Essais cliniques et pandémie : Anticorps monoclonaux et SARS-CoV-2

Cours d'Automne en Chimiothérapie Infectieuse et Vaccinologie

Anti-SARS-CoV2 Monoclonal Antibodies

Efficacy, Indications, Perspectives

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Links of interest:

- With industry
  - Janssen: anti-HIV Vaccine (consultant fees)
  - Fondation de Mécénat MSD-Avenir: Research Program on cancers
- Member of:
  - Conseil d'Orientation de la Stratégie Vaccinale : Déc. 2021 –
  - Conseil Scientifique vaccins Covid-19: Juin 2020 –
  - Ansm: Expert Externe

Anti-SARS-CoV2 Monoclonal Antibodies

- **anti-SARS-CoV2 Antibodies and Vaccines :**
  - **Neutralizing Ab and protection;**
  - **Vaccine Efficacy : Correlates of vaccinal protection and Results in Immune-suppressed patients**

- **Treatment with anti-SARS-CoV2 MAbs**
  - **anti-SARS-CoV2 monoclonal Abs and Reactivity against variants**
  - **Clinical Trials and real life efficacy**
  - **Regulatory Authorisations (ATU)**

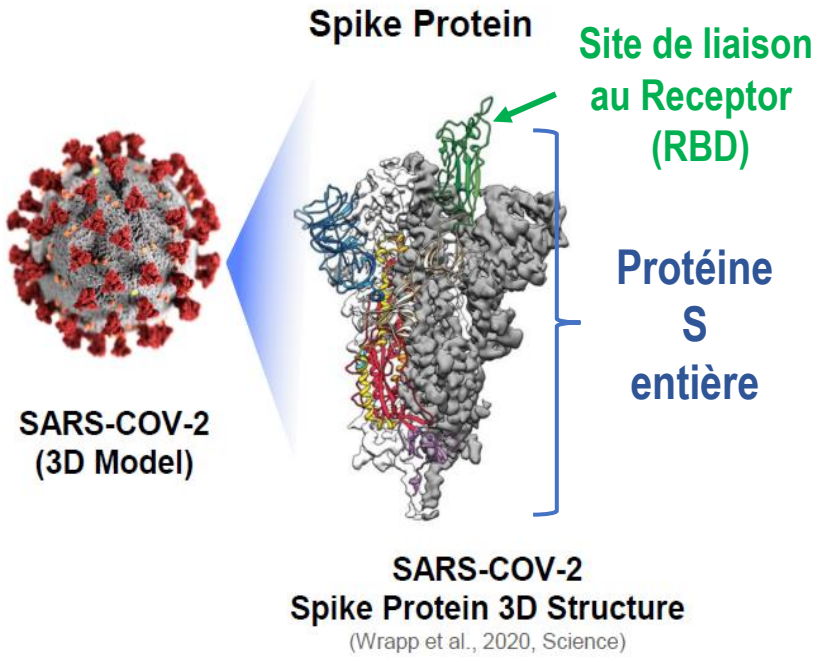
- **Prophylaxis (PEP et PrEP) with anti-SARS-CoV2 MAbs**
  - **Vaccine Responses from Immune-suppressed persons**
  - **Clinical Trials Regulatory Authorisations (ATU)**
  - **Practical issues**

Anti-SARS-CoV2 Monoclonal Antibodies

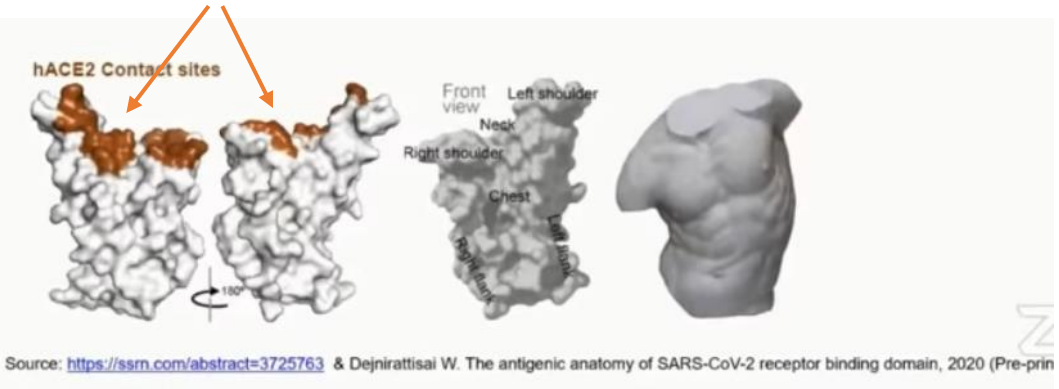
Immune Correlates of protection against severity?

- **SARS-CoV2 et Spicule S**

(Zhou P et al. Nature 2020; Wrapp et al. Science 20)



- **Antibodies:**
  - in >95% infected subjects
  - **Low levels in A-symptomatics**
- **Neutralizing Abs = Anti-Spike (RBD)**
  - **Directed against binding site RBD**
  - in convalescents, **persist > 10 mois**
  - No/low cross-reactivity with CoronaVirus



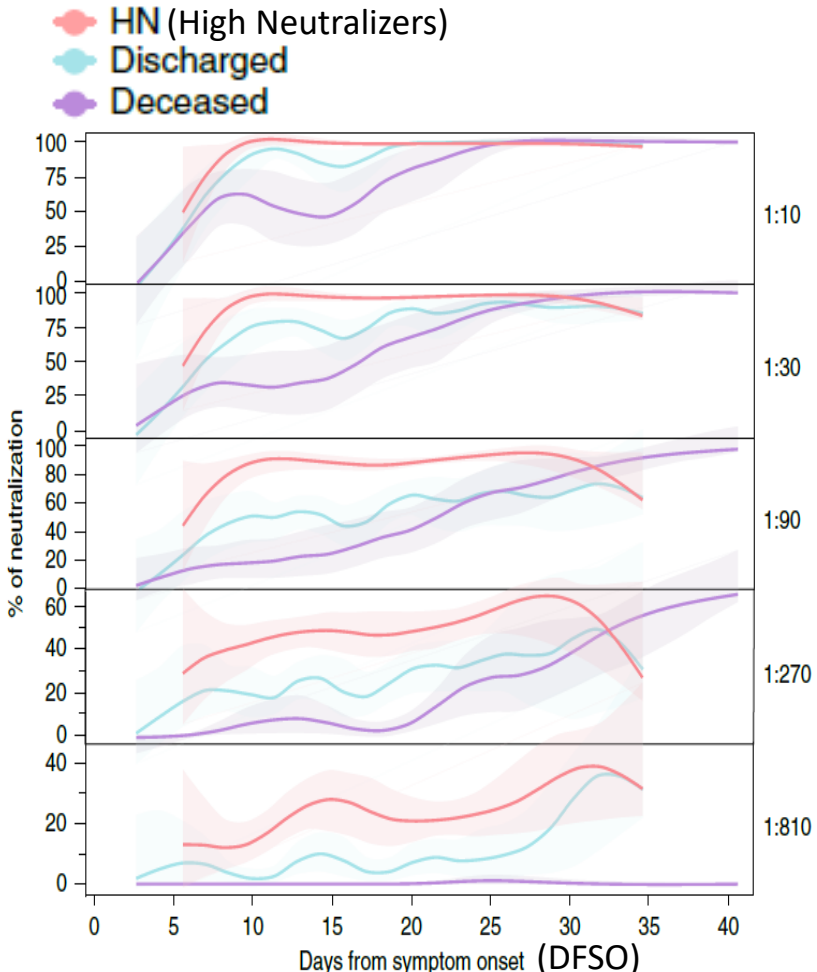
- **T cell mediated immunity : broader reactivity**

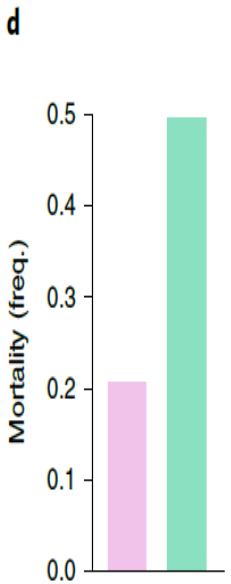
Jiang HW et al. doi: https://doi.org/10.1101/2020.03.20.20039495 medRxiv;
Jiang S et al. Trends in Immunology, May 2020;
Kai-Wang To K et al. www.thelancet.com/infection 2020
Long QX et al. Nat.Med. 2020.; Peng Y,.bioRxiv. 2020.; Wajnberg A et al., Science 2020).
Sun B et al.Emerg Microbes Infect. 2020; Ni L et al Immunity. 2020
Grifoni A et al. Cell. 2020; Vabret N et al. Immunity 2020, 52, 910.

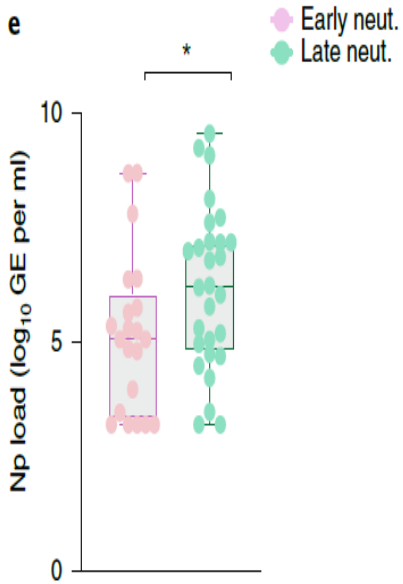
Protection conferred by Neutralizing Antibodies ?

