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Molnupiravir

U.S. Food & Drug Administration
Antimicrobial Drugs Advisory Committee

November 30, 2021

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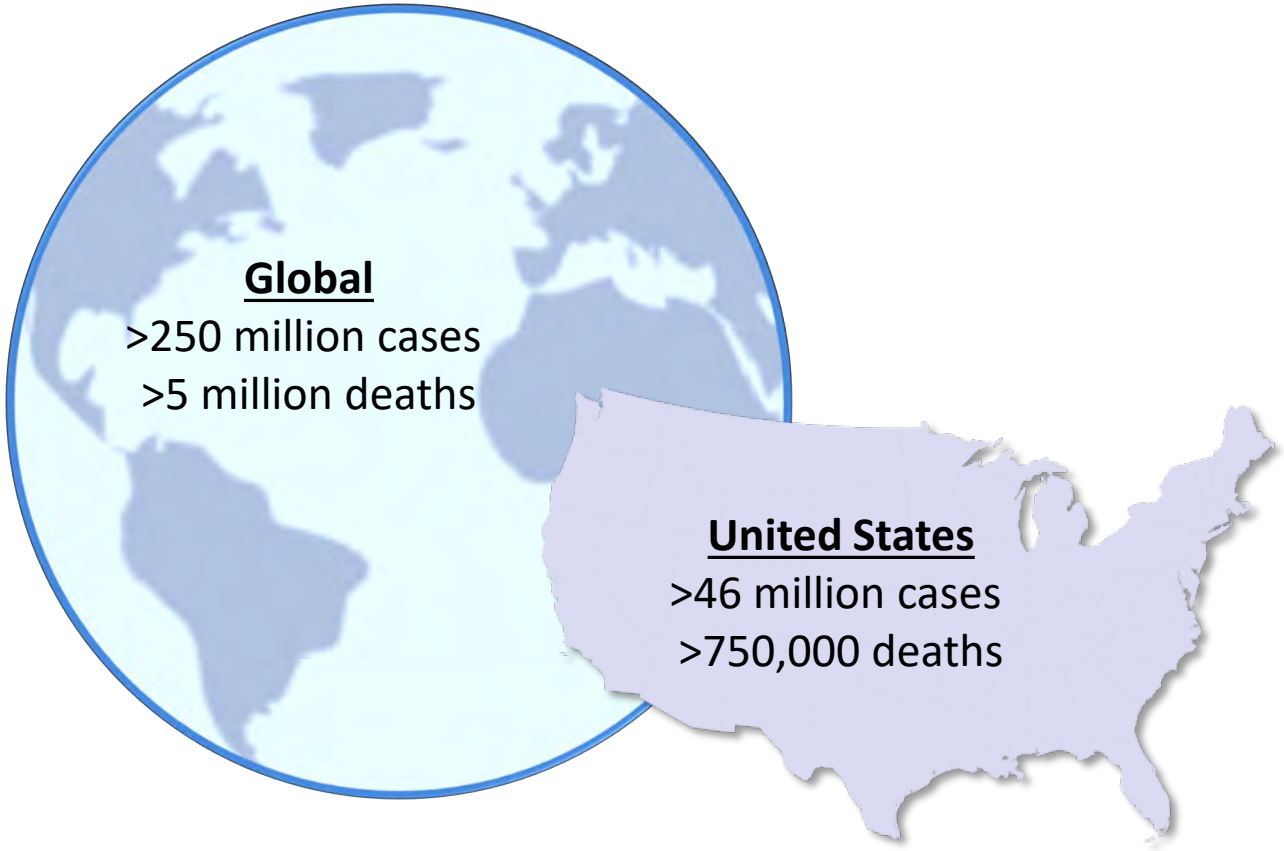
Introduction

Sean Curtis, MD, MPH

Senior Vice President, Global Regulatory Affairs and Clinical Safety
Merck & Co., Inc.

Significant Unmet Medical Need for COVID-19 Therapeutics



Many Americans remain at risk:

- Delta variant is more transmissible
- Unvaccinated
- Vaccine breakthrough infections

Treatment Across the Spectrum of COVID-19

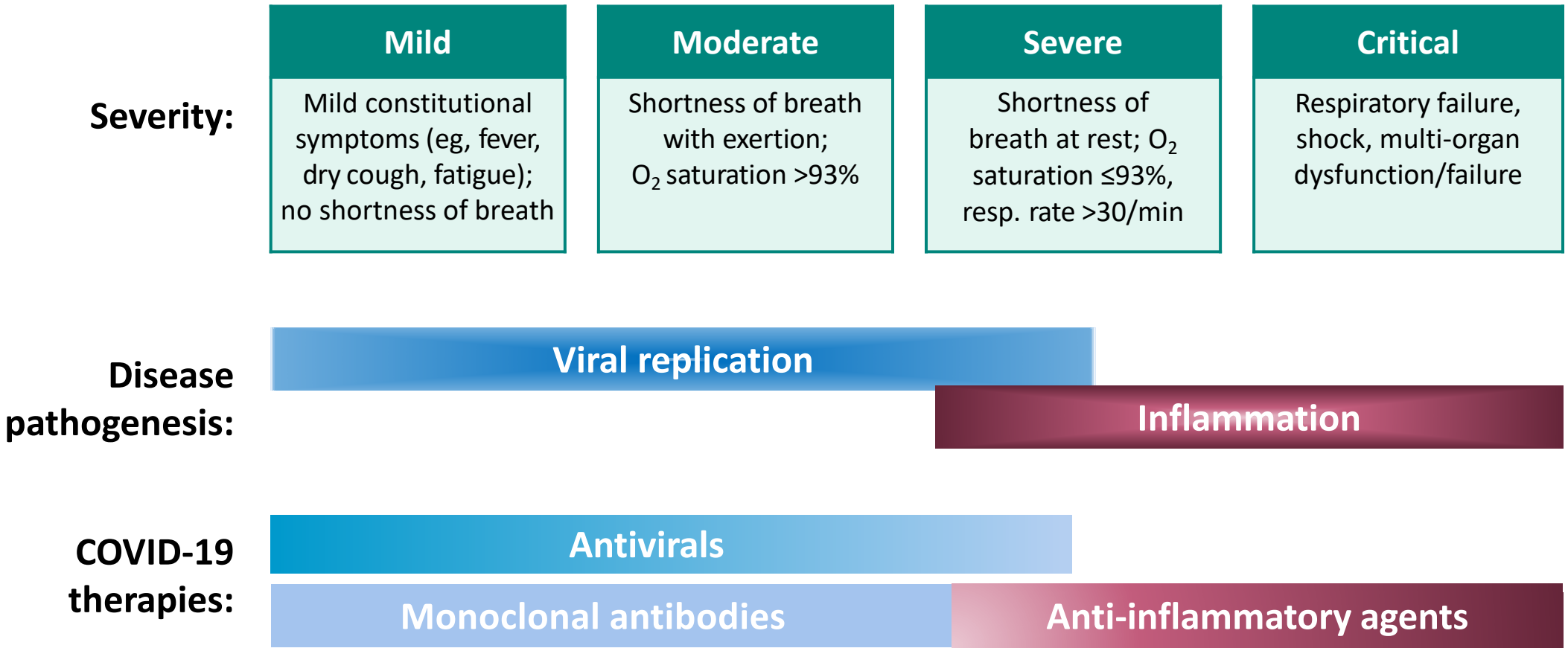


Figure adapted from RT Ghandi, et al. *N Engl J Med*.

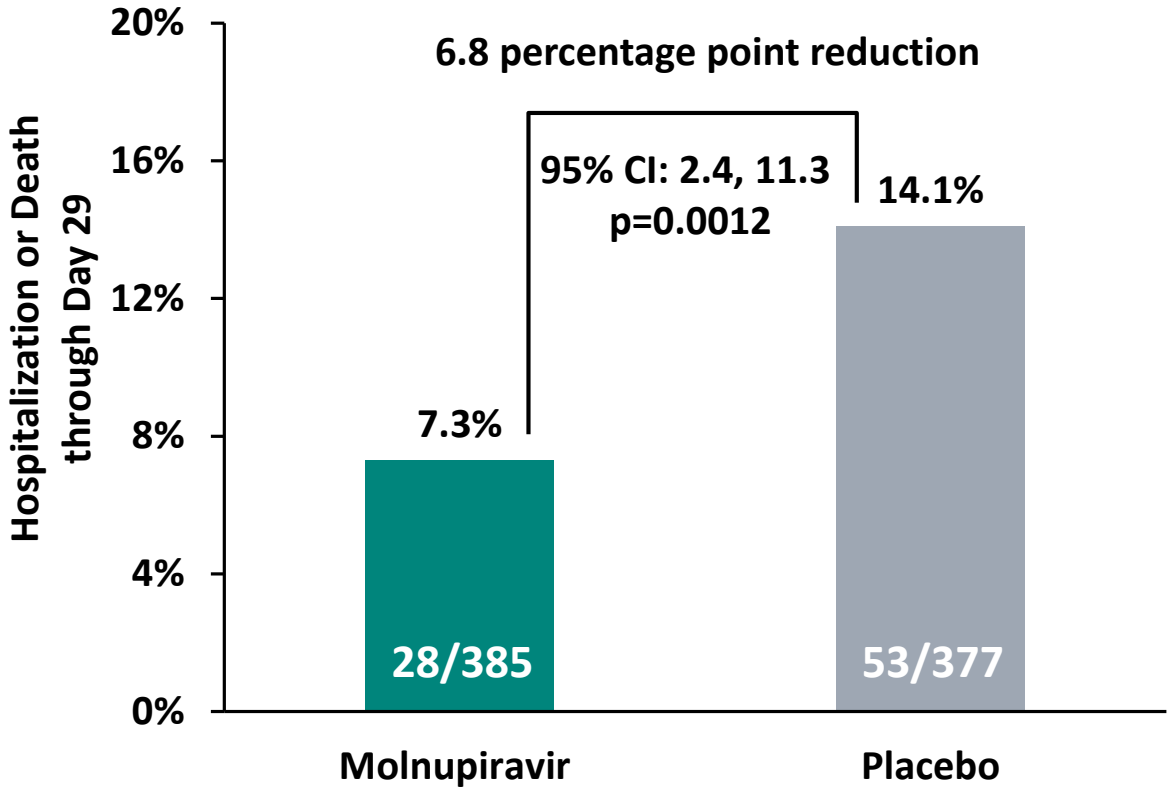
Limitations of Current COVID-19 Therapeutics

- Monoclonal antibodies are indicated for outpatients with mild to moderate COVID-19, but have significant limitations
  - Parenteral administration
  - Clinical monitoring needed during infusion and for ≥1 hour following infusion
  - Hypersensitivity reactions
  - Potential to become less effective to emerging SARS-CoV-2 variants
- Remdesivir requires intravenous administration, and is only approved for the treatment of hospitalized patients
- There are no adequate, approved oral antiviral agents available for the treatment of patients with mild to moderate COVID-19

Molnupiravir Addresses a Critical Unmet Medical Need

- Molnupiravir is an oral ribonucleoside analog that potently inhibits replication of SARS-CoV-2
- The Phase 3 trial (protocol design/endpoints agreed upon with the FDA) enrolled non-hospitalized adults with mild to moderate COVID-19, ≥1 risk factor associated with poor outcomes, and symptom onset within 5 days

Primary Efficacy Analysis (Interim Analysis)



A benefit was confirmed in supportive analysis (All Randomized Population)

Molnupiravir is an Oral Antiviral for the Treatment of COVID-19

- Proposed intended use
  - Treatment of mild to moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death
- Dosage and administration
  - 800 mg (four 200-mg capsules) orally every 12 hours for 5 days
    - No dose adjustment in patients with renal or hepatic impairment
    - No drug-drug interactions identified
  - Can be taken with or without food
  - Treatment should be initiated within 5 days of symptom onset

Merck Consultants

David Kirkland, PhD
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Agenda

Introduction	Sean Curtis, MD, MPH
Mechanism of Action	**Daria Hazuda, PhD**
Nonclinical Safety	**Kerry Blanchard, PhD**
Clinical Efficacy and Safety **Benefit-Risk Conclusion**	**Nicholas Kartsonis, MD**

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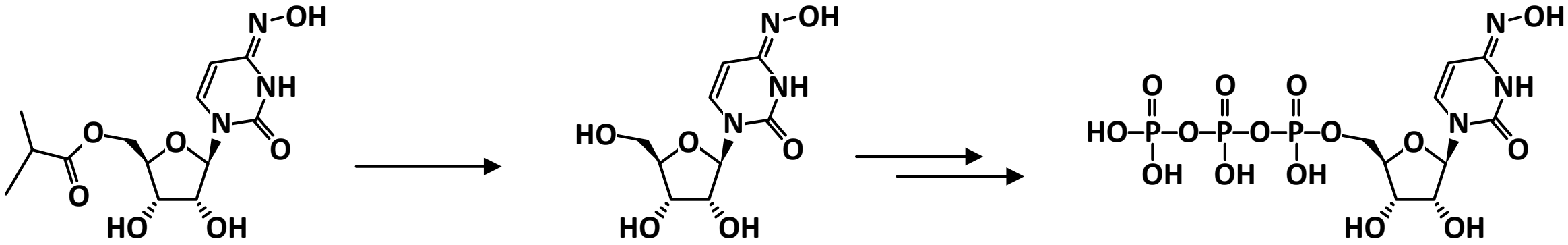
Mechanism of Action (MOA)

Daria J. Hazuda, PhD

Vice President – Infectious Disease and Vaccines
Merck & Co., Inc.

Molnupiravir Is an Oral Prodrug of N-hydroxycytidine (NHC)



Molnupiravir
(oxime tautomer)

***N*-hydroxycytidine, NHC**
(oxime tautomer)

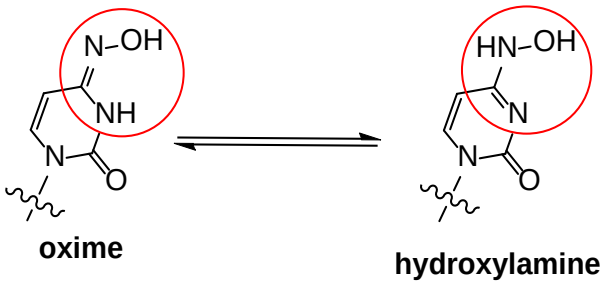
NHC-TP

Orally administered prodrug is rapidly converted by esterases to NHC in vivo

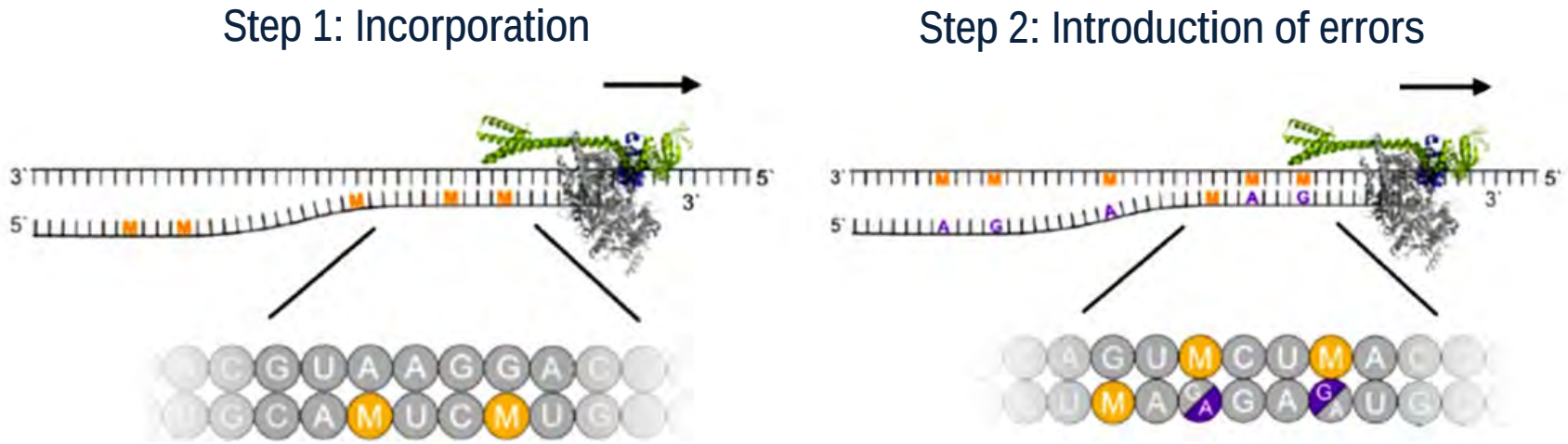
NHC is phosphorylated inside cells to NHC-TP

NHC-TP is a substrate for SARS-CoV-2 RNA polymerase and exerts its antiviral affect by introducing errors in the vRNA which impair SARS-CoV-2 replication and infection

Incorporation of NHC by Viral RNA Polymerases Results in Errors in Viral Genomes



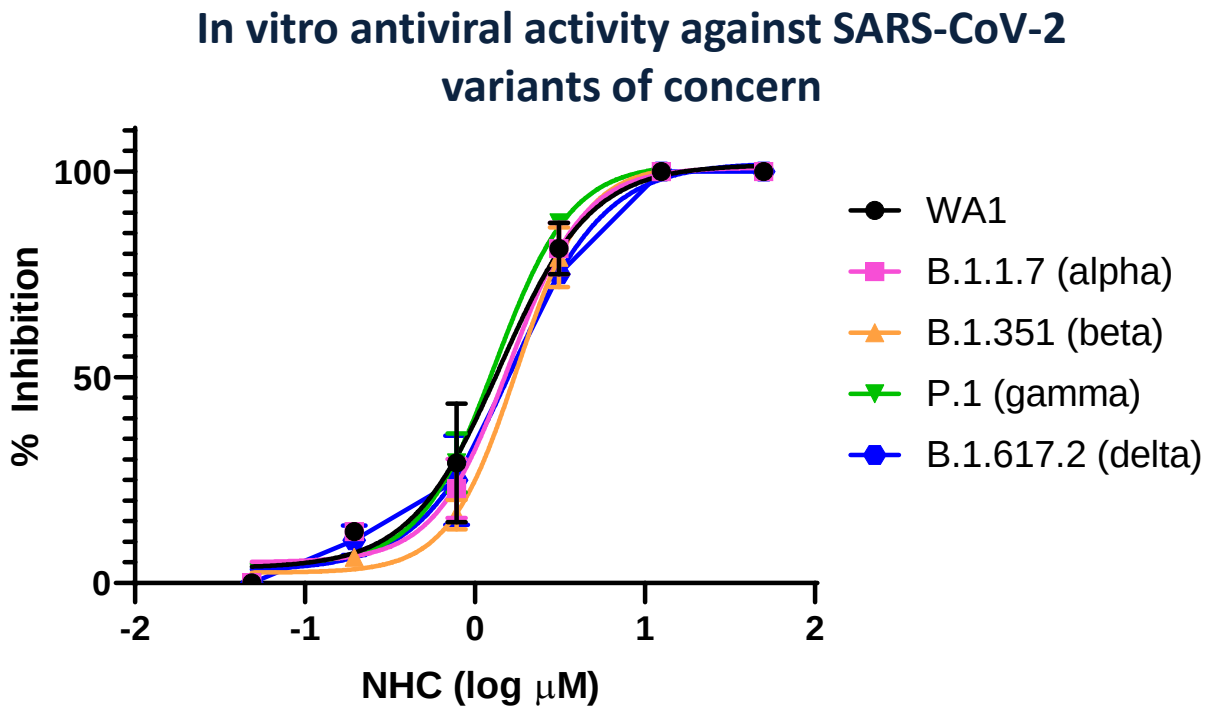
NHC and NHC-TP adopt two tautomeric forms—**oxime and hydroxylamine**—which behave either like **UTP** or **CTP**



After incorporation into the SARS-CoV-2 RNA template strand, NHC can direct the incorporation of either guanosine or adenosine, resulting in **transition errors** (C to U; U to C; G to A; A to G) in the viral RNA that impair viral replication and viral infectivity

Figure adapted from Kabinger et al. *BioRxiv*. doi.org/10.1101/2021.05.11.443555

NHC Displays Antiviral Activity Across SARS-CoV-2 Variants of Concern and Other Coronaviruses In Vitro

