Pharmacokinetics of β-d-N4-hydroxycytidine, the active metabolite of prodrug molnupiravir, in non-plasma compartments of patients with SARS-CoV-2 infection.

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ABSTRACT

Background: Molnupiravir, an orally administered prodrug of the broadly active, direct-acting antiviral, ribonucleoside analogue β-d-N4-hydroxycytidine (NHC) is a promising COVID-19 drug candidate. We characterised the pharmacokinetics of NHC in saliva, nasal secretions and tears of patients enrolled in the phase I AGILE trial (NCT04746183) to understand its potential in preventing infection and transmission.

Methods: Patients with PCR-confirmed SARS-CoV-2 infection, within 5 days of symptom onset with mild-to-moderate disease were randomised to oral molnupiravir 300, 600 or 800 mg twice daily or placebo. Plasma and non-plasma (saliva, nasal secretions and tears) samples were collected at pre-dose, 0.5, 1, 2, and 4 hours post-dose on study days 1 and 5 and molnupiravir and NHC measured by LC/MS with a lower limit of quantification of 2.5 ng/mL in all matrices. Pharmacokinetic parameters were determined by noncompartmental methods and non-plasma:plasma ratios (RNP:P; based on AUC0-4) calculated.

Results: Twelve participants (n=4 per dosing arm; 75% female) completed the study. NHC T_max ranged between 1.00-4.00 hours for saliva (n=21) and nasal swabs (n=22) and 0.50-4.00 hours (n=17) for tears compared to 1.00-2.00 hours for plasma (n=19). Median (range) saliva RNP pooled across doses was 0.03 (0.01-0.11); n=16. RNP for nasal secretions and tears were 0.21 (0.05-0.73); n=17 and 0.22 (0.09-1.05); n=12, respectively. Non-plasma and plasma concentrations were significantly correlated (p<0.0001).

Conclusion: These data provide encouraging information regarding the distribution of NHC at sites of viral transmission and have important implications for prophylactic coverage.
INTRODUCTION

There is a need for effective antivirals to treat SARS-CoV-2 infection, which if commenced in a timely manner may prevent the development of severe disease. An extended therapeutic goal of antiviral therapy is the prevention of infection in individuals that have been exposed to an infected person. Viral infection occurs through inhalation or inoculation of virus onto upper respiratory airways and mucosal surfaces. In order to be an effective prophylactic agent in such cases, drug must penetrate into sites of inoculation in sufficient quantities.

Molnupiravir (EIDD-2801; MK-4482), a prodrug of the broadly active, direct-acting antiviral, ribonucleoside analogue 14 β-d-N4-hydroxycytidine (NHC), has recently been licensed in the UK for the treatment of symptomatic COVID-19 in adults with at least one risk factor for developing severe disease. Following oral administration, molnupiravir is rapidly hydrolysed by esterases to NHC, which in turn is phosphorylated by host kinases to active metabolite EIDD-1931-5’-triphosphate (EIDD-2061) [1, 2]. AGILE, a UK platform for early-phase trials of novel COVID-19 therapies [3], has evaluated molnupiravir within its AGILE Candidate-Specific Trial (CST)-2 seamless phase Ib/IIa protocol. We previously reported phase Ib evaluation of molnupiravir across three dosing arms (300, 600 and 800 mg twice daily), establishing that a dose of 800 mg twice daily for 5 days was well-tolerated, achieving plasma concentrations within the target range extrapolated from animal models, and was suitable for progression to phase II [4], which is currently recruiting.