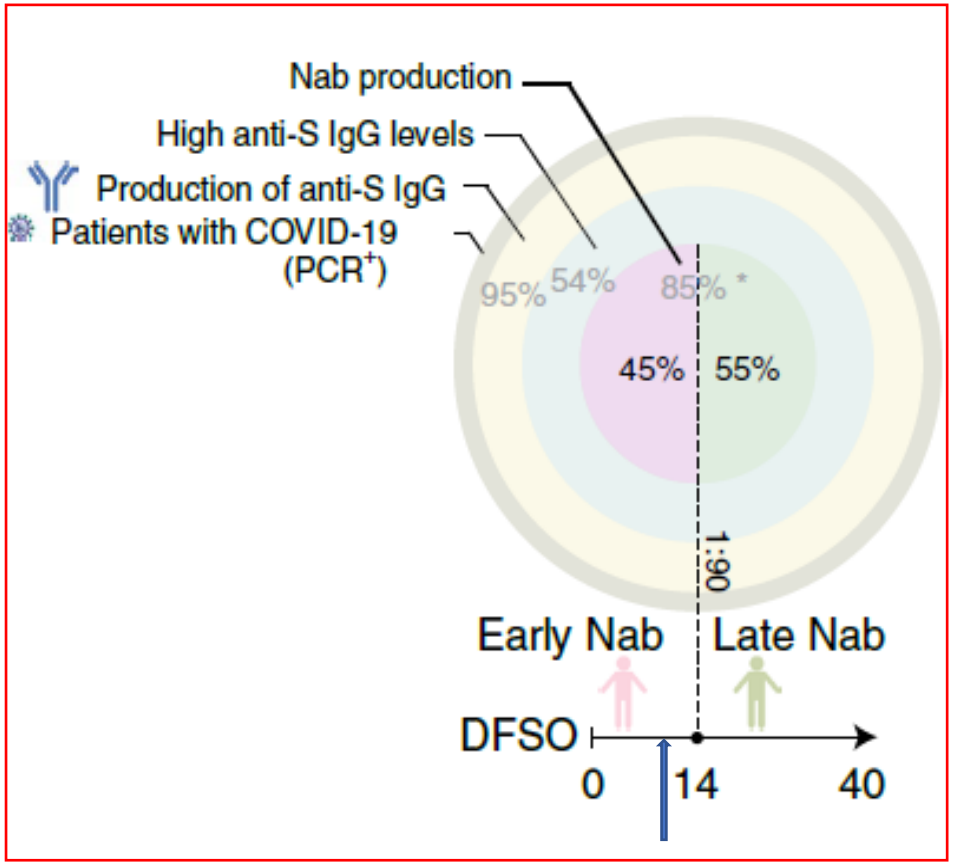
C. LUCAS et al. Nat.Med. 21

- **Viral load, severity, clinical evolution correlated :**
  - Weakly to levels of IgG anti-S ou –RBD
  - Moderately to Neutralizing Ab levels
    - **More strongly to the Kinetics of Neutralization :**



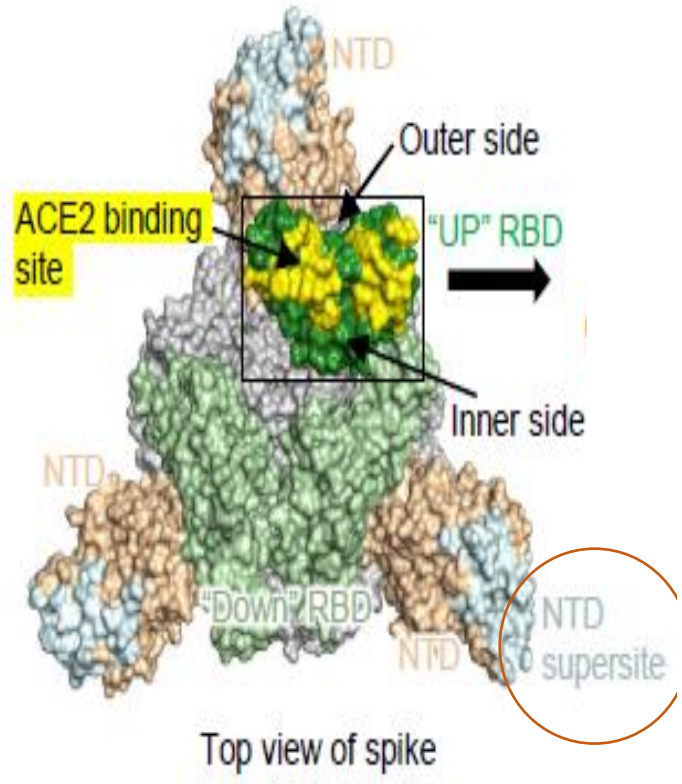






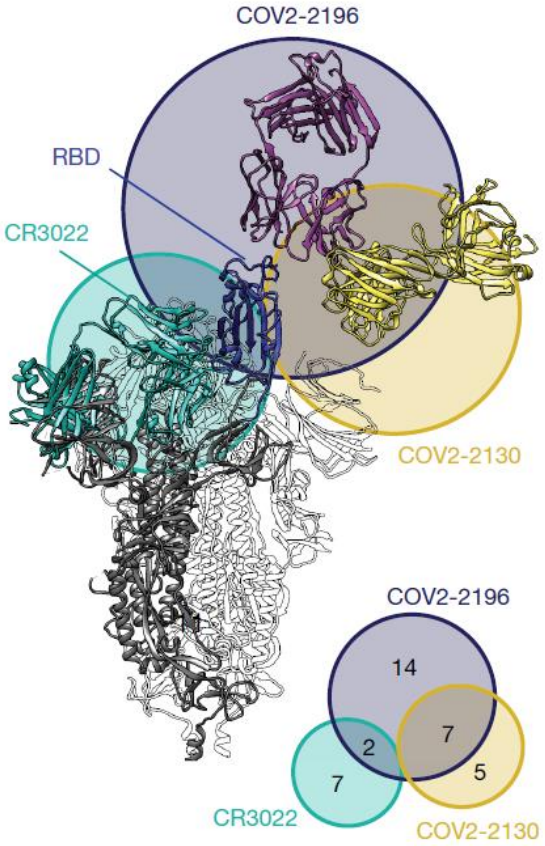
anti-SARS-CoV2 Monoclonal Antibodies

P Wang et al. BioRxiv 2020



anti-SARS-CoV2 human monoclonal Abs :

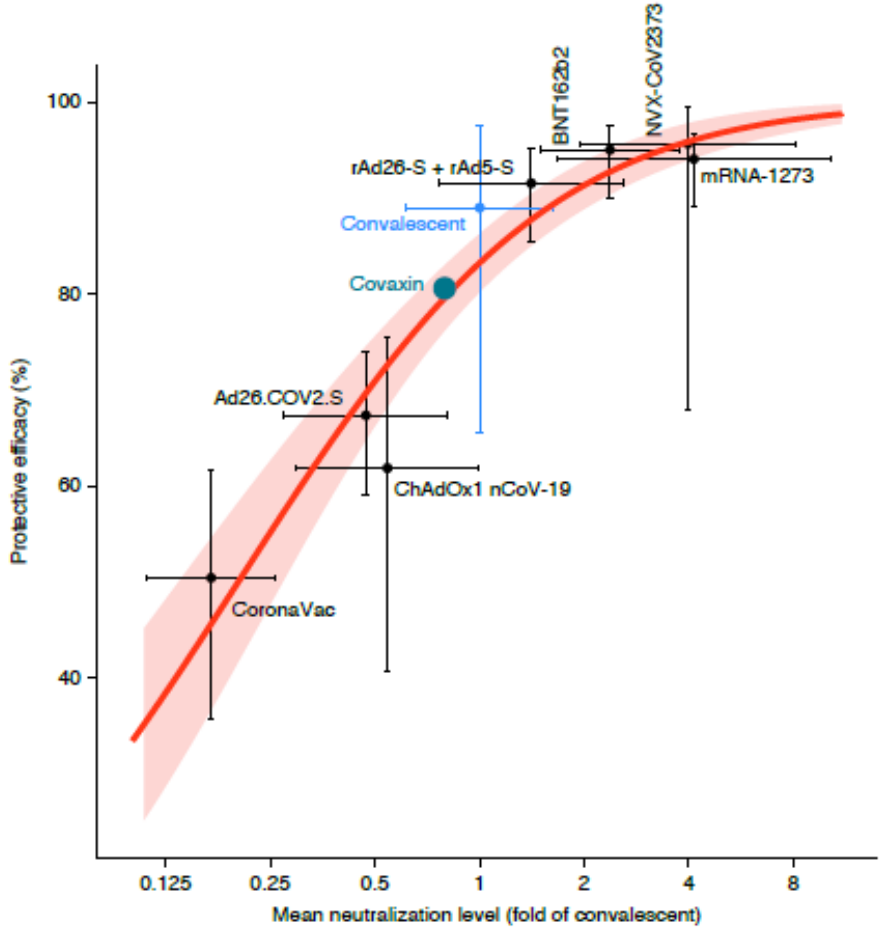
- **Isolated from convalescent B lymphocytes**
- **Cloned and selected for their potent neutralizing activity**
- **Reacting against the Spike RBD**
- **Constant Fc region genetically-modified or not for**
  - **reducing Fc-mediated functions** (ADE, ADCC..)
  - **Increasing half-life** (from 1 to 3-6 months)
- **Produced as pure mAbs**
- **Used as:**
  - **Monotherapy**
  - **or combined cocktails of 2 MAbs**



Anti-S Ab and Neutralizing Abs as Immune Correlates of Vaccine Efficacy ?

➢ **Strongly correlated to disease severity**

and predictive of protection



(Khoury S, Nat.Med. 21)

➢ **1st correlate of protection: A** UK study post-AZ

(Feng S, medRxiv 2021.06.21.21258528)