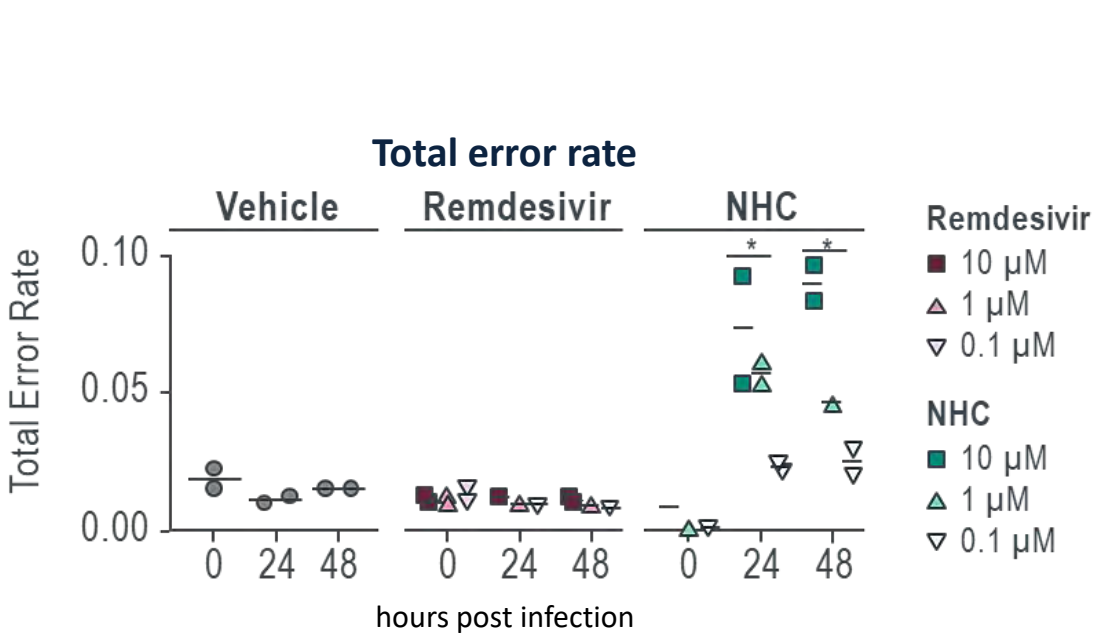


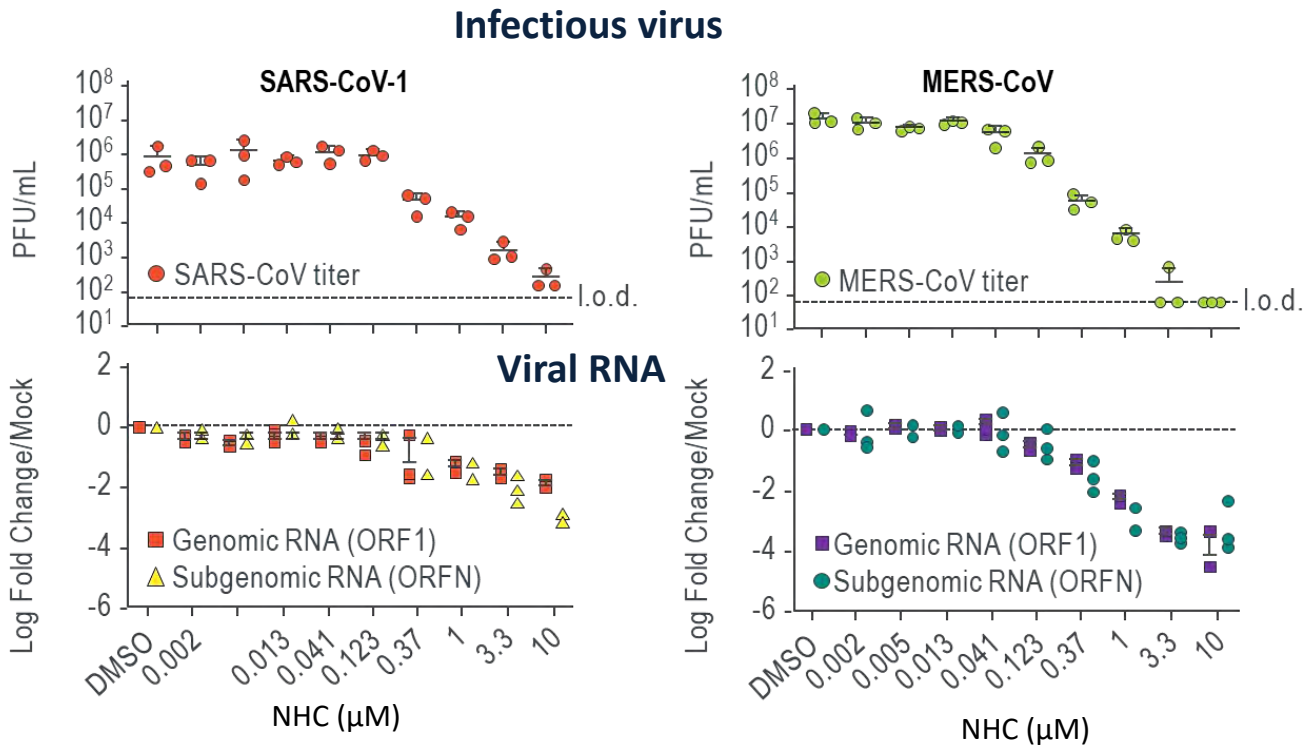
Virus	Reference
SARS-CoV-2 (WA1)	PD010-MK4482
SARS-CoV-2 (alpha)	PD010-MK4482
SARS-CoV-2 (beta)	PD010-MK4482
SARS-CoV-2 (gamma)	PD010-MK4482
SARS-CoV-2 (delta)	PD010-MK4482
SARS-CoV-1 (Urbani)	NIAID Antiviral Testing Program
SARS-CoV-1 (SARS-Cov-GFP)	Sheahan et al, 2020
MERS-CoV (MERS-nLUC)	Sheahan et al, 2020
MERS-CoV (GenBank JX869059)	Agostini et al, 2019
hCoV-OC43E	PD008-MK4482
MHV	Agostini et al, 2019

Antiviral activity IC_{50} range 0.14 to 1.77 μM

- **High barrier to the development of resistance has been demonstrated in coronaviruses (MHV and MERS-CoV), influenza, and Venezuelan equine encephalitis virus (VEEV)**
- **The antiviral activity of NHC is specific to RNA viruses; no activity against viruses which use dNTPS**

NHC Inhibits CoV Replication and Reduces the Production of Infectious Viruses as a Result of the Increased Rate of Errors



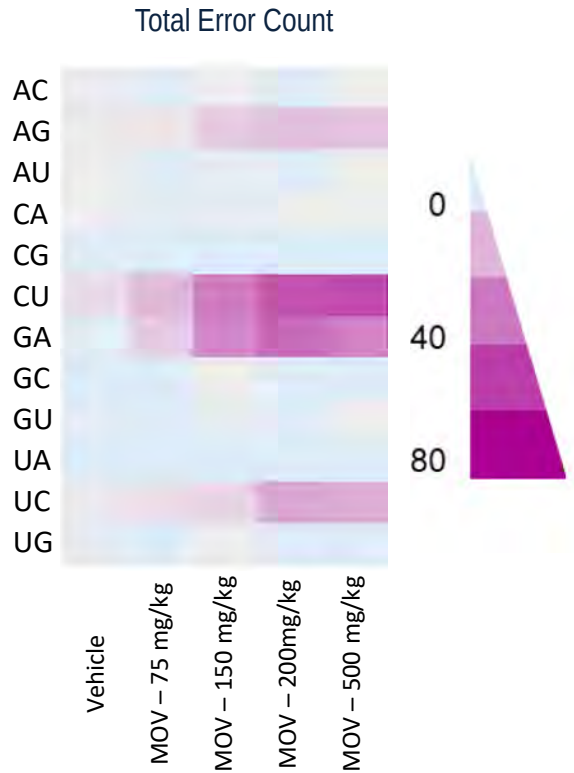


- A 3-fold increase in error rate resulted in a 138-fold decrease in infectious virus titer
- A 6-fold increase in error rate resulted in a 26,000-fold decrease in infectious virus titer

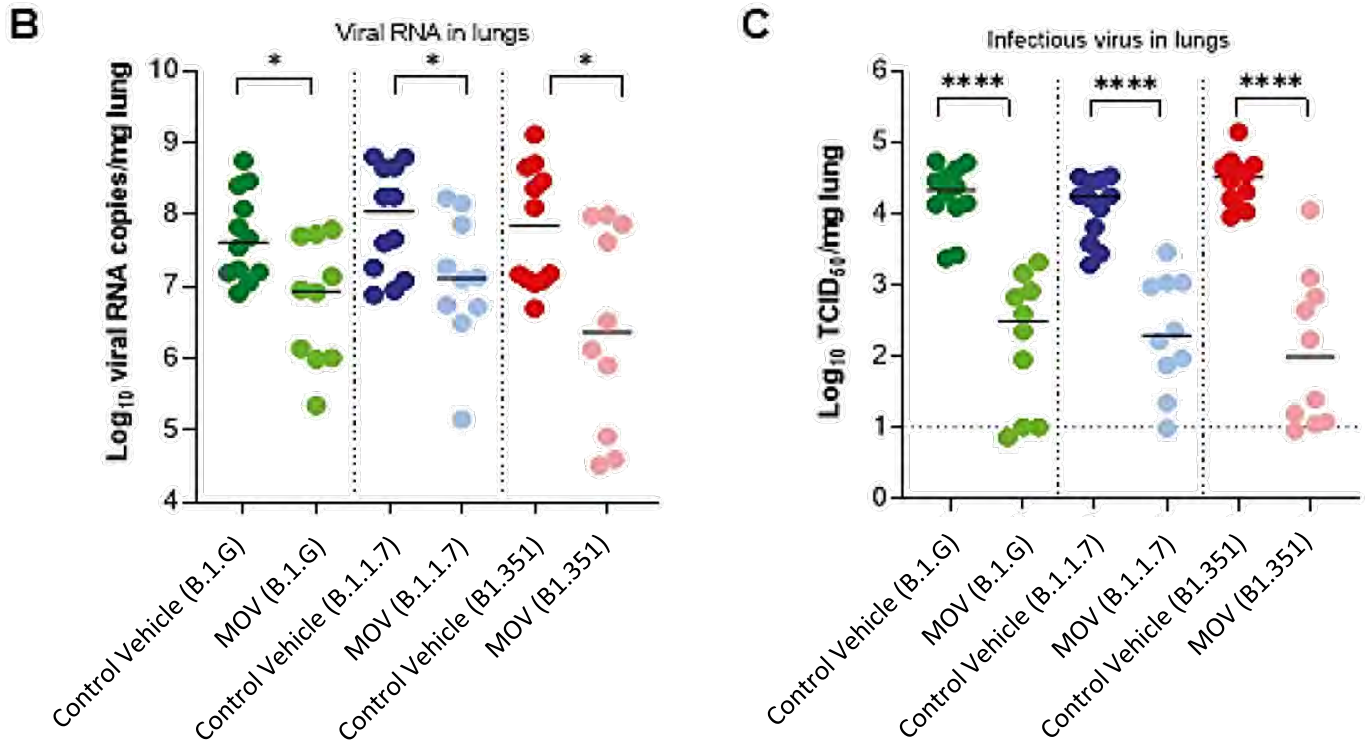
Figures reproduced from Sheahan TP, et al. 2020 *Sci Transl Med*. doi: 10.1126/scitranslamed.abb5883

Molnupiravir Inhibits SARS-CoV-2 and CoV-2 Variants in Animals, Reducing Amount of Infectious Virus in Association With Increased Errors in vRNA

Increased number of transition errors in vivo



Greater impact on infectious titers than on viral RNA levels



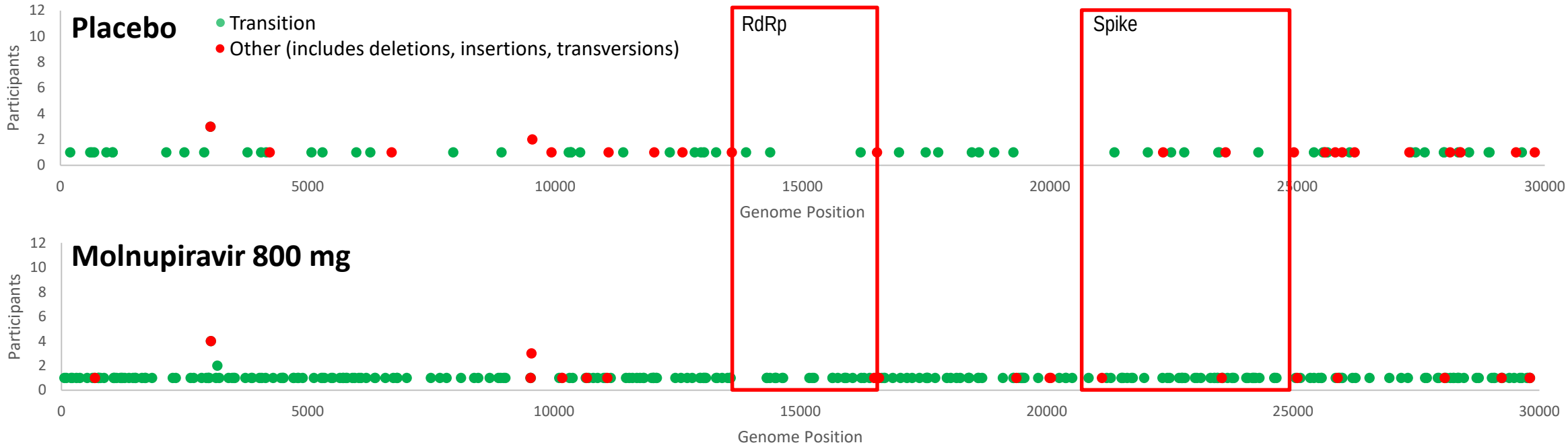
Figures adapted from Abdelnabi et al, *BioRxiv*, doi.org/10.1101/2020.12.10.419242 (left); Abdelnabi et al. *J Infect Dis*. 2021;224:749-753 (right)

Clinical Data Are Consistent With Molnupiravir Mechanism of Action

P002 Phase 2

Treatment	Number of Errors[a], count	
	Transition	Other
Placebo	64	24
Molnupiravir	289	21

- Errors observed with molnupiravir treatment were randomly distributed
- No evidence of an increased rate of transition errors at any specific position or gene including the replicase or spike



[a] Errors present at an allele frequency of 2% or more of the SARS-CoV-2 RNA sequence reads.

Treatment-Emergent Spike Substitutions in Both Molnupiravir and Placebo; Most Were Not Consistent With a Direct Effect of Molnupiravir

P002 Phase 3

Substitutions	Observed in current circulating strains	Error type
D138Y	gamma	**Transversion**
G142D	delta sub-lineages	Transition
Y144T	mu	**Transversion**
Y144Y145-TSN	mu	**Deletion/insertion**
K417T	gamma	**Transversion**
N501Y	beta, gamma, theta and alpha and delta sub-lineages	**Transversion**
H655Y	gamma	Transition
P681R	delta, kappa	**Transversion**
P681H	alpha, theta	**Transversion**
D950N	mu	Transition
G1124V	delta sub-lineages	Transition
V1176F	gamma	Transition

- Spike substitutions observed in both placebo and molnupiravir groups (4/50 vs 5/42)
- All spike substitutions observed are present in currently circulating strains
- Majority of spike substitutions were **transversions or other errors**

Molnupiravir treatment led to a more rapid decline of infectious virus, decreasing the likelihood of transmission of variants.

Molnupiravir Mechanism of Action

- Molnupiravir is an oral prodrug which is rapidly converted to NHC
- NHC-TP is a substrate for the SARS-CoV-2 RNA polymerase
- Incorporation of NHC by the SARS-CoV-2 RNA polymerase introduces transition errors into SARS-CoV-2 RNA
- Accumulation of errors in the viral RNA impacts SARS-CoV-2 replication resulting in fewer viruses and viruses which are less infectious
- Molnupiravir (and NHC) are active against SARS-CoV-2 variants of concern in vitro and in animal models
- In patients, molnupiravir treatment results in a random distribution of transition errors in SARS-CoV-2 RNA with no evidence of an increased rate of transition errors at any specific position or gene, including the replicase or spike

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Nonclinical Safety

Kerry Blanchard, PhD

FDA Advisory Committee Meeting
Molnupiravir

Nonclinical Safety Overview

Merck & Co., Inc.

Molnupiravir Was Evaluated in a Comprehensive Nonclinical Safety Program

- In vitro and in vivo safety pharmacology studies
- A battery of genotoxicity studies
- Regulatory in vivo mutagenicity follow-up assays including Pig-a and Transgenic Rodent assays
- Tolerability studies in mice, rats, rabbits, dogs, and nonhuman primates
- Repeat-dose general toxicity studies in rats up to 3 months and dogs and mice up to 1 month duration
- A comprehensive developmental and reproductive toxicology assessment

The nonclinical safety profile supports the proposed short-term use of molnupiravir for the treatment of mild to moderate COVID-19 in adults

Nonclinical Safety Topics

- Genotoxicity assessment
- Hematopoietic findings in dogs only
- Growth plate findings in rapidly growing rats
- Embryo-fetal lethality/teratogenicity in rats

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Molnupiravir Genetic Toxicology

Evidence of in vitro Mutagenicity

Low Risk of Genotoxicity in vivo

Molnupiravir Was Mutagenic *in vitro*

Regulatory GLP in vitro genotoxicity assessment

Bacteria

Bacterial mutagenicity (Ames) assay *(positive)*

In vitro mammalian cells

***In vitro* micronucleus in human lymphoblastoid TK6 cells (negative)**

External publication of non-GLP study not following regulatory guidelines

Nonstandard 32-day assay

***In vitro* HPRT in Chinese hamster cells (CHO)* (*positive*)**

In vitro signal followed up _in vivo_

* Zhou et al, 2021. HPRT assay significantly different from protocols established by regulatory testing guidelines (OECD TG 476).

Molnupiravir Was Not Genotoxic *in vivo*

Regulatory GLP *in vivo* genotoxicity assessment

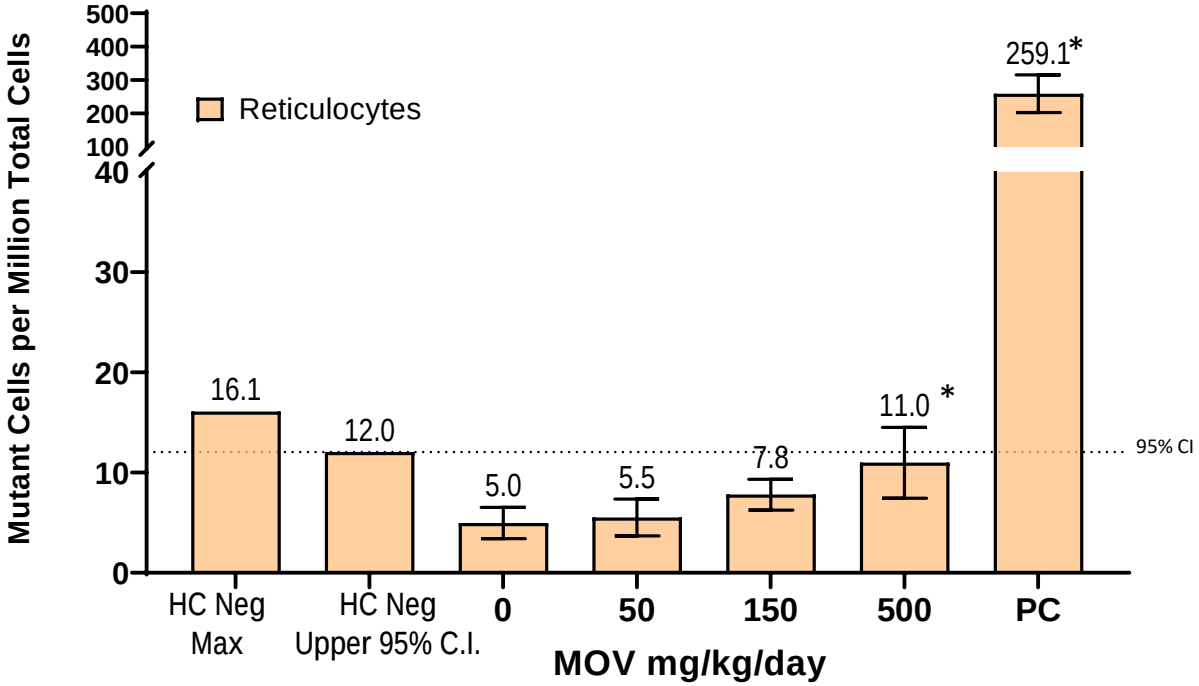
***In vivo* Rat Micronucleus Study**
No evidence of chromosomal damage

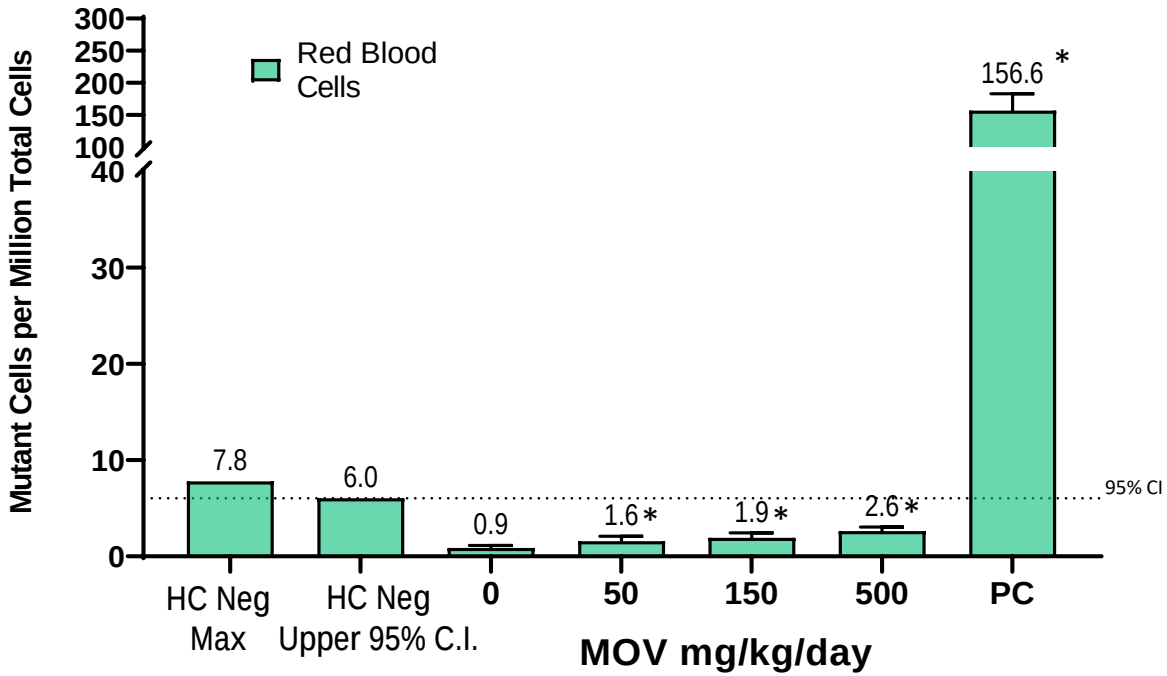
Given the *in vitro* mutagenicity signal, we advanced to additional *in vivo* mutagenicity Pig-a and transgenic (Big Blue®) rat studies

