

## **Supplementary Material**

### **Consistent effects of early remdesivir on symptoms and disease progression across at-risk outpatient subgroups: treatment effect heterogeneity in PINETREE**

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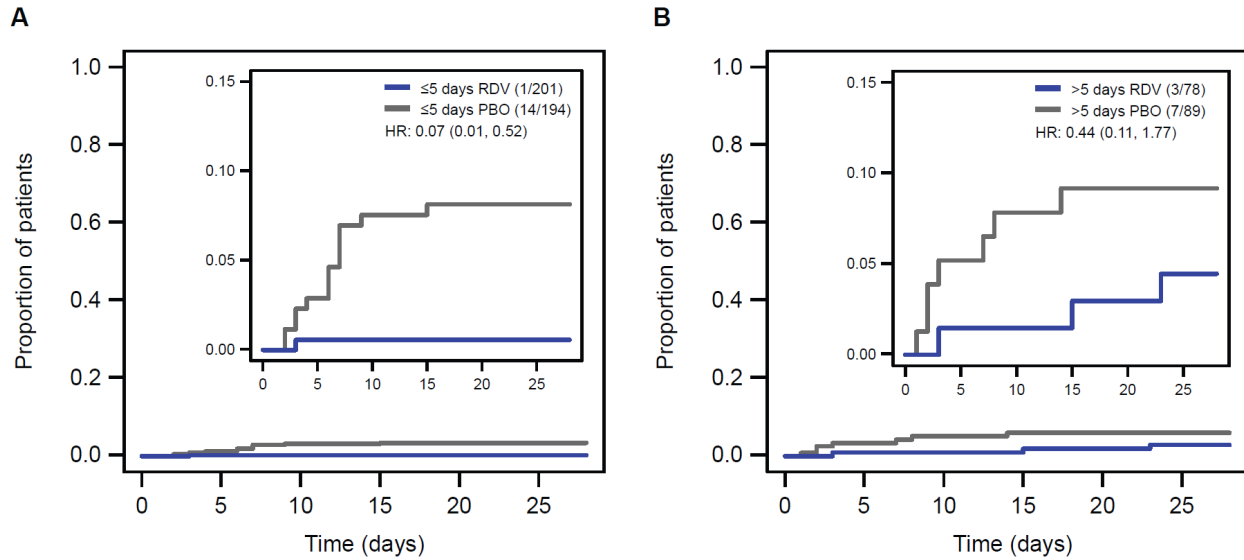
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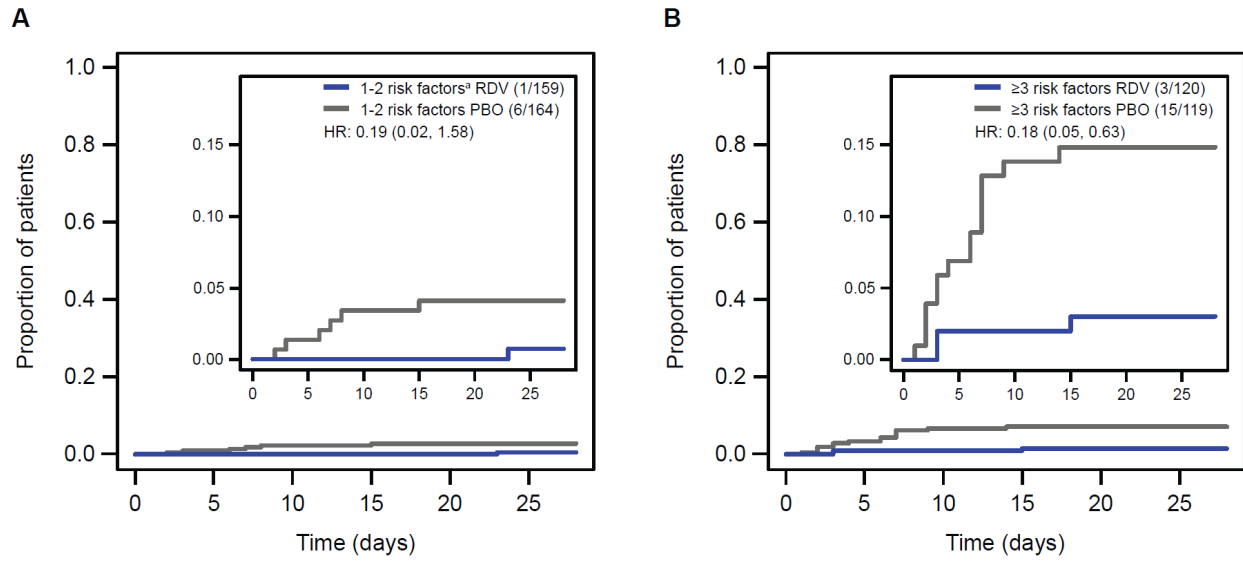
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**Supplementary Figure 1. COVID-19 MAVs stratified by time from symptom onset at treatment initiation.**



