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SCIENCE MEDICINES HEALTH

COVID-19:
the point of view of a regulatory Agency

COVID-19 inflammation and molecular imaging

Dr. Marco Cavaleri
Head of Biological Health Threats and Vaccines Strategy,
EMA

ETF establishment and composition

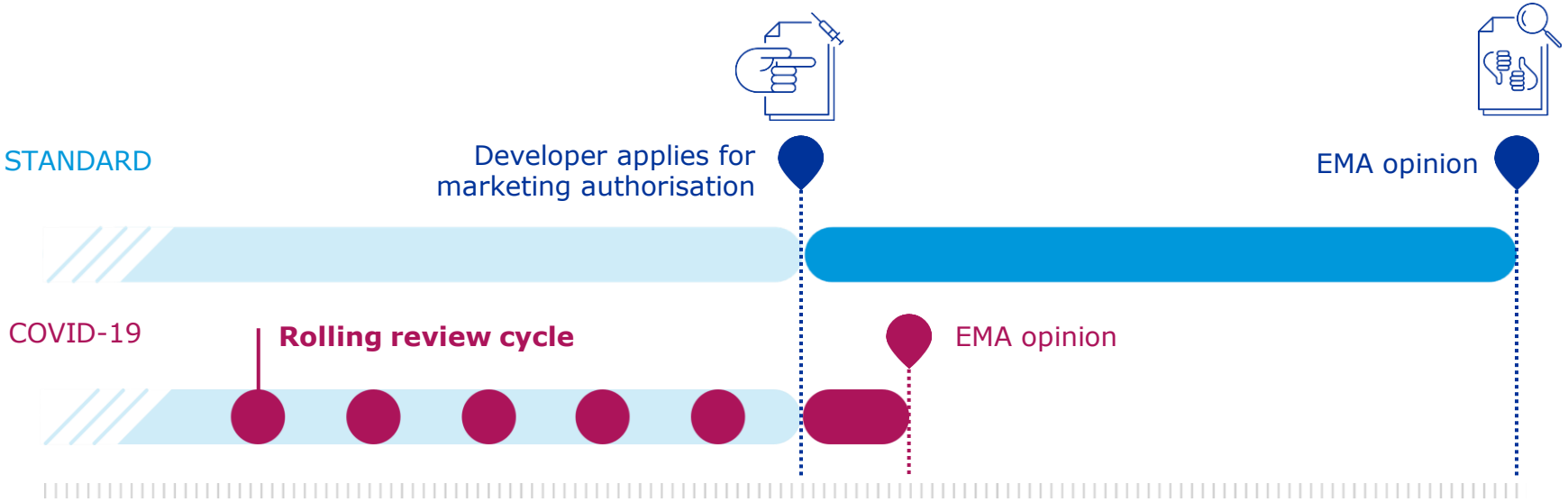
- During a public health emergency or pandemic, EMA activates its Health Threat Plan (developed based on 2009 H1N1 pandemic, 2014-2019 Ebola and Zika outbreaks).
- The Health Threat Plan includes the setting-up of a **dedicated expert group**, the EMA Pandemic Task Force (**ETF**). Current ETF activated immediately in view of emerging COVID-19
- ETF, chaired by EMA, operates as **advisory group to CHMP/PRAC/PDCO** and in cooperation with CMDh, NCAs, CTFG and the European Commission
- CORE ETF consisting of **selected experts from EMA's regulatory network** with specific expertise relevant for the therapeutic response to the health emergency (vaccinology, virology, immunology, quality, non-clinical, infectious diseases)
- ETF **membership also includes** (vice)Chairs of CHMP/PRAC/PDCO/CMDh/CTFG and members of relevant CHMP WPs, i.e. VWP, BWP, BPWP, QWP, SWP, SAWP, IDWP; RMS for NAPs, CHMP Rapps and assessors or SA coordinators for ongoing procedures and ad hoc experts; civil society reps

