domains Determined by In Vitro Flow Cytometric Assay

RBD Variant	Source of Variant	LY3819253		LY3832479	
		mAb IC50 mg/ml (95% CI)	Fold Change	mAb IC_{50} mg/ml (95% CI)	Fold Change
Wuhan	GenBank MN908947.3	0.024 (0.021, 0.028)[a]	NA	0.046 (0.039, 0.055)[a]	NA
K417N	Live virus selection (LY3832479) + GISAID at 417	0.021 (0.017, 0.025)	1	No inhibition[b]	>64
D420N	Live virus + in vitro selection (LY3832479)	0.015 (0.015, 0.016)	1	No inhibition[b]	>68

N460K	Live virus + in vitro selection (LY3832479)	0.06 (0.054, 0.065)	2	No inhibition[b]	>64
N460S	In vitro selection (LY3832479)	0.021 (0.02, 0.022)	1	No inhibition[b]	>62, >68
N460T	Live virus selection (LY3832479)	0.022 (0.017, 0.027)	1	No inhibition[b]	>64
N460Y	Live virus selection (LY3832479)	0.024 (0.019, 0.03)	1	No inhibition[b]	>64
S477N	GISAID	0.036 (0.028, 0.045)	1	0.059 (0.055, 0.065)	1
V483A	GISAID	0.05 (0.043, 0.059)	2	0.064 (0.055, 0.076)	1
E484D	Live virus selection (LY3819253)	No inhibition[b]	>118	0.142 (0.108, 0.186)	2
E484K	In vitro selection (LY3819253)	No inhibition[b]	>147, >108	0.096 (0.088, 0.11)	2
E484Q	In vitro selection (LY3819253)	No inhibition[b]	>189	0.049 (0.042, 0.056)	1
F490S	Live virus + In vitro selection (LY3819253)	No inhibition[b]	>147, >108	0.049 (0.041, 0.057)	1
Q493H	GISAID at 493	0.038 (0.034, 0.043)	2	0.035 (0.031, 0.04) 0.052 (0.048, 0.056)	1 1
Q493L	GISAID at 493	0.064 (0.051, 0.08)	3	0.127 (0.111, 0.145) 0.12 (0.097, 0.149)	3 2
Q493R	In vitro selection (LY3819253)	**No inhibition[b]**	**>108, >162**	**1.882 (1.664, 1.935)**	**42**
S494P	Live virus + In vitro selection (LY3819253)	No inhibition[b]	>147, >108	0.053 (0.048, 0.058)	1
N501T	GISAID	0.024 (0.022, 0.026)	1	0.275 (0.236, 0.347)	9
N501Y	GISAID	0.029 (0.025, 0.034)	2	0.345 (0.304, 0.461)	12
A520S	GISAID	0.023 (0.019, 0.027)	1	0.041 (0.037, 0.047)	1

No variants were isolated after combination antibody selections that contained a mutation at a single amino acid position that could result from a single nucleotide change in the codon. Nevertheless, as Q493 is a contact residue shared by both antibodies, due the observation that Q493R was isolated from the LY3819253 only selection, and the presence of naturally occurring variants at this location in the GISAID database, a panel of clones was specifically tested (Q493H, Q493L, and Q493R) for inhibition by both LY3819253 and LY3832479. Of these variants, only Q493R was able to impact inhibition of both LY3819253 and LY3832479 greater than 5-fold (see table above). LY3819253 (Bamlanivimab) was severely disrupted with no inhibition of soluble hACE2 binding observed at the highest antibody concentration (3.75 μg/ml) tested. LY3832479 (Etesevimab) inhibition was impacted, but not eliminated, with an IC_{50} of 1.882 μg /ml that represents a 42-fold shift compared to wild-type RBD.

Pseudovirus neutralization

Experiments were performed of pseudovirus neutralisation with mutants derived from: frequency of occurrence in the GISAID database, identification of escape variants from serial passage studies, and/or identification of escape variants by *in vitro* directed evolution.

Results are shown in the table below.

Table 34 - Pseudovirus Neutralization of Spike Variants in the Presence of LY3819253 and LY3832479

Spike Variant	Source of Variant	LY3819253	LY3832479

		IC_{50} µg/mL[a]	**Fold Change (≥5)[b]**	**IC_{50} µg/mL[a]**	**Fold Change (≥5)[b]**
Wuhan	Genbank MN908947.3	0.015	NA	0.095	NA
W64R	Live virus selection (LY3819253)	0.006	nc	0.066	nc
W64R/D614G	Live virus selection (LY3819253)	0.008	nc	0.08	nc
W152R	Live virus selection (LY3819253)	0.021	nc	0.129	nc
D215H/D614G	Live Virus	0.009	nc	0.089	nc
V367F	GISAID	0.005	nc	0.007	nc
K417N	Live virus selection (LY3832479) +GISAID at 417	0.016	nc	>1	>6
D420N	Live virus + In vitro selection (LY3832479)	0.039	nc	>2	>17
N439K	GISAID	0.008	nc	0.023	nc
N460K	Live virus + in vitro selection (LY3832479)	0.22	nc	>1	>11
N460K/D614G	Live virus + in vitro selection (LY3832479)	0.023	nc	>5	>24
N460S	In vitro selection (LY3832479)	0.007	nc	>20	>302
N460T	Live virus selection (LY3832479)	0.035	nc	>2	>21
N460Y	Live virus selection (LY3832479)	0.013	nc	>20	>210
N460Y/D614G	Live virus selection (LY3832479)	0.038	nc	>5	>24
G476S	GISAID	0.025	nc	0.074	nc
S477N	GISAID	0.013	nc	0.089	nc
T478I	GISAID	0.01	nc	0.095	nc
V483A	GISAID	0.466[c]	48[d]	0.094	nc
E484Q	In vitro selection (LY3819253)	>5	>890	0.118	nc
E484K	In vitro selection (LY3819253)	>20	>2360	0.428	nc
F490S	Live virus + in vitro selection (LY3819253)	>5	>590	0.071	nc
Q493R	In vitro selection (LY3819253)	**>100**	**>6666**	**22.07[c]**	**232**
Q493H	GISAID at 493	0.209	14	0.091	nc
Q493L	GISAID at 493	0.149	10	0.234	nc
S494P	live virus + In vitro selection (LY3819253)	>2	>132	0.086	nc
N501Y	GISAID	0.016	nc	0.634	5
N501T	GISAID	0.016	nc	1.4[c]	21.5
A520S	GISAID	0.029	nc	0.123	nc
D614G	GISAID	0.017	nc	0.06	nc