In this study we investigated the pharmacokinetics of molnupiravir and NHC in saliva, nasal secretions and tears, in comparison with concentrations in plasma within the phase Ib component which we report here.
METHODS

Study Design

The pharmacokinetics of molnupiravir were evaluated as part of a phase I dose-escalation study in patients with PCR-confirmed SARS-CoV-2 infection, who were within 5 days of symptom onset and presenting with mild or moderate disease (clinicaltrials.gov registration number NCT04746183). The study design has previously been described [4]. In brief, eligible individuals were randomly assigned to one of three sequential dosing cohorts - molnupiravir dosed orally at 300, 600 and 800 mg twice daily. Within each cohort, patients were randomised at a 2:1 allocation ratio to receive either molnupiravir plus standard-of-care (treatment arms; n=4 per cohort) or standard-of-care alone (control arms; n=2 per cohort). The study was approved by the UK Medicines and Healthcare product Regulatory Agency (MHRA; EudraCT 2020–001860-27) and West Midlands Edgbaston Research Ethics Committee (20/ WM/0136) and all individuals provided written informed consent. The trial was coordinated by the National Institute for Health Research (NIHR) Southampton Clinical Trials Unit (Southampton UK) with recruitment and treatment of patients taking place at the NIHR Royal Liverpool and Broadgreen Clinical Research Facility (Liverpool, UK).

Pharmacokinetic sampling

Plasma and non-plasma (saliva, nasal secretions and tears) samples were collected at pre-dose, 0.5, 1, 2, and 4 hours post-dose on study days 1 and 5 in order to characterise the single dose and steady-state pharmacokinetics of the molnupiravir and its active metabolite, NHC within these compartments.

Plasma samples were collected as previously described [5]. Saliva samples were collected using Salivette™ tubes (Sarstedt Ltd, UK). The patient was asked to chew on the Salivette
swab for approximately 60 seconds after which the swab was returned to the Salivette and centrifuged (within 30 minutes of collection) to yield liquid saliva. The saliva supernatants (50 µL) were then immediately treated with acetonitrile (acetonitrile:saliva 3:1 v/v) in order to prevent ongoing conversion (via host esterases) of the molnupiravir pro-drug to NHC.

Nasal secretions were collected using 2 x Synthetic Absorptive Matrix (SAM) strips (Mucosal Diagnostics, UK). The applicator was removed from the tube and the absorption end of the swab carefully inserted into the patient’s nostril (one each side) with the absorbent strip placed flat against the surface of the inferior turbinate for 60 seconds. The swab was then returned to its original tube and screwed in place using the applicator handle. The weight (to the nearest 0.1 mg) of each SAM strip was determined before and after sampling in order to ascertain the approximate weight of fluid absorbed.

Tears were collected using 2 x Schirmer Tear Test strips which were inserted under the patient’s lower eyelid (one in each eye) for 5 minutes. The approximate volume (to the nearest µL) was recorded immediately after collection using the graduated markings on the strip (1-35 µL) and the strip placed inside a clean labelled 2 mL polypropylene tube.

All pharmacokinetic specimens were transported and processed on wet ice and stored at -80°C within 60 minutes of collection.

**Bioanalytical Methods**

Molnupiravir and NHC concentrations in plasma and saliva were determined at the University of Liverpool Bioanalytical Facility (Liverpool, UK) using a validated LC-MS method, as described previously [5]. Similarly, NHC concentrations in nasal secretions and tears (swab
samples) were determined using an adaptation of this analytical method. In brief, 2 mL of acetonitrile:1mM ammonium acetate (50:50 v/v) was added directly to the tubes containing the swab (calibrators, quality controls and patient samples) and allowed to stand for 1 hour at room temperature. The tubes were sonicated for 30 minutes and exactly 1.8 mL transferred to clean labelled 5 mL glass tubes containing 20 μL of working internal standard solution (2.5 μg/mL $^{13}$C$_{15}$N$_2$-N4-hydroxycytidine). Samples were then vortexed, evaporated to dryness under nitrogen at ambient temperature and reconstituted with 200 μL of 1 mM ammonium acetate (adjusted to pH 4.3) ready for injection onto the LC-MS system. Standards and quality controls were freshly prepared on the day of analysis. Working solutions were prepared in 1 x phosphate-buffered saline (PBS) fresh (which served as a surrogate matrix) and 15 μL of each calibrator level pipetted onto a clean SAM or tear strip (in duplicate). The calibration curve ranged between 0.15-75 ng/sample, and was described using a weighted $(1/x^2)$ least square linear regression model.

