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Model-based dose selection for the phase 3 evaluation of molnupiravir (MOV) in the treatment of COVID-19 in adults

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Background

- There is an urgent need for effective treatment options that are easily administered and readily implementable in health systems globally to reduce the impact of COVID-19[1]
- Molnupiravir (MOV) is an orally administered ribonucleoside prodrug of β-D-N4-hydroxycytidine (NHC). NHC is converted to the pharmacologically active triphosphate form (NHC-TP), with sub-micromolar potency against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
- MOV acts by the mechanism of "viral error catastrophe", which occurs when NHC-TP is incorporated into the viral genome by the viral polymerase during replication, resulting in an accumulation of mutations in the viral RNA.[2] Once a tolerated threshold of viral RNA mutations has been exceeded, inhibition of viral replication and production of non-infectious virus lead to viral extinction
- The MOVe-OUT and MOVe-IN phase 2/3 trials are evaluating the efficacy, safety, and pharmacokinetics (PK) of MOV in adults with laboratory-confirmed COVID-19
  - Based on phase 2 results from both trials, only the outpatient trial MOVe-OUT has proceeded to phase 3, since MOV provided no clear clinical benefit to hospitalized patients[3,4]

Objectives

- To determine the optimal dose of MOV for further investigation in MOVe-OUT in adults with COVID-19,[3,4] using exposure-response modeling analyses based on multiple endpoints

Methods

Trial design and participants

- MOVe-OUT (NCT04575597, MK-4482-002) and MOVe-IN (NCT04575584, MK-4482-001) are two randomized, placebo-controlled, double-blind, multinational, dose-ranging phase 2/3 studies evaluating MOV in non-hospitalized and hospitalized adults, respectively, with laboratory-confirmed COVID-19
- MOVe-OUT enrolled non-hospitalized adults with mild or moderate COVID-19 and time since symptom onset (TSSO) ≤7 days, of whom 75% were considered high risk for severe illness due to COVID-19
  - Primary endpoints: (1) percentage of participants who are hospitalized and/or die and (2) adverse event (AE) rates
- MOVe-IN enrolled hospitalized adults with mild, moderate or severe COVID-19, who were not critically ill and had TSSO ≤10 days
  - Primary endpoints: (1) Time to sustained recovery and (2) AE rates
- MOVe-OUT and MOVe-IN evaluated MOV at 3 dose levels (200 mg, 400 mg, 800 mg) compared with placebo, administered every 12 hours for 5 days
- Plasma NHC, the primary circulating analyte, was measured predose and at 1, 3, 5, and 8 hours after the last dose in MOVe-IN and predose and 1.5 hours after the last dose in MOVe-OUT
- SARS-CoV-2 RNA viral load (VL) was measured using quantitative or qualitative polymerase chain reaction using nasopharyngeal swabs obtained at Days 1 (predose) and 3, day of the last dose, and at follow-up Days 10, 15, and 29

Exposure derived from population pharmacokinetic (popPK) model

- Individual participant-level plasma NHC exposures were estimated using a preliminary popPK model[5] developed using NHC plasma PK data from a phase 1 trial in healthy volunteers[6] as well as from MOVe-OUT and MOVe-IN

Exposure-response modeling

- Exposure-response analyses evaluated the relationship between popPK model-estimated NHC plasma exposures and virologic/efficacy outcomes using available data from MOVe-OUT and MOVe-IN, including the following key outcomes:
  - SARS-CoV-2 viral RNA mutation rate above the posthoc defined threshold threshold of either 3, 6, or 9 mutations per 10,000 nucleotides across the viral genome (approximately 30,000 nucleotides total), compared to the baseline (Day 1) sequence, during treatment
  - SARS-CoV-2 RNA titres
    - Change from baseline at Days 5, 10, 15, and 29
    - Slope of decline from baseline to Day 5
    - Proportion of participants achieving VL below the level of quantification (BLOQ) at Days 5, 10, 15, and 29
  - Percentage of participants who were hospitalized and/or died through Day 29 in MOVe-OUT (i.e., the primary endpoint of that trial)
  - Exposure-response relationships were modeled, testing several functional forms (E_{max}, sigmoidal E_{max}, linear), and all models included baseline VL as a covariate. Models were evaluated using all data as well as using subsets defined by study or TSSO (categorized as ≤5 days versus >5 days)
  - Investigations of exposure-response were not conducted for safety given the favorable tolerability profile and the lack of an identifiable safety pattern of drug related adverse events

Results

Trial population

- 302 and 304 participants were enrolled in the phase 2 components of MOVe-OUT and MOVe-IN, respectively