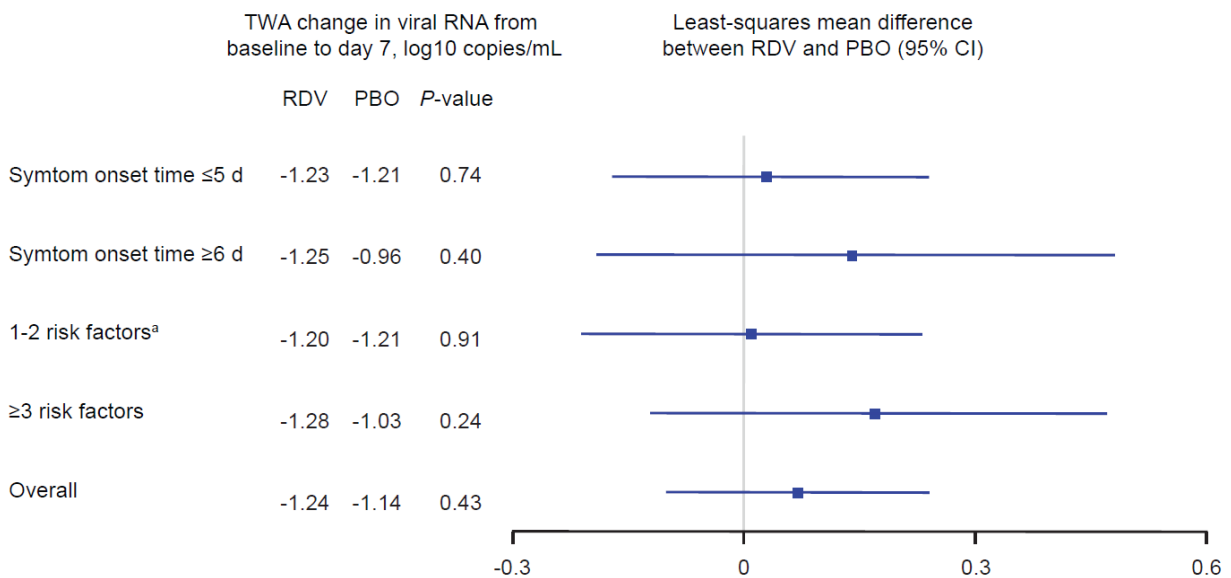
(A) Patients with  $\leq 5$  days between symptom onset and infusion. (B) Patients with  $> 5$  days between symptom onset and infusion. Abbreviations: COVID-19, coronavirus disease 2019; MAVs, medically attended visits; RDV, remdesivir; PBO, placebo; HR, hazard ratio.

**Supplementary Figure 2. COVID-19 MAVs stratified by number of baseline risk factors.**



(A) Patients with 1-2 risk factors. (B) Patients with  $\geq 3$  risk factors. Abbreviations: COVID-19, coronavirus disease 2019; MAVs, medically attended visits; RDV, remdesivir; PBO, placebo; HR, hazard ratio. <sup>a</sup>Including 1 subject without risk factor.

