

## Shionogi S-217622 (Ensitrelvir; STRIVE/INSIGHT 018A) Trial Synopsis

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| <b>Design:</b>           | <p>Treatments are needed to improve outcomes among patients hospitalized for COVID-19, including direct-acting antiviral (DAA) agents to mitigate the pathology driven by ongoing viral replication. This trial will evaluate S-217622 (ensitrelvir), an anti-SARS-CoV-2 3C-like protease inhibitor (PI) developed by Shionogi &amp; Co. Ltd.</p> <p>The study design is a randomized, placebo-controlled, multi-center international clinical trial that will evaluate the clinical efficacy of S-217622 when given in addition to standard of care (SOC) for inpatients with COVID-19. The SOC will be determined by local established guidelines and may include additional DAA (e.g., remdesivir) and immunomodulatory treatment strategies. Certain SOC treatments will be pre-specified prior to randomization.</p> |
| <b>Primary Endpoint:</b> | <p>The primary objective is to establish the safety and efficacy of S-217622 versus placebo when given in addition to SOC. The primary endpoint for this trial is the days to recovery scale assessed over 60 days (<i>DRS-60</i>). <i>DRS-60</i> is a version of the STRIVE clinical recovery scale (CRS; see master protocol), which for this trial includes daily bins for time to recovery and also captures ongoing hospitalization and death. This corresponds to 63 ordered categories: categories 0 (best) through 60 reflect time to recovery, followed by categories for “alive, not recovered” and then “death” (worst).</p>   |
| <b>Duration:</b>         | <p>Participants will be followed for 60 days following randomization for the primary endpoint. Select secondary endpoints will also be measured.</p>  |
| <b>Sample Size:</b>      | <p>This Phase 3 trial is planned to provide 80% power to detect an OR of 1.30 in <i>DRS-60</i> for S-217622 versus matched placebo, both in combination with SOC. The planned sample size is 1500 participants. Sample size may be re-estimated before enrollment is completed based on an assessment of whether the pooled estimate of the distribution across the ordinal categories of the <i>DRS-60</i> is still consistent with adequate power for the hypothesized difference. A reassessment of the magnitude of the hypothesized difference, blinded to follow-up data, may also need to be made.</p>   |
| <b>Population:</b>       | <p>Adults (<math>\geq 18</math> years) who have documented SARS-CoV-2 infection within 14 days of enrollment and are hospitalized for management of COVID-19. Inpatients at any disease stage will be eligible, including those not receiving oxygen as well as patients receiving oxygen supplementation via low-flow device, high-flow nasal cannula device,</p>  |

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|                        | non-invasive ventilation, invasive mechanical ventilation or extracorporeal membrane oxygenation at enrollment.  |
| <b>Intervention:</b>   | Randomization to S-217622 plus SOC or matched placebo plus SOC in a 1:1 allocation. Study investigational agent/placebo (S-217622) will be administered as tablets with dosing of 375 mg (3 tabs) once on Day 0 and 125 mg (1 tab) once daily on Days 1-4. All participants will receive the full 5-day course, including those who are discharged from hospitalization prior to Day 4.  |
| <b>Stratification:</b> | Randomization will be stratified by study site pharmacy and disease severity.  |
| <b>Monitoring:</b>     | An independent data and safety monitoring board (DSMB) will regularly review interim safety and efficacy data of this trial along with the conduct of other trials within the STRIVE protocol. A sponsor medical monitor will review blinded safety data. Pre-specified guidelines will be established to recommend early stopping of the trial for evidence of harm, futility, or substantial efficacy. The DSMB may recommend discontinuation of the investigational agent if the risks are judged to outweigh the benefits. |