EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Regulatory consideration for clinical development of broad-spectrum antiviral agents

Broad-spectrum anti-viral therapeutics: A key tool for pandemic preparedness, Brussels, 22nd -23rd November 2022

Dr. Marco Cavaleri
Head of Biological Health Threats and Vaccines Strategy, EMA
Chair of EMA Emergency Task Force

Treatment of viral diseases

- **As per EU regulation 726/2004, medicinal products for treatment of viral diseases in the EU must be approved by EMA via the centralised procedure**
- EMA has approved several antivirals for treatment of chronic viral diseases, mainly HIV (64 medicinal products), Hepatitis B (8 medicinal products), C (11 medicinal products) and D (1 product)
- Six antiviral agents for COVID-19, 4 antivirals for influenza, 2 monoclonal antibodies for RSV and 2 antivirals for CMV have been approved to date by EMA

Development of broad-spectrum antivirals

- **Regulatory approval must be based on an evaluation of the benefit risk balance for a specific intended use**
- An antiviral might be developed for treatment or prevention of a specific viral disease, e.g. treatment of influenza or prophylaxis of COVID-19
- There is no possibility to include in regulatory deliberations and product information data not pertinent to the intended use
- *Essential to engage early in development with EMA*

The new Emergency Task Force (ETF)

- ETF established with formal legal mandate as an **advisory and support body on medicines for public health emergencies and preparedness**
- Regulation sets out objectives and composition, but allowing flexibility & membership based on expertise
- **Strengthened** existing ETF responsibilities building on successful experience during past emergencies & COVID-19

Scientific advice and support to clinical trials

- assessed **directly** by ETF
- free of charge & fast-track for clinical trials and protocols
- **support study conduct**

Scientific reviews

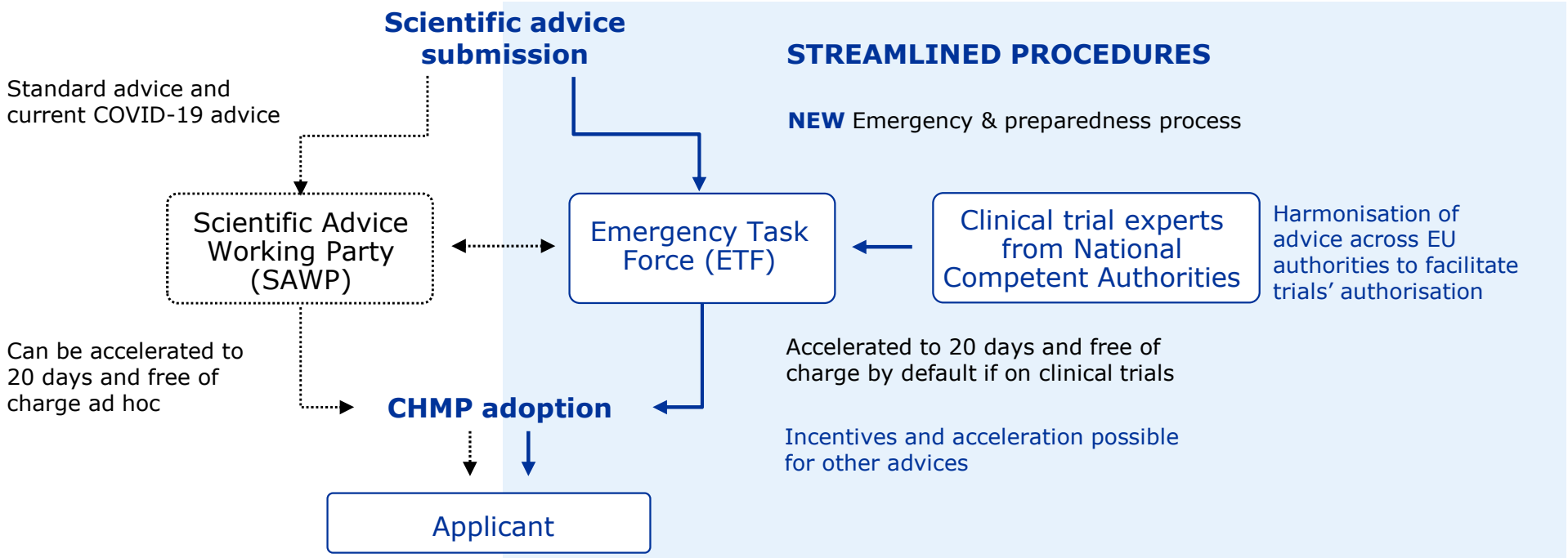
- **systematic** assessment of evidence on medicines

