EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Overview of the clinical trials that led to the authorisation of monoclonal antibody therapies in the EU

Workshop "Efficacy of monoclonal antibodies in the context of rapidly evolving SARS-CoV-2 variants"

Presented by Eugenia Di Meco on 15 December 2022
Health Threats and Vaccine Strategy

An agency of the European Union

Monoclonal antibodies authorised in EU for the treatment and/or prevention of COVID-19

Medicine	Indication	Date
Regdanvimab *Regkirona*	Treatment	November 2021
Casirivimab/Imdevimab *Ronapreve*	Pre- and post-exposure prophylaxis Treatment	November 2021
Sotrovimab *Xevudy*	Treatment	December 2021
Tixagevimab/Cilgavimab *Evusheld*	Pre-exposure prophylaxis Treatment	March 2022 September 2022

Monoclonal antibodies that received a recommendation according under Art.5(3)

Medicine	Indication	Date
Bamlanivimab/Etesevimab	Treatment	March 2021
Regdanvimab	Treatment	March 2021
Sotrovimab	Treatment	May 2021
Casirivimab/Imdevimab	Treatment	February 2021

Not licensed in EU - with a previous EUA in US (currently not authorised)

Bebtelovimab for treatment of COVID-19

Pre- and post-exposure prophylaxis

Product	Indication	Posology
Casirivimab/Imdevimab	Prevention of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg	• Post-exp: 600+600 mg IV/SC • Pre-exp: 600+600 mg IV/SC, 300+300 mg q4w
Tixagevimab/Cilgavimab	Pre-exposure prophylaxis of COVID-19 in adults and adolescents	300+300 mg IM

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COV-2069 study **Intervention:** C/I 600/600 SC vs Placebo **Population:** unvaccinated asymptomatic household contacts of symptomatic COVID-19 cases. Randomized within 96 hours from the identification of the 1st index case. Cohort A: PCR negative patients Cohort B: PCR positive patients	**PEP:** The proportion of subjects who developed symptomatic RT-qPCR confirmed COVID-19 through Day 29. **Outcome:** Cohort A primary analysis in seronegative (753-752): 1.5% vs 7.8%, 81% RRR in the treatment group vs placebo Cohort B primary analysis in seronegative (100-104): 29% vs 42.3%, 31% risk reduction in the treatment group vs placebo	
Tixagevimab/Cilgavimab	Pre-exposure prophylaxis of COVID-19 in adults and adolescents	300+300 mg IM

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Tixagevimab/Cilgavimab	Pre-exposure prophylaxis of COVID-19 in adults and adolescents	300+300 mg IM
PROVENT study **Intervention:** T/C 300/300 IM vs Placebo **Population:** Adult individuals at risk of inadequate response to active immunisation or at higher risk of infection. SARS-CoV-2 PCR positive and seropositive individuals were excluded.		**PEP:** Proportion of SARS-CoV-2 RT-PCR-positive symptomatic illness (COVID-19) through Day 183 **Outcome:** Primary analysis on PCR negative at baseline (3441-1731): 0.2% vs 1.0%, 77% RRR in the treatment group vs placebo

Treatment (1/3)

Medicine	Indication	Posology
Regdanvimab	Treatment of adults with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	40 mg/kg IV
Casirivimab/Imdevimab	Treatment of adults and adolescents with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	600+600 mg IV/SC

Treatment (1/3)

Medicine	Indication	Posology
Regdanvimab	Treatment of adults with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	40 mg/kg IV
CT-P59 3.2 **Intervention:** Reg 40mg/Kg vs Placebo **Population**: adult, symptomatic, SARS-CoV-2 confirmed patients, <=7 days of symptoms, mild-moderate infection, not requiring oxygen Sat 94%, not hospitalized, unvaccinated	**PEP:** Proportion of patients with clinical symptoms requiring hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28. **Outcome:** Primary analysis in all patient at increased risk (66.9%, 446 vs 434): 3.1% vs 11.1%, RRR 73%	
Casirivimab/Imdevimab	Treatment of adults and adolescents with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	600+600 mg IV/SC

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Casirivimab/Imdevimab	Treatment of adults and adolescents with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	600+600 mg IV/SC
COV-2067 phase 3 part **Intervention:** 600-600 IV, 1200-1200 IV, placebo **Population**: symptomatic SARS-CoV-2 confirmed patients, mild-moderate severity, not hospitalised, unvaccinated. <=7 days of symptoms, at least one risk factor for severe disease.	**PEP:** Proportion of subjects with ≥ 1 COVID-19-related hospitalisation or all cause death through Day 29. **Outcome:** mFAS (PCR+, one risk factor and seronegative): 1200 mg (1192-1193): 0.9% vs 3.4%: RRR 72.5% 2400 mg (1812 – 1790): 13% vs 4.4%: RRR 70.9%	

