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ARTICLE

A phase I, randomized, placebo-controlled study of molnupiravir in healthy Japanese to support special approval in Japan to treat COVID-19

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Abstract

Molnupiravir (MK-4482) is an oral prodrug of the antiviral ribonucleoside analog, *N*-hydroxycytidine (NHC), which has activity against RNA viruses, including severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). We conducted a phase I safety and pharmacokinetic study of molnupiravir in healthy Japanese adult participants. A sample size larger than typically used in pharmacokinetic studies was implemented to collect additional safety data in the Japanese population to support special approval for emergency use in Japan. Single doses of molnupiravir up to 1600 mg and multiple doses of 400 and 800 mg administered every 12 h (q12h) for 5.5 days were generally well-tolerated. NHC appeared rapidly in plasma and reached maximum concentration (C_{max}), with a median time to C_{max} (T_{max}) between 1.00 and 2.00 h. Area under the concentration versus time curve from zero to infinity (AUC_{0-inf}), area under the concentration versus time curve from zero to 12 h (AUC_{0-12}), and C_{max} of plasma NHC increased approximately dose proportionally. With q12h dosing, the geometric mean (GM) accumulation ratios for NHC AUC_{0-12} and C_{max} were ~1 for 400 and 800 mg. Pharmacokinetics of NHC triphosphate (NHC-TP), the active metabolite of NHC was assessed in peripheral blood mononuclear cells and also demonstrated roughly dose proportional pharmacokinetics. The GM accumulation ratios for NHC-TP AUC_{0-12} and C_{max} were ~2.5 for 400 and 800 mg. Following administration with food, only a modest reduction (24%) in plasma NHC C_{max} with comparable AUC_{0-inf} was seen, supporting administration without regard to food.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Molnupiravir (MK-4482) is a prodrug of the antiviral ribonucleoside analog, which has activity against severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). Molnupiravir is an oral drug being developed for treating patients with coronavirus disease 2019 (COVID-19). Rapid approval in Japan was desired for molnupiravir.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study evaluated the safety, tolerability, and pharmacokinetics of molnupiravir, including food effect in healthy Japanese participants. The study was conducted with a relatively larger sample size than a typical pharmacokinetic study to collect expanded Japanese safety data to support a "special approval for emergency" process in Japan.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Molnupiravir was generally well-tolerated in healthy Japanese. Area under the concentration versus time curve (AUC) and maximum concentration (C_{max}) of plasma *N*-hydroxycytidine increased approximately in a dose proportional manner. Only a modest reduction in C_{max} without a clinically meaningful change in AUC following administration with food was observed. Based on the data from this study, in conjunction with the global phase II and phase III studies, molnupiravir was approved in Japan through a "special approval for emergency" process. The therapeutic dose is 800 mg q12h and is the same as that used globally. Molnupiravir may be taken regardless of food.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The results of this study supported the "special approval for emergency" process for molnupiravir in Japan by obtaining extra safety data from healthy Japanese participants. "Special approval for emergency" process is a viable regulatory path in Japan that should be considered for new drugs to treat diseases in pandemic situations.

INTRODUCTION

There has been a pandemic of the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) virus worldwide. In Japan, ~100,000 newly infected cases were reported per day in the sixth wave (over 5 million cumulative infections as of March 1, 2022).[1] Vaccines and antibodies against SARS-CoV-2 have been developed and are playing an important role to prevent patients with coronavirus disease 2019 (COVID-19) from entering into severe illness.[2–5] However, multiple SARS-CoV-2 variants of concern have emerged, which is a significant issue in particular when mutations occur in the spike protein (a target of vaccines and antibodies).[6,7] At the time of development in mid-2021, there were several COVID-19 treatments for patients with mild to moderate disease available, such as remdesivir and monoclonal antibodies[8]; however, these drugs had limitations, including decreased efficacy against emerging variants and/or the need for i.v. administration. No oral therapy was available at that time. Hospital/clinic burden from an excessive number of patients with COVID-19[9] placed limitations on medical staff, needed for administration of i.v. drugs. As such, orally administered drugs that are less sensitive to viral mutations were desired.

Molnupiravir (MK-4482) is an oral prodrug of the antiviral ribonucleoside analog, *N*-hydroxycytidine (NHC), which has activity against a number of RNA viruses, including SARS-CoV-2.[10–13] Molnupiravir is rapidly absorbed in the gut and hydrolyzed to the parent nucleoside NHC, which is widely distributed to various tissues and then converted to the triphosphate form (NHC-TP; the pharmacologically active metabolite of NHC). Because molnupiravir is an oral drug which does not target the spike protein of SARS-CoV-2, where mutations can effect drug efficacy, its clinical development was significantly accelerated to urgently deliver an effective medication to patients in need (molnupiravir is currently approved for emergency use in Japan as well as in a number of other countries). A global phase II/III study was conducted; however, in Japan only a few patients were expected to be

enrolled due to highly limited outpatient care and strict eligibility criteria, including unvaccinated patients with increasing risk(s) of severe illness. We conducted a phase I study in healthy Japanese participants in parallel with the global phase II/III study, not only to evaluate pharmacokinetics in Japanese individuals but also to collect safety and tolerability data in the Japanese population to support approval. This study also addressed the Japanese regulatory requirement to assess the effect of food on the pharmacokinetics of the final market image formulation at the clinical dose.

METHODS

The study was conducted in compliance with the Declaration of Helsinki as well as with Good Clinical Practice regulations; the study was approved by P-One Clinic, Keikokai Medical Corp. institutional review board. Written informed consent was obtained from all participants for inclusion in the study.

Study objectives

The primary objectives of the study were to evaluate the safety and tolerability of molnupiravir as well as to evaluate the pharmacokinetic profile of NHC in plasma following single (part 1) and multiple (part 2) oral dose administration. The secondary objectives were to evaluate the effect of a high-fat meal on the bioavailability of NHC and to evaluate the pharmacokinetic profile of NHC-TP in peripheral blood mononuclear cells (PBMCs).

Study design

The study was a two-part, randomized, placebo-controlled, single-site, double-blind study of molnupiravir (final market image formulation) in healthy Japanese male adult participants. In part 1, participants were randomized to one of three panels (A, B, and C) and received a single oral dose of molnupiravir 200, 400, or 800 mg (6 per panel), respectively, or placebo (2 per panel) in a blinded fashion in the fasted state in period 1. In period 2 (minimum 11 days after dosing in period 1 to allow for washout), panel A participants received a single oral dose of molnupiravir 1600 mg ($N = 6$) or placebo ($N = 2$) and panel C participants received a single oral dose of molnupiravir 800 mg ($N = 6$) or placebo ($N = 2$) following consumption of a high-fat breakfast.