ETF recommendations

- **on medicines not yet authorised**
- on scientific or **public health matters**

Overview of ETF tasks and responsibilities

Scientific advice and support to clinical trials | Scientific reviews | Scientific recommendations



ETF preparedness activities for future emergencies

- **Monitor outbreaks and epidemics** that could become serious threats and development of countermeasures
- **Provide scientific advice to applicants for key pathogens;** such as: Ebola virus, Zika virus, pandemic influenza, chikungunya virus, coronaviruses including MERS and SARS, Arenaviruses, Anthrax, Orthopoxviruses
- **Engage with academic groups / NGOs / Public health bodies** with respect to setting up platform trials and develop specific clinical trials protocols
- **Maintain an overview of medicines in development for future emergencies**, and up- to-date information on potential radiological, chemical or bioterrorism agents
- **Coordinate activities** with relevant EU bodies including European Health Emergency Preparedness and Response Authority (DG HERA), ECDC and WHO

Update on implementation activities concerning ETF

- ETF dedicated webpage is live including composition and RoP: https://www.ema.europa.eu/en/committees/working-parties-other-groups/emergency-task-force-etf
- Update of guidance to industry for scientific advice and support to academia for CT conduct ongoing
- Reminder → two new functional mailboxes for developers and CT sponsors:

  PHEsupportCT@ema.europa.eu for CT sponsors to request EMA/ETF support for facilitating CTA and approval and sponsors agreement to conduct larger multinational trials

  PHEearlyinteractions@ema.euroma.eu for manufacturers to discuss with EMA/ETF their development programs or plans for scientific advice prior to any kind of formal submission

Global regulatory workshop on COVID-19 therapeutics #2: agreement on acceptable endpoints for clinical trials

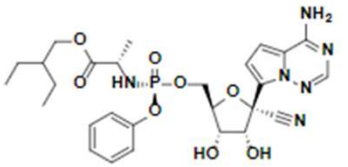
International regulators have published a report today on the acceptability of various primary endpoints in the clinical trials conducted for the development of treatments for COVID-19.

Recent Content

21 October 2022
ICMRA COVID-19 Working Group - Summary of Achievements

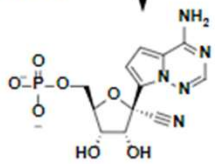
21 October 2022
ICMRA Fact Sheet

Remdesivir Is a Broad-Spectrum Antiviral Agent

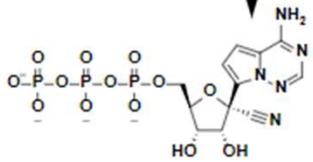


Remdesivir
(GS-5734)

Cathepsin A
Carboxylesterase



Nucleotide kinases



Triphosphate Metabolite
(Active form)

Virus Family	Virus genus	EC_{50} (µM)	Efficacy in animal model
Filoviruses	Ebola	0.14	✓
	Bundibugyo	0.19	
	Sudan	0.24	✓
	Marburg	0.06	✓
Coronaviruses	MERS	0.07	✓
	SARS	0.07	✓
Paramyxoviruses	Nipah	0.05	✓
	Measles	0.04	
	Hendra	0.06	
Flaviviruses	Dengue	0.20	
	Yellow fever	0.13	✓
	Zika	0.10	
	West Nile	1.0	
Arenaviruses	Lassa	4.5	
Bunyaviruses	RVFV	>50	
	CCHF	>20	

Warren et al. Nature 2016
Lo et al. Sci Reports 2017
Sheahan et al. Sci Transl Med 2017
Agostini et al. MBio 2018

