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DRUG DISCOVERY CASE HISTORY

An overview of the preclinical discovery and development of bamlanivimab for the treatment of novel coronavirus infection (COVID-19): reasons for limited clinical use and lessons for the future

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ABSTRACT

Introduction: In the COVID-19 pandemic emergency, research has been oriented toward the development of therapies that could cure critically ill patients and treatments that can reduce the number of hospitalized patients, in order to ease the pressure on health-care systems. Bamlanivimab, developed from human convalescent plasma, was the first monoclonal antibody to become available for emergency use in several countries. Expectations related to its use in COVID-19 patients as a single agent have been largely disregarded, especially against E484K-carrying SARS-CoV-2 variants.

Areas covered: In this drug discovery case history, the development of the drug is described starting from the identification and selection of the antibody, from the pre-clinical and clinical trials up to the post-authorization phase.

Expert opinion: Bamlanivimab has shown some efficacy in patients with mild to moderate COVID-19. Initially approved as a monotherapy, due to poor efficacy it is currently only usable in combination with etesevimab. Pharmacokinetic limitations and mainly the onset of SARS-CoV-2 variants are the main reasons for this limited clinical use. The use in preventing hospitalization also has ethical limits related to the sustainability of care, especially if, considering similar effectiveness, bamlanivimab is compared with convalescent plasma.

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1. Introduction

The identification of the pathophysiological pathways underlying severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1,2] was a leading step to the development of the treatments for COVID-19, including active and passive immunization strategies [3–5]. While in the early pandemic old drugs with potential therapeutic benefits were tested against the infection and its complications [6], parallel investigations on targeted therapeutics started all over the world [3]. In particular, the characterization of the SARS-CoV-2 portion responsible for viral entry, namely the Spike protein, represented a benchmark in COVID-19 research and drove subsequent pharmacological discovery. The Spike protein, a class I multi-domain glycoprotein exposed as a homotrimer, binds the angiotensin-converting enzyme 2 (ACE2) cellular receptor through its receptor-binding domain (RBD). The RBD upward movement allows the ACE2 receptor binding, and leads to endoproteolytic cleavage of Spike into S1 and S2 subunits. After that, virion fusion to the cell membrane and the transfer of viral genetic content into the host cell takes place [1,7]. The development of neutralizing monoclonal antibodies (mAbs), having the RBD as a target, and the ability to inhibit ACE2 receptor binding, therefore preventing SARS-CoV-2 infection [1,7,8] has appeared as a promising pharmacological strategy at once.

2. Discovery strategy and preclinical development

The attempt of achieving a passive immunization through the isolation of multiple neutralizing mAbs from peripheral blood mononuclear cells (PBMC) of donors both with active [9,10] or resolved [11–13] disease has been already made for other human pathogenic viruses such as respiratory syncytial virus (RSV), HIV, Ebolavirus, Avian H_7N_9 influenza virus, and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). MAbs have the potential of preventing and treating these emerging viruses by inhibiting entrance into host cells and subsequent virus replication [9–13]. To the best of our knowledge, palivizumab is the only mAb selected from the screening of murine convalescent blood and subsequently humanized that received a final approval for the treatment of an infectious disease, namely RSV. In the case of COVID-19, approved mAbs have been developed for the first time starting from human convalescent plasma [14,15]. Notably, the experience accumulated with MERS-CoV had a central role in the development of mAbs for SARS-CoV-2 [13].

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Article highlights

- The development of anti-COVID-19 monoclonal antibodies appeared a promising strategy to treat critically ill patients and to reduce pandemic pressure on hospitals
- Bamlanivimab was the first monoclonal antibody developed from human convalescent plasma to receive authorization for emergency use
- In the pre-clinical trial, bamlanivimab, administered IV 24 hours before intranasal and intratracheal inoculation of SARS-CoV-2, has been shown to inhibit viral load in respiratory tissues in primate models
- In clinical trials, bamlanivimab has been shown to be effective in reducing hospitalization in patients with mild to moderate COVID-19, but no efficacy in critically ill patients
- The occurrence of SARS-CoV-2 variants and some pharmacokinetic limitations are the basis of a reduced efficacy that led the FDA to withdraw the emergency authorization for bamlanivimab monotherapy, while leaving it for the bamlanivimab-etesevimab combination
- The future of COVID-19 mAb therapy is uncertain due to problems related to viral resistance, pharmacokinetics, and economic sustainability

