

**ANNEX I**

**CONDITIONS OF USE, CONDITIONS FOR DISTRIBUTION AND PATIENTS TARGETED  
AND CONDITIONS FOR SAFETY MONITORING ADRESSED TO MEMBER STATES**

**FOR**

**UNAUTHORISED PRODUCT BAMLANIVIMAB**

**AVAILABLE FOR USE**

## 1. MEDICINAL PRODUCT FOR USE

- **Name of the medicinal product for Use:** Bamlanivimab
- **Active substance(s):** Bamlanivimab
- **Pharmaceutical form:** Concentrate for solution for infusion (sterile concentrate).
- **Route of administration:** Intravenous infusion
- **Strength:** 700 mg (each vial contains 700 mg bamlanivimab in 20 mL (35 mg/mL).

## 2. NAME AND CONTACT DETAILS OF THE COMPANY

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands  
[Contact details will be added at the National level]

## 3. TARGET POPULATION

### *Bamlanivimab alone*

Bamlanivimab is indicated for the treatment of confirmed COVID-19 in patients aged 12 years and older that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe COVID-19.

### *Bamlanivimab administered together with etesevimab*

Bamlanivimab and etesevimab administered together are indicated for the treatment of confirmed COVID-19 in patients aged 12 years and older that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe COVID-19

Risk factors may include but are not limited to:

- Advanced age
- Obesity
- Cardiovascular disease, including hypertension
- Chronic lung disease, including asthma
- Type 1 or type 2 diabetes mellitus
- Chronic kidney disease, including those on dialysis
- Chronic liver disease
- Immunosuppressed, based on prescriber's assessment. Examples include: cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anemia, thalassemia, and prolonged use of immune-weakening medications.

## 4. CONDITIONS FOR DISTRIBUTION

Prescription-only medicinal product

## 5. CONDITIONS OF USE

Bamlanivimab and Etesevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis.

### **Limitation in Patients with Severe COVID-19**

Monoclonal antibodies, such as bamlanivimab and etesevimab, may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation with COVID-19.

### **5.1 Posology**

- **Dosing recommendations**

*Bamlanivimab alone*

The recommended dose for bamlanivimab in adults and paediatric patients (12 years of age and older weighing at least 40 kg) is a single infusion of 700 mg administered as soon as possible after testing positive for SARS-CoV-2 and within 10 days of symptom onset.

#### *Bamlanivimab administered together with etesevimab*

The recommended dose for bamlanivimab and etesevimab in adults and paediatric patients (12 years of age and older weighing at least 40 kg) is a single infusion of 700 mg bamlanivimab and 1,400 mg etesevimab administered as soon as possible after testing positive for SARS-CoV-2 and within 10 days of symptom onset.

#### ▪ **Treatment duration and monitoring**

Single dose.

Patients are clinically monitored during administration and observed for at least 1 hour after infusion is complete.

#### ▪ **Specific Populations**

##### *Paediatric Use*

The safety and efficacy of bamlanivimab and etesevimab in children under 12 years of age have not yet been established. No data are available. No dosage adjustment is recommended in paediatric patients who are 12 years of age and older.

##### *Geriatric use*

No dose adjustment is required in patients  $\geq$  65 years of age.

##### *Renal Impairment*

No dosage adjustment is recommended in patients with renal impairment.

##### *Hepatic impairment*

No dosage adjustment is recommended in patients with mild hepatic impairment. Bamlanivimab and etesevimab has not been studied in patients with moderate or severe hepatic impairment.

#### ▪ **Method of administration**

##### ***Bamlanivimab alone***

##### Preparation

Bamlanivimab solution for infusion should be prepared by a qualified healthcare professional using aseptic technique:

- Gather the materials for preparation:
  - Polyvinyl chloride (PVC) or polyethylene (PE)-lined PVC, sterile prefilled infusion bag. Choose one of the following sizes:
    - Prefilled 50 mL, 100 mL, 150 mL, or 250 mL infusion bag containing 0.9% Sodium Chloride Injection (see **Table 1**).
  - One 20 mL vial of bamlanivimab (700 mg/20 mL).
- Remove one bamlanivimab vial from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vial.**
- Inspect bamlanivimab visually for particulate matter and discoloration.
  - Bamlanivimab is a clear to opalescent and colourless to slightly yellow to slightly brown solution.
- Withdraw 20 mL bamlanivimab from one 20 mL vial and inject into a prefilled infusion bag containing 0.9% Sodium Chloride Injection (see **Table 1**).
- Discard any product remaining in the vial.
- Gently invert IV bag by hand approximately 10 times to mix. **Do not shake.**
- This product is preservative-free and therefore, the diluted infusion solution should be administered immediately.
  - If immediate administration is not possible, store the diluted bamlanivimab infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C) and up to 7 hours at room temperature (20°C to 25°C) including infusion time. If refrigerated,

allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.

#### Administration

Bamlanivimab infusion solution should be administered by a qualified healthcare professional.

- Gather the materials for infusion:
  - PVC or PE-lined PVC infusion set
  - Use of an in-line or add-on 0.20/0.22 micron polyethersulfone (PES) filter is strongly recommended.
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity according to the size of infusion bag used (see **Table 1**). Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of bamlanivimab with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride to ensure delivery of the required dose.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.
- If the infusion must be discontinued due to an infusion reaction, discard any unused product.
- The use of closed system transfer devices (CSTDs), elastomeric pumps, and pneumatic transport with bamlanivimab has not been studied.

**Table 1: Recommended Dilution and Administration Instructions for Bamlanivimab<sup>a</sup>**

<b>Drug<sup>a</sup>: Add 20 mL of bamlanivimab (1 vial) to a prefilled infusion bag and administer as instructed below</b>		
<b>Size of prefilled 0.9% Sodium Chloride infusion bag</b>	<b>Maximum Infusion Rate</b>	<b>Minimum Infusion Time</b>
50 mL	270 mL/hr	16 minutes
100 mL	270 mL/hr	27 minutes
150 mL	270 mL/hr	38 minutes
250 mL	270 mL/hr	60 minutes

<sup>a</sup> 700 mg of bamlanivimab (20 mL) is added to an infusion bag and administered as a single intravenous infusion.

#### ***Bamlanivimab administered together with etesevimab***

##### Preparation

Bamlanivimab and etesevimab solution for infusion should be prepared by a qualified healthcare professional using aseptic technique:

- Gather the materials for preparation:
  - PVC or PE-lined PVC, sterile prefilled infusion bag. Choose one of the following sizes:
    - Prefilled 50 mL, 100 mL, 150 mL, or 250 mL infusion bag containing 0.9% Sodium Chloride Injection (see **Table 2** and **Table 3**).
  - One vial of bamlanivimab (700 mg/20 mL) and two vials of etesevimab (700 mg/20 mL).
- Bamlanivimab and etesevimab are supplied in individual single-dose vials but are administered together using a single infusion bag.
- Remove 1 bamlanivimab vial and 2 etesevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vials.**
- Inspect both bamlanivimab and etesevimab vials visually for particulate matter and discoloration.
  - Bamlanivimab and etesevimab are clear to opalescent and colourless to slightly yellow to slightly brown solutions.
- Withdraw 20 mL from one bamlanivimab vial and 40 mL from two etesevimab vials and inject all 60 mL into a prefilled infusion bag containing 0.9% Sodium Chloride (see **Table 2** or **Table 3**).
- Discard any product remaining in the vials.
- Gently invert the bag by hand approximately 10 times to mix. **Do not shake.**
- These products are preservative-free and therefore, the diluted infusion solution should be administered immediately.
  - If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C) and up to 7 hours at room

temperature (20°C to 25°C) including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.

