Population Pharmacokinetics Analysis for Molnupiravir in Adults with COVID-19

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Introduction

- There is an urgent need for safe and effective oral treatments for COVID-19 that reduce progression to severe illness and risk of hospitalization or death
- Molnupiravir (MOV, MK-4482, EIDD-2801) is an orally available, ribonucleoside prodrug of β-D-N4-hydroxycytidine (NHC), with sub-micromolar potency against SARS-CoV-2[1]
- NHC is phosphorylated intracellularly to NHC triphosphate, its pharmacologically active form, and following its incorporation into the viral genome by the viral RNA polymerase during viral replication, it acts by inducing viral error catastrophe resulting from accumulation of deleterious mutations to a threshold beyond which the virus cannot replicate[2]
- NHC circulates in plasma and is the primary pharmacokinetics (PK) measure for the clinical program

Objectives

- To develop a population PK model for MOV using NHC plasma concentrations collected in healthy participants and participants with COVID-19
- To identify and quantify the effects of intrinsic and extrinsic factors influencing the plasma PK of NHC
- To predict the metrics of exposures used for parallel development of viral dynamics and exposure-response models

Methods

Study Design and Dose Administration

- The data used in this analysis were collected from one Phase 1 study in healthy participants (MK-4482-P004), one Phase 2a study in non-hospitalized participants with COVID-19 (MK-4482-P006), and in the Phase 2 portion of two Phase 2/3 studies in hospitalized participants with COVID-19 (MK-4482-P001) and non-hospitalized participants with COVID-19 (MK-4482-P002)
- MK-4482-P004 was an intensive PK study in healthy participants and included single ascending dose (50–2600 mg doses), food effect, and multiple ascending dose (twice-a-day [BID] 50–800 mg doses for 5 days) evaluations
- In MK-4482-P001, MK-4482-P002, and MK-4482-P006, MOV was administered at 200, 400, and 800 mg BID for 5 days to participants with COVID-19 and sparse PK samples were obtained
- Participants in the pooled dataset enrolled worldwide, albeit mostly in Europe (52.1%) and North America (28.8%)

Population Pharmacokinetics Analysis

- Exploratory analyses and presentations of data were performed using SAS Version 9.4 and KIWI Version 4
- Population modeling was performed using NONMEM, Version 7, Level 3, on an Intel cluster with the Linux operating system

Results

Data Description and Participant Characteristics

- The PK analysis dataset comprised 2952 sample records from 549 individuals – 100 healthy participants, 189 hospitalized participants with COVID-19, and 260 non-hospitalized participants with COVID-19
- 57.9% of participants were male (n=318) and 42.1% were female (n=231)
- The median (range) age was 50 years (18–91 years)
- The median (range) body weight was 80.7 kg (48–172 kg)
- Most participants identified as white (78.9%) and non-Hispanic or Latino (71.2%)
- 45.5% of participants had normal renal function, whereas 46.6% and 7.83% had mild or moderate impairment, respectively
- Using a modified Child–Pugh score (in which the encephalopathy, ascites, and internal normalization ratio were assumed to be normal), most participants had normal hepatic function (91.1%) or mild impairment (8.38%), and only 3 participants (0.55%) exhibited moderate impairment

Population Pharmacokinetics Analysis Results

- The PK of NHC was described by a linear two-compartment model with sigmoid absorption (implemented using a zero-order input process into a depot compartment followed by first-order absorption into the central compartment) and first-order elimination (Table 1, Figure 1A)

Table 1. Parameter Estimates and Standard Errors for the Final Pharmacokinetics Model

Parameter	Final Parameter Estimate		Magnitude of Variability	
	Population Mean	%RSE	Final Estimate	%RSE
CL/F				
Apparent central clearance in 80-kg participants (L/h)[a]	76.9	2.01	41.1 %CV	14.9
Power of body-weight effect (-)[a]	0.421	20.4		
VC/F				
Apparent central volume in 28-kg/m^2 BMI male participants (L)[b]	72.0	6.40	40.0 %CV	35.8
Proportional shift in female participants (-)[b]	-0.313	18.1		
Power of BMI effect (-)[b]	0.753	28.4		
Q/F				
Apparent distribution clearance (L/h)	3.35	6.73	NE	NA
VP/F				
Apparent peripheral volume (L)	70.0	14.8	NE	NA
KA				
First-order absorption rate constant (1/h)	0.830	2.81	NE	NA
D1				
Zero-order absorption duration (h)[c]	0.802	4.83	42.8 %CV	15.9
Proportional shift due to high-fat meal (-)[c]	5.68	10.4		
Proportional shift in oral solution and suspension (-)[c]	-0.644	5.71		
Proportional shift in hospitalized participants (-)	-0.265	22.4		
PHF[d]				
Probability of unknown high-fat meal (-)	0.250	FIXED	NE	NA
Residual Variability				
In Phase 1 studies	0.123	9.58	35.1 %CV	NA
In Phase 2 studies	0.268	5.33	51.7 %CV	NA
Minimum Value of the Objective Function = 38916.167				

