Montpellier, The Young Scientists Symposium
December 1, 2021

COVID-19 Treatment :
Current Therapeutic Drugs and Emerging Options

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(UMI 233 IRD, INSERM U1175, Université de Montpellier)

Recherches translationnelles sur l'infection à VIH et les Maladies infectieuses

Déclaration de potentiels liens d'intérêts : Jacques REYNES

- Consultant, ou membre d'un conseil scientifique, ou intervenant dans un symposium, ou ayant bénéficié d'un soutien pour un déplacement d'un laboratoire pharmaceutique:

  Gilead, Janssen, MSD, Pfizer, Theratechnologies, ViiV Healthcare

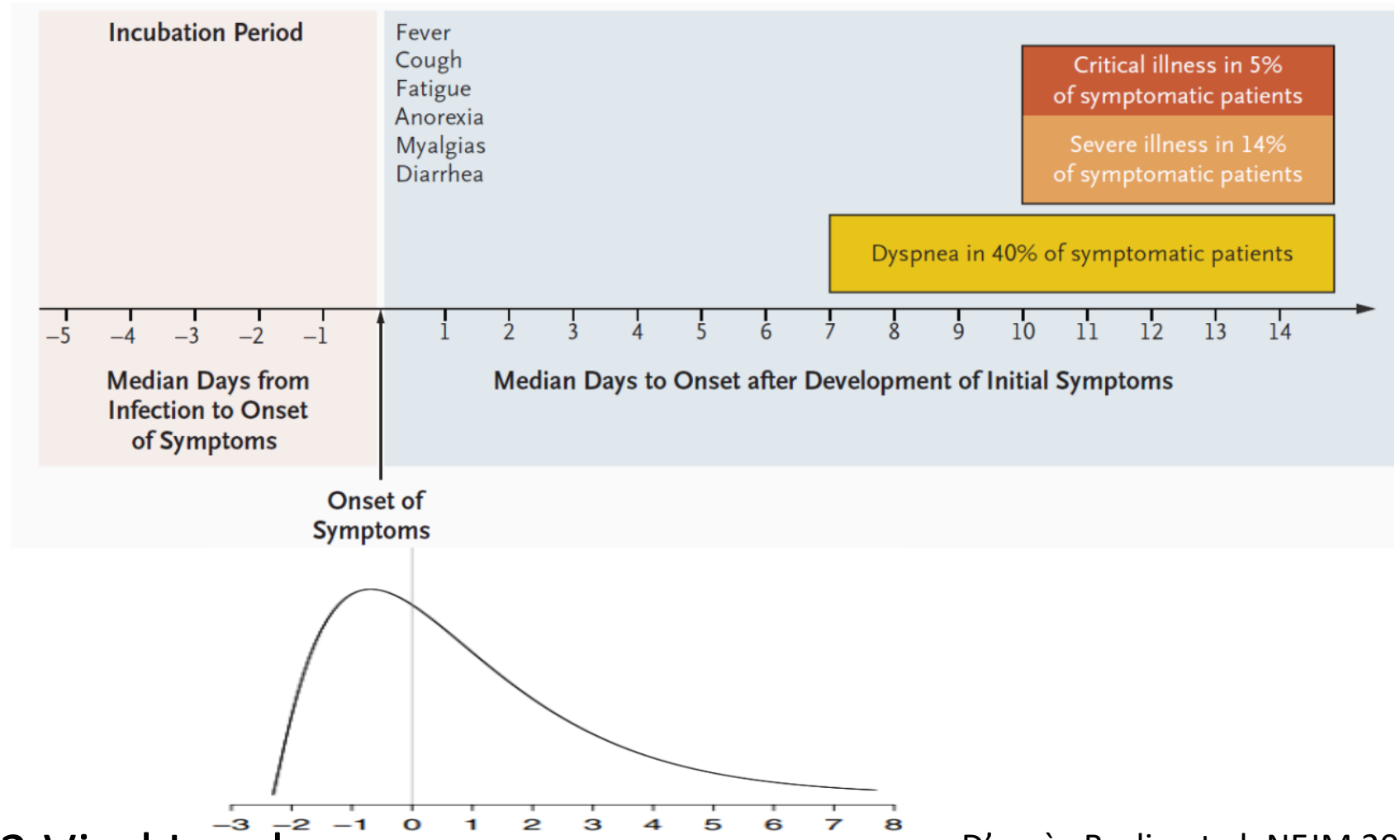
- Investigateur principal d'un essai de l'industrie pharmaceutique:

  Gilead, GSK-ViiV Healthcare, MSD

- Parts sociales ou actions dans un laboratoire pharmaceutique:

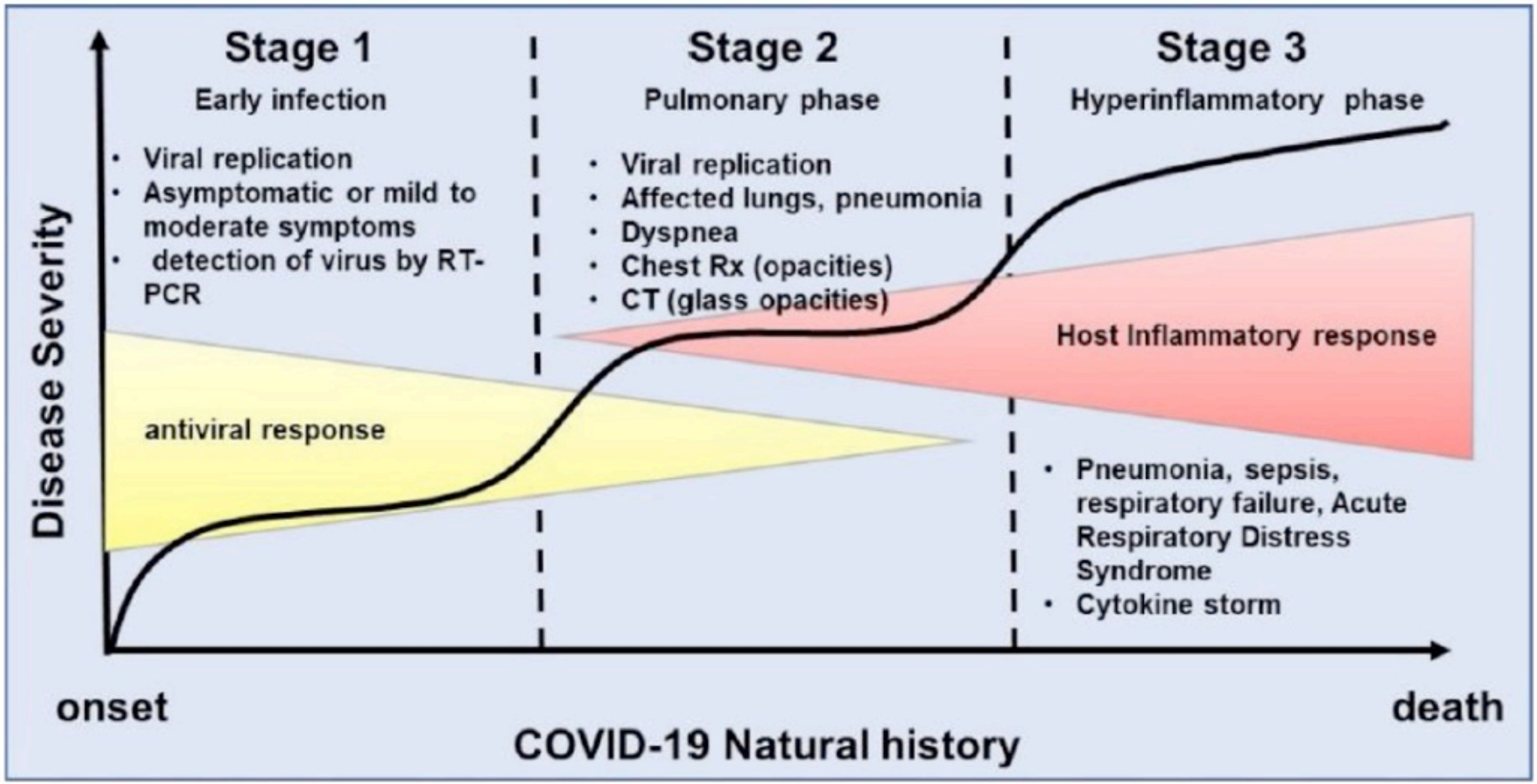
  Aucune

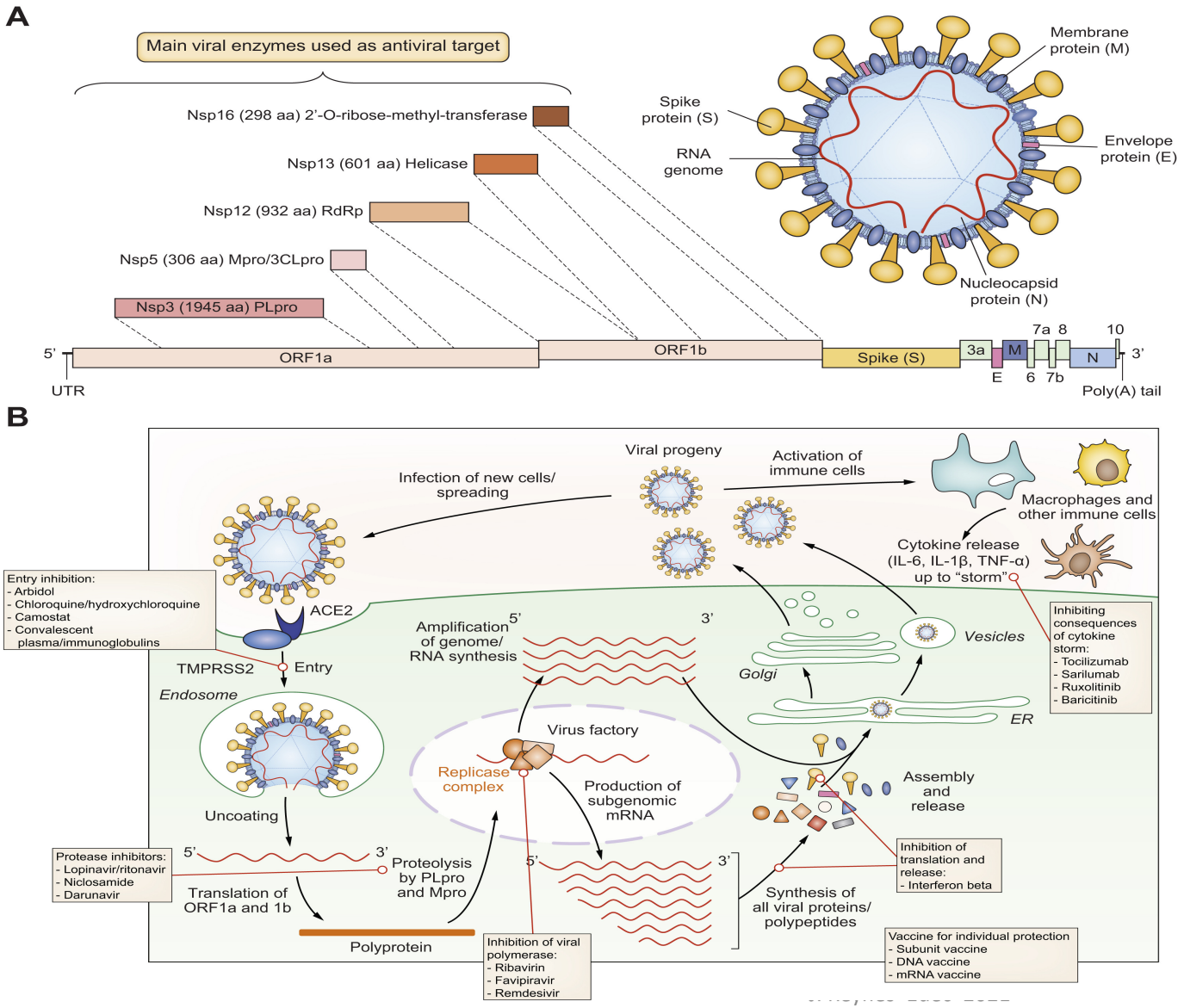
- Timeline of Symptoms of COVID-19



- SARS-CoV-2 Viral Load

D'après Berlin et al. NEJM 2020


Stage 1
Early infection
• Viral replication
• Asymptomatic or mild to moderate symptoms
• detection of virus by RT-PCR
Stage 2
Pulmonary phase
• Viral replication
• Affected lungs, pneumonia
• Dyspnea
• Chest Rx (opacities)
• CT (glass opacities)
Stage 3
Hyperinflammatory phase
Host Inflammatory response
antiviral response
• Pneumonia, sepsis, respiratory failure, Acute Respiratory Distress Syndrome
• Cytokine storm
Disease Severity
onset
death
COVID-19 Natural history



Virology,

replication cycle,

Targets for drug development

Asselah et al J Hepatol 2021

SARS-CoV-2 Antiviral Therapy

2 main sections:

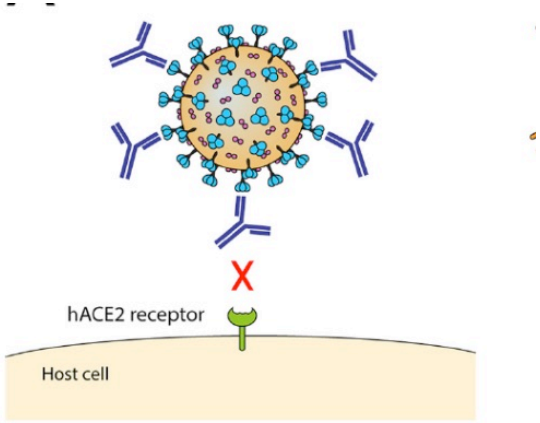
- Compounds that inhibit virus entry, including MABs

- Compounds that inhibit SARS-CoV-2 enzymes (polymerase, protease)

