Cost-effectiveness Analysis of Nirmatrelvir/Ritonavir Compared with Molnupiravir in Patients at High Risk for Progression to Severe COVID-19 in Japan

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Acceptance Code EE180

INTRODUCTION

Nirmatrelvir/ritonavir (NMV/r) and molnupiravir are oral antiviral drugs approved for the treatment of early symptomatic patients with mild-to-moderate Coronavirus disease 2019 (COVID-19) at high risk of progression to severe disease in Japan.

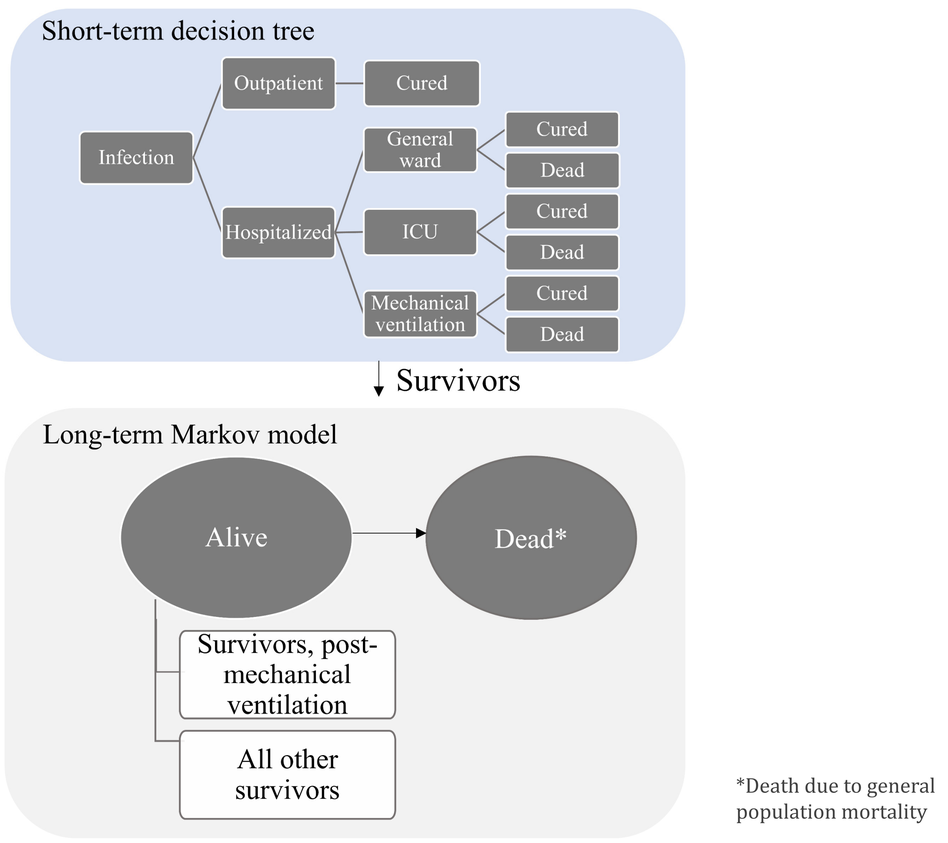
OBJECTIVES

We conducted a study to assess the cost-effectiveness of NMV/r versus molnupiravir or versus standard of care (SoC) in the antiviral eligible high risk COVID-19 positive population in Japan.

METHODS

An Excel-based cost-effectiveness analysis model was developed to describe the short-term acute infection period using a decision tree followed by a lifetime Markov model to capture the long-term impact of COVID-19 infection (Figure 1). The model was used to compare the cost-effectiveness of NMV/r compared to molnupiravir (base case) or SoC (scenario case) of patients with mild to moderate COVID-19 with risk factors for severe COVID-19 from a Japanese payer perspective.