Bamlanivimab (LY-CoV555) is a mAb developed with this rationale by AbCellera Biologics and Eli Lilly as a treatment for COVID-19. This mAb was developed starting from convalescent plasma donated from a recovered 35 years-old COVID-19 patient. About 3 weeks after the beginning of the disease signs, the PBMC were isolated. The PBMC were cryopreserved for identifying anti-Spike mAbs through two different tests, the multiplexed bead-based assay and live cell-based one. Out of 5.8 million of PBMCs screened, 4500 Abs were identified as potential candidates and 2238 single Abs were finally selected. Among these, Ab genes were sequenced and the related libraries were created. This brought to the identification of 440 high-confidence paired heavy and light chain sequences, belonging to 394 clonal families. The 4% of the identified Abs displayed cross-reactivity to both the SARS-CoV-2 and SARS-CoV Spike proteins, and 187 Abs were eligible for cloning and expression. Overall, recombinant mAbs were generated from 175 sequences cloned and they were evaluated with regard to stability, solubility, oligomerization, polydispersity, affinity, binding kinetics, binding validation, functional validation and epitope binding. Out of 24 mAbs with good properties, only 9 showed ACE2 blocking activity. When neutralization activity was tested in different *in vitro* experiments, Ab #169 (immunoglobulin G_1, IgG_1) displayed the greatest neutralization potency in the Plaque Reduction Neutralization Test (PRNT) against isolates from NextStrain clades 19A and 19B: half maximal inhibitory concentration (IC_{50}) was 0.049 µg/mL and 0.02 µg/mL, respectively. As a consequence, this mAb was selected for further investigations. Then, it was observed that its Fab portion was able to bind RBD Spike protein both in its up and down configuration [8]. Through surface plasmon resonance, this mAb showed an activity binding to the entire Spike protein and the recombinant RBD characterized by a K_D of 0.071 nM and 2.2 nM, respectively. The crystal structure of the bamlanivimab Fab showed that it binds the RBD via the amino acid residues 351, 449–450, 455–456, 470, 472, 481–489, and 492–494 of the Spike protein. This was able to inhibit Spike protein attachment to the human ACE2 with an IC_{50} value of 0.025 µg/mL. As expected for an IgG_1 mAb, bamlanivimab binds to FcγRI, FcγRIIa, FcγRIIb, and FcγRIIIa extracellular domains and to the complement protein C1q. On the contrary, no complement-dependent cytotoxicity (CDC) activity was found for bamlanivimab [8,16,17].

Reduced neutralization activity was observed when RBD variants were used in PRNTs. In particular, PRNT showed complete loss of function against WHO variants of concern (VOC) gamma (also named P.1 by PANGOLIN or 20 J/501Y.V3 by NextStrain) [18–20], beta (also named B.1.351 by PANGOLIN and 20 H/501Y.V2 by NextStrain) [18,19,21], and variants of interests (VOI) zeta (also named P.2 by PANGOLIN and 20B/S.484 K by NextStrain) [22], epsilon (also named B.1.427/B.1.419 by PANGOLIN and 21 C by NextStrain) [23,24], and iota (also named B.1.526 by PANGOLIN and 21 F by NextStrain) [25]. Efficacy of bamlanivimab was preserved against VOC alpha (also named B.1.1.7 by PANGOLIN and 20I/501Y.V1 by NextStrain) [21], but was lost in the related E484K-positive eta VOI (also named B.1.525 in PANGOLIN and 21D in NextStrain) [26]. This evidence confirms that the E484K mutation, occurring in 64 out of the 800 clades reported as of March 2021 and hence being a dramatic example of convergent evolution [27], inevitably leads to full resistance to bamlanivimab [23] as well as to many other class 2 RBD-directed mAbs [28].

With regard to the possibility of antibody-dependent enhancement (ADE) of SARS-CoV-2 infection, further investigations are needed due to both the discordance in results of *in vitro* models and the weak pharmacokinetic information in animal models (i.e. African green monkey). Nevertheless, there is no evidence of ADE in COVID-19 to date from any neutralizing antibody-based therapy [29]. When the ability to prevent viral load and replication was assessed in bronchoalveolar lavage fluid, throat and nasal swabs of rhesus monkeys, protection was found for the lower and upper respiratory tract following a single dose of bamlanivimab [8,16]. In particular, intravenous doses ≥2.5 mg/kg administered 24 hours before intranasal and intratracheal SARS-CoV-2 inoculation achieved the highest protection in infected rhesus monkeys, with timely effects first in lung and throat and then in the nasal setting owing to a late distribution of Abs into this environment [8].

After only 94 days, Ab #169, subsequently named LY-CoV555 and later bamlanivimab, was administrated for the first time in human subjects [8]. Etesevimab (LY-CoV-016) is the second mAb developed by AbCellera Biologics and Eli Lilly, characterized by the deletion of the effector function of the Fc portion through introduction of the LALA mutation. Its affinity to FcγRI, FcγRIIA allelic variant R167, or FcγRIII allelic variant V176 was scarce, and no ADCC and CDC activities were shown. Etesevimab binds to a different epitope of the RBD but since this epitope overlaps that of bamlanivimab, the two mAbs compete for binding, as displayed by co-crystal structural analysis [17].

3. Clinical development

In the Clinicaltrials.gov database and the International Clinical Trials Registry Platform (ICTRP) of the World Health Organization (WHO), 16 studies investigating bamlanivimab

for COVID-19 were retrieved [30–45]. Out of these, 10 trials involving phases from 1 to 3 were identified [31–33,35,38–43]. These involved patients with different characteristics (both outpatients with mild to moderate COVID-19 and hospitalized patients with moderate to severe COVID-19). The major characteristics of the study protocols are summarized in Table 1.