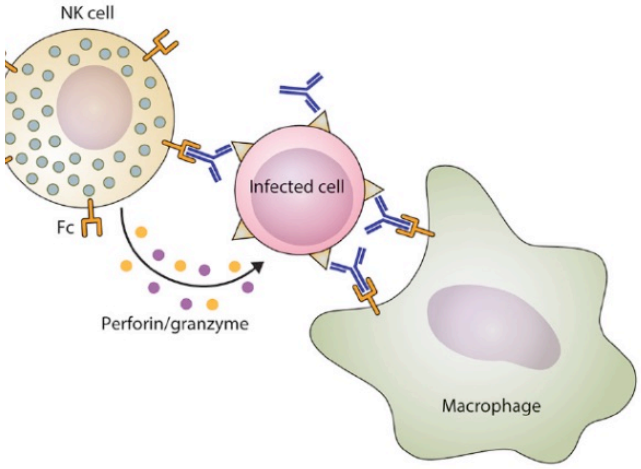
Monoclonal Antibodies (mAbs)

AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews®

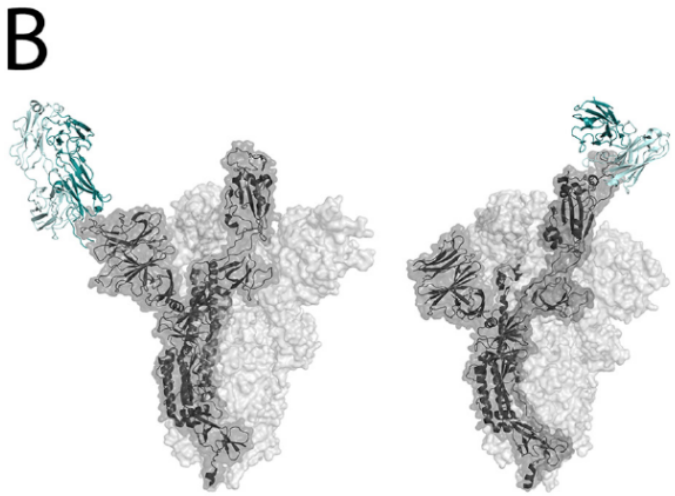
Tao et al. October 2021 Volume 34 Issue 4



Blocking entry into cells



Killing infected cells



NTD (left) and RBD (right) binding mAb Fabs comprising 2 heavy and light chains shown in cyan

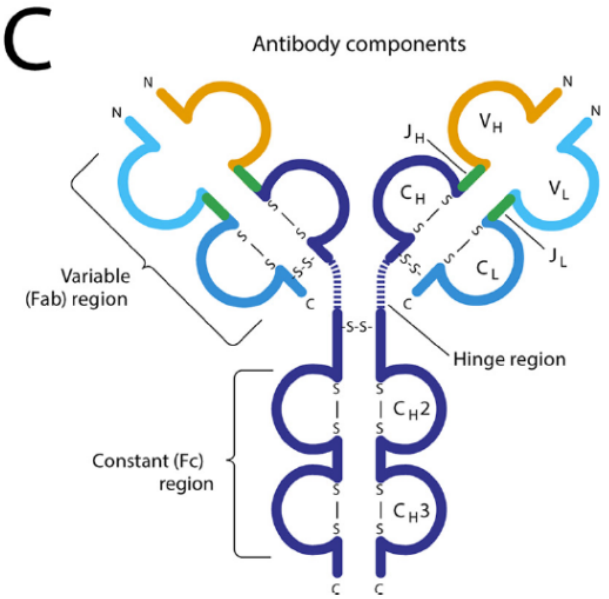
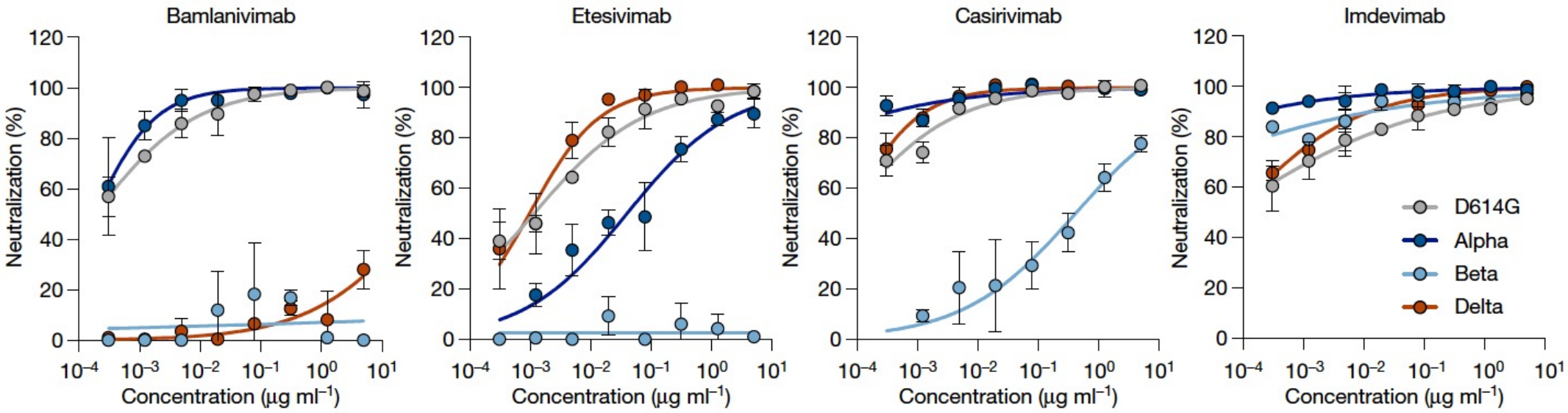


FIG 3 (A) MAbs function by directly binding to the SARS-CoV-2 spike protein to block binding to the human ACE2 receptor (neutralization) and by recruiting immune effector cells. (B) Most naturally arising SARS-CoV-2 spike antibodies and most MAbs target the receptor binding domain (RBD) while several target the N-terminal domain (NTD). (C) The MAb Fab domains are responsible for antigenic recognition whereas the Fc domains are responsible for immune effector functions. Fc-dependent recruitment of immune effector cells, including Ab-dependent cytotoxicity (ADCC) and Ab-dependent cellular phagocytosis (ADCP) may be particularly important for MAb actions against infected cells. The structures showing the RBD- and NTD-binding MAbs were obtained from entries 7K8T and 7C2L, respectively, and rendered using PyMOL.

Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization

LILLY

REGENERON/ROCHE



Beta et Delta résistants

X200 Alpha
Beta résistant

Beta résistant

Delphine Planas et al. Nature 2021

Anticorps monoclonaux

- **Bamlanivimab + Etesevimab** (Lilly)

ATU France Mars 2021, Interruption distribution en juin 2021 par Département Américain de la Santé pour inefficacité sur variant bêta (ex sud-africain) et gamma (ex brésilien), inefficacité de Bamlanivimab sur variant delata (B.1.617 ex indien). Lilly a retiré début novembre sa demande d'AMM

- **Casirivimab + Imdevimab** (REGEN-COV™, RONAPREVE*, Regeneron/Roche)

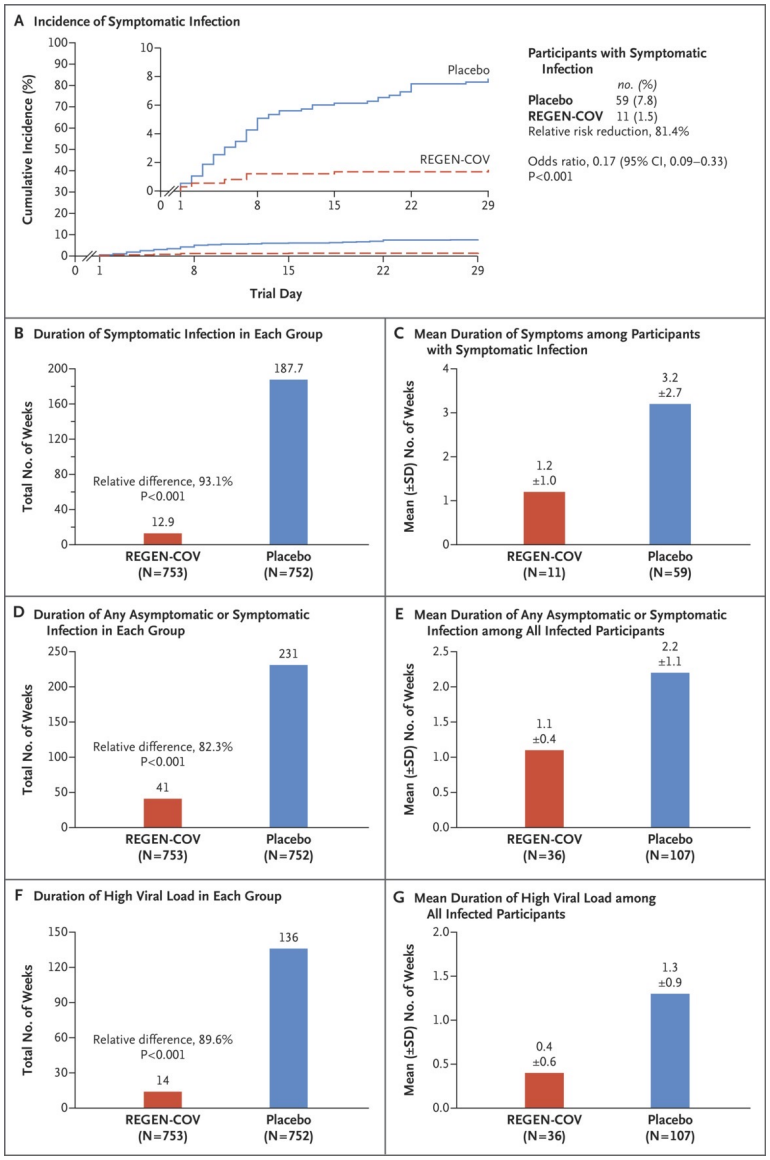
ANSM 15 mars 2021 accès tt phase précoce pour patient à risque de développer une forme grave; HAS 4 août autorisation en prophylaxie; ANSM 3 septembre élargissement aux hospitalisés nécessitant oxygénothérapie invasive et séronégatifs (immunodéprimés, risque lié à comorbidités et 80 ans et plus

- **Regdanvimab** (Regkirona*, Celltrion)

Avis favorable CMUH 12 nov 2021

- **Tixagevimab + Cilgavimab** (AZD7442, Evusheld*, AstraZeneca)
- **Sotrovimab** (ex-VIR-7831, Xevudy*, Vir Biotechnology/GSK)

Casirivimab + Imdevimab (REGEN-COV™, RONAPREVE*, Regeneron/Roche)



Original Article

Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19

N Engl J Med
Volume 385(13):1184-1195
September 23, 2021

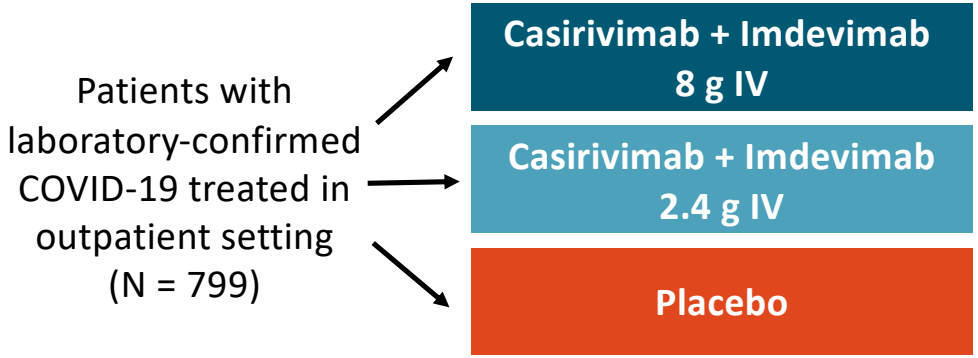
- Subcutaneous REGEN-COV (600 mg+ 600 mg) prevented symptomatic Covid-19 and asymptomatic SARS-CoV-2 infection in previously uninfected household contacts ($\leq 96\ h$) of infected persons.
- Among the participants who became infected, REGEN-COV reduced the duration of symptomatic disease and the duration of a high viral load.

Autorisation en accès précoce: préventif

Prévention de la COVID		
Prophylaxie *de l'infection à SARS-CoV-2 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*** *après un schéma vaccinal complet (au moins 3 doses) ET appartenant à l'un des* ***sous-groupes à très risque de forme sévère de COVID*** *(population définie par l'ANRS-Maladies Infectieuses Emergentes cf. tableau II)*		
Prophylaxie post-exposition chez les patients **non répondeurs[1] ou faiblement répondeurs[2]**	**Prophylaxie pré-exposition** chez les patients **non répondeurs[1]**	
Test RT-PCR négatif avant chaque administration		
1 dose unique	1 dose initiale	Dose répétée de maintenance toutes les 4 semaines
600 mg de casirivimab et 600 mg d'imdevimab administrés ensemble en une seule perfusion IV. En cas d'impossibilité d'utiliser la voie IV, injection SC consécutives possible (4 seringues)		**300 mg de casirivimab et 300 mg d'imdevimab par** perfusion administrés ensemble en une seule perfusion IV ou injection SC consécutives (2 seringues) toutes les 4 semaines.

Casirivimab + Imdevimab to Treat Nonhospitalized Patients With COVID-19

- Randomized, double-blind, placebo-controlled phase I-III trial[1-3]



- Interim analysis of phase I/II portion through September 4, 2020, included 275 patients[2]; updated phase II/III data released for 524 additional patients on October 28, 2020[3]

- Difference in average daily change in viral load through Day 7 with casirivimab + imdevimab vs placebo (n = 524)[3]
  - Patients with high viral load ($>10^7$ copies/mL): -0.68 $\log_{10}$ copies/mL (*P* <.0001)
  - All patients with detectable baseline virus: -0.36 $\log_{10}$ copies/mL (*P* = .0003)
- COVID-19–related medical visits reduced by 57% through Day 29 with casirivimab + imdevimab vs placebo (N = 799)[3]
  - 2.8% with casirivimab + imdevimab vs 6.5% with placebo (*P* = .024)

1. NCT04425629. 2. Weinreich. NEJM. 2021;384:238. 3. https://investor.regeneron.com/news-releases/news-release-details/regenerons-covid-19-outpatient-trial-prospectively-demonstrates/. Press release only, not peer reviewed.

Slide credit: clinicaloptions.com

This article was published on September 29, 2021, at NEJM.org.

