EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

COVID-19 vaccines and therapeutics

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An agency of the European Union

New data show treatment with Lilly's neutralizing antibodies bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016) together reduced risk of COVID-19 hospitalizations and death by 70 percent

- *BLAZE-1 trial met primary endpoint and key secondary endpoints with high statistical significance*
  - *Results from more than 1,000 high-risk patients were consistent with previous data*
- *Findings from BLAZE-4 trial provide data on lower doses of bamlanivimab and etesevimab together*
- *Media and investor call "SARS-CoV-2 Neutralizing Antibody Program Update" to be held at noon EST today; details below*

INDIANAPOLIS, Jan. 26, 2021 – Bamlanivimab (LY-CoV555) 2800 mg and etesevimab (LY-CoV016) 2800 mg together significantly reduced COVID-19-related hospitalizations and deaths (collectively, "events") in high-risk patients recently diagnosed with COVID-19, meeting the primary endpoint of the Phase 3 BLAZE-1 trial, Eli Lilly and Company (NYSE: LLY) announced. Across 1,035 patients, there were 11 events (2.1 percent) in patients taking therapy and 36 events (7.0 percent) in patients taking placebo, representing a 70 percent risk reduction (p= 0.0004). There were 10 deaths total, all of which occurred in patients taking placebo, and no deaths in patients taking bamlanivimab and etesevimab together.

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EMA issues advice on use of REGN-COV2 antibody combination (casirivimab / imdevimab)

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News 26/02/2021

EMA's human medicines committee (CHMP) has completed its review on the use of the monoclonal antibodies casirivimab and imdevimab to treat patients with COVID-19. This review was undertaken to provide a harmonised scientific opinion at EU level to support national decision making on the possible use of the antibodies prior to marketing authorisation. The Agency concluded that the combination also known as REGN-COV2 can be used for the treatment of confirmed COVID-19 in patients who do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19.

The medicine is given by infusion (drip) into a vein and the proposed conditions of use are available.

EMA made its recommendations following review of data including quality data and a study[1] that looked into the effects of the combination in outpatients with COVID-19 who do not need supplemental oxygen. Preliminary results indicate that the combination reduced the viral load (amount of virus in the back of the nose and throat) more than placebo (a dummy treatment) and led to fewer COVID-19-related medical visits.

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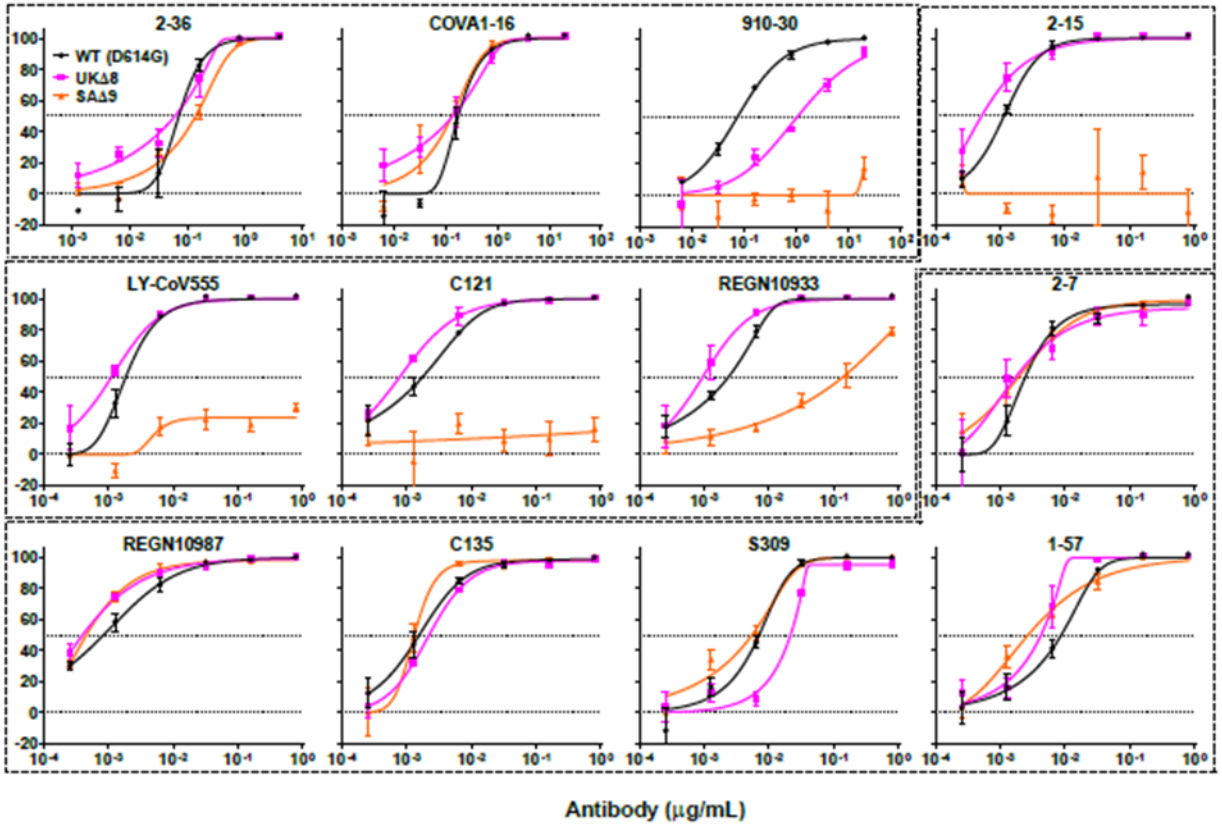
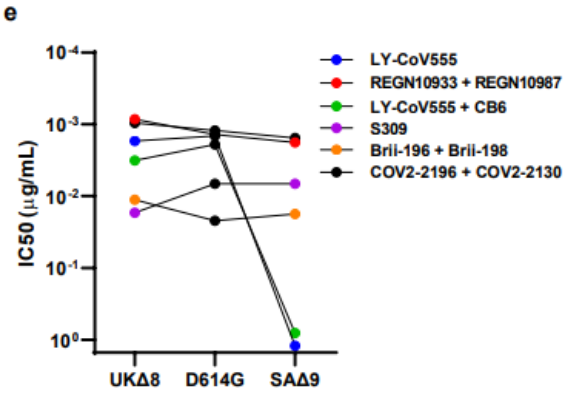
Increased resistance of SARS-COV2 variants to monoclonal antibodies