#### Administration

Bamlanivimab and etesevimab infusion solution should be administered by a qualified healthcare professional.

- Gather the materials for infusion:
  - PVC or PE-lined PVC infusion set.
  - Use of an in-line or add-on 0.2/0.22 micron PES filter is strongly recommended.
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity according to the size of infusion bag used (see **Table 2 for patients weighing ≥50 kg** or **Table 3 for patients weighing <50 kg**). Due to potential overflow of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of bamlanivimab and etesevimab injection with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride to ensure delivery of the required dose.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.
- If the infusion must be discontinued due to an infusion reaction, discard any unused product.
- The use of CSTDs, elastomeric pumps, and pneumatic transport with bamlanivimab has not been studied.

**Table 2: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion<sup>a</sup> in Patients Weighing 50 kg or More**

<b>Drug<sup>a</sup>: Add 20 mL of bamlanivimab (1 vial) and 40 mL of etesevimab (2 vials) for a total of 60 mL to a prefilled infusion bag and administer as instructed below</b>		
<b>Size of Prefilled 0.9% Sodium Chloride Infusion Bag</b>	<b>Maximum Infusion Rate</b>	<b>Minimum Infusion Time</b>
50 mL	310 mL/hr	21 minutes
100 mL	310 mL/hr	31 minutes
150 mL	310 mL/hr	41 minutes
250 mL	310 mL/hr	60 minutes

<sup>a</sup> 700 mg of bamlanivimab and 1,400 mg of etesevimab are added to the same infusion bag and administered together as a single intravenous infusion.

**Table 3: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion in Patients Weighing Less Than 50 kg**

<b>Drug<sup>a</sup>: Add 20 mL of bamlanivimab (1 vial) and 40 mL of etesevimab (2 vials) for a total 60 mL to an infusion bag and administer as instructed below</b>		
<b>Size of Prefilled 0.9% Sodium Chloride Infusion Bag</b>	<b>Maximum Infusion Rate</b>	<b>Minimum Infusion Time</b>
50 mL	310 mL/hr	21 minutes
100 mL	310 mL/hr	31 minutes
150 mL	310 mL/hr	41 minutes
250 mL <sup>b</sup>	266 mL/hr	70 minutes

<sup>a</sup> 700 mg of bamlanivimab and 1,400 mg of etesevimab are added to the same infusion bag and administered together as a single intravenous infusion.

<sup>b</sup> The minimum infusion time for patients weighing less than 50 kg who are administered bamlanivimab and etesevimab together using the 250 mL prefilled 0.9% Sodium Chloride infusion bag must be extended to at least 70 minutes to ensure safe use (endotoxin load).

## **5.2 Contraindications**

Hypersensitivity to the active substance(s) or to any of the excipients (L-histidine, L-histidine hydrochloride monohydrate, sodium chloride, sucrose, polysorbate 80, water for injection).

## **5.3 Special warnings and precautions for use**

### **Hypersensitivity**

Serious hypersensitivity reactions have occurred with bamlanivimab with and without etesevimab. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration and initiate appropriate therapy.

### **Infusion-related reactions**

Infusion-related reactions have been observed with administration of bamlanivimab with and without etesevimab. These reactions may be severe or life threatening.

If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer supportive care.

### **Clinical Worsening after Bamlanivimab Administration**

Clinical worsening of COVID-19 after administration of bamlanivimab has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to bamlanivimab use or were due to progression of COVID-19.

## **5.4 Interaction with other medicinal products and other forms of interaction**

None known. No interaction studies have been performed.

Bamlanivimab is unlikely to have any direct or indirect effect on drug metabolising enzymes. Pharmacokinetic (PK) interactions with drugs primarily renally eliminated or metabolised by CYP450 enzymes are not expected.

Bamlanivimab is a monoclonal antibody (mAb) expected to be eliminated via proteolytic degradation to amino acids. It is not anticipated to be eliminated intact in the urine nor metabolised by cytochrome P450 enzymes in the liver. Renal and hepatic impairment are not expected to affect the PK of bamlanivimab. No dose adjustment is necessary in patients with renal or hepatic impairments.

### **Immune Response**

Concomitant administration of bamlanivimab and etesevimab with COVID-19 vaccines has not been studied.

## **5.5 Pregnancy and lactation**

Bamlanivimab has not been studied in pregnant or lactating women.

Bamlanivimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the foetus.

## **5.6 Incompatibilities**

None known.

## **5.7 Overdose**

Doses up to 7000 mg (10 times the recommended dose) have been administered in clinical trials without dose-limiting toxicity. In case of overdose, initiate supportive care.

## **5.8 Shelf life**

The shelf life is 12 months when vials are stored at 2°C to 8°C.

## 5.9 Storage conditions

### Drug Product

- Vials should be stored in a refrigerator at 2°C to 8°C until time of use.
- Keep vial in outer carton in order to protect from light.
- DO NOT FREEZE or SHAKE.

### Handling of Prepared Dosing Solution

- This product is preservative free and therefore the prepared dosing solution should be used immediately
- If not used immediately, store the dosing solution under refrigeration for up to 24 hours at 2°C to 8°C and for up to 7 hours at room temperature (below 30°C) assuming dilution has taken place using acceptable aseptic techniques.
- If refrigerated, allow the dosing solution to come to room temperature prior to administration.
- Storage times include the duration of infusion.
- DO NOT FREEZE OR SHAKE the bamlanivimab infusion solution.

## 5.10 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 6. OTHER INFORMATION

### Undesirable effects:

#### Summary of the safety profile for bamlanivimab administered alone

Over 1350 subjects have been exposed to bamlanivimab in clinical trials in both hospitalized and non-hospitalized patients.

The safety of bamlanivimab is based on interim data from one Phase 2 trial of 465 ambulatory (non-hospitalized) subjects with COVID-19.

BLAZE-1 is a randomized, double-blind, placebo-controlled clinical trial in ambulatory adults with mild to moderate COVID-19 symptoms who had sample collection for the first positive SARS-CoV-2 viral infection determination within 3 days prior to the start of the infusion. Subjects were treated with a single infusion of bamlanivimab at doses of 700 mg (N=101), 2,800 mg (N=107), or 7,000 mg (N=101) or placebo (N=156).

Based on data from 309 bamlanivimab-treated subjects followed for at least 28 days after treatment, adverse events occurred in 26% of bamlanivimab-treated subjects and 28% of placebo-treated subjects. Serious adverse events occurred in 1 placebo-treated subject (1%) and in 1 bamlanivimab-treated subject (1%).

The most commonly reported adverse event was nausea. Table 2 shows adverse events reported in at least 1% of patients in any treatment group.

**Table 1: Treatment-emergent Adverse Events Reported in at Least 1% of All Subjects in BLAZE-1**

Preferred Term	Placebo (N=156) %	Bamlanivimab			
		700mg N=101 %	2,800mg N=107 %	7,000mg N=101 %	Total N=309 %
Nausea	4%	3%	4%	4%	4%
Diarrhea	5%	1%	2%	5%	3%
Dizziness	2%	3%	3%	3%	3%
Headache	2%	3%	2%	1%	2%
Pruritus	1%	2%	3%	0%	2%
Vomiting	3%	1%	3%	1%	2%

Hypersensitivity Including Anaphylaxis and Infusion-related Reactions:

Across ongoing, blinded clinical trials, a case of anaphylaxis and other cases of serious infusion-related reactions were reported with infusion of bamlanivimab. The infusions were stopped. All reactions required treatment, one required epinephrine. All events resolved. Immediate non-serious hypersensitivity events were noted for 2% of bamlanivimab-treated subjects and 1% of placebo-treated subjects in BLAZE-1. Reported events of pruritus, flushing and hypersensitivity were mild with one case of face swelling which was moderate.