The results of BLAZE-1 and ACTIVE-3 trials have been fully published in peer reviewed journals. The BLAZE-1 was a phase 2 randomized, double-blind, placebo-controlled trial that investigated the efficacy and safety of bamlanivimab in outpatients with mild to moderate COVID-19. This involved five different treatment arms: a) placebo (n = 156); b) single infusion of bamlanivimab 700 mg (n = 101); c) single infusion of bamlanivimab 2800 mg (n = 107); d) single infusion of bamlanivimab 7000 mg (n = 101); e) a single infusion combination of bamlanivimab 2800 mg and etesevimab, 2800 mg (n = 112), respectively [46]. The change in log viral load from baseline to day 11 was the primary efficacy outcome. Viral load was measured by nasopharyngeal swab followed by quantitative reverse transcriptase-polymerase chain reaction (RT-PCR). In particular, compared with placebo, the differences were not statistically significant in the three monotherapy bamlanivimab groups but a significant difference was shown in the combination therapy group (–0.57; 95% Confidence Interval, CI, – 1.00 to – 0.14, p = 0.01). Several secondary outcomes were evaluated, three evaluating viral load and five assessing improvements in signs and symptoms. Statistically significant differences were observed in changes from baseline to day 29 and 11, respectively. In particular, compared with placebo, the change from baseline to day 29 in viral load area under the curve (AUC) was significant in the bamlanivimab 2800 mg group (difference – 9.50 [95% CI, – 16.32 to – 2.68]; p = 0.006) and in the combination therapy group (difference – 17.91 [95% CI, – 25.25 to – 10.58]; p < 0.001, respectively). Improvements in mean symptom score from baseline to day 11 were statistically significant in bamlanivimab 700 mg group (mean difference, – 0.78 [95% CI, – 1.37 to – 0.20]; p = 0.009) and in combination therapy group (mean difference, – 0.60 [95% CI,–1.18 to – 0.03]; p = 0.04) compared with placebo. Symptoms improvement at day 11 was observed for bamlanivimab 700 mg and 7000 mg monotherapy, respectively (difference, 16.0% [95% CI, 3.6% to 28.4%]; p = 0.02; difference, 15.0% [95% CI, 2.6% to 27.4%]; p = 0.02) compared with placebo. However, symptom resolution at day 11 was statistically significant only for the monotherapy bamlanivimab 700 mg group (difference from baseline, 13.7% [95% CI, 1.2% to 26.1%]; p = 0.04). When COVID-19-related hospitalization or emergency department visits were analyzed, only the combination group showed a statistically significant difference compared with placebo at day 29 [difference – 4.9% (95% CI, – 8.9% to – 0.8%; p = 0.049)]. The most frequently reported adverse drug reactions (ADRs) were: nausea (3.0% for the 700 mg group, 3.7% for the 2800 mg group, 5.0% for the 7000 mg group, 3.6% for the combination therapy group, and 3.8% for the placebo), diarrhea (1.0% for the 700 mg group, 1.9% for the 2800 mg group, 5.9% for the 7000 mg group, 0.9% for the combination therapy group, and 4.5% for the placebo) and immediate hypersensitivity reactions infusion related. In particular, the last ADR occurred in six patients in the bamlanivimab monotherapy groups, two patients in the bamlanivimab and etesevimab group and one patient in the placebo group.

To understand the possible neutralizing role of mAbs and other antiviral interventions in hospitalized patients with COVID-19, the US National Institutes of Health established the ACTIV-3/TICO (Therapeutics for Inpatients with COVID-19) platform [47]. The ACTIV-3 study, comparing bamlanivimab to placebo in hospitalized patients, was the first study developed within this platform. In this study, hospitalized patients with COVID-19 were randomized in a 1:1 ratio to receive bamlanivimab or placebo. All patients received all expected supportive care, including remdesivir and, when indicated, supplemental oxygen and glucocorticoids. The interventions not allowed were those that may have provided exogenous antibodies for SARS-CoV-2, such as convalescent plasma or hyperimmune serum. Hospitalized adult patients with documented SARS-CoV-2 infection and a duration of symptoms attributable to COVID-19 lasting 12 days or less were enrolled. Patients who had received intravenous immunoglobulin, convalescent plasma from patients cured of COVID-19, or another mAb against SARS-CoV-2 were excluded from the study. Patients with organ failure or certain extra pulmonary complications were excluded. Bamlanivimab (at a dose of 7000 mg) or placebo was administered as a single intravenous infusion over 1 hour. The primary TICO protocol establishes an overall primary outcome (sustained recovery, defined as hospital discharge and out-of-hospital stay for at least 14 days, until day 90), and two outcomes on an ordinal scale measured at day 5 for futility assessment. The outcomes assessed at day 5 are termed pulmonary and pulmonary-plus outcome. The pulmonary outcome is based largely on oxygen requirements, ranging from the ability to perform all normal daily activities to death. The pulmonary-plus outcome captures the range of organ dysfunction that may be associated with COVID-19 progression, such as respiratory dysfunction and coagulation-related complications. The choice of day 5 as the primary day for evaluation was based on an assessment of ACTT-1 [48] data, which showed that remdesivir was associated with a better outcome than placebo at day 5 on an ordinal scale similar to that used in this study. On 26 October 2020, the Data and Safety Monitoring Committee recommended that enrollment be discontinued for futility after 314 patients (163 in the bamlanivimab group and 151 in the placebo group) had undergone randomization and infusion. The median interval from symptom onset was 7 days. At day 5, a total of 81 patients (50%) in the bamlanivimab group and 81 (54%) in the placebo group were in one of the two most favorable pulmonary outcome categories (Odds Ratio 0.85, 95% CI, 0.56–1.29; p = 0.45). The proportion of patients with a primary safety outcome (defined as death, serious adverse events (AEs), or clinical grade 3 or 4 AEs through day 5) was similar in the bamlanivimab group and the placebo group (19% and 14%, respectively; Odds Ratio, 1.56; 95% CI, 0.78 to 3.10; p = 0.20). The Rate Ratio for sustained recovery was 1.06 (95% CI, 0.77 to 1.47). These data indicate that patients hospitalized with COVID-19 who received a single infusion of bamlanivimab (at a dose of 7000 mg) did not have better clinical outcomes at day 5 than those who received placebo [47].