➢ **Primary Protection : 80% / symptoms**

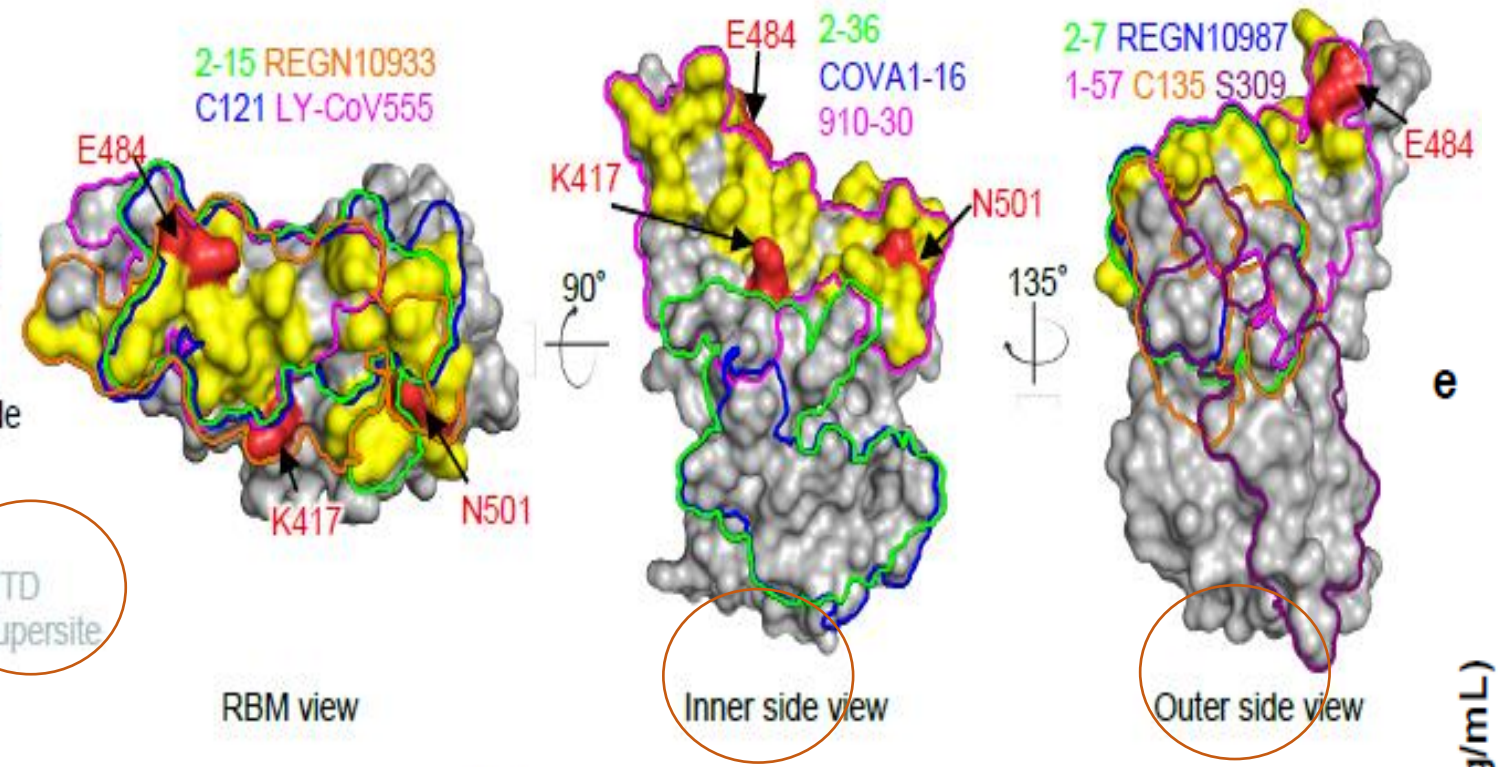
with **anti-S IgG = 264 BAU/mL** (binding antibody units)

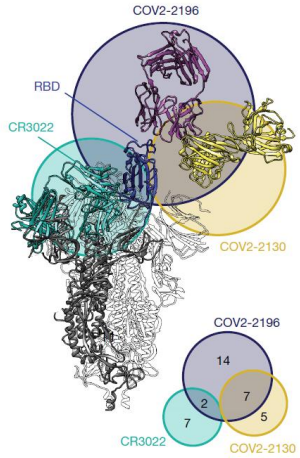
(95% CI 108, 806) , WHO international standard (NIBSC code 20/136).

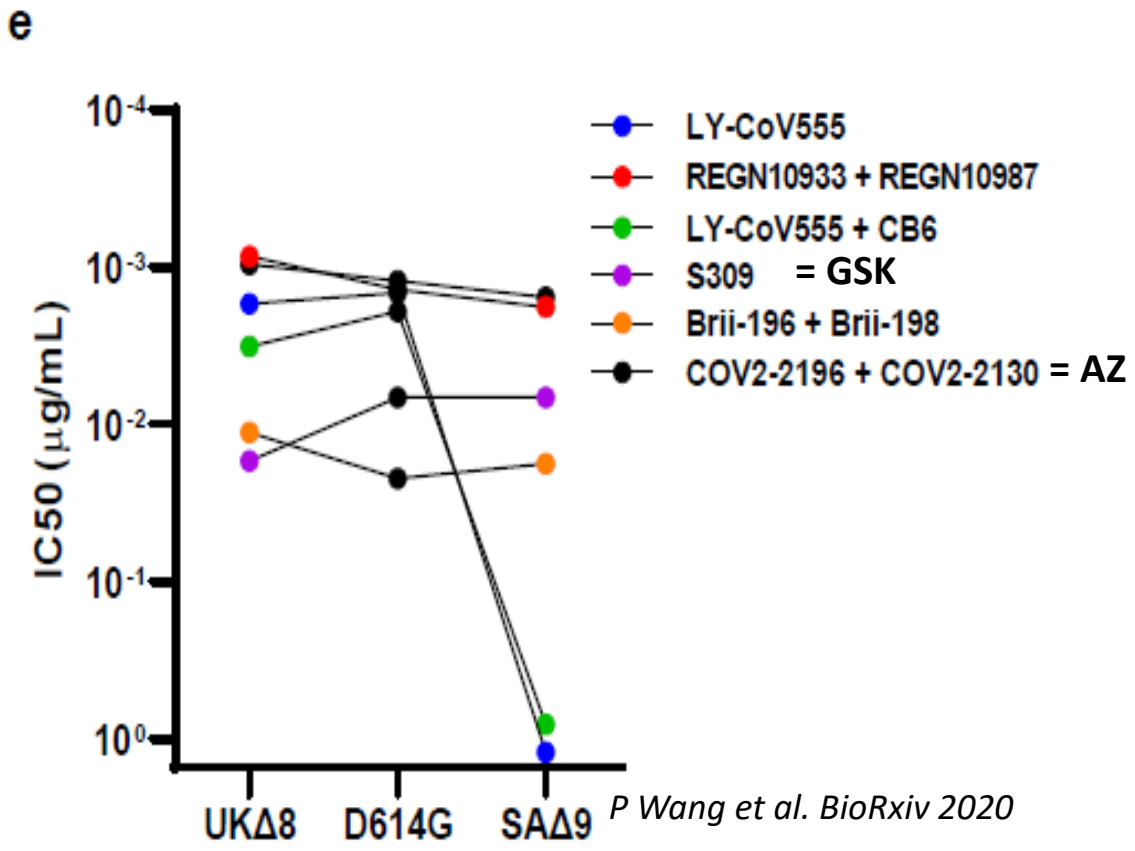
➢ Other Resuls ???

