Patient-reported symptom outcomes from COMET-ICE, a phase III study of sotrovimab for early treatment of non-hospitalized patients with COVID-19

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The COMET-ICE trial (NCT04545060) in patients (n=1057) with mild-to-moderate COVID-19 at high risk of progression to severe disease showed a clinically and statistically significant relative risk reduction (79%; 95% CI: 50%, 91%; p<0.001) in all-cause >24-hour hospitalisation or death in patients receiving sotrovimab (6/528; 1%) compared with placebo (30/529; 6%)¹

Patient-reported outcomes (PROs) are important in order to fully capture the symptom burden of COVID-19 and assess the effectiveness of treatments²

The inFLUenza-Patient Reported Outcome (FLU-PRO) measure was developed to assess the core symptoms of influenza and other viral respiratory diseases³

• An extended version (FLU-PRO Plus) has been developed to include additional commonly reported COVID-19 symptoms of loss of taste and smell⁴

• FLU-PRO Plus includes 34 items with 7 domains (nose, throat, eyes, respiratory, gastrointestinal, systemic and sense) and has been shown to be a reliable and valid instrument that is responsive to change in patients with COVID-19

Here we describe PRO results from COMET-ICE, assessed using FLU-PRO Plus

MATERIALS AND METHODS

COMET-ICE participants (randomised 1:1 sotrovimab:placebo)

Non-hospitalised adults (age ≥18 years) with symptomatic, mild-to-moderate COVID-19

Age ≥55 years OR ≥1 risk factor for disease progression: diabetes requiring medication, obesity, CKD, CHF, COPD, moderate-to-severe asthma

FLU-PRO Plus (34 items with 5-point severity score)

Administered once-daily with a 24-h recall period

Day 1 through Day 21

Symptom intensity/duration: average change in total score (measured by AUC)

Symptom alleviation

AUC, area under the curve; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease
More rapid decline in symptom severity with sotrovimab vs placebo within the first week and throughout the first 21 days after treatment

Observed Mean (± SE) FLU-PRO Plus total score by Study Day*
(higher score = more severe symptoms)

*data from Week 24 database
V, intravenous; SE, standard error
Mean decrease in FLU-PRO Plus total score statistically significantly greater with sotrovimab vs placebo at Day 7, 14 and 21

Average change from baseline (AUC) in FLU-PRO Plus total score

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=529)</th>
<th>Sotrovimab (N=528)</th>
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<tbody>
<tr>
<td><strong>AUC through Day 7^</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>399</td>
<td>412</td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>-1.98 (-2.20, -1.76)</td>
<td>-3.05 (-3.27, -2.83)</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>-1.07 (-1.38, -0.76)</td>
<td></td>
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<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td><strong>AUC through Day 14</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>373</td>
<td>385</td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>-7.04 (-7.51, -6.58)</td>
<td>-9.40 (-9.85, -8.94)</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>-2.35 (-3.00, -1.70)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td><strong>AUC through Day 21</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>345</td>
<td>379</td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>-13.34 (-14.03, -12.64)</td>
<td>-16.42 (-17.09, -15.76)</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>-3.09 (-4.05, -2.12)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
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</tbody>
</table>

^AUC through Day 7 was part of the secondary endpoint testing hierarchy; *AUC through Day 14 and Day 21 were exploratory endpoints

More negative AUC = greater symptom improvement

AUC, area under the curve; CI, confidence interval
Greater proportion of patients achieved sustained (≥48 h) symptom alleviation with sotrovimab (41%) vs placebo (34%) over the first 21 days

Proportion of patients achieving sustained (≥48 h) symptom alleviation

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=529)</th>
<th>Sotrovimab (N=528)</th>
<th>aRRR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 7*</td>
<td>Sustained, n (%)</td>
<td>31 (6%)</td>
<td>76 (14%)</td>
<td>2.51 (1.69, 3.72)</td>
</tr>
<tr>
<td>Day 14*</td>
<td>Sustained, n (%)</td>
<td>104 (20%)</td>
<td>164 (31%)</td>
<td>1.59 (1.28, 1.97)</td>
</tr>
<tr>
<td>Day 21*</td>
<td>Sustained, n (%)</td>
<td>178 (34%)</td>
<td>214 (41%)</td>
<td>1.21 (1.03, 1.41)</td>
</tr>
</tbody>
</table>

Kaplan-Meier plot of time to achieving sustained (≥48 h) symptom alleviation

Median time to sustained (≥48 h) symptom alleviation: not reached
Probability of symptom alleviation over the first 21 days: 41% in sotrovimab arm, 34% in placebo arm; log-rank test p=0.002

*Sustained symptom alleviation defined as absence of the majority of core symptoms of COVID-19 (except for cough or fatigue, where scoring no more than ‘somewhat’ in severity was allowed, and loss of smell or taste). Patients only achieved sustained symptom alleviation if they had scored questionnaires showing alleviation for 2 consecutive days.
Median time to symptom alleviation was 4 days with sotrovimab vs 6 days with placebo.

Kaplan-Meier plot of time to achieving symptom alleviation

Median time to symptom alleviation: sotrovimab, 4 days; placebo, 6 days

Probability of symptom alleviation over the first 21 days: 94.9% in sotrovimab arm, 92.9% in placebo arm; log-rank test p<0.001

Sensitivity analysis (post-hoc)*: symptom alleviation defined as having a total score ≤1 and all domain scores ≤1, excluding sense domain (FLU-PRO manual definition)

*data from Week 24 database
LIMITATIONS

Potential for bias due to missing questionnaire data

• Completed questionnaires were available from >80% of participants on Day 1 and ~50% at Day 21 in both treatment groups

Possible contributing factors include difficulties with set-up and administration of electronic questionnaires due to rapid study initiation (patients less likely to complete paper version)
CONCLUSIONS

Sotrovimab provided statistically significant and rapid (within 1 to 2 days) improvements in patient-reported COVID-19 symptoms, as measured by the FLU-PRO Plus questionnaire.

Sotrovimab increased the proportion of patients achieving symptom alleviation at any given time over 21 days.

Median time to symptom alleviation was shorter with sotrovimab (4 days) than with placebo (6 days).

Results provide further evidence for the benefits of sotrovimab in providing symptom alleviation in patients at high risk for severe morbidity and mortality from COVID-19.