Rolling review

Research & development

Standard EMA evaluation

EMA evaluation with rolling review



Procedures that are discussed by the ETF

Development support

- Early informal TCs with developers
- (ultra)Rapid scientific advice prepared by ETF and endorsed by SAWP/CHMP
- paediatric investigation plan discussed by ETF with endorsement by PDCO

Evaluation (new and repurposed products)

- Rolling review cycles: ETF discussions followed by interim CHMP opinions
- Accelerated assessment of MA applications.
  ETF expert input to CHMP assessment team
- Compassionate Use/support to national Emergency Use

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4 May 2020
EMA/213341/2020

EMA initiatives for acceleration of development support and evaluation procedures for COVID-19 treatments and vaccines

The European Medicines Agency (EMA) together with the responsible scientific committees and their working parties, and in collaboration with the European Commission, operates rapid procedures to support the development and evaluation of treatments and vaccines for COVID-19. The EMA emerging health threats plan foresees that detailed procedures are set-up to adapt different types of review activities to the needs of the health threat/crisis situation. Whilst respecting the regulatory requirements and established review principles (e.g. independence of experts), these procedures aim, within timelines that are appropriate for the public health emergency situation, to provide most efficient management of product-review activities leading to scientifically sound and robust outcomes.

EMA initiatives for acceleration of development support and evaluation procedures for COVID-19 treatments and vaccines

Conditional Marketing Authorisation

On the basis of less comprehensive data and subject to specific obligations

Scope (at least one):

- for **seriously debilitating diseases or life-threatening diseases**;
- to be used **in emergency situations**;
- **orphan** medicinal products.

Criteria (all):

- the **risk-benefit balance is positive**;
- it is likely that the applicant **will be in a position to provide comprehensive clinical data**;
- **unmet medical needs** will be fulfilled;
- the **benefit** to public health **of the immediate availability** on the market of the medicinal product concerned **outweighs the risk** inherent in the fact that additional data are still required.

'**unmet medical needs**' means a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected

Regulation (EC) No 507/2006

REVIEW

Clinical Trials for COVID-19: Can we Better Use the Short Window of Opportunity?

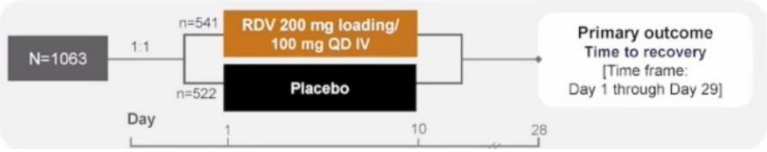
Hans-Georg Eichler[1,2,*], Marco Cavaleri[1], Harald Enzmann[3,4], Francesca Scotti[1], Bruno Sepodes[4,5], Fergus Sweeney[1], Spiros Vamvakas[1] and Guido Rasi[1,6]

