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Regulatory perspective on clinically relevant endpoints for COVID-19 and Influenza

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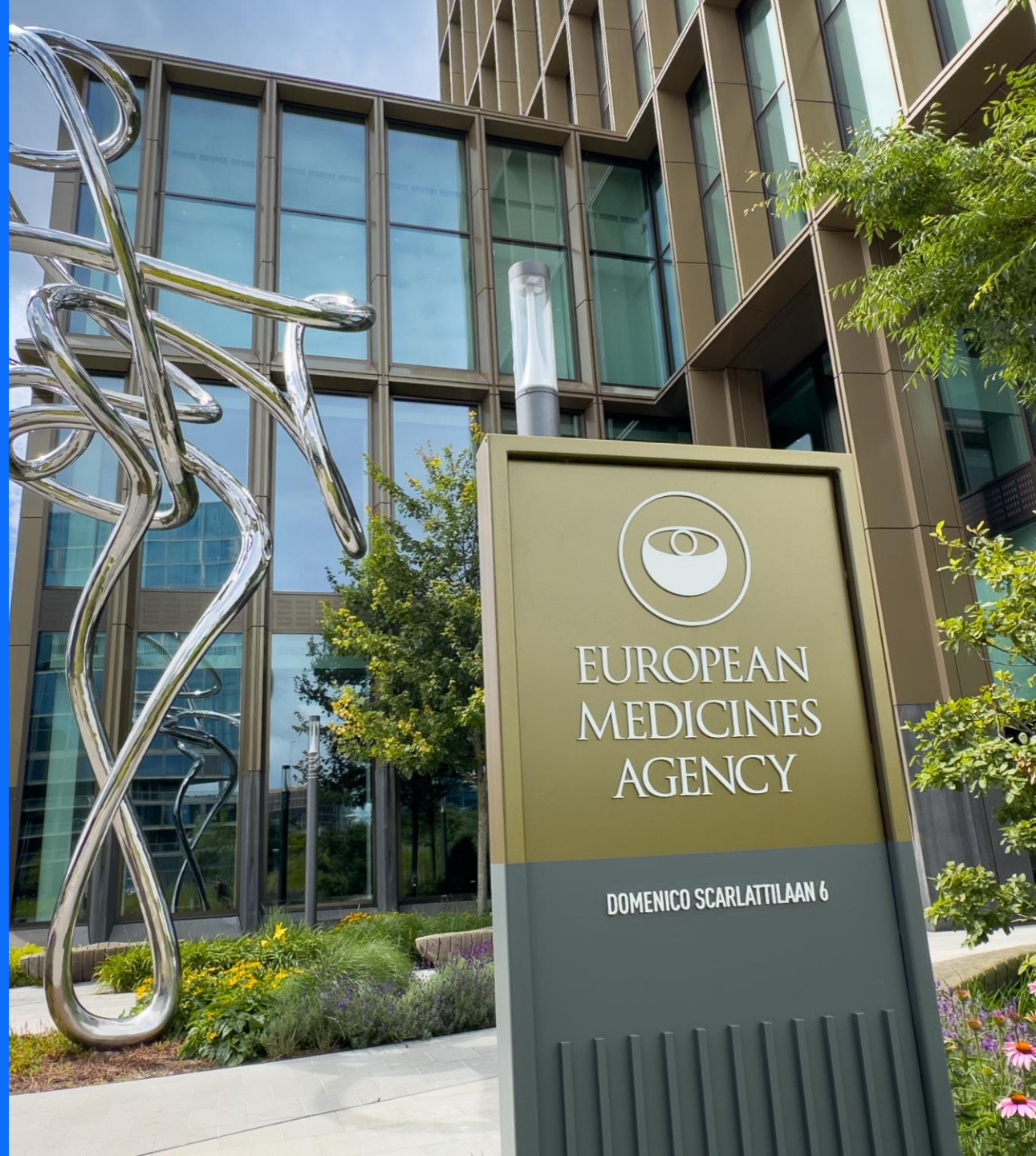
EMA workshop on primary efficacy endpoints for antivirals and monoclonal antibodies intended for the treatment of COVID-19 and Influenza



EU approved antivirals for treatment COVID-19

INN (Brand name)	MoA	Indication
Nirmatrelvir/Ritonavir (Paxlovid)	M^{pro} inhibitor	**Treatment** of coronavirus disease 2019 (**COVID-19**) in **adults** who **do not require supplemental oxygen** and who are at **increased risk** for progressing to severe COVID-19
Remdesivir (Veklury)	RdRp inhibitor	**Treatment** of coronavirus disease 2019 (**COVID-19**) in: • **adults and paediatric** patients (at least 4 weeks of age and weighing at least 3 kg) **with pneumonia requiring supplemental oxygen** (low- or high-flow oxygen or other non-invasive ventilation at start of treatment) • **adults and paediatric** patients (weighing at least 40 kg) who **do not require supplemental oxygen** and who are at **increased risk** of progressing to severe COVID-19

