EDP-235, a Potent and Once-Daily Oral Antiviral, Demonstrates Excellent Penetration into Macrophages and Monocytes with the Potential for Mitigation of Cytokine Storm in COVID-19 Patients

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EDP-235 is a Potent 3CLpro Inhibitor with Potential as a Best-in-Class Antiviral Treatment for SARS-CoV-2 Infection

- Novel, oral, directing–acting antiviral specifically designed to target the SARS-CoV-2 protease
- Nanomolar potency against emerging SARS-CoV-2 variants (including Delta & Omicron) with high barrier to resistance observed in multiple cellular models
- Generally safe and well-tolerated up to 400 mg doses for 7 days in humans
- Excellent human plasma pharmacokinetics support efficacious doses of 200 mg or 400 mg once daily (QD) without the need for boosting (e.g., ritonavir)
  - Projected to have 4x higher drug level in lung tissue compared to plasma based on preclinical animal models

<table>
<thead>
<tr>
<th>Measured Plasma Drug Multiples*</th>
<th>Predicted Lung Drug Multiples*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variant</strong></td>
<td><strong>200mg QD</strong></td>
</tr>
<tr>
<td>Alpha</td>
<td>3x</td>
</tr>
<tr>
<td>Omicron</td>
<td>7x</td>
</tr>
</tbody>
</table>

- Good distribution into key target tissues providing the potential to minimize post-treatment viral rebound and/or possible viral replication persistence linked to long COVID

*Multiples by which mean trough drug plasma levels at steady state are higher than protein adjusted EC₉₀ as measured in Vero cells
Alveolar Macrophages (AM) Play an Important Role in SARS-CoV-2 Infection

- Macrophages, including lung AM, and monocytes are the first line of defense against SARS-CoV-2.
- Several reports have suggested that SARS-CoV-2 can hijack AM and monocytes for replication and viral spread, which may, in turn, drive the cytokine storm associated with severe COVID-19.

## EDP-235: Excellent Penetration into Alveolar Macrophages (AM) in Rats

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Plasma</th>
<th>AM</th>
<th>AUC Ratio over Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{\text{max}}$ (µg/mL)</td>
<td>$\text{AUC}_{0-\infty}$ (µg-h/mL)</td>
<td>$C_{\text{max}}$ (µg/mL)</td>
</tr>
<tr>
<td>EDP-235</td>
<td>1.2</td>
<td>9.6</td>
<td>50.7</td>
</tr>
<tr>
<td>nirmatrelvir</td>
<td>1.5</td>
<td>2.7</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Single Dose PK; p.o. Formulation: 0.5% Methylcellulose (MC) in water
# EDP-235: Superior Ex Vivo Intracellular Uptake into Target Cells

## Intracellular / Extracellular Ratios in Human Cell Lines

<table>
<thead>
<tr>
<th>Compound</th>
<th>Lung Epithelial</th>
<th>Kidney Epithelial</th>
<th>Monocyte</th>
<th>Macrophage</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDP-235</td>
<td>8.7±0.6</td>
<td>18.0±0.8</td>
<td>22.7±1.4</td>
<td>30.5±2.9</td>
</tr>
<tr>
<td>nirmatrelvir</td>
<td>0.8±0.1</td>
<td>1.2±0.2</td>
<td>1.5±0.3</td>
<td>1.2±0.2</td>
</tr>
</tbody>
</table>
Conclusions

• EDP-235, a novel and potent SARS-CoV-2 3CL protease inhibitor, demonstrated excellent penetration into monocytes and macrophages, including lung alveolar macrophages.

• EDP-235 has the potential to eliminate SARS-CoV-2 replication in sentinel immune cells, thus potentially mitigating macrophage-mediated cytokine storm in COVID-19 patients.

• Phase 2 clinical trial of EDP-235 for COVID-19 treatment will initiate in 4Q of 2022.

Emerging data support a convenient EDP-235 dosing regimen, targeting one pill, once-daily effective against COVID-19 variants of concern
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Please go to Poster 1123 for more information about EDP-235