**Supplementary Figure 3. Change in NP viral RNA copy number stratified by time from symptom onset and number of baseline risk factors.**



Abbreviations: NP, nucleoprotein; TWA, time-weighted average; RDV, remdesivir; PBO, placebo; CI, confidence interval.

**Supplementary Table 1. COVID-19 Hospitalizations Based on Symptom Onset Time and Baseline Risk Factors**

|                                        | <b>Events/Number of Patients (%)</b> |               | <b>HR (95% CI)</b> |
|----------------------------------------|--------------------------------------|---------------|--------------------|
| <b>Symptom onset time, days</b>        | <b>RDV</b>                           | <b>PBO</b>    |                    |
| ≤5                                     | 1/201 (0.5%)                         | 9/194 (4.6%)  | 0.1 (0.01, 0.82)   |
| ≥6                                     | 1/78 (1.3%)                          | 6/89 (6.7%)   | 0.19 (0.02, 1.61)  |
| ≤3                                     | 0/77 (0%)                            | 5/69 (7.2%)   | NA                 |
| ≥4                                     | 2/202 (1%)                           | 10/214 (4.7%) | 0.21 (0.04, 0.94)  |
| <b>Number of baseline risk factors</b> |                                      |               |                    |
| 1- 2 <sup>a</sup>                      | 0/159 (0%)                           | 4/164 (2.4%)  | NA                 |
| ≥3                                     | 2/120 (1.7%)                         | 11/119 (9.2%) | 0.16 (0.04, 0.73)  |
| 1-3 <sup>a</sup>                       | 1/226 (0.4%)                         | 8/229 (3.5%)  | 0.14 (0.02, 1.09)  |
| ≥4                                     | 1/53 (1.9%)                          | 7/54 (13%)    | 0.14 (0.02, 1.17)  |
| Overall                                | 2/279 (0.7%)                         | 15/283 (5.3%) | 0.13 (0.03, 0.59)  |

Abbreviations: COVID-19, coronavirus disease 2019; HR, hazard ratio; CI, confidence interval; RDV, remdesivir; PBO, placebo; NA, not applicable.

<sup>a</sup>Including 1 subject without risk factor.

**Supplementary Table 2. COVID-19 Medically Attended Visits Based on Symptom Onset Time and Baseline Risk Factors**

|                                 | Events/Number of Patients (%) |               | HR (95% CI)       |
|---------------------------------|-------------------------------|---------------|-------------------|
| Symptom onset time, days        | RDV                           | PBO           |                   |
| ≤5                              | 1/201 (0.5%)                  | 14/194 (7.2%) | 0.07 (0.01, 0.52) |
| ≥6                              | 3/78 (3.8%)                   | 7/89 (7.9%)   | 0.44 (0.11, 1.77) |
| ≤3                              | 0/77 (0%)                     | 6/69 (8.7%)   | NA                |
| ≥4                              | 4/202 (2%)                    | 15/214 (7%)   | 0.26 (0.09, 0.80) |
| Number of baseline risk factors |                               |               |                   |
| 1- 2 <sup>a</sup>               | 1/159 (0.6%)                  | 6/164 (3.7%)  | 0.19 (0.02, 1.58) |
| ≥3                              | 3/120 (2.5%)                  | 15/119 (13%)  | 0.18 (0.05, 0.63) |
| 1-3 <sup>a</sup>                | 1/226 (0.4%)                  | 14/229 (6.1%) | 0.08 (0.01, 0.57) |
| ≥4                              | 3/53 (5.7%)                   | 7/54 (13%)    | 0.42 (0.11, 1.63) |
| Overall                         | 4/279 (1.4%)                  | 21/283 (7.4%) | 0.19 (0.07, 0.56) |

Abbreviations: COVID-19, coronavirus disease 2019; HR, hazard ratio; CI, confidence interval; RDV, remdesivir; PBO, placebo; NA, not applicable.