Treatment (2/3)

Medicine	Indication	Posology
Sotrovimab	Treatment of adults and adolescents with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	500 mg IV
Tixagevimab/Cilgavimab	Treatment of adults and adolescents with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	300+300 mg IM

Treatment (2/3)

Medicine	Indication	Posology
Sotrovimab	Treatment of adults and adolescents with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	500 mg IV
COMET-ICE **Intervention:** S 500 mg IV vs Placebo **Population:** adult, symptomatic, SARS-CoV-2 confirmed patients, ≤5 days symptoms, Sat >=94%, ≥1 risk factors. Unvaccinated.	**PEP:** Progression of COVID-19 as defined by hospitalisation for >24 hours for acute management of any illness or death from any cause (day 29) **Outcome:** ITT analysis (528 + 529): 1% vs 6%, RRR 79%	
Tixagevimab/Cilgavimab	Treatment of adults and adolescents with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	300+300 mg IM

Treatment (2/3)

Medicine	Indication	Posology
Sotrovimab	Treatment of adults and adolescents with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	500 mg IV

COMET-ICE
Intervention: S 500 mg IV vs Placebo
Population: adult, symptomatic, SARS-CoV-2 confirmed patients, ≤5 days symptoms, Sat >=94%, ≥1 risk factors. Unvaccinated.

PEP: Progression of COVID-19 as defined by hospitalisation for >24 hours for acute management of any illness or death from any cause (day 29)

Outcome:
ITT analysis (528 + 529): 1% vs 6%, RRR 79%

Medicine	Indication	Posology
Tixagevimab/Cilgavimab	Treatment of adults and adolescents with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	300+300 mg IM

TACKLE
Intervention: T/C 300/300 IM vs Placebo
Population: Symptomatic SARS-CoV-2 confirmed patients, mild-moderate severity, not hospitalised, unvaccinated. ≤7 days symptoms. At least 60% were to meet the protocol definition of being at high risk.

PEP: Composite of either severe COVID-19 or death from any cause by Day 29.

Outcome:
Primary analysis mFAS (not hosp, <7 days)(407-415) : 4.4% vs 8.9%, 50% RRR

Treatment (3/3)

Medicine	Indication	Posology
Bamlanivimab and Bamlanivimab/Etesevimab	Treatment of adults and adolescents with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	700 mg Bam IV 700 mg Bam + 1400 mg Ete IV

Treatment (3/3)

Medicine	Indication	Posology
Bamlanivimab and Bamlanivimab/Etesevimab	Treatment of adults and adolescents with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	700 mg Bam IV 700 mg Bam + 1400 mg Ete IV

BLAZE-1 phase 3
Intervention: B/E 2800+2800 vs placebo arm, B/E 700+1400 vs placebo arm
Population: symptomatic, SARS-CoV-2 confirmed patients, ≤3 days from diagnostic sample, not requiring oxygen, mild to moderate disease, high risk of progression

PEP: COVID-19 related hospitalization (>24 h acute care) and death from any cause (day 29)

Outcome:
Analysis 2800+2800 arm (518 vs 517): 2% vs 7%, RRR 70%
Analysis 700+1400 arm(511 vs 776): 0.8% vs 6.8%, RRR 88%

Study	Enrolment period	Viral variants	Study sites
COV-2069 (Ronapreve proph)	July 2020 – March 2021	-	Brazil, Chile, Greece, Israel, Mexico, Moldova, US
COMET-ICE (Sotrovimab)	August 2020-April 2021	Wildtype, Alpha and Epsilon	US, Brazil, Spain, Canada, Peru
BLAZE-1 phase 2 (Bamlan/Etesev)	Sept 2020 – Dec 2020	-	US
PROVENT (Evusheld proph)	Nov 2020 – March 2021	Alpha, Beta, Gamma and Delta	US, UK, Belgium, France, Spain
TACKLE (Evusheld treat)	Jan 2021 - July 2021	Alpha, Beta, Gamma and Delta	Argentina, Brazil, Czech Republic, Germany, Hungary, Italy, Japan, Mexico, Poland, Russian Federation, Spain, UK, Ukraine, US
CT-P59 part 2 (Regkirona)	Jan 2021 – May 2021	Wild type and Alpha	Hungary, Ireland, Italy, Mexico, North Macedonia, Peru, Poland, Republic of Korea, Republic of Moldavia, Romania, Serbia, Spain, Ukraine, US
COV-2067 (Ronapreve treat)	Jan 2021 – Feb 2021	-	Mexico, Romania, US