A1174V	live virus selection (LY3832479)	0.028	nc	0.168	nc

Also, in this experiment the mutation Q493R was the only one to affect the affinities of both mAbs.

Binding affinity of isolated receptor binding domain to LY3819253, LY3832479 and angiotensin-converting enzyme 2

The effect of variants in the RBD of the SARS-CoV-2 spike protein, on the monomeric binding affinities of LY3819253 (Bamlanivimab), LY3832479 (Etesevimab), and the cellular receptor ACE2 were measured by surface plasmon resonance. Results are shown in the table below.

RBD Mutation	LY3819253		LY3832479		hACE2	
	Binding Affinity (KD), at 25 °C	Fold Change (≥5)	Binding Affinity (KD), at 25 °C	Fold Change (≥5)	Binding Affinity (KD), at 25 °C	Fold Change (≥5)
Wuhan[a]	1.50 nM	NA	46.3 nM	NA	176 nM	NA
V367F	1.43 nM	nc	45.5 nM	nc	173 nM	nc
K417N	1.49 nM	nc	NB	>7	602 nM	nc
D420N	1.45 nM	nc	NB	>7	222 nM	nc
N439K	1.81 nM	nc	47.7 nM	nc	159 nM	nc
N460K	1.34 nM	nc	NB	>7	172 nM	nc
N460S	1.76 nM	nc	>300 nM[b]	>7	163 nM	nc
N460T	1.62 nM	nc	NB	>7	209 nM	nc
N460Y	1.67 nM	nc	NB	>7	308 nM	nc
G476S	2.52 nM	nc	47.2 nM	nc	169 nM	nc
S477N	1.37 nM	nc	48.1 nM	nc	70.5 nM	nc
T478I	1.30 nM	nc	41.1 nM	nc	162 nM	nc
V483A	34.3 nM	23	52.2 nM	nc	168 nM	nc
E484D	>300 nM[b]	>200	117 nM	nc	238 nM	nc
E484K	NB	>200	80.0 nM	nc	205 nM	nc
E484Q	NB	>200	54.9 nM	nc	210 nM	nc
F490S	>300 nM	>200	31.4 nM	nc	207 nM	nc
Q493H	10.7 nM	7	32.0 nM	nc	154 nM	nc
Q493L	12.7 nM	8	84.8 nM	nc	57.8 nM	nc
Q493R	**>300 nM[b]**	**>200**	**>300 nM[b]**	**>7**	**326 nM**	**nc**
S494P	>300 nM[b]	>200	51.7 nM	nc	163 nM	nc
N501T	1.73 nM	nc	>300 nM[b]	>7	433 nM	nc
N501Y	1.35 nM	nc	>300 nM[b]	>7	31.2 nM	**0.2**
A520S	1.54 nM	nc	46.0 nM	nc	168 nM	nc

Also in this experiment mutation Q439R was the only one affecting the affinities of both mAbs. Of note, no mutations negatively affected the affinity for the receptor ACE2 (the one responsible for virus entry in the cells). Only mutation N501Y was able to increase the affinity for ACE2.

In summary, from in vitro experiments with different methods, the following mutations were identified:

- F490S, S494P, E484K, and E484Q showed a reduction in susceptibility or binding activity to LY3819253, yet maintained LY3832479 activity.
- N460K resulted in a loss of susceptibility to LY3832479, but not to LY3819253.

- Only Q493R, identified in the yeast library screen as resistant to LY3819253, showed reduction in activity of both mAbs.

Importantly, Bamlanivimab seems to be the one driving the affinity for the virus, but also the one more susceptible to have a decrease affinity due to mutations.

Of note, the Q493R variant has only been identified at a low frequency of 0.005% (n=2) out of the 405,416 deposited sequences as of 24 January 2021 in the GISAID database.

From the GISAID database, some mutations were selected for surveillance, as indicated in the table below.

Table 35 -Viral Variants from Surveillance

GISAID	GISAID + modification at positions of known resistance
V367F	Q493H
N439K	Q493L
G476S	
S477N	
T478I	
V483A	
N501Y	
N501T	
A520S	
D614G	

The vast majority of the high prevalence variants identified in the GISAID database showed no change in LY3819253 and LY3832479 activity. The V483A was sensitive to neutralization by LY3819253 but showed a susceptibility shift of 48-fold compared to the Wuhan reference. At present this viral variant still has a relatively low frequency of identification in the GISAID database, 0.0173% (n=70 out of 405,416 sequences). Position N501 was found to be a position of contact for LY3832479 and is of interest due to the N501Y mutation which is contained within the B1.1.7 "UK strain" lineage. Viruses with variations of N501Y showed a minor reduction in susceptibility (5-fold), whereas the N501T showed a larger shift in susceptibility (>20-fold) compared to the Wuhan reference. LY3832479 maintained full activity to both variants at N501 as measured by pseudovirus, ACE2 competition, and binding affinity assessments.