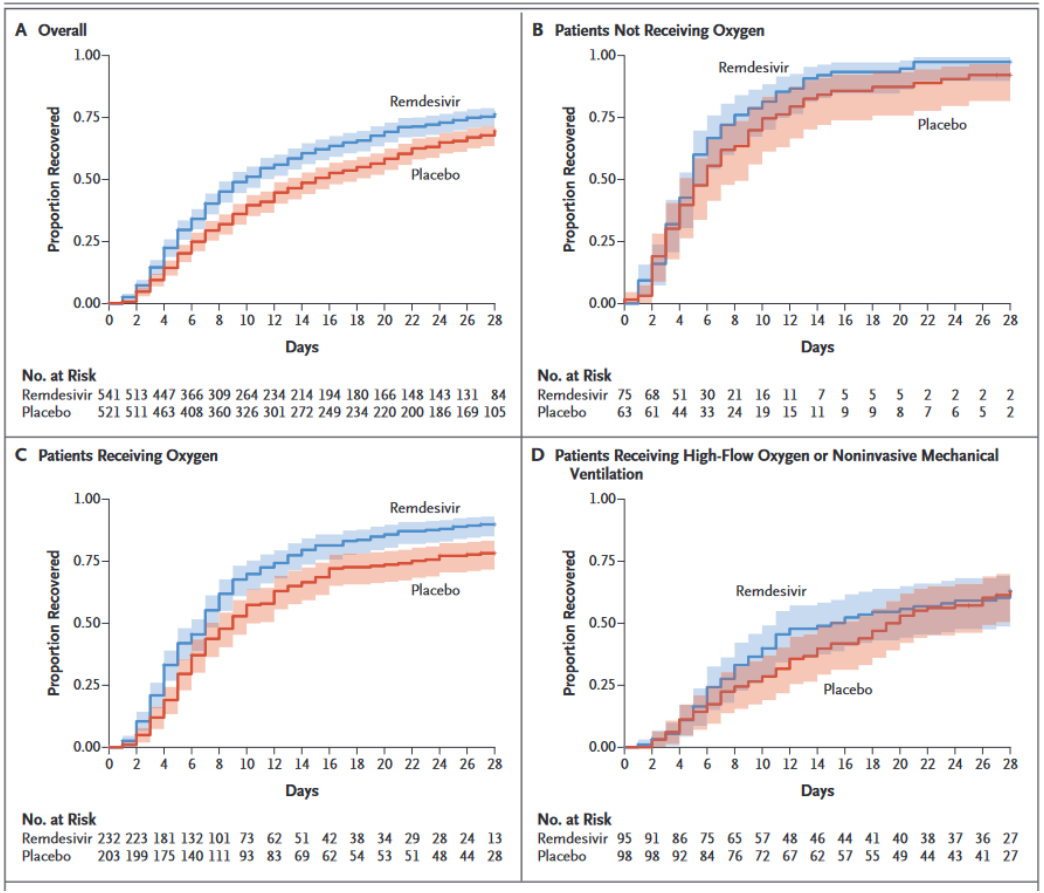
The scientific community has risen to the coronavirus disease 2019 (COVID-19) challenge, coming up with an impressive list of candidate drugs and vaccines targeting an array of pharmacological and immunological mechanisms. Yet, generating clinical evidence of efficacy and safety of these candidate treatments may be frustrated by the absence of comprehensive trial coordination mechanisms. Many small stand-alone trials and observational studies of single-agent interventions are currently running or in planning; many of these will likely not deliver robust results that could support regulatory and patient-level treatment decisions. In this paper, we discuss actions that all stakeholders in the clinical trial ecosystem need to take to ensure that the window of opportunity during this pandemic will not shut, both for patients in need of treatment and for researchers to conduct decision-relevant clinical trials.

Remdesivir
ACTT-1
(positive on TTCR)

- Phase 3,
- adaptive,
- randomized
- Double blind
- Placebo-controlled
- Multicentre
- Global trial

NCT04280705





Beigel, John H., et al. "Remdesivir for the Treatment of Covid-19 — Final Report." N. Engl. J. Med., 22 May. 2020, doi:10.1056/NEJMoa2007764.