#### Summary of the safety profile for bamlanivimab in combination with etesevimab

Approximately 1,500 subjects have been exposed to bamlanivimab and etesevimab administered together in clinical trials in ambulatory (non-hospitalized) subjects at doses of bamlanivimab 700 mg and etesevimab 1,400 mg or higher. More than 3,900 subjects have received bamlanivimab (either alone or with etesevimab) at doses ranging from 700 to 7,000 mg. Bamlanivimab and etesevimab at doses of 700 mg and 1,400 mg have been administered together to approximately 770 subjects.

The safety of bamlanivimab and etesevimab administered together is based on data from the Phase 2/3 BLAZE-1 trial of ambulatory subjects with COVID-19. The dose is bamlanivimab 700 mg and etesevimab 1,400 mg administered together.

BLAZE-1 is a randomized, double-blind, placebo-controlled clinical trial in ambulatory adults with mild to moderate COVID-19 symptoms who had sample collection for the first positive SARS-CoV-2 viral infection determination within 3 days prior to the start of the infusion.

#### *Phase 2 Data from BLAZE-1*

Five hundred seventy-seven (577) subjects were treated with a single infusion of bamlanivimab 2,800 mg and etesevimab 2,800 mg (N=112), bamlanivimab alone at doses of 700 mg (N=101), 2,800 mg (N=107), or 7,000 mg (N=101) or placebo (N=156).

Based on Phase 2 data from BLAZE-1 subjects followed for at least 28 days after treatment, adverse events occurred in 18% of subjects treated with both bamlanivimab and etesevimab and 28% of placebo-treated subjects.

Nausea was the most commonly reported adverse event, reported by 4% of subjects treated with bamlanivimab and etesevimab together and 4% treated with placebo. Pruritus and pyrexia were more frequently reported from subjects treated with both bamlanivimab and etesevimab (2% and 1%) compared to placebo (1% and 0%, respectively).

#### *Phase 3 Data from BLAZE-1*

Five hundred eighteen (518) subjects were treated with a single infusion of bamlanivimab 2,800 mg and etesevimab 2,800 mg together and 517 subjects were treated with a single infusion of placebo in Arms 7 and 8, respectively, of the BLAZE-1 Phase 3 trial. Adverse events occurred in 13% of subjects who received 2,800 mg of bamlanivimab and 2,800 mg etesevimab together, and in 12% of placebo-treated subjects. The most common adverse events were nausea, dizziness, and rash. These events each occurred in 1% of subjects treated with bamlanivimab and etesevimab and in 1% of placebo subjects.

#### Hypersensitivity Including Anaphylaxis and Infusion-related Reactions:

Across ongoing, blinded clinical trials, a case of anaphylaxis and other cases of serious infusion-related reactions were reported with infusion of bamlanivimab with and without etesevimab. The infusions were stopped. All reactions required treatment, one required epinephrine. All events resolved.

#### Other Immediate Hypersensitivity Events

In the phase 2 portion of BLAZE-1, 2% of subjects treated with bamlanivimab and etesevimab, and 1% of placebo-treated subjects experienced immediate hypersensitivity events. Reported events of pruritus, flushing and hypersensitivity were mild and one case of face swelling was moderate.

In the phase 3 portion of BLAZE-1, 1% of subjects treated with bamlanivimab and etesevimab experienced immediate hypersensitivity events, including 2 infusion-related reactions (moderate severity), 2 cases of rash (1 mild, 1 moderate), 1 infusion site rash (mild), and 1 mild case of pruritus.

#### ▪ **Summary of relevant pharmacological properties**

##### Mechanism of Action



Bamlanivimab is a potent neutralising IgG1 mAb to the spike protein of SARS-CoV-2, which blocks spike protein attachment to human ACE2 receptors, thus preventing subsequent viral entry into human cells and viral replication.

#### In Vitro Neutralisation Activities

The in vitro potency of bamlanivimab for SARS-CoV-2 was measured by detecting the neutralisation of infectious virus in a dose-response model using cultured Vero E6 cells. Bamlanivimab was shown to inhibit virus replication with an estimated  $IC_{50} = 0.03 \mu\text{g/mL}$  and an estimated  $IC_{90} = 0.09 \mu\text{g/mL}$ .

#### Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to bamlanivimab.

In vitro monoclonal antibody resistance studies have identified six amino acid substitutions at four positions (E484D/K/Q, F490S, Q493R and S494P) in the spike RBD that has a resistant phenotype to bamlanivimab as determined by determined using authentic SARS-CoV-2 neutralisation, pseudovirus neutralisation, or binding assessment.

Pseudovirus harbouring the concurrent spike substitutions present in the South African B.1.351 origin variant lineage (K417N + E484K + N501Y), and the Brazil origin P.1 variant lineage (K417T + E484K + N501Y) exhibited significantly reduced susceptibility to bamlanivimab. Bamlanivimab retained activity against pseudovirus expressing del69-70 + N501Y spike substitutions found in the UK origin B.1.1.7 variant lineage.

Genotypic and phenotypic testing are ongoing to monitor for potential bamlanivimab-resistance associated spike variations in clinical trials. To date, the observation of known bamlanivimab-resistant variants at baseline has been rare. Treatment-emergent bamlanivimab variants have been observed across all treatment groups including placebo, although the frequency of detection was higher in bamlanivimab monotherapy treatment arms compared to placebo. The clinical relevance of these findings is not known.

#### Immune Response Attenuation

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

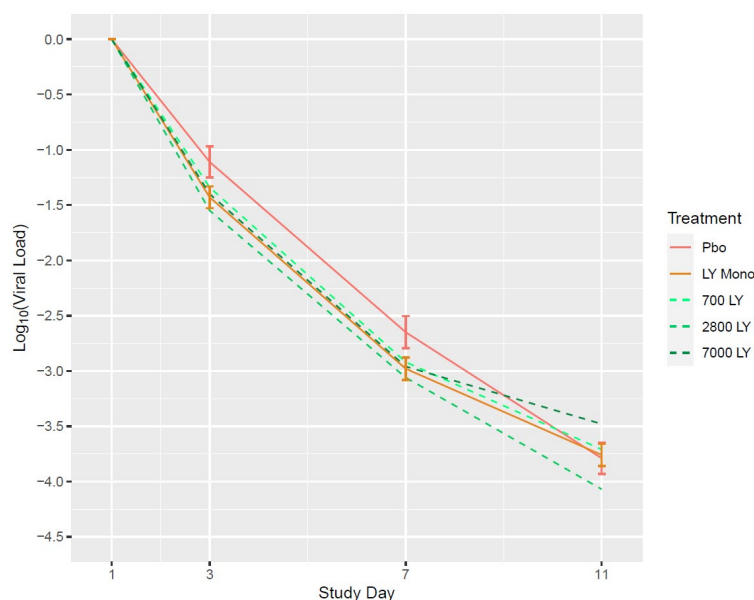
### ▪ **Summary of relevant Clinical properties**

#### ***Bamlanivimab alone***

The data supporting the use of bamlanivimab alone are based on an interim analysis from the Phase 2 part of BLAZE-1 that occurred after all enrolled subjects in Arms 1 to 4 completed at least Day 29 of the trial. BLAZE-1 is a randomized, double-blind, placebo-controlled clinical trial studying bamlanivimab for the treatment of subjects with mild to moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalised). The Phase 2 part of BLAZE-1 enrolled adult patients who were not hospitalised and had at least 1 or more COVID-19 symptoms that were at least mild in severity. Treatment was initiated within 3 days of obtaining the clinical sample for the first positive SARS-CoV-2 viral infection determination. Subjects were treated with a single infusion of bamlanivimab (at doses of 700 mg [N=101], 2,800 mg [N=107], or 7,000 mg [N=101]) or placebo (N=156).