Analysis of the activity against the known "UK" and "South Africa" variants

Table 36 - Viral Variants from Surveillance

GISAID	GISAID + modification at positions of known resistance
del69-70	Q493H
V367F	Q493L
N439K	
G476S	
S477N	
T478I	
V483A	
N501Y	
N501T	
A520S	
D614G	
N501Y + del69-70 (mutations of interest in B.1.1.7 "UK origin" lineage)	
N501Y+ K417N + E484K (mutations of interest in B.1.351 "South Africa origin" lineage)	

Table 37 - B.1.1.7 "UK origin" Lineage Related Pseudovirus Neutralization in Presence of Bamlanivimab and Etesevimab

Spike Variant	Bamlanivimab		Etesevimab		BAM + ETE (1:2 ratio)	
	IC_{50} µg/mL[b]	Fold Shift (≥5)[c]	IC_{50} µg/mL[b]	Fold Shift (≥5)[c]	IC_{50} µg/mL[b]	Fold Shift (≥5)[c]
Wuhan[a]	0.015	-	0.095	-	0.023	-
B.1.1.7 related						
N501Y	0.016	nc	0.634	5.1	0.042	nc
del69-70	0.013	nc	0.113	nc	0.03	nc
N501Y + del69-70	0.018	nc	0.757	12.1	0.041	nc
B1.1.7 spike	construction unsuccessful after multiple attempts					

Abbreviations: BAM = bamlanivimab; del= deletion; ETE = etesevimab; IC_{50} = concentration inhibiting maximal activity by 50%; nc= no change (difference was less than ≤5-fold); N = asparagine; Y = tyrosine.

a SARS-CoV-2 S Genbank MN908947.3.

b IC_{50} values presented are preliminary results of a single experiment for the del69-70 and del69-70 + N501Y or the geometric mean of multiple experiments for N501Y and weighted geometric mean for the Wuhan.

c Fold shifts are calculated comparing to the in-experiment Wuhan control or in limited cases to the weighted geometric mean of all Wuhan runs if, in-experiment, was not available. The geometric mean of the fold changes is provided if multiple experiments were performed.

Table 38 - B.1.351 "South African origin" and "Brazilian origin" Lineage Related Pseudovirus Neutralization in Presence of Bamlanivimab and Etesevimab

Spike Variant	Bamlanivimab		Etesevimab		BAM + ETE (1:2 ratio)	
	IC_{50} µg/mL[b]	Fold Shift (≥5)[c]	IC_{50} µg/mL[b]	Fold Shift (≥5)[c]	IC_{50} µg/mL[b]	Fold Shift (≥5)[c]
Wuhan[a]	0.015	-	0.095	-	0.023	-
B.1.351 related						
K417N	0.016	nc	>1	>6	0.027[d]	nc
E484K	>20	>2360	0.428	nc	0.409	17.3
N501Y	0.016	nc	0.634	5.1	0.042	nc
K417N + E484K + N501Y	>1	>130	>2	>23	>0.75	>45
B.1.351 spike	>1	>64	>2	>22	>0.75	>45
P.1 related						
K417T	0.003	nc	>2	>175	0.008	nc
E484K	>20	>2360	0.428	nc	0.409	17.3
N501Y	0.016	nc	0.634	5.1	0.042	nc
K417T + E484K + N501Y	>1	>1020	>2	>23	>1.5	>511

From this analysis the UK variants seems to negatively affect mostly Etesevimab activity, while the South Africa and Brazilian variants negatively affects both mAb, most importantly also the combination.

2.3.3. Toxicology

Bamlanivimab

The following toxicity studies were conducted: tissue cross-reactivity (TCR) studies (foetal and adult human, rat, and cynomolgus monkey tissues), a 21-day rat toxicity study, and an evaluation of antibody-dependent enhancement (ADE) in vitro and in African green monkeys.

Tissue cross-reactivity data were obtained from human, rat and NHP tissues.

Only cytoplasmatic staining was sporadically observed in human samples (axons in the cerebrum and in the spinal cord, thymic and prostatic epithelium), while both membranous and cytoplasmatic staining was observed in numerous NHP tissues. No staining was observed in rat samples, supporting the use of the rat as the nonclinical safety model. Moreover, a TCR study in human foetal tissues was also performed. Here too only cytoplasmatic staining was detected (thymus). Overall, the TCR studies do not seem to indicate concern for humans.

A 21-day repeated dose toxicological study was performed in rats, which identified no adverse findings. The NOAEL was then set at 500mg/kg/dose, which was the highest dose being tested.

Antibody-dependent enhancement of infection (ADE)

An *in vitro* evaluation of antibody-dependent enhancement of infection (ADE) was performed. ADE may occur when a virus particle bound by an antibody is internalised into a cell via binding of cell surface Fc receptors (in particularly to CD32a, FcγRIaI) to antibody Fc region. If the internalised virus is not completely neutralised, active infection of the cell and viral replication can occur. Moreover, ADE can occur also via a second mechanism involving immune-complexes leading to immune cells recruitment

and cytokine release in the airway tissue (Lee et al. 2020[15]). No indication of ADE was found in these experiments.