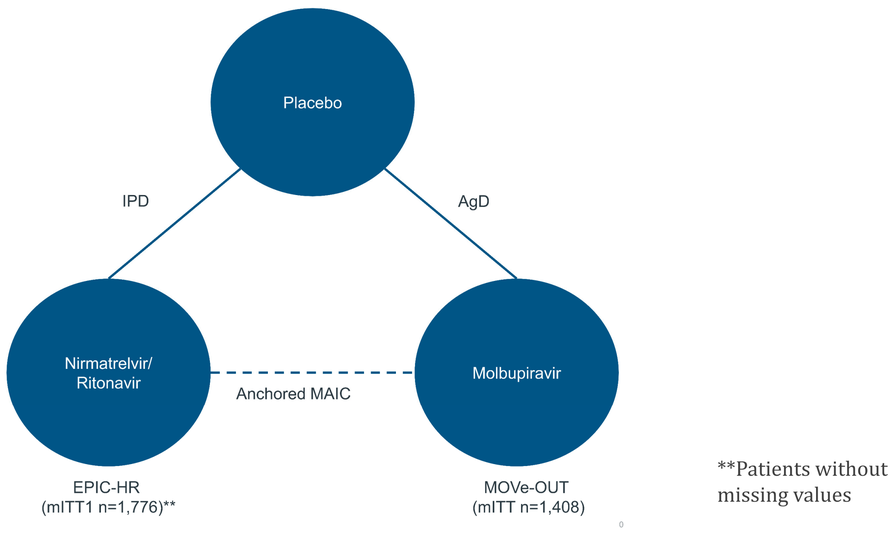
Figure 1. Hybrid cost-utility model structure, including a decision tree and Markov model



A systematic literature review (SLR) was conducted to obtain the clinical efficacy of NMV/r and molnupiravir in patients with COVID-19 till June 2023. The SLR identified two pivotal studies, viz. EPIC-HR and MOVe-OUT evaluating the efficacy and safety of NMV/r and molnupiravir, respectively. Then, as direct head-to-head clinical trials comparing the clinical efficacy of NMV/r and molnupiravir were absent, anchored matching adjusted indirect comparison (MAIC) approach was adopted (Figure 2). This is a novel technique allowing for a robust indirect comparison, by re-weighting Individual Patient Data from one study to the baseline summary statistics of another. The clinical efficacy end points (the outcome of the MAIC) of NMV/r (EPIC-HR) and molnupiravir (MOVe-OUT) was COVID-19 related hospitalization or death.

As MAIC result, NMV/r was shown to reduce the rate of COVID-19-related hospitalization or all-cause mortality by 88.16% compared to placebo group. Molnupiravir was shown to reduce this rate by 30.68% compared to placebo, as reported in MOVe-OUT (Table 1). For the clinical efficacy of NMV/r and SoC, the treatment effect of reduction of hospitalization/death was sourced from Leister-Tebbe et al. This resulted in a reduction of hospitalizations and/or deaths for NMV/r by 73.80% and 0% for SoC.

Figure 2. Conceptual figure of anchored MAIC comparing NMV/r to molnupiravir



General inputs on the proportion of hospitalized patients, deaths among ambulatory care patients, and the duration of COVID-19 symptoms from onset among vaccinated and unvaccinated patients were sourced from Japanese government data and COVID-19 registry data in Japan. Utilities were based on COVID-19 patients in Japan. Costs and health resource utilizations were estimated from hospital system data (HIS data), which includes electronic medical records and prescription data managed by IQVIA Solutions Japan G.K. One-way sensitivity analysis (OWSA) using ±20% of the parameter value and probabilistic sensitivity analysis (PSA) using 500 simulations was performed to assess the uncertainty of the model by randomly sampling the values.

