Nirmatrelwir/rytonawir w COVID-19

17.02.2022

Materiał analityczny przygotowany na potrzeby dyskusji Ekspertów Panelu Farmakoterapia w dniu 4 stycznia 2022 r.

Niniejsze opracowanie analityczne stanowi materiał dowodowy zidentyfikowany w ramach przeglądu baz informacji medycznej (PubMed, Embase, medRxiv) za okres do 3.01.2022 r. Dodatkowo przeszukano zasoby strony internetowej Europejskiej Agencji Leków (EMA).

W ramach przeprowadzonego przeglądu zidentyfikowano **1 RCT**:

- **EPIC-HR** (wyniki badania dostępne w ramach opublikowanej dokumentacji EMA)

Wyniki badania EPIC-HR zostały poddane aktualizacji w związku z ich publikacją w recenzowanym czasopiśmie – publikacja Hammond 2022 (NEJM, 16.02.2022).

Badanie EPIC-HR- metodyka (dane EMA)

<table>
<tr><th colspan="5">EPIC-HR
Interim analysis of EPIC-HR: Study of Oral PF-07321332/Ritonavir Compared With Placebo in Nonhospitalized High Risk Adults With COVID-19 (study results by EMA 22.12.2021); NCT04960202</th></tr>
<tr><th>Methodology</th><th>Population</th><th>Intervention</th><th>Control</th><th>Limitations</th></tr>
<tr><td>RCT, multicenter, double-blind, placebo-controlled, phase 2/3

South and North and America (USA: 45%), Europe, Africa, Asia

Primary analysis: participants enrolled by September 29, 2021</td><td>N=1219 (interim analysis)
Non-hospitalized patients with COVID-19
<u>Inclusion criteria:</u>
– ≥18 years
– non-hospitalized
– confirmed SARS-CoV-2 within 5 days prior to randomization
– symptom onset of ≤ 5 days
– unvaccinated
– ≥1 risk factor for progression to severe disease: diabetes, overweight (BMI > 25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically-related technological dependence, or ≥60 years of age regardless of comorbidities
<u>Exclusion criteria:</u>
– SARS-CoV-2 vaccination
– known history of prior COVID-19 infection</td><td>Ni=607 (mITT1)

PAXLOVID
(PF-07321332; nirmatrelvir) in combination with ritonavir
300 mg/100 mg
taken together orally every 12 hours for 5 days</td><td>Nc=612 (mITT1)

Placebo</td><td>– Study results not published in in a peer-reviewed journal
– Study funded by Pfizer
– Interim analysis
– No information about SoC</td></tr>
<tr><td></td><td>Male, %</td><td colspan="2">52</td><td></td></tr>
<tr><td></td><td>Age, mean [years]</td><td colspan="2">45</td><td></td></tr>
<tr><td></td><td>Age >65 years, %</td><td colspan="2">11.4</td><td></td></tr>
<tr><td></td><td>onset of symptoms ≤ 3 days from initiation of study treatment, %</td><td colspan="2">63</td><td></td></tr>
<tr><td></td><td>BMI >25 kg/m2, %</td><td colspan="2">79.4</td><td></td></tr>
<tr><td></td><td>Hypertension, %</td><td colspan="2">32.4</td><td></td></tr>
<tr><td></td><td>Diabetes mellitus, %</td><td colspan="2">12.9</td><td></td></tr>
<tr><td></td><td>Serological positive, %</td><td colspan="2">55.6</td><td></td></tr>
<tr><td></td><td>Viral load</td><td colspan="2">4.71 log10 copies/mL</td><td></td></tr>
</table>

Badanie EPIC-HR- wyniki (dane EMA)