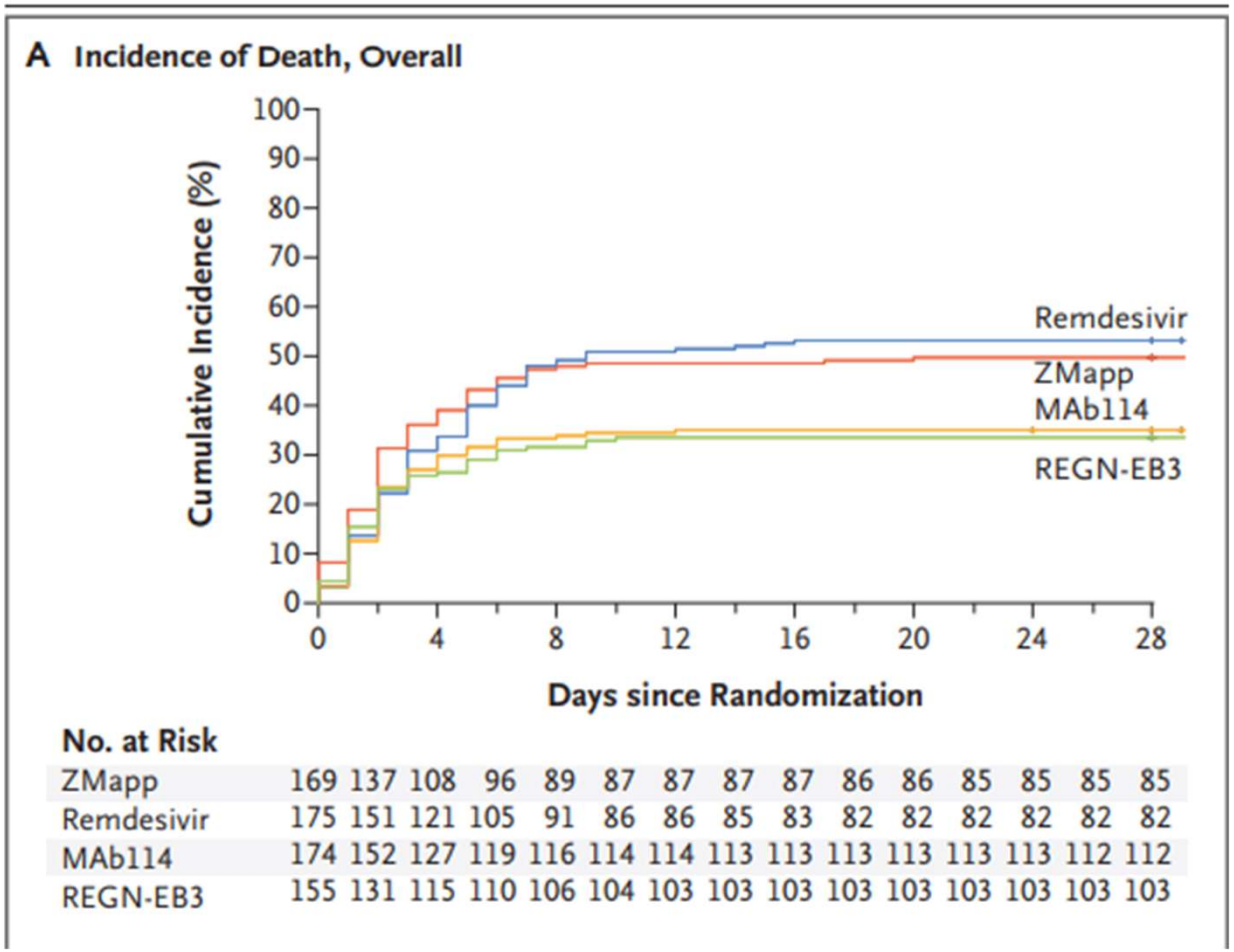
Cross et al. JCI Insight 2022
Julander et al. Antiviral Res 2022
Neyts et al., unpublished
Shi et al., unpublished

Clinical Experience with Remdesivir for COVID-19

- **Remdesivir (RDV) is approved by multiple agencies for mild or moderate COVID-19 patients who are at high risk of hospitalization and those with moderate to severe disease who are hospitalized**
- RDV is conditionally recommended by WHO for mild or moderate COVID-19 patients who are at high risk of hospitalization or severe patients who are hospitalized[1]
- Currently, global experience with RDV exceeds >11 million patients
- Populations: Pediatrics (preterm neonates and older)[2,3], pregnancy[4,5], renal insufficiency[6,7] (approved for CrCl >30, approval pending for CrCl<30 and hemodialysis), hepatic impairment[7]
- Trial experience: ACTT-1[8], SIMPLE Trials [9,10], PINETREE[11], CARAVAN[12], SOLIDARITY[13], IMPAACT 2032[14]
- Clinical safety data for RDV are primarily derived from 4 large clinical trials in participants with COVID-19 infection[8, 9-12]. RDV has an established clinical safety profile and is generally safe and well tolerated; limitations in the current SmPC include use in patients with hepatic impairment only if the potential benefit outweighs the risk and ALT<5 x ULN, and restrictions form use in those with an eGFR <30 mL/min[15]