The NEW ENGLAND JOURNAL of MEDICINE

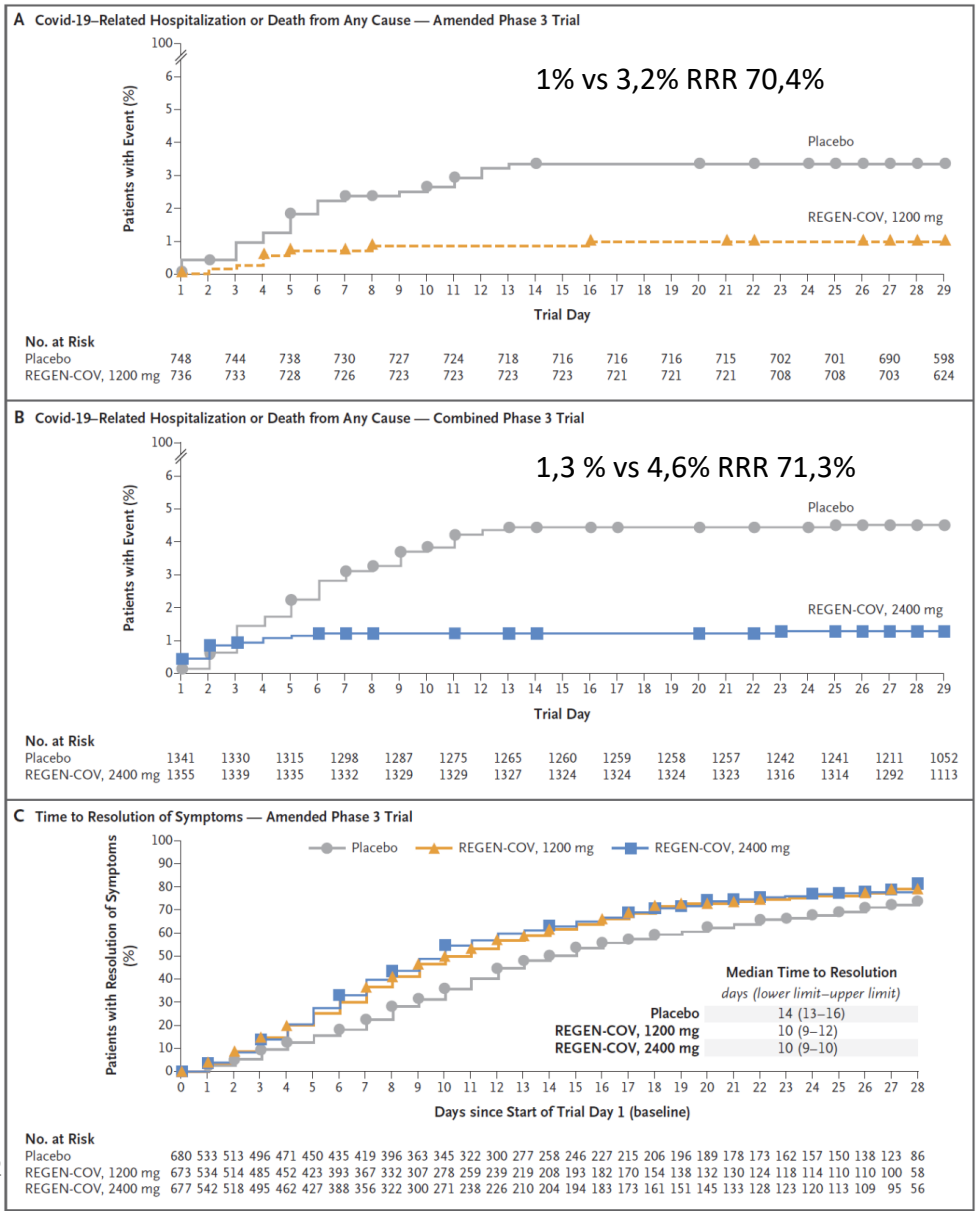
DOI: 10.1056/NEJMoa2108163

ORIGINAL ARTICLE

REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19

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

- Partie Phase 3, 4057 patients
- Patients non hospitalisés, avec facteur d'évolution vers forme grave, avec symptômes ≤ 7 jours
- Age médian 50 ans (IQR 38,59), 49% hommes
- Facteurs de risque:
  - Obésité: 58%
  - Age ≥ 50 ans : 52%
  - Maladie cardiovasculaire: 36 %
  - Maladie respiratoire, rénale, hépatique chronique : 16 %, 1%, 1%
  - Diabète: 15 %,
  - Immunodépression : 3 %,
- Sérologie COVID négative : 69%
- Durée symptômes à l'inclusion: médiane de 3j (IQR 2 - 5)



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This article was published on September 29, 2021, at NEJM.org.

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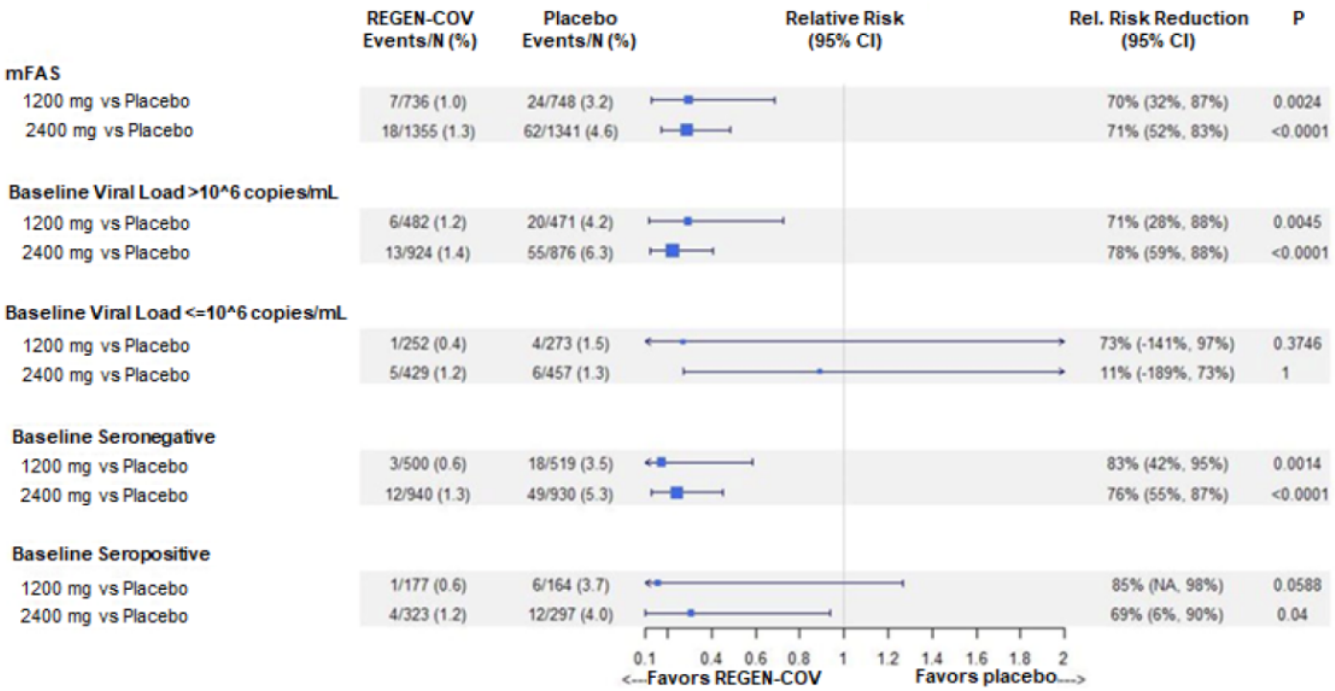
Figure S3. Forest Plots: COVID-19-related Hospitalization or All-Cause Death Through Day 29

A. Subgroups: Baseline viral load and serum antibody status



CI, confidence interval; mFAS, modified full analysis set.

Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

Running title: REGEN-COV for COVID-19

REGEN-COV 8g (casirivimab 4g + imdevimab 4g) vs usual care

Figure 2: Effect of allocation to REGEN−COV on 28−day mortality in: a) seronegative vs seropositive participants; and b) all participants

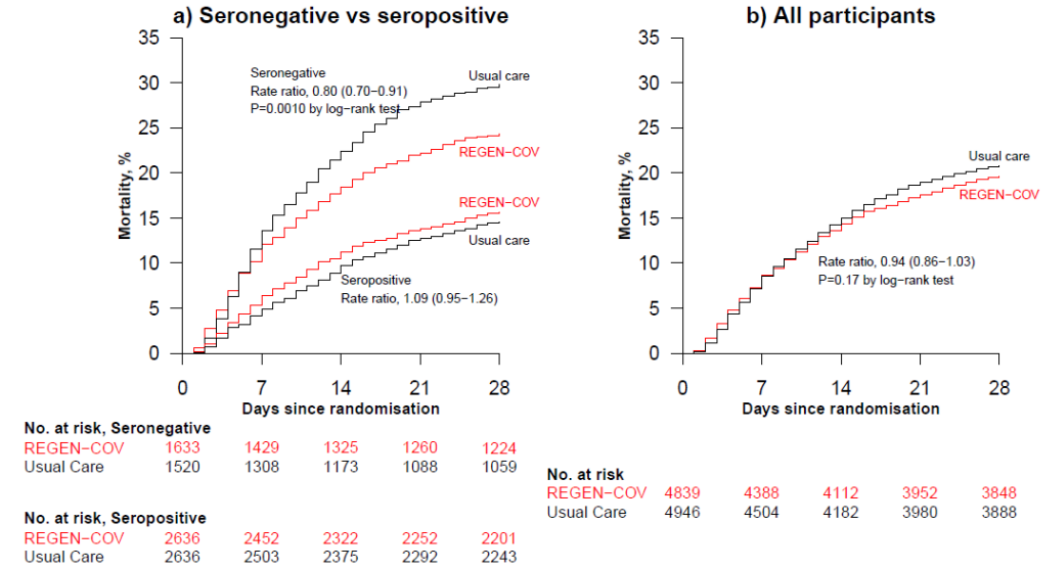


Table 2: Effect of allocation to REGEN-COV on key study outcomes among seronegative participants

	REGEN-COV (n=1633)	Usual Care (n=1520)	RR (95% CI)
Primary outcome			
Mortality at 28 days	396 (24%)	451 (30%)	0.80 (0.70-0.91)
Secondary outcomes			
Median duration of hospitalisation, days	13 (7 to >28)	17 (7 to >28)	-
Discharged from hospital within 28 days	1046 (64%)	878 (58%)	1.19 (1.08-1.30)
Invasive mechanical ventilation or death*	487/1599 (30%)	542/1484 (37%)	0.83 (0.75-0.92)
Invasive mechanical ventilation	189/1599 (12%)	200/1484 (13%)	0.88 (0.73-1.06)
Death	383/1599 (24%)	434/1484 (29%)	0.82 (0.73-0.92)

medRxiv preprint doi: https://doi.org/10.1101/2021.06.15.21258542; this version posted June 16, 2021

30 novembre 2021

Annexe : Tableau récapitulatif des posologies et voie d'administration de casirivimab et imdevimab

Dispositif	Indication		Posologie	
ATUc	**Traitement**	Patient ne nécessitant pas d'oxygénothérapie	Dose unique par perfusion IV après dilution	600 mg de Casirivimab Et 600 mg d'Imdevimab
		Patient hospitalisé avec IgG anti-Spike négatives, et nécessitant une oxygénothérapie non invasive	Dose unique par perfusion IV après dilution	4000 mg de Casirivimab Et 4000 mg d'Imdevimab
AAP	**Prophylaxie**	Pré-exposition	<u>Dose initiale</u> Perfusion IV après dilution ou SC	600 mg de Casirivimab Et 600 mg d'Imdevimab
			<u>Doses mensuelles subséquentes</u> Perfusion IV après dilution ou SC	300 mg de Casirivimab Et 300 mg d'Imdevimab
		Post-exposition	Dose unique Perfusion IV après dilution ou SC en cas d'impossibilité d'utiliser la voie IV	600 mg de Casirivimab Et 600 mg d'Imdevimab

- **Patients ne nécessitant pas d'oxygénothérapie du fait de la COVID-19** : le traitement doit être instauré dès que possible après l'obtention du test RT-PCR au SARS-CoV-2 positif et dans un délai maximum de 5 jours après le début des symptômes.
  OU
- **Patients hospitalisés du fait de la COVID-19 et séronégatifs** (IgG anti-Spike) :
  - nécessitant une oxygénothérapie non invasive conventionnelle du fait de la COVID-19 ou,
  - nécessitant une oxygénothérapie non invasive haut débit du fait de la COVID-19.
- Patients étant à risque élevé d'évolution vers une forme grave de la maladie à savoir les populations suivantes telles que définies par l'ANRS-Maladies Infectieuses Emergentes :

●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

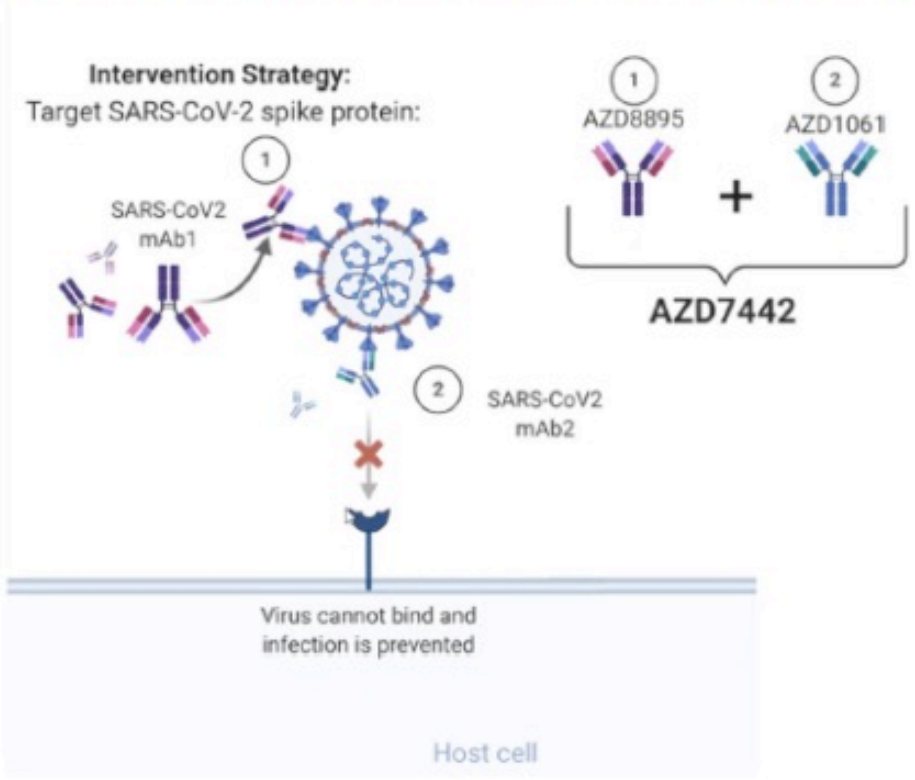
● Les patients à risque de complications :