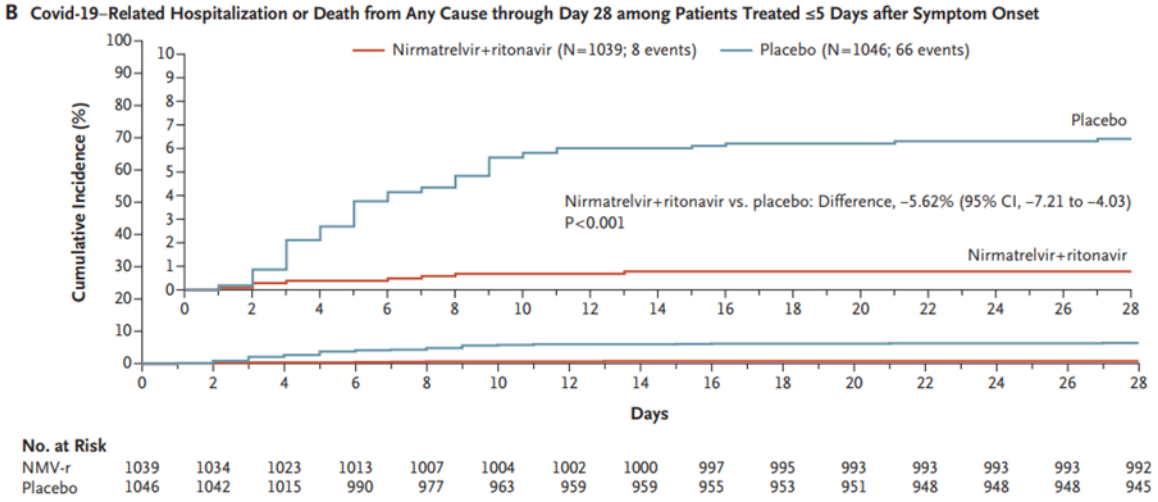
Results							
Outcome				PAXLOVID	Placebo	Statistical variability of differences	
event			follow-up (days)			relative parameter (95% CI)	absolute parameter (95% CI)
Hospitalization or death n/N (%)	mITT (≤3 days)		28	3/389 (0.8)	27/385 (7)	**^RR=0.11 (0.03; 0.36)**	**^NNT=17**
	mITT1 (≤5 days)	Total		6/607 (1)	41/612 (6.7)	**^RR=0.15 (0.06; 0.34)**	**^NNT=18**
		Serology negative		5/256 (2)	36/272 (13.2)	**^RR=0.15 (0.06; 0.37)**	**^NNT=9**
		Serology positive		1/344 (0.3)	5/332 (1.5)	^RR=0.19 (0.02; 1.64)	-
		>3 days		3/218 (1.4)	14/227 (6.2)	**^RR=0.22 (0.06; 0.77)**	**^NNT=21**
Mortality, n/N (%)	mITT (≤3 days)		28	0/369 (0)	7/385 (1.8)	^RR=0.07 (0.00; 1.21)	-
	mITT1 (≤5 days)			0/607 (0)	10/612 (1.6)	**^RR=0.05 (0.00; 0.82)**	**^NNT=62**
Treatment-emergent AEs, %			nd	19	21	-	-
SAEs, %				1.7	6.6	-	-
Discontinuation due to AEs, %				2.1	4.1	-	-
Conclusions: PAXLOVID (PF-07321332; ritonavir) was found to reduce the risk of hospitalization or death by 89% compared to placebo in non-hospitalized high-risk adults with COVID-19.							