EU approved antivirals for treatment of Influenza

INN (brand name)	INN (brand	Indication
Baloxavir Marboxil (Xofluza)	cap-dependent endonuclease (CEN) inhibitor	**Treatment** of **uncomplicated influenza** in patients aged 3 weeks and above. **Post-exposure prophylaxis** of influenza in individuals aged 3 weeks and above. Xofluza should be used in accordance with official recommendations
Zanamivir IV (Dectova)	Neuraminidase inhibitors	**Treatment** of **complicated and potentially life-threatening influenza A or B virus infection** in adult and paediatric patients (aged ≥6 months) when: • The patient's influenza virus is known or suspected to be resistant to anti-influenza medicinal products other than zanamivir, and/or • Other anti-viral medicinal products for treatment of influenza, including inhaled zanamivir, are not suitable for the individual patient. Dectova should be used in accordance with official guidance.
Oseltamivir (Tamiflu)	Neuraminidase inhibitors	• **Treatment of influenza** in adults and children including full term neonates who present with symptoms typical of influenza, when influenza virus is circulating in the community. Efficacy has been demonstrated when treatment is initiated within two days of first onset of symptoms. • **Post-exposure prevention** in individuals 1 year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community. The appropriate use of Tamiflu for prevention of influenza should be determined on a case by case basis by the circumstances and the population requiring protection. • In **exceptional situations** (e.g. in case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) **seasonal prevention** could be considered in individuals one year of age or older. • **Post-exposure prevention** of influenza in **infants less than 1 year** of age during **a pandemic influenza outbreak**
Zanamivir inhaled (Relanza) (Approved at MS level)	Neuraminidase inhibitors	• **Treatment of influenza A and B** in adults and children (≥ 5 years) who present with symptoms typical of influenza when influenza is circulating in the community. • **Post-exposure prophylaxis of influenza A and B** in adults and children (≥ 5 years) following contact with a clinically diagnosed case in a household (see section 5.1 for children aged 5-11 years). • In **exceptional circumstances**, Relenza may be considered for **seasonal prophylaxis of influenza A and B** during a **community outbreak** (e.g. in case of a mismatch between circulating and vaccine strains and a pandemic situation).
Amatadine and rimantadine (Approved at MS level	M2 inhibitors	**Chemoprophylaxis** and **chemotherapy** against **influenza type A.** Resistance and ineffectiveness of rimatedine against influenza B → no longer widely used

Challenges on designing clinical studies

How to generate robust clinical data needed for regulatory approval?

How to define appropriate patient populations?

What are clinically feasible and relevant primary efficacy endpoints?

How to generate robust clinical data needed for regulatory approval?

- Well-designed, controlled randomised clinical trials to generate **robust and reliable efficacy data needed for approval**
- **Feasibility issue** concerning the **conduct of randomised clinical trials (RCT)** in a **high-risk and the mild moderate population**

Issues relate to:

- **Feasibility** of demonstrating efficacy due to overall **low event rates for progression and decreased impact on symptoms resolution**→ hamper enrolment in outpatient and in patient trials with established primary efficacy endpoints
- **Ethical concerns** of conducting placebo-controlled studies in high-risk patients due to available treatment options
- **Difficulties** of conducting **non-inferiority studies with active comparator → challenge** of deriving a reliable **NI margin**

What is the appropriate study population and study design ?

Regulatory considerations – Define patient population

What is the **optimal patient population** to demonstrate efficacy of antivirals?

What are **risk factors** for severe disease?

The **population** chosen **impact** the choice of **endpoint**

Immunocompromised patients have an **unmet medical need** and may **benefit most** from an antiviral → how to design studies?

What is the appropriate study population?