PK

- NHC exhibited dose-proportional PK, with exposures comparable across all evaluated demographic/clinical factors (including age, gender, body-mass index, body weight, ethnicity, and renal impairment status), supporting the use of the same dose in all participants in phase 3[5]

Table 1. Summary of exposure-response modeling (MOVe-OUT/MOVe-IN pooled)

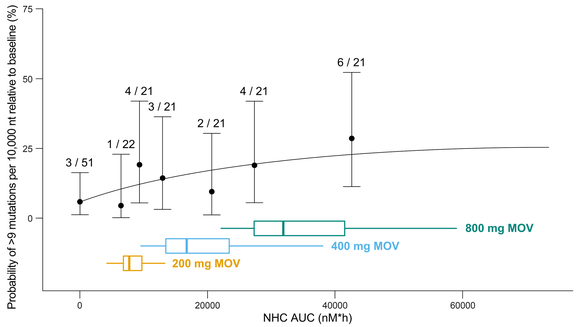
Exposure-response relationship identified				
		Pooled MOVe-IN/ MOVe-OUT	MOVe-OUT	TSSO ≤5 days in MOVe-IN/ MOVe-OUT
Mutation rate*	Above threshold of 3	p<0.05	Not tested due to small sample size	
	Above threshold of 6	p<0.05		
	Above threshold of 9	p<0.10		
Viral RNA	CFB on Day 5	Not significant	p<0.10	p<0.05
	CFB on Day 10	Not significant	Not significant	p<0.10
	CFB on Day 15	p<0.10	p<0.05	Not significant
	CFB on Day 29	Not significant	Not significant	Not significant
	Slope of decline from baseline to Day 5	Not significant	p<0.10	p<0.10
	Proportion of BLOQ at Day 5	Not significant	Not significant	p<0.05
	Proportion of BLOQ at Day 10	Not significant	Not significant	Not significant
	Proportion of BLOQ at Day 15	p<0.05	p<0.10	p<0.05
	Proportion of BLOQ at Day 29	p<0.10	p<0.10	p<0.10
Clinical efficacy	Hospitalization rate	Not applicable	p<0.05	Not applicable

*Threshold of either 3, 6 or 9 mutations per 10,000 nucleotides across the viral genome. Defined post hoc.
BLOQ, below the level of quantification; CFB, change from baseline.

Exposure-response analyses

- The mutation rate exposure-response was best described by logistic regression using an E_{max} model
- An increased SARS-CoV-2 mutation rate was observed in participants receiving any MOV dose compared with those receiving placebo, consistent with the proposed mechanism of action for MOV. The highest mutation rate post treatment was observed in the 800 mg group, with the drug effect reaching apparent saturation at 800 mg (Figure 1). The rate of mutations does not appear to be correlated with time from symptom onset to initiation of treatment

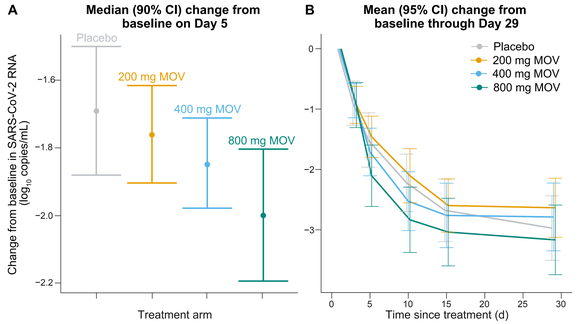
Figure 1. Model-estimated relationship between NHC plasma exposure and the probability of achieving >9 mutations/10,000 nucleotides of SARS-CoV-2 RNA (from nasopharyngeal swab, relative to baseline) at the end of treatment (MOVe-OUT/MOVe-IN pooled)



AUC, area under the curve; MOV, molnupiravir; NHC, β-D-N4-hydroxycytidine

- Exposure-response analyses suggest that 800 mg MOV resulted in a larger VL change from baseline, a steeper slope of VL decline, and a higher proportion of participants achieving VL BLOQ than placebo, 200 mg MOV, or 400 mg MOV in non-hospitalized participants enrolled in MOVe-OUT and in participants with TSSO ≤5 days pooled across both trials
- An exposure-response (nominal p value=0.10) was identified for MOVe-OUT and subset of TSSO ≤5 days for VL change from baseline at Day 5 and for slope of VL decline (Table 1). Exploration of VL change from baseline at Day 10 and 15 suggested a stronger exposure-response relationship than was seen in change from baseline at Day 5. Overall, these results were consistent with an enhanced rate of VL decline during the 5-day treatment period
- At 800 mg, mean VL change from baseline versus placebo in MOVe-OUT was -0.39 and -0.04 (log10 copies/mL) at Day 5 and Day 10, respectively. In the subgroup of TSSO ≤5 days in MOVe-OUT, mean VL change from baseline at 800 mg versus placebo was -0.71 and -0.60 (log10 copies/mL) at Day 5 and Day 10, respectively
  - This magnitude of VL change from baseline at 800 mg is in the range previously reported with monoclonal antibodies authorized for COVID-19 treatment, including casirivimab/imdevimab[7] and bamlanivimab/etesevimab[8]
- The model-estimated virologic reduction from baseline suggests that the 800 mg dose provides a larger VL reduction than 200 mg or 400 mg, with this result most evident in the data from participants with TSSO ≤5 days (Figure 2)