Molnupiravir in a 28-day Rat Pig-a Mutation Assay

Prospective criteria for clear negative or positive	
Statistical difference from control	YES
Statistical trend	NO
Exceeds historical controls 95% CI	NO

- Equivocal result as it was not a clear positive or negative result
- All values within historical 95% confidence interval

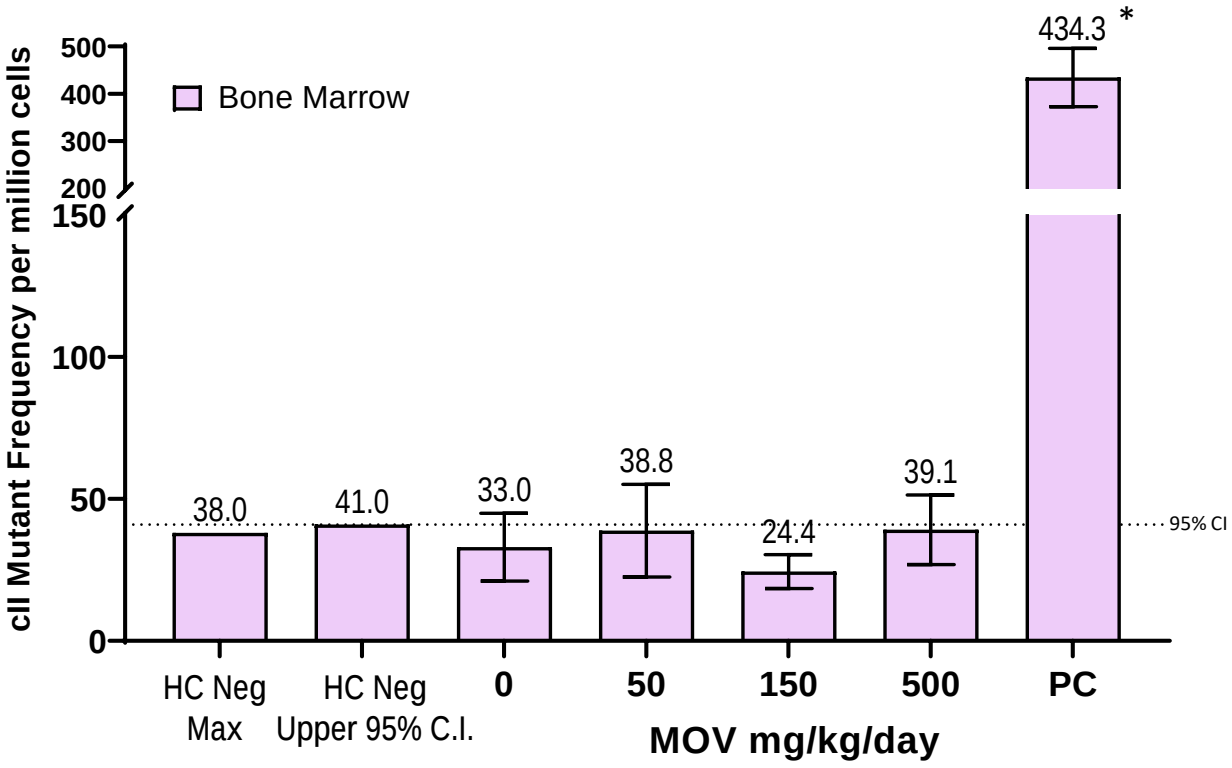


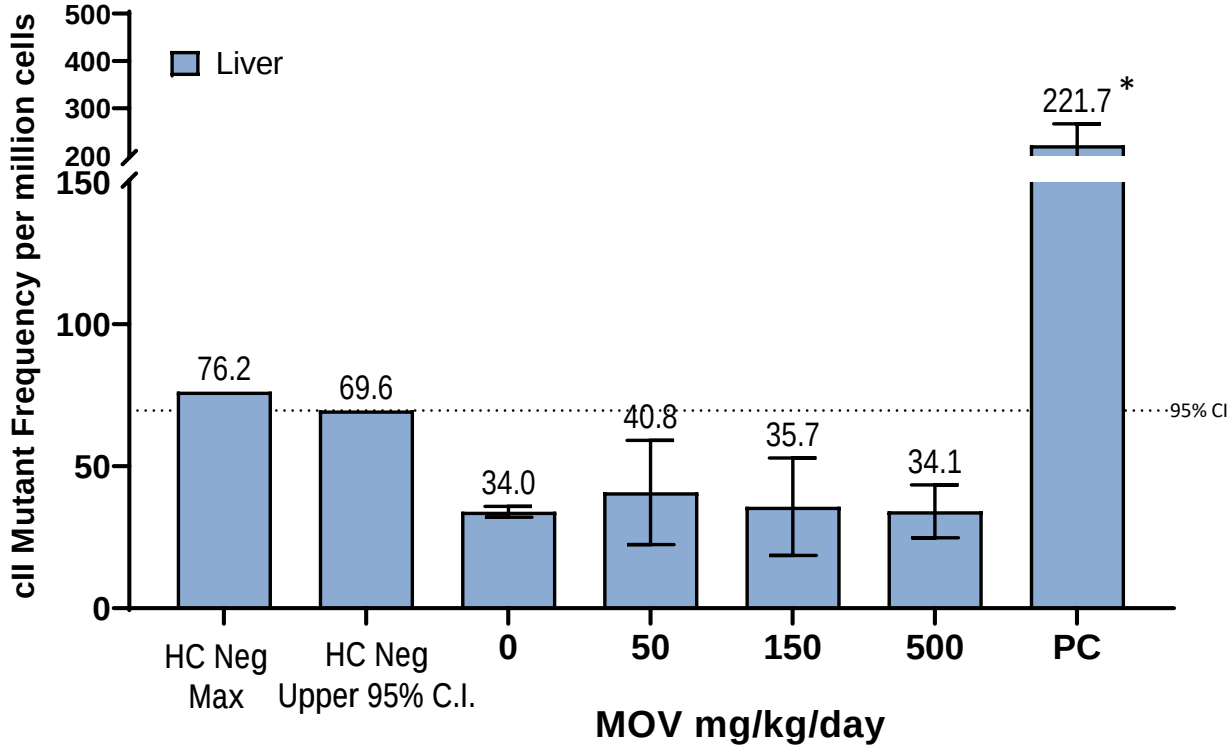


HC=historical control; PC=positive control, Ethyl nitrosourea (ENU); *p<0.05

Molnupiravir in a Transgenic Rodent Mutation Assay (28-day Big Blue®)

- No increase in mutation frequency in slow (liver) and rapidly (bone marrow) proliferating tissues
- Gold Standard assay for *in vivo* mutagenesis





HC=historical control; PC=positive control, Ethyl nitrosourea (ENU); *p<0.05

Molnupiravir *in vivo* Genotoxicity Assessment

Clear Negative – *in vivo* micronucleus rat assay
Equivocal – Pig-a 28-day rat assay
Clear Negative - Gold standard Transgenic Rodent assay

Based on totality of data, molnupiravir has low risk for genotoxicity *in vivo*

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Hematopoietic Findings

Hematopoietic Findings in Dogs Only – Similar Findings Not Observed in Humans

Hematopoietic Findings Observed in Dogs Only

- Hematopoietic findings in 1-month dog study
  - Mild hematologic findings on Day 7
  - Severe pancytopenia and bone marrow depletion after ≥2 wk of continuous exposure
  - Bone marrow and hematologic findings were reversible
- Similar hematopoietic findings not observed in other nonclinical species
  - Rats (9× for 12 wk), mice (19× for 4 wk), rabbits (29× for 2 wk) or nonhuman primates (4× for 1 wk)
    - NOTE: (fold above clinical NHC AUC and duration of treatment)
- Closely monitored in clinical trials – similar findings not observed

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Increased Growth Plate Thickness

Growth Plate Findings in Rapidly Growing Rats—Not Relevant in Adults

Increased Growth Plate Thickness (Rat Only) Not Relevant to Adults

- In 1-month studies, no effects on growth plates in mice, rats, or dogs
- In a 3-month rat study
  - Dose-dependent increased thickness of growth plate observed in rapidly growing rats
  - Increased thickness of growth plate associated with decreased bone formation
  - No effect on cortical bone or articular cartilage
- These findings are not relevant to adults since growth plate is no longer present in the mature skeleton of humans

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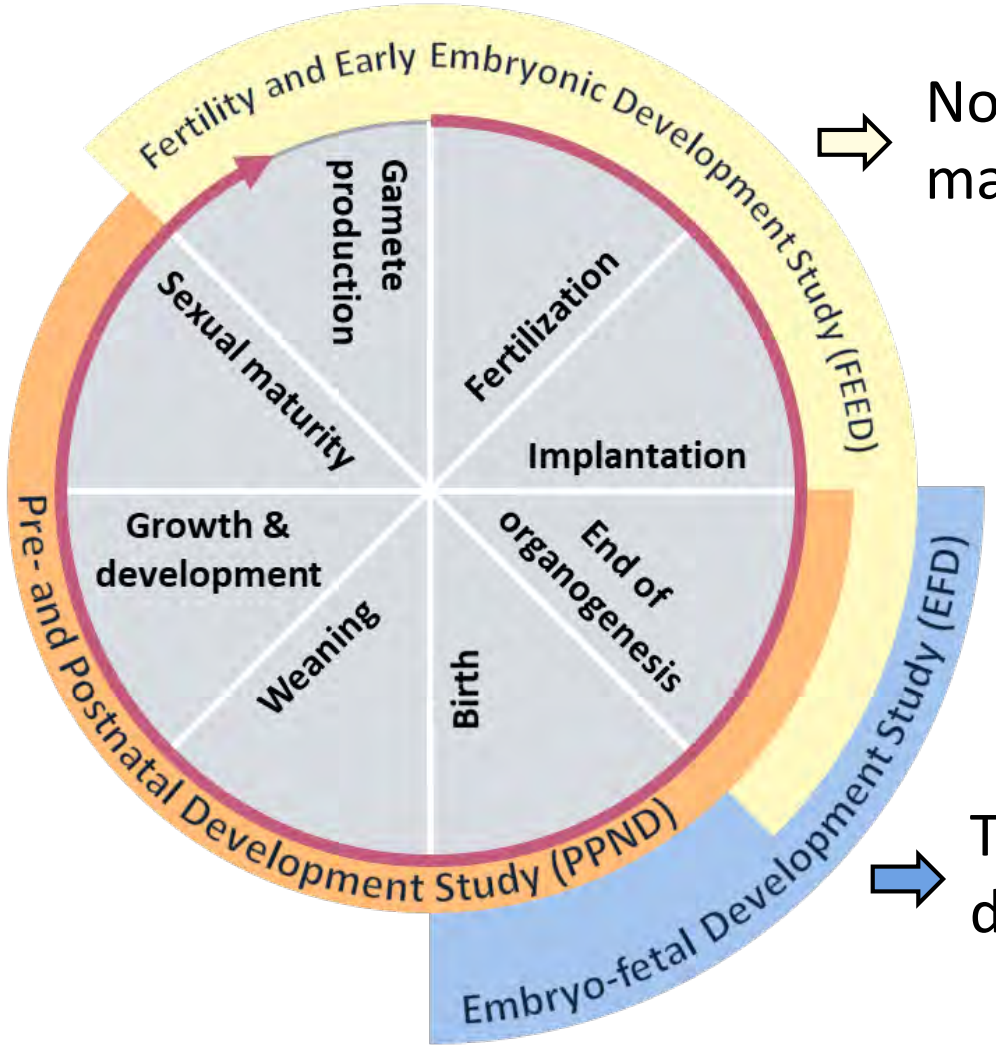
Assessment of Developmental and Reproductive Toxicology

Embryo-fetal Lethality/Teratogenicity in Rats at a Maternally Toxic Dose—Not Recommended for Use in Pregnancy

Reproductive Life Cycle and DART Study Types



No effects on female or male fertility

No effects on offspring

Toxic effects on developing fetuses

Embryo-fetal Lethality and Teratogenicity in Rats at NHC Exposure Above Human Exposure

Species	Dose, mg/kg/day	NHC exposure multiple (AUC)	Developmental effects
Rat	1000[a]	8×	Embryo-fetal lethality and teratogenicity Reduced fetal body weights[b]
	500	3×	Reduced fetal body weights[b]
	250	0.8×	None
Rabbit	750	18×	Reduced fetal body weights[b]
	400	7×	None

[a] Excessive maternal toxicity in some but not all rats in the pEFD study.
[b] Delayed ossification called treatment-related in rats; ossification in rabbit fetuses was within expected range.

Based on these findings, molnupiravir is not recommended for use during pregnancy

Summary

The nonclinical safety profile supports the proposed short-term use of molnupiravir for the treatment of mild to moderate COVID-19 in adults

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Overview of Clinical Development

Nicholas Kartsonis, MD

Senior Vice President, Clinical Research
Merck & Co., Inc.

Molnupiravir's (MOV) Clinical Development Program Provides a Comprehensive Evaluation of Its Use in the Treatment of COVID-19

Healthy Volunteers Phase 1 (P004)

- Single dose (SD)/Multiple dose (MD) trial
- MOV up to 1600 mg SD and 800 mg BID × 5.5 days
- N=130
- **Complete**

Outpatients with COVID Phase 2 (P006)

- Outpatient adults with mild or moderate COVID
- Dose escalation
- Placebo (PBO) vs MOV BID × 5 days
- N=204
- **Complete**

Outpatients with COVID Phase 1/2 (P005)

- AGILE (UK)
- Outpatient adults with mild or moderate COVID
- PBO vs MOV × 5 days BID
- Dose finding Phase 1 N=18 (complete)
- N=132/180 in Phase 2
- **Enrollment ongoing**

Inpatients with COVID Phase 2 (P007)

- Inpatient adults (non-ICU/mechanically ventilated) with COVID
- Dose escalation
- PBO vs MOV BID × 5 days
- N=65/84
- **Enrollment ongoing**

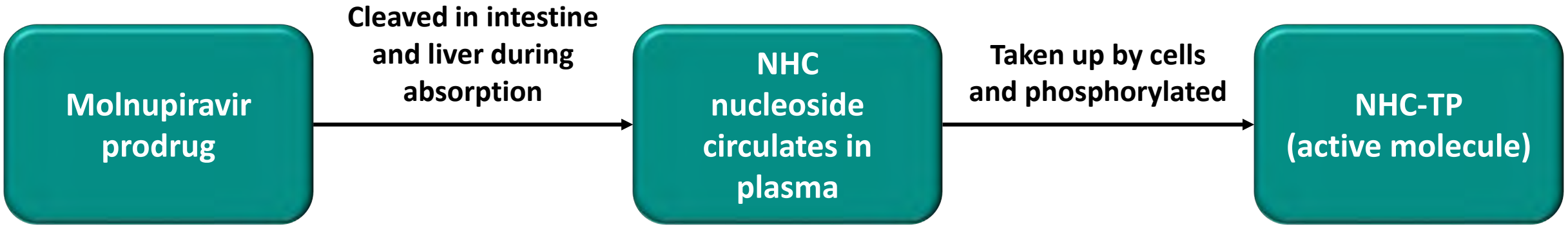
Outpatients with COVID Phase 2/3 (P002, MOVe-OUT)

- Outpatient adults with mild or moderate COVID
- PBO vs MOV BID × 5 days
- Phase 2: PBO vs MOV 200, 400, or 800 mg, 1:1:1:1
- Phase 3: PBO vs MOV 800 mg, 1:1
- N=302 (Phase 2), 1433 (Phase 3)
- **Complete**

Inpatients with COVID Phase 2/3 (P001, MOVe-IN)

- Hospitalized adults with mostly moderate or severe COVID
- PBO vs MOV BID × 5 days
- Phase 2: PBO vs MOV 200, 400, or 800 mg, 1:1:1:1
- N=304 (Phase 2), Phase 3 not conducted
- **Complete**

The Pharmacokinetic (PK) Properties of Molnupiravir Are Well Understood



- Molnupiravir is rapidly absorbed and converted to NHC (NHC T_{max} ~1.5 hr)
  - Limited molnupiravir observed in plasma
- Elimination is via metabolism to native uridine and cytidine
  - No expected drug-drug interactions
  - NHC is not a substrate, inhibitor, or inducer of major metabolic enzymes or a substrate or inhibitor of transporters
- No expected effect of renal or hepatic impairment on PK

The PK Properties of NHC Allow for Use of Molnupiravir as an Oral Option to Treat COVID-19

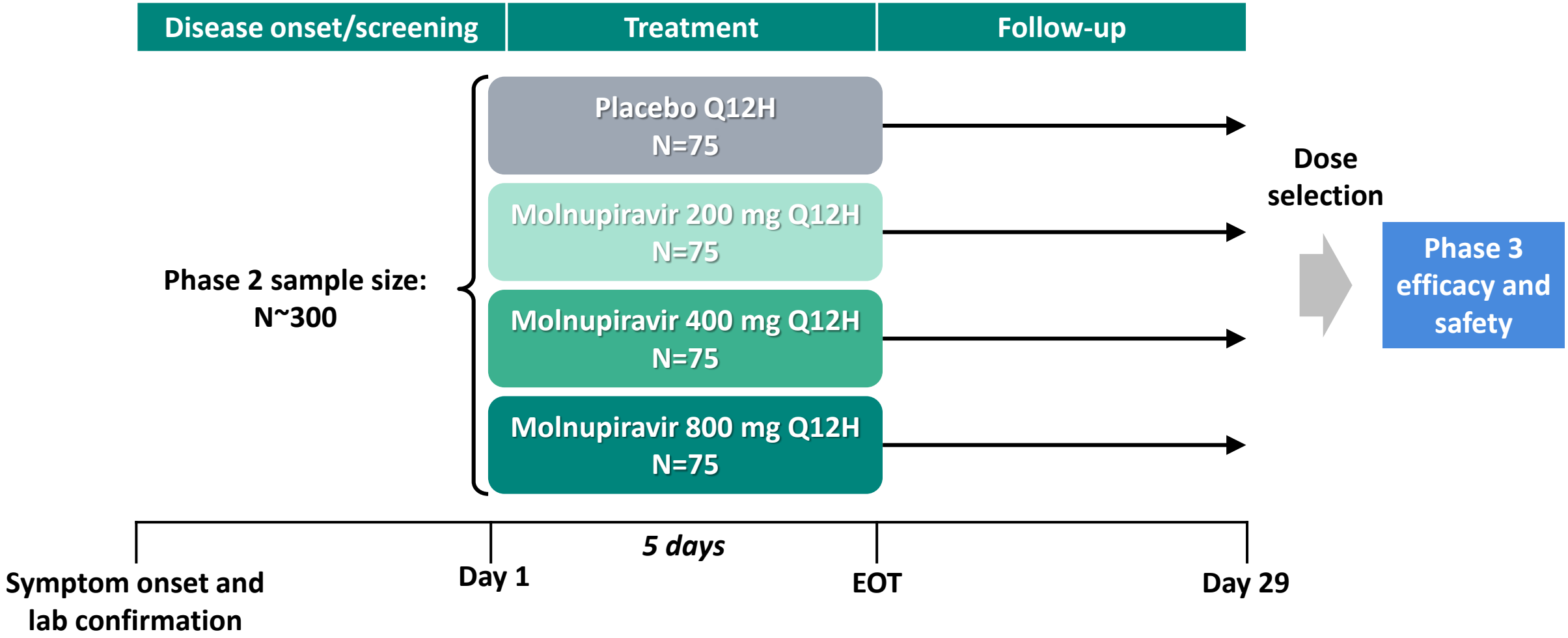
Phase 1 Study of Single and Multiple Doses in Healthy Participants (P004)

Population PK Analysis of NHC Data from Phase 1 and Phase 2 Studies

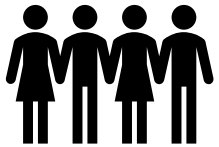
- Exposure increases dose proportionally
- Limited accumulation (<10%) after Q12H dosing due to 3.3-hour effective half-life ($t_{1/2}$)
- Limited renal elimination (≤3% of dose)
- No meaningful effect of food on PK
- <2-fold effect of demographic intrinsic factors

Merck's Phase 2/3 Studies Were Designed to Support Molnupiravir Dose Selection and Demonstrate Clinical Efficacy and Safety in COVID-19

Design of each Phase 2/3 study:



The Phase 2 Portion of the Outpatient Study (P002, MOVe-OUT) Was Designed to Facilitate Dose Selection



- Adults (≥18 years) with mild/moderate COVID-19
- Symptomatic + positive SARS-CoV-2 test result ≤7 days prior to study entry
- Symptom duration ≤7 days at entry

- Randomized, double-blind
- 200, 400, 800 mg molnupiravir vs placebo BID for 5 days (~75 per arm)
- Randomization stratified by symptom duration at entry and increased risk status

- Primary Endpoint: Hospitalization or death through Day 29
- Other endpoints to inform dose selection: viral load, infectivity, and viral nucleotide substitution analysis

- Number of sites who screened in Phase 2: 58
- Number of countries: 12 (including the United States)
- Total Phase 2 Recruitment: 303

The Phase 2 portion of P001 (MOVe-IN) evaluated COVID-19 in hospitalized participants with COVID-19

Dose Selection for Molnupiravir Was Ultimately Based on Data From Three Different Sources