<sup>a</sup>Including 1 subject without risk factor.

**Supplementary Table 3. COVID-19 Symptom Alleviation by Symptom Onset Time and Baseline Risk Factors**

|                                        | <b>Events/Number of Patients (%)</b> |              | <b>RR (95% CI)</b> |
|----------------------------------------|--------------------------------------|--------------|--------------------|
| <b>Symptom onset time, days</b>        | <b>RDV</b>                           | <b>PBO</b>   |                    |
| ≤5                                     | 45/123 (37%)                         | 24/120 (20%) | 1.9 (1.16, 3.13)   |
| ≥6                                     | 16/46 (35%)                          | 9/45 (20%)   | 2.32 (0.94, 5.72)  |
| ≤3                                     | 17/41 (41%)                          | 9/40 (22%)   | 1.99 (0.88, 4.54)  |
| ≥4                                     | 44/128 (34%)                         | 24/125 (19%) | 1.91 (1.16, 3.15)  |
| <b>Number of baseline risk factors</b> |                                      |              |                    |
| 1- 2 <sup>a</sup>                      | 46/104 (47%)                         | 17/99 (17%)  | 2.79 (1.6, 4.86)   |
| ≥3                                     | 15/65 (23%)                          | 16/66 (24%)  | 0.99 (0.49, 2.00)  |
| 1-3 <sup>a</sup>                       | 54/137 (39%)                         | 28/142 (20%) | 2.07 (1.31, 3.28)  |
| ≥4                                     | 7/32 (22%)                           | 5/23 (22%)   | 1.22 (0.38, 3.88)  |
| Overall                                | 61/169 (36%)                         | 33/165 (20%) | 1.92 (1.26, 2.93)  |

Abbreviations: COVID-19, coronavirus disease 2019; RR, rate ratio; CI, confidence interval; RDV, remdesivir; PBO, placebo.

<sup>a</sup>Including 1 subject without risk factor.

**Supplementary Table 4. SARS-CoV-2 Lineages Determined at Baseline**

| <b>Pango Lineage<br/>(WHO<br/>nomenclature)</b> | <b>Number of participants, n (% out of participants with baseline<br/>sequencing data available)</b> |                     |                        |
|-------------------------------------------------|------------------------------------------------------------------------------------------------------|---------------------|------------------------|
|                                                 | <b>RDV (n = 119)</b>                                                                                 | <b>PBO (n =138)</b> | <b>Total (n = 257)</b> |
| B.1.2                                           | 35 (29.4%)                                                                                           | 43 (31.2%)          | 78 (30.4%)             |
| B.1.1.7 (Alpha)                                 | 21 (17.6%)                                                                                           | 27 (19.6)           | 48 (18.7%)             |
| B.1.429 (Epsilon)                               | 9 (7.6%)                                                                                             | 14 (10.1%)          | 23 (8.9%)              |
| B.1.243                                         | 8 (6.7%)                                                                                             | 2 (1.4%)            | 10 (3.9%)              |
| B.1.427                                         | 4 (3.4%)                                                                                             | 2 (1.4%)            | 6 (2.3%)               |
| B.1.234                                         | 2 (1.7%)                                                                                             | 3 (2.2%)            | 5 (1.9%)               |
| B.1.311                                         | 1 (0.8%)                                                                                             | 4 (2.9%)            | 5 (1.9%)               |
| B.1                                             | 0                                                                                                    | 4 (2.9%)            | 4 (1.6%)               |
| B.1.1.519                                       | 3 (2.5%)                                                                                             | 1 (0.7%)            | 4 (1.6%)               |
| B.1.240                                         | 3 (2.5%)                                                                                             | 1 (0.7%)            | 4 (1.6%)               |
| B.1.526 (Iota)                                  | 2 (1.7%)                                                                                             | 2 (1.4%)            | 4 (1.6%)               |
| B.1.561                                         | 1 (0.8%)                                                                                             | 3 (2.2%)            | 4 (1.6%)               |
| B.1.577                                         | 3 (2.5%)                                                                                             | 1 (0.7%)            | 4 (1.6%)               |
| B.1.595                                         | 2 (1.7%)                                                                                             | 2 (1.4%)            | 4 (1.6%)               |
| B.1.596                                         | 0                                                                                                    | 4 (2.9%)            | 4 (1.6%)               |
| B.1.623                                         | 4 (3.3%)                                                                                             | 0                   | 4 (1.6%)               |
| Other <sup>a</sup>                              | 22 (18.5%)                                                                                           | 25 (18.1%)          | 47 (18.3%)             |