-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 autoimmunes
-Myopathies avec capacité vitale forcée <70%
-Autres pathologies rares définies par les filières de santé maladies rares (FSMR)
-Trisomie 21

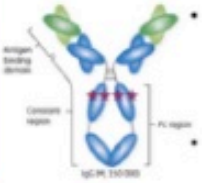
●Les patients de 80 ans et plus

Tixagevimab + Cilgavimab (AZD7442, Evusheld*, AstraZeneca)

AZD7442: a long-acting monoclonal antibody (LAAB) combination for prevention and treatment of COVID-19



Half-Life Extension



- Substitutions in Fc domain of IgGs can change FcRn recycling ('YTE')
- Increased half-life 4x (20 vs 70-100 days[1,2])

Fc Effector Knockout

- Antibody-dependent enhancement (ADE) of disease can be elicited by SARS-CoV/other CoV Abs
- L234F/L235E/P331S triple substitutions (TM) ablates effector function of antibodies[3]

[1]Mallory RM et al, Biologicals (2017)
[2]Robbie et al, AAC (2013)
[3]Oganesyan et al , ACDBC (2008)

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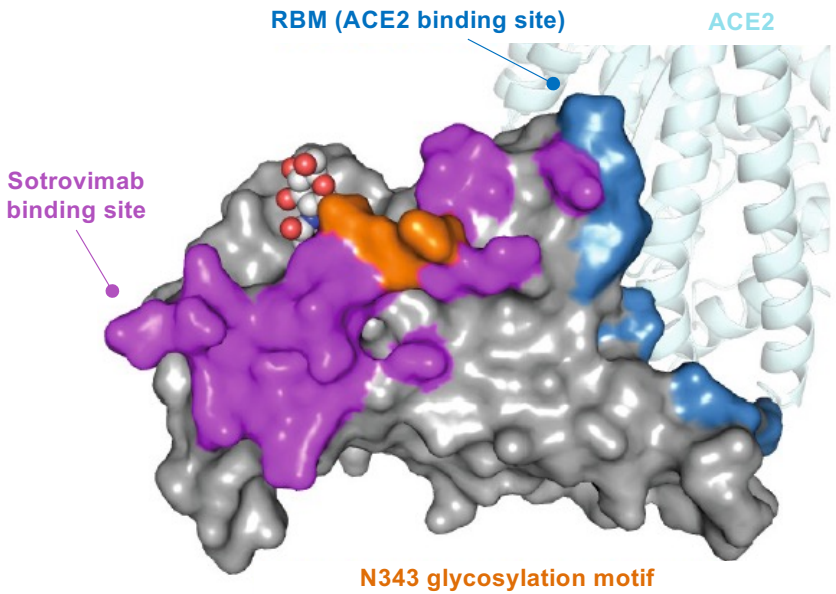
Sotrovimab (ex-VIR-7831, Xevudy*, Vir Biotechnology/GSK)

Sotrovimab, isolated from a survivor of SARS-CoV-1, has broad activity against sarbecoviruses



The illustration has been reproduced with the permission of Springer: Pinto D, et al. *Nature* 2020;583:290–5. Copyright © 2020

Sotrovimab binds to an epitope in the RBD near to, but not in, the RBM (ACE2 binding site)[1]

The RBM is poorly conserved between SARS-CoV-1 and SARS-CoV-2[2]

A mAb that binds to the RBM may have a higher chance of escape[1]

*Sotrovimab is based on parental mAb S309
ACE2, angiotensin-converting enzyme 2; mAb, monoclonal antibody; RBD, receptor binding domain; RBM, receptor binding motif; SARS, severe acute respiratory syndrome; SARS-CoV-1, severe acute respiratory syndrome coronavirus 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

1. Pinto D, et al. *Nature* 2020;583:290–5; 2. Jaimes JA, et al. *J Mol Biol* 2020;432:3309–25

RESEARCH SUMMARY

Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab

Gupta A et al. DOI: 10.1056/NEJMoa2107934

CLINICAL PROBLEM

Highly effective treatments are needed for Covid-19 in patients at increased risk for severe disease. Sotrovimab is an engineered human monoclonal antibody that neutralizes SARS-CoV-2 and numerous other sarbecoviruses in vitro. However, its effects on clinical outcomes in high-risk outpatients with Covid-19 are unknown.

CLINICAL TRIAL

Design: A phase 3, multinational, randomized, double-blind, placebo-controlled trial examined the efficacy and safety of sotrovimab in high-risk outpatients with mild-to-moderate Covid-19.

Intervention: 868 ambulatory patients with Covid-19 and symptom onset within the previous 5 days were randomly assigned to receive a single 1-hour intravenous infusion of sotrovimab (500 mg) or saline placebo. Patients were at high risk for disease progression because they were ≥55 years of age or they had conditions such as diabetes for which medication was warranted, obesity, or chronic kidney disease. The primary outcome was hospitalization (for >24 hours) for any cause or death through day 29.

RESULTS

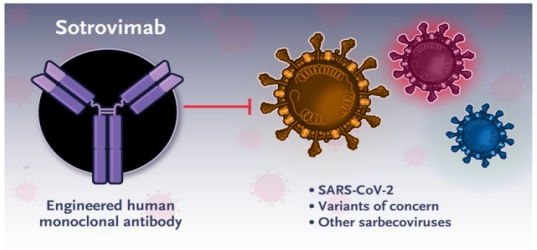
Efficacy: In a prespecified interim analysis involving 583 patients who underwent randomization through mid-January 2021, those assigned to sotrovimab were significantly less likely to have a primary-outcome event than those assigned to placebo. The benefit was attributed to a reduction in hospitalization.

Safety: No safety signals were identified.

LIMITATIONS AND REMAINING QUESTIONS

- Just three patients in the sotrovimab group were hospitalized; accordingly, patient or disease characteristics associated with treatment failure are unknown.
- Rare adverse events may not have been observed given the modest size of the safety analysis population.
- Sotrovimab has in vitro activity against SARS-CoV-2 variants of concern; whether this will translate into treatment efficacy as the virus continues to evolve is unknown.

Links: Full Article | NEJM Quick Take



Primary Outcome: Hospitalization for >24 Hours or Death

Outcome	Sotrovimab N=291	Placebo N=292
Hospitalization for any cause through day 29	3	21
Death from any cause through day 29	0	1

Adverse Events (Safety Analysis Population)

Event	Sotrovimab N=430	Placebo N=438
Any adverse event	73	85
Any serious adverse event	7	26
Any infusion-related reaction	6	5

CONCLUSIONS

Among high-risk outpatients with mild-to-moderate Covid-19, a single infusion of the monoclonal antibody sotrovimab lowered the risk of disease progression without an increase in adverse events.

Gupta A et al. N Engl J Med 2021;385:1941-1950 (Published on October 27, 2021)

Sotrovimab (500 mg IV): essai de phase 3 COMET-ICE

- Patients non hospitalisés symptomatiques (≤ 5 jours)
- Réduction significative (RR 85%, p = 0,002) *vs* placebo (1% vs 7%) du risque d'hospitalisation ou décès à J29 chez les **patients adultes à haut risque souffrant de la COVID-19 légère à modérée**.
- Résultats finaux RRR 79%

- **Evaluation de l'administration IM** dans le traitement des **formes légères à modérées (**≤ 7 jours): Press Release 12 nov 2021

Essai COMET-TAIL 500 mg IV vs 500 mg Im vs 250 mg IM

- Arrêt bras 250 mg IM (comité indépendant)
- Hospit ou décès: 500 mg IV: 2,7% vs 500 mg IM: 1,3%

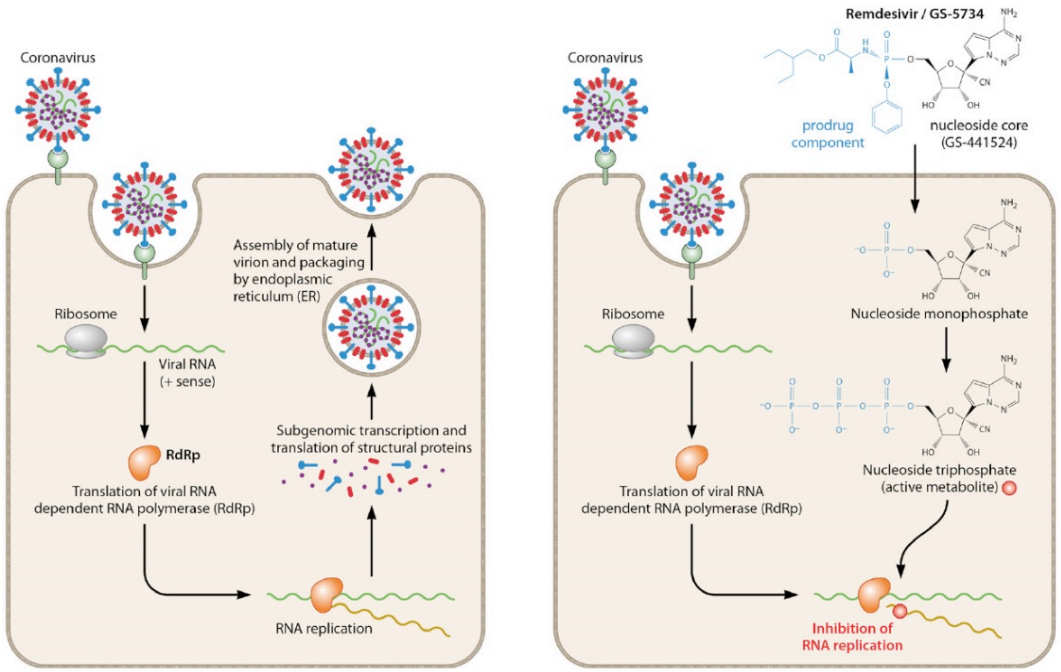
(différence ajustée 1,07% < marge non infériorité de 3,5%)

J. Reynes 1dec 2021

Antiviraux

- Remdésivir (Veklury*, Gilead)
- Molnupiravir (Lagevrio*, MSD)
- PF-07321332 (Paxlovid*, Pfizer)

Mécanismes d'action
Remdésivir et Molnupiravir



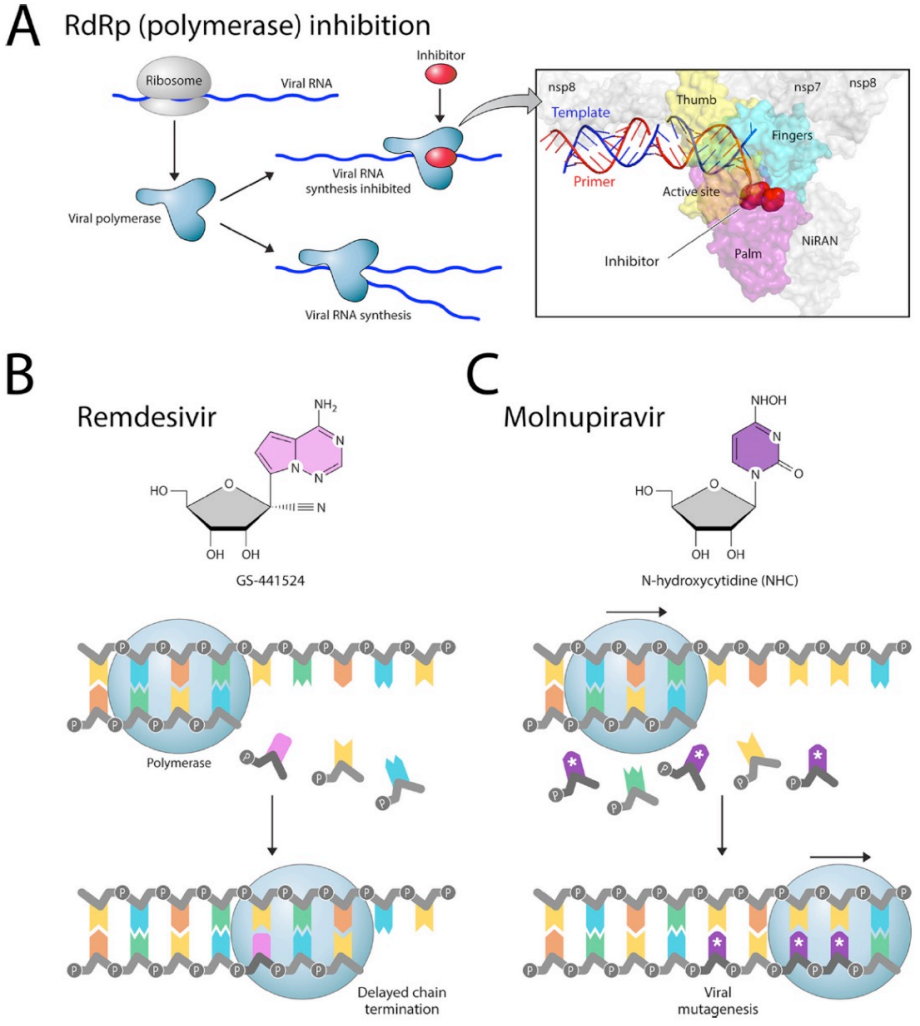


FIG 1 RNA-dependent RNA polymerase (RdRp) inhibition. (A) Coronavirus RdRp enzymes catalyze genome copying and the transcription of multiple subgenomic RNAs. The RdRp-associated replication-transcription complex contains two accessory proteins (nsp7 and nsp8) and an exonuclease (not shown). (B) Remdesivir is a prodrug of GS-441524 which inhibits RdRp by causing delayed chain termination. (C) Molnupiravir is a prodrug of *N*-hydroxycytidine, which causes lethal viral mutagenesis.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

This article was published on May 22, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2007764

Remdesivir for the Treatment of Covid-19 — Preliminary Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

METHODS

We conducted a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults hospitalized with Covid-19 with evidence of lower respiratory tract involvement. Patients were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only.