The risk of ADE for Bamlanivimab was also evaluated *in vivo* in the African green monkey model. It was reported that ADE is dependent on the mAb-dose: sub-neutralising doses show higher incidence of ADE (Lee et al. 2020). It is acknowledged that a group of animals treated with a low dose of Bamlanivimab (0.05 mg/kg) sub-optimal for the virus neutralisation was also included in the study. The animals included in this group showed higher viral loads as well as more severe clinical signs (viral pneumonia), compared with the high-dose group treated with 20mg/kg Bamlanivimab. The difference of such parameters between low-treated and control group was not reported. Notably, only one death in the low treatment group was reported. Further data was provided on this death and overall, the results seem to indicate that the moribundity status of the animal was rather caused by the SARS CoV-2 infection, as no signs of ADE (in particular, no increase in viral load) and no escape mutations were identified in the animal.

Moreover, the occurrence of viral mutations was also investigated. A small number of animals treated with Bamlanivimab exhibited mutations in the region of the virus which encodes the RBD region of the S protein (S494P and Q493K). These mutations were not observed in animals treated with control IgG and located in the binding epitope of Bamlanivimab. However, these mutations were present both in the low and in the high treated groups. It was concluded that in the study there was no evidence of development of escape mutants due to sub-neutralising dose and the risk of ADE for Bamlanivimab was assessed as being low. Furthermore, Eli Lilly is currently monitoring "Cases Involving Events Related to Disease Progression Occurring During or Shortly After Infusion" in a "post-authorisation" setting following the in Emergency-Use-Authorisation (EUA) in the USA. 28 cases were so far documented. From the additional non-clinical data provided (BTDR481, report 20256103 and BTDR491), the risk of ADE, as well as the risk of the worsening of the disease caused by escape-mutants in animals seem low.

Etesevimab

TK data from a 2-week, single IV dose, non-GLP toxicology study in cynomolgus macaques demonstrated that Etesevimab has an average observed clearance of 0.22 to 0.25 mL/hr/kg and a plasma $t_{1/2}$ of approximately 6.5 to 10.5 days. TK data were determined in a 3-week, repeat-dose GLP study in cynomolgus monkeys (IV doses of 25, 75, or 205 mg/kg of etesevimab on Days 1, 4, 7, 10, 13, and 20). The TK results showed no gender difference in C_{max} or AUC. C_{max} and AUC were dose related on all study days. Accumulation, with accumulation factors of 8- to 12-fold, was observed by study Day 20 following twice-weekly dosing for a total of 6 doses (Study report P20-S055-RD). The study reports were not submitted, therefore the validity of the methods could not be verified, the data however show a PK behaviour typical of a mAb.

TCR studies were performed in human (adult and foetal) tissues as well as in cynomolgus monkey tissues. No staining was detected and cynomolgus monkey was selected as relevant species for the toxicology program. A GLP-compliant, 3-week repeat-dose toxicity and toxicokinetic study in cynomolgus monkeys was performed, which evidenced no treatment related adverse findings. As such, the NOAEL dose was considered being the maximum dose (205mg/kg). The risk of Etesevimab in inducing ADE *in vitro* and *in vivo* was also evaluated. Of note, some additional experiments were performed, compared with Bamlanivimab, that is somehow surprising, considering that Etesevimab has no Fc effector function due to the LALA mutation, therefore the risk should be reduced in comparison to Bamlanivimab. The risk of *in vivo* ADE for Etesevimab was also evaluated in the African green monkey model. No sign of ADE was reported.

[15] Lee, W.S., Wheatley, A.K., Kent, S.J. *et al.* Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies. *Nat Microbiol* **5,** 1185–1191 (2020). https://doi.org/10.1038/s41564-020-00789-5

Combination

Studies to assess PK parameters for Bamlanivimab and Etesevimab administered together were not provided.

No toxicologic study was performed using the combination of Bamlanivimab together with Etesevimab.

It was reported that mixture of LY3819253 and LY3832479 does not mediate ADE in Raji, THP-1, ST486 or primary macrophage cells.

The combination was administered prophylactically in African green monkeys. at 0.05, 0.5, or 20 mg/kg each or isotype controls. Reduction in viral loads in the treated animals was observed and no signs of ADE were reported.

2.4. Quality aspects

2.4.1. Introduction

This medicinal product is a combination pack containing two monoclonal antibodies as active substances, Bamlanivimab (LY3819253, LY-CoV555) and Etesevimab (LY3832479, LY-CoV016).

Bamlanivimab and Etesevimab finished products are presented as concentrates for solution for infusion in separate vials. Each vial contains 700 mg of each monoclonal antibody in 20 mL, corresponding to a concentration of 35 mg/mL). Bamlanivimab and Etesevimab are formulated with a L-histidine buffer, sucrose, polysorbate 80, sodium chloride and water for injection. The formulations do not contain preservatives.

Bamlanivimab and Etesevimab must be administered as a single intravenous infusion immediately after dilution with 0.9% sodium chloride.

2.4.2. Active Substance

General Information

Bamlanivimab and Etesevimab are IgG1 kappa anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) recombinant monoclonal antibodies targeting overlapping but different epitopes of the receptor binding domain (RBD) of the spike (S) protein. They exhibit neutralisation activity. The blockage of the S protein interaction with angiotensin-converting enzyme 2 (ACE2) prevents subsequent viral entry into human cells and viral replication.

Bamlanivimab and Etesevimab contain a single N-linked glycosylation site on each heavy chain.

Etesevimab presents amino acid substitutions in the Fc region (L234A, L235A) to reduce effector function. Bamlanivimab is unmodified in the Fc region.

The biological and physico-chemical properties have been described.

Manufacture, process controls and characterisation

Manufacture

Information regarding the manufacturing and testing sites and their EU GMP status was provided. Proof of EU GMP compliance for all sites will be expected at the time of marketing authorisation application (MAA).

