Remdesivir for the treatment of Covid-19 – Preliminary report.

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This study presents the preliminary results of a multi-centre randomized controlled trial of Remdesivir versus placebo in adults hospitalized with Covid-19 and evidence of lower respiratory tract involvement.

QUESTION The PICO of the study is as follows;

P – adults hospitalized with Covid-19 and evidence of lower respiratory tract involvement
I – Remdesivir
C – placebo
O – time to recovery (discharge from hospital or hospitalization only for infection control purposes)

METHODS Adults hospitalized at 60 trial sites and 13 subsites with laboratory confirmed SARS-CoV-2 were randomly assigned in a 1:1 ratio to Remdesivir (intravenous 200mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or matching placebo (intravenous normal saline). Analysis was stratified by study site and disease severity (severe and mild-moderate disease). The primary outcome was the time to recovery defined as the first day on which a participant satisfied categories 1,2, or 3 on an 8-category scale (category 1; not hospitalized with no limitations of activities, category 2; not hospitalized but limitation of activities or home oxygen requirement or both, category 3; hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care (hospitalization was for infection control reasons)).

RESULTS preliminary results were available for 1059 of 1063 randomised participants. The median number of days between symptom onset and randomisation was 9 (interquartile range 6-12) and 88% of participants had severe disease at enrolment (the majority of these with baseline score of 6). Median recovery time was 11 days (95%CI 9-12) with Remdesivir and 15 days (95% CI 13-29) with placebo. The rate ratio of 1.32 95% CI 1.12-1.55 reflects a 32% improvement in recovery with Remdesivir. Mortality by 14 days was 7.1% with Remdesivir and 11.9% with placebo (hazard ratio 0.70 95% CI 0.47-1.04). Serious adverse events occurred in 114/538 (21%) in the Remdesivir group and 141/521 (27%) in the placebo group.

DISCUSSION The following points were discussed;

Some key information was missing from the main text (e.g. inclusion/ exclusion criteria, randomisation block size). Though this information was reported in the supplementary data, it was difficult to find. Randomisation, blinding and follow-up appeared adequate.

The initial primary study outcome – difference in clinical status among patients treated with Remdesivir compared to placebo at day 15 – became a secondary outcome during the trial. The change was made in light of emerging data on the protracted nature of disease, and concern that a single assessment at day 15 would have missed differences. Though the data for the initial outcome is presented in the trial report, clinicians present felt that difference in clinical status is the more clinically useful outcome.

Time to recovery was reported for prespecified subgroups (Fig 2) including duration of symptoms before randomisation, which found a larger rate ratio for recovery in participants randomised during the first 10 days after onset. However, statistical advice was that these analyses should be cautiously interpreted (and tests of interaction would have been useful).

The Kaplan-Meier curve for survival in the overall population (Figure S3 Panel A) shows that approximately 10% of participants in both arms died during the trial. However the number of participants at risk reduces by more than 10% after 15-18 days indicating limited follow up of most of the study population. With few participants in the 'tails' of the curve, interpretation drawn from this area of the curve is unreliable (curves should have been truncated at about 24 days).

It was noted that though this was a publicly funded trial, Gilead Sciences (Remdesivir manufacturer) employees participated in protocol development and regular meetings. Given the limited availability of the drug, it was felt this was acceptable. It was noted Gilead's royalty free sharing of the molecule (until emergency declared over or credible alternative available).

OVERALL SUMMARY The results of the trial are promising but based on preliminary analysis with limited follow-up. Existing research analysing studies stopped early for benefit, has shown effects are overestimated and as such the results of this study should be interpreted cautiously. The results of The Solidarity Trial (which will have approximately similar numbers in the Remdesivir arm as in this trial) and further follow up of participants in this trial, will provide more definitive data on the effectiveness of Remdesivir as a treatment for coronavirus disease 2019.