Supplemental Digital Content

Supplemental digital content has been provided by the authors to give readers additional information about their work.

Supplement to: Remdesivir for Severe COVID-19 versus a Cohort Receiving Standard of Care

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For the GS-US-540-5773 and GS-US-540-5807 Investigators
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Supplemental Digital Content 2. Additional methods of the GS-US-540-5807 study

Primary endpoint (use of the ordinal scale)

The ordinal scale methodology was selected for the primary endpoint as it prioritizes patient recovery and survival outcomes, and is recommended by the National Institute for Health and Care Excellence Guide for COVID-19 evidence collection [1] and the WHO R&D Blueprint expert group [2]. The scale was a modified version of that used by Cao et al. in the study of lopinavir–ritonavir in severe COVID-19 [3], and that proposed by the draft WHO R&D Blueprint COVID-19 Therapeutic Trial Synopsis [2]. Variations of the ordinal scale have been used previously in influenza trials [4, 5] and are being implemented into other ongoing COVID-19 studies (e.g. NCT04315948, NCT04280705, and NCT04332991).

Secondary endpoints

The secondary endpoints of GS-US-540-5807 are: proportion of oxygen saturation >94% on room air on day 14; proportion of negative SARS-CoV-2 polymerase chain reaction test on day 14; proportion of subjects on room air on day 14; proportion of clinical improvement from day 1 on a 7-point ordinal scale on day 14; proportion of ≥1-point improvement in clinical status on day 14; proportion of the use of mechanical ventilation/ECMO (extracorporeal membrane oxygenation); and duration of hospitalization (days).

Data collection, missing data, abstraction, and management

Data collection

On days 1, 7 (±1) and 14 (±2) and at discharge, data on vital signs, radiographic findings, laboratory testing, oxygenation status, clinical status on the 7-point ordinal scale, and COVID-19 treatments were collected. On day 28, oxygenation and imaging were collected (where available). Date of death and presumed cause of death were recorded up to day 28.
|                          | Day 1 | Day 7 (±1) and 14 (±2) or last observation |
|--------------------------|-------|-------------------------------------------|
| Medical history          | X     |                                           |
| Pregnancy test           | X     |                                           |
| Vital signs (SpO\textsubscript{2}, temperature) | X (plus body weight and height) | X |
| Laboratory testing (includes white blood cell count, creatinine, total bilirubin, AST, ALT, SARS-CoV-2 testing) | X (plus radiographic findings) | X |
| Oxygenation (includes oxygen supplementation) | X | X |
| Ordinal scale            | X     | X                                         |
| Treatments for CovidCOVID-19 | X | X |

ALT, alanine transferase; AST, aspartate transferase; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

**Outliers**

Outliers were identified during the data management and data analysis process, but no sensitivity analyses were done to evaluate the impact of outliers on efficacy or safety outcomes.

**Data abstraction**

Pseudonymised data were retrospectively abstracted from electronic and non-electronic medical records and entered into a secure electronic care report form or transferred via secure server.
Data management

Electronic Case Report Forms (eCRFs) were developed by Gilead Clinical Data Management and Electronic Data Capture (EDC) Programmers using the Medidata Rave EDC System to capture data generated at the sites. The eCRFs were reviewed by study team members and validated by Gilead Clinical Data Management and EDC Programming prior to use. CRF Completion Guidelines containing data entry and data handling instructions were provided to each site. An alternative data collection method was utilized for some sites which entailed transferring data from sites’ clinical data records (electronic medical record systems) to Gilead via a secure server. A Data Transfer Guide was provided to the sites detailing the data elements to be included in the transfer and instructions for securely transferring the data. Data validation checks and listings were developed and reviewed by Gilead, focusing on key data elements impacting the study endpoints defined in the protocol to ensure data quality. Any data discrepancies were queried, tracked, and documented until they were resolved.
**Supplemental Digital Content 3. Description of full analysis set**

The primary analysis set for the efficacy comparison of the remdesivir-cohort compared with standard-of-care treated patients (non-remdesivir-cohort) is the full analysis set (FAS). The FAS consists of: ex-Italy patients in the FAS from GS-US-540-5773 with non-missing day 1 and day 14 clinical status (7-point ordinal scale) after applying imputation rules; and patients in the All Enrolled Analysis Set from Study GS-US-540-5807 with non-missing day 1 and day 14 clinical status (7-point ordinal scale) after applying the analysis visit window and imputation rules, with a stabilized weight after the inverse probability treatment weighting (IPTW) was applied.

