A Pharmacokinetic Modeling Approach to Evaluate the Current Dosing Recommendations for Molnupiravir, a Novel Oral SARS-CoV-2 Antiviral, in the Egyptian Population.

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BACKGROUND – Molnupiravir for Treatment of SARS-CoV-2

- Molnupiravir, a prodrug of the antiviral N-hydroxycytidine (NHC), is one of the limited treatment options that has recently gained emergency use authorization by the US FDA for treating mild-to-moderate SARS-CoV-2 cases.[1]
- Middle Eastern Populations show distinct Genetic Makeup in Drug Metabolizing Enzymes which could lead to different exposures compared to other ethnic groups.[2]
- While NHC is shown to follow linear pharmacokinetics with similar exposures in healthy and SARS-CoV-2 subjects, its pharmacokinetics has not been characterized in the Egyptian population.[3]

AIMS – Evaluate the Current Molnupiravir Dosage in Achieving Therapeutic Targets in the Egyptian Population

- We aimed to develop a population pharmacokinetic model for NHC and evaluate through simulations the current molnupiravir dosage of 800 mg twice daily for five days in the Egyptian population.
- An open label, single arm pharmacokinetic study was conducted.

METHODS – Population Pharmacokinetic Modeling & Simulation for NHC Using Non-linear Mixed Effect Modeling

- Twelve healthy volunteers received 800 mg molnupiravir oral dose.
- Model development using non-linear mixed effect modeling and internal validation using bootstrapping and visual predictive check were conducted in MonolixSuite.
- Simulation-based maximum concentration (C_{max}) "the safety metric" and area under the curve ($AUC_{0\text{-}12h}$) "the efficacy metric" were computed for 1000 virtual subjects.
- Geometric mean ratios (GMR) and 90% confidence intervals (CI) compared to previously reported values were calculated

RESULTS – Transit Compartment Model for Absorption & One Compartment with Linear Elimination for Disposition

Table 1. Baseline demographic characteristics for healthy volunteers (n = 12)

Characteristic	Summary statistics
Age, years, mean (SD)	33 (6.1)
Weight, kg, mean (SD)	81.5 (11.60)
Creatinine, mg/dL, mean (SD)	0.77 (0.07)
ALT, IU/L, mean (SD)	28.2 (7.7)
AST, IU/L, mean (SD)	27.9 (5.9)
Total plasma protein, mg/dL, mean (SD)	6.8 (0.21)
Sex, Males, n (%)	12 (100%)

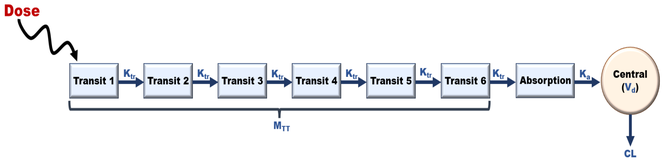

Figure 1: A schematic presentation of NHC population pharmacokinetic model

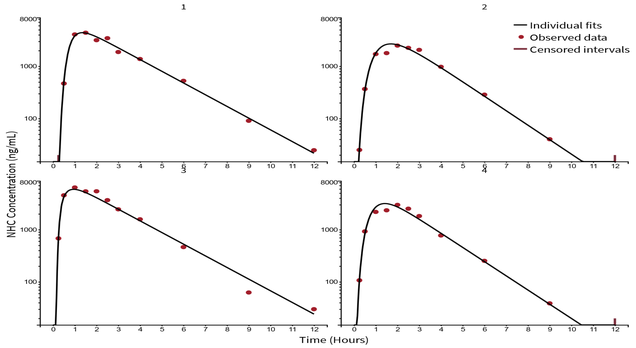

Figure 2: Individual predictions of NHC population pharmacokinetic model in representative sample of subjects

Table 2. Population PK parameter estimates and their associated Bootstrap estimates