Table 1. Phase I–III clinical trials recorded in Clinicaltrial.gov database and International Clinical Trials Registry Platform (ICTRP) of the World Health Organization (WHO) for bamlanivimab up to July 7th2021.

Clinicaltrial.gov identifier	Study design and type of control	Date, start – end	Efficacy outcome measures	Enrolled participants	Population	Treatment groups (dosage, route)
NCT04701658 [41]	Phase 2 – interventional study	January 2021 – June 2021	Experience of COVID-19-related hospitalization or death	With mild to moderate COVID-19; not hospitalized; 12 years and older	3000	Experimental: Bamlanivimab (IV) Control: standard of care
NCT04537910/ J2X-MC-PYAG [31]	Phase 1 – randomized, placebo-controlled	September 2020 – December 2020	PK	From 18 years to 60 years; healthy	25	Experimental: Bamlanivimab (700 mg, sc) No Intervention: standard of care (700 mg, sc)
NCT04411628/ J2W-MC-PYAA [44]	Phase 1 – randomized, placebo-controlled, double-blind	May 2020 – August 2020	Serious Adverse Event(s); PK	Hospitalized with COVID-19 moderate or severe	24	Experimental: LY3819253 Bamlanivimab (700 mg, 2800 mg, 7000 mg, IV) Comparator: Placebo
NCT04634409 (BLAZE-4)/ J2X-MC-PYAH [45]	Phase 2, placebo-controlled, double-blind, randomized, single dose trial	October 2020 – April 2021	SARS-CoV-2 Viral Load Greater than 5.27	Ambulatory adults (18–64 years) with mild to moderate COVID-19	500	Bamlanivimab (700 mg) Bamlanvinimab+ Etesevimab Bamlanivimab+ Etesevimab (700 mg+1400 mg) Bamlanivimab+ Etesevimab (2800 mg+2800 mg) Placebo
NCT04497987/ J2X-MC-PYAD [32]	Phase 3, randomized, double-blind, placebo controlled study	August 2020 – June 2021	COVID-19 within 21 days of detection Part 1: goal of achieving ~33 events (in each of the primary and key secondary endpoints) in the prevention population Part 2: goal of achieving ~56 events on each of the primary and key secondary endpoints in the prevention cohort	Residents and staff of skilled nursing or assisted living facilities; prevention and treatment cohorts (from 18 years)	≤5000 (maximum sample size) Part 1 will randomize up to 1700 participants	Placebo **Part 1**: Bamlanivimab (4200 mg) **Part 2: Prevention Cohort** Bamlanvinimab(700 mg) Bamlanivimab+ Etesevimab **Treatment Cohort** Bamlanivimab(700 mg) Bamlanivimab+ Etesevimab (2800 mg+2800 mg)
NCT04427501/ J2W-MC-PYAB (BLAZE-1) [33]	Phase 2, randomized, double-blind, placebo controlled trial	November 2019 – May 2021	(1) COVID-related hospitalization or death from any cause (2) Change from Baseline to day 11 in SARS-CoV-2 viral load (3) SARS-CoV-2 viral load greater than a pre-specified threshold	Mild to moderate COVID-19; participants in arms 7 & 8 have at least 1 risk factor for developing severe COVID-19 (from 12 years)	1060	Bamlanivimab (700 mg) Bamlanivimab (2800 mg) Bamlanivimab (7000 mg) Bamlanivimab+ Etesevimab (2800 mg+2800 mg) Placebo

(*Continued*)

Table 1. (Continued).

