Triple Combination of Interferon beta-1b, Lopinavir-Ritonavir, and Ribavirin in Treatment of Adults with COVID-19 (Hong Kong)

Published Data – Multicenter, prospective, open-label, randomized, phase 2 trial

### Study Design

**Background:** Multicenter, prospective, open-label, randomized, phase 2 trial comparing triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin to lopinavir-ritonavir only in patients hospitalized with COVID-19. Patients were randomized in a 2:1 ratio with no stratification.

**Location:** Hong Kong (February 10-March 20, 2020)

**Inclusion Criteria (n = 127)**
- Age ≥18 years
- National Early Warning Score 2 (NEWS2) ≥1
- Symptom duration ≤14 days upon recruitment
- Laboratory-confirmed SARS-CoV-2 infection by RT-PCR via NP swab

**Exclusion Criteria:**
- Second- and third-degree heart block
- Severe depression
- Pregnancy

**Treatment Arms**
- Combination Arm: Lopinavir-ritonavir + ribavirin + Interferon beta-1b + standard of care
- Control Arm: Lopinavir-ritonavir 400-100 mg PO BID + standard of care

Interferon beta-1b, Lopinavir-Ritonavir, and Ribavirin in Treatment of Adults with COVID-19: Study Design

**Study Design**

- **Primary Endpoint**
  - Time to achieve negative RT-PCR for SARS-CoV-2 in NP swab sample

- **Secondary Endpoints**
  - Time to NEWS2 of 0
  - Daily NEWS2 and sequential organ failure assessment (SOFA) score
  - Length of hospitalization
  - 30-day mortality

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Arms and Interventions

Lopinavir-ritonavir 400-100 mg orally + ribavirin 400 mg orally every 12 hours, and interferon beta-1b 1 mL subcutaneously on alternate days for 14 days* (n = 86)

or

Lopinavir-ritonavir 400-100 mg orally every twelve hours for 14 days (n = 41)

### Interferon beta-1b, Lopinavir-Ritonavir, and Ribavirin in Treatment of Adults with COVID-19: Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>LPV-RTV, IFN-beta 1b, RBV* (n = 86)</th>
<th>LPV-RTV Only (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (IQR)</td>
<td>51.0 (31.0–61.3)</td>
<td>52.0 (33.5–62.5)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>45 (52%)</td>
<td>23 (56%)</td>
</tr>
<tr>
<td>Coexisting conditions, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (27%)</td>
<td>13 (32%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 (13%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>NEWS2 Score, n (IQR)</td>
<td>2 (1-2)</td>
<td>2 (2-2)</td>
</tr>
<tr>
<td>SOFA Score, n (IQR)</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Days from onset to treatment, median (IQR)</td>
<td>5 (4–7)</td>
<td>4 (3–8)</td>
</tr>
</tbody>
</table>

*Abbreviations: LPV = Lopinavir, RTV = ritonavir, IFN = interferon, RBV = ribavirin

Interferon beta-1b, Lopinavir-Ritonavir, and Ribavirin in Treatment of Adults with COVID-19: Results

Comparison Between Combination and Control Groups: Days to Achieve Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>LPV-RTV, IFN-beta 1b, RBV* (n=86)</th>
<th>LPV-RPV Only (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative RT-PCR</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>NEWS2 Score of 0</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>SOFA score of 0</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Hospital Duration</td>
<td>9</td>
<td>14.5</td>
</tr>
</tbody>
</table>

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### Interferon beta-1b, Lopinavir-Ritonavir, and Ribavirin in Treatment of Adults with COVID-19: Results

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<tr>
<th>Endpoint</th>
<th>LPV-RTV, IFN-beta 1b, RBV* (n = 86)</th>
<th>LPV-RPV Only (n = 41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint, days (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Time to negative RT-PCR in NP Swab</td>
<td>7 (5–11)</td>
<td>12 (8–15)</td>
<td>0.0010</td>
</tr>
<tr>
<td><strong>Secondary Endpoints, days (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Time to NEWS2 Score of 0</td>
<td>4 (3–8)</td>
<td>8 (7–9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>- Time to SOFA score of 0</td>
<td>3.0 (1.0–8.0)</td>
<td>8.0 (6.5–9.0)</td>
<td>0.041</td>
</tr>
<tr>
<td>- Duration of hospital days</td>
<td>9·0 (7.0–13.0)</td>
<td>14.5 (9.3–16.0)</td>
<td>0.016</td>
</tr>
<tr>
<td>- 30-day mortality</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

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Interferon beta-1b, Lopinavir-Ritonavir, and Ribavirin in Treatment of Adults with COVID-19: Results

• **Primary Endpoint: Median time to SARS-CoV-2 negative NP swab**
  - Significantly shorter in combination group than control group (HR 4.37 [95% CI 1.86-10.24], p=0.001)
  - No statistically significant difference between treatment groups in patients who started treatment ≥7 days after symptom onset

• **Secondary Endpoints**
  - Statistically significant outcomes in combination group for:
    • Time to achieve NEWS2 and SOFA score of 0
    • Median length of hospital stay

• **Time to achieve negative viral load across all samples collected**
  - No statistically significant differences between treatment groups in patients who started treatment ≥7 days after symptom onset (except NEWS2 score on Day 5)

Adverse events were reported in 41 of 86 (48%) patients in combination group and 29 of 41 (49%) in control group.

Side effects were generally mild and self-limiting.

No serious adverse events were reported in combination group.

1 patient in the control group had a serious adverse event requiring discontinuation of treatment.

Interferon beta-1b, Lopinavir-Ritonavir, and Ribavirin in Treatment of Adults with COVID-19: Authors’ Conclusions

Interpretation: “Early triple antiviral therapy was safe and superior to lopinavir–ritonavir alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19. Future clinical study of a double antiviral therapy with interferon beta-1b as a backbone is warranted”.