1. BMJ 2020;370:m3379
2. Ahmed et al., Remdesivir in the treatment of children 28 days to < 18 years of age hospitalized with COVID-19 in the CARAVAN study. Abstract presented at ECCMID 2022; Lisbon.
3. Goldman et al., Compassionate Use of Remdesivir in Children With Severe COVID-19. Pediatrics. 2021 May;147(5):e2020047803.
4. Burwick et al., Compassionate Use of Remdesivir in Pregnant Women With Severe Coronavirus Disease 2019. Clin Infect Dis. 2021 Dec 6;73(11):e3996-e4004.
5. Brooks et al., IMPAACT 2032: REMDESIVIR PK & SAFETY in PREGNANT and NON-PREGNANT WOMEN with COVID-19. Topics in Antiviral Medicine ; 30(1 SUPPL):267, 2022.
6. Ogbuagu et al., Acute Kidney Injury in Particiants with Moderate Covid-19treated with RDV vs SOC, CROI March 6-10 2021, Poster395
7. Webb et al., Safety of Remdesivir vs Placebo in Nonhospitalized Patients with COVID-19 CROI March 6-10 2021, Poster 456
8. Beigel et al., Remdesivir for the Treatment of Covid-19 — Final Report, N Engl J Med 2020; 383:1813-1826
9. Goldman et al., Remdesivir for 5 or 10 Days in Patients with Severe Covid-19, N Engl J Med 2020; 383:1827-1837
10. Spinner et al., Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19, JAMA. 2020;324(11):1048-1057
11. Gottlieb et al., Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients, N Engl J Med 2022; 386:305-315
12. Ahmed et al., Remdesivir in the treatment of children 28 days to < 18 years of age hospitalized with COVID-19 in the CARAVAN study. Abstract presented at ECCMID 2022; Lisbon.
13. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med 2021; 384(6): 497-511.
14. Brooks et al., IMPAACT 2032: REMDESIVIR PK & SAFETY in PREGNANT and NON-PREGNANT WOMEN with COVID-19. Topics in Antiviral Medicine 30 (Suppl.): 267 abstr. 676, No. 1, Mar 2022.
15. https://www.ema.europa.eu/en/documents/product-information/veklury-epar-product-information_en.pdf

BUT efficacy across viral diseases needs to be shown



No. at Risk

ZMapp	169	137	108	96	89	87	87	87	87	86	86	85	85	85	85
Remdesivir	175	151	121	105	91	86	86	85	83	82	82	82	82	82	82
MAb114	174	152	127	119	116	114	114	113	113	113	113	113	113	112	112
REGN-EB3	155	131	115	110	106	104	103	103	103	103	103	103	103	103	103

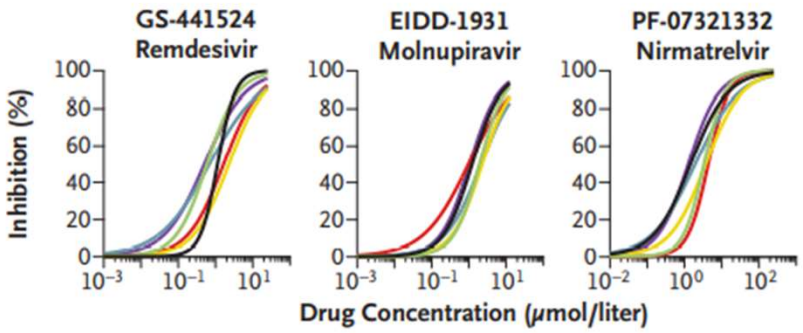
[A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics (nejm.org)]

Impact of virus variants on activity of antivirals vs Mabs SARS-COV2

B Neutralization Efficacy of Monoclonal Antibodies

	REGN10987 Imdevimab	REGN10933 Casirivimab	COV2-2196 Tixagevimab	COV2-2130 Cilgavimab	S309 Sotrovimab Precursor	LYCoV1404 Bebtelovimab	REGN10987 plus REGN10933	COV2-2196 plus COV2-2130
	$FRNT_{50}$ (ng/ml)							
Ancestral strain: SARS-CoV-2/UT-NC002-1T/Human/2020/Tokyo	1.87	4.01	3.17	5.36	16.71	3.31	4.89	5.35
Delta: hCoV-19/USA/WI-UW-5250/2021	4.31	7.15	4.63	8.93	255.55	1.72	3.26	10.57
Omicron BA.2: hCoV-19/Japan/UT-NCD1288-2N/2022	653.29	>50,000	2020.05	27.12	>50,000	6.9	390.97	38.93
Omicron BA.5: hCoV-19/Japan/TY41-702/2022	174.78	>50,000	>50,000	70.34	>50,000	3.03	394.6	92.62
Omicron BA.4.6: hCoV-19/USA/WI-UW-12757/2022	322.57	>50,000	>50,000	>50,000	>50,000	3.8	258.83	>10,000
Omicron BA.4.6: hCoV-19/USA/WI-UW-12767/2022	307.11	>50,000	>50,000	>50,000	>50,000	2.26	426.89	>10,000