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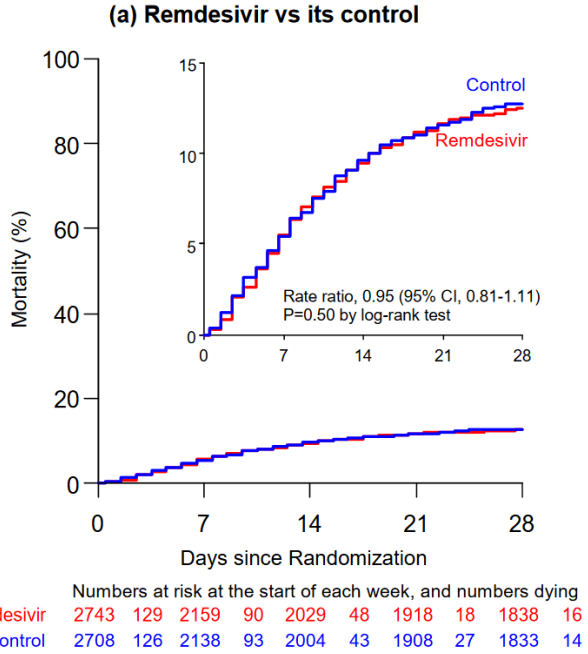
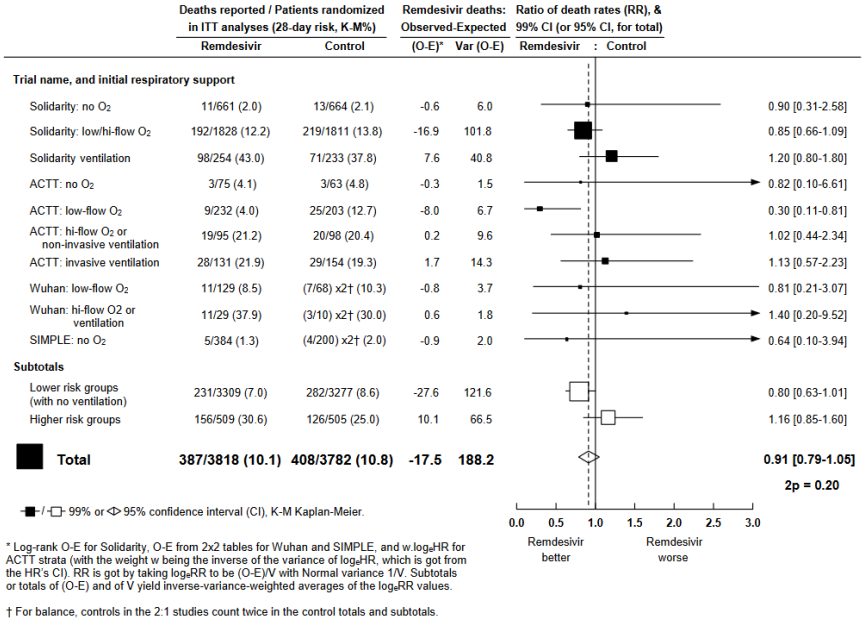
RDV-Solidarity trial





* Log-rank O-E for Solidarity, O-E from 2x2 tables for Wuhan and SIMPLE, and w.$\log_e$HR for ACTT strata (with the weight w being the inverse of the variance of $\log_e$HR, which is got from the HR's CI). RR is got by taking $\log_e$RR to be (O-E)/V with Normal variance 1/V. Subtotals or totals of (O-E) and of V yield inverse-variance-weighted averages of the $\log_e$RR values.

† For balance, controls in the 2:1 studies count twice in the control totals and subtotals.

COVID-19 SOLIDARITY

"Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results." medRxiv, 15 Oct. 2020, p. 2020.10.15.20209817, doi:10.1101/2020.10.15.20209817.

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18 September 2020
EMA/483739/2020

EMA endorses use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation

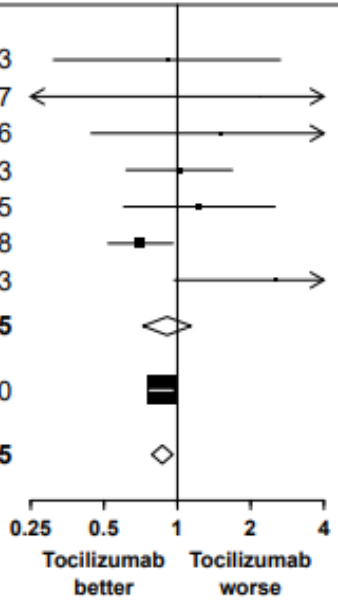
EMA's human medicines committee (CHMP) has completed its review of results from the RECOVERY study arm that involved the use of the corticosteroid medicine dexamethasone in the treatment of patients with COVID-19 admitted to hospital, and has concluded that dexamethasone can be considered a treatment option for patients who require oxygen therapy (from supplemental oxygen to mechanical ventilation).