Virologic data

- Viral load
- Infectivity
- Viral nucleotide substitution analysis

Clinical efficacy and safety data from 4 studies

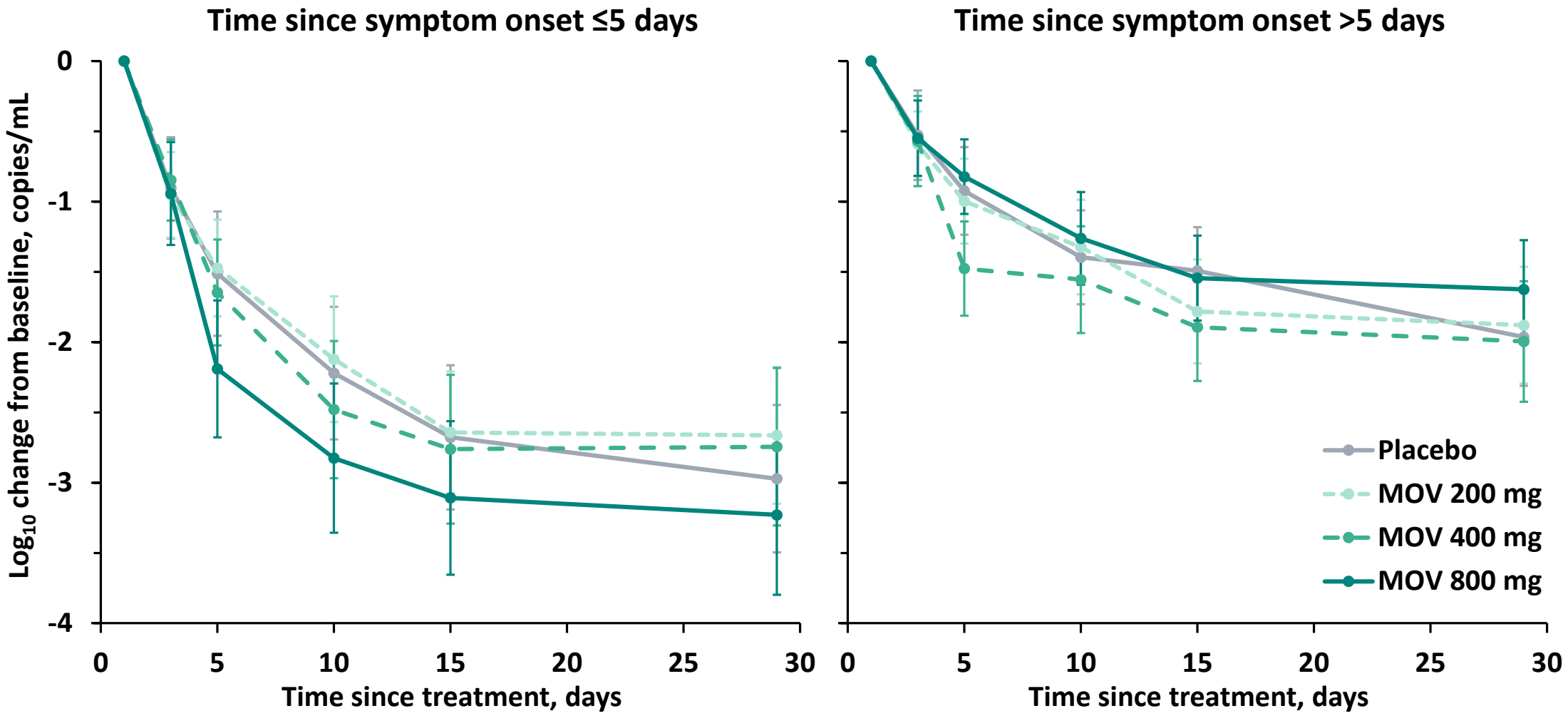
- Ph1 (P004)
- Ph2 (P002 Phase 2 portion, P001 Phase 2 portion, and P006)

PK

- Population PK
- Exposure-response analyses

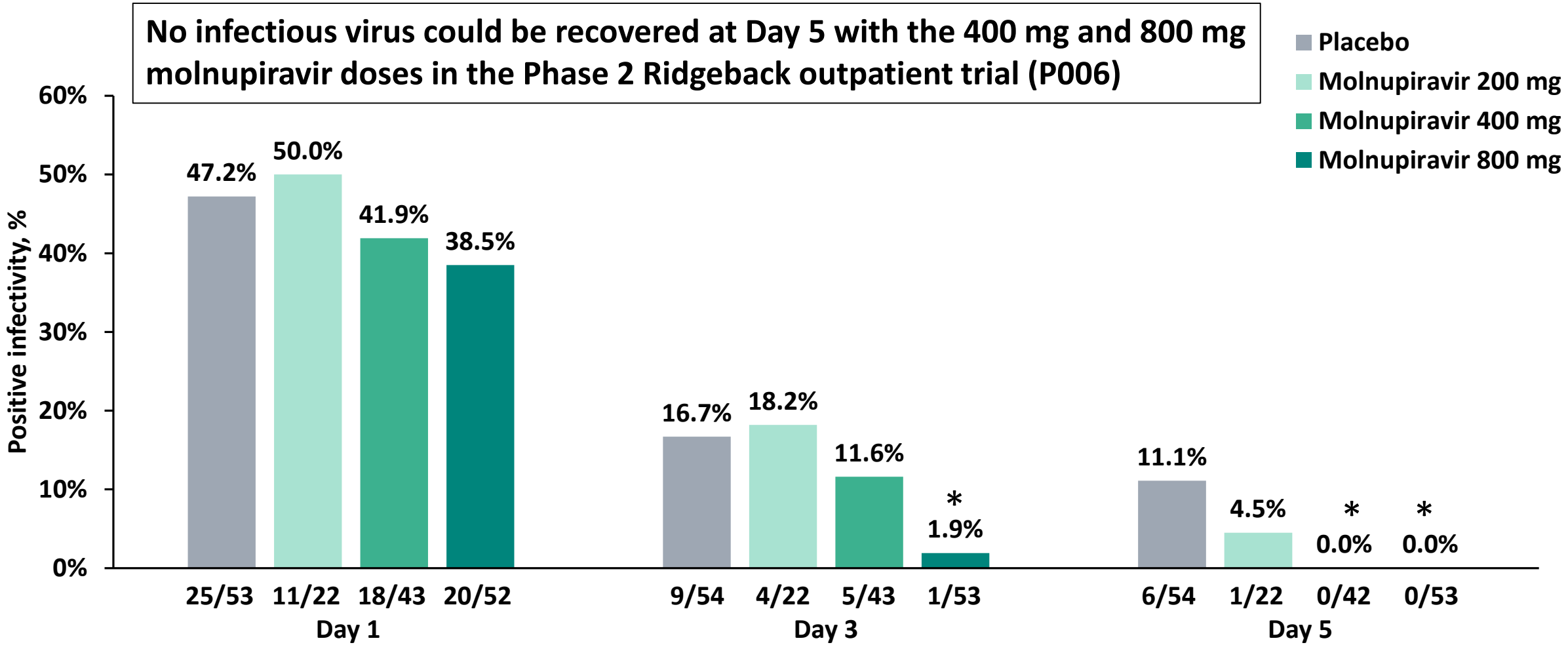
Reduction in Viral Load Was Largest for the 800-mg Molnupiravir Dose

P001 and P002 Phase 2



Lower Percentages of Participants Treated With Molnupiravir Had Positive Viral Cultures

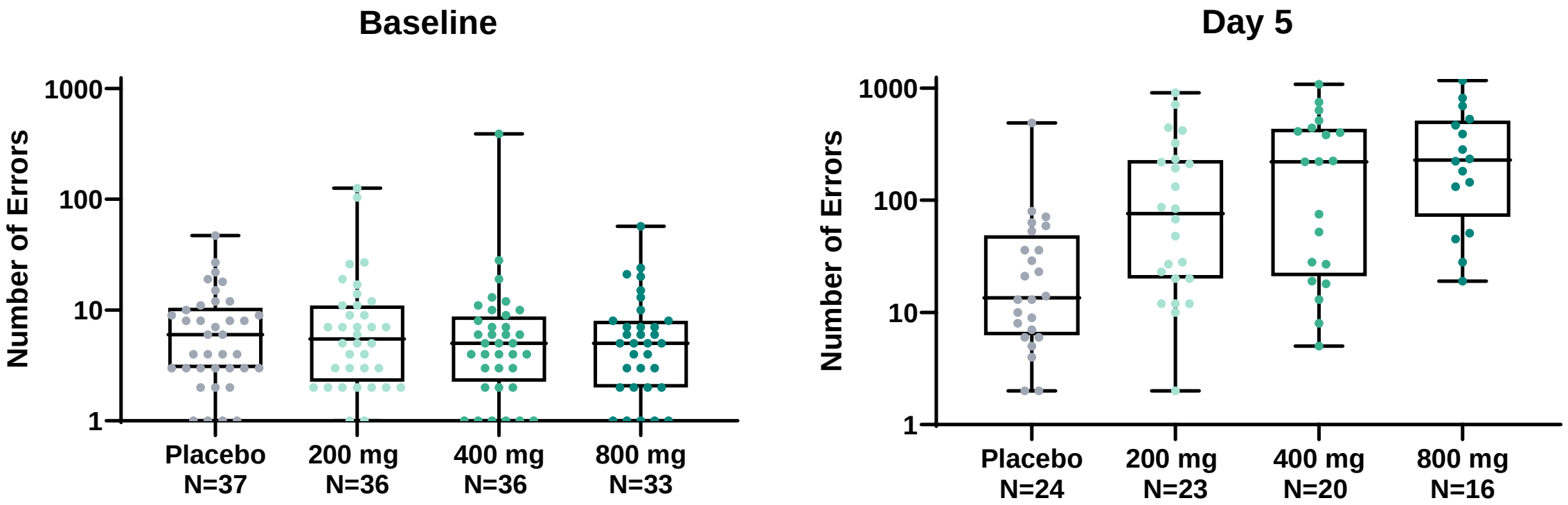
P006 Phase 2



* p<0.05 (molnupiravir dose vs placebo).

The Number of Low-frequency Nucleotide Substitutions Increases With Increasing Molnupiravir Dose

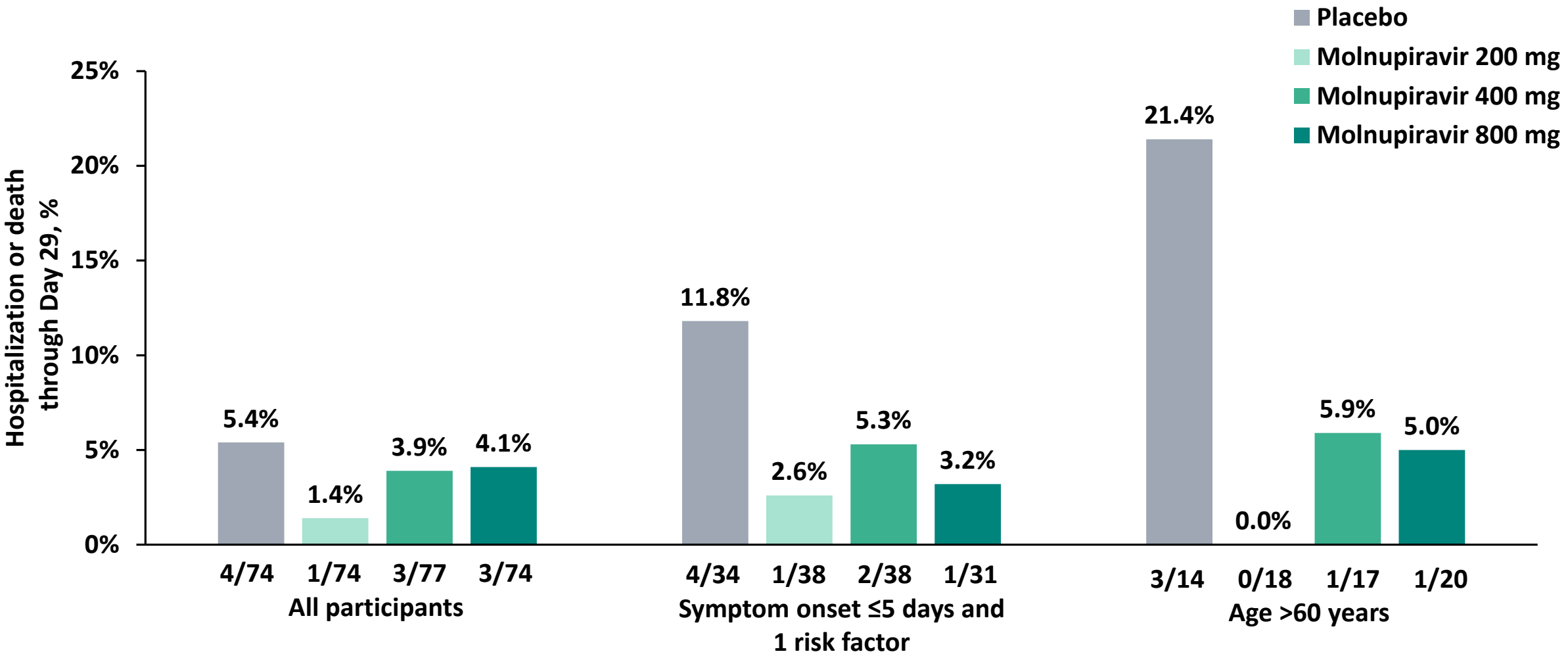
P002 Phase 2



Each point represents the number of substitutions in one participant. Boxes are drawn between the 25th and 75th percentiles of the data. The central horizontal lines correspond to the median.

Molnupiravir Was Associated With Fewer Hospitalizations and Deaths in the Phase 2 Portion of P002 (MOVe-OUT)

P002 Phase 2



The Phase 3 Design of Protocol 002 Was Modified to Focus on At-risk Outpatients and Those Earlier in the Course of Disease

Non-hospitalized adults with mild or moderate COVID-19

- Laboratory-confirmed SARS-CoV-2 infection ≤5 days prior to randomization
- Onset of COVID-19 signs/symptoms ≤5 days prior to randomization

Patient population

- All at increased risk for severe illness from COVID-19
  - >60 years of age, active cancer, CKD, COPD, obesity (BMI ≥30), serious heart conditions (CAD, heart failure, cardiomyopathies), diabetes mellitus
- Unvaccinated against SARS-CoV-2
- N=1550

Stratification

- Time from symptom onset to randomization (≤3 days, >3 [4-5] days)

Dose

- Molnupiravir 800 mg every 12 hours for 5 days vs placebo, randomized 1:1

Phase 3 Design of Protocol 002 Included a Comprehensive Evaluation of Efficacy

Efficacy endpoints

Primary: All-cause hospitalization (≥24 hours) or death through Day 29

Secondary: Improvement/progression of patient-reported signs/symptoms of COVID-19 through Day 29
WHO 11-point ordinal scale measuring COVID-19 severity at pre-specified timepoints

Exploratory: SARS-CoV-2 RNA titers at pre-specified timepoints

Efficacy evaluation

- Modified Intention-to-Treat (mITT) population
- Formal hypothesis testing evaluation of primary endpoint based on risk difference
- Planned interim analysis to assess efficacy/futility based on ~50% of the planned Phase 3 enrollment (N=775/1550) with an alpha spending function that controlled the type I error rate at $\alpha = 0.025$ (one sided), with a criterion to declare early efficacy of $p < 0.0092$
- **The external Data Monitoring Committee (eDMC) recommended stopping enrollment early as statistical significance was met, demonstrating superior efficacy of molnupiravir**

Demographics Were Balanced Across the Two Groups

P002 Phase 3 (Interim Analysis and All Randomized Populations)

	Participants, n (%)			
	Interim Analysis Population		All Randomized Population	
	Molnupiravir N=387	Placebo N=388	Molnupiravir N=716	Placebo N=717
Sex				
Male	187 (48)	217 (56)	332 (46)	366 (51)
Female	200 (52)	171 (44)	384 (54)	351 (49)
Age, yr				
18-49	274 (71)	271 (70)	484 (68)	465 (65)
50-64	82 (21)	80 (21)	159 (22)	170 (24)
65-74	24 (6)	24 (6)	49 (7)	59 (8)
≥75	7 (2)	13 (3)	24 (3)	23 (3)
Mean	43.2	44.2	44.4	45.3
Median	41.0	43.0	42.0	44.0
Range	18-87	18-88	18-90	18-88

Race and Ethnicity Were Balanced Across the Two Groups

P002 Phase 3 (Interim Analysis and All Randomized Populations)

	Participants, n (%)			
	Interim Analysis Population		All Randomized Population	
	Molnupiravir N=387	Placebo N=388	Molnupiravir N=716	Placebo N=717
Race				
American Indian or Alaska Native	20 (5)	9 (2)	60 (8)	44 (6)
Asian	7 (2)	11 (3)	26 (4)	23 (3)
Black or African American	27 (7)	20 (5)	40 (6)	35 (5)
White	194 (50)	209 (54)	400 (56)	413 (58)
Multiple	139 (36)	139 (36)	190 (27)	202 (28)
Ethnicity				
Hispanic or Latino	224 (58)	228 (59)	355 (50)	356 (50)
Not Hispanic or Latino	163 (42)	159 (41)	355 (50)	358 (50)

Baseline COVID-19 Characteristics Were Balanced Across the Two Groups

P002 Phase 3 (Interim Analysis and All Randomized Populations)

	Participants, n (%)			
	Interim Analysis Population		All Randomized Population	
	Molnupiravir N=387	Placebo N=388	Molnupiravir N=716	Placebo N=717
Time from symptom onset to randomization				
≤3 days	191 (49)	190 (49)	342 (48)	342 (48)
>3 days	196 (51)	198 (51)	374 (52)	375 (52)
Median days	4.0	4.0	4.0	4.0
Risk factors for severe illness from COVID-19				
≥1 risk factor	385 (99)	384 (99)	712 (99)	712 (99)
Age >60 years	51 (13)	55 (14)	119 (17)	127 (18)
Active cancer	6 (2)	11 (3)	13 (2)	16 (2)
Chronic kidney disease	14 (4)	20 (5)	38 (5)	46 (6)
Chronic obstructive pulmonary disease	7 (2)	22 (6)	22 (3)	35 (5)
Obesity (BMI ≥30)	306 (79)	287 (74)	538 (75)	518 (72)
Serious heart condition	42 (11)	36 (9)	86 (12)	81 (11)
Diabetes mellitus	48 (12)	57 (15)	107 (15)	121 (17)
Baseline disease severity				
Mild	222 (57)	212 (55)	395 (55)	390 (54)
Moderate	162 (42)	174 (45)	315 (44)	323 (45)

Virologic Assessments Confirm the Trial Was Enrolled at the Time of Widely Circulating Variants

P002 Phase 3 All Randomized Population

Most common clades (~55% of samples sequenced as of Nov 19)

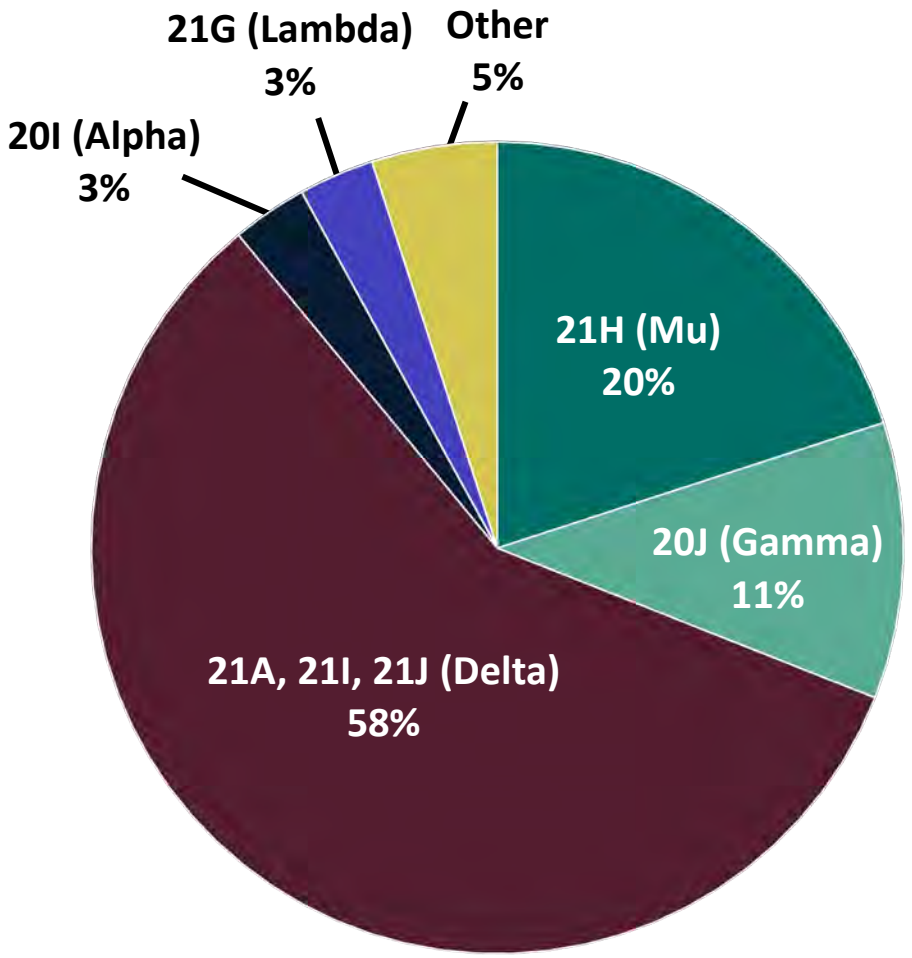
- 21A, 21I, 21J [*Delta strains, India, B.1.617.2*] (58%)
- 21H [*Mu strain, South America, B.1.621*] (20%)
- 20J [*Gamma strain, Brazil, P.1*] (11%)

Most participants had SARS-CoV-2 RNA detected in a nasopharyngeal swab (86%)