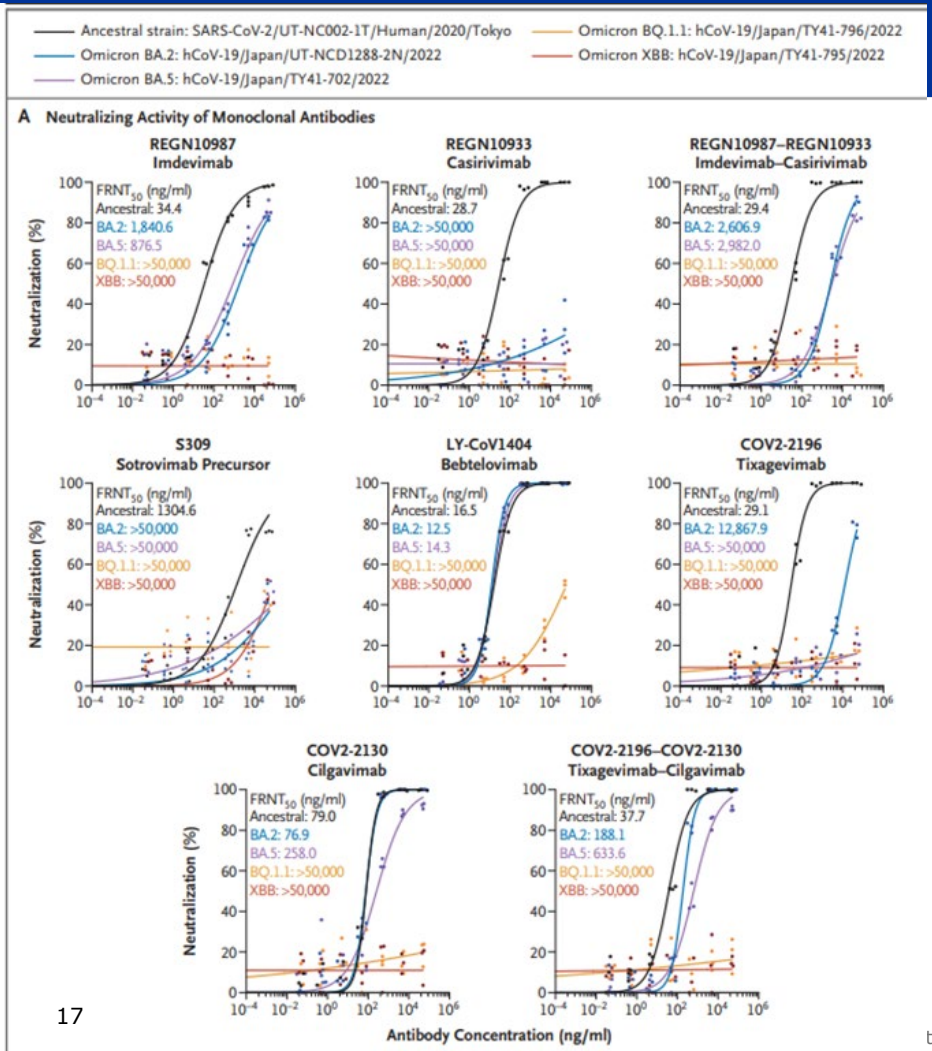
Conclusions (1/2):

- Clinical studies have demonstrated efficacy of monoclonal antibodies only in the context of **prophylaxis** and for the **treatment** of patients in the **early stage of the disease (not requiring supplemental oxygen)**

- **Primary endpoints:**
  - Prophylaxis: Proportion of symptomatic confirmed infection
  - Treatment: Disease progression, COVID-19 related hospitalizations, all cause deaths.

Conclusions (2/2)

- Studies performed prevalently in **high-risk patients** when placebo-controlled designs could still be conducted.
- Efficacy shown in **unvaccinated and/or seronegative** patients.
- Available data do not allow to directly establish efficacy in several **underrepresented subpopulations** (immunosuppressed, elderly). Very limited evidence on pregnant women, breastfeeding, adolescents and children.
- Efficacy shown against **viral variants no longer circulating** and that could be potently neutralized by the monoclonal antibodies.



Efficacy of Antiviral Agents against Omicron Subvariants BQ.1.1 and XBB (nejm.org)

EUROPEAN MEDICINES AGENCY
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9 December 2022
EMA/931457/2022
Emergency Task Force

ETF statement on the loss of activity of anti-spike protein monoclonal antibodies due to emerging SARS-CoV-2 variants of concern

ETF warns that monoclonal antibodies may not be effective against emerging strains of SARS-CoV-2 | European Medicines Agency (europa.eu)

Any questions?

Further information

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