Badanie EPIC-HR (Hammond 2022)- metodyka

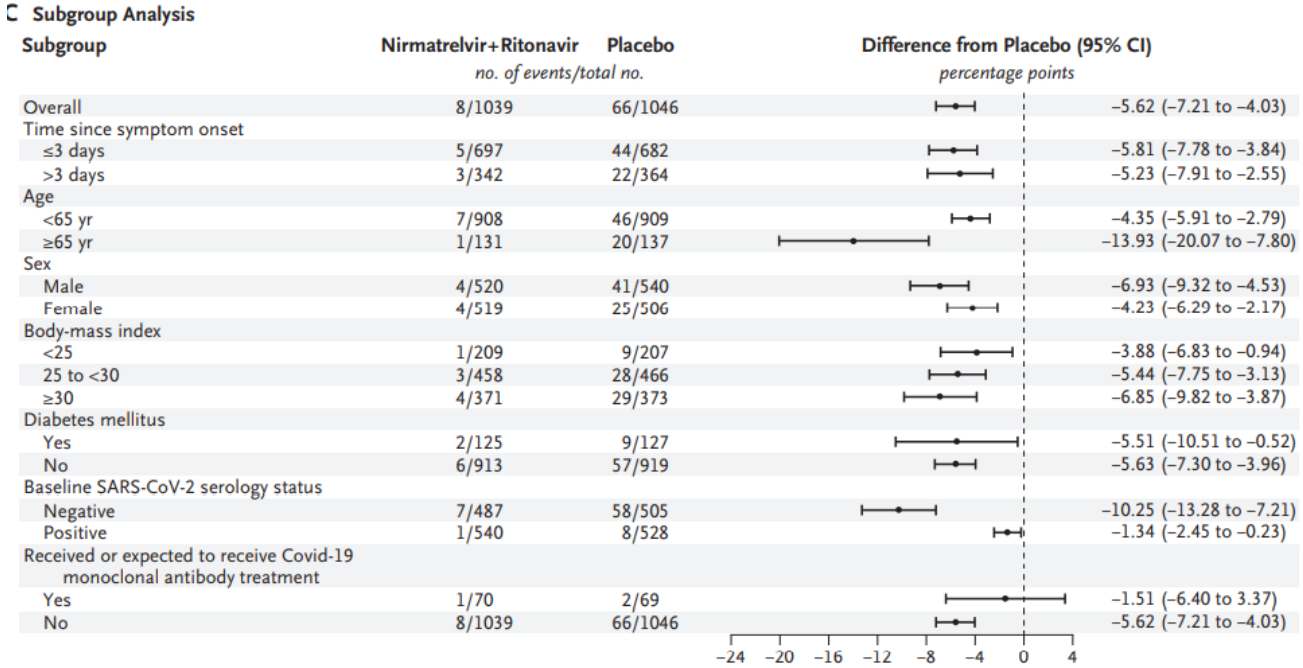
EPIC-HR (Hammond 2022)					
Oral Nirmatrelvir for High-Risk. Nonhospitalized Adults with Covid-19 (The new England journal of medicine. 16 Feb 2022); NCT04960202					
Methodology	**Population**		**Intervention**	**Control**	**Limitations**
RCT, double blind, Phase 2-3 Randomization: 1:1 Stratification: by geographic region and by receipt or expected receipt of Covid-19 monoclonal antibodies multicenter – 21 countries, 5 continents Study conduction: July 16 - December 9, 2021	N= 2246 Inclusion criteria: – ≥18 yrs, – confirmed symptomatic SARS-CoV-2 infection ≤5 days before randomization, – ≥1 symptom of COVID-19 on the day of randomization, – ≥ 1 factor associated with an increased risk of severe COVID 19 Exclusion criteria: – >5 days earlier confirmed SARS-CoV-2 infection or hospitalization for Covid-19, – anticipated need for hospitalization within 48 hours after randomization, – prior receipt of convalescent Covid-19 plasma or SARS-CoV-2 vaccine.		Ni=1120 N=697 (modified ITT population*) N=1109 (safety analysis population) 300 mg of nirmatrelvir plus 100 mg of ritonavir (a pharmacokinetic enhancer) orally administered every 12 hours for 5 days	Nc=1126 N=682 (modified ITT population*) N=1115 (safety analysispopulation) placebo every 12 hours for 5 days	– the trial is restricted to unvaccinated persons – supported by Pfizer
	Age (Median. range) – y		45.00 (18.00; 86.00)	59.00 ± 1.79	
	Male sex - %		50.5	51.7	
	Race or ethnic group (%)	White	71.4	71.7	
		Black	5.4	4.4	
		Asian	13.8	14.3	
		Other or unknown	9.4	9.6	
	Time since first symptom- median (range), days		3 (0; 7)	3 (0; 9)	
	Covid-19 monoclonal antibody treatment - % of patients		6.2	6.2	
	Serology status: negative - %		46.2	47.7	
	Viral load ≥104 copies/ml - %		60.4	60.0	

Badanie EPIC-HR (Hammond 2022)- wyniki

Results					
Outcome		PAXLOVID	Placebo	Statistical variability of differences	
event	follow-up (days)			relative parameter (95% CI)	absolute parameter (95% CI)
Hospitalization for Covid-19 (in a modified ITT population) – n/N (%)	28	5/697 (0.72)	44/682 (6.45)	**0.11 (0.04; 0.28)**	**18 (4; 27)**
Death form any cause (in a modified ITT population) – n/N (%)		0	9/682 (1.32)	**0.05 (0.003; 0.883)**	**76 (46; 234)**
Hospitalization for Covid-19 – n/N (%) – in population treated ≤5 days after onset of symptoms	28	8/1039 (0.77)	66/1046 (6.31)	**0.12 (0.06; 0.25)**	**19 (15; 26)**
Death form any cause – n/N (%) - in population treated ≤5 days after onset of symptoms		0	12/1046 (1.15)	**0.04 (0.002; 0.679)**	**88 (55; 212)**



Badanie EPIC-HR (Hammond 2022)- wyniki cd.

Results					
Outcome		**PAXLOVID**	**Placebo**	**Statistical variability of differences**	
event	**follow-up (days)**			**relative parameter (95% CI)**	**absolute parameter (95% CI)**
					
Any adverse events — n/N (%)	34	251/1109 (22.6)	266/1115 (23.9)	0.95 (0.81; 1.10)	-
Serious adverse event – n/N (%)		18/1109 (1.6)	74/1115 (6.6)	0.24 (0.15; 0.41)	20 (16; 30)
Maximum grade 3 or 4 adverse event - n/N (%)		45/1109 (4.1)	93/1115 (8.3)	0.49 (0.34; 0.69)	24 (16; 44)
Grade 5 adverse event (death) - n/N (%)		0	13/1115 (1.2)	0.037 (0.002; 0.626)	85 (55; 197)
Discontinued drug or placebo because of adverse event - n/N (%)		23/1109 (2.1)	47/1115 (4.2)	0.49 (0.3; 0.8)	47 (28; 145)

Authors' conclusions: Treatment of symptomatic Covid-19 with nirmatrelvir plus ritonavir resulted in a risk of progression to severe Covid-19 that was 89% lower than the risk with placebo, without evident safety concerns.