- 7% were undetectable
- Remainder (7%) were unknown

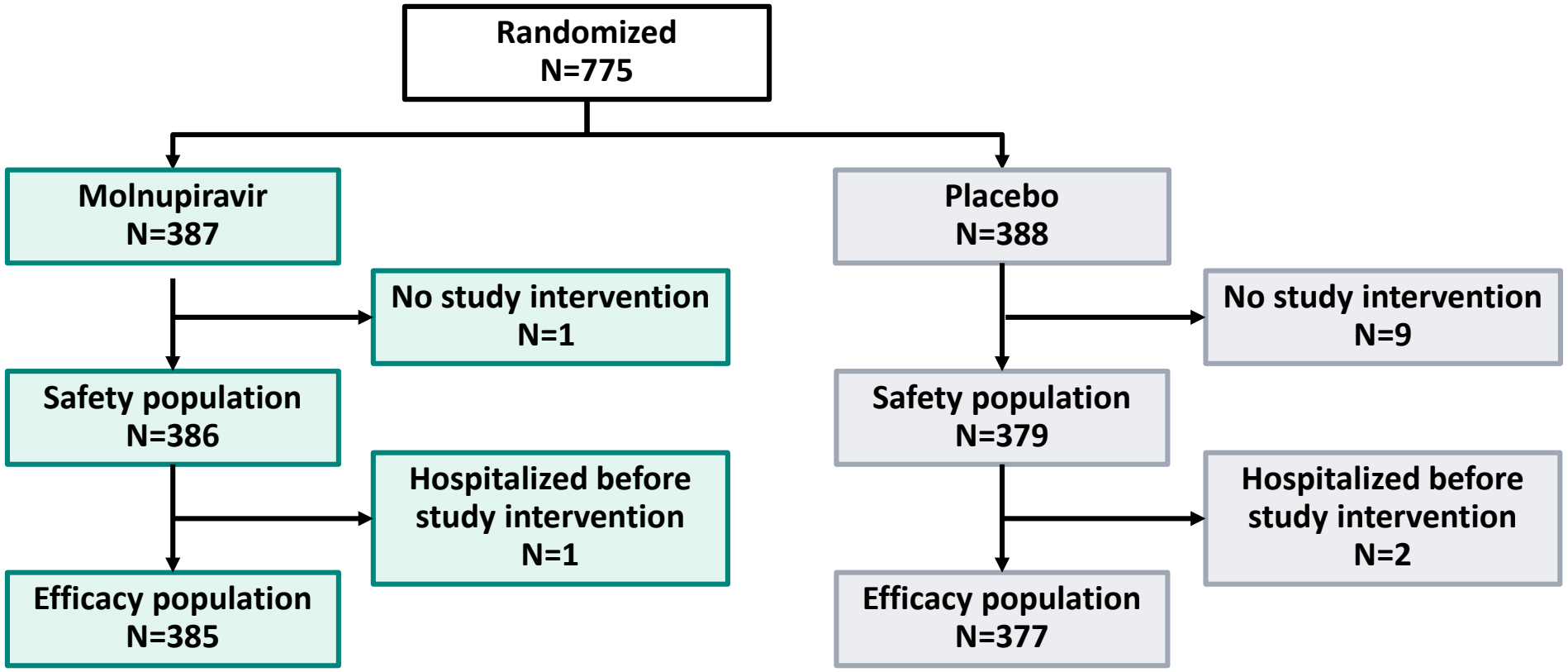
Some participants had positive SARS-CoV-2 baseline antibody status (20%)

Baseline SARS-CoV-2 clades



Few Participants Were Excluded from the Efficacy Analyses

P002 Phase 3 Interim Analysis Population

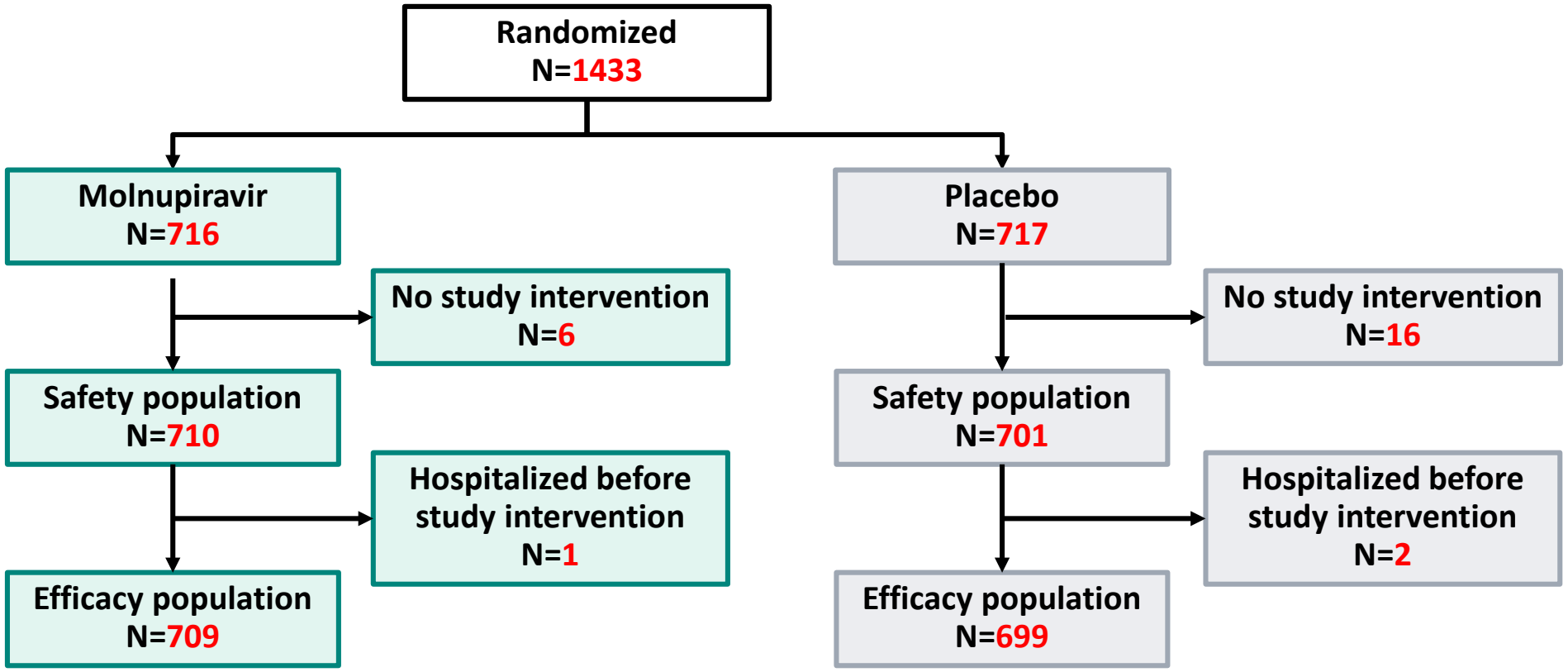


371 Completed study intervention
15 Discontinued
385 With survival status obtained though Day 29
369 Completed follow-up through Day 29

355 Completed study intervention
24 Discontinued
376 With survival status obtained though Day 29
358 Completed follow-up through Day 29

Few Participants Were Excluded from the Efficacy Analyses

P002 Phase 3 All Randomized Population



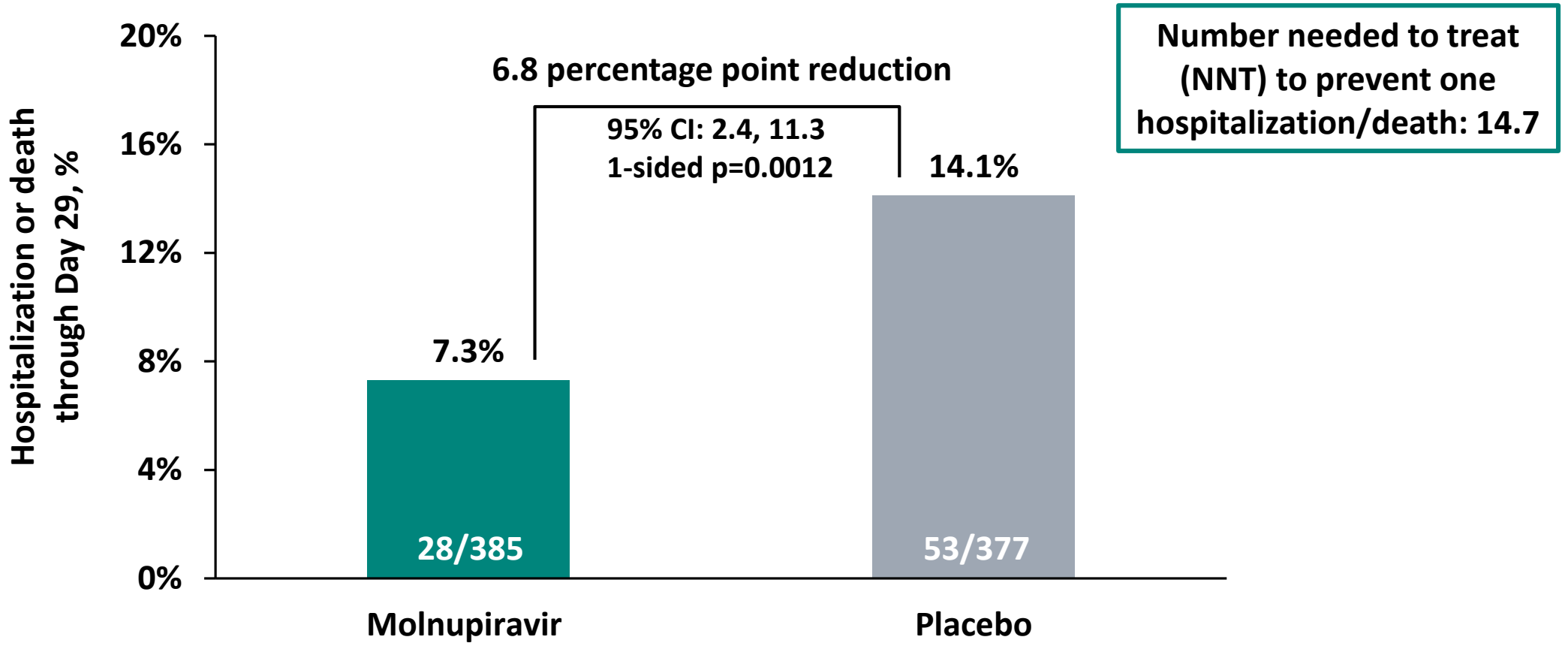
680 Completed study intervention
30 Discontinued
709 With survival status obtained though Day 29
680 Completed follow-up through Day 29

665 Completed study intervention
36 Discontinued
698 With survival status obtained though Day 29
672 Completed follow-up through Day 29

The Primary Efficacy Endpoint Was Met At the Interim Analysis – eDMC Recommended Further Enrollment be Stopped

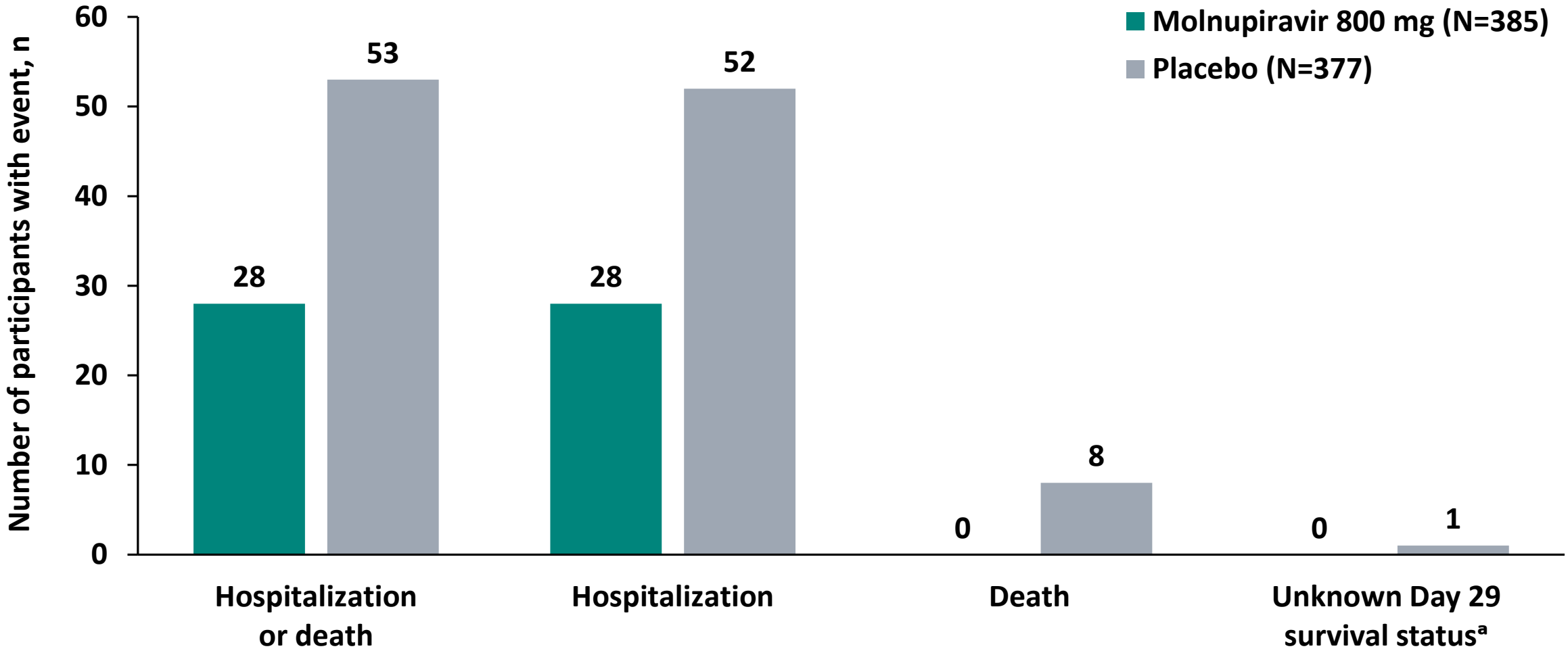
P002 Phase 3 Interim Analysis Population

Molnupiravir Significantly Reduces the Risk of Hospitalization or Death Through Day 29



All 8 Participants Who Died Through Day 29 Were in the Placebo Group and Were Hospitalized Prior to Death

P002 Phase 3 Interim Analysis Population

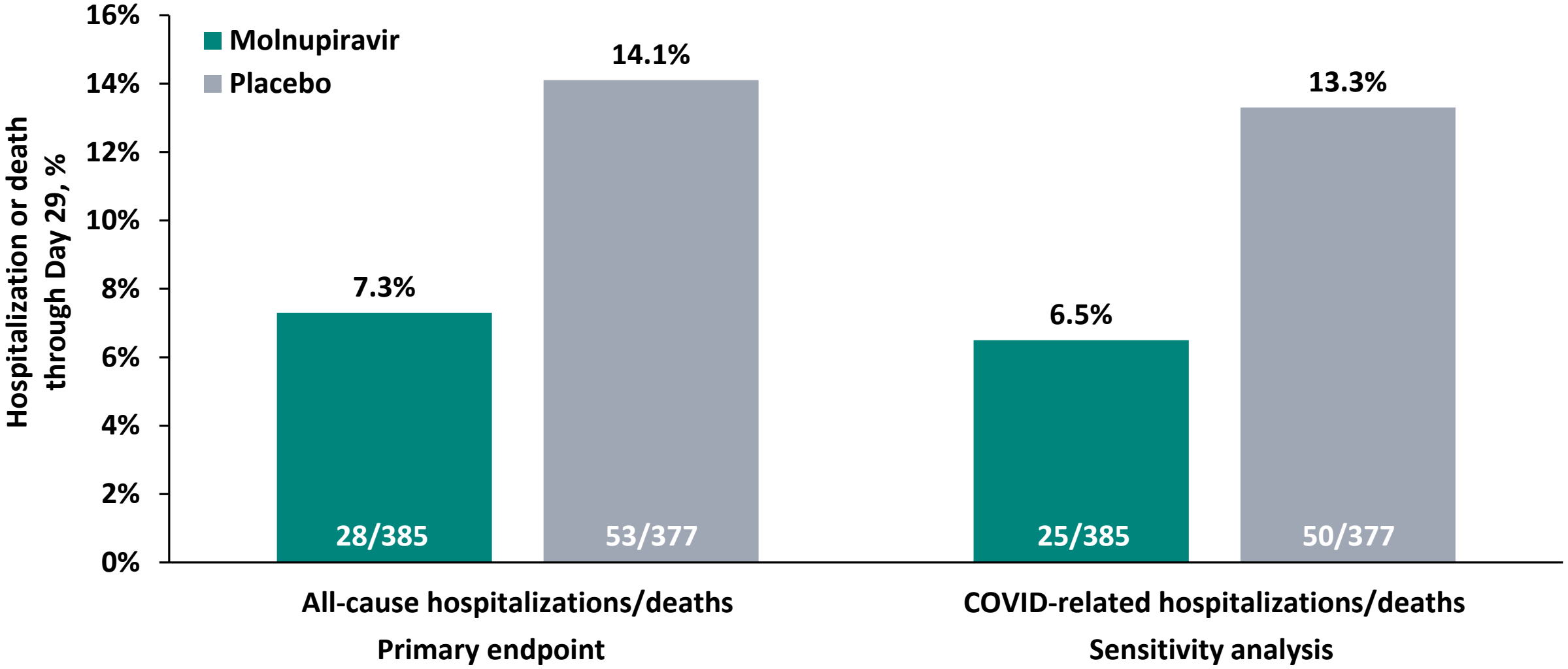


N=number of participants in MITT population; n=number of participants with the corresponding event.

[a] Unknown Day 29 survival status is counted as hospitalization or death in the primary analysis for the primary efficacy endpoint.

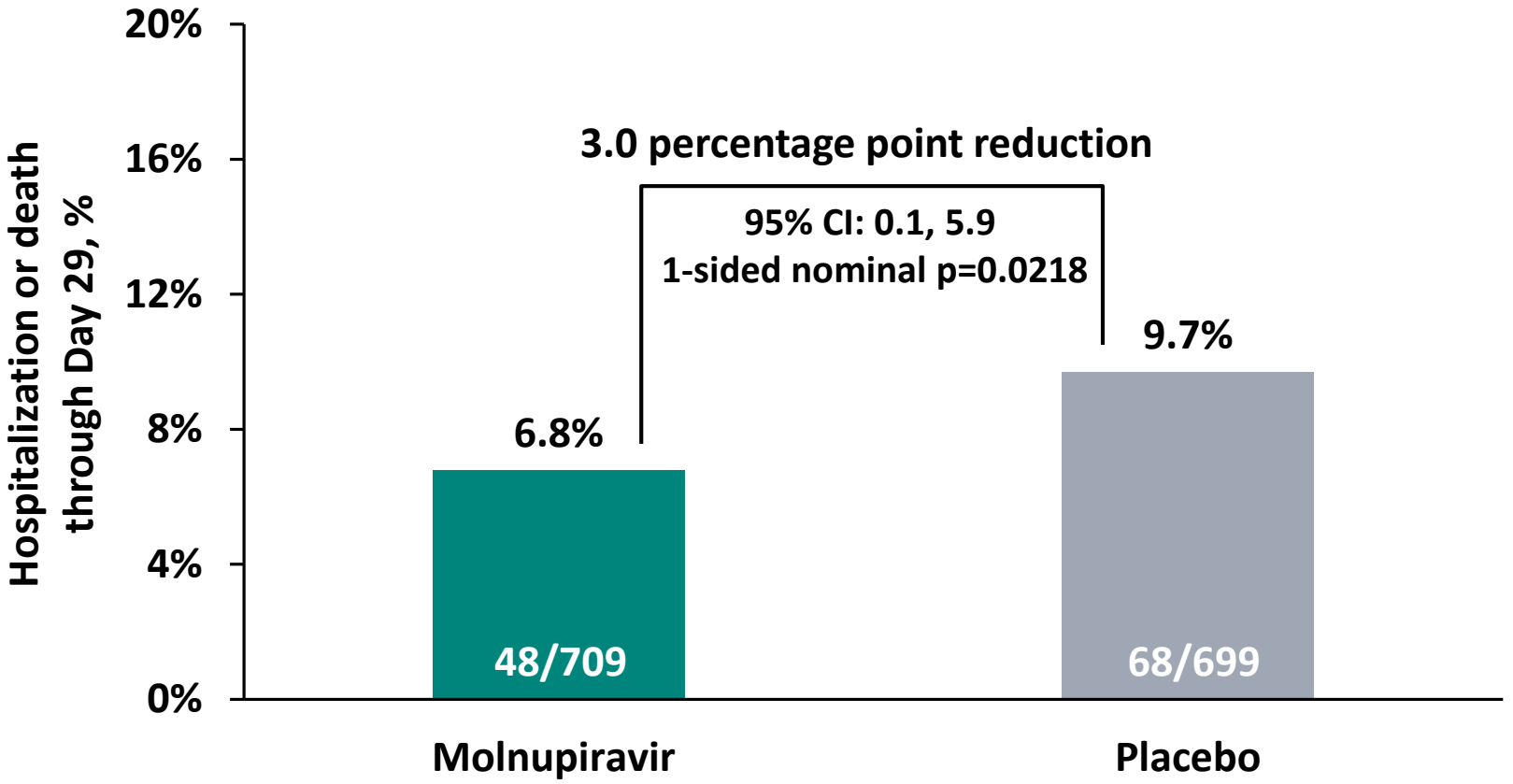
A Sensitivity Analysis Focused on COVID-related Endpoints Shows a Consistent Reduction in the Molnupiravir Group