https://doi.org/10.1101/2021.01.25.428137
doi: bioRxiv preprint

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TOCILIZUMAB – RECOVERY

	Treatment allocation			
	Tocilizumab (n=2022)	Usual care (n=2094)	RR (95% CI)	p value
Primary outcome				
Total: 28-day mortality	596 (29%)	694 (33%)	0.86 (0.77-0.96)	0.0066
Secondary outcomes				
Median time to being discharged alive, days	20	>28		
Discharged alive from hospital within 28 days	1093 (54%)	990 (47%)	1.22 (1.12-1.34)	<0.0001
Receipt of invasive mechanical ventilation or death*	571/1754 (33%)	687/1800 (38%)	0.85 (0.78-0.93)	0.0005
Invasive mechanical ventilation	215/1754 (12%)	273/1800 (15%)	0.81 (0.68-0.95)	0.01
Death	471/1754 (27%)	552/1800 (31%)	0.88 (0.79-0.97)	0.01
Subsidiary clinical outcomes				
Receipt of ventilation†	233/935 (25%)	242/933 (26%)	0.96 (0.82-1.12)	0.61
Non-invasive ventilation	222/935 (24%)	223/933 (24%)	0.99 (0.84-1.17)	0.94
Invasive mechanical ventilation	45/935 (5%)	63/933 (7%)	0.71 (0.49-1.03)	0.07
Successful cessation of invasive mechanical ventilation‡	91/268 (34%)	94/294 (32%)	1.07 (0.80-1.43)	0.64
Use of haemodialysis or haemofiltration§	103/2003 (5%)	142/2075 (7%)	0.75 (0.59-0.96)	0.02

Data are n(%), n/N (%), or median (interquartile range). RR=rate ratio for the outcomes of 28-day mortality, hospital discharge and successful cessation of invasive mechanical ventilation, and risk ratio for other outcomes. * Analyses include only those on no ventilator support or non-invasive ventilation at second randomisation. † Analyses include only those on no ventilator support at second randomisation. ‡ Analyses restricted to those on invasive mechanical ventilation at second randomisation. § Analyses exclude those on haemodialysis or haemofiltration at second randomisation.

RECOVERY_Tocilizumab_MainPaper_medRxiv (1253)

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Tuesday, December 22, 2020

NIH ACTIV Trial of blood thinners pauses enrollment of critically ill COVID-19 patients

Three clinical trial platforms working together to test the effects of full doses of anticoagulants (blood thinners) in COVID-19 patients have paused enrollment for one group of patients. Among critically ill COVID-19 patients requiring intensive care unit (ICU) support, therapeutic anticoagulation drugs did not reduce the need for organ support. Enrollment continues for mode COVID-19 patients in the trials.