Bamlanivimab and Etesevimab are produced in CHO cells. For Bamlanivimab, a two-tiered cell banking system of master cell bank (MCB) and working cell bank (WCB) is in place. For Etesevimab, a WCB has not yet been established. After thawing of a MCB or WCB vial, the cells are grown in a series of seed train bioreactors to generate sufficient cell mass to seed the production bioreactor. Purification is performed with a series of chromatography steps, tangential flow filtration / ultrafiltration steps and viral inactivation and filtration steps.

The manufacturing processes are considered standard for the production of monoclonal antibodies.

Control of materials

The list of raw materials used in the manufacture of Bamlanivimab and Etesevimab was provided.

Available characterisation data for the MCB and WCB, in line with ICH Q5D, was provided. The data presented is acceptable in the context of this procedure.

Control of critical steps and intermediates

Critical steps and critical process parameters (CPPs) have not been defined yet. The manufacturing processes are controlled by preliminary in-process testing and controls. The bulk harvests are tested in line with ICH Q5A requirements.

Process validation

No formal validation of the active substance manufacturing processes has been performed yet. This is acceptable in the context of this procedure and the COVID-19 pandemic. Formal process validation studies will be expected at the time of MAA.

Manufacturing process development

A number of significant changes were introduced during development. Some information to support these changes was provided with this procedure.

For Etesevimab, the Company confirmed which version of the active substance manufacturing process and finished product manufacturing process will be used in the context of this procedure and for the future MAA.

However, extensive comparability/bridging data, in accordance with ICH Q5E, will be expected at the time of MAA, including detailed comparison of process performance, side-by-side comparisons, extended characterisation and stability (for example forced degradation studies). For Etesevimab, the observed differences with certain quality attributes resulting from development changes will have to adequately addressed at the time of MAA with quality, preclinical and clinical data as appropriate.

Characterisation

Analytical characterisation was performed to provide an understanding of the physicochemical properties of Bamlanivimab and Etesevimab, including identity, secondary and tertiary structure, molar mass, molecular weight, size heterogeneity, purity and glycosylation profile.

Effector function characterisation determined that Bamlanivimab binds human FCγ receptors I, IIa, IIb, and IIIa and the complement component C1q and shows antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). Bamlanivimab did not show complement-dependent cytotoxicity (CDC).

Effector function characterisation determined that Etesevimab did not bind human FCγ receptors I, IIa, and IIIa and showed no ADCC or CDC activity. The binding activity of Etesevimab to FcRn was confirmed.

Data on virus neutralisation for Bamlanivimab and Etesevimab were presented in the non-clinical part of the documentation.

Characterisation data for process- and product-related impurities for Bamlanivimab and Etesevimab was provided. Certain impurities are controlled at release.

Overall, characterisation of Bamlanivimab and Etesevimab is considered adequate in the context of this procedure. Additional data will be expected at the time of MAA.

Specification

Specifications with preliminary acceptance criteria for Bamlanivimab and Etesevimab are set in accordance with ICH Q6B and include control of identity, purity and impurities, potency and other general tests. The justification provided for the specifications is acceptable in the context of this procedure. It is expected that the test panel and acceptance criteria will be revised at the time of MAA as more experience is gained and more data is available.

Analytical procedures

The suitability of the methods commensurate with stage of development was demonstrated for Bamlanivimab and Etesevimab and some validation data was provided

Batch analyses

Representative batch analyses data was provided for the manufacturing process of Bamlanivimab and Etesevimab. All pre-defined acceptance criteria were met.

Reference standard

The information provided on the reference standards for Bamlanivimab and Etesevimab is acceptable in the context of this procedure. Additional data will be expected at the time of MAA.

Container closure

The container closure systems for Bamlanivimab and Etesevimab were described. Results from extractables/leachables studies will be expected at the time of MAA.

Stability

Overall, limited stability data for Bamlanivimab and Etesevimab active substances is presented. The Company provided shelf life extension protocols and committed to inform EMA in case of out-of-trend or out-of-specification results. The Company also committed to perform a stability study for each GMP batch placed on stability according to an approved stability protocol.
Bamlanivimab and Etesevimab active substances are stored frozen and the currently proposed shelf lives are considered acceptable in the context of this procedure, Additional stability data will be expected at the time of MAA.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Bamlanivimab and Etesevimab finished products are presented as concentrates for solution for infusion in separate Type I glass vials: 700 mg in 20 mL volume (concentration of 35 mg/mL) for each monoclonal antibody.

Bamlanivimab and Etesevimab finished products contain no novel excipient or excipients of human or animal origin. The excipients - L-histidine and L-histidine hydrochloride monohydrate (buffer with target pH 6.0), sodium chloride (tonicity agent used in bamlanivimab formulation only), sucrose (stabilising agent), polysorbate 80 (stabilising agent) and water for injection – are compendial and commonly used for the formulation of biopharmaceuticals. The two formulations do not contain preservatives. The solution for each vial is clear to opalescent, colourless to slightly yellow to slightly brown.

The qualitative and quantitative compositions for Bamlanivimab and Etesevimab finished products were provided and are considered adequate.

Each vial contains an overfill to ensure complete withdrawal of the volume stated on the label.

Pharmaceutical development

Information on formulation development was provided together with comparability data to support various changes introduced during manufacturing process development.

The vials and stoppers for Bamlanivimab/Etesevimab are commonly used for other medicinal products.

A co-mixing study was conducted to assess the physical and chemical compatibility of Bamlanivimab and Etesevimab finished products upon mixing together. Study results support combining in the same bag for intravenous administration without impact to product quality attributes for up to 8 hours at room temperature.