➢ Detection threshold for anti-Sseropositivity = 30 BAU/mL

anti-SARS-CoV2 Mabs epitopes and reactivity against and Variants



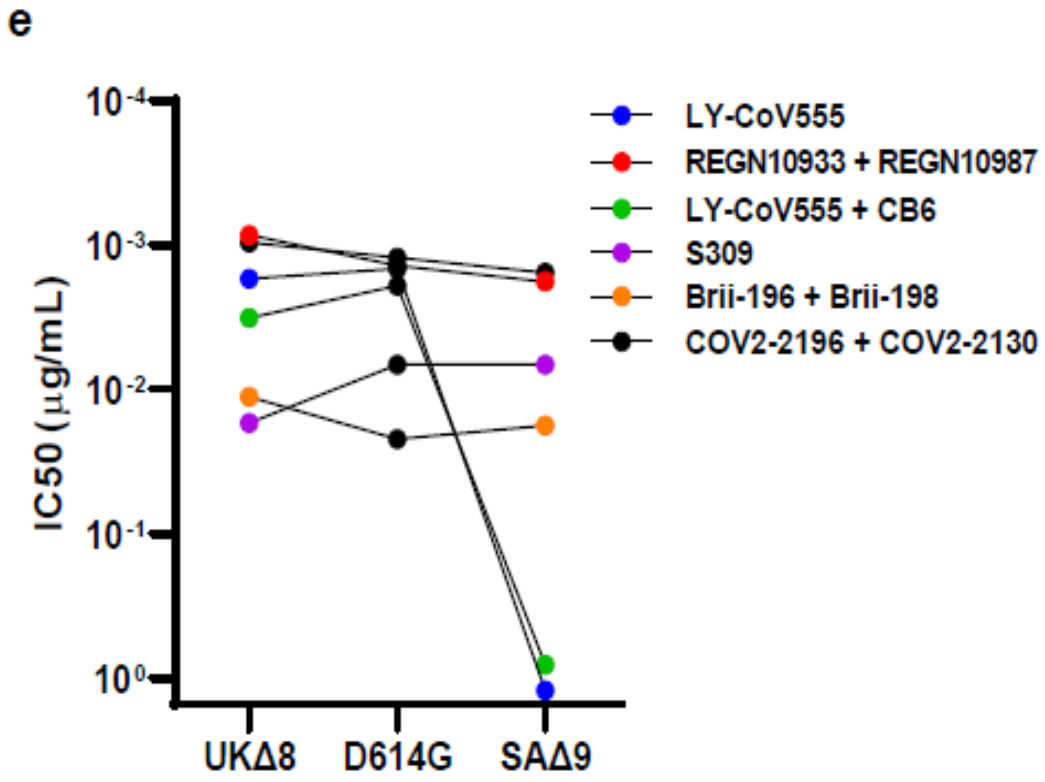




P Wang et al. BioRxiv 2020

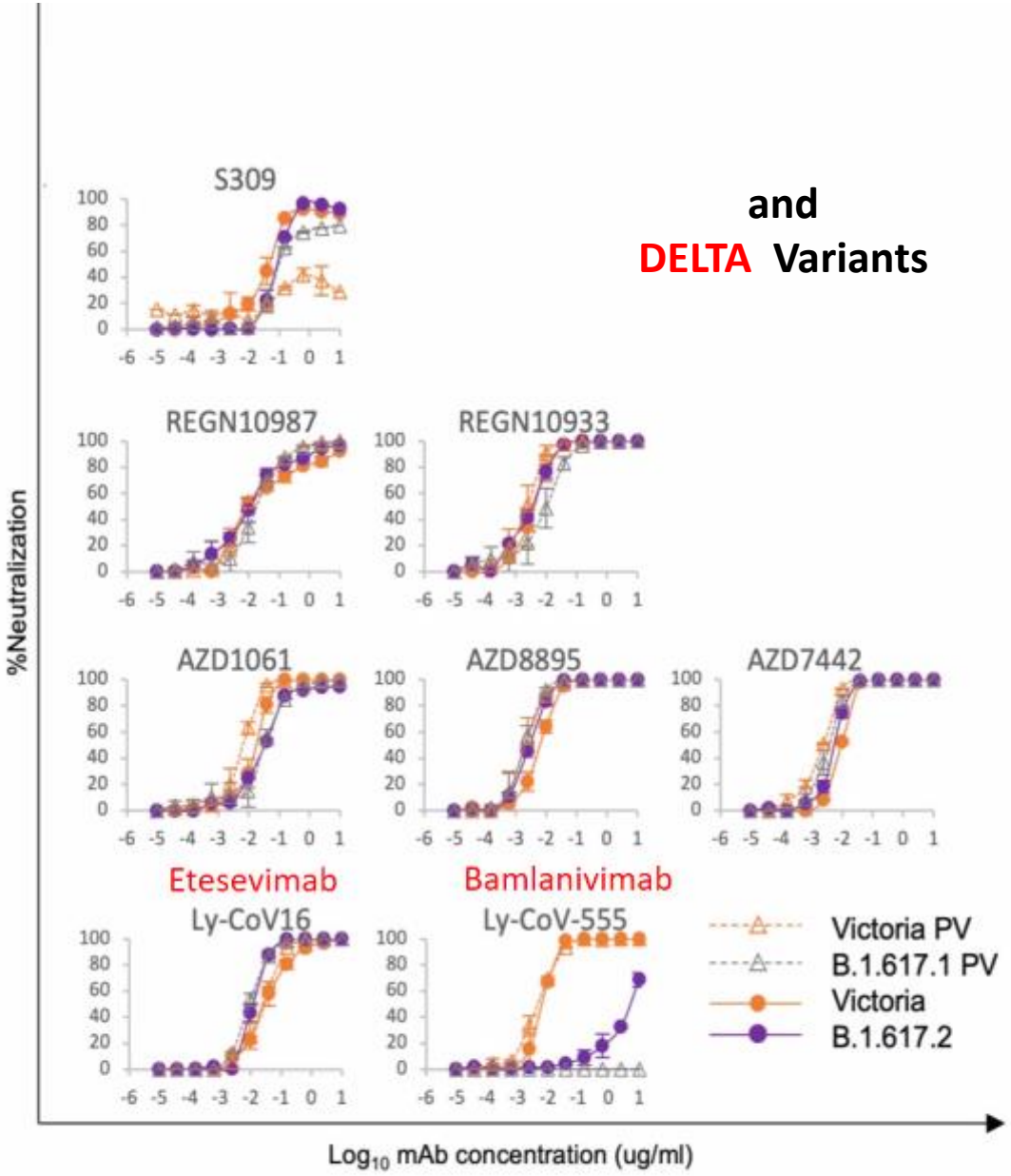
anti-SARS-CoV2 Mabs and Variants

Neutralizing Efficacy of Mab cocktails / variants



P Wang et al. BioRxiv 2020

and
DELTA Variants



Vir

Regeneron

AstraZeneca

Lilly

Chang Liu et al., Cell, 2021

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D'après J Potet, MSF : **Jan. 2021**

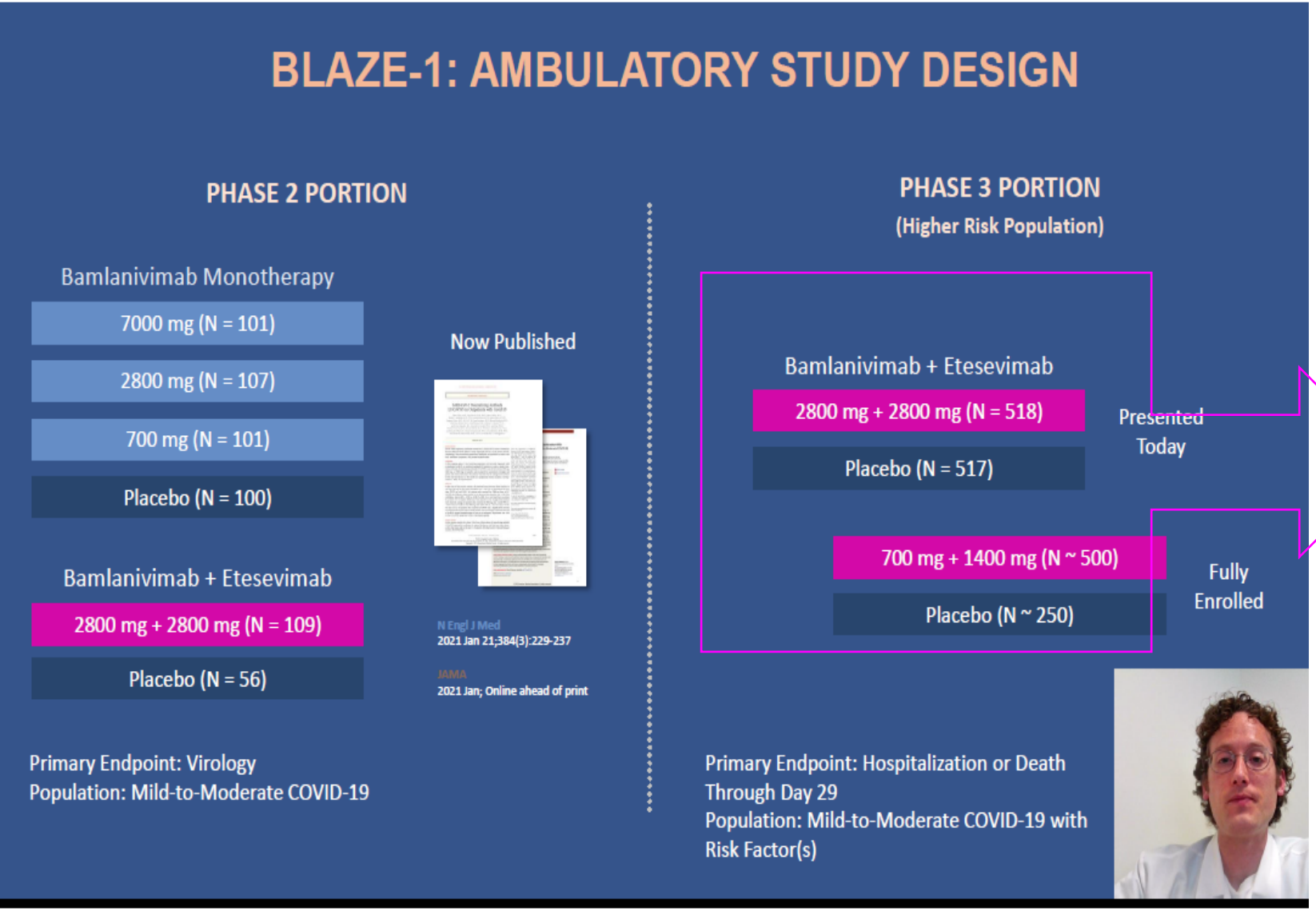
Trial readout | Regulatory approval | Trial updates

Clinical update | Emerging Therapeutics Evidence

Asset class	Asset		Use case	Summary of results and workstream actions / implications	Source
mAbs	LY-CoV555 (Bamlanivimab) and LY-CoV016 (Etesevimab) ***New combination***		*Mild*	• *Jan 26* – **BLAZE-1** preliminary results (Ph3) demonstrate combination significantly reduced COVID-19-related hospitalizations and deaths in high-risk pts (70% reduction, p= 0.0004). Requires 1 hour infusion with dilution. • In addition, initial results from **BLAZE-4** looking at viral load, PD and PK demonstrate lower doses of combo are similar to higher doses used in BLAZE-1, with plans to explore lower doses *Strong efficacy data, await results on variant impact*	Company announcement
	LY-CoV555 (Bamlanivimab)		*PEP, PrFP* *Mild*	• *Jan 21* – **BLAZE-2** preliminary results (Ph3 in mild pt) of 8 weeks follow-up showed significantly lower frequency of symptomatic COVID-19 in Bamlanivimab treatment arm vs placebo (odds ratio 0.43, p=0.00021). For sub-groups of nursing home residents' results suggest 80 percent lower risk of contracting COVID-19. EUA update expected soon. *Strong efficacy data but unlikely to be actionable for ACT-A given impact of variants on asset*	Company announcement
	REGN-COV (Casirivimab/ imdevimab) *Combination*		*PrEP/ PEP* *Mild*	• *Jan 26* –REGN-COV preliminary Ph3 results for antibody cocktail, used as a passive vaccine for the prevention of COVID-19 in high risk pt resulted in 100% prevention of symptomatic infection and approx. 50% lower overall rates of infection, and associated with lower disease burden, no significance figures quoted, unclear of effect on variants. REGN-COV given as injection, not infusion. *Strong efficacy data, await clinical results on variant impact (pre-clinical data demonstrates combo unaffected by UK and SA variant[1])*	Company announcement
	LY-CoV555 (Bamlanivimab) & VIR-7831 (Sotrovimab) ***New combination***		*Mild*	• *Jan 28* – Eli Lilly company announcement that **BLAZE-4** is to be expanded to include Bamlanivimab (LY-CoV555) together with GSK's VIR-7831, with **BLAZE-4** study completion date Apr 21 according to clinicaltrials.gov *Continue tracking for trial read-outs, explore across asset combination potentials*	Company announcement

1. Wang et al. (David Ho's lab) Increased Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7 to Antibody Neutralization, 26/1/21 biorxiv.

Anti-SARS-CoV2 Therapeutic monoclonal antibodies
First Phase II/III clinical trials : **BLAZE-1** bamlanivimab + etesevimab



CROI 2021 Bi-Therapy Eli-Lilly

- **2800+1400mg : N= 517**
  - **71% reduction Hospitalisation**
  - **Réduction de CV (p<0.001)**
- **1400+700mg: …**

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Extension Phase 3 BLAZE-1 bamlanivimab + etesevimab :

N = 769 patients high risk

Covid mild / moderate

n=511; placebo: n=258.

Results :

- 4 evts vs 15 in placebo

  = 87% RR (p<0.0001).