[a]The typical apparent clearance ($\overline{CL}$) for an individual with weight $WTKG$ can be calculated as follows:

$$\overline{CL} = 76.9 \times (WTKG/80)^{0.421}$$

[b]The typical apparent central volume of distribution ($\overline{VC}$) for a male ($SEXF$=0) and female ($SEXF = 1$) individual with body mass index weight BMI can be calculated as follows:

$$\overline{VC} = 72 \times (1 - 0.313 \times SEXF) \times (BMI/28)^{0.753}$$

[c]The typical duration of the zero-order absorption process ($\overline{D1}$) for a healthy/non-hospitalized participant ($INPAT$=0) and hospitalized participant ($INPAT$=1) individual receiving MK-4482 as a capsule ($FSOL$=0) or an oral solution or suspension ($FSOL$=1) in fasted conditions (HFM=0) or after a high-fat meal (HFM=1) can be calculated as follows:

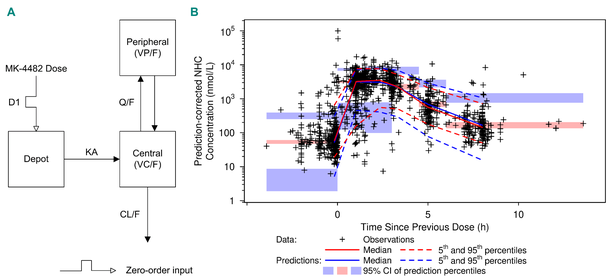
$$\overline{D1} = 0.802 \times (1 + 5.68 \times HFM) \times (1 - 0.644 \times FSOL) \times (1 - 0.265 \times INPAT)$$

[d]Mixture modeling was used to assign a food status in participants for whom the information was not recorded
Note: Shrinkage estimates: 9.0% for IIV in CL, 36.6% for IIV in VC, and 39.0% for IIV in D1

BMI, body mass index; CL, elimination clearance; %CV, coefficient of variation expressed as a percent; D1, duration of the zero-order absorption process; F, bioavailability; IIV, interindividual variability; KA, first-order absorption rate constant; NA, not applicable; NE, not estimated; %RSE, relative standard error expressed as a percent; PHF, probability of high-fat meal; Q, distribution clearance; VC, apparent central volume; VP, apparent peripheral volume

- Interindividual variability (IIV) was estimated for the elimination clearance (CL), apparent central volume (VC), and the duration of the zero-order absorption process (D1), although the last two IIV terms were only estimated in participants from MK-4482-P004 and participants from MK-4482-P001 contributing >2 samples. Distinct residual variability models were implemented for healthy participants and participants with COVID-19. All model parameters were estimated precisely (relative standard error expressed as a percent [%RSE] <29% for fixed effects and <36% for random effects) and without correlation (Table 1)
- Predictive performance of the selected model was assessed by (prediction corrected) visual predictive checks. In participants with COVID-19, the model predictions tracked the median and the variance in observed NHC concentrations generally well, with a slight underprediction at the lower end of the concentration range, which may be related to the inclusion of outlier observations in the analysis dataset (Figure 1B)

Figure 1. (A) Schematic of the Pharmacokinetics Model for Plasma NHC Following MOV Administration and (B) Visual Predictive Check Plot for the Final Pharmacokinetics Model in Participants With COVID-19[a]



[a]Medians and percentiles are plotted at the median time since previous dose of the data observed within each time since previous dose interval.
CI, confidence interval; CL, apparent elimination clearance; D1, duration of the zero-order absorption process; F, bioavailability; KA, first-order absorption rate constant; NHC, β-d-N4-hydroxycytidine; Q, apparent distribution clearance; VC, apparent central volume; VP, apparent peripheral volume