As is normal for clinical trials, these trials are overseen by independent boards that routinely review the data experts in ethics, biostatistics, clinical trials, and blood clotting disorders. Informed by the deliberations of the the trial sites have paused enrollment of the most critically ill hospitalized patients with COVID-19. A potential group could not be excluded. Increased bleeding is a known complication of full-dose anticoagulation. The tri to undertake additional analyses which will be made available as soon as possible.

Full-dose blood thinners decreased need for life support and improved outcomes in hospitalized COVID-19 patients in international trial

JANUARY 22, 2021 — Full dose anti-coagulation (blood thinner) treatments given to patients hospitalized for COVID-19 reduced the requirement of vital organ support in a large clinical trial conducted worldwide. With large numbers of COVID-19 patients requiring hospitalization, this treatment is expected to reduce the pressure in intensive care units around the world.

Three clinical trial platforms spanning five continents in over 300 hospitals, have been working together since May 2020 to urgently test whether there is a greater benefit of full doses of heparin (blood thinners) to treat adults hospitalized for non-critical COVID-19 illness compared to the lower dose typically administered to prevent blood clots in hospitalized patients.

Based on the interim results of more than 1300 moderately ill patients admitted to hospital, findings showed that full doses of blood thinners were not only safe, but superior to the doses normally given to prevent blood clots in hospitalized patients. Moderately ill patients are those not in ICU and who did not receive organ support such as mechanical ventilation at trial enrollment. The trial investigators are now working as fast as possible to make the full results of the study available so clinicians can make informed decisions about treating their COVID-19 patients.

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COLCHICINE EFFICACY

ColCorona

ITT Population **Clinical Outcome**	**Colchicine N=2235 n (%)**	**Placebo N=2253 n (%)**	**Odds Ratio (95% CI)**	**P-value**
Primary Composite Endpoint				
Composite of death or hospitalization due to COVID-19 infection	104 (4.7)	131 (5.8)	0.79 (0.61-1.03)	0.08
Patients with PCR-proven COVID-19 **Clinical Outcome**	**Colchicine N=2075 n (%)**	**Placebo N=2084 n (%)**	**Adjusted Odds Ratio (95% CI)**	**P-value**
Primary Composite Endpoint				
Composite of death or hospitalization due to COVID-19 infection	96 (4.6)	126 (6.0)	0.75 (0.57-0.99)	0.04
Secondary Endpoints				
Death	5 (0.2)	9 (0.4)	0.56 (0.19-1.66)	0.29
Hospitalization due to COVID-19 infection	93 (4.5)	123 (5.9)	0.75 (0.57-0.99)	0.04
Need for mechanical ventilation	10 (0.5)	20 (1.0)	0.50 (0.23-1.07)	0.07