Clinicaltrial.gov identifier	Study design and type of control	Date, start – end	Efficacy outcome measures	Enrolled participants	Population	Treatment groups (dosage, route)
NCT04518410/ ACTIV-2 [34]	Phase 2/3, randomized, blinded, controlled, platform trial	August 2020 – December 2021	(1) Duration of COVID-19 symptoms (2) Post-treatment presence of SARS-CoV-2 RNA at Day 3 (3) Post-treatment presence of SARS-CoV-2 RNA at Day 7 (4) Post-treatment presence of SARS-CoV-2 RNA at Day 14 (5) Post-treatment presence of SARS-CoV-2 RNA at Day 21 (6) Post-treatment presence of SARS-CoV-2 RNA at Day 28 (7) Cumulative incidence of death from any cause or hospitalization **Safety:** (1) Incidence of new AE ≥ Grade 3 (2) Proportion of participants with new AE ≥ Grade 3	Ambulatory patients with mild to moderate COVID-19 (from 18 years)	220 for phase 2 N = 1000 per arm for phase 3, inclusive of the patients enrolled in the phase 2 portion of the trial Outpatient adults positive for SARS-CoV-2	Bamlanivimab (7000 mg initially, dose then changed to 700 mg) Placebo
NCT04501978/ ACTIV-3 [35]	Phase 3, randomized, blinded, controlled platform study with two stages	August 2020 – July 2022	(1) Pulmonary ordinal outcome (disease severity stratum 1) (2) Pulmonary ordinal outcome (disease severity stratum 1) (3) Time from randomization to sustained recovery	Patients hospitalized for COVID-19 (from 18 years)	1000 Stage 1, N = 150 participants Inpatient adults with COVID-19 symptoms, without organ failure Stage 2, N = 500 participants (including those from Stage 1)	Bamlanivimab (7000 mg) Placebo
NCT04790240 [38]	The trial (phase 1/2) uses medicinal herbs to direct T cells to engulf the COVID-19 virus and protect the organs well	February 2021 – March 2023	(1) Recovering damaged organ (2) Inhibiting inflammation (3) Preventing the antibody depositing on antigen	Patients with marks positive COVID-19 diagnosed in the past 1–20 days during the registration	120	Treatment group: Medications (remdesevir, colchicine, anti-SARS-CoV-2 monoclonal antibodies, bamlanivimab, Casirivimab, Imedevimab) and medical herbs Control group: remdesevir, colchicine, anti-SARS-CoV-2 monoclonal antibodies, bamlanivimab, Casirivimab, Imedevimab
NCT04840459 [39]	Use of monoclonal antibodies for the treatment of mild to moderate COVID-19 in non-hospitalized setting (phase 2)	November 2020 – December 2021	(1) Rate of recovery after monoclonal antibody therapy (2) Determine if hospitalization occurred after monoclonal antibody administration	Patients from 12 years with positive results of direct SARS-CoV-2 viral testing at high risk for progression to severe COVID-19 and/or hospitalization	1000	Bamlanivimab (Single IV infusion 700 mg) Casirivimab (10 mL) +Imdevimab (10 mL)

AE: Adverse events; IV: intravenous; N: number; PK: Pharmacokinetic; sc: subcutaneous

A US randomized double blind phase III trial was conducted on 966 resident and staff of skilled nursing and assisted living facilities with at least one index case, enrolled between August and November 2020, and followed up to January 2021. This study showed that bamlanivimab significantly reduced the incidence of COVID-19 in the prevention population compared with placebo (8.5%vs 15.2%; odds ratio, 0.43 [95% CI, 0.28–0.68]; P < .001; absolute risk difference, −6.6 [95% CI, −10.7 to −2.6] percentage points). No deaths related to COVID-19 were reported in the bamlanivimab vs five in the placebo group [49].

On November 9th, 2020 bamlanivimab obtained its first emergency use authorization (EUA) by U.S. Food and Drug Administration (FDA), both as monotherapy or in combination with etesevimab [50].

In Europe, the two neutralizing mAbs are currently under rolling review by the European Medicine Agency (EMA) [51].

4. Post-launch

The FDA has issued the EUA for the use of the unapproved mAb bamlanivimab for the treatment of mild to moderate COVID-19 in adult and pediatric patients (>12 years old) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to hospitalization and/or severe COVID-19. Bamlanivimab, is still under investigation, and collecting post-launch data is essential [50]. EMA's human medicines committee (CHMP) has started a rolling review on data collected for bamlanivimab used alone or in combination with etesevimab [51]. The Agency is reviewing available data on the use of bamlanivimab to treat patients with COVID-19 who do not require oxygen supplementation and who are at high risk of progressing to severe COVID-19.

To date, in the Clinicaltrials.gov database and the ICTRP of the WHO there are three phase 4 clinical trials [34,36,44], one expanded access program [30] and two observational studies [37,45] evaluating effectiveness and safety of bamlanivimab (Table 2). All of these studies started between January and March 2021 and, with the possible exception of the extended program for which little information is available, no results are available yet.

Real-world data about the use of bamlanivimab after EUA are scarce [52–54]. The study by Webb BJ et al. [52] described real-world effectiveness and tolerability of monoclonal antibodies against SARS-COV-2 for ambulatory patients with early COVID-19 at high risk of hospitalization. The study was conducted in infusion centers and urgent care clinics in the United States using target trial emulation and casual inference methodology. Patients were included in pre- (July 1–27 November 2020) and post- (28 November 2020–28 January 2021) mAbs implementation groups. Among the included patients, 594 high-risk early-symptomatic adults with positive COVID-19 test receiving the mAbs (479 and 115 were treated with bamlanivimab and casirivimab/imdevimab, respectively) were compared to 5536 controls through inverse probability of treatment weighting analysis, and to 7404 patients of the pre-implementation cohort using propensity-weighted interrupted time series analysis. The results showed that treatment with monoclonal antibody was associated with fewer subsequent hospitalization and emergency department (ED) visits (odds ratio 0.69, 95% CI 0.60–0.79). In the period after the implementation, the probability of hospitalization or ED access decreased by 0.7% per day, 95% CI 0.03–0.10%, $p < 0.001$. Authors observed six different infusion-associated AEs for bamlanivimab: two were classified as serious (chest pain and syncope), and four not serious (oral tingling, pruritus without rush, rigors and nausea plus emesis). The study by Rainwater-Lovett et al. [53] was in line with these results. Authors evaluated 598 COVID-19 patients (270 treated with bamlanivimab and 328 untreated) and found that the risk of ED visits or hospitalization was 82% lower in patients who received the mAb than untreated subjects (95% CI 66–94%). Despite results corroborated effectiveness and safety evidence deriving from clinical trials, their reliability is limited due to observational nature of data and to the reduced sample size.