Based on the review of available data, EMA is endorsing the use of dexamethasone in adults and adolescents (from 12 years of age and weighing at least 40 kg) who require supplemental oxygen therapy. Dexamethasone can be taken by mouth or given as an injection or infusion (drip) into a vein. In all cases, the recommended dose in adults and adolescents is 6 milligrams once a day for up to 10 days.

Figure 4: Tocilizumab vs usual care in patients hospitalised with COVID − Meta−analysis of mortality in RECOVERY and other trials

	Deaths / Patients randomised (%)		Observed−Expected		Ratio of death rates, RR (95% CI)
	Tocilizumab	Usual care	(O−E)*	Var(O−E)	
COR−IMUNO TOCI	7/64 (10.9)	8/67 (11.9)	−0.3	3.3	0.91 (0.31−2.65)
RCT−TCZ−COVID−19	2/60 (3.3)	1/66 (1.5)	0.6	0.7	2.17 (0.22−21.3)
BACC Bay	9/161 (5.6)	(3/82) x2† (3.7)	1.0	2.6	1.51 (0.44−5.13)
COVACTA	58/294 (19.7)	(28/144) x2† (19.4)	0.3	15.3	1.02 (0.62−1.68)
EMPACTA	26/249 (10.4)	(11/128) x2† (8.6)	1.6	7.5	1.23 (0.60−2.52)
REMAP−CAP	98/353 (27.8)	142/402 (35.3)	−14.2	40.8	0.71 (0.52−0.96)
TOCIBRAS	14/65 (21.5)	6/64 (9.4)	3.9	4.3	2.51 (0.97−6.50)
Subtotal: 7 trials	**214/1246 (17.2)**	**241/1307 (18.4)**	**−7.2**	**74.5**	**0.91 (0.72−1.14)**
RECOVERY	596/2022 (29.5)	694/2094 (33.1)	−48.2	316.0	0.86 (0.77−0.96)
All trials	**810/3268 (24.8)**	**935/3401 (27.5)**	**−55.4**	**390.5**	**0.87 (0.79−0.96) p=0.005**

Heterogeneity between RECOVERY and previous trials: χ^2_1=0.2



RECOVERY_Tocilizumab_MainPaper_medRxiv (1253)

GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study

Giacomo De Luca, Giulio Cavalli, Corrado Campochiaro, Emanuel Della-Torre, Piera Angelillo, Alessandro Tomelleri, Nicola Boffini, Stefano Tentori, Francesca Mette, Nicola Farina, Patrizia Rovere-Querini, Annalisa Ruggeri, Teresa D'Aliberti, Paolo Scarpellini, Giovanni Landoni, Francesco De Cobelli, John F Paolini, Alberto Zangrillo, Moreno Tresoldi, Bruce C Trapnell, Fabio Ciceri, Lorenzo Dagna

hyperinflammation, defined as elevation of serum inflammation markers C-reactive protein (CRP) to 100 mg/L or more (normal range <6 mg/L) or ferritin to 900 µg/L or more (normal range 30–400 µg/L), in the presence of any increase in lactate dehydrogenase (LDH; normal range 125–220 U/L).

Mavrilimumab for severe COVID-19

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Department of Medicine (ARK, MS, NW) and Department of Infectious Diseases (PKT), All India Institute of Medical Sciences, New Delhi, 110029 India

We read with interest the Article by Giacomo De Luca and colleagues[1] in *The Lancet Rheumatology*, in which the authors showed that mavrilimumab treatment was associated with improved clinical outcomes compared with standard care in non-mechanically ventilated patients with severe COVID-19 pneumonia and systemic hyperinflammation. However, we would like to highlight important limitations of the study

First, the authors used arbitrary cut-off points in continuous variables (serum C-reactive protein, ferritin, and lactate dehydrogenase) for selecting patients with hyperinflammation.[2] Such cut-offs were not derived from or validated in any predictive or prognostic studies in patients with COVID-19 that we are aware of.[3]

1 De Luca G, Cavalli G, Campochiaro C, et al. GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study. *Lancet Rheumatol* 2020; **2**: e465–73.