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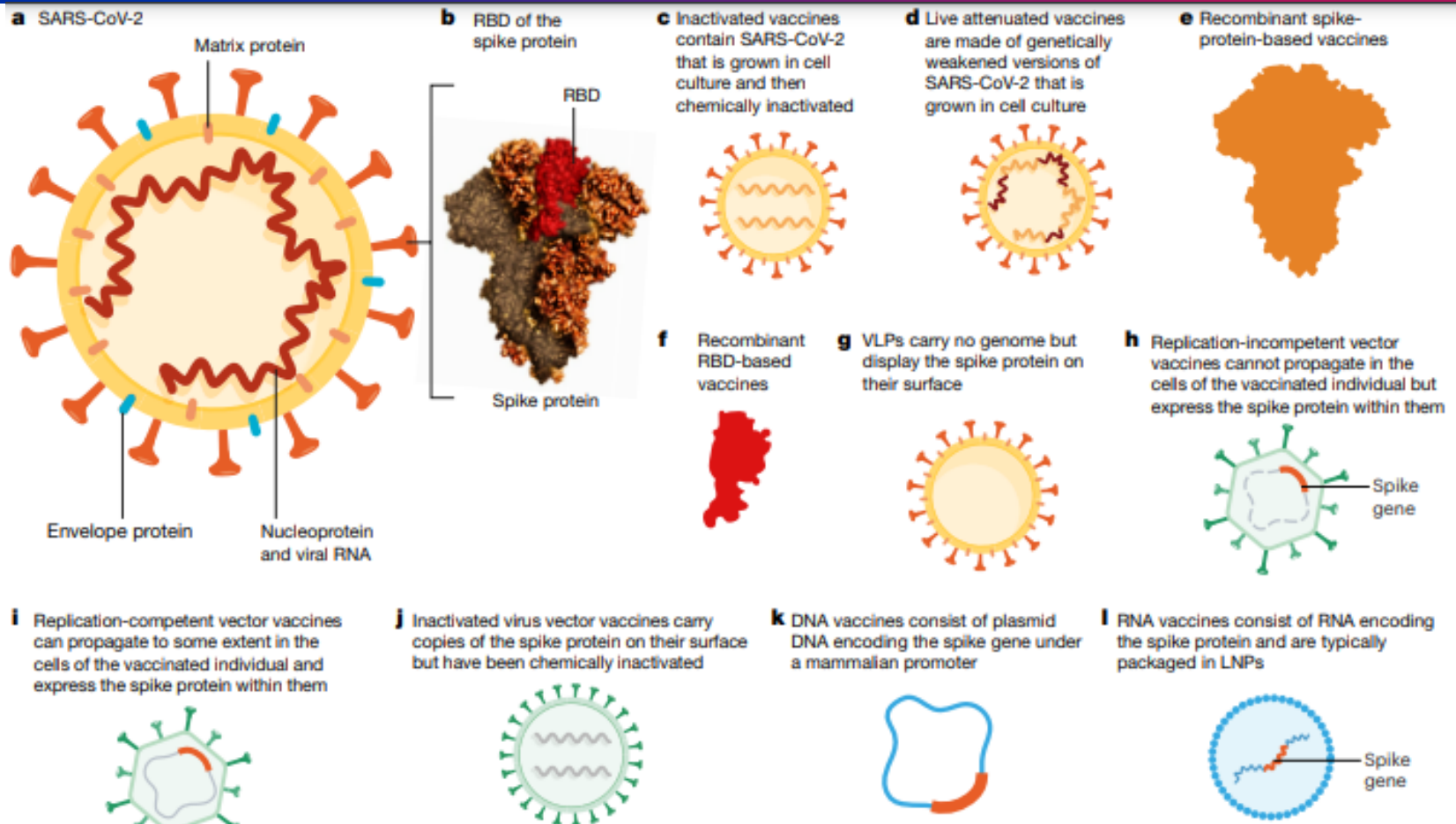

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Vaccine	Doses	Dose interval	Overall level of protection (%)	Storage temperature (doses per vial)
Comirnaty	2 doses (0.3 mL each)	3 weeks after the first dose	95.0 (95% CI -90.0, 97.9)	-90 °C to -60 °C (6 doses per vial)
COVID-19 Vaccine Moderna	2 doses (0.5 mL each)	28 days after the first dose	94.1 (95% CI - 89.3, 96.8)	-25ºC to -15ºC (10 doses per vial)