In part 2, participants were randomized to receive multiple oral doses of 400 or 800 mg molnupiravir (15 per panel) or placebo (5 per panel) every 12 h (q12h) for 5.5 days (total of 11 doses per participant) in a blinded fashion. The first and last dose of study interventions (day 1 morning and day 6 morning, respectively) were administered in the fasted condition.

In both part 1 and part 2, plasma and PBMC samples were collected for assessment of NHC and NHC-TP, respectively. Molnupiravir concentrations in plasma were not evaluated because they were generally below the limit of quantification in previous studies, as molnupiravir is rapidly hydrolyzed to NHC during absorption.[14] Pharmacokinetic samples were collected on days 1 parts 1 and 2 and day 6 part 2 predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 15 h (part 1 and day 6 part 2 only), 24 h (part 1 and day 6 part 2 only) postdose and predose on day 4 (part 2 only) for NHC; and predose, 1.5, 3, 5, 8, 12, and 24 h (part 1 and day 6 part 2 only) postdose and predose on day 4 (part 2 only) for NHC-TP. Participants in both part 1 and part 2 were followed for safety throughout the study, until ~14 days following administration of the last dose of study intervention. In addition, the participants were verbally contacted to confirm contraceptive requirements 90 days (within +1 week) after the last study intervention.

Participants

Healthy Japanese male participants aged 20–60 years with body mass index of 18.5–24.9 kg/m^2 were eligible for entry. Participants agreed to refrain from donating sperm and followed contraception requirements during the intervention period and for at least 90 days after the last dose of study intervention. Participants may have been excluded based on smoking history, alcoholic beverage consumption, caffeine consumption, disease history, and medication needs. Only male participants were included as past data have indicated that there is no meaningful difference in pharmacokinetics between men and women.[14,15]

Bioanalytical methods

Plasma concentrations of NHC and PBMC concentrations of NHC-TP were determined using validated liquid chromatography/tandem mass spectrometry (LC–MS/MS) methods. Plasma NHC and PBMC NHC-TP assays were performed by Labcorp Early Development Laboratories and Clinical Pharmacology Analytical Laboratory at The Johns Hopkins University School of Medicine, respectively.

For NHC in plasma, the analytical method was based on an automated 96-well format protein precipitation. The LC–MS/MS system consisted of a Waters Acquity

UPLC system and a Sciex API-6500+ mass spectrometer. Chromatographic separation was achieved using gradient elution on Acquity UPLC BEH Amide column (100 mm × 2.1 mm, 1.7 μm) and mobile phases: A = water containing 25 mM ammonium formate and formic acid (100:0.5), and B = acetonitrile with formic acid (100:0.1) at a flow rate of 0.7 ml/min. The MS/MS quantitation was performed using Multiple Reaction Monitoring transitions monitored at m/z 258.1 → 126.0 for NHC and m/z 263.1 → 126.0 for the internal standard (IS). The lower limit of quantitation (LLOQ) for this method was 1 ng/ml with a linear calibration range from 1 to 1000 ng/ml using a 100 μl plasma sample. EDTA was used as the anticoagulant and plasma samples were stored at −70°C.

NHC-TP was measured in PBMCs lysed in 70% methanol via sample dilution and evaporation. Briefly, 100 μl of PBMC lysate was pipetted into a 96-well plate; 25 μl of IS in 70% methanol was added to each sample. Specimens were evaporated to dryness under a stream of a nitrogen stream. Samples were re-constituted in 100 μl of water. Twenty microliters of the reconstituted solution were introduced into a Shimadzu Nexera X2 HPLC system (Shimadzu Corporation) interfaced with a QTRAP 6500 mass analyzer with an ESI source (SCIEX; serial no. BL28671410). Chromatographic separation occurred using a Scherzo SM-C18, 3 × 50 mm column with a 3.0 μm particle size (Imtakt USA) with a mobile phase system of 50 mM ammonium formate: 5 mM ammonium hydroxide (mobile phase A) and 80 mM ammonium formate: 8 mM ammonium hydroxide in 80:20 water: acetonitrile (mobile phase B). Analytes were eluted under a gradient; the assay was operated at a flow rate of 0.75 ml/min. NHC-TP was monitored in multiplexed selective reaction monitoring and negative ionization modes. NHC-TP and NHC-TP-IS were monitored at the following transitions: NHC-TP: 497.600 → 158.700 m/z; NHC-TP-IS: 502.800 → 158.700 m/z. The LLOQ for this method was 1 pmol/sample with a linear calibration range from 1 to 1500 pmol/sample.

The accuracy of the bioanalytical method was determined using incurred sample re-analysis, during which it was observed that >67% of results had a relative percentage difference within the acceptable criteria of ±20%.[16]

Statistical analysis

Safety

The all participants as treated population consisted of all participants who received at least one dose of treatment. This population was used for assessments of safety.

Summary statistics and plots were generated for safety assessment.

Pharmacokinetics

The per-protocol population consisted of the subset of participants who complied with the protocol sufficiently to ensure that generated data would likely exhibit the effects of treatment, according to the underlying scientific model. All of the participants were compliant with the study procedures and had available data from at least one treatment. This population was used for assessments of pharmacokinetics.

Prior to performing pharmacokinetic analyses, PBMC NHC-TP concentrations were corrected for cell count as follows[17]:

$$\mu\text{M}\ (\text{mol}/10^6\,\text{L}) = (\text{concentration in pmol/sample})/\left[(\text{cell count in } 10^6 \text{ cells/mL}) * (0.1\,\text{ml/sample})\right] * (5 \text{ cells/pL}).$$

Pharmacokinetic parameter values were determined by using a noncompartmental approach using Phoenix WinNonlin Built 8.1.0.3530. Maximum concentration (C_{max}), trough concentration (C_{trough} or C12), and time to maximum concentration (T_{max}) values were obtained directly from the concentration-time data. The area under the concentration versus time curve from zero to infinity (AUC_{0-inf}), AUC to the last measurable point (AUC_{0-last}), and AUC from zero to 12 h (AUC_{0-12}) were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear up, log down calculation method option in Phoenix WinNonlin). AUC_{0-inf} was calculated as the sum of AUC_{0-last} and $C_{est,last/\lambda z}$, where AUC_{0-last} is the AUC to the last measurable concentration, $C_{est,last}$ is the estimated concentration corresponding to the time of the last measurable concentration, and λz is the apparent first-order terminal elimination rate constant. The apparent terminal half-life ($t_{½}$) was calculated as the quotient of the ln of two and λz (ln [2]/λz), where λz was calculated from the slope of the linear regression of the terminal log-linear portion of the plasma concentration versus time profile. At least three consecutive timepoints in the terminal log-linear phase, excluding T_{max}, were used for determination of the apparent $t_{½}$. Following multiple dose administration, the effective $t_{½}$ was calculated as ln [2]/k by determining k based on the accumulation ratio (AR) of AUC_{0-12} and dosing interval (tau) together with the following equation: AR = 1/(1-exp[−k * tau]). The AR was calculated based on C_{max} and AUC_{0-12} on day 1 versus day 6.