Table 1. COVID-19-related hospitalization or all-cause death before/after matching

	Intervention			Placebo (PBO)			Total ESS	n/r - PBO (A)	Mol – PBO (B)	A – B	Lower 95% CI	Upper 95% CI
	Total	Outcomes*		Total	Outcomes*							
	n	n	%	n	n	%	n					
MOVe-OUT AgD	709	45	6.35%	699	64	9.16%						
EPIC HR before matching	875	8	0.91%	901	60	6.66%						
EPIC HR after matching			1.18%			10.00%	223	-8.83%	-2.81%	-6.02%	-8.83%	-3.17%

*COVID-19-related hospitalization or all-cause death

RESULTS

1. Base case and scenario case results

- The base case results over a lifetime time horizon showed that the incremental cost-effectiveness ratio (ICER) was JPY 164,934 (USD 1,165.12) per QALY gained, which was lower than the willingness-to-pay threshold in Japan (JPY 5,000,000/QALY [USD 35,320.71/QALY]) (Table 2).
- A scenario analysis showed that by changing the comparator from molnupiravir to SoC, the ICER for NMV/r was JPY 3,646,821 / USD 25,761.66 per QALY gained, which was lower than the threshold in Japan (Table 2).

2. OWSA and PSA results of base case and scenario case

- OWSA of base case and scenario case showed All the results showed that the ICER was less than JPY 5,000,000 /QALY (USD 35,320.71 /QALY).
- In PSA, the results of the cost-effectiveness acceptability curve showed that the probability that the ICER was below the willingness-to-pay of JPY 5,000,000 /QALY (USD 35,320.71 /QALY) was 100.00% for base case and 78.00% for scenario case.

Table 2. Base case and scenario analysis results

	Intervention/ comparator	QALY	Incremental QALY	Cost (JPY [USD])	Incremental cost (JPY [USD])	ICER (JPY [USD]/QALY)
Base case	NMV/r	15.752	0.013	¥6,248,014 ($44,136.86)	¥2,185 ($15.44)	¥164,934 ($1,165.12)
	Mol	15.739		¥6,245,829 ($44,121.42)		
Scenario case	NMV/r	15.751	0.025	¥6,251,137 ($44,158.92)	¥89,570 ($632.73)	¥3,646,821 ($25,761.66)
	SoC	15.726		¥6,161,567 ($43,526.19)		

LIMITATION

The target population in this analysis was conditioned on taking into account the prevalence of SARS-CoV-2 variants in Japan (since the Omicron strain epidemic) and vaccination status. However, in the SLR, the only randomized controlled trials of NMV/r and molnupiravir that met the criteria were the EPIC-HR and MOVe-OUT studies, which were conducted in unvaccinated subjects before the Omicron strain dominance period.

CONCLUSION

Our cost-utility analysing demonstrates that NMV/r improves quality of life and increases health care costs when compared to either molnupiravir or SoC. These benefits are gained from reductions in hospitalization and death driven by the higher effectiveness compared to the comparator. As the Japanese government stopped public funding for anti-COVID drugs since April 2024, the findings of this study provide important evidence for the cost-effectiveness of NMV/r from a Japanese payer perspective.

Abbreviations: AgD, aggregated data; COVID-19, Coronavirus disease 2019; CI, confidence interval; ESS, effective sample size; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; IPD, individual patient data; LY, life year; MAIC, matching adjusted indirect comparison; Mol, molnupiravir; NMV/r, nirmatrelvir/ritonavir; n/r, nirmatrelvir/ritonavir; OWSA, one-way sensitivity analysis; PBO, placebo; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; SLR, systematic literature review; SoC, standard of care.

Declaration of conflicting interests: A Yuasa and K Murata are full-time employees of Pfizer Japan Inc. H Matsuda and Y Kado are full-time employees of IQVIA Solutions Japan G.K., which received funding from Pfizer Japan Inc. to undertake the research outlined in this study. Y Fujii and M Yoshida are full-time employees of Pfizer R&D Japan. T Mugwagwa is a full-time employee of Pfizer Inc. Y Gu reports lecture fees not related to the submitted work from Pfizer Japan Inc., bioMérieux Japan Ltd., Nippon Becton Dickinson Company Ltd., and Gilead Sciences Inc., advisory fee from Pfizer Japan Inc., advisory fees not related to the submitted work from bioMérieux Japan Ltd., and research grants not related to the submitted work from MSD K.K. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the poster apart from those disclosed.