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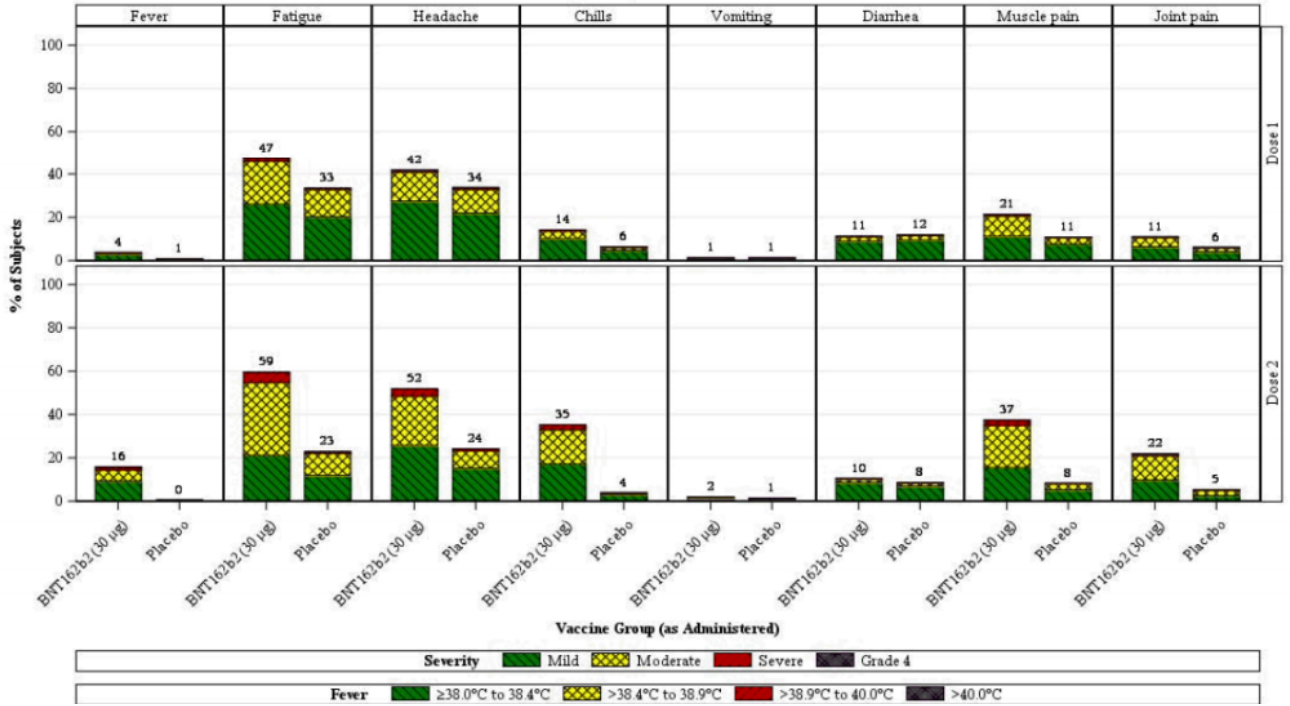
Comirnaty safety

https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf

Systemic reactions

Table 15 Subjects Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose, Age Group 16-55 Years – Reactogenicity Subset for Phase 2/3 Analysis– Safety Population



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Moderna vaccine

2.7. Risk Management Plan

Safety specification

Summary of safety concerns

The applicant has submitted an RMP including the following summary of safety concerns:

Important identified risks	Anaphylaxis
Important potential risks	Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breast-feeding Long-term safety Use in immunocompromised subjects Interaction with other vaccines Use in frail subjects with unstable health conditions and co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in subjects with autoimmune or inflammatory disorders

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ChAdOX1 COVID-19 vaccine

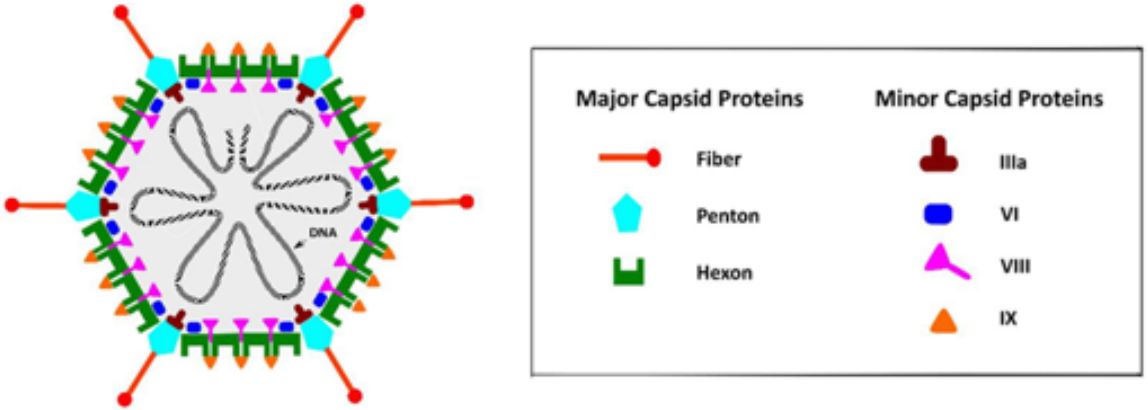

Figure 2 Structure of the nCOV-19 spike protein gene expression cassette (6214 bp)

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Table 2 COVID-19 Vaccine AstraZeneca efficacy against COVID-19[a]

Population	COVID-19 Vaccine AstraZeneca		Control		Vaccine efficacy % (95% CI)[b]
	N	Number of COVID-19 cases, n (%)	N	Number of COVID-19 cases, n (%)	
Licensing regimen					
4 – 12 weeks (28 to 84 days)	5,258	64 (1.2)	5,210	154 (3.0)	59.5 (45.8, 69.7)

N = Number of subjects included in each group; n = Number of subjects having a confirmed event; CI = Confidence Interval;

[a] Efficacy endpoint was based on confirmed COVID-19 cases in subjects aged 18 years and over who were seronegative at baseline, who had received two doses and were on-study ≥15 days post second dose.