The effect of food on NHC exposures was estimated by obtaining the geometric mean (GM) ratio (fed/fasted) and 90% confidence interval for C_{max} and AUC_{0-inf} at the dose level administered in both the fasted and fed state. Similarly, the least squares mean differences (day 6 – day 1) and 90% confidence intervals from the models were back-transformed to obtain the GM accumulation ratios (day 6/day 1) and 90% confidence intervals for C_{max} and AUC_{0-12}.

An exploratory assessment of dose proportionality of NHC C_{max}, AUC_{0-12}, and AUC_{0-inf} was conducted. Separately for each parameter, linear mixed effects models with ln(dose) as a fixed effect and participant as a random effect was used to obtain the slope estimate associated with ln(dose). A least-squares estimate and 95% confidence interval for the slope associated with ln(dose) was obtained from the model.

RESULTS

Participant characterization

In part 1, 25 participants were randomized, and all completed the study (one participant discontinued study intervention and was replaced). The participant who discontinued withdrew consent in period 1 of part 1 for personal reasons after receiving a single dose of molnupiravir 800 mg in the fasted state and completed subsequent follow-up procedures. The replacement participant participated in both period 1 and period 2 of part 1. In part 2, 40 participants were randomized, and all completed the study (two participants discontinued study intervention and were not replaced). Participant disposition is shown in Figure S1. The study intervention groups were comparably balanced for all demographic characteristics (Table S1).

Safety

Single dose administration of molnupiravir up to 1600 mg and multiple dose administration of molnupiravir 400 and 800 mg q12h for 5.5 days were generally well-tolerated in healthy Japanese male adult participants. There were no serious adverse events (AEs) or events of clinical interest.

In part 1 (single dose), two participants out of 25 (8.0%) reported three AEs after receiving molnupiravir, including dermatitis in one participant and increased lipase and amylase in another participant (Table 1). There were no AEs in the placebo group. In part 2 (multiple dose), 13 participants out of 40 (32.5%) reported 15 AEs (Table 2). Toxic skin eruption (three participants) was most frequently reported in the molnupiravir group. In the placebo group, decreased hemoglobin (one participant) was reported. Listing of AEs in part 1 and part 2 are shown in Table S2 and Table S3, respectively. All the AEs were mild in intensity except two events: one moderate dermatitis was reported in one participant who received a single dose of molnupiravir 200 mg and one moderate toxic skin eruption was reported in one participant who received multiple doses of molnupiravir 800 mg q12h for 5 days. The participant who reported moderate dermatitis also received a single dose of molnupiravir 1600 mg without recurrence of dermatitis.

There was one AE (moderate toxic skin eruption) resulting in discontinuation of study intervention (multiple dose panel molnupiravir 800 mg). The toxic skin eruption

TABLE 1 Participants with AEs (incidence >0% in one or more treatment groups) part 1

	Placebo	MOV 200 mg	MOV 400 mg	MOV 800 mg (fasted)	MOV 800 mg (fed)	MOV 1600 mg
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Participants in population	8	6	6	7	6	6
With one or more AEs	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
With no AEs	8 (100.0)	5 (83.3)	5 (83.3)	7 (100.0)	6 (100.0)	6 (100.0)
Investigations	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Amylase increased	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Lipase increased	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dermatitis	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Every participant is counted a single time for each applicable row and column.

MedDRA version 24.1.

Abbreviations: AEs, adverse events; MOV, Molnupiravir.

TABLE 2 Participants with AEs (incidence >0% in one or more treatment groups) part 2

	Placebo *n* (%)	Molnupiravir 400 mg *n* (%)	Molnupiravir 800 mg *n* (%)
Participants in population	10	15	15
With one or more adverse events	1 (10.0)	4 (26.7)	8 (53.3)
With no adverse events	9 (90.0)	11 (73.3)	7 (46.7)
Cardiac disorders	0 (0.0)	0 (0.0)	1 (6.7)
Postural orthostatic tachycardia syndrome	0 (0.0)	0 (0.0)	1 (6.7)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	1 (6.7)
Stomatitis	0 (0.0)	0 (0.0)	1 (6.7)
Investigations	1 (10.0)	1 (6.7)	3 (20.0)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	1 (6.7)
Amylase increased	0 (0.0)	1 (6.7)	0 (0.0)
Blood creatine phosphokinase increased	0 (0.0)	0 (0.0)	2 (13.3)
Hemoglobin decreased	1 (10.0)	0 (0.0)	0 (0.0)
Nervous system disorders	0 (0.0)	1 (6.7)	0 (0.0)
Dizziness postural	0 (0.0)	1 (6.7)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	5 (33.3)
Dyshidrotic eczema	0 (0.0)	0 (0.0)	1 (6.7)
Eczema nummular	0 (0.0)	0 (0.0)	1 (6.7)
Toxic skin eruption	0 (0.0)	0 (0.0)	3 (20.0)
Vascular disorders	0 (0.0)	2 (13.3)	0 (0.0)
Orthostatic hypotension	0 (0.0)	2 (13.3)	0 (0.0)

Note: Every participant is counted a single time for each applicable row and column.

MedDRA version 24.1.

Abbreviation: AEs, adverse events.

occurred on day 4 prior to the evening dose administration and resolved on day 14 following treatment with betamethasone butyrate propionate and fexofenadine hydrochloride. The participant received 10 doses of molnupiravir 800 mg and discontinued study intervention after the day 5 evening dose.

No clinically meaningful trends were observed for changes in clinical laboratory values, vital signs, or 12-lead electrocardiograms (ECGs) as a function of dose or treatment.

Pharmacokinetic analysis

Summary pharmacokinetic statistics of NHC in plasma following single oral dose administration of molnupiravir are shown in Table 3. The arithmetic mean plasma concentration-time profiles of NHC following single oral dose administration of molnupiravir are presented in Figure 1. NHC appeared rapidly in plasma and reached C_{max} with a median T_{max} between 1.00 and 2.00 h (fasted). Following peak plasma concentrations, NHC decreased in a biphasic manner, with a shorter distribution phase followed by a longer terminal phase with a half-life of ~4–8 h. The full NHC pharmacokinetic profile at 200 mg was not characterized due to concentrations in the terminal phase falling below the LLOQ of the assay (1.00 ng/ml). Dynamics of clearance for the 200 mg dose appear somewhat erratic likely secondary to variability associated with a small sample size.

Administration of molnupiravir in the fed state delayed the median NHC T_{max} by 1.5 h and reduced C_{max} by 24% when compared to administration in the fasted state (Table 4). However, AUC_{0-inf} was comparable.