Results from extractables/leachables studies will be expected at the time of MAA.

Manufacture of the product and process controls

Manufacture

The manufacturing and testing sites and their EU GMP status were provided. Proof of EU GMP compliance for all sites will be expected at the time of MAA. The Company will also be expected to identify a valid site responsible for EU batch certification.

During finished product manufacturing, Bamlanivimab and Etesevimab finished products are processed separately. The finished product manufacturing processes represent a standard fill-finish process. The individual processing steps are adequately described. Each monoclonal antibody is independently filled into separate vials.

Critical steps and CPPs have not been defined yet. The manufacturing processes are controlled by preliminary in-process testing and controls.

Process validation

No formal validation of the active substance manufacturing processes has been performed yet. Aseptic filling is validated by media fill simulations. This is acceptable in the context of this procedure and the COVID-19 pandemic. Formal process validation studies will be expected at the time of MAA.

Product specification

Specifications with preliminary acceptance criteria for Bamlanivimab and Etesevimab finished products are set in accordance with ICH Q6B and include control of identity, purity and impurities, potency and other general tests. The justification provided for the specifications is acceptable in the context of this procedure. It is expected that the test panel and acceptance criteria will be revised at the time of MAA as more experience is gained and more data is available.

The Company is reminded that at the time of the MAA, a risk evaluation concerning the presence of nitrosamine impurities in the finished product should be provided, applying the principles outlined in Questions and answers on "Information on nitrosamines for marketing authorisation holders" (EMA/409815/2020 or current version) and Nitrosamine Impurities - Final Outcome of Article 5(3) (EMA/369136/2020 or current version). In case there is an identified risk of the presence of nitrosamines, the Company will have to immediately start confirmatory testing and evaluating possible sources of contamination, together with a proposal of an appropriate method and acceptable levels of control of nitrosamines in the specification.

Analytical procedures

The suitability of the methods commensurate with stage of development was demonstrated for Bamlanivimab and Etesevimab finished products and some validation data was provided.

Batch analyses

Representative batch analyses data was provided for the manufacturing process of Bamlanivimab and Etesevimab finished products. All pre-defined acceptance criteria were met.

Reference standard

The same reference standards as for Bamlanivimab and Etesevimab active substances are used.

Stability of the product

A preliminary shelf life for Bamlanivimab and Etesevimab finished products of 12 months when stored at 2°C to 8°C in the original carton and protected from light is proposed. The data presented to support this shelf life is limited and relies on extrapolation of real time data available at the time of this procedure. This is considered acceptable in the context of this procedure and the COVID-19 pandemic. At the time of MAA, shelf life determination should be based on ICH Q5C principles and additional stability data will be expected.

The Company provided shelf life extension protocols and committed to inform EMA in case of out-of-trend or out-of-specification results. The Company also committed to perform a stability study for each GMP batch placed on stability according to an approved stability protocol.

In the absence of preservative, Bamlanivimab and Etesevimab finished products should be diluted and administered immediately after opening of the vials. If immediate administration is not possible, the diluted infusion solution may be stored for up to 7 hours at room temperature (up to 30°C) or refrigerated between 2°C to 8°C for up to 24 hours, including infusion time. If refrigerated, the infusion solution should be allowed to equilibrate to room temperature for approximately 20 minutes prior to administration.

Adventitious agents

No animal- or human-derived raw materials with a risk for virus or TSE contamination are used in the manufacture and no risk materials were used for the generation of the antibody-producing cell lines and cell banks.

Cell banks were characterised according to ICH Q5A guideline and routine screening of adventitious viruses was implemented.

A sufficient viral clearance capacity was demonstrated for the downstream manufacturing processes. Validation studies indicated efficient virus inactivation/removal.

The submitted information indicates adequate adventitious agents evaluation safety.

2.4.4. Discussion

In general, the extent of information on quality provided by the Company corresponds to the level of a dossier for an investigational medicinal product.

The design of the manufacturing processes for the active substances and finished products is standard. However, critical steps have not been defined, process validation data are not yet available and only preliminary criteria for process controls and active substance and finished product specifications are set. In addition, considering the number of changes introduced during their development, the Company is expected to provide extensive comparability data at the time of MAA. This is considered of critical importance.

Additional data for the characterisation of the active substances will also be expected at the time of MAA.

The Company provided several references to platform knowledge in order to support manufacture and current control strategy. A justification for such approach will be expected at the time of MAA.

Stability data to support the currently proposed active substance and finished product shelf lives is limited and relies on extrapolation, which is acceptable in the context of this procedure and the COVID-19 pandemic.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Bamlanivimab/Etesevimab is considered acceptable in the context of this procedure and the COVID-19 pandemic, when used in accordance with the conditions of use.

3. Overall conclusions

Quality aspects

Considering the data provided by the Company on the manufacture, characterisation, pharmaceutical development, control and stability of the active substances and finished products, the overall quality of Bamlanivimab/Etesevimab is acceptable in the context of this procedure and the COVID-19 pandemic, when used in accordance with the conditions of use.

Non-clinical aspects

Non-clinical studies performed on pharmacology, pharmacokinetics and toxicology were submitted. Surface plasmon resonance (SPR) experiments were performed in order to characterise the binding activities. Co-crystal structural analysis of Bamlanivimab and Etesevimab were preformed, which indicated that the two mAbs bind to two different but overlapping epitopes of the Receptor Binding Site

(RBD) of the SARS-CoV-2-S protein. As a consequence, they compete with one another for the binding of the Spike protein. ADCC and CDC activities were not detected for both antibodies. No sign of ADE was reported, *in vitro* or *in vivo*.