[b] CI not adjusted for multiplicity.

Vaccine efficacy was 62.6% (95% CI: 50.9; 71.5) in participants receiving two recommended doses with any dose interval (ranging from 3 to 23 weeks), in a pre-specified analysis.

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ChAdOX1 vaccine - immunogenicity

Subgroup	Timepoint	Statistic	SD/SD Control	SD/SD AZD1222
	Baseline	n /N[sub:b]	515 / 994	551 / 1104
Age 18-64		**GMT**	**20.36**	**20.10**
		(95% CI)	(20.00, 20.71)	(19.90, 20.31)
	Post Dose 1	n/N[sub:b]	522/994	500/1104
		GMT	**20.37**	**59.03**
		(95% CI)	(19.99, 20.76)	(52.87, 65.90)
	Post Dose 2	n/N[sub:b]	501/994	497/1104
		GMT	**21.49**	**173.71**
		(95% CI)	(20.67, 22.33)	(156.52, 192.78)
Age ≥65	Baseline	n /N[sub:b]	81 / 172	78 / 216
		GMT	**20.00**	**20.00**
		(95% CI)	(NE, NE)	(NE, NE)
	Post Dose 1	n/N[sub:b]	77/172	75/216
		GMT	**21.11**	**37.10**
		(95% CI)	(18.96, 23.49)	(29.26, 47.05)
	Post Dose 2	n/N[sub:b]	193/380	192/394
		GMT	**21.07**	**109.21**
		(95% CI)	(18.98, 23.38)	(77.58, 153.73)

Validated PSVNA50 age and interval

Visit Window	Statistic	SDSD AZD1222 < 6 wks N=677	SDSD AZD1222 6-8 wks N=239	SDSD AZD1222 9-11 wks N=169	SDSD AZD1222 ≥ 12 wks N=235
Baseline	N	246	131	100	152
	GMT	**20.000**	**20.434**	**20.000**	**20.000**
	95% CI for GMT	(NE, NE)	(19.58, 21.32)	(NE, NE)	(NE, NE)
	Min, Max	20.00, 20.00	20.00, 333.72	20.00, 20.00	20.00, 20.00
Day 28 post the first dose	N	243	109	91	132
	GMT	**50.565**	**53.040**	**59.106**	**65.783**
	95% CI for GMT	(43.44, 58.86)	(42.00, 66.97)	(45.64, 76.55)	(52.67, 82.17)
	Min, Max	20.00, 5440.37	20.00, 2061.91	20.00, 1961.43	20.00, 1634.36
Day 28 post the second dose	N	202	112	94	141
	GMT	**105.373**	**177.862**	**199.164**	**268.381**
	95% CI for GMT	(88.67, 125.22)	(145.13, 217.97)	(165.55, 239.60)	(221.71, 324.87)
	Min, Max	20.00, 6863.67	20.00, 2350.68	20.00, 2142.76	20.00, 7725.75

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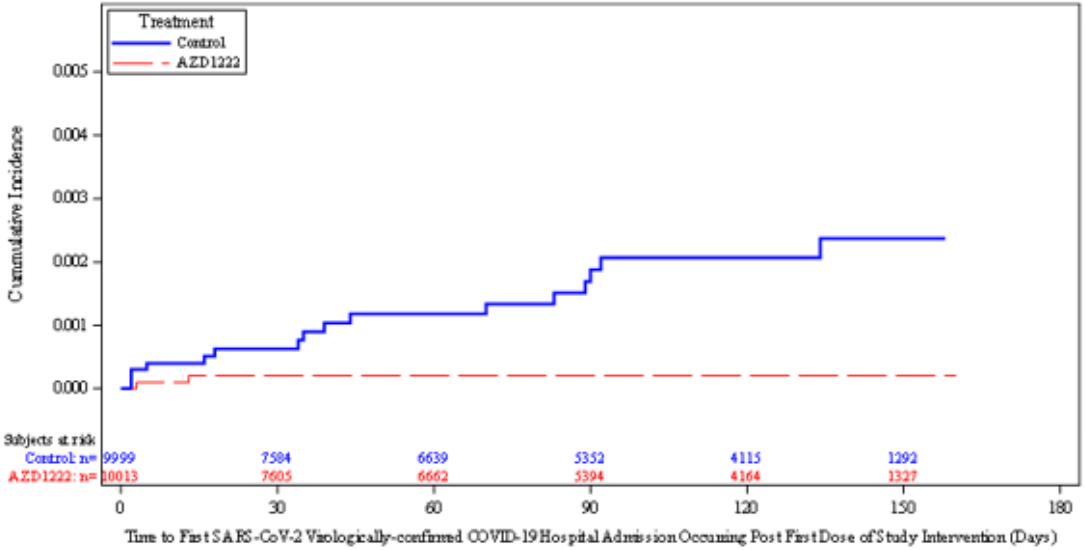
ChAdOx1 vaccine – severe disease