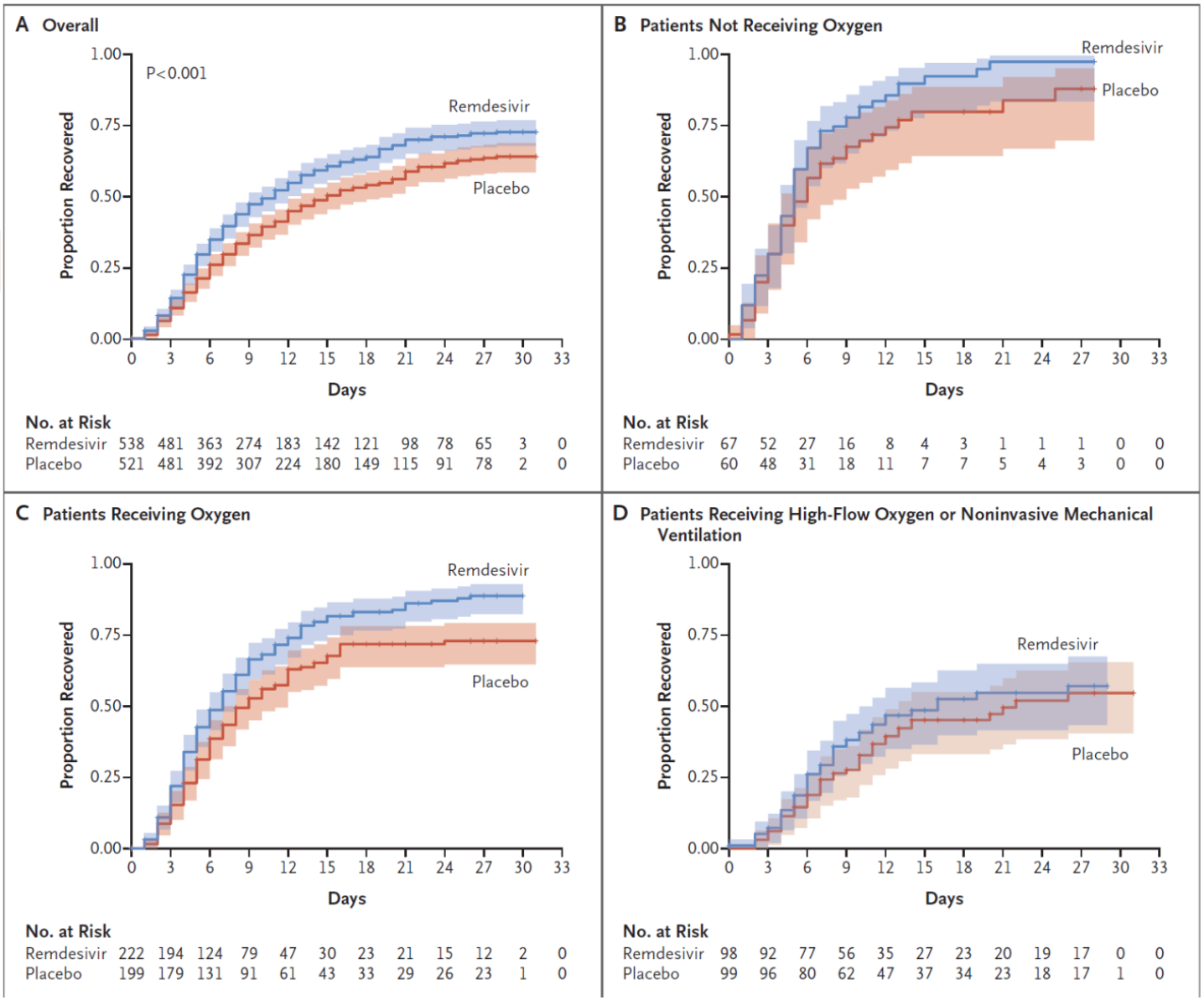
RESULTS

A total of 1063 patients underwent randomization. The data and safety monitoring board recommended early unblinding of the results on the basis of findings from an analysis that showed shortened time to recovery in the remdesivir group. Preliminary results from the 1059 patients (538 assigned to remdesivir and 521 to placebo) with data available after randomization indicated that those who received remdesivir had a median recovery time of 11 days (95% confidence interval [CI], 9 to 12), as compared with 15 days (95% CI, 13 to 19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; P<0.001). The Kaplan-Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04). Serious adverse events were reported for 114 of the 541 patients in the remdesivir group who underwent randomization (21.1%) and 141 of the 522 patients in the placebo group who underwent randomization (27.0%).

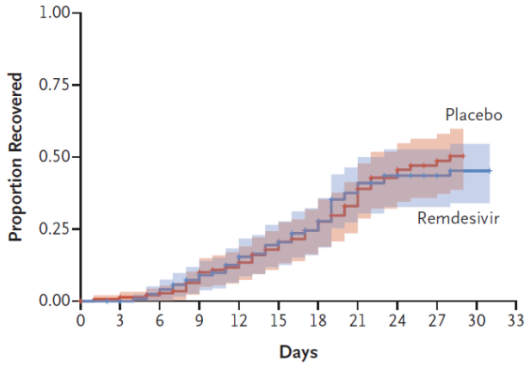
CONCLUSIONS

Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with Covid-19 and evidence of lower respiratory tract infection. (Funded by the National Institute of Allergy and Infectious Diseases and others; ACTT-1 ClinicalTrials.gov number, NCT04280705.)

Figure 2 (facing page). Kaplan–Meier Estimates of Cumulative Recoveries.



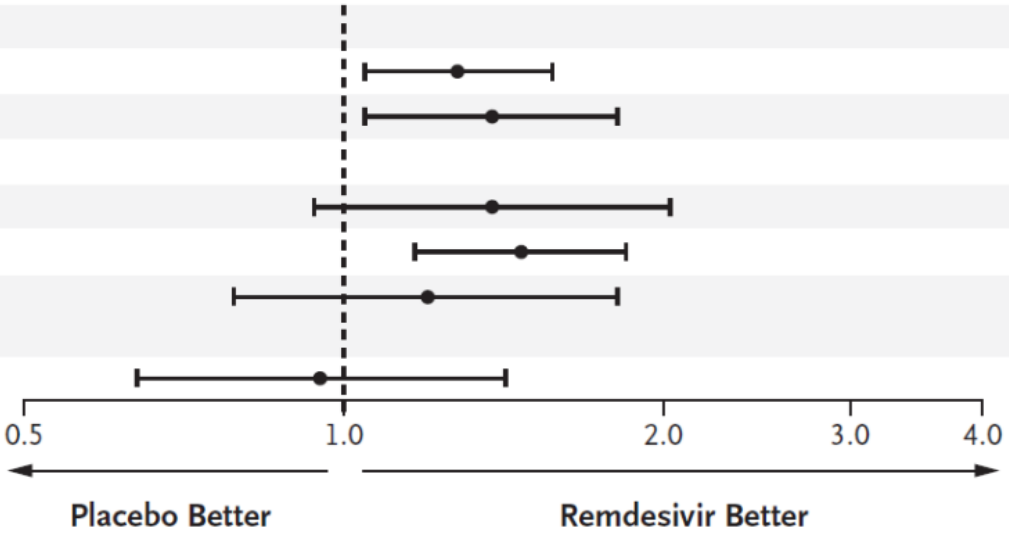
E Patients Receiving Mechanical Ventilation or ECMO



No. at Risk

Remdesivir	125	124	120	111	91	80	71	55	42	34	1	0
Placebo	147	145	141	127	102	91	73	56	41	33	0	0

Subgroup	No. of Patients	Recovery Rate Ratio (95% CI)
Symptoms duration		
≤10 days	664	1.28 (1.05–1.57)
>10 days	380	1.38 (1.05–1.81)
Baseline ordinal score		
4 (not receiving oxygen)	127	1.38 (0.94–2.03)
5 (receiving oxygen)	421	1.47 (1.17–1.84)
6 (receiving high-flow oxygen or noninvasive mechanical ventilation)	197	1.20 (0.79–1.81)
7 (receiving mechanical ventilation or ECMO)	272	0.95 (0.64–1.42)

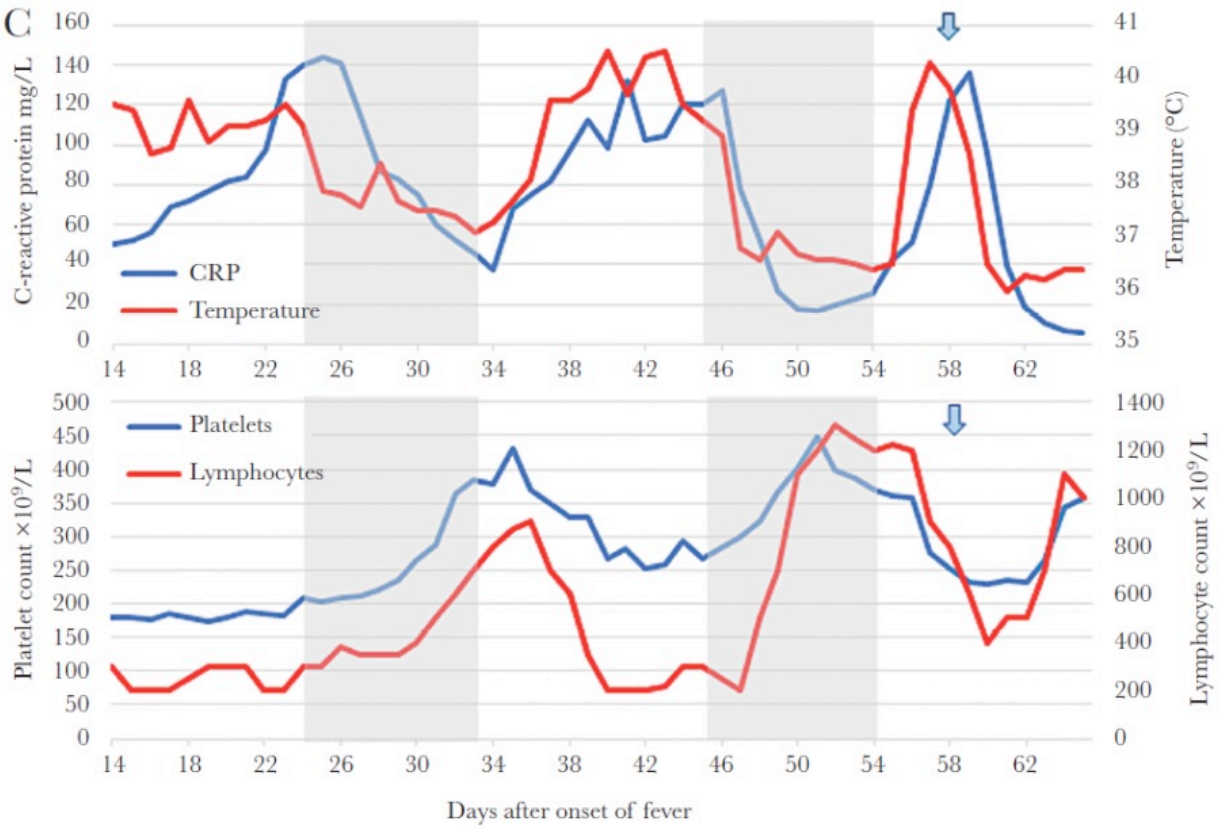


The Journal of Infectious Diseases

BRIEF REPORT

Persistent COVID-19 in an Immunocompromised Patient Temporarily Responsive to Two Courses of Remdesivir Therapy

Marie Helleberg,[1] Carsten Utoft Niemann,[2] Kasper Sommerlund Moestrup,[1] Ole Kirk,[1] Anne-Mette Lebech,[1] Clifford Lane,[3] and Jens Lundgren[1]



Received 8 June 2020; editorial decision 14 July 2020; accepted 17 July 2020; published online July 23, 2020.