Abbreviations: WHO, World Health Organization; RDV, remdesivir; PBO, placebo.

<sup>a</sup>Lineages observed in <4 participants include B.1.110.3, B.1.177, B.1.369, and P.1 (Gamma) observed in 3 participants each, B.1.177.12, B.1.564, B.1.582, B.1.637, and XB observed in 2 participants each, and A.2.5, B.1.1, B.1.1.135, B.1.1.192, B.1.1.231, B.1.1.316, B.1.1.328, B.1.1.337, B.1.1.517, B.1.111, B.1.160, B.1.170, B.1.177.21, B.1.232, B.1.241, B.1.265, B.1.280, B.1.396, B.1.438.4, B.1.568, B.1.575.1, B.1.609, C.23, Q.3, and R.1 observed in 1 participant each.

**Supplementary Table 5. Remdesivir EC<sub>50</sub> Against SARS-CoV-2 Omicron BA.2.12.1, BA.4.6 and BF.5 Subvariants Based on Anti-nucleoprotein ELISA Results**

| Variant<br>(Lineage)    | Isolate <sup>a</sup>                            | RDV EC <sub>50</sub> (nM) |                 |                 |                 |                              | EC <sub>50</sub> fold<br>change<br>from<br>reference <sup>c</sup> |
|-------------------------|-------------------------------------------------|---------------------------|-----------------|-----------------|-----------------|------------------------------|-------------------------------------------------------------------|
|                         |                                                 | Replicate                 |                 |                 |                 | Mean<br>±<br>SD <sup>b</sup> |                                                                   |
|                         |                                                 | 1 <sup>st</sup>           | 2 <sup>nd</sup> | 3 <sup>rd</sup> | 4 <sup>th</sup> |                              |                                                                   |
| Reference<br>WA1<br>(A) | hCoV-19/USA-<br>WA1/2020                        | 161.0                     | 161.8           | 161.7           | 130.7           | 154 ± 15                     | 1.0                                                               |
| Omicron<br>(BA.2.12.1)  | hCoV-<br>19/USA/NY-<br>MSHSPSP-<br>PV56475/2022 | 34.6                      | 31.1            |                 |                 | 33 ± 3                       | 0.20                                                              |
| Omicron<br>(BA.4.6)     | hCoV-<br>19/USA/MD-<br>HP35538/2022             |                           |                 | 88.4            | 95.1            | 92 ± 5                       | 0.64                                                              |
| Omicron<br>(BF.5)       | hCoV-<br>19/USA/MD-<br>HP34985/2022             |                           |                 | 117.1           | 151.1           | 134 ± 24                     | 0.94                                                              |

Abbreviations: ELISA, enzyme-linked immunoassay; EC<sub>50</sub>, half-maximal effective concentration; SD, standard deviation.

<sup>a</sup>Clinical isolates were obtained from BEI Resources (<https://www.beiresources.org/>).

<sup>b</sup>Values are the mean ± SD of the results of at least 2 independent experiments.

<sup>c</sup>The fold change from SARS-CoV-2 reference WA1 strain (lineage A) was calculated for each experiment.