P002 Phase 3 Interim Analysis Population



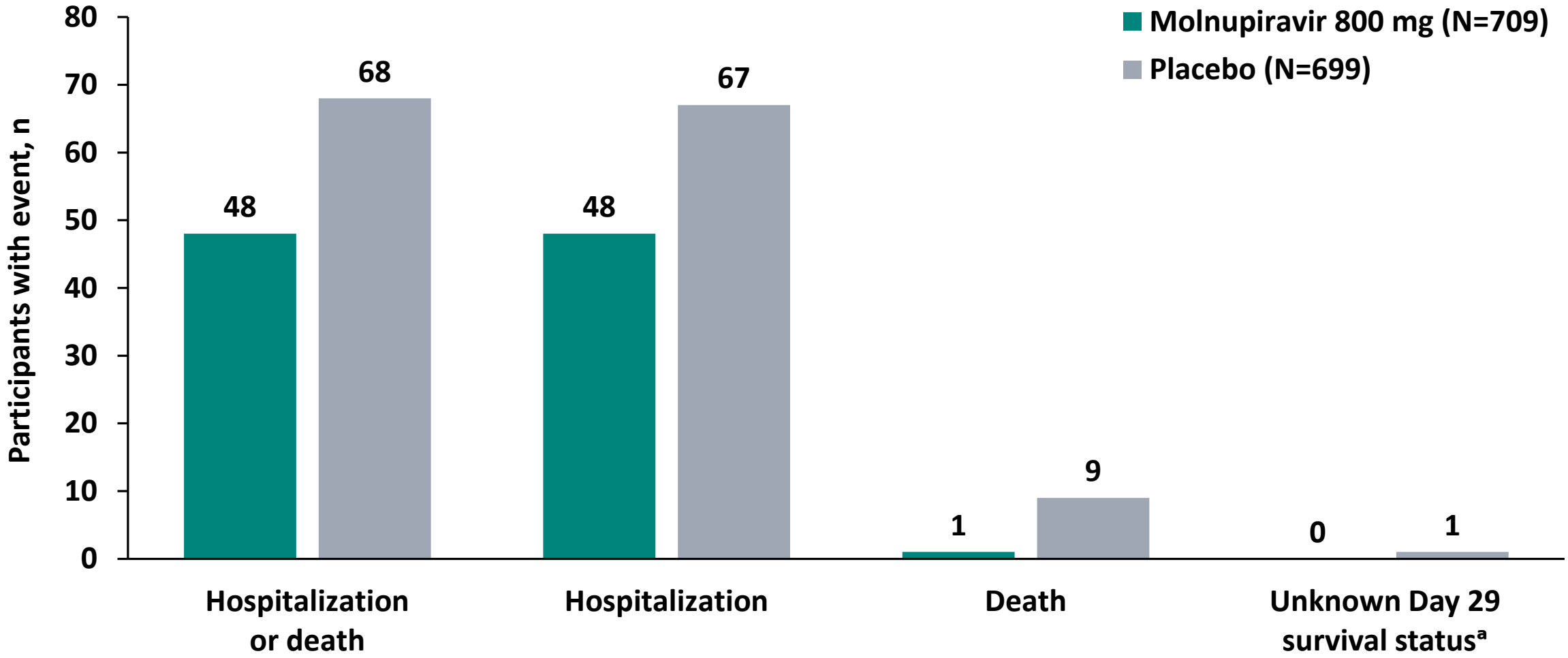
Supportive Analysis in the All Randomized Population Confirms that Molnupiravir Reduces the Risk of Hospitalization or Death through Day 29

P002 Phase 3 All Randomized Population



Nine of the Ten Participants Who Died Through Day 29 Were in the Placebo Group

P002 Phase 3 All Randomized Population

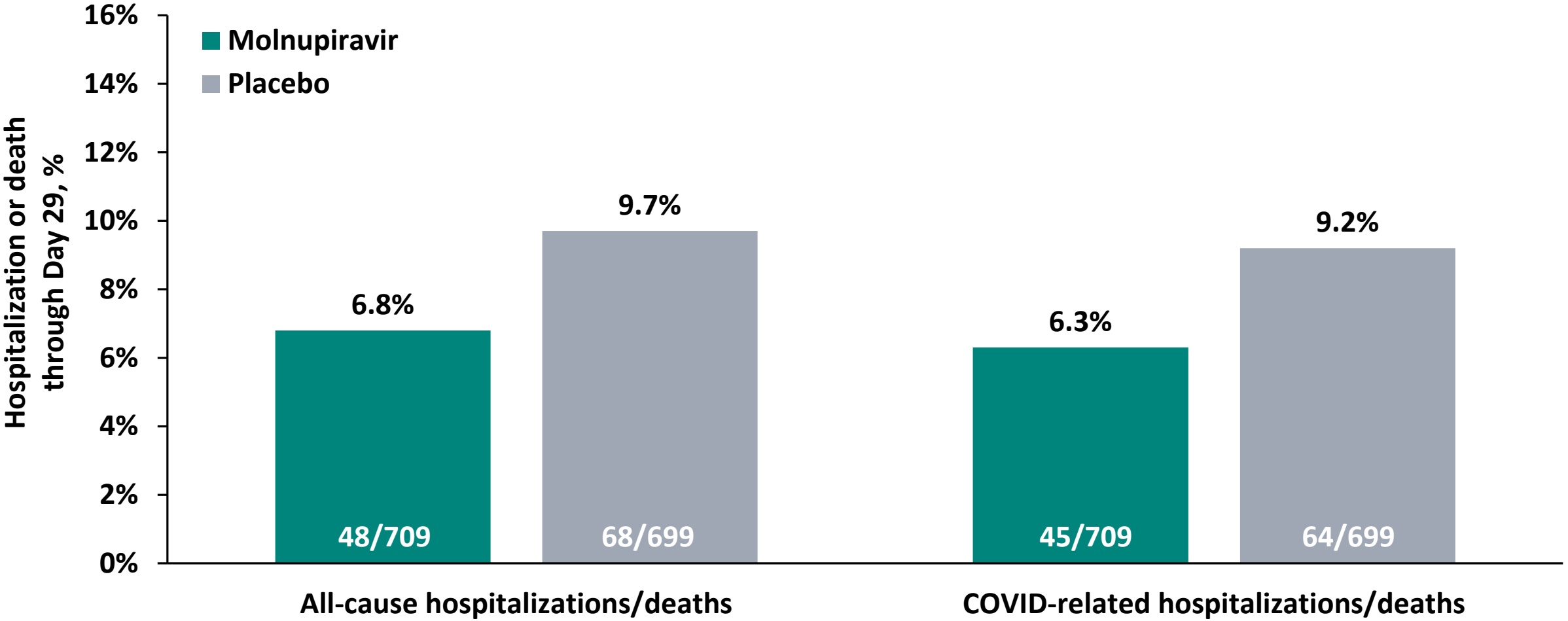


N=number of participants in MITT population; n=number of participants with the corresponding event.

[a] Unknown Day 29 survival status is counted as hospitalization or death.

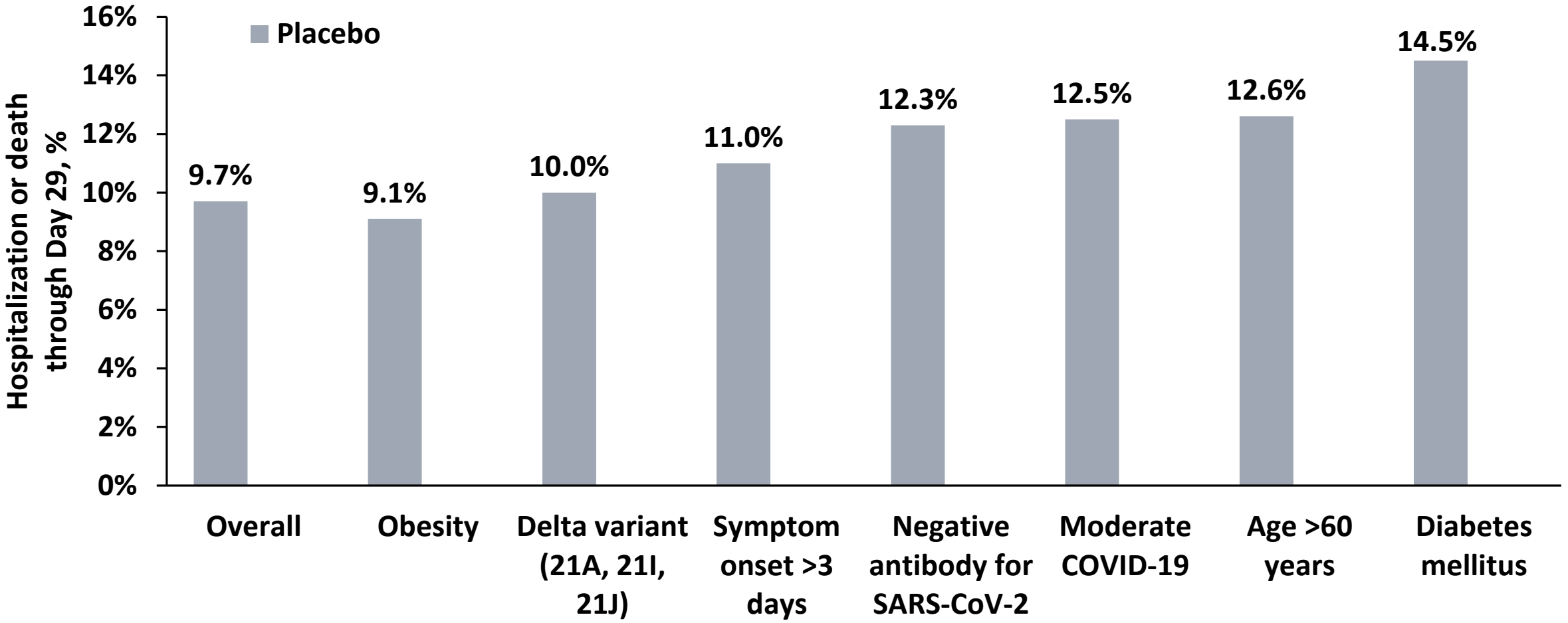
A Sensitivity Analysis Focused on COVID-related Endpoints Shows a Consistent Reduction in the Molnupiravir Group

P002 Phase 3 All Randomized Population



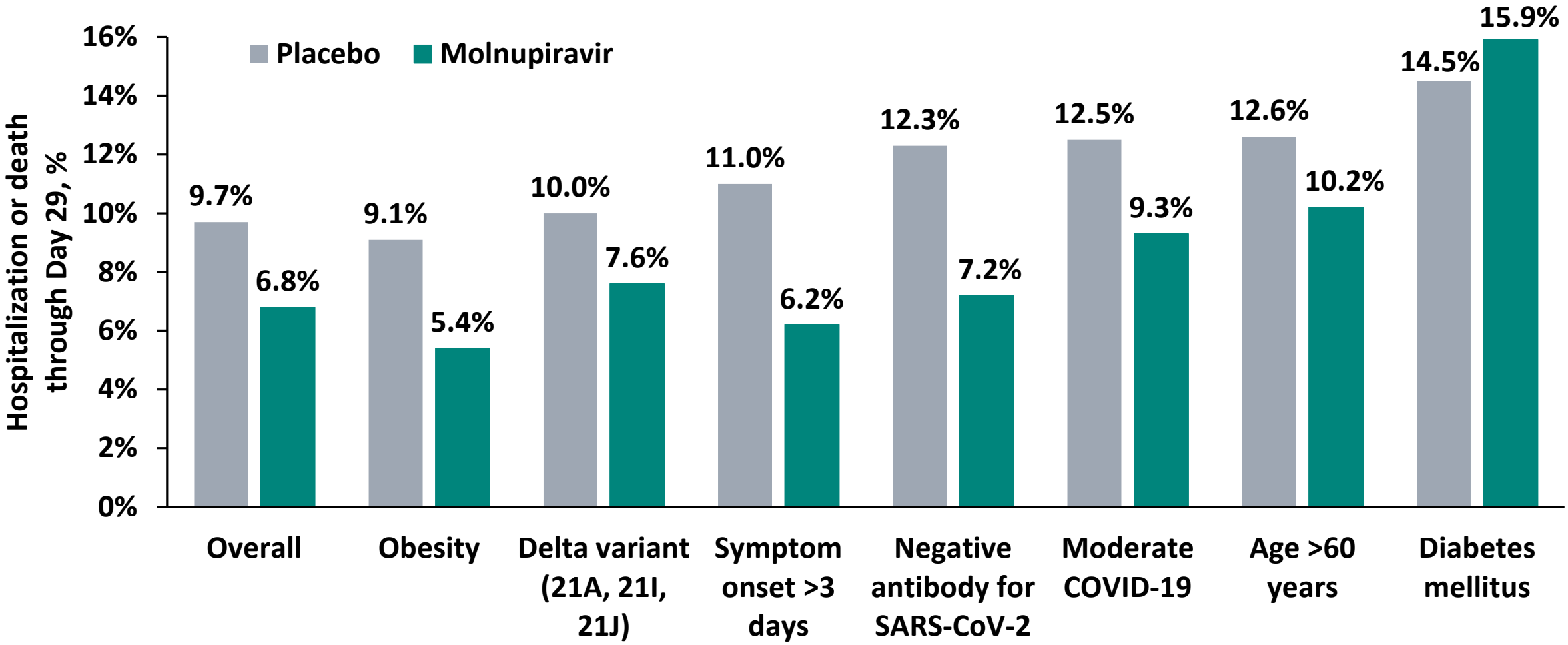
A Review of the Event Rate in the **Placebo Group** by Underlying Risk Factor Confirms That the Trial Enrolled High-risk Patients

P002 Phase 3 All Randomized Population



For Most Key Subgroups, A Lower Proportion of Participants in the Molnupiravir Group Were Hospitalized or Died

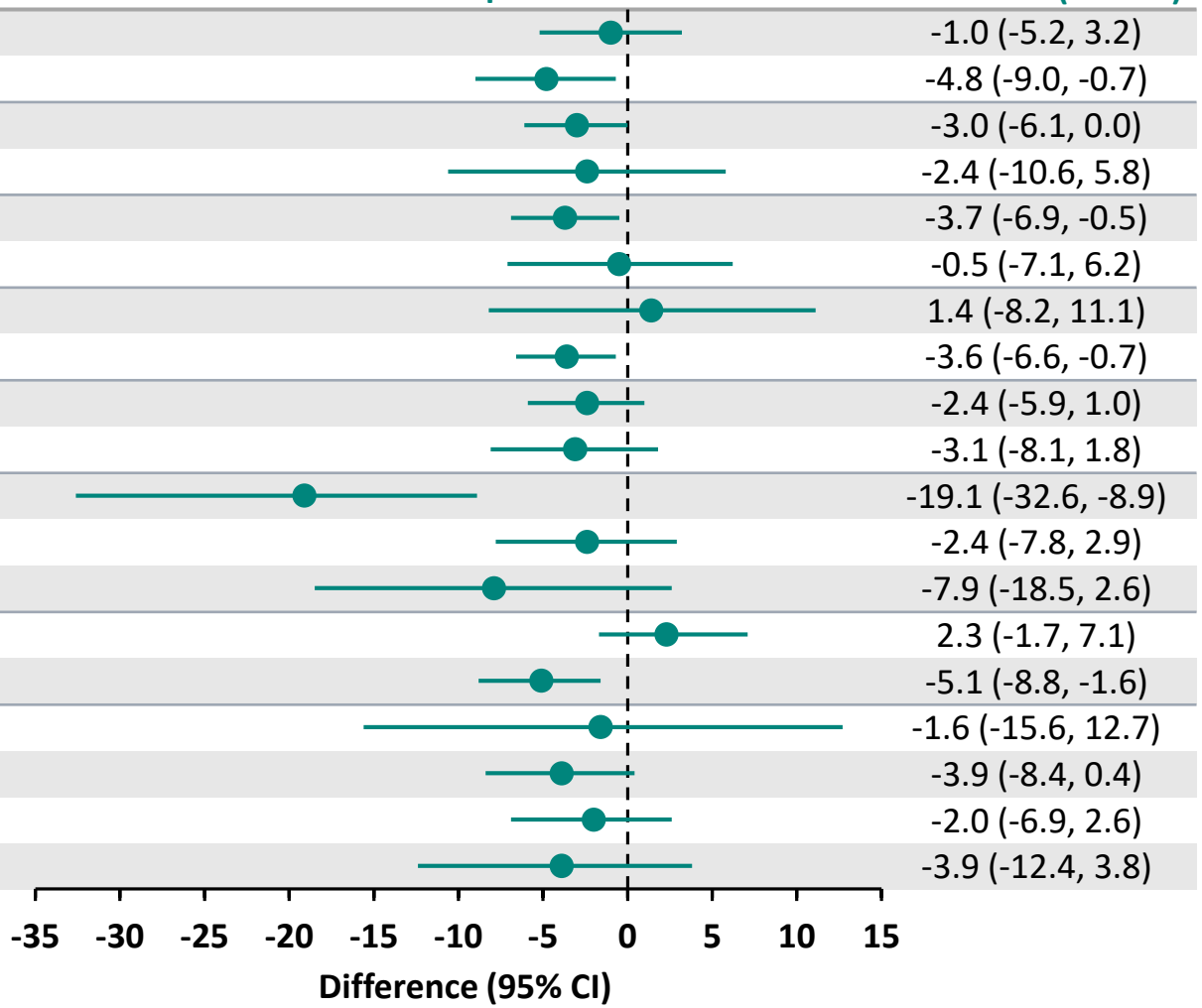
P002 Phase 3 All Randomized Population



Efficacy Results Were Consistent Across Subgroups

P002 Phase 3 All Randomized Population

Subgroup		% (Events*/Participants) Molnupiravir	% (Events*/Participants) Placebo	Difference (95% CI)
Time from symptom onset to randomization, days	≤3	7.4 (25/339)	8.4 (28/335)	-1.0 (-5.2, 3.2)
	>3	6.2 (23/370)	11.0 (40/364)	-4.8 (-9.0, -0.7)
Age, yr	≤60	6.1 (36/591)	9.1 (52/572)	-3.0 (-6.1, 0.0)
	>60	10.2 (12/118)	12.6 (16/127)	-2.4 (-10.6, 5.8)
Obesity (BMI ≥30)	Yes	5.4 (29/535)	9.1 (46/507)	-3.7 (-6.9, -0.5)
	No	10.9 (19/174)	11.5 (22/192)	-0.5 (-7.1, 6.2)
Diabetes mellitus	Yes	15.9 (17/107)	14.5 (17/117)	1.4 (-8.2, 11.1)
	No	5.1 (31/602)	8.8 (51/582)	-3.6 (-6.6, -0.7)
Baseline COVID severity	Mild	4.8 (19/395)	7.2 (27/376)	-2.4 (-5.9, 1.0)
	Moderate	9.3 (29/311)	12.5 (40/321)	-3.1 (-8.1, 1.8)
Most common baseline variants/clades	Gamma	0.0 (0/37)	19.1 (9/47)	-19.1 (-32.6, -8.9)
	Delta	7.6 (18/237)	10.0 (22/221)	-2.4 (-7.8, 2.9)
	Mu	8.0 (6/75)	15.9 (13/82)	-7.9 (-18.5, 2.6)
Baseline antibody status	Positive	3.7 (5/136)	1.4 (2/146)	2.3 (-1.7, 7.1)
	Negative	7.2 (39/541)	12.3 (64/520)	-5.1 (-8.8, -1.6)
Region	N. America	9.5 (4/42)	11.1 (5/45)	-1.6 (-15.6, 12.7)
	Latin America	6.7 (22/329)	10.6 (34/321)	-3.9 (-8.4, 0.4)
	Europe	5.7 (13/229)	7.7 (18/233)	-2.0 (-6.9, 2.6)
	Africa	4.4 (4/90)	8.3 (7/84)	-3.9 (-12.4, 3.8)

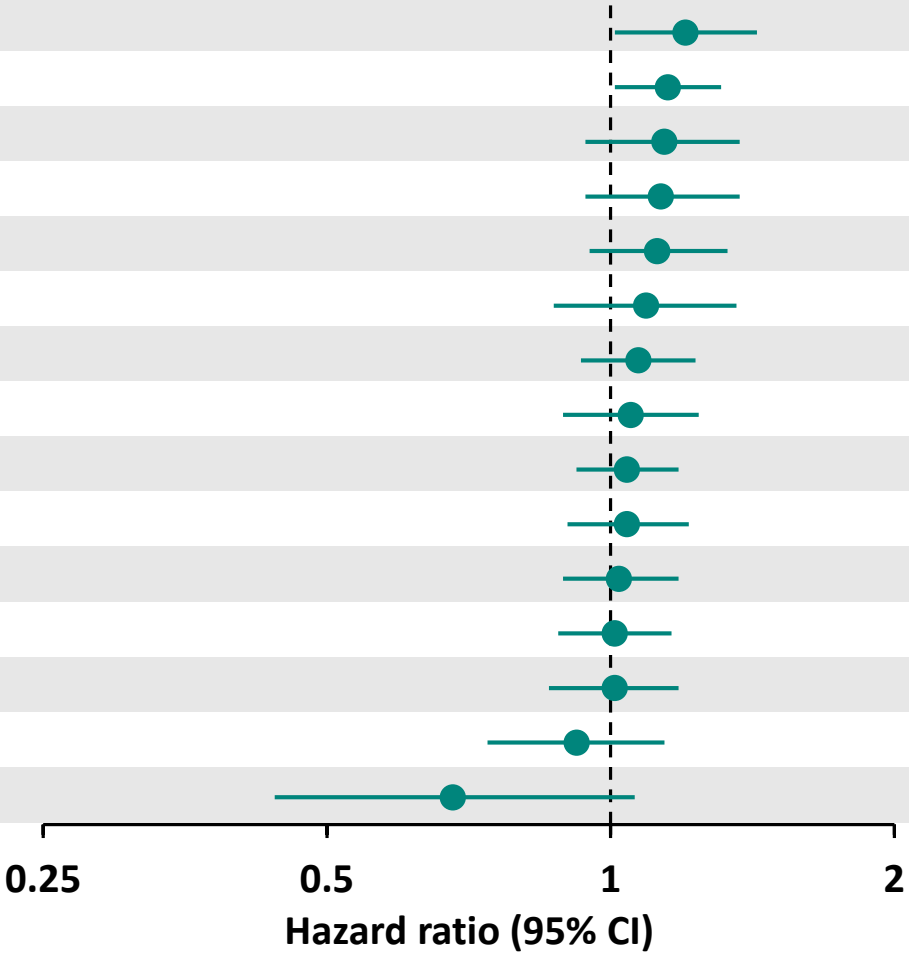


* Number of hospitalizations/deaths through Day 29.