- The impact of the covariate effects included in the final plasma NHC PK model was evaluated based on distribution of exposure metrics (trough concentration [C_{trough}], maximum concentration [C_{max}], and area under the NHC concentration versus time curve from 0 to 12 h postdose [AUC_{0-12}]), predicted assuming a hypothetical 800 mg BID dosing regimen for 5.5 days (Table 2)

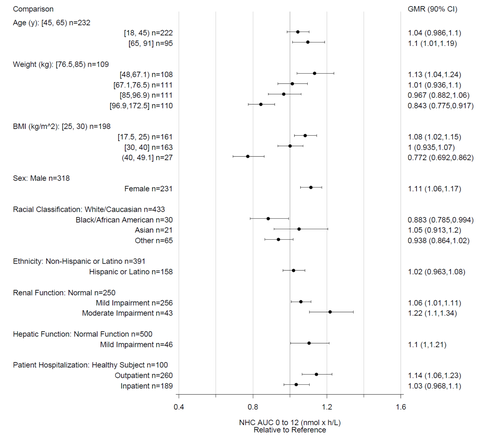
Table 2. Distribution of Model-Predicted NHC Exposures After 5.5 Days of 800 mg MOV Twice Daily, by Study

Variable	MK-4482-P001	MK-4482-P002	MK-4482-P004	MK-4482-P006	Overall	Participants With COVID-19[a]
Maximum Concentration (nmol/L)						
Geom. mean (%CV)	8990 (36.9)	NA	10400 (20.7)	NA	9460 (32.6)	8990 (36.9)
n	178		100		278	178
Trough Concentration (nmol/L)						
Geom. mean (%CV)	110 (123)	132 (141)	87.7 (55.7)	117 (73)	113 (113)	120 (124)
n	189	194	100	66	549	449
AUC_{0-12} (nmol x h/L)						
Geom. mean (%CV)	30100 (38)	33200 (46.9)	29100 (22.3)	33200 (27.6)	31300 (38.3)	31900 (41)
n	189	194	100	66	549	449

[a]Excludes data from Study MK-4482-P004
AUC_{0-12}, area under the NHC concentration versus time curve from 0 to 12 h postdose; %CV, coefficient of variation expressed as a percent; Geom., geometric; MOV, molnupiravir; n, number of participants; NA, not applicable; NHC, β-D-N4-hydroxycytidinem

- The sizes of intrinsic factor effects on MOV PK were generally modest in size and unlikely to be clinically relevant (Figure 2). Further evaluation of the clinical relevance is planned once Phase 3 data are available

Figure 2. Forest Plot of Geometric Mean Ratios (90% Confidence Intervals) for Model-Predicted AUC_{0-12} After 800 mg MOV Twice Daily



n is the number of subjects in each group. [or] indicates respective endpoint is included in the interval. (or) indicates respective endpoint is not included in the interval
AUC_{0-12}, area under the NHC concentration versus time curve from 0 to 12 h postdose; BMI, body mass index, CI, confidence interval; GMR, geometric mean ratio; MOV, molnupiravir; NHC, β-d-N4-hydroxycytidine

Conclusions

- A linear two-compartment model with sigmoid absorption and first-order elimination was found to adequately describe the plasma PK of NHC after single and repeated BID dosing of MOV
- No statistical differences in NHC PK were found between healthy participants and non-hospitalized participants with COVID-19. A slight increase in the rate of absorption in hospitalized participants with COVID-19 did not impact the extent of absorption
- A high-fat meal delayed the absorption of MOV but did not alter the extent of absorption
- Body size (body weight or body mass index) was a statistically significant predictor of CL/F and VC/F. Increases in body-size metrics were generally associated with decreases in C_{max}, C_{trough}, and AUC_{0-12}
- Age had minimal impact on NHC exposures over the range of observed age (18–91 years)
- NHC exposures were slightly increased (≤11%) in females compared to males
- No statistically significant effect of ethnicity or self-identified racial group on NHC PK was found
- Mild renal impairment did not substantially impact NHC exposures. Effect of moderate renal impairment was modest (22% increase in AUC_{0-12}), with a larger 63% increase in C_{trough}
- Based on a limited number of participants with mild impairment (<10% of the analysis population), hepatic function did not appear to substantially influence NHC exposure

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Trial Registration/Funding Information: Registered at Clinicaltrials.gov (NCT04575584 and NCT04575597)