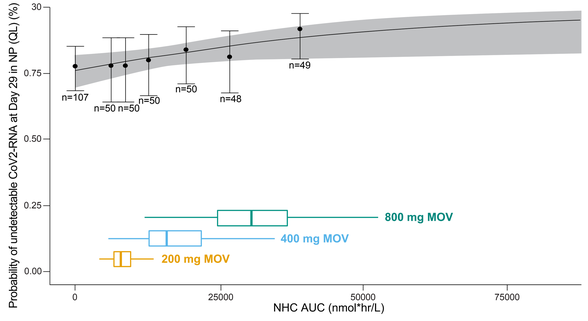
Figure 2. (A) Model-estimated relationship between NHC plasma exposure and viral load reduction from baseline at end of treatment and (B) actual viral load reduction over time, both by dose received in participants with ≤5 days from COVID-19 sign/symptom onset to randomization (MOVeOUT/MOVe-IN pooled)



CI, confidence interval; MOV, molnupiravir; NHC, β-D-N4-hydroxycytidine

- The exposure-response analysis evaluating the probability of achieving undetectable SARS-CoV-2 provided evidence of a drug effect at Day 5 in the subset of TSSO ≤5 days (data not shown) and in all data at Day 15 (data not shown) and Day 29 (Figure 3)

Figure 3. Exposure-response analysis of probability of BLOQ (Day 29): logistic regression model-estimated exposure-response relations for probability of negative VL on Day 29 (MOVeOUT/MOVe-IN pooled)

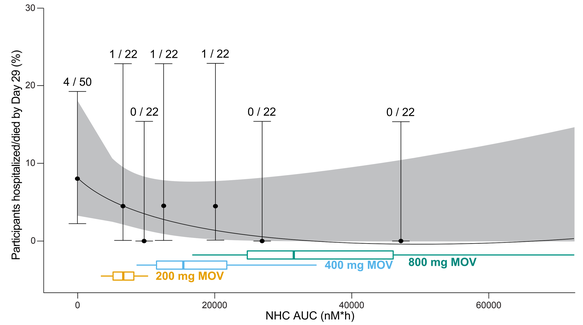


AUC, area under the curve; BLOQ, below the level of quantification; CI, confidence interval; MOV, molnupiravir; NHC, β-D-N4-hydroxycytidine; NP, nasopharyngeal; VL, viral load.

- In MOVe-OUT participants who had a TSSO of ≤5 days, there was a non-significant trend (p=0.098) towards a reduction in hospitalizations/deaths through Day 29 with increasing MOV exposure, suggesting that the 800 mg dose provides a greater clinical effect than lower doses (Figure 4)
- These results should be interpreted with caution given the small sample size, the number of events, and non-significant exposure-response relationships for some endpoints, but they suggest a potential drug and dose effect and the importance of early treatment on clinical outcome

Figure 4. Model-estimated relationship between NHC plasma exposure and the probability of hospitalization/death by Day 29 in non-hospitalized participants with ≤5 days from COVID-19 sign/symptom onset to randomization (MOVe-OUT trial only)

AUC, area under the curve; MOV, molnupiravir; NHC, β-D-N4-hydroxycytidine



Conclusions

- Based on the totality of the virologic and safety data, and trends in the clinical efficacy seen in MOVe-OUT, the 800 mg every 12 hours dose has been selected for further evaluation in the phase 3 component of MOVe-OUT
  - The MOV 800 mg dose provided a greater magnitude of virologic effect compared with 200 mg or 400 mg. Exposure-response analyses using available data showed that the 800 mg dose provided a substantial drug effect which some analyses suggested may be near maximal
  - Although there was no statistically significant exposure-response relationship observed in MOVe-OUT with respect to the primary endpoint of hospitalization or death, hospitalization rates and overall risk reduction were in the range of those seen with monoclonal antibodies in the outpatient population

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