  4 deaths: Placebo

- **Reduction in VL CV**

2800/2800 **700/1400**

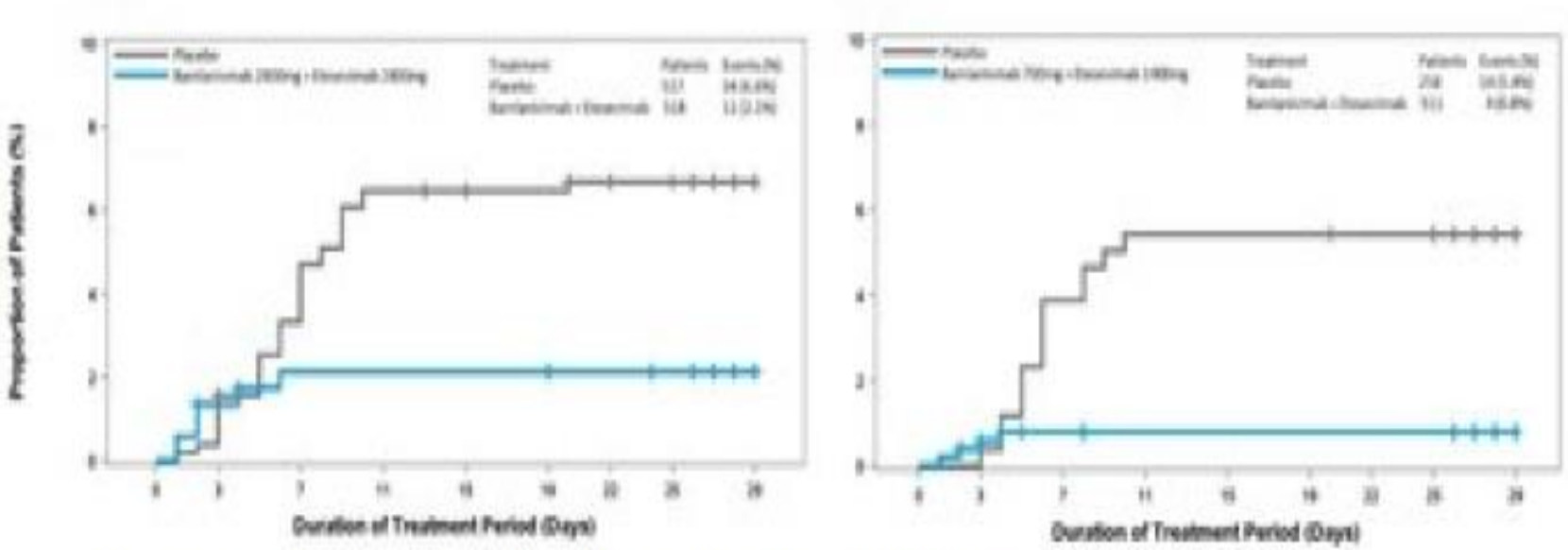


Figure 1: Time to COVID-19 related hospitalization

REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19

D.M. Weinreich, S. Sivapalasingam, T. Norton, S. Ali, H. Gao, R. Bhore,

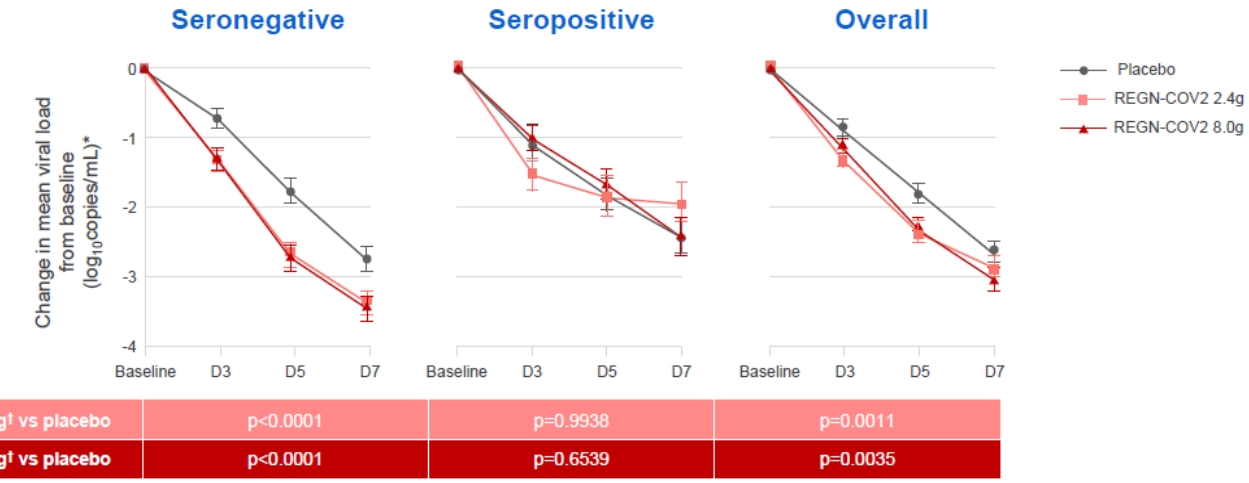
The NEW ENGLAND JOURNAL of MEDICINE
DOI: 10.1056/NEJMoa2035002

Randomized Study: Cocktail vs Placebo:
2 doses (2,4 & 8 mg)

- **Inclusion Criteria**
  - > 18 yo
  - **Symptoms < 7d**
- **Primary End-points:**
  - **Ph2: Viral Load**
  - **Ph3: medical intervention Needs < D29**

Cohorts	1 = 275	2 = 524
Age.	44	41
Obesity	42%	34%
≥1 risk Fact.	**64%**	**59%**

Significantly reduced viral load in both seronegative and overall populations



2.4g† vs placebo	p<0.0001	p=0.9938	p=0.0011
8.0g† vs placebo	p<0.0001	p=0.6539	p=0.0035

➢ **Anti-viral efficacy if EARLY treatment**
= before host's immune response

Treatment benefits (medically attended visits in pts with Risk Factors)

	placebo	RGN 2.4 (215)	RGN 8.0 (219)
No Risk factors	2.2%	3.7%	2.3%
≥1 risk factor	**9.2%**	**2.2%**	**3%**

➢ **75% reduction (p=0.001)**

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Real-World Effectiveness and Tolerability of Monoclonal Antibodies for Ambulatory Patients with Early COVID-19

BJ Webb et al.

preprint doi: https://doi.org/10.1101/2021.03.15.21253646

13 534 patients dont:

- **594 Mabs** (MonoT Eli-L : 80%; Bi-T RGNR: 19.5%)
- Controles : contemporains, historiques

- **Age** median : 61 ans
- **Facteurs de risque**: médiane: 4/patient
  (Immunosuppression: 4.3%)
- **Ambulatoires**
- **Formes Minimes /Modérées**
  depuis <7j

Critere Primaire: Hospit. ou SAU:

- **Mabs: 12.6% vs 18.4% controles**
  RR = 0.69

Tolérance:

- SAE: 0.3%

➢ **Standard of care aux USA**

Variable	All	Monoclonal treatment group	Contemporaneous control group	Pre-Implementation cohort
N=	13534	594	5536	7404
Age, years, mean (SD)	61 (15)	65 (13)	62 (15)	60 (15)
Female, n (%)	6064 (44.8)	240 (40.4)	2531 (45.7)	3293 (44.5)
Total Comorbidities, median (IQI)	4 (3-5)	5 (3-6)	4 (3-5)	4 (3-5)
Individual Comorbidities, n (%)				
Immunosuppression[b]	579 (4.3)	34 (5.7)	236 (4.3)	309 (4.2)
Diabetes mellitus	6719 (49.6)	390 (65.7)	2656 (48.0)	3673 (49.6)
Coronary artery disease	1346 (9.9)	82 (13.8)	529 (9.6)	735 (9.9)
Active malignancy	440 (3.3)	23 (3.9)	191 (3.5)	226 (3.1)
Chronic pulmonary disease	7183 (53.1)	347 (58.4)	2928 (52.9)	3908 (52.8)
Chronic kidney disease	2612 (19.3)	188 (31.6)	1077 (19.5)	1347 (18.2)
Chronic liver disease	3546 (26.2)	170 (28.6)	1476 (26.7)	1900 (25.7)
Cerebrovascular disease	2176 (16.1)	117 (19.7)	904 (16.3)	1155 (15.6)
Hypertension	10699 (79.1)	537 (90.4)	4392 (79.3)	5770 (77.9)
Chronic neurological disease	2141 (15.8)	93 (15.7)	903 (16.3)	1145 (15.5)
Congestive heart failure	2033 (15.0)	145 (24.4)	15% (827 (14.9)	1061 (14.3)
Cardiac arrhythmia	5677 (41.9)	294 (49.5)	2323 (42.0)	3060 (41.3)
Obesity[c]	8323 (61.5)	397 (66.8)	3416 (61.7)	4510 (60.9)
Outcomes, n (%)				
Emergency Department visit (14 days)	2442 (18.0)	71 (12.0)	944 (17.1)	1427 (19.3)
Hospital Admission (14 days)	1412 (10.4)	23 (3.9)	538 (9.7)	851 (11.5)
Mortality (14 days)	129 (1.0)	1 (0)	57 (1.0)	71 (1.0)
Composite outcome (14 days)	2618 (19.3)	75 (12.6)	1018 (18.4)	1525 (20.6)

Treatment with anti-SARS-CoV2 Mabs : Early Access in France

- March 8th 21 (extension 8/6/21): **ATU "de cohorte"** for Eli-Lilly and Regeneron/Roche MAbs**:**
  - Indication : treatment of **confirmed COVID-19 symptomatic or not**
  - treatment instaured asap after positive PCR : **within 5 days post first symptoms or post-1st positive PCR**
  - In patients > **12yo not requiring O2** for COVID-19 **AND:**

Accès précoce aux anticorps monoclonaux en France

- Extension de la population éligible pour les bithérapies intervenue le 8 juin 2021 qui peuvent être dorénavant utilisées chez les patients à partir de 12 ans

- **Les patients ayant un déficit de l'immunité lié à une pathologie ou à des traitements :**
  - Chimiothérapie en cours
  - Transplantation d'organe solide
  - Allogreffe de cellules souches hématopoïétiques
  - Maladie rénale avec DFG <30 mL/min ou dialyse
  - Lupus systémique ou vascularite avec traitement immunosuppresseur
  - Traitement par corticoïde >10 mg/jour d'équivalent prednisone pendant plus de 2 semaines
  - Traitement immunosuppresseur incluant rituximab
  - Infection par le VIH non contrôlée ou stade SIDA
- **Les patients à risque de complications :**
  - Obésité (IMC>30),
  - BPCO et insuffisance respiratoire chronique,
  - Hypertension artérielle compliquée,
  - Insuffisance cardiaque,
  - Diabète (de type 1 et de type 2),
  - Insuffisance rénale chronique,
  - Fibrose pulmonaire idiopathique
  - Sclérose latérale amyotrophique
  - Pathologies rares du foie y compris hépatites auto-immunes
  - Myopathies avec capacité vitale forcée <70%
  - Autres pathologies rares définies par les filières de santé maladies rares (FSMR)
  - Trisomie 21
- **Les patients de 80 ans et plus**

New Extension of therapeutic ATUc with anti-SARS-CoV2 Mabs 3/9/2021

- **RECOVERY** trial : **4000mg** each Roche Mab as add-on:
  - Primay endpoint: death at D28, in **seronegative** patients (IgG anti-S) at randomisation
    - ➢ **reduction of mortality all causes by 20 %**

      Deaths: 24% in group Ab vs 30 %; RR : 0,80 (IC 95 % : 0,70-0,91 ; p=0,001.