The neutralization capacity of Bamlanivimab was assessed in-vitro using SARS-CoV2 material of different origins. The *in vitro* efficacy (viral neutralisation) was also assessed for the combination, with the US and Italy isolate. The neutralisation potency of the combination seems better than Etesevimab alone and comparable to Bamlanivimab alone. Several escape mutations for both Bamlanivimab and Etesevimab, were identified. There were no shared mutations between the two mAbs. However, the mutation Q493R, identified in the yeast library screen as resistant to Bamlanivimab, showed reduction in activity of both mAbs. Of note, the Q493R variant has only been identified at a low frequency of 0.005% (n=2) out of the 405,416 deposited sequences as of 24 January 2021 in the GISAID database.

Analysis of the activity against the known "UK" and "South Africa" variants indicates that the UK variants seems to negatively affect mostly Etesevimab activity, while the South Africa variants negatively affects both mAb, most importantly also the combination. This result is reflected in the "conditions for use".

Clinical aspects

Results from the ongoing Phase 2/3 study Blaze-1 (or PYAB) were considered for the assessment of the potential use of Bamlanivimab monotherapy as a single administration of 700mg i.v and bamlanivimab/etesevimab combination as a single administration of 700mg + 1400mg i.v. for the treatment of COVID-19. PYAB is a randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of Bamlanivimab and Etesevimab in participants with mild to moderate COVID-19.

PK/PD modelling was used to derive an IC90 value and to conduct deterministic simulations to support dosing and to obtain a better understanding of the treatment effect. For monotherapy, as expected, simulations indicate that treatment effect is greater for patients who are treated earlier during the course of disease. All doses of Bamlanivimab (700 mg, 2800 mg and 7000mg) had a significant effect in increasing the elimination rate of the virus ($p<0.001$). This effect was not dose dependent. The model indicates that Bamlanivimab resulted in approximately 1.5 days shorter time to viral clearance relative to placebo.

The serum concentration IC90 estimate from the viral dynamic model was 2.3 µg/mL (upper 95% CI). This value compares well with the in vitro 95% CI of 0.029-0.265 µg/mL, after accounting for 6.5% lung penetration (0.446-4.1 µg/mL). The IC90 estimate should be interpreted with caution since there was no significant difference between the doses of 700, 2800 and 7000 mg IV for virology; this implies the need for a better characterization of the exposure-response relationship (for the lower doses). Further simulations showed that a single dose of 200 mg Bamlanivimab would equally suffice to result in serum concentrations above the IC90 (and even above IC99) over a 28-day period and would be reached by 90% of the patients. Clinical results from Study PYAB indicate that all 3 doses of Bamlanivimab administered alone (700, 2800, and 7000 mg), when compared to placebo, were modestly effective at reducing viral load, decreasing the time to symptom improvement and resolution, as well as decreasing the frequency of COVID-19-related ER visits and hospitalisations. Thus, given the very flat dose-response and PK/PD relationships, the selection of the lowest dose (700mg) of Bamlanivimab as recommended dose for monotherapy can be accepted.

The PYAB study was initially planned as a non-confirmatory dose-finding study for bamlanivimab monotherapy. The primary endpoint of the PYAB study was to demonstrate the effect of bamlanivimab alone and in combination with etesevimab on the viral load reduction.

For the phase 2 part of the study, a statistically significant effect for the chosen primary endpoint of change from baseline to Day 11 in $\log_{10}$ viral load could not be demonstrated in any of the monotherapy groups. However, assessment of the treatment effect with respect to this endpoint is hampered by the fact that patients receiving placebo were also able to effectively reduce viral load by Day 11. Results in the *post hoc* defined subgroups (patients with high viral load and high-risk for severe COVID-19 disease) were presented but should be treated with great care. The secondary endpoint of viral load reduction at day 7 provides some signs of a treatment effect as an increased viral reduction was seen at this time-point for all bamlanivimab doses compared to placebo.

The number of patients with bamlanivimab monotherapy who progressed to COVID-19-related hospitalizations or emergency room visits (secondary endpoint) was smaller than in the placebo control. Due to the small sample size (309 in all bamlanivimab monotherapy arms, 101 thereof with the proposed posology of 700mg) the low event rate for hospitalization or death, and the lack of a type 1 error control, a definitive conclusion on this effect cannot be drawn. However, based on the preliminary data set now assessable, it would appear to suggest that bamlanivimab monotherapy could potentially be used for the treatment of COVID-19 based on the following rational:

Bamlanivimab shows neutralization activity of live virus in vitro with high binding affinity to the viral S protein. While a significant effect of bamlanivimab in reducing viral load at day 11 was not demonstrated in the Blaze-1 study, there was a consistent trend for viral load reduction at day 7 and a positive trend on COVID-related hospitalizations or emergency room visits. The safety profile does not raise major safety concerns for patients. While the limitations of the data are acknowledged, taking into consideration the totality of the evidence and the use in an emergency setting, CHMP considered that bamlanivimab monotherapy could potentially be a treatment option for patients at high risk of progressing to severe COVID-19.

Efficacy of Etesevimab/Bamlanivimab (2800 mg each) combination in the treatment of patients under risk for severe COVID-19 disease was assessed in a confirmatory phase-3 part of study PYAB.