**Pharmacokinetic Data Analysis**

Concentrations of NHC in plasma and saliva were measured in ng/mL, whereas nasal and tear swab NHC were quantified using a ng/sample calibration curve, and converted to ng/mL based on swab volume in μL.

Following administration of 300, 600 and 800 mg doses of molnupiravir, NHC concentrations on study day 1 and 5 in each sampling matrix, at each nominal time point [pre-dose (0), 0.5, 1, 2, 4 hours post-dose] were described using summary statistics such as geometric mean (90% CI), mean, standard deviation, median and range. Samples below the lower limit of quantification of the assay (LLQ; <2.5 ng/mL) at pre-dose on day 1 were included as 0 ng/mL, whereas those <LLQ beyond pre-dose on day 1 were included as LLQ/2 (1.25 ng/mL).
NHC pharmacokinetic parameters, area under the concentration-time curve 0-4 hours (AUC0-4), maximum concentration (Cmax) and time to maximum concentration (Tmax) were determined using non-compartmental modelling methods (Phoenix 64, WinNonlin, v. 8.3, Certara, Princeton, NJ, USA). NHC accumulation ratio (RAC) in non-plasma samples from day 1 to 5 were determined for each molnupiravir dose (Day 5 AUC0-4/Day 1 AUC0-4). Intercompartmental ratios of non-plasma to plasma (RNP:P) were calculated on day 1 and 5 for each dose using the plasma compartment as reference (non-plasma AUC0-4/plasma AUC0-4). Results were expressed as geometric mean (CV%). Patients without a full pharmacokinetic profile between 0-4 hours were excluded from the summary statistics for AUC0-4, and those with sample(s) missing between 0-2 hours were excluded from Cmax and Tmax summary statistics.

Linear regression was performed to evaluate the relationship between NHC concentrations in plasma and non-plasma compartments. Concentrations below assay LLQ were excluded. Data were log transformed and analysed using IBM SPSS Statistics (v. 25.0, IBM Corporation, Armonk, NY, USA).

RESULTS

Patients

Of the twelve participants (n=4 per dosing arm) with pharmacokinetic data, 9/12 (75%) were female, median (range) baseline age, weight and BMI were 50 years (22-80), 79 kg (54-134) and 29 kg/m² (21-51) and time from onset of symptoms to randomisation and start of treatment was 5 days (3-5).
Ten of the twelve individuals (83%) completed the full treatment schedule. One patient in the 300 mg cohort took only 1 of 2 tablets for the second and third dose and a participant in the 800 mg cohort withdrew after the second dose; however, collected pharmacokinetic data were included.

**Non-plasma samples**

Of note, prodrug molnupiravir was detected at very low concentrations in only 31/106 (29%) plasma and 12/114 (11%) saliva samples [median (range) 5.89 (2.59-27.53 ng/mL) and 4.86 (2.63-31.44 ng/mL, respectively] and therefore not measured in swab samples.

In total, 111/114 saliva samples, 112/112 nasal swabs and 97/106 tear test strip concentrations were included. Three saliva samples were excluded due to an incorrect volume of acetonitrile added during processing and n=10 tear samples did not have a recorded volume for conversion to ng/mL. All pre-dose concentrations on day 1 (n=12 per matrix) were <LLQ, as were three 0.5 hour and one 1 hour saliva sample and n=1 tear test strip sample at 0.5 hour post-dose. Additionally, seven pre-dose saliva samples, three nasal swab (n=1 at 0, 2 and 4 hours post-dose) and tear strip concentrations (n=2 at 0 hours, n=1 at 4 hours) on day 5 were below LLQ.