➢ **EMA**: favorable to early access for patients at high risk for severe Covid : https://www.ema.europa.eu/en/news/ema-issues-advice-use-regn-cov2-antibody-combination-casirivimab-imdevimab

- ➢ Italy : 6/8/21: early access in patients *>12 yo hospitalized for COVID-19 and* ***seroNEGATIVE for anti-SRAS-CoV-2 IgG,***

➢ **Extension of Therapeutic ATUc:** Ansm 3/9/2021**:**

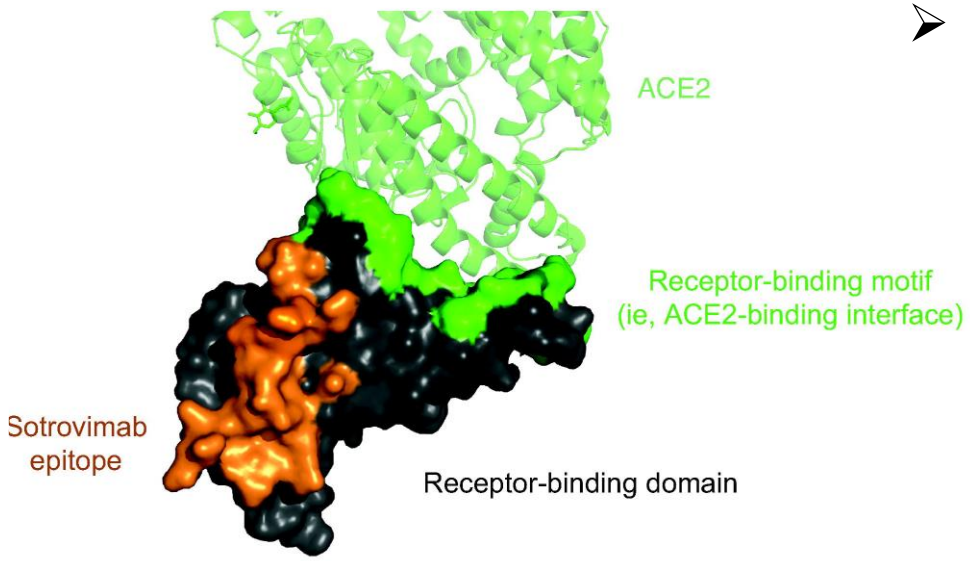
- ➢ **Patients hospitalized for COVID-19 AND seroNegatives** (IgG anti-S) at entry :
  - with non invasive oxygénotherapy (conventional or high flow) for COVID-19
  - at high risk of severity in previous ATU indications

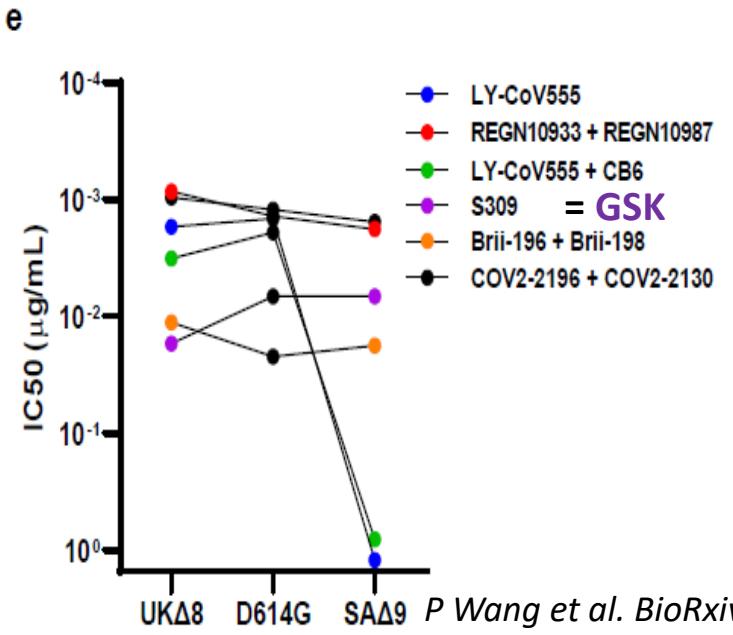
What's next? SARS-CoV-2 Neutralizing Antibody Sotrovimab

Anil Gupta et al. doi: https://doi.org/10.1101/2021.05.27.21257096

- A peculiar anti-SARS-CoV Monoclonal: **developed from a SARS-CoV 2003 patient** ,
  - **cross-reacting with SARS-CoV2**
  - **directed against a conserved epitope below the RBD**

    = not affected by RBD mutations





P Wang et al. BioRxiv 2020

Early Covid-19 Treatment With SARS-CoV-2 Neutralizing Antibody Sotrovimab

Anil Gupta et al. doi: https://doi.org/10.1101/2021.05.27.21257096

- **COMET-ICE**
  Phase II/III trial

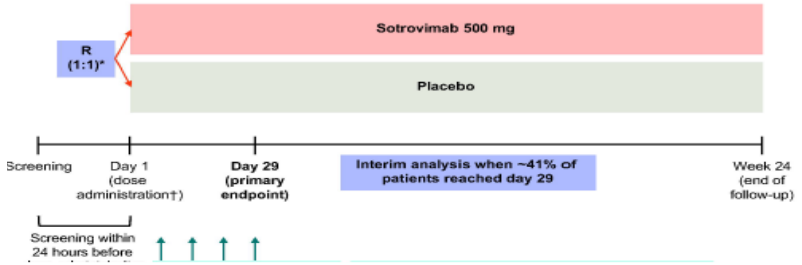


Table 1. Baseline Demographic and Disease Characteristics (ITT Population)

Characteristic	Sotrovimab (N = 291)	Placebo (N = 292)	Total (N = 583)
Age – yr, median (range)	53.0 (18-96)	52.5 (18-88)	53.0 (18-96)
≥65 yr – no. (%)	63 (22)	65 (22)	128 (22)
>70 yr – no. (%)	33 (11)	32 (11)	65 (11)
Male gender – no. (%)	135 (46)	131 (45)	266 (46)
Body-mass index† – mean (SD)	32.0 (6.4)	32.1 (6.3)	32.1 (6.3)
Duration of symptoms‡ – no. (%)			
≤3 days	167 (57)	171 (59)	338 (58)
4-5 days	123 (42)	121 (41)	244 (42)
Any risk factor for Covid-19 progression – no. (%)	291 (100)	290 (>99)	581 (>99)
Age ≥55 yr	135 (46)	141 (48)	276 (47)
Diabetes requiring medication	66 (23)	66 (23)	132 (23)
Obesity (body-mass index >30†)	182 (63)	187 (64)	369 (63)
Chronic kidney disease (eGFR <60 by MDRD)	1 (<1)	4 (1)	5 (<1)
Congestive heart failure (NYHA class II or more)	1 (<1)	3 (1)	4 (<1)
Chronic obstructive pulmonary disease	14 (5)	10 (3)	24 (4)
Moderate to severe asthma	46 (16)	46 (16)	92 (16)
Number of concurrent risk factors for Covid-19 progression – no. (%)			
0	0	2 (<1)	2 (<1)
1	170 (58)	168 (58)	338 (58)
2	91 (31)	86 (29)	177 (30)
≥3	30 (10)	36 (12)	66 (11)

Early Covid-19 Treatment With SARS-CoV-2 Neutralizing Antibody Sotrovimab

Anil Gupta et al. doi: https://doi.org/10.1101/2021.05.27.21257096

- COMET-ICE Phase II/III trial
- **85% Prevention of Hospitalizations or Deaths**

Table 2. Summary of Efficacy Outcomes Through Day 29 (ITT Population)

	Sotrovimab (N = 291)	Placebo (N = 292)
Primary outcome		
Hospitalized >24 hours or death for any cause – no. (%)	3 (1)	21 (7)
Hospitalized >24 hours for any cause	3 (1)	21 (7)
Death by any cause	0	1 (<1)
Alive and not hospitalized – no. (%)	284 (98)	270 (92)
Missing – no. (%)	4 (1)	1 (<1)
Withdrew consent prior to dosing – no. (%)	3 (1)	1 (<1)
Percent reduction (97.24% CI), P value	85% (44% to 96%); P = 0.002	

Other clinical outcomes*		
Emergency room visit, hospitalization, or death for any cause – no. (%)	6 (2)	28 (10)
Emergency room visit for any cause	2 (<1)	8 (3)
Hospitalized for any cause	4 (1)†	21 (7)
Death by any cause	0	1 (<1)

Therapeutic anti-SARS-CoV2 Monoclonal antibodies : What's next?

- AZD7442 :
  - **Discovery : Ongoing Phase III trial in hospitalized moderate patients < 9 days post-symptoms**
    Clinical Primary endpoint : D15
  - **TACKLE Phase III,** randomised, blinded, placebo-controlled, multi-centre trial assessing :
    - **Safety and Efficacy** of 600mg **IM** dose of AZD7442 vs placebo for **outpatients :**
      - N= 903 randomised (1:1: AZD7442 : n = 452) or placebo (n = 451)
      - mild-to-moderate COVID-19 and **symptomatic for 7 days** or less and PCR+ **< 3 days prior to D1**.
      - **13% > 65 years, 90% = co-morbidities and high risk factors** (cancer, diabetes, obesity, chronic lung disease or asthma, cardiovascular disease or immunosuppression)

    ➢ *Press release October 11th 2021* Primary efficacy endpoint = severe COVID-19 or death through D29.

