Supplementary Materials for

A phase 2a clinical trial of molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus

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The PDF file includes:

Tables S1 to S11

Other Supplementary Material for this manuscript includes the following:

Reproducibility Checklist
Table S1. Time to SARS-CoV-2 Viral RNA Negativity in Participants Who Were Negative for Antibodies at Baseline

|                | 200 mg Molnupiravir | 400 mg Molnupiravir | 800 mg Molnupiravir | Placebo |
|----------------|---------------------|---------------------|---------------------|---------|
| Participants with Response, n/N (%) | 16/17 (94.1) | 26/34 (76.5) | 32/32 (100) | 34/44 (77.3) |
| Median time to response (95% CI), days | 22.0 (15.0, 29.0) | 26.0 (15.0, 28.0) | 14.0 (13.0, 14.0) | 27.0 (15.0, 28.0) |
| Log-rank p-value | 0.87 | 0.48 | 0.001 | |

Abbreviations: CI = confidence interval; n = number of observations; N = number of participants; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Table S2. Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

| System Organ Class                              | Molnupiravir 200 mg (N=23) | Molnupiravir 400 mg (N=62) | Molnupiravir 800 mg (N=55) | Placebo (N=62) |
|-------------------------------------------------|----------------------------|----------------------------|----------------------------|----------------|
| Preferred Term                                  | n  (%)  E                  | n  (%)  E                  | n  (%)  E                  | n  (%)  E      |
| Subjects with at Least 1 Adverse Event          | 11 (47.8) 16               | 20 (32.3) 42               | 11 (20.0) 21               | 18 (29.0) 31   |
| Nervous system disorders                        | 4 (17.4) 4                 | 6 (9.7) 10                 | 2 (3.6) 2                  | 3 (4.8) 4      |
| Headache                                        | 1 (4.3) 1                  | 3 (4.8) 4                  | 2 (3.6) 2                  | 3 (4.8) 3      |
| Dizziness                                       | 2 (8.7) 2                  | 1 (1.6) 3                  | 0                          | 0              |
| Parasthesia                                     | 0                          | 2 (3.2) 2                  | 0                          | 0              |
| Cerebrovascular accident                        | 0                          | 1 (1.6) 1                  | 0                          | 0              |
| Syncope                                         | 1 (4.3) 1                  | 0                          | 0                          | 0              |
| Migraine                                        | 0                          | 0                          | 1 (1.6) 1                  | 0              |
| Investigations                                  | 2 (8.7) 3                  | 5 (8.1) 8                  | 3 (5.5) 6                  | 4 (6.5) 6      |
| Alanine aminotransferase increased              | 0                          | 2 (3.2) 2                  | 2 (3.6) 2                  | 2 (3.2) 2      |
| Aspartate aminotransferase increased            | 0                          | 1 (1.6) 1                  | 2 (3.6) 2                  | 1 (1.6) 1      |
| Blood creatinine increased                      | 0                          | 3 (4.8) 3                  | 0                          | 0              |
| Blood alkaline phosphatase increased            | 0                          | 0                          | 1 (1.8) 1                  | 0              |
| Blood glucose decreased                         | 1 (4.3) 1                  | 0                          | 0                          | 1 (1.6) 1      |
| Blood glucose increased                         | 0                          | 0                          | 1 (1.8) 1                  | 0              |
| Creatinine renal clearance decreased            | 1 (4.3) 2                  | 0                          | 0                          | 1 (1.6) 1      |
| Haemoglobin decreased                           | 0                          | 1 (1.6) 1                  | 0                          | 0              |