**NHC non-plasma pharmacokinetics**

NHC pharmacokinetic parameters are summarised (Table 1). Geometric mean concentration-time profiles per dosing cohort, stratified by study day are shown (Figure 1) and individual profiles illustrated in the supplementary material (Supplementary Figure 1).
NHC $T_{\text{max}}$ ranged between 1.00-4.00 hours for saliva (n=21) and nasal swabs (n=22) and 0.50-4.00 hours (n=17) for tears compared to 1.00-2.00 hours for plasma (n=19). Nasal and tear NHC $R_{\text{AC}}$ from single dose to day 5 was below unity for 8/9 and 5/6 patients, respectively. $R_{\text{AC}}$ was variable for saliva, but appeared not to accumulate for the 800 mg dose (Table 1). NHC saliva concentrations were approximately 3% that of plasma [median (range) $R_{\text{NP:P}}$ pooled across doses: 0.03 (0.01-0.11); n=16]; the majority of individual ratios were between 0.01-0.04 (n=12). Individual patient NHC $R_{\text{NP:P}}$ for nasal secretions and tears were more variable, particularly for tears (CV%: 60, 70 and 92% for saliva, nasal and tears $R_{\text{NP:P}}$, respectively) and overall approximately 6-fold higher than saliva $R_{\text{NP:P}}$ [median (range) $R_{\text{NP:P}}$ nasal: 0.21 (0.05-0.73); n=17, tears: 0.22 (0.09-1.05); n=12]. Geometric mean (CV%) NHC $R_{\text{NP:P}}$, stratified by molnupiravir dose and study day are described (Table 1).

**Correlation between plasma and non-plasma compartments**

NHC concentrations in saliva and nasal secretions were significantly associated with paired plasma concentrations on day 1 and day 5 ($p < 0.0001$ for all linear regression analyses) with similar correlation coefficient values between study days (Figure 2), whereas a statistically significant relationship was observed for paired tear and plasma NHC concentrations on day 5 ($r^2 = 0.360, p < 0.0001$) but not day 1 ($r^2 = 0.028, p = 0.314$; Figure 2).
DISCUSSION

SARS-CoV-2 is primarily transmitted through viral particles contained in droplets and aerosols expelled through the mouth and nose [6]; it is therefore important to also understand drug pharmacokinetics at the sites of initial viral exposure such as the throat, nose and eye. Molnupiravir is the first orally direct-acting antiviral agent licensed for early treatment of mild-to-moderate COVID-19 disease in adults with at least one risk factor for developing severe disease. Molnupiravir is currently under phase II evaluation within AGILE including mild-to-moderate COVID-19 without risk factors and in both unvaccinated and vaccinated patients. Furthermore, molnupiravir is also being investigated for prophylactic use in household contacts of symptomatic COVID-19 patients (MOVe-AHEAD; NCT04939428). Knowledge of drug accumulation within the upper airways and in mucosal secretions will inform and support future research in this area.

We observed concentrations of NHC in saliva that were 3% that of plasma, whereas exposure in nasal secretions and tears was higher at approximately 20% that of plasma (based on AUC₀₋₄ ratios). Of the measured saliva, nasal and tear samples, 6, 50 and 61%, respectively were within or above the NHC EC₉₀ against SARS-CoV-2 in primary human airway epithelia cultures [7, 8] (approximately 0.5-1 µM ≈ 130-260 ng/mL), suggesting therapeutic concentrations are potentially attained within the nasal and ocular compartments, but not in saliva. However, it is important to note that without established pharmacokinetic/pharmacodynamic relationships or virological data further studies are warranted to determine whether efficacious targets, or indeed prophylactic targets, are obtained in non-plasma compartments.
A strong correlation between saliva and plasma NHC concentrations implies (assuming a one compartment model) that salivary accumulation is dependent on the plasma drug concentration. Mucosal permeability and protein binding are major factors in determining salivary drug accumulation, since only unbound drug is available for diffusion into saliva [9]. Of note, NHC exists predominantly in unbound form in plasma (unbound fraction ≥0.99) (*personal communication, Ridgeback Biotherapeutics*) and *in vitro* studies demonstrated that molnupiravir and NHC are not substrates for efflux transporters ABCB1 (p-glycoprotein), ABCC2 (multidrug resistance-associated protein 2; MRP2) or ABCG2 (breast cancer resistance protein, BCRP; *personal communication, Ridgeback Biotherapeutics*), suggesting salivary excretion of NHC is potentially modulated by other factors relating to the characteristics of the drug or surrounding milieu. Passage of drugs into non-plasma compartments not only depends on physiochemical properties, protein binding or molecule size, it can also be attributed to factors such as pH (e.g. mouth), inflammation (e.g. eye) and flow rate. For example, pharmacokinetics of drug in tears may be affected due to increased lacrimation or infection. Higher turnover or flow rate of saliva, compared to nasal secretions and tears may also contribute to the lower concentrations observed. Additionally, the marked variability in nasal and tear NHC concentrations could be related to the challenging collection procedures, particularly for tears, and the accuracy of swab volume for conversion from ng/sample to ng/mL.