Primary efficacy endpoints of approved drugs

29-day Mortality	• **Remdesivir**
Hospitalisation and all cause mortality through D28	• **Remdesivir** and **Paxlovid** (different time on onset of symptoms ≤ 7 days and ≤3 days)
Time to clinical response	• **Zanamivir iV** (**composite of viral sign stabilisation** (temperature, oxygen saturation, respiratory status, heart rate and systolic blood pressure) **or hospital** discharge)
Time to recovery D28	• **Remdesivir** (**discharged** from hospital (with or w/o limitations of activity or home oxygen requirements) or **hospitalised** but not requiring supplemental oxygen and no longer requiring ongoing medical care
Clinical improvement	• **Remdesivir**: **clinical status on Day 14** assessed on a 7-point ordinal scale ranging from hospital discharge to increasing levels of oxygen and ventilatory support to death
Time to resolution of symptoms (TTRS), Time to alleviation of symptoms	• **Baloxavir** (cough, sore throat, headache, nasal congestion, feverishness/chills, muscle or joint pain, and fatigue), 21.5 hours, all symptoms absent or mild • **Zanamivir** inhaled (time to alleviation of clinically significant signs and symptoms of influenza (fever/feverishness, headache, myalgia, cough and sore throat), 24 hours, all symptoms none or mild • **Oseltamivir** (feverish feeling, myalgia, headache, sore throat, cough, overall discomfort, and nasal stuffiness or runny nose) 24 hours, all symptoms mild or none
Incidence of laboratory-confirmed, symptomatic influenza	• **Oseltamivir**, **Baloxavir** and **Zanamivir inhaled**

Can the established primary efficacy endpoints generate robust clinical efficacy data for approval in the current epidemiological situation?

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Do trial design issues impact the TTRS outcome?

	Nirmatrelvir/RTV EPIC-SR	Obeldesivir OAKTREE	Ensitrelvir SCORPIO-SR
Study design	Placebo controlled, double blinded RCT	Placebo controlled, double blinded RCT	Placebo-controlled, double-blinded RCT
Population	• Symptomatic standard risk and vaccinated high-risk outpatients, • **≤ 5 days** of positive test • At least **one COVID-19 symptom**	• Standard risk of developing severe illness outpatients • ≤**3 days** of positive test • **≥2 symptoms**	• Symptomatic patients (aged 12 to <70 years) with mild to moderate COVID-19 • **≤ 120 hours** of positive test • At least **one symptom**
Number of participants enrolled	**1296** participants enrolled	**1900 patients** were planned	**1821** participants enrolled, 1030 randomised
Primary efficacy endpoint	Time to **sustained alleviation** of **all targeted** COVID-19 symptoms D28	Time to COVID-19 **symptom alleviation** by Day 29	Time to **resolution of the composite of 5 COVID-19 symptoms** D28
Time of study conduct/Variant	Aug 2021 – July 2022 Delta and Omicron	Feb. 2023 –Jan. 2024 Omicron XBB, JN.1	February 10 -July 10, 2022 Omicron, BA.1, BA.2, BA.4, BA.5
Number of symptoms	**11**	**9**	**5**
Definition of sustained alleviation	The **first of four consecutive days** during which all symptoms that have been scored: moderate or severe at baseline => mild or absent Mild or absent at baseline => absent	**Change in severity** of all targeted symptoms first of **48 consecutive hours** that have been scored: moderate or severe at baseline => mild or none mild or none at baseline => none	Change of severe symptoms at baseline => have remained improved to moderate or better, moderate symptoms at baseline => have remained improved to mild or better, and mild symptoms at baseline =>have remained mild or better **for 24 hours**.
Statistics	**Log-rank test**, Alpha **0.05 significance level**, only if stat. significant	**Stratified log-rank test** with stratification factor included, 2-sided **significance level of 0.05** to compare treatment differences **Kaplan-Meier-method,** median time to symptom alleviation **per treatment group** including 95% CI	*Peto-Prentice generalized Wilcoxon test*, with 80% power and a 2-sided **significance level of 0.05.** Primary analysis population: < 72 hours of positive viral test results

References: EPIC-SR: Nirmatrelvir for Vaccinated or Unvaccinated Adult Outpatients with Covid-19 | New England Journal of Medicine
OAKTREE: P-2036. Obeldesivir for Treatment of COVID-19 in Adults and Adolescents Without Risk Factors for Progression to Severe Disease: the OAKTREE Study – PMC
SCORPIO-SR: Efficacy and Safety of 5-Day Oral Ensitrelvir for Patients With Mild to Moderate COVID-19: The SCORPIO-SR Randomized Clinical Trial | Infectious Diseases | JAMA Network Open | JAMA Network