C Inhibitory Activity of Antiviral Drugs



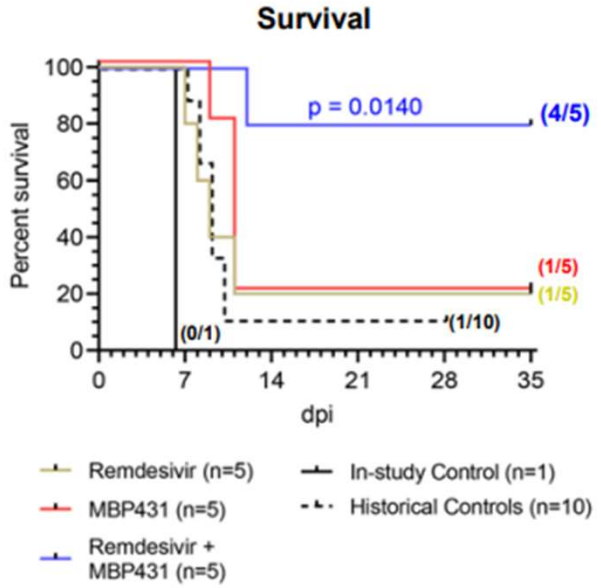
D Viral Susceptibility to Drug

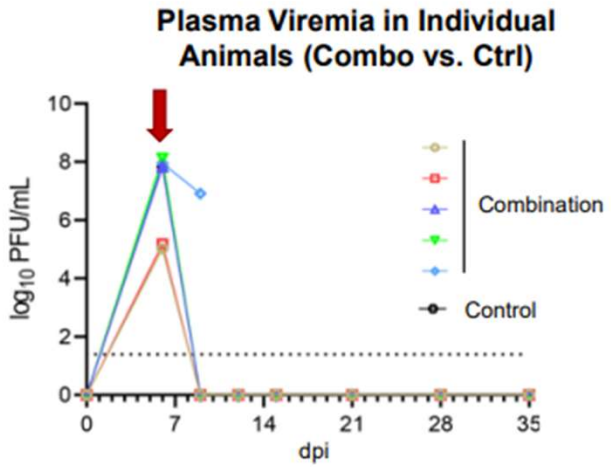
	GS-441524 Remdesivir	EIDD-1931 Molnupiravir	PF-07321332 Nirmatrelvir
	IC_{50} (μmol/liter)		
Ancestral strain: SARS-CoV-2/ UT-NC002-1T/Human/2020/Tokyo	1.23	1.46	1.08
Delta: hCoV-19/USA/ WI-UW-5250/2021	0.61	1.85	3.29
Omicron BA.2: hCoV-19/ Japan/UT-NCD1288-2N/2022	2.68	6.60	3.69
Omicron BA.5: hCoV-19/Japan/ TY41-702/2022	0.78	8.36	2.01
Omicron BA.4.6: hCoV-19/USA/ WI-UW-12757/2022	1.95	8.38	4.43
Omicron BA.4.6: hCoV-19/USA/ WI-UW-12767/2022	0.54	2.62	1.29

Relevance of combination therapy

Remdesivir + Monoclonal Antibody in Rhesus Monkeys Infected with SUDV

- SUDV (Sudan ebolavirus, Gulu variant) infection in rhesus monkeys, 1000 pfu i.m.
- Treatment initiated on Day 6 post infection (N=5/group):
  - Single dose MBP431 (15mg/kg) i.v.
  - Once-daily Remdesivir (10/5 mg/kg) i.v. for 12 days
  - Combination





Cross, et al (2022). Combination therapy with remdesivir and monoclonal antibodies protects nonhuman primates against advanced Sudan virus disease. JCI Insight, 7(10)

Conclusions

- Medicinal products for treatment of viral diseases **must be approved by EMA in the EU**
- **Antivirals need to be developed and approved for specific viral diseases** treatment and/or prevention
- Approval of broad-spectrum antivirals for specific viral disease use **enhances the potential rapid use during outbreaks and epidemics due to other viruses**, based on availability of commercial product manufacturing, characterisation of safety and dose
- **ETF provides a suitable platform for scientific advice on the development of new antiviral agents** in preparedness and during emergencies
- **ETF ready to engage with academia and clinical trials networks on platform clinical trials**
- **International cooperation among regulators, e.g. ICMRA, WHO and stakeholders is crucial** for rapid development of promising antivirals

Latest updates on ETF on EMA's corporate website: Emergency Task Force (ETF) | European Medicines Agency (europa.eu)

ema.europa.eu

@EMA_News

European Medicines Agency

Marco.Cavaleri@ema.europa.eu