The baseline demographics and disease characteristics were well balanced across bamlanivimab and placebo treatment groups. The mean duration of symptoms was 5 days. The mean viral load by cycle threshold (CT) was 24 at baseline.

While viral load was used to define the primary endpoint in this Phase 2 trial (Figure 1), signs that bamlanivimab may be effective came from a predefined secondary endpoint of COVID-19-related hospitalisations, emergency room visits or death within 28 days after treatment. A lower proportion of bamlanivimab-treated subjects progressed to COVID-19-related hospitalisation or emergency room visits compared to placebo-treated subjects (Table 4). Results for this endpoint were suggestive of a relatively flat dose-response relationship.



**Figure 1: SARS-CoV-2 viral load change from baseline by visit.**

**Table 4: Proportion of Subjects with Events of Hospitalisation or Emergency Room Visits within 28 Days After Treatment**

Treatment	N <sup>a</sup>	Events	Proportion of Subjects %
Placebo	156	9	5.8%
bamlanivimab 700 mg	101	1	1.0%
bamlanivimab 2800 mg	107	2	1.9%
bamlanivimab 7000 mg	101	2	2.0%
All bamlanivimab doses	309	5	1.6%

<sup>a</sup> N = number of treated patients in analysis.

The absolute risk reduction for bamlanivimab compared to placebo is greater in subjects at higher risk of hospitalisation according to the high risk criteria (Table 5). These data were generated by post-hoc analysis.

**Table 5: Proportion of Subjects with Events of Hospitalisation or Emergency Room Visits for Subjects at Higher Risk of Hospitalisation<sup>a</sup>**

Treatment	N <sup>b</sup>	Events	Proportion of Subjects %
Placebo	68	7	10.3%
bamlanivimab 700 mg	46	1	2.2%
bamlanivimab 2800 mg	45	1	2.2%
bamlanivimab 7000 mg	44	2	4.5%
All bamlanivimab doses	135	4	3.0%

<sup>a</sup> This data was generated by post-hoc analysis not pre-defined in the study protocol

<sup>b</sup> N = number of treated patients in analysis.

The median time to symptom improvement as recorded in a trial specific daily symptom diary was 6 days for bamlanivimab-treated subjects, as compared with 8 days for placebo-treated subjects. Symptoms assessed were cough, shortness of breath, feeling feverish, fatigue, body aches and pains, sore throat, chills, and headache. Symptom improvement was defined as symptoms scored as moderate or severe at baseline being scored as mild or absent, and symptoms scored as mild or absent at baseline being scored as absent.

#### ***Bamlanivimab administered together with etesevimab***

The data supporting the use of bamlanivimab together with etesevimab are based on analyses of data from the Phase 2/3 BLAZE-1 trial (NCT04427501) and the Phase 2 BLAZE-4 trial (NCT04634409). Both trials are evaluating the safety and efficacy of bamlanivimab and etesevimab together for treatment of subjects with mild to moderate COVID-19. BLAZE-1 provides clinical efficacy data from subjects receiving 2,800 mg bamlanivimab and 2,800 mg of etesevimab together

### Data from BLAZE-1

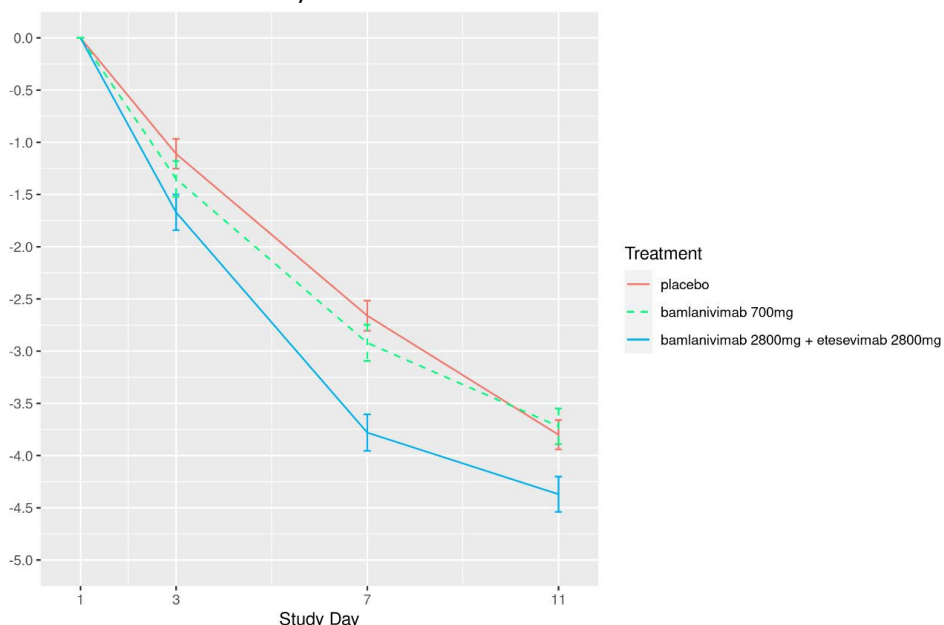
BLAZE-1 is an ongoing randomized, double-blind, placebo-controlled clinical trial studying bamlanivimab and etesevimab administered together for the treatment of subjects with mild to moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalised). BLAZE-1 enrolled adult subjects who were not hospitalised and had at least 1 or more COVID-19 symptoms that were at least mild in severity. Treatment was initiated within 3 days of obtaining the clinical sample for the first positive SARS-CoV-2 viral infection determination.

### Phase 2 Data from BLAZE-1

In the Phase 2 portion of the trial, subjects were treated with a single infusion of bamlanivimab 2,800 mg and etesevimab 2,800 mg (N=112), bamlanivimab alone (at doses of 700 mg [N=101], 2,800 mg [N=107], or 7,000 mg [N=101]) or placebo (N=156). The data are from an interim analysis after all enrolled subjects in these arms completed at least Day 29 of the trial.

The baseline demographics and disease characteristics were well balanced across treatment groups. The mean duration of symptoms was 5 days. The mean viral load by CT was 24 at baseline.

While viral load was used to define the primary endpoint in this Phase 2 trial (Figure 2), signs that bamlanivimab and etesevimab may be effective came from a predefined secondary endpoint of COVID-19-related hospitalisations or emergency room visits or death within 28 days after treatment. A lower proportion of bamlanivimab and etesevimab-treated subjects progressed to COVID-19-related hospitalisation or emergency room visits compared to placebo-treated subjects (Table 6). No deaths occurred in any treatment arm.



**Figure 2: SARS-CoV-2 Viral Load Change from Baseline by Visit from the Phase 2 Portion of BLAZE-1.**

**Table 6: Proportion of Subjects with Events of Hospitalisation or Emergency Room Visits within 28 Days After Treatment**

Treatment	Na	Events	Proportion of Subjects %
Placebo	156	9	5.8%
Bamlanivimab and etesevimab <sup>b</sup>	112	1	0.9%
Bamlanivimab <sup>c</sup> 700 mg	101	1	1.0%

<sup>a</sup> N = number of treated patients in analysis.