The exploratory analysis of dose proportionality following single dose administration (fasted) showed

TABLE 3 Summary statistics for pharmacokinetics of NHC in plasma and NHC-TP in PBMC following single oral dose administration of molnupiravir in healthy Japanese male participants, part 1

Pharmacokinetic parameter	Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg (fasted)	Molnupiravir 800 mg (fed)	Molnupiravir 1600 mg
NHC					
N	6	6	7	6	6
AUC_{0-inf} (h•ng/ml)[a,d]	2280 (2000, 2600)	6410 (5550, 7410)	12,400 (10,900, 14,200)	13,700 (12,000, 15,800)	25,300 (22,200, 28,900)
AUC_{0-last} (h•ng/ml)[a]	2280 (1990, 2600)	6390 (5520, 7390)	12,400 (10,800, 14,200)	13,700 (11,900, 15,700)	25,300 (22,100, 28,900)
AUC_{0-12} (h•ng/ml)[a]	2270 (1990, 2600)	6350 (5490, 7350)	12,300 (10,800, 14,100)	13,600 (11,900, 15,600)	25,100 (22,000, 28,700)
C_{max} (ng/ml)[a]	1240 (984, 1560)	3160 (2450, 4090)	4750 (3750, 6030)	3610 (2830, 4600)	7650 (6070, 9640)
T_{max} (h)[b]	1.00 (0.50, 5.00)	1.00 (1.00, 1.50)	1.50 (0.52, 2.50)	3.00 (2.00, 3.00)	2.00 (1.00, 2.00)
$t_{½}$ (h)[c,d]	1.28 (13.9)	8.37 (15.1)	3.95 (113.3)	3.74 (78.5)	5.50 (57.1)
NHC-TP					
N	5	6	7	6	6
AUC_{0-inf} (h•μM)[a,d]	NC	478 (339, 674)	937 (664, 1320)	1670 (1180, 2350)	1890 (1300, 2760)
AUC_{0-last} (h•μM)[a]	56.5 (34.5, 92.7)	273 (174, 428)	648 (427, 985)	553 (352, 869)	1250 (795, 1960)
AUC_{0-12} (h•μM)[a]	52.9 (35.5, 78.7)	205 (143, 295)	419 (292, 603)	303 (211, 436)	785 (546, 1130)
C_{max} (μM)[a]	10.1 (7.01, 14.7)	27.9 (19.6, 39.8)	68.2 (49.2, 94.6)	44.1 (31.3, 62.2)	88.1 (62.6, 124)
T_{max} (h)[b]	8.00 (3.03, 12.02)	3.00 (1.50, 5.00)	5.00 (5.00, 5.02)	4.00 (3.00, 5.03)	4.00 (3.00, 8.00)
$t_{½}$ (h)[c,d]	NC	15.1 (49.5)	13.1 (25.7)	37.6 (85.6)	13.4 (14.9)

Note: The *N* for AUC_{0-inf}, AUC_{0-12}, and $t_{½}$ of molnupiravir-800 mg fasted in NHC-TP is 6. The *N* for AUC_{0-inf} and $t_{½}$ of molnupiravir-1600 mg in NHC-TP is 5.

NHC-TP AUC_{0-inf} had >25% extrapolated in five participants at 400 mg (five out of six participants), four participants at 800 mg fasted (four out of six participant), six participants at 800 mg fed (six out of six participants), and five participants at 1600 mg SD (five out of five participants).

Abbreviations: %CV, percent coefficient of variation; AUC_{0-inf}, area under the concentration versus time curve from zero to infinity; C_{max}, maximum concentration; NC, not calculated due to insufficient data; NHC, *N*-hydroxycytidine; NHC-TP, *N*-hydroxycytidine triphosphate; PBMC, peripheral blood mononuclear cell; $t_{½}$, terminal half-life; T_{max}, time to maximum concentration.

[a]Back-transformed least squares mean and 95% confidence interval from mixed effects model performed on natural log-transformed values.

[b]Median; minimum, maximum.

[c]Geometric mean (GM %CV).

[d]These values should be interpreted with caution as sampling duration was likely not sufficient to fully characterize the terminal elimination phase of the profile.

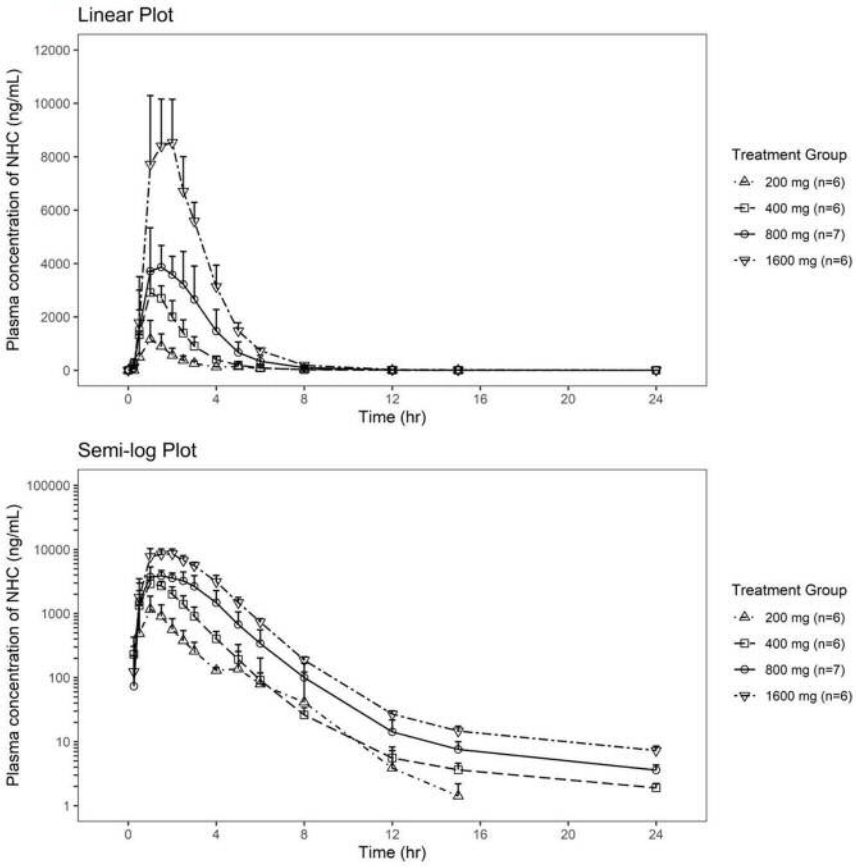

FIGURE 1 Mean plasma concentration-time profiles for NHC following single oral dose administration of molnupiravir (fasted state) to healthy Japanese male participants (part 1). Arithmetic mean + SD. Top: Linear plot, bottom: semi-log plot; $n = 6$ beyond 8 h at 800 mg. NHC, *N*-hydroxycytidine.