Patients in the FAS from GS-US-540-5773 are defined as those who are randomized into Part A of the study (first 400 patients) and have received at least 1 dose of remdesivir. The All Enrolled Analysis Set for Study GS-US-540-5807 includes all patients from Study GS-US-540-5807 who meet the study inclusion criteria and the exclusion criteria listed below that match the exclusion criteria from Study GS-US-540-5773. If data for an exclusion criterion listed below is missing or unknown for a patient, this patient will be considered not meeting that exclusion criterion:

- On venous-arterial ECMO at day 1 visit
- ALT or AST greater than 5 x upper limit of normal at day 1 visit
- Creatinine clearance less than 50 mL/min using the Cockcroft-Gault formula at day 1 visit
- Pregnancy
- Breastfeeding
**Supplemental Digital Content 4. Exclusion of Italian patients**

As of April 10, 2020 (the interim analysis data cut-off), data from Study GS-US-540-5807 were mainly from US sites and did not include any data from patients in Italy. At the time of the cut-off, the epidemiological data coming from Italy suggested a considerably higher mortality rate than that seen in other countries [6], possibly due to an overwhelmed healthcare system or for another unknown reason. Additionally, data from the remdesivir compassionate use cohort suggested an unexplained higher mortality from Italian than non-Italian sites (Gilead data on file). Thus, there was a concern at the time of data cut-off that the inclusion of Italian patients from GS-US-540-5773 in the remdesivir-cohort, in the absence of Italian patients in the non-remdesivir-cohort, could potentially have introduced a severe bias to the analysis, which the inverse probability treatment weighting would not be able to balance. Therefore, an *a priori* decision was made to exclude patients from Italy from the interim analysis. However, it is planned to include Italian patients from both studies in a future analysis, after Italian patients have been recruited into GS-US-540-5807.
Supplemental Digital Content 5. Distribution balance for propensity score without (Figure A) and with hydroxychloroquine (Figure B)

Balance diagnostic plot illustrating the standardized difference between patients in Studies 5807 and 5773 (x-axis) for each variable included in IPTW analysis (y-axis). The plot demonstrates balance between cohorts before and after weighting.

Based on the propensity score calculated for each subject, subjects with their propensity score outside of the common support region (overlap in the range of propensity scores across the remdesivir-and non-remdesivir-cohorts) were trimmed and not included in the analysis. After the stabilized IPTW (using propensity score) was applied, all the baseline factors included in the propensity score model were well balanced with the absolute standardized difference <0.1 except for chronic obstructive pulmonary disease (absolute standardized difference=0.2, Figure A). For the sensitivity analysis, that included hydroxychloroquine in the propensity score, the standardized difference for hydroxychloroquine was improved, but other important factors were further imbalanced (Figure B).

Figure A: Balanced diagnostic plot of baseline factors before and after IPTW - without hydroxychloroquine in the propensity score
Figure B: Balanced diagnostic plot of baseline factors before and after IPTW - with hydroxychloroquine in the propensity score.
### Supplemental Digital Content 6. Summary of potential medications for COVID-19 treatment

| Group                          | Medication                                                                 |
|--------------------------------|-----------------------------------------------------------------------------|
| Azithromycin                   | Azithromycin                                                               |
|                                | Azithromycin dihydrate                                                      |
| Biologic                       | Interferon                                                                 |
|                                | Interferon beta                                                            |
|                                | Investigational drug                                                       |
|                                | Plasma                                                                      |
|                                | Sarilumab                                                                  |
|                                | Siltuximab                                                                 |
|                                | Tocilizumab                                                                |
| HIV protease inhibitor         | Atazanavir sulfate                                                         |
|                                | Cobicistat                                                                 |
|                                | Cobicistat; darunavir                                                      |
|                                | Cobicistat; darunavir ethanolate                                            |
|                                | Cobicistat; elvitegravir; emtricitabine; tenofovir                          |
|                                | Cobicistat; elvitegravir; emtricitabine; tenofovir alafenamide fumarate     |
|                                | Darunavir                                                                  |
|                                | Lopinavir; ritonavir                                                       |
| Hydroxychloroquine group       | Aminoquinolines                                                            |
|                                | Chloroquine                                                                |
|                                | Hydroxychloroquine                                                         |
|                                | Hydroxychloroquine sulfate                                                 |
| Ribavirin                      | Ribavirin                                                                   |
Supplemental Digital Content 7. Inverse probability of treatment weighting (IPTW) method and weighted sample size