| Oxygen saturation decreased                     | 0                          | 1 (1.6) 1                  | 0                          | 0              |
| Blood pressure increased                        | 0                          | 0                          | 0                          | 1 (1.6) 1      |
| Gastrointestinal disorders                      | 1 (4.3) 1                  | 7 (11.3) 8                 | 0                          | 5 (8.1) 6      |
| Nausea                                          | 1 (4.3) 1                  | 2 (3.2) 2                  | 0                          | 1 (1.6) 1      |
| Abdominal pain                                  | 0                          | 1 (1.6) 1                  | 0                          | 2 (3.2) 2      |
| Abdominal pain upper                            | 0                          | 1 (1.6) 1                  | 0                          | 1 (1.6) 1      |
| Diarrhoea                                       | 0                          | 1 (1.6) 1                  | 0                          | 1 (1.6) 1      |
| Gastrooesophageal reflux disease                | 0                          | 1 (1.6) 1                  | 0                          | 1 (1.6) 1      |
| Hyperaesthesia teeth                            | 0                          | 1 (1.6) 1                  | 0                          | 0              |
| Oral mucosal exfoliation                        | 0                          | 1 (1.6) 1                  | 0                          | 0              |
| Respiratory, thoracic and mediastinal disorders | 1 (4.3) 1                  | 2 (3.2) 3                  | 2 (3.6) 2                  | 1 (1.6) 1      |
| Cough                                           | 0                          | 2 (3.2) 2                  | 1 (1.8) 1                  | 0              |
| Acute respiratory failure                       | 0                          | 0                          | 1 (1.8) 1                  | 0              |
| Asthma                                           | 1 (4.3) 1                  | 0                          | 0                          | 0              |
| Dyspnoea                                        | 0                          | 1 (1.6) 1                  | 0                          | 0              |
| Hypoxia                                         | 0                          | 0                          | 0                          | 1 (1.6) 1      |
| Psychiatric disorders                           | 2 (8.7) 2                  | 1 (1.6) 1                  | 1 (1.8) 2                  | 4 (6.5) 4      |
| Insomnia                                        | 2 (8.7) 2                  | 1 (1.6) 1                  | 1 (1.8) 2                  | 4 (6.5) 4      |
| Condition                                               | n | E (in parentheses) | n | E (in parentheses) | n | E (in parentheses) |
|---------------------------------------------------------|---|--------------------|---|--------------------|---|--------------------|
| General disorders and administration site conditions   | 0 | 2 (3.2) 4          | 1 | (1.8) 2           | 3 | (4.8) 3           |
| Chest discomfort                                       | 0 | 1 (1.6) 2          | 0 |                   | 1 | (1.6) 1           |
| Chills                                                  | 0 | 0                 | 1 | (1.8) 1           | 0 |                   |
| Pyrexia                                                 | 0 | 0                 | 1 | (1.8) 1           | 0 |                   |
| Vessel puncture site bruise                            | 0 | 1 (1.6) 2          | 0 |                   | 0 |                   |
| Non-cardiac chest pain                                 | 0 | 0                 | 0 |                   | 1 | (1.6) 1           |
| Peripheral swelling                                    | 0 | 0                 | 0 |                   | 1 | (1.6) 1           |
| Infections and infestations                            | 0 | 2 (3.2) 2          | 1 | (1.8) 1           | 1 | (1.6) 1           |