<sup>b</sup> The doses for bamlanivimab and etesevimab were bamlanivimab 2,800 mg and etesevimab 2,800 mg.

<sup>c</sup> Results for other doses of bamlanivimab were suggestive of a flat dose-response relationship for this endpoint.

The absolute risk reduction for bamlanivimab and etesevimab-treated subjects compared to placebo is greater in subjects at higher risk of hospitalisation according to the high risk criteria (Table 7). These data were generated by post-hoc analysis.

**Table 7: Proportion of Subjects with Events of Hospitalisation or Emergency Room Visits within 28 Days After Treatment <sup>a</sup>**

Treatment	N <sup>b</sup>	Events	Proportion of Subjects %
Placebo	68	7	10.3%
Bamlanivimab and etesevimab <sup>C</sup>	38	1	2.6%
Bamlanivimab <sup>d</sup> 700 mg	46	1	2.2%

<sup>a</sup> This data was generated by post-hoc analysis not pre-defined in the study protocol

<sup>b</sup> N = number of treated patients in analysis.

<sup>c</sup> The doses for bamlanivimab and etesevimab were bamlanivimab 2,800 mg and etesevimab 2,800 mg.

<sup>d</sup> Results for other doses of bamlanivimab were suggestive of a flat dose-response relationship for this endpoint.

The median time to symptom improvement as recorded in a trial specific daily symptom diary was 6 days for bamlanivimab and etesevimab-treated subjects, as compared with 8 days for placebo-treated subjects. Symptoms assessed were cough, shortness of breath, feeling feverish, fatigue, body aches and pains, sore throat, chills, and headache. Symptom improvement was defined as symptoms scored as moderate or severe at baseline being scored as mild or absent, and symptoms scored as mild or absent at baseline being scored as absent.

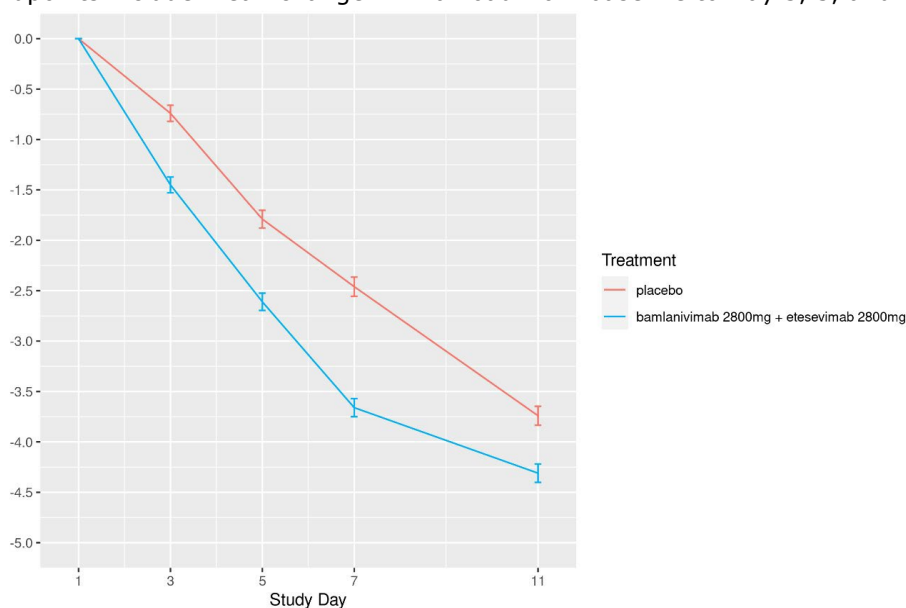
### Phase 3 Data from BLAZE-1

In the Phase 3 portion of the trial, subjects were treated with a single infusion of bamlanivimab 2,800 mg and etesevimab 2,800 mg (N=518), or placebo (N=517). All of the patients enrolled in these dose arms met the criteria for high-risk.

The baseline demographics and disease characteristics were well balanced across treatment groups. The mean duration of symptoms was 4 days. The mean viral load by CT was 24 at baseline.

The primary endpoint was the proportion of subjects with COVID-19 related hospitalisation (defined as  $\geq 24$  hours of acute care) or death by any cause by Day 29. Events occurred in 36 subjects treated with placebo (7%) as compared to 11 events in subjects treated with bamlanivimab 2,800 mg and etesevimab 2,800 mg together (2%) [ $p < 0.001$ ; not controlled for multiple testing across treatment arms], a 70% relative risk reduction or 5% absolute risk reduction. There were 10 deaths in subjects treated with placebo and no deaths in subjects treated with bamlanivimab 2,800 mg and etesevimab 2,800 mg together.

Secondary endpoints include mean change in viral load from baseline to Day 3, 5, and 7 (Figure 3).



**Figure 3: SARS-CoV-2 Viral Load Change from Baseline by Visit from the Phase 3 Portion of BLAZE-1.**

## **7. CONDITIONS FOR SAFETY MONITORING**

This medicine is subject to additional monitoring. This enables new safety information to be identified quickly. Healthcare Professionals are asked to report any suspected adverse reactions. For information on reporting side effects, see section 6.

## **8. DATE OF CHMP OPINION**

**Note for agency: Presume this will be completed by the agency**

**ANNEX I**

**CONDITIONS OF USE, CONDITIONS FOR DISTRIBUTION AND PATIENTS TARGETED  
AND CONDITIONS FOR SAFETY MONITORING ADRESSED TO MEMBER STATES**

**FOR**

**UNAUTHORISED PRODUCT ETESEVIMAB**

**AVAILABLE FOR USE**

## 1. MEDICINAL PRODUCT FOR USE

- **Name of the medicinal product for Use:** Etesevimab
- **Active substance(s):** Etesevimab
- **Pharmaceutical form:** Concentrate for solution for infusion (sterile concentrate).
- **Route of administration:** Intravenous infusion
- **Strength:** 700 mg (Each vial contains 700 mg Etesevimab in 20 mL (35 mg/mL).

## 2. NAME AND CONTACT DETAILS OF THE COMPANY

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands

[Contact details will be added at the National level]

## 3. TARGET POPULATION

Bamlanivimab and etesevimab administered together are indicated for the treatment of confirmed COVID-19 in patients aged 12 years and older that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe COVID-19

Risk factors may include but are not limited to:

- Advanced age
- Obesity
- Cardiovascular disease, including hypertension
- Chronic lung disease, including asthma
- Type 1 or type 2 diabetes mellitus
- Chronic kidney disease, including those on dialysis
- Chronic liver disease
- Immunosuppressed, based on prescriber's assessment. Examples include: cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anemia, thalassemia, and prolonged use of immune-weakening medications.

## 4. CONDITIONS FOR DISTRIBUTION

Prescription-only medicinal product

## 5. CONDITIONS OF USE

Bamlanivimab and Etesevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis.

### Limitation in Patients with Severe COVID-19

Monoclonal antibodies, such as bamlanivimab and etesevimab, may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation with COVID-19.

### 5.1 Posology

#### Dosing recommendations

The recommended dose for in adults and paediatric patients (12 years of age and older weighing at least 40 kg) is a single infusion of 700 mg bamlanivimab and 1,400 mg etesevimab administered as soon as possible after testing positive for SARS-CoV-2 and within 10 days of symptom onset.