SmPC

There were 0 (0.0%; N=5,258) cases of COVID-19 hospitalisation in participants who received two doses of COVID-19 Vaccine AstraZeneca (≥15 days post dose 2) as compared to 8 (0.2%; N=5,210) for control, including one severe case (WHO Severity grading ≥6), reported for control. In all participants who received at least one dose, as from 22 days post dose 1, there were 0 (0.0%, N=8,032) cases of COVID-19 hospitalisation in participants who received COVID-19 Vaccine AstraZeneca, as compared to 14 (0.2%, N=8,026), including one fatality, reported for control.

Cumulative Incidence Plot for Time to First SARS-CoV-2 Virologically Confirmed Symptomatic COVID-19 Hospital Admission Occurring Post First Dose (Any Dose for Efficacy Analysis Set, Any Serostatus)



The time to first SARS-CoV-2 virologically confirmed COVID-19 occurring post first dose of study intervention, in days, has been calculated as follows: Date of SARS-CoV-2 virologically confirmed test – (date of first dose of study intervention + 1. For censored participants, the censoring time is from date of first dose of study intervention to last observed time during the analysis period.

The observation period for the endpoint was post first dose up to 1 year in study.

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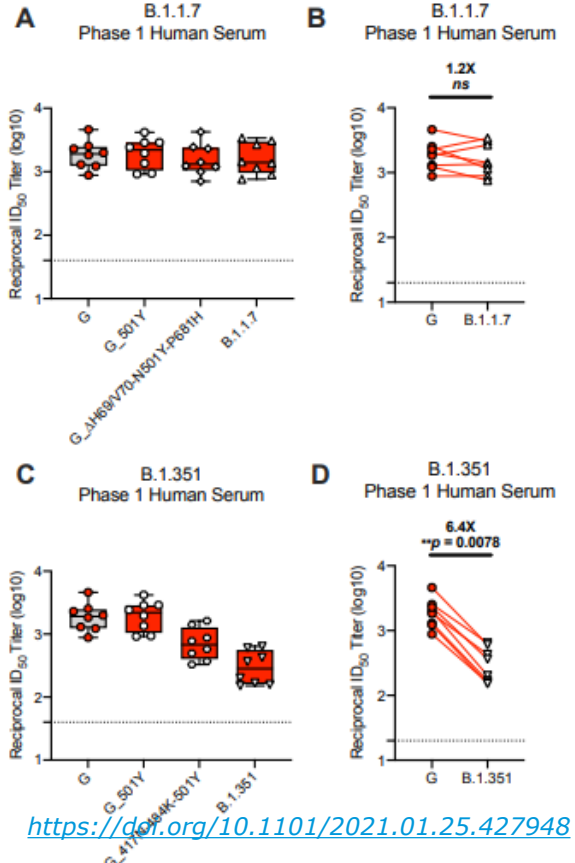
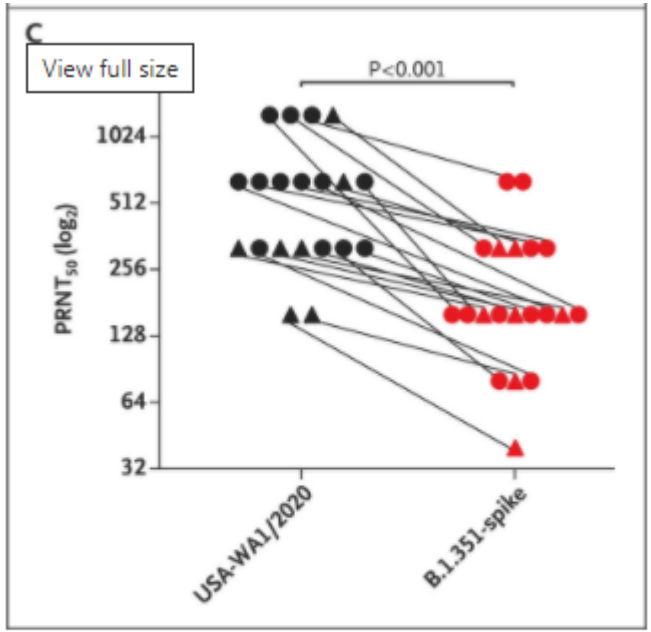
Cross-neutralisation - mRNA vaccines vs B.1.1.7 and B.1.351



https://doi.org/10.1101/2021.01.25.427948



Serum Neutralization of Variant Strains of SARS-CoV-2 after the Second Dose of BNT162b2 Vaccine.