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J. Reynes 1dec 2021

Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial

Florence Ader, Maude Bouscambert-Duchamp, Maya Hites, Nathan Peiffer-Smadja, Julien Poissy, Drifa Belhadi, Alpha Diallo, Minh-Patrick Lê, Gilles Peytavin, Thérèse Staub, Richard Greil, Jérémie Guedj, Jose-Artur Paiva, Dominique Costagliola, Yazdan Yazdanpanah, Charles Burdet, France Mentré*, and the DisCoVeRy Study Group*

In this randomised controlled trial, the use of remdesivir for the treatment of hospitalised patients with COVID-19 was **not associated with clinical improvement at day 15 or day 29, nor with a reduction in mortality, nor with a reduction in SARS-CoV-2 RNA**

Together with previous evidence, results from the DisCoVeRy trial **do not support the use of remdesivir in hospitalised patients with COVID-19 in a population with symptoms for more than a week and requiring oxygen support**

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Journal of Antimicrobial Chemotherapy

Impact of remdesivir according to the pre-admission symptom duration in patients with COVID-19

Carolina Garcia-Vidal[1]†, Rodrigo Alonso[1]†, Ana M. Camon[1], Celia Cardozo[1], Laia Albiach[1], Daiana Agüero[1], M. Angeles Marcos[2,3], Juan Ambrosioni[1], Marta Bodro[1], Mariana Chumbita[1], Lorena de la Mora[1], Nicole Garcia-Pouton[1], Gerard Dueñas[1], Marta Hernandez-Meneses[1], Alexy Inciarte[1], Genoveva Cuesta[2,3], Fernanda Meira[1], Laura Morata[1], Pedro Puerta-Alcalde[1], Sabina Herrera[1], Montse Tuset[4], Pedro Castro[5], Sergio Prieto-Gonzalez[6], Alex Almuedo-Riera[3,7], Josep Mensa[1], José Antonio Martínez[1], Gemma Sanjuan[1,8], J. M. Nicolas[5], A. del Rio[1], José Muñoz[3,7], Jordi Vila[2,3], Felipe Garcia[1] and Alex Soriano[1]* on behalf of the Hospital Clinic of Barcelona COVID-19 Research Group‡

Table 2. Independent predictors associated with 30 day mortality

Variable	OR (95% CI)	*P*
Age >66 years	8.763 (5.232–14.676)	0.001
Chronic renal failure	2.442 (1.622–3.677)	0.001
Pre-admission duration of symptoms		
>6 days	1	–
4–6 days	1.588 (1.042–2.422)	0.031
≤3 days	2.587 (1.722–3.887)	0.001
Oxygen saturation ≤94%	1.631 (1.108–2.398)	0.013
Respiratory rate >21 bpm	3.068 (2.080–4.525)	0.001
Mechanical ventilation	1.820 (1.170–2.829)	0.008
Creatinine >0.92 mg/dL	1.803 (1.208–2.693)	0.004
Lymphocyte count ≤800 cells/mm^3	1.650 (1.156–2.358)	0.006
C-reactive protein >7.52 mg/dL	1.956 (1.353–2.828)	0.001
Remdesivir	0.382 (0.218–0.671)	0.001

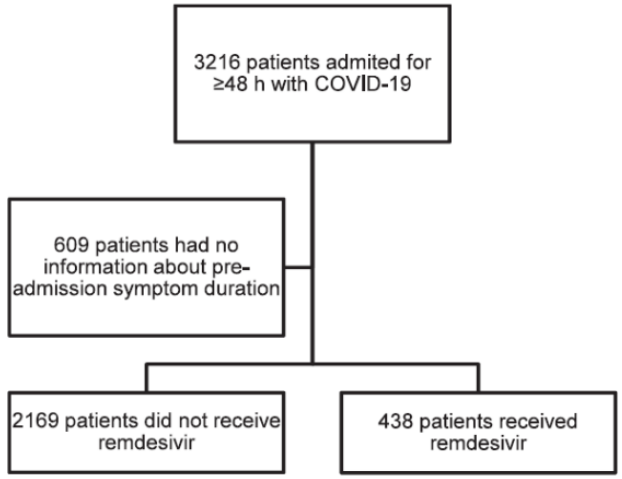

Figure 1. Flowchart of the population selected for the analysis.

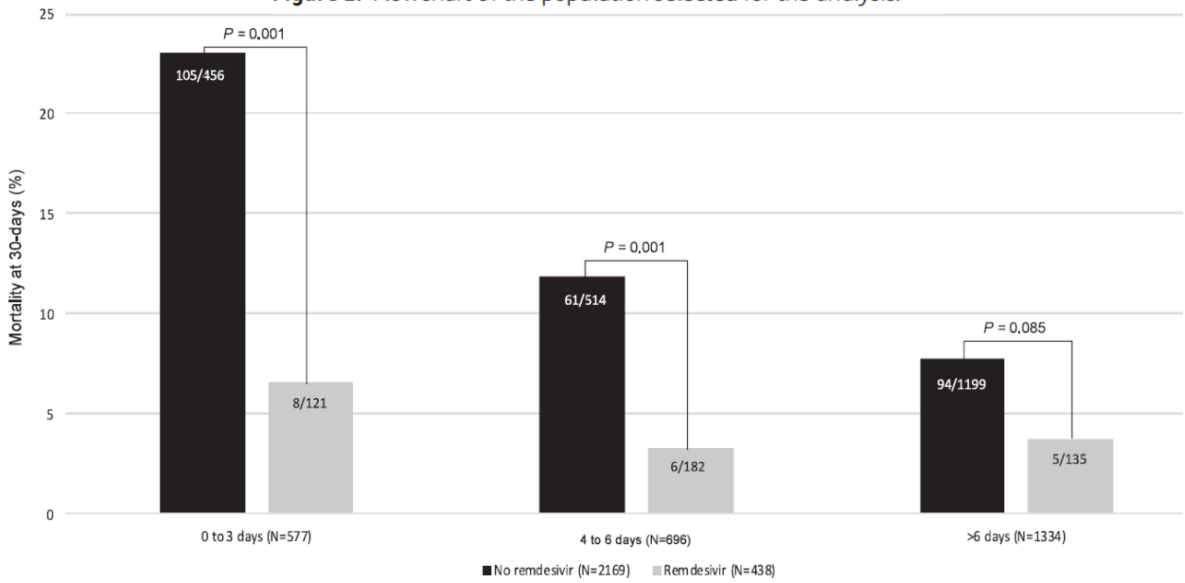

Figure 2. Mortality rate at 30 days by remdesivir treatment and the pre-test duration of symptoms (proportion comparisons using χ^2 test).

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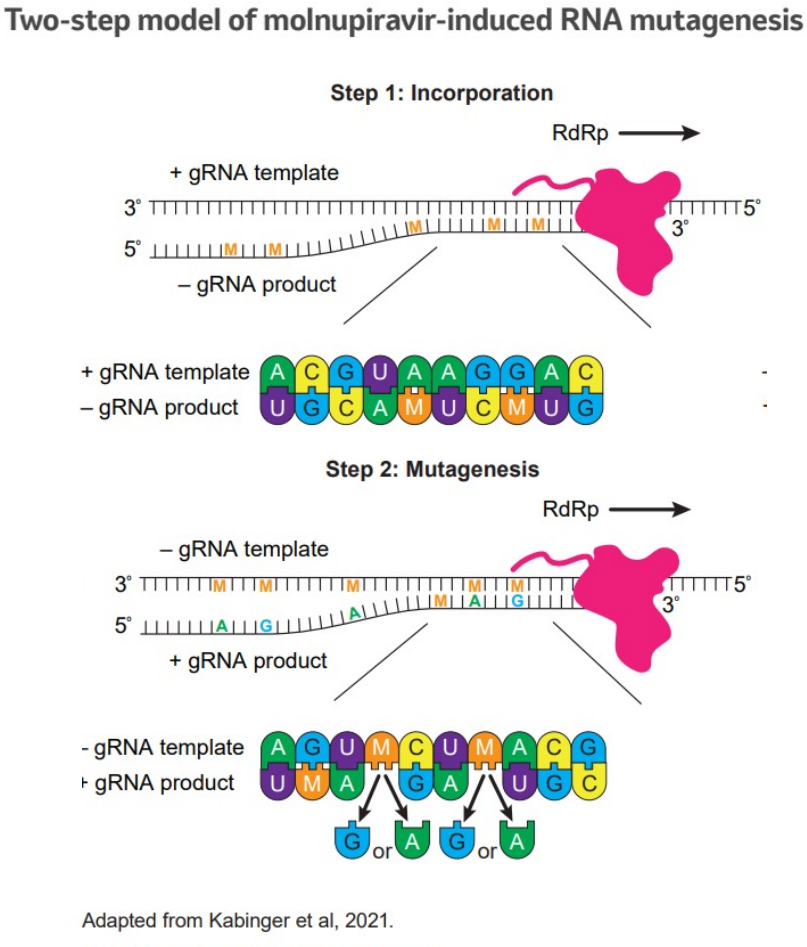
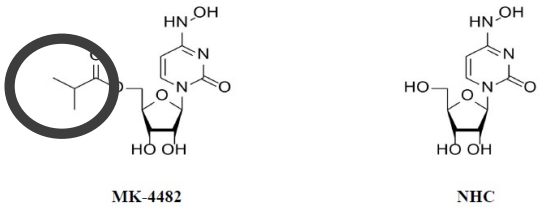
Molnupiravir (MK-4482, ex-EIDD-2801, Lagevrio*, MSD)

Molnupiravir
Mécanisme d'action



Adapted from Kabinger et al, 2021.

Prodrogue de l'analogue ribonucléosidique EIDD-1931
(NHC = β-D-N^4-hydroxycytidine)



MOV → NHC → NHC-TP (forme active dans cellules)

Antiviral oral à large spectre agissant contre :

- 3 CoV transmis à l'homme : SARS-CoV-1, MERS-CoV, SARS-CoV-2
- Autres virus à ARN (grippe, Ebola, Zika, Dengue, Chikungunya, EEV…)

Mécanisme d'action

- **Inhibition de l'ARN polymérase** en mimant les ribonucléosides de l'ARN (C ou U) et entraînant des erreurs dans la réplication de l'ARN viral
- **Ne cible pas la protéine spike**

Sheahan TP, et al. Sci Transl Med. 2020;12(541).

Molnupiravir maintains antiviral activity against SARS-CoV-2 variants in vitro and in early clinical studies

Jay A Grobler[1]; Julie Strizki[1]; Nicholas Murgolo[1]; Wei Gao[1]; Youfang Cao[1]; Ying Zhang[1]; Jiejun Du[1]; Manoj Nair[2]; Yaoxing Huang[2]; Yang Luo[2]; Daria Hazuda[1]; David Ho[2]

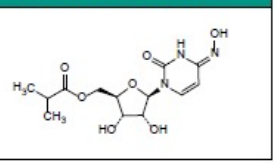
[1]Merck & Co., Inc., Kenilworth, NJ, USA; [2]Aaron Diamond AIDS Research Center, Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA

Background

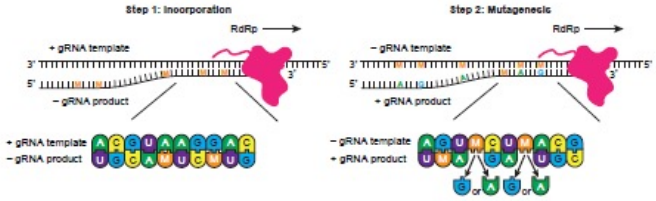
Molnupiravir (MK-4482): Summary of characteristics

- Molnupiravir (MOV, MK-4482) is an orally administered prodrug of the nucleoside N-hydroxycytidine (NHC)
- NHC has broad antiviral activity against a range of RNA viruses, including severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative virus of coronavirus infectious disease 2019 (COVID-19)[1-4]
- NHC-TP acts by a mechanism known as viral error catastrophe. NHC-TP incorporation into the viral RNA by the viral polymerase results in an accumulation of errors in the SARS-CoV-2 genome, leading to inhibition of replication[5]
- NHC has potent antiviral activity against SARS-CoV-2[3]
  - Active against remdesivir-resistant coronavirus variants[6,7]
- High barrier to the development of antiviral resistance[6,8]
- Scalable manufacturing process[9]
- Merck is conducting a Phase 2/3 trial to study the efficacy and safety of molnupiravir for the treatment of non-hospitalized patients with COVID-19 with symptom duration ≤5 days and at least one risk factor for progression to severe disease (NCT04575597)

Molnupiravir
(MK-4482, formerly EIDD-2801), an investigational oral prodrug of the ribonucleoside analog NHC



Two-step model of molnupiravir-induced RNA mutagenesis



Adapted from Kabinger et al, 2021.

- NHC-TP acts by inducing viral error catastrophe. NHC-TP is a competitive alternative substrate for the viral RNA polymerase. Due to its ability to pair with either guanosine or adenosine, NHC-TP can substitute for either cytidine triphosphate (CTP) or uridine triphosphate (UTP), respectively, for incorporation into nascent viral RNA. When present in a template strand, NHC directs incorporation of either guanosine or adenosine leading to accumulation of mutations in the viral RNA that results in inhibition of replication

Objective

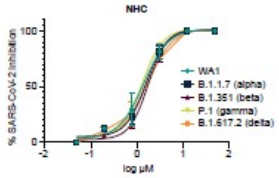
We characterized MOV activity against variants by assessing antiviral activity in vitro and virologic response from the Phase 2 clinical trial (MOVe-IN) and the Phase 2 portion of the Phase 2/3 clinical trial (MOVe-OUT) for treatment of COVID-19.

Methods

- Within the clinical trials, participants were randomized 1:1:1:1 to receive molnupiravir 200 mg, 400 mg, or 800 mg, or placebo twice daily for 5 days, stratified by time since sign/symptom onset (TSSO) and being at increased risk for severe illness from COVID-19
  - 304 adults requiring in-hospital treatment for COVID-19 and symptom onset ≤10 days were randomized to the MOVe-IN clinical trial
  - 302 adults with mild/moderate COVID-19 and symptom onset ≤7 days were randomized to the Phase 2 portion of the MOVe-OUT clinical trial
- Antiviral potency of NHC (β-D-N^4-hydroxycytidine) (IC_{50}) against several SARS-CoV-2 variants was determined in Vero E6 cells infected with virus at MOI ~0.1 by monitoring cytopathic effect (CPE)
- Sequences of SARS-CoV-2 from study participants were amplified from nasopharyngeal swabs by PCR, and next-generation sequencing (NGS) was performed on samples with viral genome RNA of >22,000 copies/mL amplified by primers covering full-length genome with Ion Torrent sequencing to identify clades represented in trial participants
- Longitudinal SARS-CoV-2 RNA viral load from nasopharyngeal swabs in participants enrolled in MOVe-IN and MOVe-OUT was analyzed based on SARS-CoV-2 genotype
- SARS-CoV-2 clades were assigned using clade.nextstrain.org

Results

Figure 1. NHC is equally active against variants of concern



	NHC IC_{50} (μM)				
	WA1 (US A)	B.1.1.7 (alpha)	B.1.351 (beta)	P.1 (gamma)	B.1.617.2 (delta)
	1.41	1.59	1.77	1.32	1.68

Figure 2. Current circulating SARS-CoV-2 clades are represented in molnupiravir clinical participants

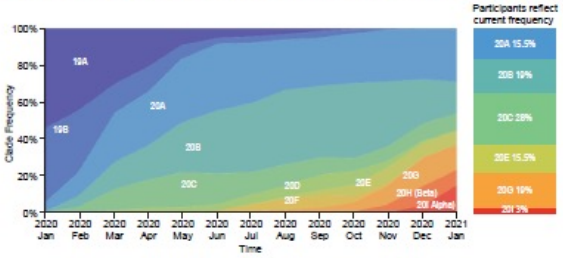
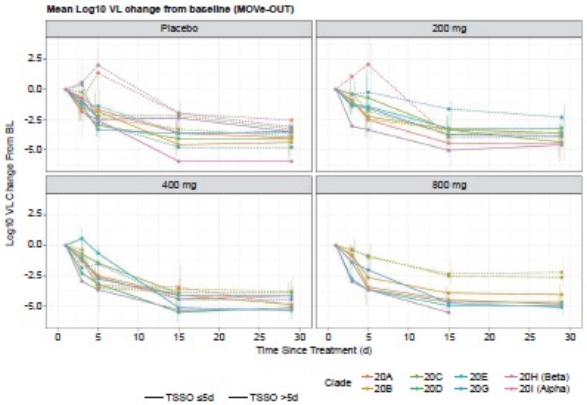


Figure 3. Virologic response is greater in participants with time since symptom onset ≤5 days

Virologic response by clade and TSSO



- Combined modeling data from MOVe-IN and MOVe-OUT support the selection of molnupiravir 800 mg every 12h as the optimum dose for further evaluation in the phase 3 component of MOVe-OUT

Conclusions

- Distribution of clades in participants in MOVe-IN and MOVe-OUT was representative of those circulating globally at the time of collection (Oct 2020–Jan 2021)
- Both in vitro and clinical data suggest that spike protein substitutions do not impact antiviral activity of MOV and suggest molnupiravir's potential for the treatment of SARS-CoV-2 variants, particularly when initiated early in the course of illness

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Presented at IDWeek 2021; September 29-October 3, 2021.