2 Dawson NV, Weiss R. Dichotomizing continuous variables in statistical analysis: a practice to avoid. *Med Decis Making* 2012; **32**: 225–26.

3 Wynants L, Van Calster B, Collins GS, et al. Prediction models for diagnosis and prognosis of COVID-19 infection: systematic review and critical appraisal. *BMJ* 2020; **369**: m1328.

4 Calfee CS, Delucchi KL, Sinha P, et al. Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. *Lancet Respir Med* 2018; **6**: 691–98.

EMA issues advice on use of sotrovimab (VIR-7831) for treating COVID-19

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News 21/05/2021

EMA's human medicine
sotrovimab (also know
undertaken to provide
possible use of the an

The Agency concluded
(aged 12 years and a
who are at risk of pro

The medicine is given

EMA issues advice on use of regdanvimab for treating COVID-19

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News 26/03/2021

EMA's human medicines
regdanvimab (also know
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antibody prior to marketi
treatment of confirmed C
are at high risk of progre

The medicine is given by

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)
casirivimab and imdevimab to treat patients
harmonised scientific opinion at EU level to s
antibodies prior to marketing authorisation.
COV2 can be used for the treatment of confir
oxygen and who are at high risk of progressi

The medicine is given by infusion (drip) into

EMA issues advice on use of antibody combination (bamlanivimab / etesevimab)