    ➢ **50% reduction in risk of developing severe COVID-19 or death (**18/407 events in AZD7442 vs 37/415 in placebo)

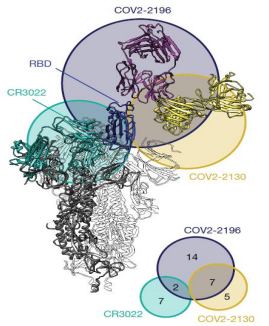
    ➢ **Good safety profile**

    ➢ prespecified analysis of treatment **within 5 days of symptom**

    ➢ **67% reduction in risk of developing severe COVID-19 or death** vs placebo

    - 9/253 events in AZD7442 vs 27/251 in placebo

    ➢ FDA submission for EUA : early Oct 21



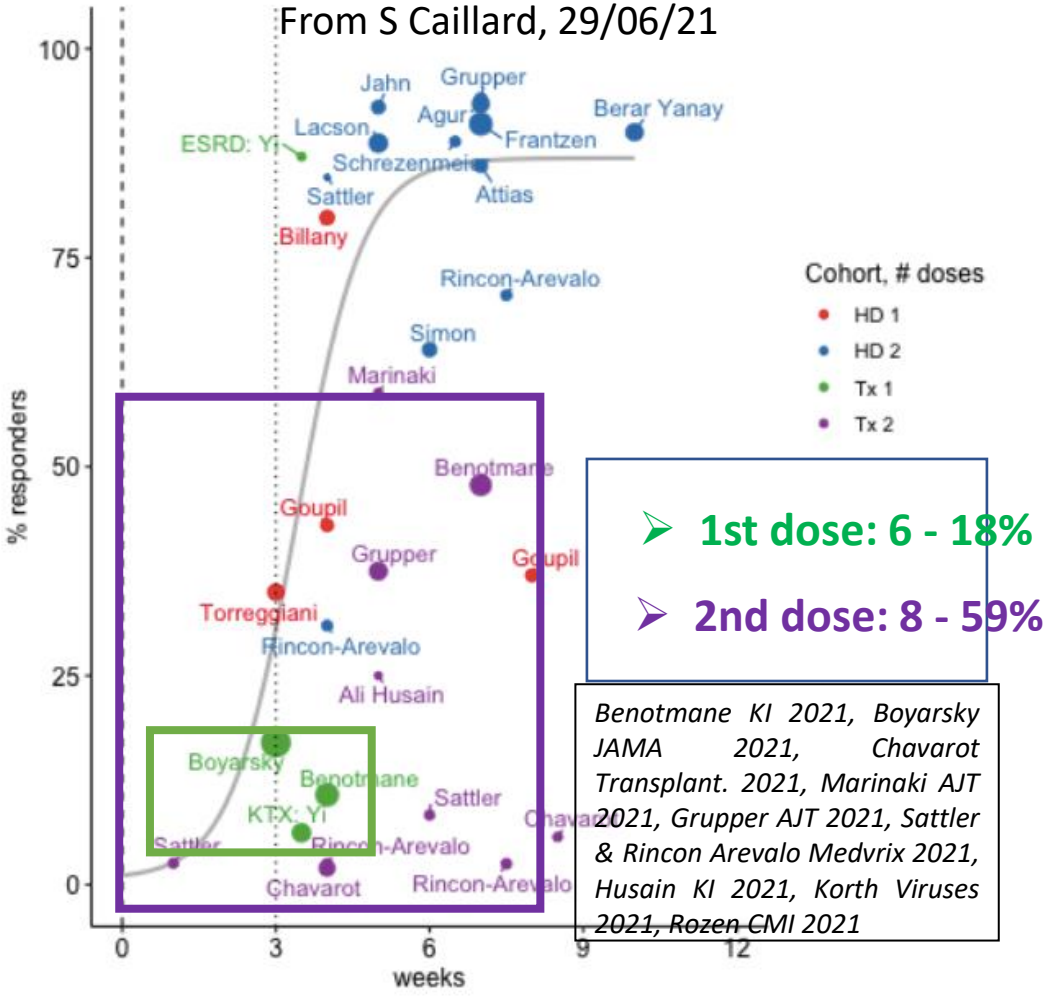
Cocktail AZ (*Zost et al. Nature 20*

Can anti-SARS-CoV2 Mabs help protect Vaccine Non Responders ?

Synthesis of current french datas

Kidney Transplants

From S Caillard, 29/06/21



- 1st dose: 6 - 18%
- 2nd dose: 8 - 59%

Benotmane KI 2021, Boyarsky JAMA 2021, Chavarot Transplant. 2021, Marinaki AJT 2021, Grupper AJT 2021, Sattler & Rincon Arevalo Medvrix 2021, Husain KI 2021, Korth Viruses 2021, Rozen CMI 2021

Transplants and others

	Post-dose 2		Post-dose 3	
	Non Responders	**Poor Responders**	**Non Responders**	**Poor Responders**
SOT (SFT) kidney	**50%**	**40%**	**25%**	**40%**
CLL (FILO)	**50%**	**40%**	**25%**	**40%**
CSH Allografts (SFGM-TC)	**20%**		**18%** (<250 BAU)	**30% in NR post dose 2**
Anti-CD20 *(Deepak et al. Sokratis et al.) (C Besson)*	**>35%**			***50%***

- **2 situations post complete vaccine scheme (2 or 3 doses) :**
  - **Total failure** = No Response (Ac anti-S <30 BAU/mL)
  - **Partial Failure** = Low Titers (Ab anti-S << 250 BAU/mL).

anti-Covid19 Prophylaxis with anti-SARS-CoV2 Mabs : Clinical Trials

➢ **PEP (Post-Exposure Prophylaxis): Prevention of symptoms** :

- Bamlanivimab IV: in high risk contacts (non immunosuppressed) : OR : 0.43 p<0.01 *(M Cohen, JAMA, 21)*

  Not active on Delta but Etesimab and cocktail still active (Monotherapy)

- AZD7442 IM : **in about 75% in PCR-negative contacts** *(communiqué de presse AZ 15/6/21)*

anti-Covid19 Prophylaxis with anti-SARS-CoV2 Mabs : Clinical Trials

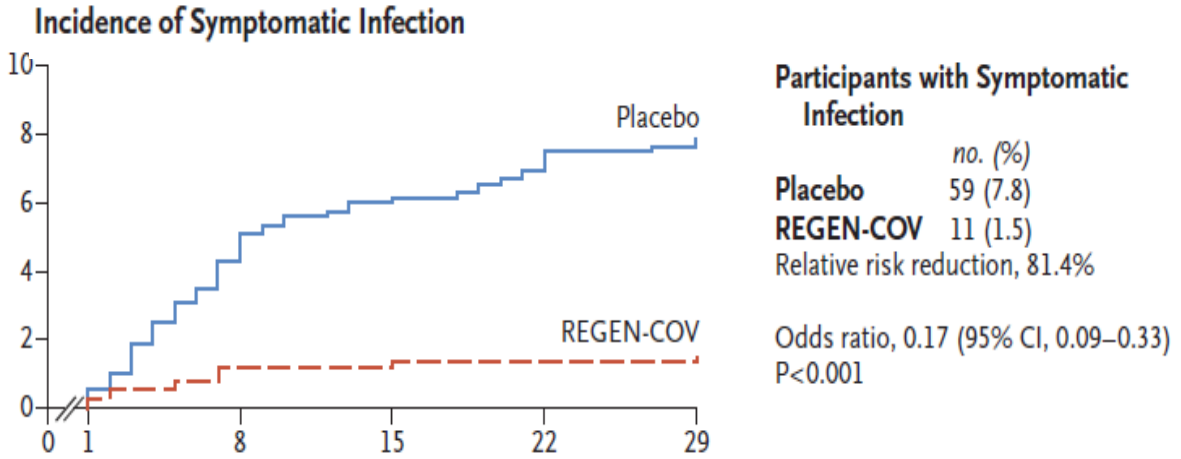
➢ PEP (Post-Exposure Prophylaxis): Prevention of symptoms :

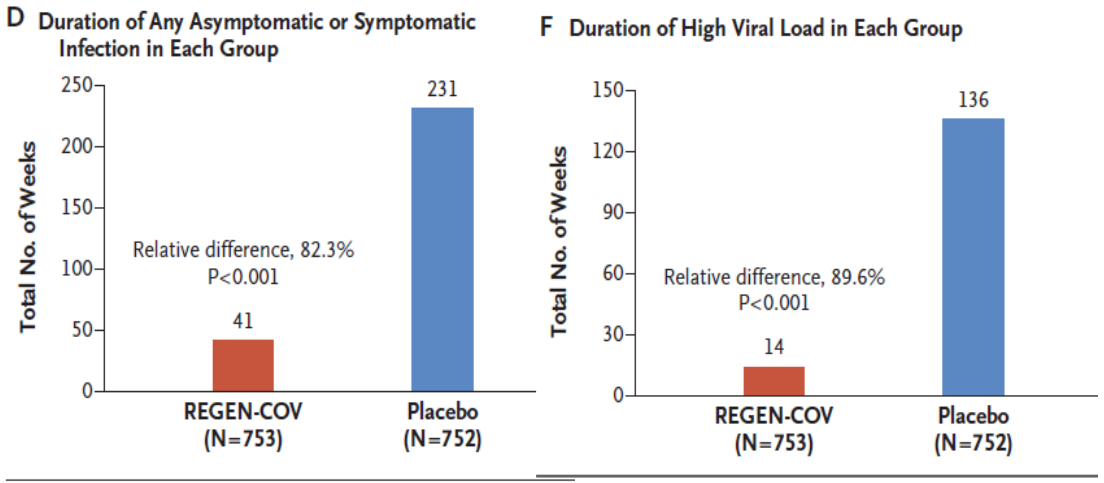
- **Casirivimab-Indevimab SC: in 81% PCR-negative contacts :**

(MS O'Brien, medRxiv. 2021 Jun 14;2021.06.14.21258569)

Table 1. Demographic and Clinical Characteristics of the Seronegative Population at Baseline.*

Characteristic	REGEN-COV (N=753)	Placebo (N=752)
Age		
Mean (range) — yr	43.2 (12–87)	42.7 (12–92)
High risk of Covid-19 — no. (%)		
Any high-risk factor	238 (31.6)	221 (29.4)
≥65 yr of age	76 (10.1)	55 (7.3)
BMI ≥35	99 (13.1)	104 (13.8)
Chronic kidney disease	17 (2.3)	11 (1.5)
Diabetes	58 (7.7)	45 (6.0)
Immunosuppressive disease	5 (0.7)	2 (0.3)
Receipt of immunosuppressive therapy	4 (0.5)	11 (1.5)
≥55 yr of age with cardiovascular disease, hypertension, or COPD	99 (13.1)	90 (12.0)





anti-Covid19 Prophylaxis with anti-SARS-CoV2 Mabs : Clinical Trials

- **PEP (Post-Exposure Prophylaxis):**

Casirivimab-Indevimab SC:

(MS O'Brien, medRxiv. 2021 Jun 14;2021.06.14.21258569)

83.5% of participants = PCR negative at D0
and 73% = SeroNegative

Table 2. Primary and Key Secondary Efficacy End Points.*

End Point	REGEN-COV (N=753)	Placebo (N=752)
Primary end point: symptomatic RT-qPCR–confirmed SARS-CoV-2 infection, broad-term definition†		
No. of participants (%)	11 (1.5)	59 (7.8)
Relative risk reduction — %	81.4	—
Odds ratio (95% CI)	0.17 (0.09–0.33)	—
P value‡	<0.001	—
Viral load >10^4 copies/ml§		
No. of participants/total no. (%)	12/745 (1.6)	85/749 (11.3)
Relative risk reduction — %	85.8	—
Odds ratio (95% CI)	0.13 (0.07–0.24)	—
P value‡	<0.001	—
Duration of symptomatic RT-qPCR–confirmed SARS-CoV-2 infection, broad-term definition		
Total no. of wk	12.9	187.7
Total duration/1000 participants — wk	17.1	249.6
Relative difference vs. placebo — %¶	93.1	—
P value‖	<0.001	—
Mean duration of symptoms/participant with symptomatic infection — wk	1.2±1.0	3.2±2.7
Duration of high viral load (>10^4 copies/ml) among all participants§		
Total no. of wk	14.0	136.0
Total duration/1000 participants — wk	18.8	181.6
Relative difference vs. placebo — %¶	89.6	—
P value‖	<0.001	—
Mean duration of high viral load/infected participant — wk	0.4±0.6	1.3±0.9
Duration of any RT-qPCR–confirmed symptomatic or asymptomatic SARS-CoV-2 infection		
Total no. of wk	41.0	231.0
Total duration/1000 participants — wk	54.4	307.2
Relative difference vs. placebo — %¶	82.3	—
P value‖	<0.001	—
Mean duration of overall infection/infected participant — wk	1.1±0.4	2.2±1.1
Any RT-qPCR–confirmed symptomatic or asymptomatic SARS-CoV-2 infection		
No. of participants (%)	36 (4.8)	107 (14.2)
Relative risk reduction — %	66.4	—
Odds ratio (95% CI)	0.31 (0.21–0.46)	—
P value**	<0.001	—

anti-Covid19 Prophylaxis with anti-SARS-CoV2 Mabs : Clinical Trials

➢ Primary Prophylaxis (PrEP): Prevention of symptomaticCovid-19 :

- **AZD7442** : *(Press release 20/8/21):*

  ➢ **Reduces risk of symptomatic COVID-19 by 77%** (IC 9: 46-90) / au placebo:

  N= 5 197, 1 dose IM (n = 3 460) 300mg in 2 IM.

  >75 % subjects at high risk of severe COVID-19 (Immunosuppressed, diabete, obesity, cardiopathy, BPCO, Chronic renal insuffisiency, chronichepatitis).

  ➢ Severe Covid: Gp AZD7442: N=0 / Placebo: N=3 with 2 deaths.

  ➢ Good safety

Recommandations by ANRS-MIE for **Primary and Post-exposure prophylaxis**

(Recommandations **évolutives** du Groupe MAbTher : 25/7/2021)

➢ **Subjects at very high risk for severe Covid19 AND not responding adequately to Vaccines**

(complete scheme 2 or 3 doses) **due to their immunodepression:**

- **Priority**: **Non Responders: seronegative** (Ab anti-S *<30 BAU)* AND :
  - **SOT recipients,**
  - **Allogénic CSH grafts recipients**
  - **Lymphoïd Hemopathies: CLL treated or not, NHL and myelomas under treatment** (including CAR-T cell or bi-phenotypic Abs).
  - **Anti-CD20 whatever the indication,** or BTK inhibitors, azathioprine, cyclophosphamide, mycophenolate mofetil
  - **Primary Immune Deficiency**
  - **Other indications :** **Oncology (some immunosuppressive treatments)** or Hemodialysis

    Any SeroNegative Vaccinated patient at high risk of severe COVID-19

- **Inadequate Ab Response to Vaccine** : Same patients with : **anti-S IgG < 260 BAU** (*hypothétical threshold for protection currently available susceptible to modifications with future datas)*

ansm

30/7/2021

- **L'ANSM atteste de la forte présomption d'efficacité et de sécurité du médicament RONAPREVE (casirivimab et imdevimab) dans les indications thérapeutiques suivantes :**

« L'association casirivimab et imdevimab est indiquée en prophylaxie pré ou post-exposition de la COVID-19 chez les patients adultes et les enfants âgés de 12 ans et plus, n'ayant pas développé du fait de leur immunodépression une réponse vaccinale satisfaisante à un schéma complet de vaccination [i.e patients non-répondeurs (séronégatifs ou titre d'anticorps anti-S <30 BAU) ou faiblement répondeurs (titre d'anticorps anti-S <260 BAU)] **ET** appartenant à l'un des sous-groupes à très haut risque de forme sévère de COVID-19 tels que définis par l'ANRS-Maladies Infectieuses Emergentes:

- Receveurs de greffes d'organes solides
- Receveurs d'une greffe allogénique de cellules souches hématopoïétiques
- Hémopathies lymphoïdes : leucémies lymphoïdes chroniques traitées ou non, lymphomes non hodgkiniens et myélomes sous traitement, y compris les patients receveurs de thérapie cellulaire génique de type CAR-T cell ou d'anticorps thérapeutiques bi-phénotypiques
- Patients recevant un traitement par anticorps anti-CD20 ou inhibiteurs de BTK ou azathioprine, cyclophosphamide et mycophenolate mofetil
- Sujets porteurs d'un déficit immunitaire primitif
- Patients séronégatifs après un schéma vaccinal complet ou non éligibles à la vaccination **et** qui présentent une immunodépression sévère **et** qui sont à haut risque de forme grave de COVID-19.

Dans le cadre d'une administration en prophylaxie post-exposition, les sujets cas-contact doivent avoir la confirmation d'un test RT-PCR négatif avant l'administration. Le casirivimab et l'imdevimab doivent être administrés simultanément dès que possible après l'exposition confirmée au SARS-CoV-2.
En contexte d'urgence, les patients tels que définis ci-dessus n'ayant pas reçu un schéma vaccinal complet ou avec une exposition à un patient COVID-19 dans les 7 jours après la dernière dose, peuvent également bénéficier de la prophylaxie post-exposition sans attendre le résultat de la sérologie.

Dans le cadre d'une administration en prophylaxie pré-exposition, le casirivimab et l'imdevimab doivent être administrés simultanément et de façon répétée toutes les 4 semaines dès lors qu'il existe un risque d'être exposé au SARS-CoV-2. Les patients doivent avoir la confirmation d'un test RT-PCR négatif avant chaque administration.

Cette indication est susceptible d'évoluer en fonction de l'état des connaissances scientifiques et du contexte épidémiologique. »

Préconisations
- IV for PEP
- SC for PrEP

3/8/2021 : **Early Access Authorization for Ronapreve® (casirivimab/imdevimab)**

- in 12 yo i**n prophylaxis** :

- **Post-ExposURE (PEP)**
  - Severely **Immunosuppressed patients Non or Weak Responders to a complete scheme of vaccination** or non éligible to vaccination with high risk of severe Covid-19 (Indications ANRS-MIE).
  - Cocktail of 2 MAbs in contacts **asap after negative PCR** or in emergency if uncomplete vaccination

- **Pre-Exposure (PrEP)**
  - Severely **Immunosuppressed patients Non Responders to a complete scheme of vaccination** or non éligible to vaccination with high risk of severe Covid-19 (Indications ANRS-MIE).
  - Cocktail of 2 MAbs **every 4 weeks as long as exposed** .
  - *Because of insufficient data, this authorization is not extended to Weak Responders* .

- Advice susceptible to be modified as a function of scientific and epidemiological data

- Estimated target Population : 130 000 immunosuppressed patients non-responding to a complete vaccination scheme

National Prospective Cohort
for Primary and Post-Exposure Prophylaxis by anti-SARS-CoV2 MAbs

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- **Co-PI:** Prs V Levy (Hématologie, Avicenne), G Blancho (Transplantation Rénale, Nantes), G Martin-Blondel (Infectiologie, Toulouse)
- **Promotion: APHP : URC : Avicenne** (ou Bichat)
- **Methodology : Equipe URC AVC**
- **Follow-up : monthtly:**
- **Biostatistics & data Analysis: F. Mentré (Equipe Inserm, Bichat).**
- ***Cohort "Sous l'égide de l'ANRS"***

Anti-Covid19 anti-SARS-CoV2 Mabs

TREATMENT TO PREVENT DISEASE

- **Cocktails recommended** (or broad spectrum)
- Efficacy :
  - in high risk outpatients : 50 - 75%
  - In seronegative hospitalized patients : 20%
- Good safety profile
- Indications :
  - Prevention of disease in outpatients:
    - < 5 days post-symptoms or post-infection
    - Non O2-dependent
    - Immune deficiency or other High risk factors or > 80y
  - Prevention of severe disease or death in hospitalized
    - Seronegative, O2 dependent (non invasive)

PROPHYLAXIS

- **Cocktails recommended** (or broad spectrum)
  - ½ life: 1 month : Caserivimab+Indevimab
    3 months : AZD7442
- Efficacy : Pre and Post-Exposure : about 75%
- Indications :
  - Currently :
    - PEP: Caserivimab+Indevimab SC or IV for Non and Weak Responders to Vaccines
    - PrEP : Caserivimab+Indevimab SC for Non Responders
  - Future?
    - PEP : Caserivimab+Indevimab SC ?
    - PrEP: AZD 7442 IM once a year (?)

➢ **FUTURE ? Respective indications of oral anti-viral drugs vs Mabs???**

Anti-SARS-CoV2 MabTher Reacting group:

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- Jeremie Guedj
- Nathan Pfeiffer-Smadja
- Florence Ader
- Bruno Hoen
- Alexandre Duvignaud
- Laurence Weiss
- Guillaume Martin-Blondel,
- Jacques-Eric Gottenberg,
- Olivier Saint-Lary,
- Odile Launay,