J. Reynes 1dec 2021

Efficacité MOV démontrée sur l'ARN viral et les particules virales infectieuses

Différents modèles animaux pertinents évalués

Modèle animal et référence de l'étude / Moment d'initiation du traitement (BID)	Pré-infection (-12h)	Au moment de l'infection (-1h et T0)	Post-infection				Inhibition de la transmission virale
			+12h	+24h	+36h	+48h	
Souris humanisée - *Wahl, A. et al. Nature 2021* SARS-CoV-2 infection is effectively treated and prevented by EIDD-2801	+			+		+	
Furet - *Cox RM, et al. Nat Microbiol. 2020* Therapeutically administered ribonucleoside analogue MK-4482/EIDD-2801 blocks SARS-CoV-2 transmission in ferrets			+		+		+
Hamster syrien - *Abdelnabi, R. et al. bioRxiv preprint 2021* Molnupiravir (EIDD-2801) inhibits SARS-CoV-2 replication and enhances the efficacy of favipiravir in a Syrian hamster infection model		+		+			

Molnupiravir (Lagevrio*, MSD)

- Modèle animal (furet): réduction de la charge virale et arrêt de la transmission dans les 24h[1]
  - **Réduction significative (p<0,001) de la charge virale** dans les voies aériennes supérieures **12h après administration du traitement** quelle que soit la dose administrée
  - Indétectabilité des particules infectieuses **24 à 36h après le début du traitement**
- Données virologiques évaluées chez des patients ambulatoires (phase 2a)[2]
- N = 202, < 7 jours début des symptômes
- *Culture virale*
  - J5: absence de virus infectieux (0/53) détecté chez les patients traités (MOV 800 mg BID) vs 11,1% (6/54) placebo; p = 0,03

Charge virale

- Clairance virale (médiane en jours): 14 jours (MOV 800 mg BID) vs 27 jours (placebo); p = 0,001*

- Développement clinique
  - *Approche curative*
    - Phase 2b: essai MOVe-IN, chez les patients hospitalisés (résultats 04/2021)
    - **Phase 2b/3 : essai MOVe-OUT chez les patients ambulatoires (résultats 10/2021)**
  - *Approche préventive post-exposition*
    - Phase 3: essai MOVe-AHEAD, prévention des cas contacts (débuté en 08/21)

*Chez les patients présentant un taux d'Ac antinucléocapside négatif à l'inclusion

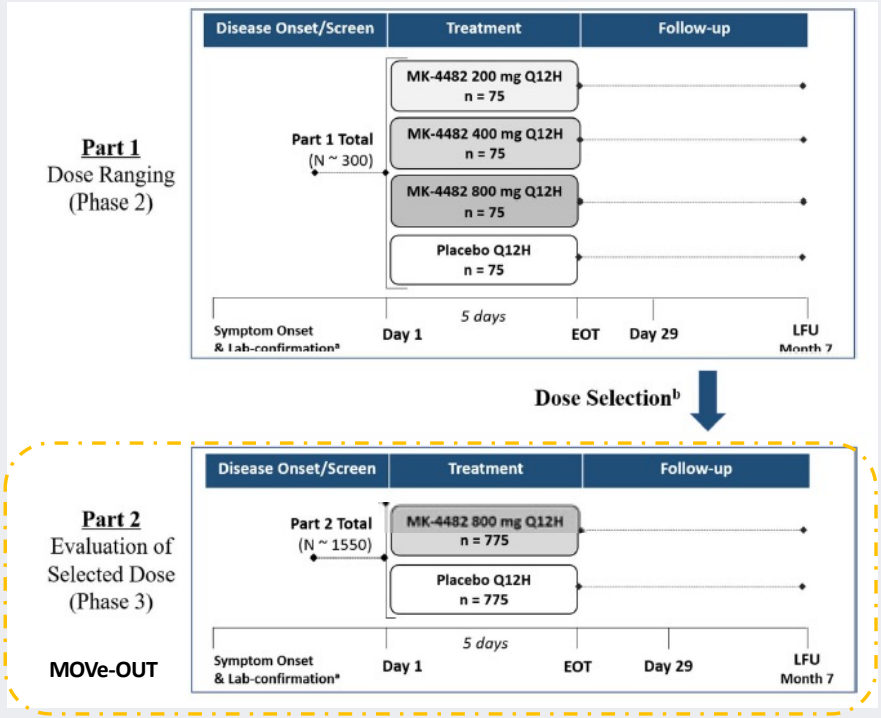
1- Cox. Nat Microbiol. 2021;6:11
2- Fischer. medRxiv. 2021 Jun 17;2021.06.17.21258639

Programme Molnupiravir

Essai *MOVe-OUT (patients ambulatoires): Essai de phase 2b/3*

Design de l'étude MOVe-OUT

Administration orale **2 fois par jour** pendant **5 jours**
avec un suivi jusqu'à J29



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Objectifs de l'étude

	MK4482-002 / MOVe-OUT
Primary Efficacy objective	Objective : To evaluate efficacy of MK-4482 compared to placebo as assessed by the percentage of participants who are hospitalized and/or die from randomization through Day 29 (superiority) Endpoint : Hospitalization or death D29
Primary safety objective	Objective : To evaluate the safety and tolerability of MK-4482 compared to placebo. Endpoint : •Adverse events •Adverse events leading to discontinuation of study intervention

	MOVe-OUT Phase 2b	MOVe-OUT Phase 3
Profil Patient	▪ PCR+ documentée <7J ▪ Au moins 1 symptôme COVID <7J ▪ Forme légère à haut risque de s'aggraver ou Forme modérée	▪ PCR+ documentée ≤ 5J ▪ Au moins 1 symptôme COVID ≤ 5J ▪ Au moins 1 FR d'évoluer vers une forme sévère qqs forme (légère ou modérée)
Recrutement Monde	**302 participants**	**1434 participants* (90% objectif fixé:1550)**

* Clôture prématurée du recrutement de MOVe-OUT sur recommandation du DMC après consultation de la FDA au regard des résultats intermédiaires positifs de l'essai

FR: facteur de risque

Molnupiravir

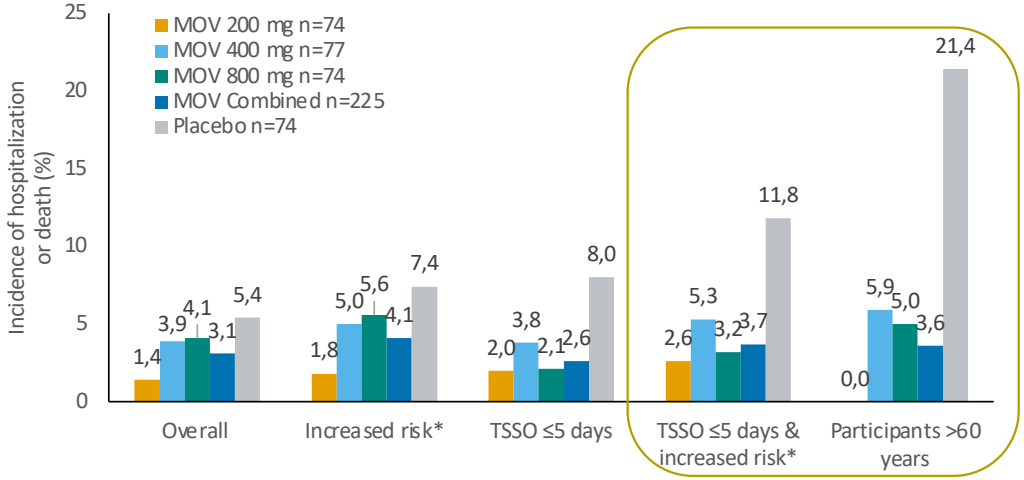
*MOVe-OUT (ambulatoire): Analyse intermédiaire **phase 2b** ECCMID 2021*

N= 302 patients adultes en ambulatoire, symptômes ≤ 7 jours avant randomisation (75 MOV 200, 77 MOV 400, 76 MOV 800 et 74 PCB)

Caractéristiques des patients

- **MOV 800**: 27,5% de +60 ans
- **≤ 5 jours post-symptôme ou signe d'infection**: 66,7 % des patients MOV
- **≥ 1 FR (obésité, âge, diabète)**: 75,9%

EFFICACITE CLINIQUE (mITT) ► Réduction de l'incidence d'hospitalisations ou de décès MOV *vs.* placebo jusqu'à J29, en particulier sous-groupes

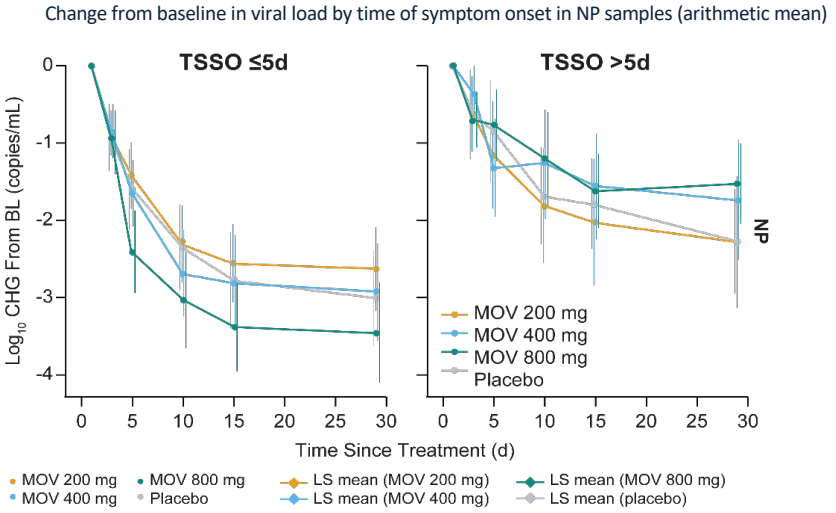


Nombre d'événements rapportés non suffisant pour déterminer une significativité sur l'effet clinique

TSSO: time since onset of covid-19 signs/symptoms to randomization. **mITT population**: included all randomized participants who received ≥1 dose of study medication and was based on the study medication to which participants were randomized.

MOV généralement bien toléré durant toute l'étude (Ø signal MOV 800)
+ Bénéfice clinique présumé en stade précoce, en particulier chez patients avec symptômes dans les 5 jours avant la randomisation et FR associés
+ Effet antiviral plus important MOV 800

EFFICACITE ANTIVIRALE (mITT) ► Réduction plus rapide et plus importante de la charge virale en SARS-CoV-2 MOV vs. placebo chez patients avec symptômes ≤ 5J avant la randomisation



BL, baseline. D, day. EOT, end of treatment. LS, least squares. mITT, modified intent-to-treat. MOV, molnupiravir. NP, nasopharyngeal. TSSO, time since symptom onset

CARAGO Y, ET AL. PHASE 2 RESULTS FROM A RANDOMIZED, CONTROLLED, PHASE 2/3 STUDY EVALUATING MOLNUPIRAVIR FOR TREATMENT OF COVID-19 IN NON-HOSPITALIZED ADULTS (MOVE-OUT) PRESENTED AT 31ST ECCMID, 12 JULY, 2021.