Following 5 days of dosing, NHC did not to accumulate in plasma [4] or non-plasma compartments. Accumulation is associated with the elimination rate of drug in relation to the dosing interval. Although we could not determine the elimination rate constant or half-life of NHC (due to truncated sampling) a value of 7 hours has been reported in the literature (n=4 healthy volunteers, 800 mg twice daily) [10], and in the absence of enzyme induction or
inhibition, suggests that NHC would not accumulate. Low accumulation in non-plasma compartments could indicate that elimination is dependent upon that of the plasma.

NHC appeared to exhibit a similar absorption and elimination profile in the matrices studied, confirmed by statistically significant linear relationships between NHC in plasma with that in non-plasma compartments (with the exception of tears on day 1). The strong correlation in pharmacokinetics between saliva and plasma suggests the former may be utilised as non-invasive sampling in support of clinical studies.

There are a number of limitations. We utilised a sampling schedule for a truncated pharmacokinetic profile (0-4 hours) to limit infection risk. Missing samples led to a number of exclusions from the analysis, particularly for evaluation of $R_{NP:P}$, contributed to data variability and limited data interpretation. Finally, the active triphosphate metabolite, EIDD-2061 was not quantified. Despite the limitations these data add to our understanding of NHC pharmacokinetics, principally at sites of COVID-19 infection.

To our knowledge this is the first report describing significant accumulation of NHC in nasal secretions and tears, and to a lesser extent saliva. These data support the evaluation of molnupiravir as prophylaxis for SARS-CoV-2 infection.
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CONFLICT OF INTEREST

SK has received research funding from ViiV Healthcare, Gilead Sciences, and Merck for the Liverpool HIV Drug Interactions programme and for clinical studies unrelated to the submitted work.

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WG has received funding from the Wellcome Trust.

WH is a cofounder, owner and advisor of/to Ridgeback Biotherapeutics.
WP is employed by Ridgeback Biotherapeutics.

All other authors have none to declare.
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Table 1 Geometric mean (CV%) NHC pharmacokinetic parameters from plasma, saliva, nasal swabs and tear strips of SARS-CoV-2 infected patients following single (Day 1) and multiple dose (Day 5) molnupiravir 300 mg, 600 mg and 800 mg twice daily (n=4 per dosing arm unless stated otherwise).