TABLE 4 Assessment of food effect on NHC AUC_{0-inf} and C_{max} in plasma following single oral dose administration of molnupiravir 800 mg under fed and fasted conditions in healthy Japanese male participants, part 1

Pharmacokinetic parameter	Molnupiravir 800 mg Fed			Molnupiravir 800 mg Fasted			Fed/Fasted	
	N	GM	95% CI	*N*	GM	95% CI	GMR	90% CI
AUC_{0-inf} (h•ng/ml)[a]	6	13,700	(12,000, 15,800)	7	12,400	(10,900, 14,200)	1.11	(1.02, 1.20)
C_{max} (ng/ml)[a]	6	3610	(2830, 4600)	7	4750	(3750, 6030)	0.76	(0.67, 0.86)

Abbreviations: AUC_{0-inf}, area under the concentration versus time curve from zero to infinity; CI, confidence interval; C_{max}, maximum concentration; GM, geometric mean; GMR, least-squares geometric mean ratio; NHC, *N*-hydroxycytidine.

[a]Back-transformed least squares mean and 95% confidence interval from mixed effects model performed on natural log-transformed values.

that NHC AUC_{0-inf}, AUC_{0-12}, and C_{max} increased roughly in a dose proportional manner across the dose levels of 200 to 1600 mg, with AUC_{0-inf} and AUC_{0-12} slope estimates slightly >1 and C_{max} slightly less than one (Table 5).

Summary pharmacokinetic statistics of NHC-TP in PBMCs following single oral dose administration of molnupiravir are shown in Table 3. The arithmetic mean PBMC concentration-time profiles of NHC-TP following single oral dose administration of molnupiravir (fasted) are presented in Figure 2. NHC-TP PBMC concentrations reached C_{max} with a median T_{max} between 3.00 and 8.00 h, and NHC-TP was eliminated with a GM apparent $t_{½}$ of

TABLE 5 Assessment of dose proportionality for NHC C_{max}, AUC_{0-inf}, and AUC_{0-12} in plasma following single oral administration of molnupiravir 200, 400, 800 and 1600 mg (fasted state) in healthy Japanese male participants ($N = 6/7$), part 1

Pharmacokinetic parameter	Slope estimate (95% CI)
C_{max} (ng/ml)	0.866 (0.755, 0.978)
AUC_{0-inf} (h•ng/ml)	1.152 (1.092, 1.213)
AUC_{0-12} (h•ng/ml)	1.150 (1.089, 1.211)

Abbreviations: AUC_{0-inf}, area under the concentration versus time curve from zero to infinity; AUC_{0-12}, area under the concentration versus time curve from zero to 12 h; CI, confidence interval; C_{max}, maximum concentration; NHC, *N*-hydroxycytidine.

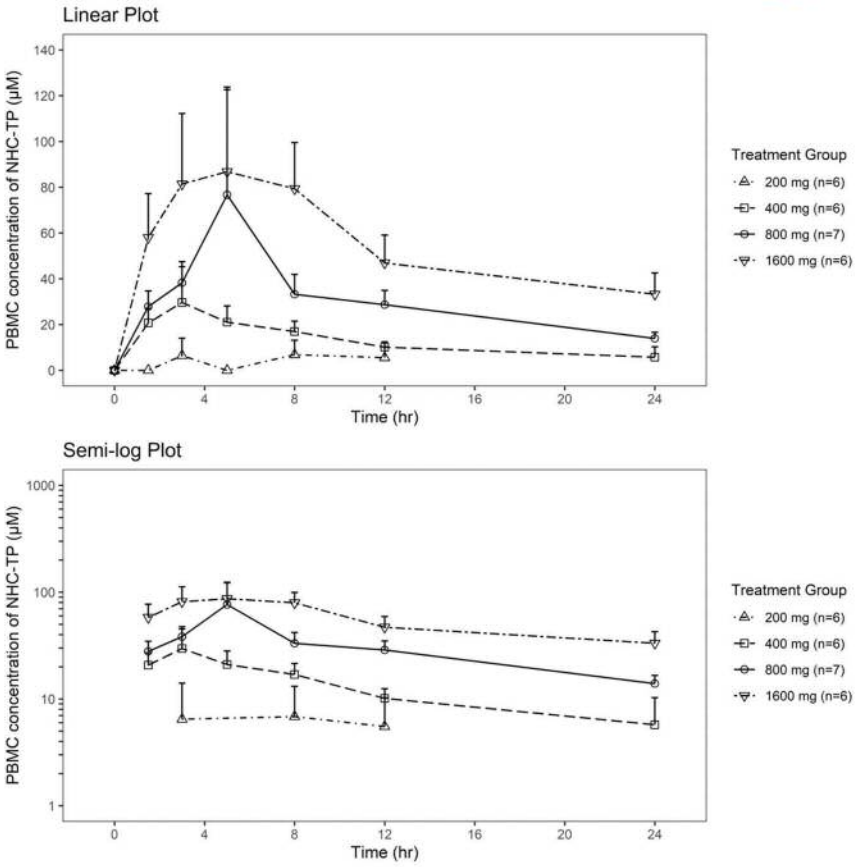

FIGURE 2 Mean PBMC concentration-time profiles for NHC-TP following single oral dose administration of molnupiravir (fasted state) to healthy Japanese male participants (part 1). Arithmetic mean + SD. Top: Linear plot, bottom: semi-log plot; $n = 6$ beyond 8 h at 800 mg. NHC-TP, *N*-hydroxycytidine triphosphate; PBMC, peripheral blood mononuclear cell.

approximately 13–15 h. NHC-TP exposure generally increased in a dose proportional manner.

Summary pharmacokinetic statistics for NHC in plasma and NHC-TP in PBMCs following multiple oral dose administration of molnupiravir (400 and 800 mg) q12h for 5.5 days are shown in Table 6. GM apparent $t_{½}$ of plasma NHC was 11.5 and 10.2 h after the last dose of 400 and 800 mg, respectively. No meaningful accumulation of NHC was observed following multiple oral dose administration, indicating that the terminal phase does not contribute meaningfully to accumulation after multiple dose administration. Based on the dosing interval of 12 h and limited GM accumulation ratios of 1.03 and 1.05 for AUC_{0-12} at 400 and 800 mg, effective $t_{½s}$ were calculated as 2.35 h and 2.73 h, respectively. NHC-TP PMBC concentrations reached C_{max} with a median T_{max} between 3.00 and 5.00 h, and NHC-TP was eliminated with a GM apparent $t_{½}$ of ~16 to 19 h on day 6. The accumulation ratio (day 6/day 1) was ~2.5 for AUC_{0-12} and C_{max}. These results are consistent with the $t_{½}$ of NHC-TP and q12h dosing.