In an early matched study on 468 patients by Bariola et al., patients receiving bamlanivimab were less likely to experience hospitalization or mortality (OR 0.31) and hospitalization or emergency department visit without hospitalization (OR 0.50). The impact of bamlanivimab was more pronounced in prevention of hospitalization (among all age groups, OR 0.35) than mortality or emergency department visit without hospitalization, and most strongly associated with patients age 65 years and older (primary outcome OR 0.28) [55].

Ganesh *et al.* run a retrospective propensity-score matched study on 2,335 patients who received single-dose bamlanivimab infusion at Mayo Clinic facilities. Patients who received bamlanivimab had lower all-cause hospitalization rates at days 14 (1.5% vs 3.5%; OR 0.38), 21 (1.9% vs 3.9%; OR, 0.46), and 28 (2.5% vs 3.9%; OR, 0.61). Secondary exploratory outcomes included lower intensive care unit admission rates at days 14 (0.14% vs 1%; OR, 0.12), 21 (0.25% vs 1%; OR: 0.24) and 28 (0.56% vs 1.1%; OR: 0.52), and lower all-cause mortality at days 14 (0% vs 0.33%), 21 (0.05% vs 0.4%; OR, 0.08) and 28 (0.11% vs 0.44%; OR, 0.01) [56].

Webb et al. reported that, among 13,534 high-risk adult outpatients with symptomatic, laboratory-confirmed COVID-19 within 7 days of symptom onset propensity-weighted probability of emergency department visit or hospitalization decreased by 0.7% per day under bamlanivimab [52]. In a metanalyis by Wafa et al., bamlanivimab-etesevimab decreased viral load but did not improve hospital discharge at day 28–30 [57].

Following the outbreak of COVID-19 pandemic, the FDA has developed a specific section of the FDA Adverse Event Reporting System (FAERS) Public Dashboard dedicated to drugs that have obtained the EUA [58]. The tool now ensures frequent updates of AEs reports submitted to FAERS. Despite the existence of a report does not establish a causal relationship between drug and AEs, the reporting system is useful to monitor safety issues surrounding the drug. In this pandemic context, it assumes a helpful value to supplement evidence about the new drugs under evaluation. The COVID-19 EUA FAERS Public Dashboard [58] recorded 4,323 reports of AEs for bamlanivimab monotherapy as of July 7th, 2021 (998 and 3,682 received in 2020 and in 2021, respectively). Table 3 shows the distribution of the most reported AEs according to age groups. Among the 2,847 reported serious cases, death

Table 2. Phase IV studies recorded in Clinicaltrial.gov database and International Clinical Trials Registry Platform (ICTRP) of the World Health Organization (WHO) for bamlanivimab up to July 7th2021.

Clinicaltrial.gov identifier	Study design and type of control	Date, start – end	Efficacy outcome measures	Enrolled participants	Population	Treatment groups (dosage, route)
NCT04656691 [40]	Phase 4 – open-label, pragmatic, single-dose	January 2021 – May 2021	Hospitalization rates documenting adverse events after infusion	Participants with mild to moderate COVID-19; 65 years and older	7500	Bamlanivimab (700 mg IV)/
NCT04603651 / J2X-MC-Y001 [30]	Expanded access program	/	/	12 years and older (with risk factors), 65 years and older	/	/
NCT04796402 (B-EPIC) [36]	A pragmatic eight week phase 4 study of bamlanivimab/LY-CoV555 for emergency passive immunity against COVID-19	March /2021-March 2021	Any incidence of admission to hospital for >24 hours in the 28 days following first positive test for SARS-CoV2	High-risk for hospitalization in patients with SARS-CoV -2	576	Standard of care (indicated by care provider) Bamlanivimab (700 mg/20 mL IV over at least one hour once daily)
NCT04790786 [37]	A pragmatic evaluation of monoclonal antibody treatments in participants with covid-19 illness (Observational study)	March 2021-December 2022	Days alive and free from hospitalization	Patients that are both living and not in the hospital will meet criteria to be counted in this outcome	5000	Bamlanivimab (700 mg IV one within 10 days of COVID-19 symptom onset) Casirivimab+Imdevimab (1200 mg IV of each drug (2400 mg total) one within 10 days of COVID-19 symptom onset) Bamlanivimab+Etesevimab (700 mg/20 mL IV of each drug one within 10 days of COVID-19 symptom onset)
NCT04885452 [43]	Prospective, multicentric, non comparative study aiming to evaluate the clinical and virological evolution of high-risk patients infected with SARS-CoV-2 (Observational study)	May 2021 – July 2022	Percentage of patients hospitalized (if the patient was outpatient) or whose hospitalization was extended for complications from COVID-19 within 1 month of symtoms' onset.	Patients infected with SARS-CoV-2	2000	casirivimab/imdevimab bamlanivimab/etesevimab Other treatments authorized for emergency use
NCT04748588 [42]	Randomized, open-label, controlled clinical trial: standard-of-care (control) vs bamlanivimab (phase 4)	February 2021 – January 2023	(1) Proportion of participants requiring mechanical ventilation or not surviving to hospital discharge (2) in-hospital death (3) Need for mechanical ventilation (4) Need for new intensive care admission (5) Need for new oxygen administration	Adults with laboratory-confirmed SARS-CoV-2 infection nosocomially acquired	648	Bamlanivimab (Single IV infusion 700 mg) Standard of care

IV:intravenous;

Table 3. Distribution of the most reported suspected adverse drug reactions for bamlanivimab monotherapy in the FDA Adverse Event Reporting System according to age groups up to July 7th, 2021.