- **Treatment duration and monitoring**

Single dose.

Patients are clinically monitored during administration and observed for at least 1 hour after infusion is complete.

- **Specific Populations**

*Paediatric Use*

The safety and efficacy of bamlanivimab and etesevimab in children under 12 years of age have not yet been established. No data are available. No dosage adjustment is recommended in paediatric patients who are 12 years of age and older.

#### *Geriatric use*

No dose adjustment is required in patients  $\geq 65$  years of age.

#### *Renal Impairment*

No dosage adjustment is recommended in patients with renal impairment.

#### *Hepatic impairment*

No dosage adjustment is recommended in patients with mild hepatic impairment. Bamlanivimab and etesevimab has not been studied in patients with moderate or severe hepatic impairment.

### ▪ **Method of administration**

#### Preparation

Bamlanivimab and etesevimab solution for infusion should be prepared by a qualified healthcare professional using aseptic technique:

- Gather the materials for preparation:
  - Polyvinyl chloride (PVC) or polyethylene (PE)-lined PVC, sterile prefilled infusion bag. Choose one of the following sizes:
    - Prefilled 50 mL, 100 mL, 150 mL, or 250 mL infusion bag containing 0.9% Sodium Chloride Injection (see **Table 1** and **Table 2**).
  - One vial of bamlanivimab (700 mg/20 mL) and two vials of etesevimab (700 mg/20 mL).
- Bamlanivimab and etesevimab are supplied in individual single-dose vials but are administered together using a single infusion bag.
- Remove 1 bamlanivimab vial and 2 etesevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vials.**
- Inspect both bamlanivimab and etesevimab vials visually for particulate matter and discoloration.
  - Bamlanivimab and etesevimab are clear to opalescent and colourless to slightly yellow to slightly brown solutions.
- Withdraw 20 mL from one bamlanivimab vial and 40 mL from two etesevimab vials and inject all 60 mL into a prefilled infusion bag containing 0.9% Sodium Chloride (see **Table 1** or **Table 2**).
- Discard any product remaining in the vials.
- Gently invert the bag by hand approximately 10 times to mix. **Do not shake.**
- These products are preservative-free and therefore, the diluted infusion solution should be administered immediately.
  - If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C) and up to 7 hours at room temperature (20°C to 25°C) including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.

#### Administration

Bamlanivimab and etesevimab infusion solution should be administered by a qualified healthcare professional.

- Gather the materials for infusion:
  - PVC or PE-lined PVC infusion set.
  - Use of an in-line or add-on 0.2/0.22 micron polyethersulfone (PES) filter is strongly recommended.
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity according to the size of infusion bag used (see **Table 1 for patients weighing  $\geq 50$  kg** or **Table 2 for patients weighing  $< 50$  kg**). Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.



- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of bamlanivimab and etesevimab injection with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride to ensure delivery of the required dose.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.
- If the infusion must be discontinued due to an infusion reaction, discard any unused product.
- The use of CSTDs, elastomeric pumps, and pneumatic transport with bamlanivimab has not been studied.

**Table 1: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion<sup>a</sup> in Patients Weighing 50 kg or More**

<b>Drug<sup>a</sup>: Add 20 mL of bamlanivimab (1 vial) and 40 mL of etesevimab (2 vials) for a total of 60 mL to a prefilled infusion bag and administer as instructed below</b>		
<b>Size of Prefilled 0.9% Sodium Chloride Infusion Bag</b>	<b>Maximum Infusion Rate</b>	<b>Minimum Infusion Time</b>
50 mL	310 mL/hr	21 minutes
100 mL	310 mL/hr	31 minutes
150 mL	310 mL/hr	41 minutes
250 mL	310 mL/hr	60 minutes

<sup>a</sup> 700 mg of bamlanivimab and 1,400 mg of etesevimab are added to the same infusion bag and administered together as a single intravenous infusion.

**Table 2: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion in Patients Weighing Less Than 50 kg**

<b>Drug<sup>a</sup>: Add 20 mL of bamlanivimab (1 vial) and 40 mL of etesevimab (2 vials) for a total 60 mL to an infusion bag and administer as instructed below</b>		
<b>Size of Prefilled 0.9% Sodium Chloride Infusion Bag</b>	<b>Maximum Infusion Rate</b>	<b>Minimum Infusion Time</b>
50 mL	310 mL/hr	21 minutes
100 mL	310 mL/hr	31 minutes
150 mL	310 mL/hr	41 minutes
250 mL <sup>b</sup>	266 mL/hr	70 minutes

<sup>a</sup> 700 mg of bamlanivimab and 1,400 mg of etesevimab are added to the same infusion bag and administered together as a single intravenous infusion.

<sup>b</sup> The minimum infusion time for patients weighing less than 50 kg who are administered bamlanivimab and etesevimab together using the 250 mL prefilled 0.9% Sodium Chloride infusion bag must be extended to at least 70 minutes to ensure safe use (endotoxin load).

## **5.2 Contraindications**

Hypersensitivity to the active substance(s) or to any of the excipients (L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80, water for injection)

## **5.3 Special warnings and precautions for use**

### **Hypersensitivity**

Serious hypersensitivity reactions have occurred with bamlanivimab and etesevimab together. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration and initiate appropriate therapy.

### **Infusion-related reactions**

Infusion-related reactions have been observed with administration of bamlanivimab and etesevimab together. These reactions may be severe or life threatening.

If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer supportive care.

### **Clinical Worsening after Bamlanivimab Administration**

Clinical worsening of COVID-19 after administration of bamlanivimab alone has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to bamlanivimab use or were due to progression of COVID-19.

### **5.4 Interaction with other medicinal products and other forms of interaction**

None known. No interaction studies have been performed.

Bamlanivimab and etesevimab are not renally excreted or metabolised by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

#### **Immune Response**

Concomitant administration of bamlanivimab and etesevimab with COVID-19 vaccines has not been studied.

### **5.5 Pregnancy and lactation**

Bamlanivimab and etesevimab have not been studied in pregnant or lactating women.

Bamlanivimab and etesevimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the foetus.

### **5.6 Incompatibilities**

None known.

### **5.7 Overdose**

Doses up to 7,000 mg of bamlanivimab (10 times the recommended dose) or 7,000 mg of etesevimab (5 times the recommended dose) have been administered in clinical trials without dose-limiting toxicity. In case of overdose, initiate supportive care.

### **5.8 Shelf life**

The shelf life is 12 months when vials are stored at 2°C to 8°C.

### **5.9 Storage conditions**

#### **Drug Product**

- Vials should be stored in a refrigerator at 2°C to 8°C until time of use.
- Keep vial in outer carton in order to protect from light.
- DO NOT FREEZE or SHAKE.

#### **Handling of Prepared Dosing Solution**

- This product is preservative free and therefore the prepared dosing solution should be used immediately
- If not used immediately, store the dosing solution under refrigeration for up to 24 hours at 2°C to 8°C and for up to 7 hours at room temperature (below 30°C) assuming dilution has taken place using acceptable aseptic techniques.
- If refrigerated, allow the dosing solution to come to room temperature prior to administration.
- Storage times include the duration of infusion.

DO NOT FREEZE OR SHAKE the bamlanivimab infusion solution.