DISCUSSION

Molnupiravir is a prodrug with antiviral activity against SARS-CoV-2, where early treatment reduces the risk of hospitalization or death in patients with COVID-19.[18] We evaluated molnupiravir pharmacokinetics and safety in a phase I study in healthy Japanese participants to support use in Japanese patients. In the present study, molnupiravir was generally well-tolerated following single and multiple dose administration. In addition, the pharmacokinetics of NHC in plasma and NHC-TP in PBMC were characterized. Based on the data from this study, in conjunction with global phase II and phase III data, molnupiravir was approved for use in Japan under the "special approval for emergency" process.[19] The therapeutic dose is 800 mg q12h, which is the same dose and schedule used world-wide. Molnupiravir can be taken regardless of food and without drug–drug interaction considerations[15,20]; a favorable profile for patients with COVID-19 without the added burden of food considerations or to those who require concomitant medications.

The pharmacokinetics of molnupiravir were assessed in non-Japanese participants prior to this investigation.[14] Similar to our reported findings, NHC appeared rapidly in plasma, with a median T_{max} between 1.00 and 2.00 h. Estimates of $t_{½}$ in the present study ranged from 10 to 11 h; however, this value should be interpreted with caution as sampling duration was likely not sufficient to fully characterize the terminal elimination phase of the profile. Meanwhile, there was no meaningful accumulation

TABLE 6 Summary statistics for pharmacokinetics of NHC in Plasma and NHC-TP in PBMC following multiple oral dose administration of molnupiravir q12h for 5.5 days in healthy Japanese male participants, part 2

Pharmacokinetic parameter	Day 1			Day 6			Accumulation ratio (day 6 /day 1)[e]	
	N	GM	95% CI	*N*	GM	95% CI	GMR	90% CI
NHC (Molnupiravir 400 mg)								
AUC_{0-12} (h•ng/ml)[a]	15	5240	(4790, 5730)	15	5410	(4950, 5920)	1.03	(0.99, 1.08)
C_{max} (ng/ml)[a]	15	2340	(2080, 2620)	15	2320	(2070, 2600)	0.99	(0.91, 1.08)
T_{max} (h)[b]	15	1.50	(1.00, 2.00)	15	1.50	(1.00, 2.00)		
$t_{½}$ (h)[c,d]				15	11.5	(18.6)		
C_{trough} (ng/ml)[c]	15	4.53	(38.6)	15	8.60	(31.1)		
NHC (Molnupiravir 800 mg)								
AUC_{0-12} (h•ng/ml)[a]	15	12,100	(11,100, 13,300)	13	12,700	(11,600, 13,900)	1.05	(1.00, 1.10)
C_{max} (ng/ml)[a]	15	5000	(4450, 5610)	13	4660	(4130, 5260)	0.93	(0.85, 1.02)
T_{max} (h)[b]	15	1.50	(1.00, 2.00)	13	1.50	(1.00, 2.50)		
$t_{½}$ (h)[c,d]				13	10.2	(49.4)		
C_{trough} (ng/ml)[c]	15	11.0	(35.9)	13	21.5	(30.8)		
NHC-TP (Molnupiravir 400 mg)								
AUC_{0-12} (h•μM)[a]	15	156	(132, 183)	15	387	(329, 456)	2.49	(2.19, 2.83)
C_{max} (μM)[a]	15	21.0	(16.9, 26.0)	15	48.9	(39.5, 60.6)	2.33	(1.89, 2.89)
T_{max} (h)[b]	15	3.00	(1.50, 5.00)	15	3.00	(0.00, 8.00)		
$t_{½}$ (h)[c,d]				13	16.4	(42.2)		
C_{trough} (μM)[c]	15	8.89	(26.8)	15	21.0	(30.0)		
NHC-TP (Molnupiravir 800 mg)								
AUC_{0-12} (h•μM)[a]	15	364	(309, 429)	13	964	(812, 1140)	2.65	(2.31, 3.03)
C_{max} (μM)[a]	15	48.4	(39.1, 59.9)	13	117	(93.1, 147)	2.42	(1.93, 3.02)
T_{max} (h)[b]	15	3.00	(1.50, 5.00)	13	5.00	(1.50, 8.00)		
$t_{½}$ (h)[c,d]				12	19.2	(28.4)		
C_{trough} (μM)[c]	15	22.1	(34.2)	13	66.2	(38.4)		

Abbreviations: %CV, percent coefficient of variation; AUC_{0-12}, area under the concentration versus time curve from zero to 12 h; CI, confidence interval; C_{max}, maximum concentration; GM, geometric mean; NHC, *N*-hydroxycytidine; NHC-TP, *N*-hydroxycytidine triphosphate; PBMC, peripheral blood mononuclear cell; $t_{½}$, terminal half-life; T_{max}, time to maximum concentration.

[a]Back-transformed least squares mean and 95% confidence interval from mixed effects model performed on natural log-transformed values.

[b]Median; minimum, maximum.

[c]Geometric mean (GM% CV).

[d]These values should be interpreted with caution as sampling duration was likely not sufficient to fully characterize the terminal elimination phase of the profile.

[e]Back-transformed least squares mean difference and 90% confidence interval from mixed effects model performed on natural log-transformed values.

of NHC in plasma after q12h dosing, suggesting that the $t_{½}$ does not contribute meaningfully to accumulation after multiple dose administration. The effective $t_{½}$ that was calculated based on the accumulation ratio and dosing interval of q12h, was 2 to 3 h, supporting q12h dosing of molnupiravir. AUC_{0-inf} and C_{max} of plasma NHC increased in an approximately dose proportional manner. In the present study, administration of molnupiravir with a high-fat meal delayed median T_{max} for NHC by 1.5 h and reduced C_{max} by 24% when compared to administration in the fasted state. However, AUC_{0-inf} was comparable, which indicates that the rate, but not the extent, of absorption is slightly lower in the fed state. Similar results were seen in healthy non-Japanese participants. These data support molnupiravir administration without regard to food.

NHC AUC_{0-12}, AUC_{0-inf}, and C_{max} were slightly higher in our study than pharmacokinetic parameter values in non-Japanese healthy participants. The apparent difference in NHC exposure between studies needs further investigation via integrated population pharmacokinetic assessments, which may reveal factors that can influence

molnupiravir pharmacokinetics across diverse populations. NHC-TP exposures in PBMCs (representing concentrations of the active form in target tissue) correlated with NHC plasma concentrations at doses of 200–1600 mg (including the clinical dose of 800 mg). The observed correlation supports utilizing NHC in plasma as a valid pharmacokinetic measure in the clinic.

Toxic skin eruption was the most frequently reported AE following multiple dose administration of molnupiravir with one discontinuation reported. A similar finding of discontinuation due to rash was observed in one participant in a study in non-Japanese subjects.[14] Intensity of these AEs were mild to moderate and recovered by steroid treatment and antihistamines. In the larger COVID-19 patient population study, skin and subcutaneous tissue disorder AEs were not frequently reported (those that occurred in ≥2% of participants).[18] Due to the limited size of our study, ethnic sensitivity of skin findings is not clear and continued surveillance is supported. In our study and phase I studies in non-Japanese participants, there were no serious drug-related AEs, and there were no clinically meaningful trends in clinical laboratory values, vital signs, or 12-lead ECGs.