	Unit	Final Model Results		Bootstrap Results	
		Estimate	RSE (%)	Median	95% CI
K_{tr}	hr^{-1}	14.43	29.2	15.4	7.9, 32.9
M_{TT}	hr	0.49	12.3	0.48	0.35, 0.66
K_a	hr^{-1}	2.32	24.4	2.06	1.3, 4.7
CL	L/ hr·70 kg	75.17	4.27	83.5	71.3, 95.3
V_d	L/70 kg	118.13	5.32	128.8	97.2, 154.9
residual error	%	19	8.69	19.5	15.8, 23.8

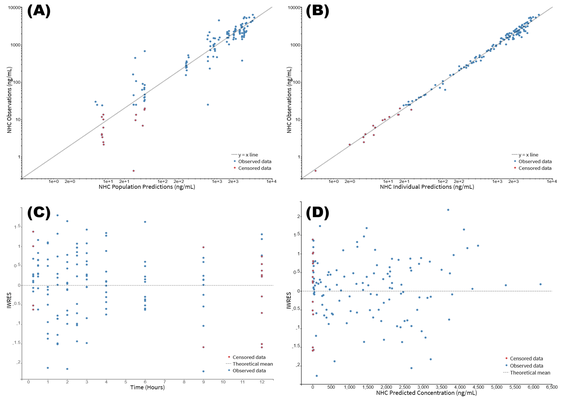

Figure 3: Diagnostic plots of NHC population pharmacokinetic model

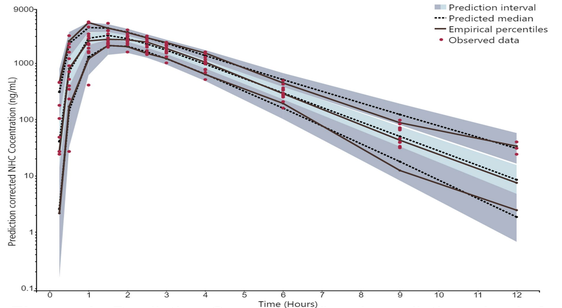

Figure 4: Prediction-Corrected Visual predictive check for the population pharmacokinetic model

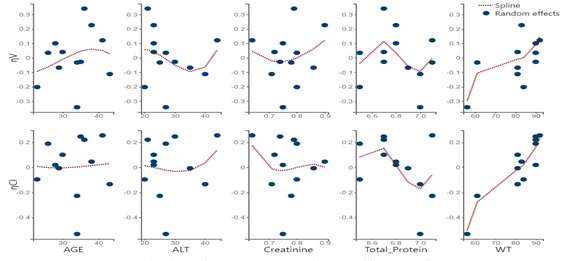

Figure 5: Correlation between random effects of PK parameters and clinically meaningful covariates.

- A total of 132 NHC plasma concentrations were analyzed. Six transit compartments for absorption and one-compartment with weight on apparent clearance (CL/F) and volume of distribution (V_d/F) for disposition best described NHC's pharmacokinetics.
- The population estimates for mean transit time, first-order absorption rate constant, CL/F and V_d/F were 0.49 hours, 2.32 $hour^{-1}$, 75.12 L/hour·70 kg and 118 L/70 kg, respectively.
- Geometric means of simulation-based C_{max} and $AUC_{0\text{-}12}$ were 3827 ng/mL (GMR = 1.05; 90% CI= 0.96-1.15) and 9320 ng.hr/mL (GMR = 1.04; 90% CI= 0.97-1.11), respectively

CONCLUSIONS- Dose Adjustment is Not Required for Egyptian Population

- Population pharmacokinetic model was developed for NHC.
- Simulations showed that current molnupiravir dosage can achieve the therapeutic targets and dose adjustment may not be required for the Egyptian population.
- The developed model could be used in the future to refine molnupiravir's dosage once further therapeutic targets are identified

REFERENCES

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3EMA Assessment report, Use of molnupiravir for the treatment of COVID-19, EMA/719664/2021 Corr. 1, Committee for Medicinal Products for Human Use (CHMP), 2021.