For Most Signs/Symptoms, ***Sustained Improvement or Resolution*** Was More Likely for Participants Treated With Molnupiravir

P002 Phase 3 All Randomized Population

Signs/Symptoms through Day 29	Participants* Molnupiravir	Participants* Placebo	HR (95% CI)
Loss of smell	323	318	1.20 (1.01, 1.43)
Fatigue (tiredness)	528	538	1.15 (1.01, 1.31)
Shortness of breath or difficulty breathing	260	258	1.14 (0.94, 1.37)
Loss of taste	262	242	1.13 (0.94, 1.37)
Sore throat	296	318	1.12 (0.95, 1.33)
Diarrhea	166	158	1.09 (0.87, 1.36)
Nasal congestion (stuffy nose)	429	439	1.07 (0.93, 1.23)
Chills	279	308	1.05 (0.89, 1.24)
Cough	574	570	1.04 (0.92, 1.18)
Feeling hot or feverish	372	386	1.04 (0.90, 1.21)
Headache	429	472	1.02 (0.89, 1.18)
Muscle or body aches	454	460	1.01 (0.88, 1.16)
Rhinorrhea (runny nose)	347	348	1.01 (0.86, 1.18)
Nausea	171	176	0.92 (0.74, 1.14)
Vomiting	38	49	0.68 (0.44, 1.06)

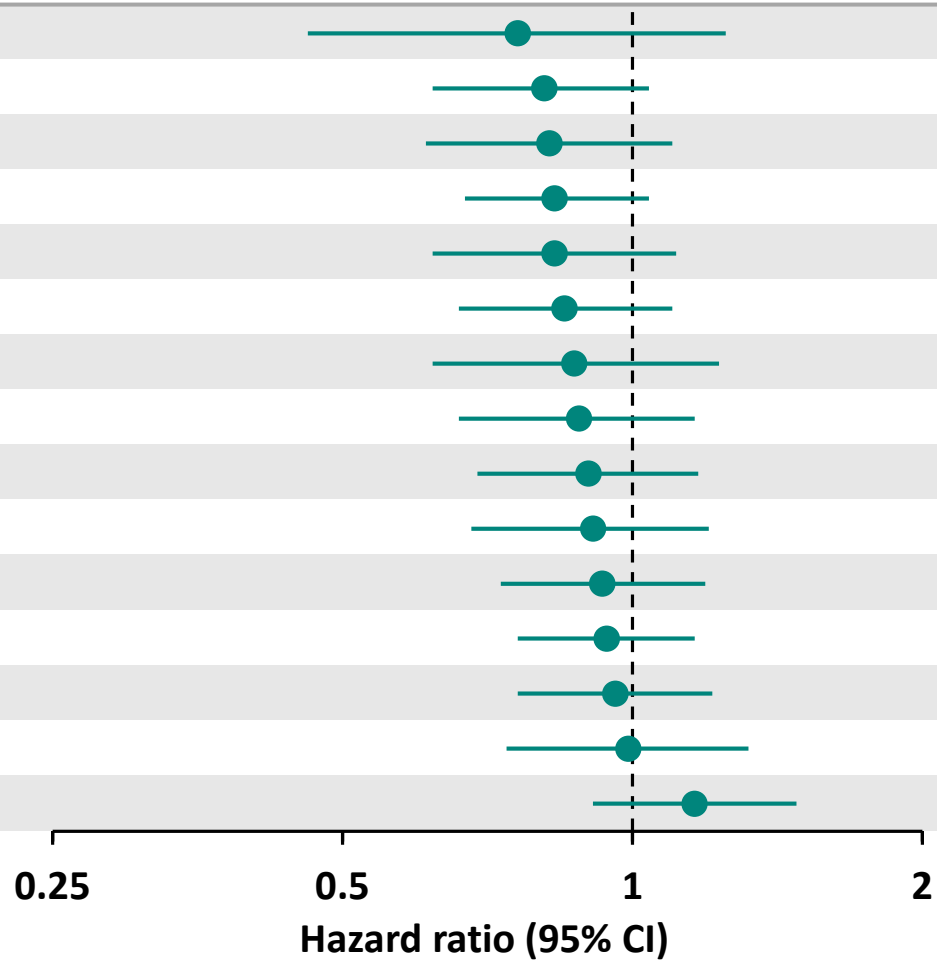


* Number of participants who had the corresponding sign/symptom at baseline.

For Most Signs/Symptoms, ***Progression*** Was Less Likely for Participants Treated With Molnupiravir

P002 Phase 3 All Randomized Population

Signs/Symptoms through Day 29	Participants*		HR (95% CI)
	Molnupiravir	Placebo	
Vomiting	702	692	0.76 (0.46, 1.25)
Loss of smell	385	372	0.81 (0.62, 1.04)
Diarrhea	695	691	0.82 (0.61, 1.10)
Cough	688	672	0.83 (0.67, 1.04)
Feeling hot or feverish	676	673	0.83 (0.62, 1.11)
Nasal congestion (stuffy nose)	682	664	0.85 (0.66, 1.10)
Chills	679	676	0.87 (0.62, 1.23)
Sore throat	695	681	0.88 (0.66, 1.16)
Rhinorrhea (runny nose)	694	690	0.90 (0.69, 1.17)
Loss of taste	461	433	0.91 (0.68, 1.20)
Headache	640	640	0.93 (0.73, 1.19)
Shortness of breath or difficulty breathing	701	681	0.94 (0.76, 1.16)
Fatigue (tiredness)	659	637	0.96 (0.76, 1.21)
Nausea	688	686	0.99 (0.74, 1.32)
Muscle or body aches	655	640	1.16 (0.91, 1.48)

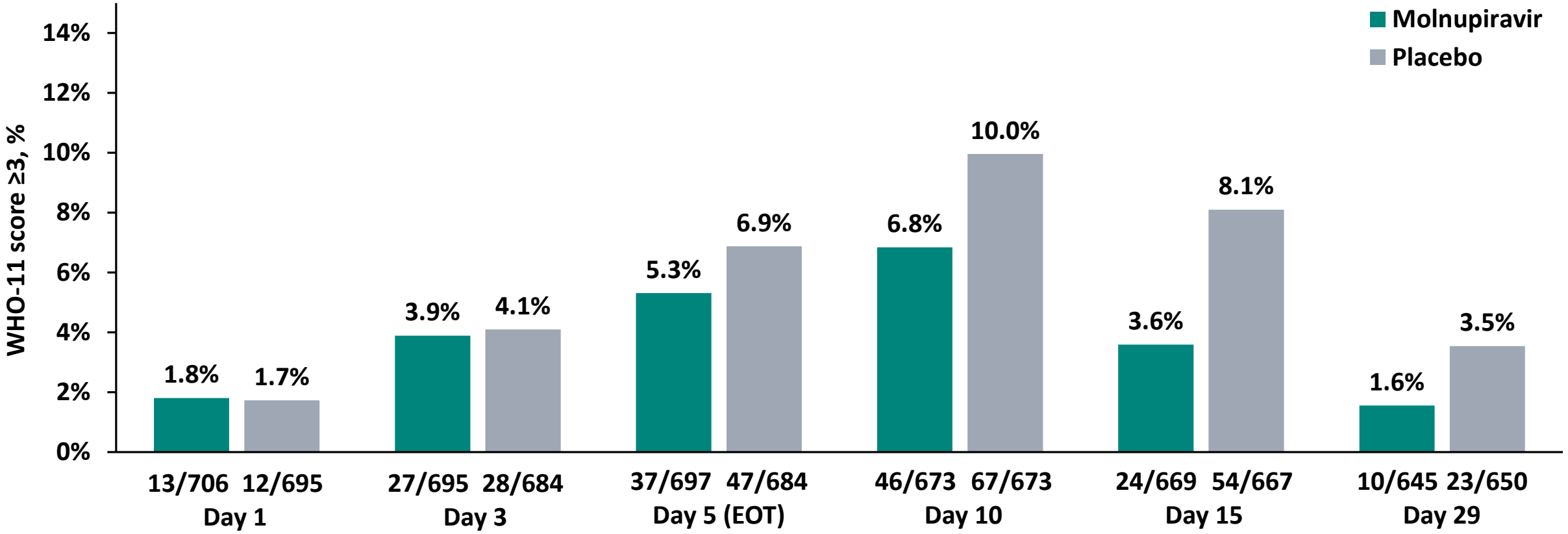


* Number of participants who had absent or non-severe sign/symptom at baseline.

The Benefit of Treatment With Molnupiravir Was Supported by Results of the WHO 11-point Ordinal Scale

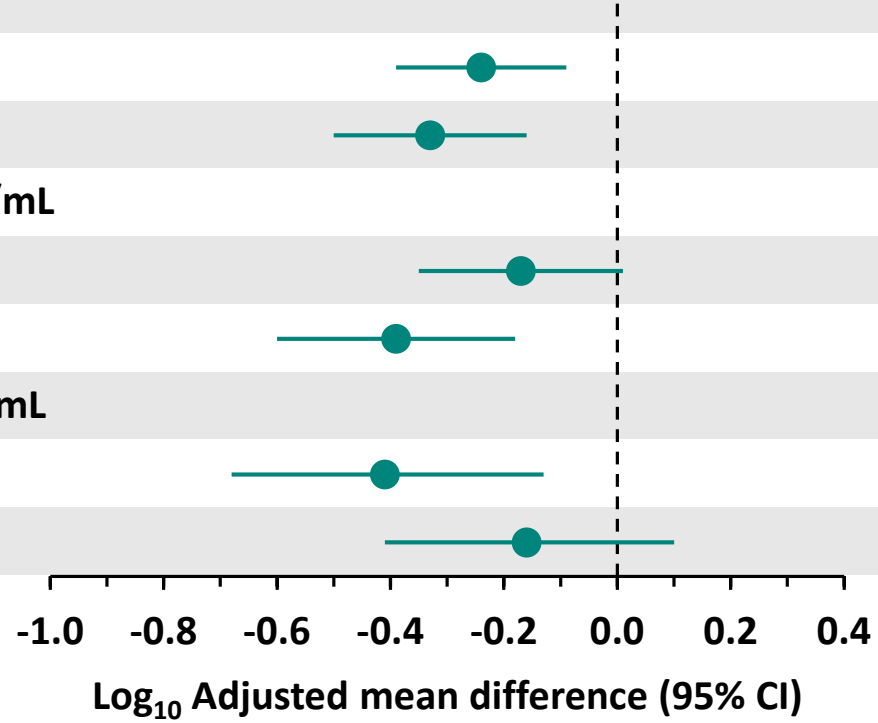
P002 Phase 3 All Randomized Population

A lower percentage of participants who received molnupiravir showed worse outcomes on the WHO 11-point ordinal scale compared with those who received placebo; the largest observed differences occurred at Days 10 and 15



Treatment With Molnupiravir Was Associated With a Greater Decrease in Mean SARS-CoV-2 RNA From Baseline to Days 3 and 5

P002 Phase 3 All Randomized Population



	Adjusted mean difference (Log_{10}) (95% CI)	Adjusted relative reduction, % (95% CI)
Overall		
Day 3	-0.24 (-0.39, -0.09)	42% (19%, 59%)
Day 5	-0.33 (-0.50, -0.16)	53% (31%, 68%)
Higher viral load at baseline, >10^6 copies/mL		
Day 3	-0.17 (-0.35, 0.01)	32% (-2%, 55%)
Day 5	-0.39 (-0.60, -0.18)	59% (34%, 75%)
Lower viral load at baseline, ≤10^6 copies/mL		
Day 3	-0.41 (-0.68, -0.13)	61% (26%, 79%)
Day 5	-0.16 (-0.41, 0.10)	31% (-26%, 61%)

Efficacy Summary

Clinical outcomes

- Molnupiravir significantly reduces the risk of hospitalization or death through Day 29
- Nine of the 10 deaths through Day 29 occurred in the placebo group
- Molnupiravir was associated with improved clinical outcomes based on self-reported COVID-19 signs/symptoms and WHO 11-point ordinal scale

Virologic response

- Molnupiravir was associated with lower mean SARS-CoV-2 RNA at Days 3 and 5 compared with placebo
- Phase 2 results demonstrated molnupiravir reduces percentage of participants with infectious virus compared with placebo and leads to increase in viral substitutions, consistent with proposed mechanism of action

To Date, Based on Unblinded Analyses, the Safety of Molnupiravir Has Been Evaluated in 1,393 Adults

	Unblinded participants, n	
Study	**Any dose of molnupiravir**	**Molnupiravir 800 mg Q12H**
P002 (Phase 2/3)	Phase 3: 710 Phase 2: 225	Phase 3: 710 Phase 2: 74
P006 (Phase 2a)	140	55
P001 (Phase 2)	218	72
P004 (Phase 1)	100	6
Total	**1393**	**917**

Molnupiravir Was Well Tolerated Following a 5-day Treatment Course

P002 Phase 3 All Randomized Population

	Participants, n (%)		
	Molnupiravir N=710	Placebo N=701	Difference vs placebo, % (95% CI)
≥1 adverse event (AE)	216 (30)	231 (33)	-2.5 (-7.4, 2.3)
No AEs	494 (70)	470 (67)	2.5 (-2.3, 7.4)
Drug-related[a] adverse events (DRAE)	57 (8)	59 (8)	-0.4 (-3.3, 2.5)
Serious adverse events (SAE)	49 (7)	67 (10)	-2.7 (-5.6, 0.2)
Serious DRAEs	0 (0)	1 (<1)	-0.1 (-0.8, 0.4)
Death	**2 (<1)**	**12 (2)**	**-1.4 (-2.7, -0.5)**
Discontinued drug due to an AE	10 (1)	20 (3)	-1.4 (-3.1, 0.1)
Discontinued drug due to a DRAE	4 (1)	3 (<1)	0.1 (-0.8, 1.1)
Discontinued drug due to a SAE	5 (1)	13 (2)	-1.2 (-2.5, 0.0)
Discontinued drug due to a serious DRAE	0 (0)	0 (0)	0.0 (-0.5, 0.5)

[a] Determined by the investigator to be related to the drug.

Incidence of Specific AEs Was Similar Across Groups, With the Most Common Events Pertaining to COVID-19

P002 Phase 3 All Randomized Population

Incidence ≥1.5% in Either Group

	Participants, n (%)	
	Molnupiravir N=710	**Placebo N=701**
COVID-19 (worsening)	56 (8)	69 (10)
COVID-19 pneumonia	45 (6)	67 (10)
Diarrhea	16 (2)	21 (3)
Nausea	13 (2)	6 (1)
Pneumonia bacterial	14 (2)	11 (2)
ALT increased	12 (2)	12 (2)

Incidence of Drug-related[a] Adverse Events in the Molnupiravir Group Was Low and Similar Across Groups

P002 Phase 3 All Randomized Population

Incidence ≥1% in the Molnupiravir Group

	Participants, n (%)	
	Molnupiravir N=710	Placebo N=701
Diarrhea	12 (2)	15 (2)
Nausea	10 (1)	5 (1)
Dizziness	7 (1)	5 (1)

[a] Determined by the investigator to be related to the drug.

Most Serious Adverse Events Were Related to Worsening COVID-19

P002 Phase 3 All Randomized Population

Serious Adverse Events Observed in ≥2 Participants in Either Group

	Participants, n (%)	
	Molnupiravir N=710	Placebo N=701
COVID-19 (worsening)	35 (5)	53 (8)
COVID-19 pneumonia	27 (4)	42 (6)
Respiratory failure	6 (1)	9 (1)
Pneumonia bacterial	3 (<1)	2 (<1)
Pneumonia	2 (<1)	0 (0)
Acute respiratory failure	0 (0)	2 (<1)

Hematologic Laboratory Parameters Also Show No Particular Concern for the Use of Molnupiravir

P002 Phase 3 All Randomized Population

Grade ≥3 Hematologic Effects

	Participants, n/m (%)	
	Molnupiravir N=710	Placebo N=701
Hemoglobin (g/dL) <9.0 (M) or <8.5 (F)	2/615 (<1)	4/616 (1)
Lymphocytes (10^9/L) <0.50	12/610 (2)	22/616 (4)
Absolute neutrophil count (10^9/L) <0.60	0/446 (0)	0/435 (0)
Platelets (10^9/L) <50	0/607 (0)	1/605 (<1)
Leukocytes (10^9/L) <1.50	2/615 (<1)	1/616 (<1)

M=males; F= females

Safety Summary

- Molnupiravir 800 mg Q12H for 5 days is generally well tolerated
  - Compared with placebo, molnupiravir has a
    - Similar incidence of overall AEs and low incidence of individual AEs
    - Lower incidence of SAEs and deaths in recipients of molnupiravir
- No evidence of hematologic toxicity for molnupiravir in clinical studies
- No safety concerns have been identified throughout clinical development program
- Totality of safety database supports use of molnupiravir for proposed intended use

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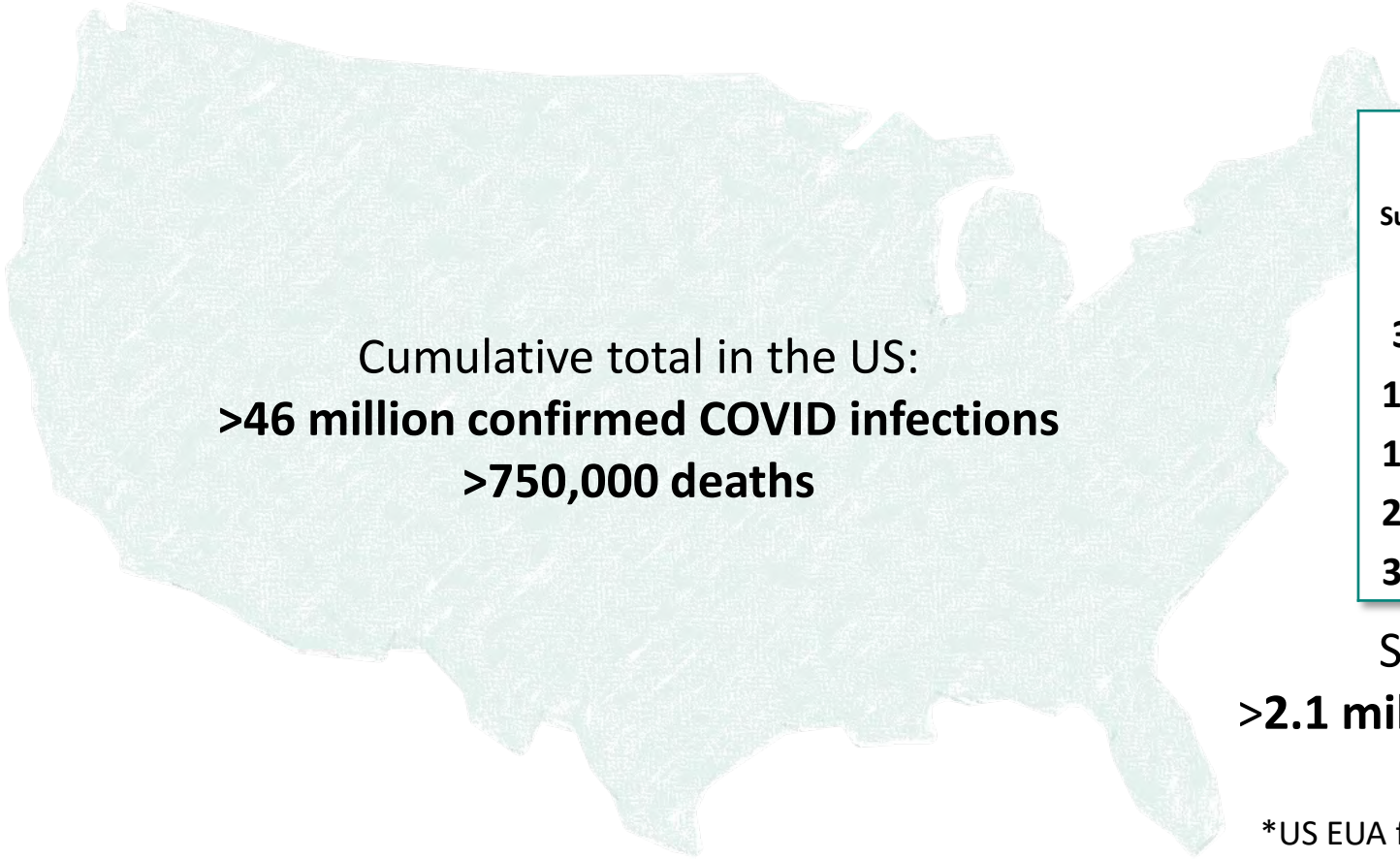
INVENTING FOR LIFE

Benefit-Risk

Nicholas Kartsonis, MD

Senior Vice President, Clinical Research
Merck & Co., Inc.