| Parameter | 300 mg | 600 mg | 800 mg |
|-----------|--------|--------|--------|
|           | Day 1  | Day 5  | Day 1  | Day 5  | Day 1  | Day 5  |
| **Plasma** |        |        |        |        |        |        |
| AUC$_{0-4}$ (ng.h/mL) | 3031 (45)$^\#$ | 2328$^\$ | 5690 (22)$^*$ | 4368 (41) | 8187 (30) | 7005 (21)$^*$ |
| C$_{max}$ (ng/mL) | 1488 (31)$^*$ | 1048 (17)$^\#$ | 2440 (17) | 1865 (61) | 3447 (32) | 3546 (13)$^*$ |
| T$_{max}$ (h) | 2.00 (1.00-2.00)$^*$ | 1.00 (1.00-1.00)$^\#$ | 1.00 (1.00-2.00) | 1.00 (1.00-2.00) | 2.00 (2.00-2.00) | 2.00 (2.00-2.00)$^\$ |
| R$_{AC}$ | NA | NC | NA | 0.91 (7)$^*$ | NA | 0.93 (20)$^*$ |
| **Saliva** |        |        |        |        |        |        |
| AUC$_{0-4}$ (ng.h/mL) | 65 (109)$^*$ | 106 (93)$^*$ | 143 (120) | 106 (77)$^*$ | 289 (52) | 237 (36)$^*$ |
| C$_{max}$ (ng/mL) | 29 (113)$^*$ | 41 (98) | 73 (127) | 48 (76)$^*$ | 134 (48) | 109 (27)$^*$ |
| T$_{max}$ (h) | 1.00 (1.00-2.00)$^*$ | 1.50 (1.00-2.00) | 2.00 (1.00-2.00) | 2.00 (2.00-4.00)$^*$ | 2.00 (1.00-2.00) | 2.00 (2.00-2.00)$^\$ |
| R$_{AC}$ | NA | 1.62 (31)$^*$ | NA | 0.59 (58)$^\$ | NA | 1.00 (13)$^*$ |
| R$_{NP,P}$ | 0.03 (62)$^\#$ | 0.03$^\$ | 0.04 (79)$^*$ | 0.03 (51)$^\$ | 0.04 (33) | 0.03 (18)$^*$ |
| **Nasal Swabs** |        |        |        |        |        |        |
| AUC$_{0-4}$ (ng.h/mL) | 1061 (38)$^*$ | 673 (27)$^*$ | 629 (64) | 716 (67) | 2164 (50) | 1611 (73)$^*$ |
| C$_{max}$ (ng/mL) | 805 (70)$^*$ | 484 (60) | 365 (75) | 321 (65) | 1076 (43) | 738 (87)$^*$ |
| Parameter               | 1.00 (1.00-1.00)<sup>*</sup> | 1.00 (1.00-2.00)<sup>*</sup> | 1.00 (1.00-2.00) | 1.00 (1.00-4.00) | 1.50 (1.00-2.00) | 2.00 (2.00-4.00)<sup>*</sup> |
|------------------------|-----------------------------|-----------------------------|-----------------|-----------------|-----------------|-----------------------------|
| $T_{\text{max}}$ (h)   | 0.50 (0.50-2.00)<sup>*</sup> | 1.00 (0.50-2.00)<sup>*</sup> | 2.00 (0.50-4.00)<sup>*</sup> | 1.50 (1.00-2.00)<sup>*</sup> | 1.00 (1.00-1.00)<sup>*</sup> | 1.00 (0.50-1.00)<sup>*</sup> |
| $R_{\text{AC}}$       | NA                          | 0.63 (39)<sup>*</sup>       | NA              | 0.58 (47)<sup>*</sup> | NA              | 0.90 (30)<sup>*</sup>       |
| $R_{\text{NP-P}}$     | 0.41 (73)<sup>#</sup>      | 0.23<sup>$§</sup>          | 0.17 (27)<sup>*</sup> | 0.17 (112)      | 0.26 (26)       | 0.23 (67)<sup>*</sup>       |

**Tear Strips**

| Parameter               | 1731 (44)<sup>*</sup> | 1071 (38)<sup>*</sup> | 1137 (96)<sup>*</sup> | 749 (50)<sup>#</sup> | 1934 (90)<sup>*</sup> | 722<sup>$§</sup> |
|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
| $AUC_{0-4}$ (ng.h/mL)  | 908 (58)<sup>*</sup>   | 674 (53)<sup>*</sup>   | 411 (100)<sup>*</sup> | 508 (84)               | 985 (95)<sup>*</sup>  | 1267 (40)<sup>*</sup>   |
| $C_{\text{max}}$ (ng/mL) | 0.50 (0.50-2.00)<sup>*</sup> | 1.00 (0.50-2.00)<sup>*</sup> | 2.00 (0.50-4.00)<sup>*</sup> | 1.50 (1.00-2.00)<sup +#</sup> | 1.00 (1.00-1.00)<sup>*</sup> | 1.00 (0.50-1.00)<sup>*</sup> |
| $R_{\text{AC}}$       | NA                     | 0.62 (43)<sup>*</sup>  | NA                     | 1.12 (85)<sup>#</sup>   | NA                     | 0.80<sup>$§</sup>       |
| $R_{\text{NP-P}}$     | 0.77 (36)<sup>#</sup> | 0.39<sup>$§</sup>      | 0.20 (76)<sup>*</sup>  | 0.17 (47)<sup>*</sup>   | 0.26 (121)<sup>*</sup> | 0.10<sup>$§</sup>       |