This Phase 3 part which was submitted to proof the efficacy of Bamlanivimab in combination with Etesevimab was initially planned as a Phase 2 study with PHVL as primary endpoint. Over multiple amendments a clinical endpoint (hospitalization or death) was added as second primary endpoint and later as sole endpoint. The number and extent of changes of the Phase 3 part of the study render the confirmatory nature of this study at least questionable. Furthermore, the Phase 3 part under review enrolled patients to three arms: Arm 7 (bamlanivimab 2800 mg + etesevimab 2800 mg), Arm 9 (bamlanivimab 700 mg + etesevimab 1400 mg-data not yet available and not presented), and a shared placebo control (Arm 8). While multiplicity control *within* Arm 7 and *within* Arm 9 over primary and key secondary endpoints was planned, *no multiplicity control over the two dosing regimen* was in place. In total, 518 subjects received combination treatment in this part of the study.

Etesevimab 2800 mg + Bamlanivimab 2800 mg treatment showed a statistically significant effect in an endpoint that is considered to be clinically relevant (i.e. proportion of participants who experience COVID-19 related hospitalization or death from any cause by day 29). When looking on these results, it has to be kept in mind that the number of events counted for this endpoint was overall low - based on currently available data the absolute risk reduction is assumed to be not more than 5%.

Etesevimab 2800 mg + bamlanivimab 2800 mg treatment resulted in a robust improvement of viral load compared to placebo throughout the respective treatment arms of study PYAB analyzed at

present. Furthermore, sustained symptom resolution was shortened by 1 day. However, the clinical relevance of the observed effects remains debatable. Besides, sample size in study PYAB was relatively small given the relatively low incidence of hospitalization or death even in a population at high risk for severe COVID-19 for the combination treatment. The data submitted was restricted to 1 dosing regimen (2800 mg+2800 mg). In total, 518 subjects received combination treatment in the phase-3 portion of the study leading to 36 (placebo) vs 11 (Bamlanivimab 2800 mg + Etesevimab 2800 mg) hospitalizations or deaths. Phase-2 portion of the study randomized additional 112 subjects in the combination treatment arm, but was designed as a phase-2 biomarker study. Among these participants no deaths occurred under bamlanivimab/etesevimab combination therapy; One (1) event of COVID-19-related hospitalization occurred.

Clinical data to support the proposed treatment regime of 700mg bamlanivimab + 1400mg etesevimab are not yet available**.** Instead, the Applicant provided data from the treatment regime of a single IV infusion of 2800 mg of bamlanivimab and 2800 mg of etesevimab. This is justified by a population modelling of combined PK and viral load data from Study PYAB interim analyses. Only data from 2800/2800 mg were used for PK/PD modelling. Overall, the analyses supported that a dose of 700 mg bamlanivimab and 1400 mg of etesevimab administered together is expected to achieve a similar maximum viral load reduction as observed at higher doses of bamlanivimab and etesevimab together. At these doses, bamlanivimab and etesevimab will both maintain drug concentrations above the respective IC90 of viral reduction in 90% of the patient population for at least 21 days. Based on this modelling as well as pop PK and PK data, the extrapolation to the posology for adolescents weighing at least 40 kg is also acceptable.

In conclusion, 700 mg bamlanivimab in combination with 1400 mg etesevimab could be used as treatment for mild to moderate COVID-19 in patients on high risk for progression to severe disease.

Safety aspects

In study PYAB, treatment with bamlanivimab and bamlanivimab/etesevimab was well tolerated overall with a safety profile comparable to placebo. Most TEAEs in Study PYAB were mild to moderate in severity under both, bamlanivimab monotherapy (each dose tested) and bamlanivimab/etesevimab combination treatment. Under monotherapy, the frequency of moderate events was slightly lower, whereas severe events were a little more frequent compared to placebo. Under etesevimab 2800 mg + bamlanivimab 2800 mg treatment, the frequency compared to placebo was lower for both, moderate and severe events. No deaths occurred under treatment with bamlanivimab monotherapy in any dose or given in combination with etesevimab in the ongoing study so far. Whereas no event of cardiac disorders was reported under placebo treatment in the phase 3 portion of study PYAB, four (4) such events were reported under bamlanivimab/etesevimab combination treatment, namely atrial flutter, ventricular extrasystoles, myocardial infarction, and atrial fibrillation. It is also known that COVID-19 infection itself may cause cardiovascular toxicity (Khan, 2020; Costa, 2020; Ragab, 2020; Driggin, 2020). Thus, based on currently available data the impact of bamlanivimab/etesevimab combination therapy on cardiac risk cannot be evaluated conclusively.

Based on currently available data (no analysis presented for phase-3 portion of the trial), the risk of hypersensitivity, anaphylaxis, infusion-related reactions under bamlanivimab monotherapy and bamlanivimab/etesevimab combination treatment cannot be assessed conclusively. Therefore, appropriate precautions should be taken during infusion. Furthermore, no ADA data are available at present and, thus, the impact on PK, efficacy and safety cannot be assessed. Based on the fact that both antibodies are fully human and a single infusion is envisaged, the risks to subjects from ADA may be theoretically considered low.

Based on data available at present, there are no serious concerns about patients' safety, keeping in mind that long-term safety data are pending and overall number of subjects treated under clinical trial conditions is currently low.

The Committee considered that this medicine, once it is authorised for use, should be subject to additional monitoring. This enables to stimulate the ADR reporting in order for new safety information to be identified quickly. Healthcare Professionals will be asked to report any suspected adverse reactions.

Overall conclusions

Considering the data provided by the Company on quality aspects, preclinical aspects and the provided clinical dataset, bamlanivimab monotherapy and combination therapy of bamlanivimab/etesevimab might provide a therapeutic option for the treatment of confirmed COVID-19 in patients aged 12 years and older that do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19 in the context of this procedure and the COVID-19 pandemic, when used in accordance with the conditions of use.