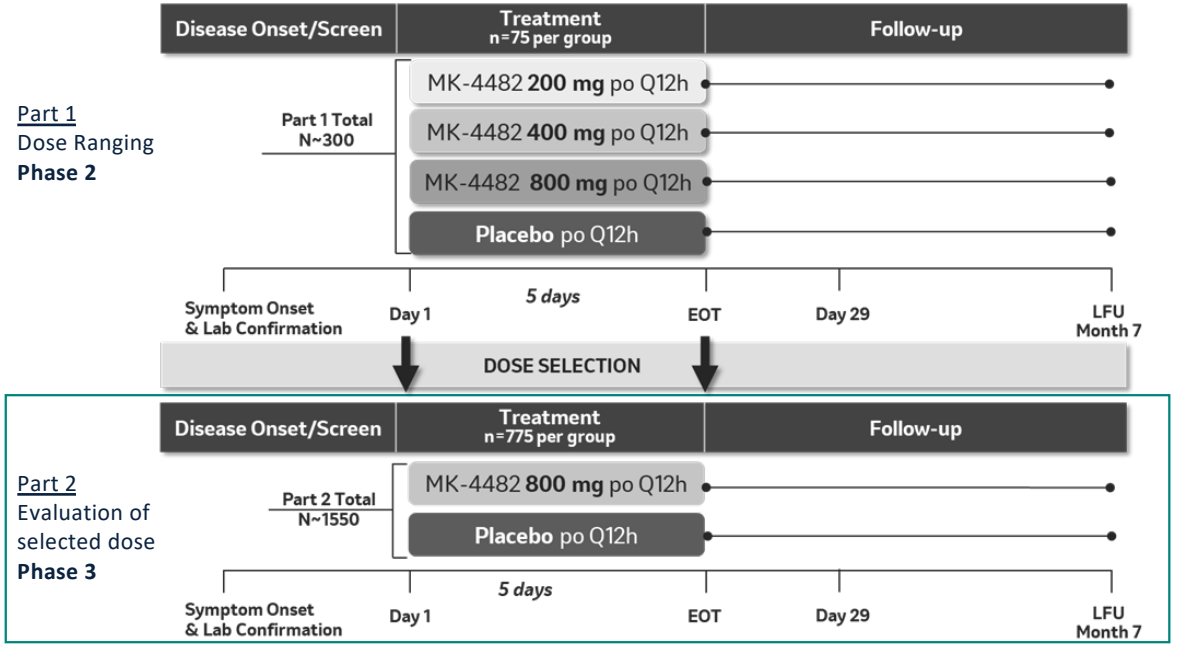
MOVe-OUT **Phase 3** Study Design

Study Population

- **Non-hospitalized adults with mild or moderate COVID-19**
  - **Laboratory-confirmed SARS-CoV-2** infection with sample collection and initial onset of COVID-19 **signs/symptoms ≤5 days prior to randomization**
  - **≥ 1 sign/symptom** of COVID-19
- **All** participants **at increased risk** for severe illness from COVID-19
  - >60 years of age
  - Active cancer
  - CKD
  - COPD
  - Obesity (BMI ≥ 30)
  - Serious heart conditions (CAD, heart failure, cardiomyopathies)
  - Diabetes mellitus

Stratification

- Time since symptom onset to randomization (≤3 days, >3 days)



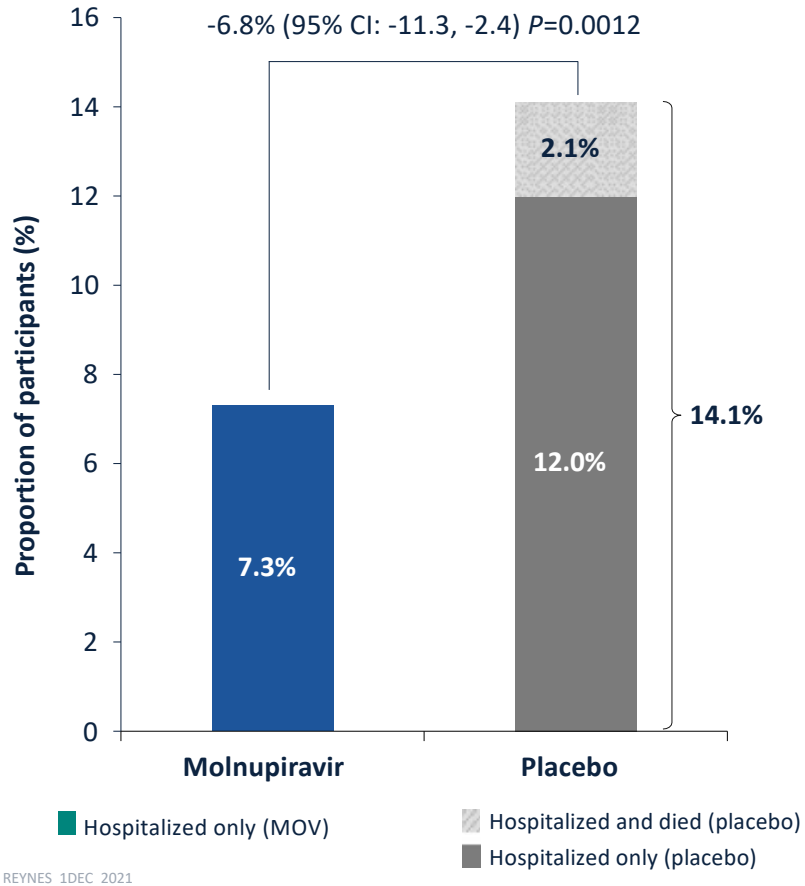
A planned interim analysis evaluated data from 775 participants who were initially enrolled in Phase 3 on or prior to August 5, 2021

Johnson MG, et al. Poster #2968. Presented at Virtual ASTMH; Nov 2021

MOVe-OUT Analyse intermédiaire Phase 3

Données d'efficacité – critère principal

Hospitalizations and/or deaths through Day 29 (MITT)



J. REYNES 1DEC 2021

Clinical Efficacy

- The proportion of participants who were hospitalized and/or died through Day 29 was significantly lower in the MOV (7.3%) than the placebo group (14.1%)
  - **Absolute risk reduction of 6.8 % (95% CI: 2.4, 11.3; P=0.0012)**
  - NNT=14,7
- No participants in the MOV group died
- 8 participants in the placebo group died through Day 29 (all-cause mortality rate: 2.1%), all of whom were hospitalized prior to death

Johnson MG, et al. Poster #2968. Presented at Virtual ASTMH; Nov 2021

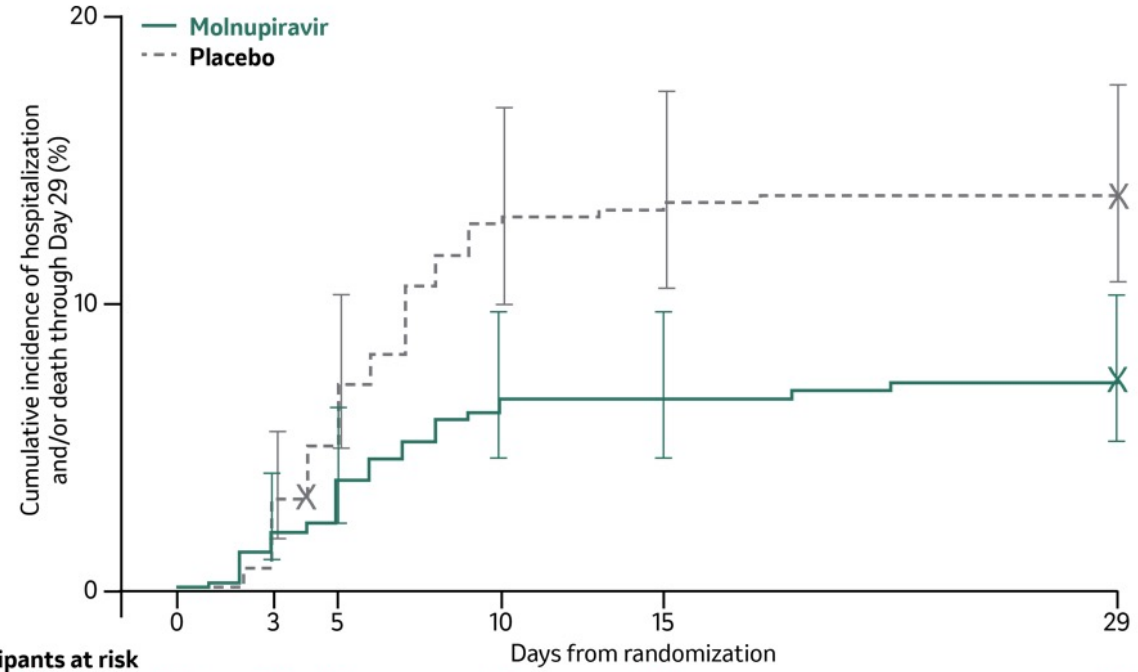
MOVe-OUT Analyse intermédiaire Phase 3

Données d'efficacité – cinétique du critère principal

Time to hospitalization and/or death through Day 29, demonstrating a **hazard ratio of 0.51 (95% CI: 0.32, 0.81)** for molnupiravir versus placebo

Réduction significative de 50% du risque d'hospitalisation ou décès à J29

Time to hospitalization and/or death through Day 29 (MITT)



Number of participants at risk						
Molnupiravir	385	380	376	361	359	357
Placebo	377	374	357	328	326	324

No. of events inside time period						
Molnupiravir	5	4	15	2	2	0
Placebo	3	16	29	2	2	0

Kaplan-Meier curve with 95% confidence intervals.
X indicates censored values. CI, confidence interval.

Johnson MG, et al. Poster #2968. Presented at Virtual ASTMH; Nov 2021

Avis CHMP du 19 Novembre 2021

“EMA issues advice on use of Lagevrio (molnupiravir) for the treatment of COVID-19”

“The **Target Population** indicated in the Conditions of Use is : Lagevrio is indicated for the treatment of **COVID-19 in adults** who **do not require supplemental oxygen** and who are **at increased risk of developing severe COVID-19**.

Lagevrio should be administered **as soon as possible** after diagnosis of COVID-19 and **within 5 days of the start of symptoms**.

The medicine, which is available as capsules, should be taken **twice a day for 5 days**.”

The most common side effects reported during treatment and within 14 days after the last dose were **diarrhoea**, **nausea**, **dizziness** and **headache**, all of which were either mild or moderate.

Not recommended during pregnancy and in women who can become pregnant and are not using effective contraception : **effective contraception** needed during treatment and for 4 days after the last dose.

Breastfeeding should be interrupted during treatment and for 4 days after treatment.

J. REYNES 1DEC 2021

MSD

RIDGEBACKBIO

News Release

FOR IMMEDIATE RELEASE

MSD and Ridgeback Biotherapeutics Provide Update on Results from MOVe-OUT Study of Molnupiravir, an Investigational Oral Antiviral Medicine, in At Risk Adults With Mild-to-Moderate COVID-19

KENILWORTH, N.J. & MIAMI, Nov. 26, 2021 – MSD (NYSE: MRK), a trade name of Merck & Co., Inc, Kenilworth, NJ, USA, and Ridgeback Biotherapeutics today provided an update on the MOVe-OUT study of molnupiravir (MK-4482, EIDD-2801), an investigational oral antiviral medicine for COVID-19. Data are now available from all enrolled participants (n=1433). In this study population, molnupiravir reduced the risk of hospitalization or death from 9.7% in the placebo group (68/699) to 6.8% (48/709) in the molnupiravir group, for an absolute risk reduction of 3.0% (95% confidence interval [CI]: 0.1, 5.9; nominal p-value=0.0218) and a relative risk reduction of 30% (relative risk 0.70; 95% CI: 0.49, 0.99). Nine deaths were reported in the placebo group, and one in the molnupiravir group. The adverse event profile for molnupiravir remained consistent with the profile reported at the planned interim analysis.

Science First release: 2 November 2021 RESEARCH ARTICLES

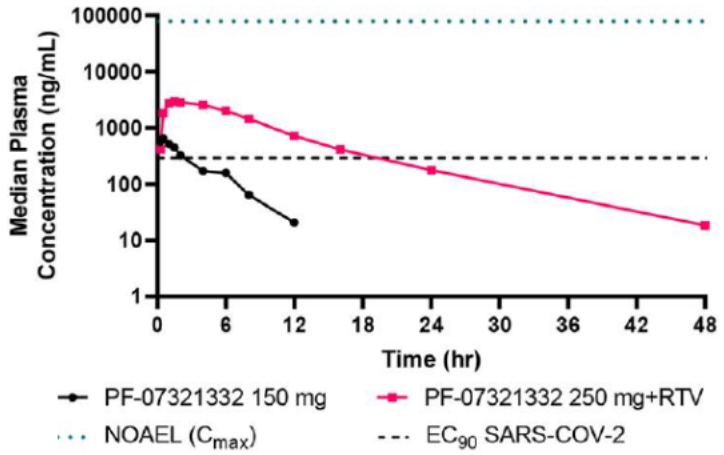
Cite as: Owen *et al.*, *Science* 10.1126/science.abl4784 (2021).

An oral SARS-CoV-2 M^{pro} inhibitor clinical candidate for the treatment of COVID-19

Dafydd R. Owen[1]*, Charlotte M. N. Allerton[1], Annaliesa S. Anderson[2], Lisa Aschenbrenner[3], Melissa Avery[3], Simon Berritt[3], Britton Boras[4], Rhonda D. Cardin[2], Anthony Carlo[3], Karen J. Coffman[3], Alyssa Dantonio[3], Li Di[3], Heather Eng[3], RoseAnn Ferre[4], Ketan S. Gajiwala[4], Scott A. Gibson[5], Samantha E. Greasley[4], Brett L. Hurst[5], Eugene P. Kadar[3], Amit S. Kalgutkar[1], Jack C. Lee[3], Jisun Lee[3], Wei Liu[4], Stephen W. Mason[2]†, Stephen Noell[3], Jonathan J. Novak[3]‡, R. Scott Obach[3], Kevin Ogilvie[3], Nandini C. Patel[1], Martin Pettersson[1]§, Devendra K. Rai[2], Matthew R. Reese[3], Matthew F. Sammons[1], Jean G. Sathish[2], Ravi Shankar P. Singh[1], Claire M. Steppan[3], Al E. Stewart[4], Jamison B. Tuttle[1], Lawrence Updyke[1], Patrick R. Verhoest[1], Liuqing Wei[3], Qingyi Yang[1], Yuao Zhu[2]

[1]Pfizer Worldwide Research, Development & Medical, Cambridge, MA 02139, USA. [2]Pfizer Worldwide Research, Development & Medical, Pearl River, NY 10965, USA. [3]Pfizer

COVID-19. Here, we report the discovery and characterization of PF-07321332, an orally bioavailable SARS-CoV-2 main protease inhibitor with in vitro pan-human coronavirus antiviral activity and excellent off-target selectivity and in vivo safety profiles. PF-07321332 has demonstrated oral activity in a mouse-adapted SARS-CoV-2 model and has achieved oral plasma concentrations exceeding the in vitro antiviral cell potency in a phase I clinical trial in healthy human participants.



PF-07321332 + Ritonavir

Paxlovid*

J. Reynes 1dec 2021

- **Press release Pfizer 5 nov 2021**

Données analyse intermédiaire portant sur 1219 patients non hospitalisés, à risque de forme grave, symptômes < 5 j

Réduction de 89% du risque d'hospitalisation ou décès pour patients traités dans 3 premiers jours, hospitalisation 0,8% (3/389) vs 7% (27/385).

Résultats similaires dans 5 premiers j

Arrêt recrutement à 70% des 3000 prévus

Deux autres essais:

EPIC-SR: tt risque standard

EPIC-PEP : prophylaxie post-exposition

Montpellier 2021

Reynes Oct 2021