A Tremendous and Urgent Unmet Medical Need Remains for Safe, Effective Oral Agents for the Treatment of COVID-19



Cumulative total in the US:

>46 million confirmed COVID infections

>750,000 deaths

October 2021

Sun	Mon	Tue	Wed	Thu	Fri	Sat
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

Since 09-Oct-21* in the US:

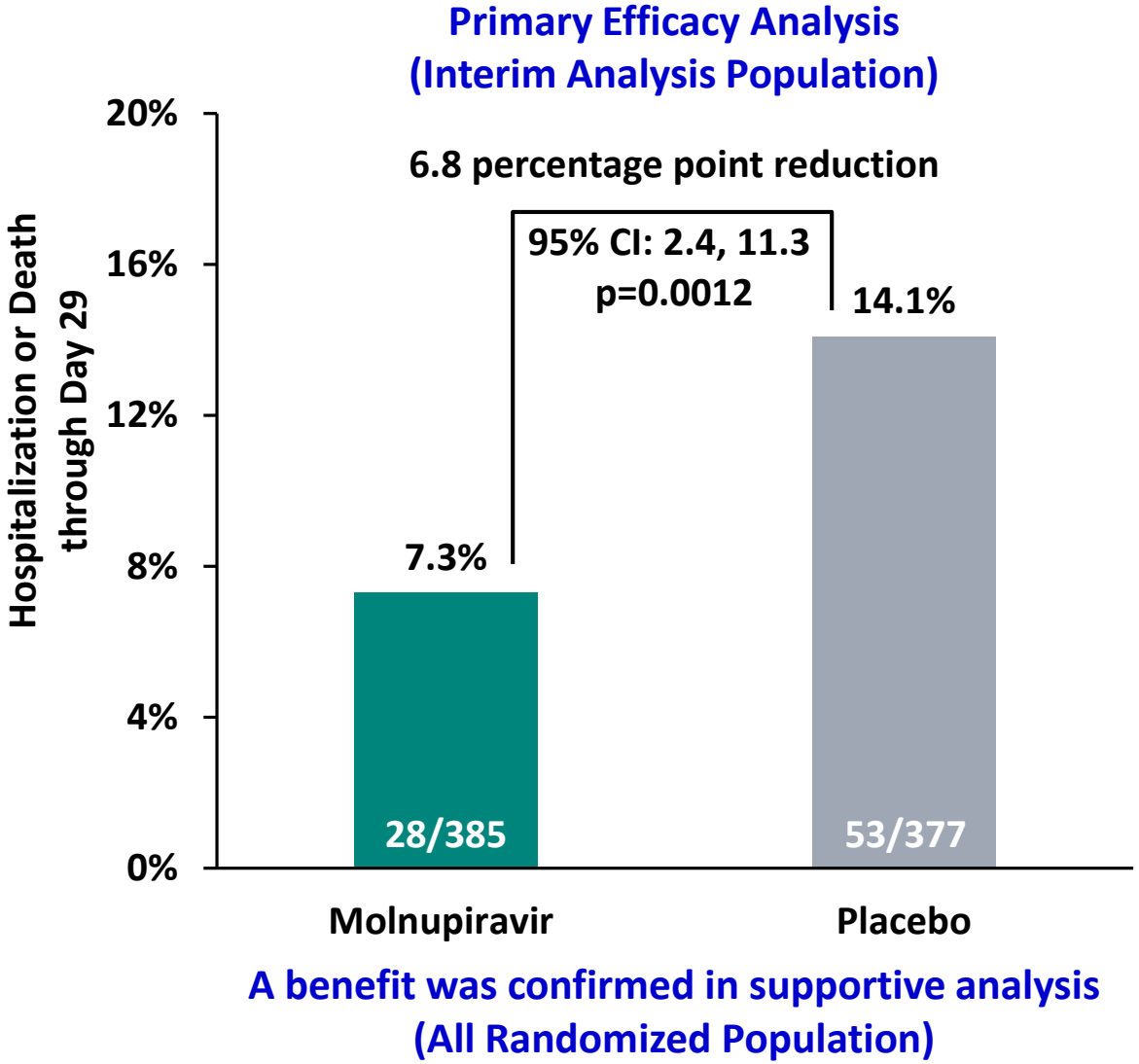
>2.1 million confirmed COVID infections

>35,000 deaths

*US EUA for molnupiravir was submitted on 08-Oct-21

Molnupiravir, an Oral Antiviral Therapy, Provides Substantial Benefit to Patients With COVID-19

- Significant reduction in risk of hospitalization or death in outpatients at risk of progressing to severe illness
- Efficacy results consistent across all viral variants assessed to date
- Sustained improvement or resolution of patient-reported signs and symptoms of COVID-19
- Orally administered, without changes in administration based on intrinsic or extrinsic factors



The Safety Profile of Molnupiravir Has Been Comprehensively Assessed and Supports Use in the Proposed Intended Use

The Totality of the Data Supports Use of Molnupiravir for the Proposed Intended Use

Treatment of Mild to Moderate Coronavirus Disease 2019 (COVID-19) in Adults With Positive Results of Direct SARS-CoV-2 Testing, and Who Are at High Risk for Progressing to Severe COVID-19, Including Hospitalization and/or Death

MERCK
INVENTING FOR LIFE

Molnupiravir
Supportive Slides

Overall Safety

P001 Phase 2

The proportion of participants with AEs, drug-related AEs (per investigator), SAEs, and AEs leading to study intervention discontinuation were comparable for the intervention groups.

	Molnupiravir 200 mg		Molnupiravir 400 mg		Molnupiravir 800 mg		Molnupiravir Combined		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	73		73		72		218		75	
with one or more adverse events	40	(54.8)	36	(49.3)	45	(62.5)	121	(55.5)	46	(61.3)
with no adverse event	33	(45.2)	37	(50.7)	27	(37.5)	97	(44.5)	29	(38.7)
with drug-related[a] adverse events	8	(11.0)	6	(8.2)	10	(13.9)	24	(11.0)	16	(21.3)
with serious adverse events	11	(15.1)	9	(12.3)	13	(18.1)	33	(15.1)	12	(16.0)
with serious drug-related adverse events	1	(1.4)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)
who died	6	(8.2)	4	(5.5)	4	(5.6)	14	(6.4)	2	(2.7)
discontinued drug due to an adverse event	0	(0.0)	1	(1.4)	0	(0.0)	1	(0.5)	0	(0.0)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	1	(1.4)	0	(0.0)	1	(0.5)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

AE Leading to Death

P001 Phase 2

Dose	AE terms
200 mg N = 73	Bacteremia
	Respiratory Failure
	COVID-19
	COVID-19/Respiratory Failure
	COVID-19/Acute Respiratory Failure
	COVID-19/Bacterial Pneumonia
400 mg N = 73	Shock
	Septic Shock
	COVID-19 pneumonia
	Cardiac Arrest

Dose	AE terms
800 mg N = 72	COVID-19 pneumonia
	Acute Respiratory Distress Syndrome
	COVID-19/Acute Respiratory Failure
	COVID-19/Acute Respiratory Failure
Placebo N = 75	Pulmonary Sepsis
	COVID-19 pneumonia

None of the deaths was drug related per investigator

- 12/16 had severe COVID-19 at baseline
- 13/16 were >60 years of age
- 14/16 had underlying co-morbidities
- 12/16 had duration of symptoms >5 days

Incidence of Deaths in Other Hospitalized COVID-19 Studies (Focused on Non-intubated Patients with Moderate or Severe COVID-19)

P001 Phase 2

Placebo		Active Agent		
Study	**Incidence of Death At Day 29**	**Study**	**Active Agent**	**Incidence of Death At Day 29**
Remdesivir Hospitalized Study	13%	Remdesivir Hospitalized Study	Remdesivir	8%
RECOVERY Dexamethasone Study	22% (18% no O_2 at baseline)	Remdesivir 5 vs. 10 Day Trial	Remdesivir (5 d) Remdesivir (10 d)	0% 6%
RECOVERY Hydroxychloroquine Study	24% (13% no O_2 at baseline)	RECOVERY Dexamethasone Study	Dexamethasone	22% (14% no O_2 at baseline)
SOLIDARITY Study	9% (range 7-11%)	SOLIDARITY Study	Remdesivir	9%

Beigel et al., NEJM 2020; Golman et al., NEJM 2020; RECOVERY Collaborative Group, NEJM 2021; RECOVERY Collaborative Group, NEJM, 2020; WHO Solidarity Trial, NEJM 2021;

Outcomes Based on Continued Treatment After Hospitalization

P002 Phase 3 All Randomized Population

	Participants, n (%)	
	Molnupiravir N=12	Placebo N=22
Oxygen use within 29 days of randomization	6 (50)	20 (91)
Ventilation use within 29 days of randomization	1 (8)	4 (18)
Death	1 (8)	2 (9)
Mean Duration of Hospitalization (days)*	8.3	12.2

* Does not include 1 (8.3%) participant in the Molnupiravir group and 2 (9.1%) participants in the Placebo group who died prior to being discharged from the hospital.

Baseline Characteristics in Participants With Diabetes Mellitus

P002 Phase 3 All Randomized Population

		Molnupiravir N=107	Placebo N=121
Region, n (%)	North America	7 (6.5)	7 (5.8)
	Latin America	59 (55.1)	65 (53.7)
	Europe	18 (16.8)	22 (18.2)
	Asia Pacific	8 (7.5)	7 (5.8)
	Africa	15 (14.0)	20 (16.5)
Time from symptom onset to randomization, n (%)	≤3 days	46 (43.0)	51 (42.1)
	>3 days	61 (57.0)	70 (57.9)
	Median (range)	4.0 (1-5)	4.0 (1-5)
Risk factors for severe illness from COVID-19, n (%)	≥1 risk factor	107 (100.0)	121 (100.0)
	Age >60 yr	26 (24.3)	30 (24.8)
	Active cancer	3 (2.8)	3 (2.5)
	Chronic kidney disease	7 (6.5)	7 (5.8)
	Chronic obstructive pulmonary disease	3 (2.8)	4 (3.3)
	Obesity (BMI ≥30)	63 (58.9)	57 (47.1)
	Serious heart condition	16 (15.0)	14 (11.6)
	Diabetes mellitus	107 (100.0)	121 (100.0)
Baseline COVID severity, n (%)	Mild	47 (43.9)	54 (44.6)
	Moderate	60 (56.1)	67 (55.4)
	Severe	0	0
	Unknown	0	0

2 additional risk factors: MOV 25% vs placebo 18%

Hospitalization or Death in Those with Diabetes Mellitus and Other Risk Factors

P002 Phase 3 All Randomized Population

	Participants, n/m (%)					
	Molnupiravir 800 mg N=107		Placebo N=117		Difference, % (95% CI)	
Diabetes mellitus with						
No additional risk factor	4/25	(16.0)	5/35	(14.3)	1.7	(-16.8, 22.7)
1 other additional risk factor	7/55	(12.7)	11/61	(18.0)	-5.3	(-18.8, 8.5)
2 other additional risk factors	6/19	(31.6)	1/15	(6.7)	24.9	(-3.4, 49.5)
3 or more other additional risk factors	0/8	(0.0)	0/6	(0.0)	0.0	(-40.8, 34.1)

Primary Endpoint by Country (At Least 20 Participants Enrolled)

P002 Phase 3 All Randomized Population

Incidence of hospitalization or death through Day 29 by country
modified Intent-to-Treat population

Country	Participants, n/m (%) Molnupiravir N=709	Placebo N=699	Difference, % (95% CI)
Brazil	1/34 (2.9)	9/40 (22.5)	-19.6 (-35.2, -4.7)
Chile	1/20 (5.0)	2/18 (11.1)	
Colombia	10/136 (7.4)	18/139 (12.9)	-5.6 (-13.1, 1.6)
Guatemala	5/55 (9.1)	0/58 (0.0)	9.1 (2.5, 19.6)
Mexico	4/83 (4.8)	5/66 (7.6)	-2.8 (-12.4, 5.4)
Philippines	4/13 (30.8)	3/13 (23.1)	
Russian Federation	11/155 (7.1)	15/176 (8.5)	-1.4 (-7.4, 4.7)
South Africa	3/89 (3.4)	7/83 (8.4)	-5.1 (-13.5, 2.2)
Ukraine	0/59 (0.0)	2/48 (4.2)	-4.2 (-14.0, 2.1)
United States	4/41 (9.8)	5/45 (11.1)	-1.4 (-15.5, 13.2)

Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.
Treatment difference and 95% CI were not calculated for subgroups with small sample sizes (<25 per treatment group) as per the protocol statistical analysis plan.
m=number of participants in the modified intent-to-treat population with the corresponding group; n=number of participants died or hospitalized through Day 29.
[a] The corresponding confidence interval is based on Miettinen & Nurminen method.

The SARS-CoV-2 Polymerase and Exonuclease are Conserved Across Viral Variants

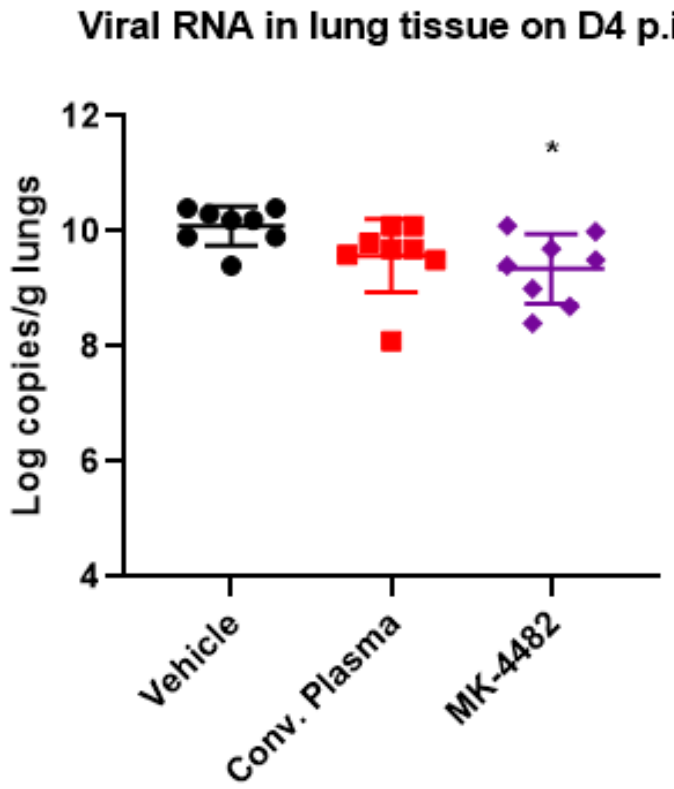
- The viral replicase genes nsp12 and nsp14 are well conserved across variants
- NHC shows similar antiviral activity against all variants evaluated to date, including WA-1, Alpha, Beta, Gamma, Delta, Lambda and Mu

Polymerase (nsp12) Amino Acid Position	Wu-1	Clade 21 A (delta)	Clade 21J (delta)	Omicron
323	P	L	L	L
671	G	S	S	G

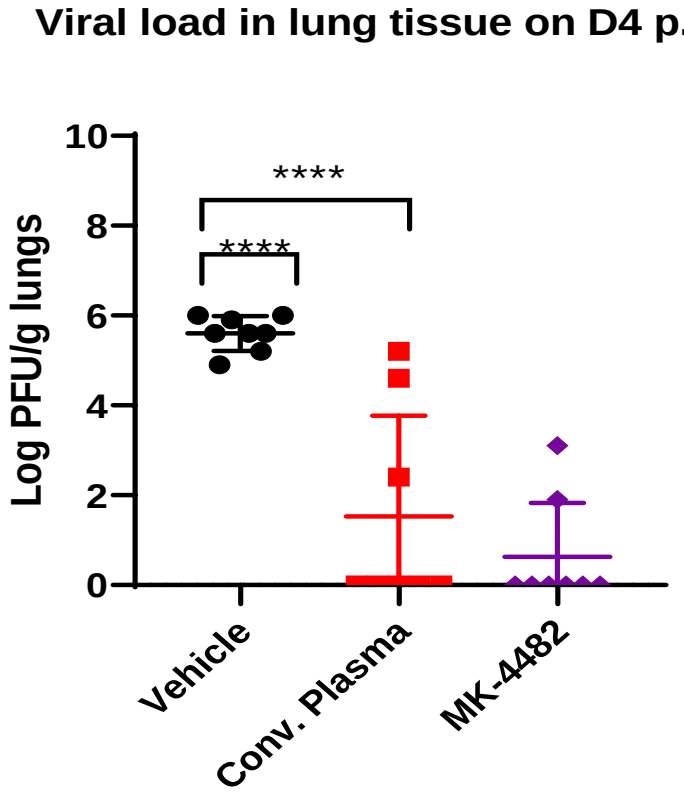
Exonuclease (nsp14) Amino Acid Position	Wu-1	Clade 21 A (delta)	Clade 21J (delta)	Omicron
42	I	I	I	V
394	A	A	V	A

MOV Treatment Results in Marked Reduction in Infectious Virus Relative to Viral RNA titers in Lungs of SARS-CoV-2 Infected Mice

MOV dosed 200 mg/kg BID



* p<0.05, MK-4482 vs. Vehicle.



**** p<0.0001, Conv. Plasma or MK-4482 vs. Vehicle.

Primary Efficacy by Clade

P002 Phase 3 All Randomized Population

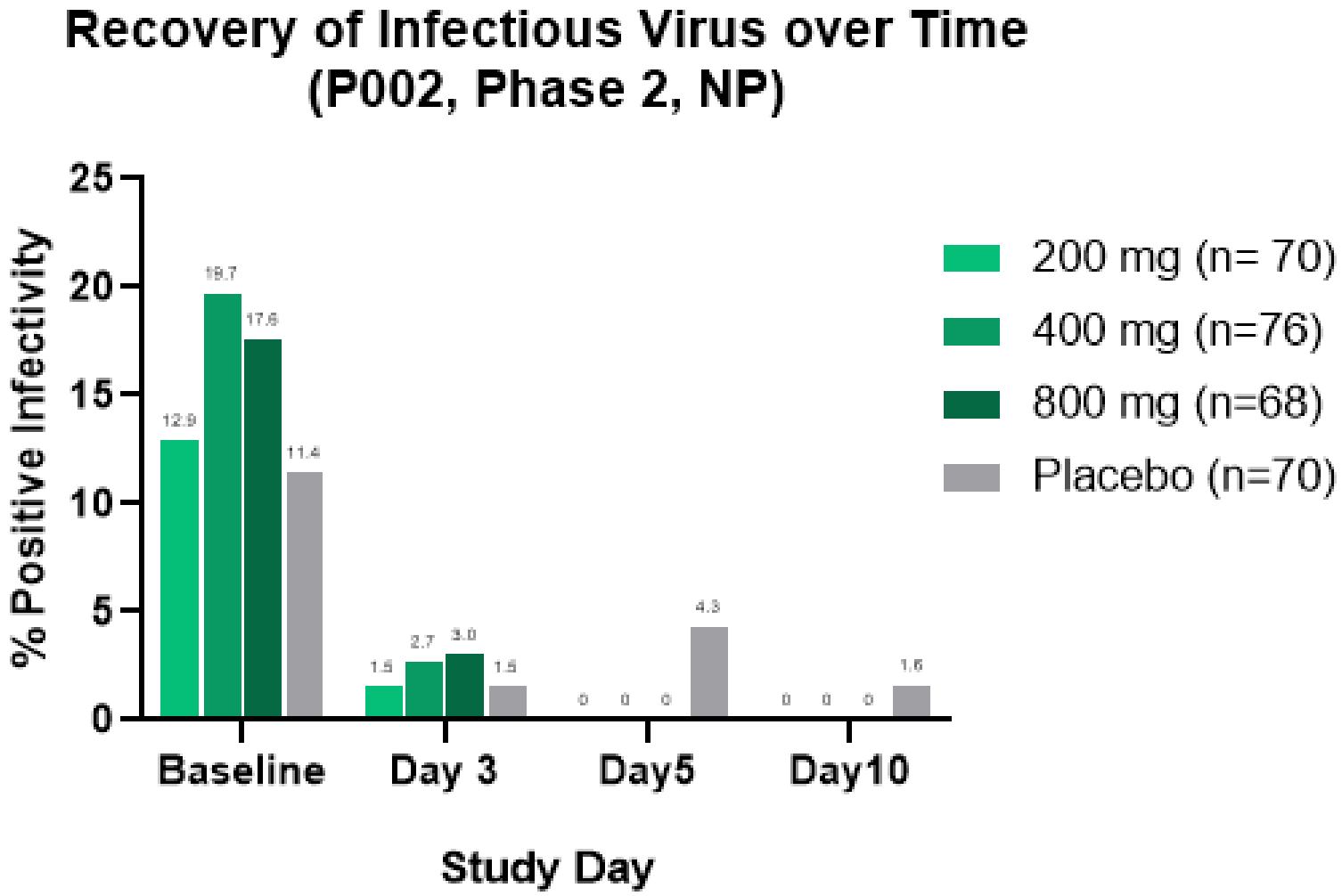
Incidence of hospitalization or death through Day 29 by Clade
modified Intent-to-Treat population

	Participants, n/m (%)		
Clade Designation	Molnupiravir N=709	Placebo N=699	Difference, % (95% CI)
20J (Gamma)	0/37 (0.0)	9/47 (19.1)	-19.1 (-32.6, -8.9)
21H (Mu)	6/75 (8.0)	13/82 (15.9)	-7.9 (-18.5, 2.6)
21A, 21I, 21J (Delta)	18/237 (7.6)	22/221 (10.0)	-2.4 (-7.8, 2.9)
Other	5/47 (10.6)	7/38 (18.4)	-7.8 (-24.4, 7.4)
Unknown	19/313 (6.1)	17/311 (5.5)	0.6 (-3.2, 4.4)
Total	48/709 (6.8)	68/699 (9.7)	-3.0 (-5.9, -0.1)

Unknown row includes participants with unavailable sequence data and participants with unknown clade designation.

No Infectious Virus Was Recovered from Any MOV Treated Participant by Study Day 5 and Day 10

P002 Phase 2



Primary Endpoint by VL (Qualitative Assay) at Baseline

P002 Phase 3 All Randomized Population

Incidence of hospitalization or death through Day 29 by VL (qualitative assay) at baseline
Modified Intent-to-Treat population

Baseline SARS-CoV-2 qualitative assay viral load S	Participants, n/m (%) MOV 800 mg N=709	Placebo N=699	Difference, % (95% CI)[a]
Detectable	45/614 (7.3)	61/613 (10.0)	-2.6 (-5.8, 0.5)
Undetectable	0/54 (0.0)	0/51 (0.0)	0.0 (-7.1, 6.7)
Unknown	3/41 (7.3)	7/35 (20.0)	-12.7 (-29.9, 2.9)

Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.
m=number of participants in the modified intent-to-treat population with the corresponding group.
n=number of participants died or hospitalized through Day 29.
[a] The corresponding confidence interval is based on Miettinen & Nurminen method.

Acute Care Visits

P002 Phase 3 All Randomized Population