Neutralizing Activity of BNT162b2-Elicited Serum — Preliminary Report | NEJM

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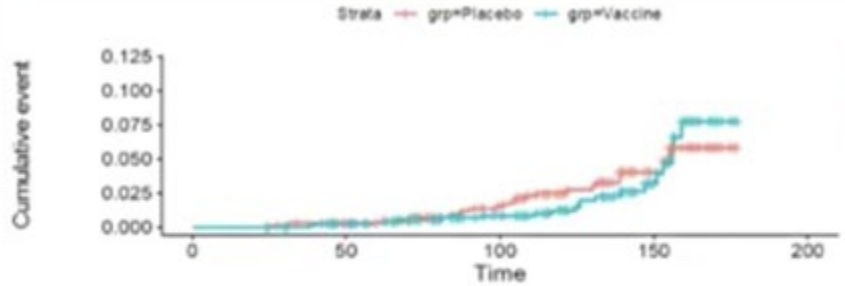
ChAdOx1-nCoV19 not efficacious in protecting against mild to moderate Covid-19 due to the B.1351 variant.



No significant risk reduction in mild-moderate Covid-19 from B.1.351 variant occurring at least 14 days after 2nd dose of ChAdOx1/nCoV19.

Baseline N-protein IgG	Total number of cases	Placebo n/N (%)	Vaccine n/N (%)	Vaccine efficacy (95%CI)
Primary endpoints: All severity COVID-19 clinical >14 days post-boost				
Negative	42	23/717 (3.2%)	19/750 (2.5%)	21.9% (-49.9 to 59.8)
Secondary endpoint: All severity COVID-19 clinical disease due to B1.351 variant >14 days post-boost				
Negative	39	20/714 (2.3%)	19/748 (2.5%)	10.4% (-78.8 to 54.8)

Submitted for peer review

zoom

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Requirements for variant vaccines based on already approved/in use vaccines

- Preparatory discussions with other regulatory agencies, i.e. EMA, FDA, HC and WHO and in an ICMRA workshop
- It was possible to agree on key elements of vaccine development
- An EMA Reflection Paper has been released 25 February 2021
- Discussion with developers of vaccines already approved in the EU has started to define development plans

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Requirements for variant vaccines based on already approved/in use vaccines

There must be a justification for the relevance of the variant(s) included in a variant vaccine intended for use in the EU based on disease surveillance and characterisation of strains circulating at the time of selecting the variant(s).

As soon as there is a global forum established to support SARS-CoV-2 strain selection for vaccines (e.g. by the WHO), the recommendations made should be consulted when selecting the variant strain(s).

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Requirements for variant vaccines based on already approved/in use vaccines -clinical

The efficacy of a monovalent or a multivalent variant vaccine against the variant strain(s) may be inferred from provision of immunogenicity data:

i. After primary vaccination with the variant vaccine; and

ii. After a single dose of the variant vaccine when given to subjects who previously received primary vaccination with the parent vaccine.

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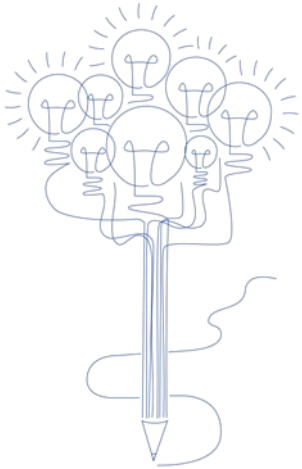
Summary of activities



181 therapeutics in discussion with EMA

50 vaccines identified for interaction

Rapid scientific advice proceeding for advanced vaccines and therapeutics (76 completed – 3 in the pipeline)

referral 5.3 to support Emergency use of monoclonal antibodies for outpatients

Guidance on variant vaccines issued

Discussions ongoing for CMA of additional vaccines

Post-authorisation studies for effectiveness and safety

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