$T_{\text{max}}$ expressed as median (range)

<sup>*</sup>n=3, <sup>#</sup>n=2, <sup>$§</sup>n=1

NA: not applicable; NC: not calculated due to missing samples on Day 1 or 5 preventing calculation of $AUC_{0.4}$; $AUC_{0.4}$: area under the concentration-time curve over 0 hours (pre-dose) to 4 hours post-dose; $C_{\text{max}}$: maximum concentration; $T_{\text{max}}$: time of maximum concentration; $R_{\text{AC}}$: accumulation ratio from day 1 to day 5 ($Day_{5} AUC_{0.4}/Day_{1} AUC_{0.4}$); $R_{\text{NP-P}}$: intercompartmental ratio of non-plasma to plasma ($non$-plasma $AUC_{0.4}$/plasma $AUC_{0.4}$)
FIGURE LEGENDS

**Figure 1** Geometric mean NHC concentrations over time from saliva (closed points, solid line), nasal swabs (open points, solid line) and tear strips (closed points, broken line) of individuals with SARS-CoV-2 following (A) single dose (Day 1) and (B) multiple dose (Day 5) molnupiravir 300 mg (circles), 600 mg (squares) and 800 mg (diamonds) twice daily. Data are expressed on a log-linear scale.

**Figure 2** Matched NHC concentrations from (A) saliva, (B) nasal swabs and (C) tear strips versus plasma concentrations following single dose (Day 1; left pane) and multiple dose (Day 5; right pane) molnupiravir 300 mg, 600 mg and 800 mg twice daily. Concentrations at each dose were pooled, log10 transformed and analysed using linear regression; $p \leq 0.05$ was considered statistically significant.
Figure 1

(A) NHC (ng/mL) vs. Time post-dose (h) for Molnupiravir 300 mg; saliva, Molnupiravir 600 mg; saliva, Molnupiravir 800 mg; saliva, Molnupiravir 300 mg; nasal, Molnupiravir 600 mg; nasal, Molnupiravir 800 mg; nasal, Molnupiravir 300 mg; tears, Molnupiravir 600 mg; tears, Molnupiravir 800 mg; tears.

(B) NHC (ng/mL) vs. Time post-dose (h) for Molnupiravir 300 mg; saliva, Molnupiravir 600 mg; saliva, Molnupiravir 800 mg; saliva, Molnupiravir 300 mg; nasal, Molnupiravir 600 mg; nasal, Molnupiravir 800 mg; nasal, Molnupiravir 300 mg; tears, Molnupiravir 600 mg; tears, Molnupiravir 800 mg; tears.
Figure 2

(A) $r^2 = 0.677$
$p < 0.0001$

(B) $r^2 = 0.502$
$p < 0.0001$

(C) $r^2 = 0.028$
$p = 0.314$

$\log(\text{Saliva concentration})$

$\log(\text{Plasma concentration})$

$\log(\text{Nasal swab concentration})$

$\log(\text{Plasma concentration})$

$\log(\text{Tear concentration})$

$\log(\text{Plasma concentration})$

$r^2 = 0.648$

$p < 0.0001$

$r^2 = 0.360$

$p < 0.0001$

$r^2 = 0.677$

$p < 0.0001$

$r^2 = 0.602$

$p < 0.0001$