| Pneumonia                                              | 0 | 1 (1.6) 1          | 1 | (1.8) 1           | 0 |                   |
| Oral herpes                                             | 0 | 1 (1.6) 1          | 0 |                   | 0 |                   |
| Genital herpes                                          | 0 | 0                 | 0 |                   | 1 | (1.6) 1           |
| Musculoskeletal and connective tissue disorders         | 1 | (4.3) 1            | 1 | (1.6) 1           | 1 | (1.8) 1           | 1 | (1.6) 2           |
| Arthralgia                                              | 0 | 1 (1.6) 1          | 0 |                   | 0 |                   |
| Back pain                                               | 1 | (4.3) 1            | 0 |                   | 0 |                   |
| Myalgia                                                 | 0 | 0                 | 1 | (1.8) 1           | 1 | (1.6) 1           |
| Musculoskeletal chest pain                              | 0 | 0                 | 0 |                   | 1 | (1.6) 1           |
| Skin and subcutaneous tissue disorders                 | 0 | 2 (3.2) 3          | 1 | (1.8) 1           | 2 | (3.2) 2           |
| Rash                                                    | 0 | 1 (1.6) 1          | 1 | (1.8) 1           | 0 |                   |
| Pruritus                                                | 0 | 1 (1.6) 1          | 0 |                   | 1 | (1.6) 1           |
| Skin burning sensation                                 | 0 | 1 (1.6) 1          | 0 |                   | 0 |                   |
| Hyperhidrosis                                           | 0 | 0                 | 0 |                   | 1 | (1.6) 1           |
| Cardiac disorders                                       | 0 | 1 (1.6) 1          | 1 | (1.8) 1           | 0 |                   |
| Cardiac flutter                                         | 0 | 1 (1.6) 1          | 0 |                   | 0 |                   |
| Supraventricular tachycardia                           | 0 | 0                 | 1 | (1.8) 1           | 0 |                   |
| Ear and labyrinth disorders                            | 2 | (8.7) 2            | 0 |                   | 1 | (1.6) 1           |
| Ear pain                                                | 1 | (4.3) 1            | 0 |                   | 0 |                   |
| Vertigo                                                 | 1 | (4.3) 1            | 0 |                   | 0 |                   |
| Ear discomfort                                          | 0 | 0                 | 0 |                   | 1 | (1.6) 1           |
| Injury, poisoning and procedural complications           | 1 | (4.3) 2            | 0 | 1 (1.8) 1         | 1 | (1.6) 1           |
| Accidental overdose                                     | 0 | 0                 | 1 | (1.8) 1           | 0 |                   |
| Arthropod bite                                          | 1 | (4.3) 1            | 0 |                   | 0 |                   |
| Muscle strain                                           | 1 | (4.3) 1            | 0 |                   | 0 |                   |
| Alcohol poisoning                                       | 0 | 0                 | 0 |                   | 1 | (1.6) 1           |
| Blood and lymphatic system disorders                    | 0 | 0                 | 1 | (1.8) 1           | 0 |                   |
| Anaemia                                                 | 0 | 0                 | 1 | (1.8) 1           | 0 |                   |
| Eye disorders                                           | 0 | 0                 | 1 | (1.8) 1           | 0 |                   |
| Blepharitis                                             | 0 | 0                 | 1 | (1.8) 1           | 0 |                   |
| Metabolism and nutrition disorders                      | 0 | 1 (1.6) 1          | 0 |                   | 0 |                   |
| Hyponatraemia                                           | 0 | 1 (1.6) 1          | 0 |                   | 0 |                   |