System organ class	Reactions	Age groups Cases (n)	0–1 m	2 m-2 y	12–17y	18–64y	65–85y	>85y	Unknown
General disorders and administration site conditions	Pirexia, chills, fatigue	1.878	-	2	8	599	814	135	320
Respiratory, thoracic and mediastinal disorders	Dispnea, cough, hypoxia	1.470	1	-	11	549	680	97	132
Nervous system disorders	Headache, dizziness, tremor	992	1	1	3	359	433	64	131
Investigations	Oxygen saturation decreased	918	1	3	3	307	439	91	74
Gastrointestinal disorders	Nausea, diarrhea, vomiting	823	-	-	-	264	378	60	121
Infections and infestations	Pneumonia, COVID-19	784	1	-	6	296	355	41	85
Injury, poisoning and procedural complications	Infusion related reaction, intentional product use issue	673	-	1	11	287	264	44	66
Skin and subcutaneous tissue disorders	Rash, hyperidrosis, pruritus	482	1	1	3	230	161	14	72
Cardiac disorders	Tachycardia, atrial fibrillation	409	-	-	2	131	209	43	24
Vascular disorders	Hypotension, hypertension, flushing	368	1	-	4	163	147	21	32
Psychiatric disorders	Confusional state, mental status changes	339	-	-	1	86	175	41	36

Y: years; m:months; n: number

cases were 264 and about 60% were aged between 66 and 85 years old with no gender differences. Death events were usually described in a clinical picture including cardiovascular, cardiac, and respiratory complications. About 20% of reported cases of death had information on concomitant treatments, which were likely attributable to therapies for chronic diseases or for COVID-19 (e.g. remdesivir or corticosteroids). Several important details such as time elapsed between bamlanivimab administration and events, drug dosage, or patients' clinical picture were not available. Of note, these characteristics are essential to establish a causal relationship between bamlanivimab and any suspected AEs reported in the FAERS. Some reported AEs to bamlanivimab suggest that its post-marketing safety profile could be partially in line with that observed in the BLAZE-1 study, that reported nausea, diarrhea, dizziness, headache, pruritus, with vomiting as the most commonly reported (2–4% of subjects) AEs [46,59].

In March 2021, the FDA updated the 'Antiviral Resistance' section of the Fact Sheet for Healthcare Providers for the bamlanivimab by adding information of efficacy against SARS-CoV-2 variants harboring RBD mutations [60]. A sustained increase in SARS-CoV-2 variants has been demonstrated, and different mutations of RBD are arising, making the virus able to escape mAbs targeting the RBD, including bamlanivimab [23]. Due to the unknown clinical impact following the current spread of the virus variants, the U.S. government halted the administration of bamlanivimab alone, allowing provider sites to order the combination bamlanivimab/etesevimab or etesevimab alone to combine with the residual stock of bamlanivimab [61]. The combination of bamlanivimab and etesevimab received the EUA for the same disease condition described for the use of bamlanivimab alone in February 2021 [60,62]. Therapy with both bamlanivimab and etesevimab is expected to prevent treatment failure and/or accelerated viral evolution [60]. According to this scenario, on April 16th, 2021, the FDA decided for the revocation of the EUA for bamlanivimab as monotherapy, stating that the benefits no longer outweigh the potential risks [63]. The EUA remained for the combination with etesevimab. Of note, bamlanivimab is being investigated in combination with VIR-7831 in patients with early manifestation of COVID-19 in the phase 2 BLAZE-4 trial [39]. The available results showed that the co-administration of bamlanivimab and VIR-7831 [3] demonstrated a 70% relative reduction ($p < 0.001$) in persistently high viral load on day 7 compared to placebo, reaching the primary endpoint. This combination will be further investigated, especially for potential protection against known variants of SARS-CoV-2 [64]. The last update of National Institute of Health (NIH) guidelines on July 8th, 2021 recommended against the use of the combination bamlanivimab-etesevimab in patients with mild to moderate COVID-19 who are at risk of clinical progression due to an increase in the prevalence of potentially resistant variants [65]. Previously, this mAb cocktail approach was used to develop the combination casirivimab/indevimab (REGN-COV), which obtained EUA by FDA in November 2020 for the same indications authorized for bamlanivimab/etesevimab. REGN-COV is made up of two mAbs binding different non-overlapping epitopes of spike RBD of SARS-CoV-2. Currently, both with REGN-COV and bamlanivimab/etesevimab are expected to remain available for emergency use to face therapeutic concerns due to the potential for further viral variants [63]. Similar approaches are represented by the long-acting mAb cocktail AZD7442 (including AZD8895 and AZD1061) [66,67], and the combinations C135 plus C144 [68], and VIR-7831 associated with VIR-7832 [69].

Further studies are needed, including comparative ones, to confirm the effectiveness and the safety profile.