From this comparison with non-Japanese study data (sufficient exposure and similar safety profile), it is supported that the clinical dose for Japanese patients is the same as the dose selected for the global program.

To achieve a rapid approval for molnupiravir in Japan, utilization of the "special approval for emergency" process was considered for clinical development. The process defined in the "Pharmaceutical and Medical Devices Act" article 14–3 does not specifically require Japanese data; however, based on the precedent that limited Japanese data have been requested to gain approval with this process, Japanese data were collected. For this program, there was a strategic plan for Japan to join the global phase II/III study, although only a few patients were expected to be enrolled due to differences in medical practice for the treatment of COVID-19. The global phase II/III study was an outpatient study which required rapid identification of vaccine naïve patients with COVID-19; however, in Japan, the majority of patients were treated on an inpatient basis at the time of study conduct. Access to patients at disease onset was challenging due to varied polymerase chain reaction testing practices. Furthermore, SARS-CoV-2 vaccination uptake was rapidly progressing.

To support the special new drug application in Japan, extra safety data from Japanese healthy participants was considered important. Twenty participants (15:5 participants for molnupiravir and placebo) each for two arms were enrolled in part 2 (multiple dose) of the present phase I study, the size of which is relatively larger than a typical Japanese pharmacokinetics study (8–10 participants per cohort randomized in a 3:1 or 4:1 ratio such that 6–8 subjects receive the active therapy[21]). In the global phase III study, only eight Japanese patients were enrolled, whereas 1433 patients were ultimately enrolled.[18] From a regulatory perspective, the present phase I study provided additional safety and tolerability data at the clinical dose (800 mg q12h) in the Japanese population and expanded clinical experience.

In conclusion, the pharmacokinetics of NHC in plasma and NHC-TP in PBMCs together with the favorable safety profile of molnupiravir in healthy Japanese participants supported the selection of the clinical dose (800 mg q12h without regard to food) for marketing authorization in Japan.

Although molnupiravir has been successfully approved in Japan and elsewhere, there are some limitations of the present study and the molnupiravir clinical development program. Molnupiravir was approved by utilizing the "special approval for emergency" process based on limited clinical data. Whereas the present phase I study provided additional safety data by accommodating a relatively larger study design than typical, the study sample size was small and limited to male participants, although past data have indicated that there is no meaningful difference in pharmacokinetics between men and women.[14,15] Overall, clinical experience remains limited in the Japanese patient population. Continuous surveillance of clinical use of molnupiravir is required as a postmarketing assessment to ensure the safety of molnupiravir in Japanese patients being treated for COVID-19.

AUTHOR CONTRIBUTIONS

K.N., K.F., C.H., I.A., H.Y., H.U., N.Y., Y.T., and N.U. wrote the article. K.N., K.F., C.H., I.A., H.Y., H.U., N.Y., Y.T., B.M.M., P.K.W., K.E.D., M.I., and S.A.S. designed the research. K.N., K.F., C.H., I.A., H.Y., H.U., N.Y., Y.T., and K.F. performed the research. K.N., K.F., C.H., I.A., H.Y., H.U., N.Y., Y.T., B.M.M., P.K.W., K.E.D., M.I., S.A.S., and N.U. analyzed the data.

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CONFLICT OF INTEREST

K.N., K.F., C.H., I.A., H.Y., H.U., N.Y., Y.T., B.M.M., P.K.W., K.E.D., M.I., and S.A.S. are currently or former employees

of MSD K.K., Tokyo, Japan, or Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and may hold stock and/or stock option of Merck & Co., Inc., Rahway, NJ, USA. K.F. received institutional study grant from MSD K.K., Tokyo, Japan. N.U. is a contract adviser to MSD K.K., Tokyo, Japan. As an Associate Editor for *Clinical & Translational Science*, Naoto Uemara was not involved in the review or decision process for this paper.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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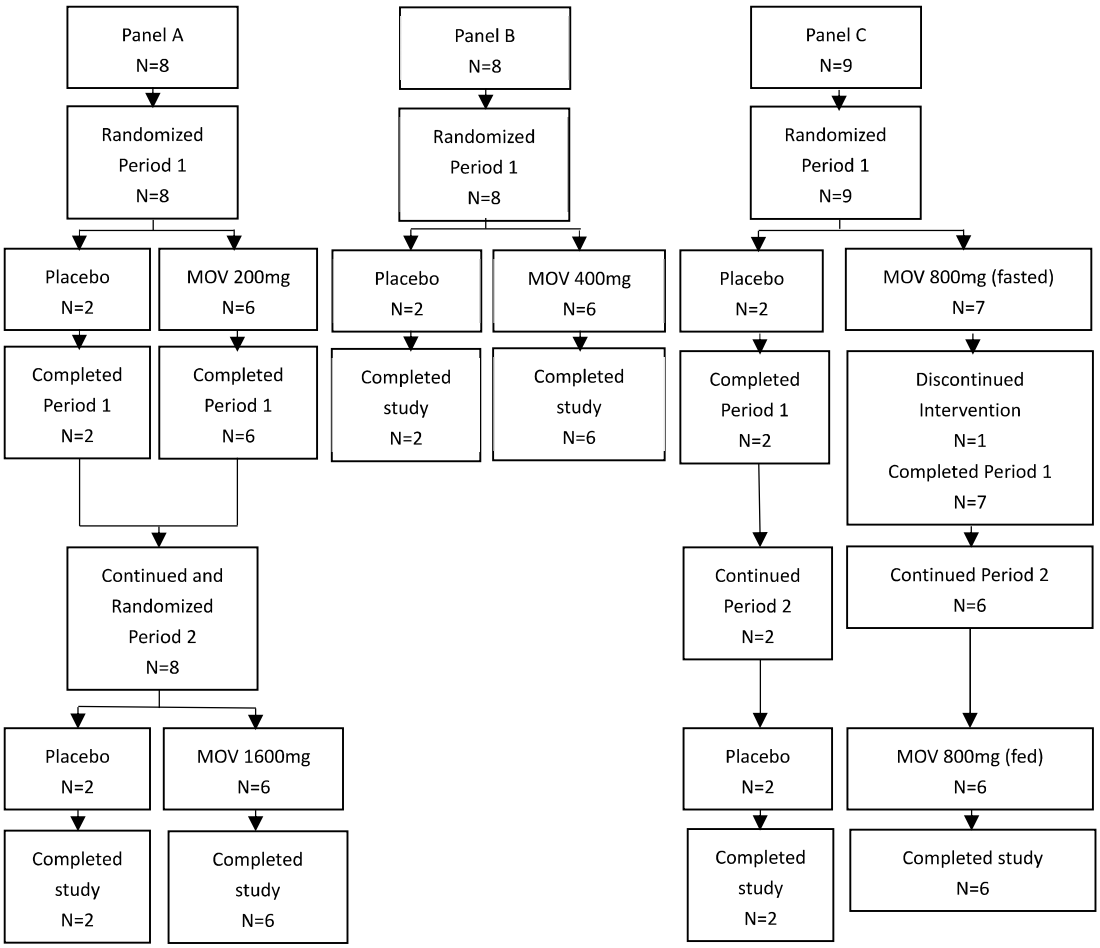
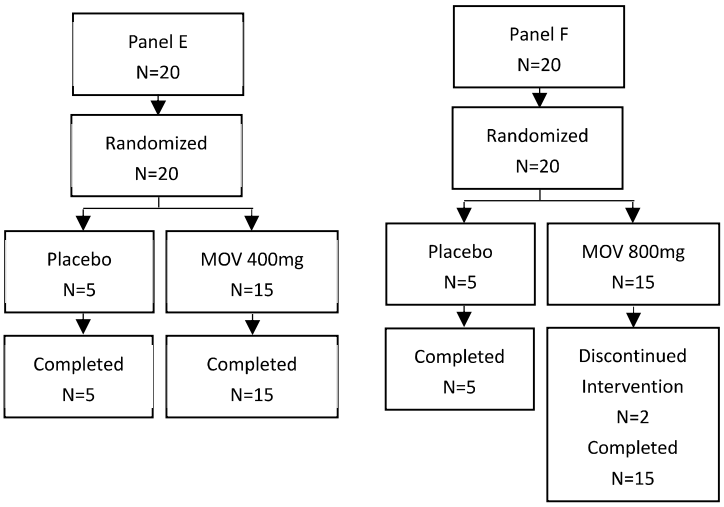
Figure S1 Participant Disposition