n = number of participants; E = number of events.
### Table S3. Summary of SARS-CoV-2 Infectivity for Participants Who Had Infectious Virus Isolation at Baseline

|                  | 200 mg Molnupiravir | 400 mg Molnupiravir | 800 mg Molnupiravir | Placebo |
|------------------|---------------------|---------------------|---------------------|---------|
|                  | N = 11               | N = 18               | N = 20               | N = 25  |
| Day 3, n/N (%)   | 4/11 (36.4)          | 5/18 (27.8)          | 1/20 (5.0)           | 7/25 (28.0) |
| Fishers exact p-value | 0.70                | >0.99               | 0.06                |         |
| Dose response p-value |                    |                     | 0.06                |         |
| Day 5, n/N (%)   | 1/11 (9.1)           | 0/18 (0.0)           | 0/20 (0.0)           | 6/25 (24.0) |
| Fishers exact p-value | 0.40                | 0.03                | 0.03                |         |
| Dose response p-value |                    |                     | 0.004               |         |

Abbreviations: n = number of observations; N = number of participants; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
|                       | 200 mg Molnupiravir (N = 9) | 400 mg Molnupiravir (N = 17) | 800 mg Molnupiravir (N = 20) | Placebo (N = 24) |
|-----------------------|-----------------------------|-----------------------------|-----------------------------|-----------------|
| **Day 3, n/N (%)**    | 2/9 (22.2)                  | 5/17 (29.4)                 | 1/20 (5.0)                  | 7/24 (29.2)     |
| *Fishers exact p-value* | >0.99                      | >0.99                       | 0.05                        |                 |
| *Dose response p-value* |                            |                            | 0.07                        |                 |
| **Day 5, n/N (%)**    | 0/9 (0.0)                   | 0/17 (0.0)                  | 0/20 (0.0)                  | 6/24 (25.0)     |
| *Fishers exact p-value* | 0.16                       | 0.03                        | 0.02                        |                 |
| *Dose response p-value* |                            |                             | 0.003                       |                 |

Abbreviations: n = number of observations; N = number of participants; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
### Table S5. Summary of SARS-CoV-2 Infectious Virus Isolation: 800 mg Molnupiravir Compared with Concurrent Placebo Recipients

| Number of Positive Subjects | 800 mg Molnupiravir | Placebo |
|-----------------------------|---------------------|---------|
| Day 1, n/N (%)              | 20/52 (38.5%)       | 8/17 (47.1%) |
| *p*-value                   | 0.58                |         |
| Day 3, n/N (%)              | 1/53 (1.9)          | 2/18 (11.1%) |
| *p*-value                   | 0.16                |         |
| Day 5, n/N (%)              | 0/53 (0.0)          | 3/18 (16.7%) |
| *p*-value                   | 0.014               |         |
| Day 7, n/N (%)              | 0/52 (0.0)          | 1/18 (5.6%)  |
| *p*-value                   | 0.26                |         |

Abbreviations: n = number of observations; N = number of participants.
| Day, n/N | 200 mg Molnupiravir | 400 mg Molnupiravir | 800 mg Molnupiravir | Placebo |
|---------|----------------------|----------------------|----------------------|---------|
| Day 3   | least squares mean (SE) | -1.141 (0.183) | -1.196 (0.132) | -1.157 (0.129) | -0.877 (0.150) |
|         | Difference in least squares mean | -0.263 | -0.319 | -0.280 |         |
|         | 95% CI | -0.734, 0.207 | -0.714, 0.076 | -0.670, 0.111 |         |
|         | p-value | 0.27 | 0.11 | 0.16 |         |
| Day 5   | least squares mean (SE) | -1.874 (0.183) | -2.101 (0.132) | -2.191 (0.129) | -1.578 (0.150) |
|         | Difference in least squares mean | -0.296 | -0.523 | -0.613 |         |
|         | 95% CI | -0.767, 0.174 | -0.917, -0.128 | -1.004, -0.223 |         |
|         | p-value | 0.22 | 0.010 | 0.002 |         |
| Day 7   | least squares mean (SE) | -2.447 (0.183) | -2.582 (0.137) | -2.967 (0.129) | -2.284 (0.152) |
|         | Difference in least squares mean | -0.163 | -0.298 | -0.683 |         |
|         | 95% CI | -0.635, 0.308 | -0.702, 0.105 | -1.075, -0.290 |         |
|         | p-value | 0.50 | 0.15 | <0.001 |         |
| Day 14  | least squares mean (SE) | -3.579 (0.183) | -3.412 (0.136) | -3.601 (0.129) | -3.343 (0.155) |
|         | Difference in least squares mean | -0.236 | -0.069 | -0.257 |         |
|         | 95% CI | -0.711, 0.239 | -0.475, 0.337 | -0.654, 0.140 |         |
|         | p-value | 0.33 | 0.74 | 0.20 |         |