5. Conclusion

The development of bamlanivimab was apparently based on a robust rationale. This mAb, selected starting from convalescent plasma, has demonstrated *in vitro* and *in vivo* pharmacodynamic and pharmacokinetic characteristics that have pushed it toward clinical trials. However, in the latter phase, the antibody showed some benefits in non-critically-ill COVID-19 patients, and no benefit in those hospitalized with more severe conditions. Nevertheless, FDA authorized this drug for emergency use in patients with mild to moderate COVID-19,

both for monotherapy and combined use with another mAb, etesevimab. In Europe, EMA has initiated the rolling review. The good safety profile of the drug was confirmed in the post-authorization period. However, the onset of resistance related to the spread of SARS-CoV-2 variants with the risk of therapeutic failure led to the FDA's decision to suspend the EUA for monotherapy, leaving it only for the combination with etesevimab. Clinical trials still ongoing will determine the future of this drug in COVID-19 therapy.

6. Expert opinion

Since the early phase of the pandemic, the two major and more urgent medical needs for health-care systems were an effective treatment for critically ill patients and a treatment that could prevent COVID-19-related hospitalization. The development of bamlanivimab and other mAbs against SARS-CoV-2 was driven by both these needs. Although the rationale was apparently robust and the procedures that led to the selection of the antibody definitely appropriate, the antibody failed in part to meet expectations.

From a clinical perspective, the expected effectiveness of bamlanivimab in hospitalized and intensive care unit patients was not met, while some benefits were observed in patients with mild to moderate COVID-19. The authorization in emergency use for these latter subjects has created the problem of defining which patients could be suitable candidates for these treatments due to the higher risk of experiencing complications requiring hospitalization. Even if we would be able to identify them, the number of patients we need to treat to achieve a mitigation of the pressure on hospitals is likely too high to preserve the economic sustainability of health-care systems in many Countries. Furthermore, convalescent plasma can provide largely similar benefits with far lower costs [70].

There are at least two main reasons explaining why bamlanivimab failed in the goal of significantly reducing the hospital pressure.

First, the emergence and expansion of E484K-carrying SARS-CoV-2 variants resistant to bamlanivimab had been at least partially underestimated. This is probably because a better containment of the epidemic was envisaged with the social distancing measures adopted in many Countries. Nevertheless, the spread of the virus has had such characteristics as to favor the rapid onset of numerous local variants. These have been allowed to leave their borders, due to political decisions taken in the interest of social and economic stability in all countries. While convalescent plasma, hyperimmune serum and vaccine-elicited antibodies are by nature polyclonal and hence less prone to immune escape, mAbs target single epitopes, which could easily mutate under selective pressure. The strategy of antibody cocktails could represent a temporary solution (cocktails cannot escape resistance for long time if occurrence of variants is too frequent), although their economic sustainability should be carefully considered: resistance to the bamlanivimab-etesevimab cocktail due to Q493R mutation has indeed already been reported, although fitness of such strain remains unconfirmed [71]. Additionally, mAb development takes time and is slow to readapt to variants of concern, while new convalescent plasma collections can be readily restarted soon after the appearance of new variants. Secondly, if one of the purpose of developing bamlanivimab was the treatment of critically ill patients, the rationale was probably unreliable. Indeed, these patients are hospitalized because they are hypoxic due to lung inflammation. Although we can expect some benefits from blocking the infection in the lungs with bamlanivimab, it was improbable that neutralizing mAbs could be able to reverse the inflammatory process. Furthermore, in the hypothesis that the infection could have been countered in the lungs, it is reasonable to expect that the neutralizing concentrations quickly reach these tissues. To the best of our knowledge, there are no pharmacokinetic studies that can confirm that the antibody concentration in these tissues is comparable with those showing efficacy in *in vitro* pharmacodynamic models, or that the expected concentration in the lungs is achieved timely to improve the clinical picture. In particular, bamlanivimab is an IgG_1, and these immunoglobulins cannot be secreted to mucosal tissue like IgA and IgM. It has been demonstrated that systemically administered IgG levels in bronchoalveolar lavage (BAL) can be approximately 1,000 times lower than levels of IgG in serum [72]. Furthermore, the injury of the respiratory tissue by inflammatory processes probably determines a further limitation to bioavailability. To the best of our knowledge, results of published pre-clinical test conducted in primate models showed that this mAb can reduce viral load in the respiratory mucosa when administered before viral intranasal and intratracheal inoculation. This means that the mAb could be effective when the virus is in the plasmatic phase of the infection. Unfortunately, the time window in which the viral infection is in this phase is likely narrow, and consequently, even the choice of the appropriate timing for administration of the mAb could be complicated. This hypothesis is in line with the efficacy observed in subject with mild to moderate symptoms in the early phases of the infection. It is reasonable that in a situation in which urgency in drug development had not been an essential requirement, more animal tests would have been conducted, and possible hypothetical bioavailability problems would have been verified.

In evaluating the history of the development of bamlanivimab, it is important to remember that we are facing the uncharted terrain of the first pandemic of the modern era in which, for the first time in history, global-scale immunization is being attempted. In relation to the extraordinary and emergency circumstances in which the antibody was developed, it was certainly possible that something went wrong. Unfortunately, if our hypotheses about the reason for the current limited use of bamlanivimab are correct, they likely apply to different anti-SARS-CoV-2 mAbs. Nevertheless, the experience acquired with the use of bamlanivimab was worthy for optimizing future approach to viral infections. It is possible that the strategy of developing neutralizing antiviral mAbs, will be more successful with other types of infections, especially those where the contagion is less rapid and the onset of variants less frequent. Also, special categories of patients such those that

cannot be immunized with active strategies due to efficacy (e.g. immunodepressed patients) or safety issues (e.g., hypersensitivity) could have a great benefit from neutralizing mAbs.

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