### **5.10 Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **6. OTHER INFORMATION**

### **▪ Undesirable effects:**

#### Summary of the safety profile

Approximately 1,500 subjects have been exposed to bamlanivimab and etesevimab administered together in clinical trials in ambulatory (non-hospitalized) subjects at doses of bamlanivimab 700 mg and etesevimab 1,400 mg or higher. More than 3,900 subjects have received bamlanivimab (either alone or with etesevimab) at doses ranging from 700 to 7,000 mg. Bamlanivimab and etesevimab at doses of 700 mg and 1,400 mg have been administered together to approximately 770 subjects

The safety of bamlanivimab and etesevimab administered together is based on data from the Phase 2/3 BLAZE-1 trial of ambulatory subjects with COVID-19. The dose is bamlanivimab 700 mg and etesevimab 1,400 mg administered together.

BLAZE-1 is a randomized, double-blind, placebo-controlled clinical trial in ambulatory adults with mild to moderate COVID-19 symptoms who had sample collection for the first positive SARS-CoV-2 viral infection determination within 3 days prior to the start of the infusion.

#### *Phase 2 Data from BLAZE-1*

Five hundred seventy-seven (577) subjects were treated with a single infusion of bamlanivimab 2,800 mg and etesevimab 2,800 mg (N=112), bamlanivimab alone at doses of 700 mg (N=101), 2,800 mg (N=107), or 7,000 mg (N=101) or placebo (N=156).

Based on Phase 2 data from BLAZE-1 subjects followed for at least 28 days after treatment, adverse events occurred in 18% of subjects treated with both bamlanivimab and etesevimab and 28% of placebo-treated subjects.

Nausea was the most commonly reported adverse event, reported by 4% of subjects treated with bamlanivimab and etesevimab together and 4% treated with placebo. Pruritus and pyrexia were more frequently reported from subjects treated with both bamlanivimab and etesevimab (2% and 1%) compared to placebo (1% and 0%, respectively).

#### *Phase 3 Data from BLAZE-1*

Five hundred eighteen (518) subjects were treated with a single infusion of bamlanivimab 2,800 mg and etesevimab 2,800 mg together and 517 subjects were treated with a single infusion of placebo in Arms 7 and 8, respectively, of the BLAZE-1 Phase 3 trial. Adverse events occurred in 13% of subjects who received 2,800 mg of bamlanivimab and 2,800 mg etesevimab together, and in 12% of placebo-treated subjects. The most common adverse events were nausea, dizziness, and rash. These events each occurred in 1% of subjects treated with bamlanivimab and etesevimab and in 1% of placebo subjects.

#### Hypersensitivity Including Anaphylaxis and Infusion-related Reactions:

Across ongoing, blinded clinical trials, a case of anaphylaxis and other cases of serious infusion-related reactions were reported with infusion of bamlanivimab with and without etesevimab. The infusions were stopped. All reactions required treatment, one required epinephrine. All events resolved.

#### Other Immediate Hypersensitivity Events

In the phase 2 portion of BLAZE-1, 2% of subjects treated with bamlanivimab and etesevimab, and 1% of placebo-treated subjects experienced immediate hypersensitivity events. Reported events of pruritus, flushing and hypersensitivity were mild and one case of face swelling was moderate.

In the phase 3 portion of BLAZE-1, 1% of subjects treated with bamlanivimab and etesevimab experienced immediate hypersensitivity events, including 2 infusion-related reactions (moderate severity), 2 cases of rash (1 mild, 1 moderate), 1 infusion site rash (mild), and 1 mild case of pruritus.

### **▪ Summary of relevant pharmacological properties**

#### Mechanism of Action

Etesevimab is a recombinant neutralising human IgG1k mAb to the spike protein of SARS-CoV-2, with amino acid substitutions in the Fc region (L234A, L235A) to reduce effector function. Etesevimab binds the spike protein with a dissociation constant  $K_D = 6.45$  nM and blocks spike protein attachment to the human ACE2 receptor with an  $IC_{50}$  value of 0.32 nM (0.046  $\mu\text{g/mL}$ ).

Bamlanivimab is also a recombinant neutralising human IgG1k mAb to the spike protein of SARS-CoV-2 and is unmodified in the Fc region. Bamlanivimab and etesevimab bind to different but overlapping epitopes in the receptor binding domain (RBD) of the S-protein. Using both antibodies together is expected to reduce the risk of viral resistance.

#### Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to both bamlanivimab and etesevimab.

In vitro monoclonal antibody resistance studies have identified six amino acid substitutions at three positions (K417N, D420N, and N460K/S/T/Y) in the spike RBD that has a resistant phenotype to etesevimab and six amino acid substitutions at four positions (E484D/K/Q, F490S, Q493R and S494P) that has a resistant phenotype to bamlanivimab as determined using authentic SARS-CoV-2 pseudovirus neutralisation, or binding assessment. Resistant variants were not identified when bamlanivimab and etesevimab were tested together using the same methodologies. All identified bamlanivimab and etesevimab resistant variants maintained susceptibility to bamlanivimab and etesevimab together, except for the E484K, E484Q, and Q493R substitutions, which resulted in susceptibility shifts using a pseudovirus neutralisation assay.

Pseudovirus harbouring the concurrent spike substitutions present in the South African B.1.351 origin variant lineage (K417N + E484K + N501Y), and the Brazil origin P.1 variant lineage (K417T + E484K + N501Y) exhibited significantly reduced susceptibility to etesevimab alone, bamlanivimab alone, and bamlanivimab and etesevimab together. Bamlanivimab alone and bamlanivimab and etesevimab together retained activity against pseudovirus expressing del69-70 + N501Y spike substitutions found in the UK origin B.1.1.7 variant lineage.

Genotypic and phenotypic testing are ongoing to monitor for potential bamlanivimab and etesevimab-resistance associated spike variations in clinical trials. To date, the observation of known etesevimab and/or bamlanivimab-resistant variants at baseline has been rare. The frequency of detection was lower in the bamlanivimab with etesevimab together treatment group compared to that of bamlanivimab monotherapy treatment group. The clinical relevance of these findings is not known.

#### Immune Response Attenuation

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection

#### **Summary of relevant Clinical properties**

The data supporting the use of bamlanivimab together with etesevimab are based on analyses of data from the Phase 2/3 BLAZE-1 trial (NCT04427501) and the Phase 2 BLAZE-4 trial (NCT04634409). Both trials are evaluating the safety and efficacy of bamlanivimab and etesevimab together for treatment of subjects with mild to moderate COVID-19. BLAZE-1 provides clinical efficacy data from subjects receiving 2,800 mg bamlanivimab and 2,800 mg of etesevimab together.