Abbreviations: CI = confidence interval; n = number of observations; N = number of participants; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SE = standard error.
Table S7. Change from Baseline in SARS-CoV-2 Viral Load (log_{10} copies/mL)

|                  | 800 mg Molnupiravir | Placebo |
|------------------|----------------------|---------|
|                  | N = 53               | N = 18  |
| Day 3, n/N       | 51/53                | 16/18   |
| Least squares mean (SE) | -0.955 (0.094)  | -0.638 (0.166) |
| Difference in least squares mean | -0.316 |       |
| 95% CI           | -0.696, 0.063        |         |
| p-value          | 0.101                |         |
| Day 5, n/N       | 52/53                | 17/18   |
| Least squares mean (SE) | -1.673 (0.093)  | -1.297 (0.160) |
| Difference in least squares mean | -0.376 |       |
| 95% CI           | -0.744, -0.008       |         |
| p-value          | 0.045                |         |

Abbreviations: CI = confidence interval; n = number of observations; N = number of participants; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SE = standard error.
### Table S8. Summary of Time to Patient Reported General Physical Health At least Very Good (Safety Population)

|                           | Pooled Molnupiravir Groups (N=140) | Placebo (N=62) |
|---------------------------|-----------------------------------|---------------|
| **Number (%) Subjects with Response:** | 90 (64.3)                        | 41 (66.1)     |
| **Time to Response (days)** |                                   |               |
| 25% (95% CI)              | 8.0 (6.0, 9.0)                    | 6.0 (5.0, 9.0) |
| Median (95% CI)           | 14.0 (13.0, 21.0)                 | 15.0 (12.0, 18.0) |
| 75% (95% CI)              | NE                               | NE            |
| **Log Rank p-value**      | 0.5856                           |               |

Abbreviations: CI = confidence interval; N = number of participants; NE = not estimated
Table S9. Summary of COVID-19-Related Medical Visits (Safety Population)

|                      | Molnupiravir 200 mg (N=23) | Molnupiravir 400 mg (N=62) | Molnupiravir 800 mg (N=55) | Placebo (N=62) |
|----------------------|-----------------------------|-----------------------------|-----------------------------|----------------|
|                      | n (%)                        | n (%)                       | n (%)                       | n (%)          |
| Participants with a COVID-19-related medical visit |                             |                             |                             |                |
| Yes                  | 3 (13.0)                     | 4 (6.5)                     | 5 (9.1)                     | 5 (8.1)        |
| No                   | 20 (87.0)                    | 58 (93.5)                   | 50 (90.9)                   | 57 (91.9)      |
| p-value              | 0.6768                       | >.9999                      | >.9999                      |                |

Abbreviations: COVID-19 = coronavirus disease 2019; n = number of observations; N = number of participants
Table S10. Missing Data for SARS-CoV-2 Infectious Virus

| Visit Before       | Visit After | Imputation of Infectivity Result |
|--------------------|-------------|---------------------------------|
| Negative           | Negative    | Negative                        |
| Positive           | Positive    | Positive                        |
| Negative or missing| Positive    | Positive*                       |
| Missing            | Negative    | Missing                         |
| Any value          | Missing     | Missing                         |

* For participants with missing baseline assessments and reported the first post baseline value as positive, the baseline was imputed as positive.
Table S11. Missing Data for Time to SARS-CoV-2 Viral RNA Negativity

| Visit Before       | Visit After       | Imputation of Undetectable SARS-CoV-2 RNA |
|--------------------|-------------------|------------------------------------------|
| BLQ/BLD            | BLD or BLQ        | Negative                                 |
| >BLQ               | BLD or BLQ        | Positive                                 |
| BLD/BLQ or missing | >BLQ              | Positive*                                |
| Missing            | BLD or BLQ        | Missing                                  |
| Any value          | Missing           | Missing                                  |

Abbreviations: BLD = below limit of detection; BLQ = below limit of quantification; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
* For participants with missing baseline assessments who reported the first post baseline value as >BLQ, the baseline was imputed as >BLQ (positive).