Results of studies

	Nirmatrelvir/RTV EPIC-SR	Obeldesivir OAKTREE	Ensitrelvir SCORPIO-SR
PEP	Time to sustained symptom resolution of all targeted symptoms: Nirmatrelvir/RTV : **12 days** (11-13) Placebo: **13 days** (12-14) **P=0.60**	Median time to symptom alleviation: Obeldesivir: **5.9 days** (95% CI, 5.4-6.1) Placebo: **6.0 days** (95% CI, 5.8-6.3) **P = 0.068**	Time to resolution of 5 symptoms (72h randomisation): Ensitrelvir: 167.9 hours Placebo: 192.9 hours **-24.3 hours, p = 0.04** **No statistical significance** in patients randomized within 120 hours of disease onset
SEP	Hospitalisation and Death at D28 Nirmatrelvir/RTV : N=5 Placebo: N=10 Study failed	Time to symptom resolution: Obeldesivir: **9.2 days** [95% CI 8.9-10.0] PBO: **9.3 days** [95% CI 8.9-10.1] **P = 0.56.** Viral load reduction: Obeldesivir: viral load reduction with least squares mean treatment differences of **D3: -0.31** (P < 0.0001) log10 copies/mL **D5: -0.18** (P = 0.0037) log10 copies/mL Study failed	Time to resolution of 12 symptoms: Ensitrelvir 125 mg: **179.2 hours** (-34 hours, p = 0.07) 250 mg: **184.9** (-28.3 hours, p=0.08) Placebo: **213.2** hours **Not significant** Time to resolution of 14 symptoms: Ensitrelvir 125 mg: **187.8 hours** (-44.1 hours, **p = 0.03)** 250 mg: **190.3** (-41.5 hours, p=0.05) Placebo: **231.8** hours **No statistical significance** in in those enrolled within 120 hours

TTRS endpoint for COVID-19 does not seem to work anymore

References: EPIC-SR: Nirmatrelvir for Vaccinated or Unvaccinated Adult Outpatients with Covid-19 | New England Journal of Medicine
OAKTREE: P-2036. Obeldesivir for Treatment of COVID-19 in Adults and Adolescents Without Risk Factors for Progression to Severe Disease: the OAKTREE Study – PMC
SCORPIO-SR: Efficacy and Safety of 5-Day Oral Ensitrelvir for Patients With Mild to Moderate COVID-19: The SCORPIO-SR Randomized Clinical Trial | Infectious Diseases | JAMA Network Open | JAMA Network

Regulatory considerations on TTRS endpoints

Clinical relevance/impact of different definitions ?

Clinical relevance of a 24 hours reduction in symptoms?

TTRS **worked** for Influenza antivirals

TTRS **does not work** for COVID antivirals in current epidemiological situation

What endpoint to use for treatment options?

Regulatory considerations on virological endpoints

Issue on viral load:

- **Magnitude of response** is **dependent on** several factors, including host-factors, virus types/variants and time from onset of symptoms prior to treatment initiation.
- **Clinical evidence** of correlation of viral load with clinical benefit **not consistently shown**

For COVID-19:

- **Lack of data**
- **Divergent evidence** of correlation between viral load reduction and clinical efficacy, e.g. remdesivir, nirmatrelvir/ritonavir and molnupiravir

For Influenza:

- **Divergent evidence** of correlations between viral load reduction and clinical efficacy, e.g. outpatients and hospitalised patients

Presently not sufficient evidence to support the use of viral load reduction as surrogate endpoint for the confirmation of clinical efficacy for regulatory decision making

Pre- and post-exposure prophylaxis

- Influenza antivirals have been approved for post-exposure prophylaxis based on a primary efficacy endpoint of:

Incidence of laboratory-confirmed, symptomatic influenza

- Mabs for COVID-19 have been approved for pre-exposure prophylaxis based on a primary efficacy endpoint of:

Incidence of laboratory-confirmed, symptomatic COVID-19

- No COVID-19 antiviral has to date been approved for pre-postexposure prophylaxis

Having approved antivirals for pre- and post exposure prophylaxis for Influenza and COVID-19 is important

Potential new endpoints - Blocking viral transmission as in CENTERSTONE study

Potential **public health benefit** of **blocking viral transmission**

Clinical relevance?

→ Health benefit **not related** to the **treated patient**

Relevance of **not blocking** symptomatic transmission?

Relevance of **baseline immunity?**

Could this be an interesting endpoint also in terms of pandemic preparedness?

Reference: Efficacy of Baloxavir Treatment in Preventing Transmission of Influenza | New England Journal of Medicine

Regulatory considerations to be addressed

Need of well-designed, controlled randomised clinical trials to generate **robust and reliable efficacy data** for approval of treatment and prevention options

Need for **alignment on outcome measures**, e.g. development of Core outcome Sets?

Context of use of antivirals

Relevance and **usefulness** of **established** and **alternative primary efficacy endpoints** for regulatory approval

How to define **appropriate patient population** for clinical trials?

How to address **feasibility concerns** on conducting RCTs?

Outcomes of the workshop will inform EMA guidelines on COVID-19 and Influenza

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Thank you

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