Part 1



Part 2



MOV = Molnupiravir

Table S1 Study demographics

Part 1 (single dose)							
	Placebo	MOV 200 mg	MOV 400 mg	MOV 800 mg (fasted)	MOV 800 mg (fed)	MOV 1600 mg	Total
Number of Participants*	8	6	6	7	6	6	25
Age (Years)							
Median	51.0	52.5	53.0	51.0	48.5	53.5	51.0
Range	28 to 57	21 to 59	31 to 57	24 to 57	24 to 57	21 to 59	21 to 59
Weight (kg)							
Mean	63.0	62.9	62.3	65.6	64.8	62.1	63.4
SD	5.9	6.8	5.5	3.9	3.4	5.8	5.2
Height (cm)							
Mean	169.1	169.5	167.8	170.9	170.0	168.8	169.4
SD	2.9	4.9	3.1	2.8	1.8	4.6	3.4
BMI (kg/m^2)							
Mean	22.2	22.1	21.8	22.3	22.2	22.0	22.1
SD	2.0	1.8	1.8	1.6	1.8	1.7	1.7

Part 2 (multiple dose)				
	Placebo	MOV 400 mg	MOV 800 mg	Total
Number of Participants	10	15	15	40
Age (Years)				
Median	49.5	42.0	45.0	45.0
Range	24 to 59	20 to 59	21 to 57	20 to 59
Weight (kg)				
Mean	61.6	63.8	61.9	62.5
SD	4.0	6.1	4.5	5.0
Height (cm)				
Mean	169.3	169.9	167.4	168.8
SD	5.4	5.4	3.5	4.8
BMI (kg/m2)				
Mean	21.7	22.1	22.1	22.0
SD	1.4	1.7	1.5	1.5

*Of the 25 participants in Part 1, 14 contributed to more than one group (refer to study design).
MOV, Molnupiravir; SD, Standard deviation; BMI, Body Mass Index.

Table S2 Listing of Individual Adverse Events (Part 1)

Adverse Event MedDRA Preferred Term	Intensity	Serious AE Criteria	Related	Action Taken
MK-4482 200 mg				
Dermatitis	Moderate	N	N	None
MK-4482 400 mg				
Amylase increased	Mild	N	Y	N/A
Lipase increased	Mild	N	Y	N/A

Serious AE Criteria: Y^1 = Results in Death, Y^2 = Life threatening, Y^3 = Persistent or Significant Disability/Incapacity , Y^4 = Requires or prolongs hospitalization, Y^5 = Congenital Anomaly or Birth Defect , Y^6 = Involves Cancer, Y^7 = Occurred with overdose, Y^8 = Other Medically important event, N = Not Serious

Related: Investigator-assessed relationship of the adverse event to study medication. Y = RELATED, N = NOT RELATED

Action Taken: Discontinued = DRUG WITHDRAWN, Interrupted = DRUG INTERRUPTED, Reduced = DOSE REDUCED, Increased = DOSE INCREASED, None = DOSE NOT CHANGED, N/A = NOT APPLICABLE.

Table S3 Listing of Individual Adverse Events (Part 2)

Adverse Event MedDRA Preferred Term	Intensity	Serious AE Criteria	Related	Action Taken
MK-4482 400 mg				
Amylase increased	Mild	N	Y	None
Dizziness postural	Mild	N	N	N/A
Orthostatic hypotension	Mild	N	N	None
Orthostatic hypotension	Mild	N	N	N/A
MK-4482 800 mg				
Alanine aminotransferase increased	Mild	N	N	N/A
Blood creatine phosphokinase increased	Mild	N	Y	N/A
Blood creatine phosphokinase increased	Mild	N	Y	None
Dyshidrotic eczema	Mild	N	N	N/A
Eczema nummular	Mild	N	N	N/A
Postural orthostatic tachycardia syndrome	Mild	N	N	None
Stomatitis	Mild	N	N	None
Toxic skin eruption	Mild	N	Y	N/A
Toxic skin eruption	Moderate	N	Y	Discontinued
Toxic skin eruption	Mild	N	Y	None
Placebo				
Haemoglobin decreased	Mild	N	N	N/A

Serious AE Criteria: Y^1 = Results in Death, Y^2 = Life threatening, Y^3 = Persistent or Significant Disability/Incapacity , Y^4 = Requires or prolongs hospitalization, Y^5 = Congenital Anomaly or Birth Defect , Y^6 = Involves Cancer, Y^7 = Occurred with overdose, Y^8 = Other Medically important event, N = Not Serious

Related: Investigator-assessed relationship of the adverse event to study medication. Y = RELATED, N = NOT RELATED

Action Taken: Discontinued = DRUG WITHDRAWN, Interrupted = DRUG INTERRUPTED, Reduced = DOSE REDUCED, Increased = DOSE INCREASED, None = DOSE NOT CHANGED, N/A = NOT APPLICABLE.