#### **Data from BLAZE-1**

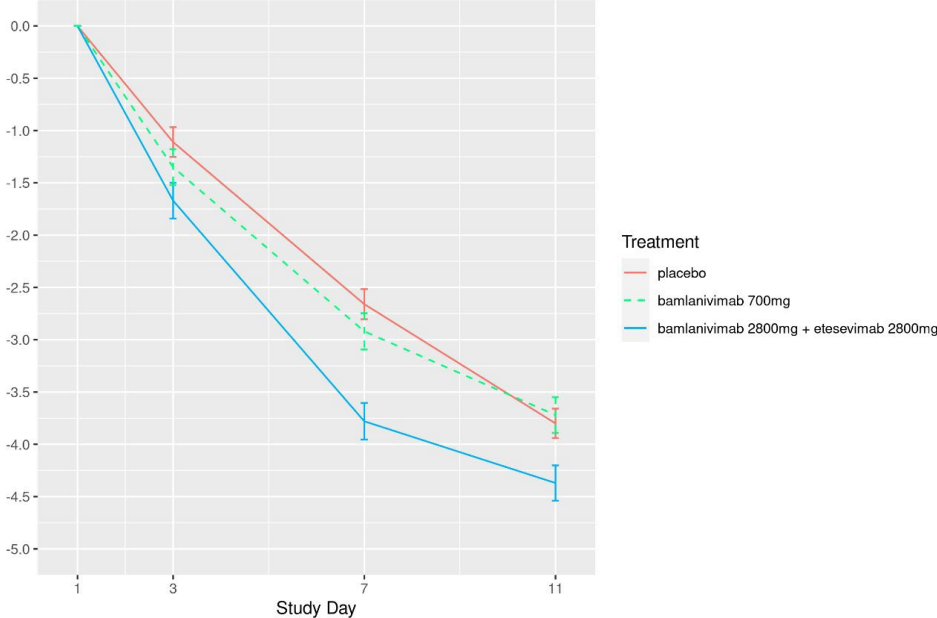
BLAZE-1 is an ongoing randomized, double-blind, placebo-controlled clinical trial studying bamlanivimab and etesevimab administered together for the treatment of subjects with mild to moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalised). BLAZE-1 enrolled adult subjects who were not hospitalised and had at least 1 or more COVID-19 symptoms that were at least mild in severity. Treatment was initiated within 3 days of obtaining the clinical sample for the first positive SARS-CoV-2 viral infection determination.

#### *Phase 2 data from BLAZE-1*

In the Phase 2 portion of the trial, subjects were treated with a single infusion of bamlanivimab 2,800 mg and etesevimab 2,800 mg (N=112), bamlanivimab alone (at doses of 700 mg [N=101], 2,800 mg [N=107], or 7,000 mg [N=101]) or placebo (N=156). The data are from an interim analysis after all enrolled subjects completed at least Day 29 of the trial.

The baseline demographics and disease characteristics were well balanced across treatment groups. The mean duration of symptoms was 5 days. The mean viral load by CT was 24 at baseline.

While viral load was used to define the primary endpoint in this Phase 2 trial (Figure 1), signs that bamlanivimab and etesevimab may be effective came from a predefined secondary endpoint of COVID-19-related hospitalisations or emergency room visits within 28 days after treatment. A lower proportion of bamlanivimab and etesevimab-treated subjects progressed to COVID-19-related hospitalisation or emergency room visits compared to placebo-treated subjects (Table 3). No deaths occurred in any treatment arm.



**Figure 1: SARS-CoV-2 Viral Load Change from Baseline by Visit from the Phase 2 Portion of BLAZE-1.**

**Table 3: Proportion of Subjects with Events of Hospitalisation or Emergency Room Visits within 28 Days After Treatment**

Treatment	N <sup>a</sup>	Events	Proportion of Subjects %
Placebo	156	9	5.8%
Bamlanivimab and etesevimab <sup>b</sup>	112	1	0.9%
Bamlanivimab <sup>c</sup> 700 mg	101	1	1.0%

<sup>a</sup> N = number of treated patients in analysis.

<sup>b</sup> The doses for bamlanivimab and etesevimab were bamlanivimab 2,800 mg and etesevimab 2,800 mg.

<sup>c</sup> Results for other doses of bamlanivimab were suggestive of a flat dose-response relationship for this endpoint.

The absolute risk reduction for bamlanivimab and etesevimab-treated subjects compared to placebo is greater in subjects at higher risk of hospitalisation according to the high risk criteria (Table 4). These data were generated by post-hoc analysis.

**Table 4: Proportion of Subjects with Events of Hospitalisation or Emergency Room Visits within 28 Days After Treatment <sup>a</sup>**

Treatment	N <sup>b</sup>	Events	Proportion of Subjects %
Placebo	68	7	10.3%
Bamlanivimab and etesevimab <sup>b</sup>	38	1	2.6%
Bamlanivimab <sup>c</sup> 700 mg	46	1	2.2%

<sup>a</sup> This data was generated by post-hoc analysis not pre-defined in the study protocol

<sup>b</sup> N = number of treated patients in analysis.

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<sup>d</sup> Results for other doses of bamlanivimab were suggestive of a flat dose-response relationship for this endpoint.

The median time to symptom improvement as recorded in a trial specific daily symptom diary was 6 days for bamlanivimab and etesevimab-treated subjects, as compared with 8 days for placebo-treated subjects. Symptoms assessed were cough, shortness of breath, feeling feverish, fatigue, body aches and pains, sore throat, chills, and headache. Symptom improvement was defined as symptoms scored as moderate or severe at baseline being scored as mild or absent, and symptoms scored as mild or absent at baseline being scored as absent.

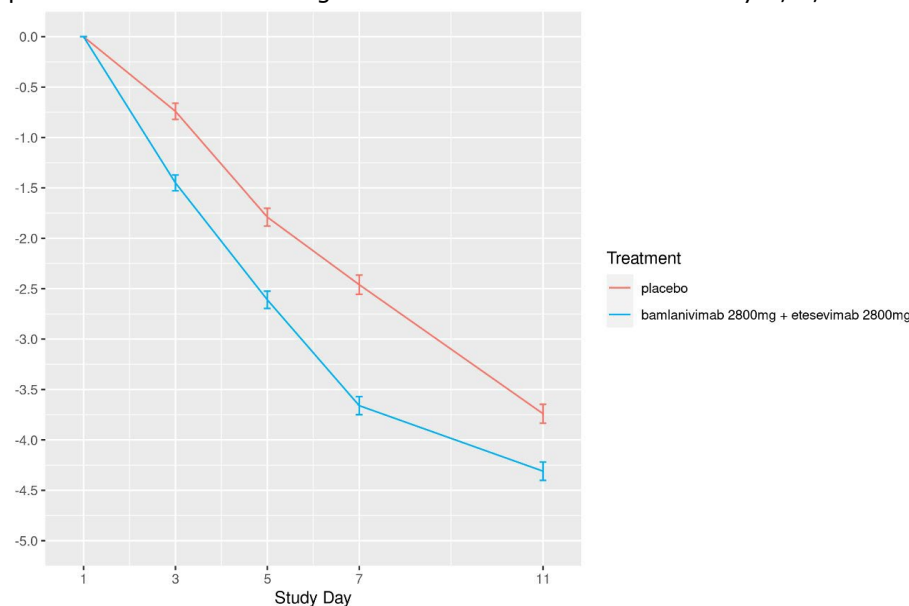
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The primary endpoint was the proportion of subjects with COVID-19 related hospitalisation (defined as  $\geq 24$  hours of acute care) or death by any cause by Day 29. Events occurred in 36 subjects treated with placebo (7%) as compared to 11 events in subjects treated with bamlanivimab 2,800 mg and etesevimab 2,800 mg together (2%) [ $p < 0.001$  not controlled for multiple testing across treatment arms], a 70% relative risk reduction or 5% absolute risk reduction. There were 10 deaths in subjects treated with placebo and no deaths in subjects treated with bamlanivimab 2,800 mg and etesevimab 2,800 mg together.

Secondary endpoints include mean change in viral load from baseline to Day 3, 5, and 7 (Figure 2).



**Figure 2: SARS-CoV-2 Viral Load Change from Baseline by Visit from the Phase 3 Portion of BLAZE-1.**

## 7. CONDITIONS FOR SAFETY MONITORING

This medicine is subject to additional monitoring. This enables new safety information to be identified quickly. Healthcare Professionals are asked to report any suspected adverse reactions. For information on reporting side effects, see section 6.

## 8. DATE OF CHMP OPINION

**Note for agency: Presume this will be completed by the agency**