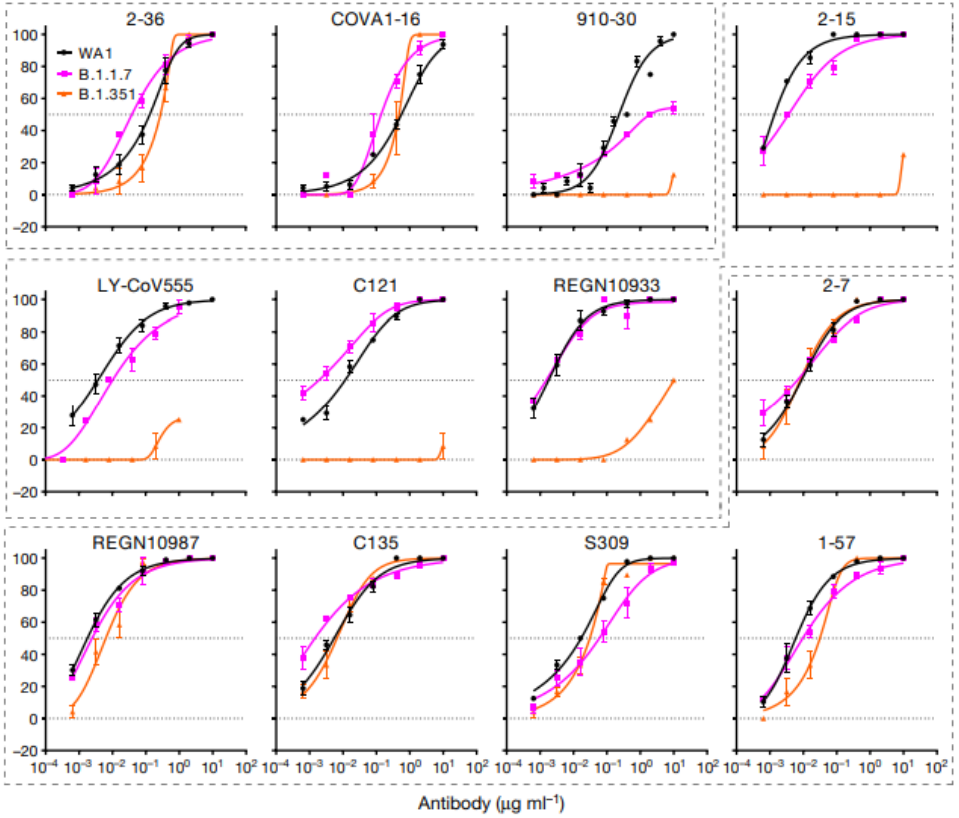
Share

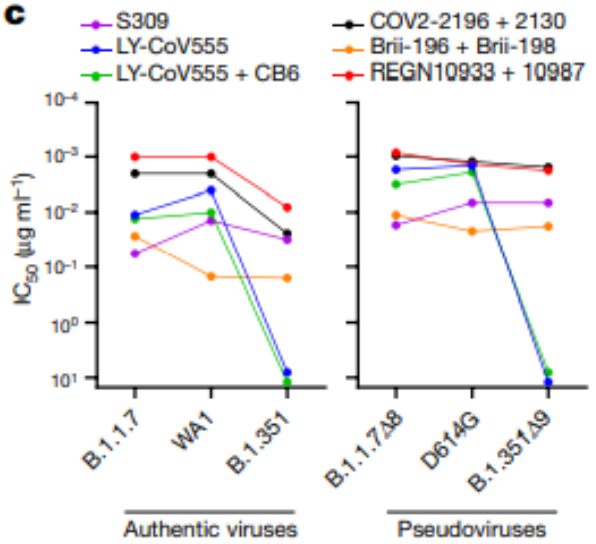
News 05/03/2021

EMA's human medicines committee (CHMP) has completed its review on the use of the monoclonal antibodies bamlanivimab and etesevimab 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.

4 monoclonal antibodies products with neutralising activity received scientific opinion to support emergency use before approval and have started rolling Review

Increased resistance of SARS-COV2 variants to monoclonal antibodies





Wang, P., Nair, M.S., Liu, L. *et al.* Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature* **593,** 130–135 (2021). https://doi.org/10.1038/s41586-021-03398-2

EMA advises against use of ivermectin for the prevention or treatment of COVID-19 outside randomised clinical trials

Share

News 22/03/2021

EMA has reviewed the latest evidence on the use of ivermectin for the prevention and treatment of COVID-19 and concluded that the available data do not support its use for COVID-19 outside well-designed clinical trials.

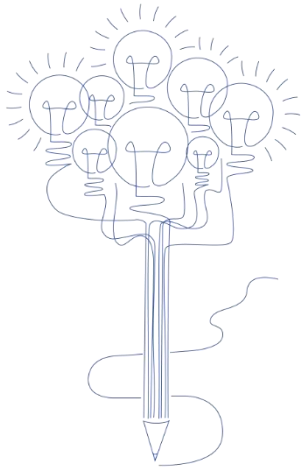
In the EU, ivermectin tablets are approved for treating some parasitic worm infestations while ivermectin skin preparations are approved for treating skin conditions such as rosacea. Ivermectin is also authorised for veterinary use for a wide range of animal species for internal and external parasites.

Ivermectin medicines are not authorised for use in COVID-19 in the EU, and EMA has not received any application for such use.[1]

EMA therefore concluded that use of ivermectin for prevention or treatment of COVID-19 cannot currently be recommended outside controlled clinical trials. Further well-designed, randomised studies are needed to draw conclusions as to whether the product is effective and safe in the prevention and treatment of COVID-19.

This EMA public health statement has been endorsed by the COVID-19 EMA pandemic Task Force (COVID-ETF), in light of the ongoing discussions on the use of ivermectin in the prevention and treatment of COVID-19.

Summary



250 medicines and vaccines for COVID interacted with EMA

Only 2 drugs currently approved: VEKLURY and dexamethasone

Need of therapeutics for different domains:

- antivirals for outpatient use

- agents addressing inflammation/tissue damage/coagulation providing benefit in patients with severe/critical COVID

Studies in specific populations according to stage of disease and use of biomarkers for more personalised treatments

Importance of proper pharmacology investigations, proof-of-concept studies and dose selection

Randomised controlled trials for determining benefits and risks

Studies of adequate size to demonstrate clinical benefit – relevance of clinical trial networks