To balance the baseline characteristics of the remdesivir and non-remdesivir cohorts and to minimise losses in sample size and thus statistical power, the inverse probability of treatment weighting (IPTW) method was applied to form a synthetic sample in which the distribution of baseline characteristics was independent of treatment. The IPTW used to estimate the average treatment effect (ATE) for the $i^{th}$ patient was calculated as follows:

$$w_i = \frac{T_i}{PS_i} + \frac{1 - T_i}{1 - PS_i}$$

where $T_i$ is the treatment indicator for the $i^{th}$ subject which is 1 for subjects from the remdesivir cohort, 0 for subjects from the non-remdesivir cohort, $PS_i$ is the propensity score for the $i^{th}$ subject, the probability that the $i^{th}$ subject is assigned to the remdesivir cohort. However, one concern with IPTW is that if a subject from the treatment group has a propensity score close to 0 or a subject from the control group has a propensity score close to 1, the IPTW ATE weight can be large, which may lead to the estimate of treatment effect with a large variance. As a result, in order to reduce the potential large variance, stabilized IPTW ATE weight for the $i^{th}$ subject was used in the analysis, which is defined as:

$$w_{i,\text{stabilized}} = \frac{T_i}{PS_i} \cdot p_t + \frac{1 - T_i}{1 - PS_i} \cdot (1 - p_t)$$

where $p_t$ is the proportion of subjects in the treatment group, which is equal to the number of subjects in the treatment group divided by the sum of the number of subjects in the treatment and control groups.

After applying the IPTW method, the weighted sample size, as the sum of the weights, was expected to modestly change from the original sample size: some of the subjects’ weights were smaller than 1, e.g. the first 10 subjects in the example table below; whereas some of the subjects’ weights were larger than 1, e.g. last 10 subjects in the table below. In this example, the pre-weighted sample size was 20 patients from each study. After weighting, the sample size for study 5807 is 19.3 and for study 5773 is 20.05.

| Patient Number* | Study 5773 patient weight | Study 5807 patient weight |
|----------------|---------------------------|---------------------------|
| 1              | 0.83                      | 0.79                      |
| 2              | 0.83                      | 0.79                      |
| 3              | 0.84                      | 0.79                      |
| 4              | 0.84                      | 0.79                      |
| 5              | 0.84                      | 0.79                      |
| 6              | 0.85                      | 0.79                      |
|    | 0.86 | 0.79 |
|----|------|------|
| 8  | 0.86 | 0.79 |
| 9  | 0.87 | 0.79 |
| 10 | 0.87 | 0.79 |
| 11 | 1.15 | 1.13 |
| 12 | 1.15 | 1.13 |
| 13 | 1.15 | 1.13 |
| 14 | 1.15 | 1.13 |
| 15 | 1.15 | 1.13 |
| 16 | 1.15 | 1.13 |
| 17 | 1.16 | 1.17 |
| 18 | 1.16 | 1.17 |
| 19 | 1.16 | 1.17 |
| 20 | 1.16 | 1.17 |

| Total patient number | Patient number after weighting | Patient number after weighting |
|----------------------|--------------------------------|-------------------------------|
| 20                   | 20.05                          | 19.31                         |

*Patient numbers are for example purposes and do not represent any actual patient identification numbers.*
Supplemental Digital Content 8. Distribution of patients by country and mortality outcome

In study 5807, there were no patients enrolled in Germany, Spain, Hongkong, and Taiwan and a higher proportion of patients from the US versus Study 5773. Conversely, in Study 5773, there were no patients from the UK. Although there are differences in recovery rate on day 14 between countries, the overall recovery rate was mainly driven by the US population, as the majority of patients were enrolled in the US for both cohorts. After weighting, 286/312 (91.7%) subjects for study 5773 and 745/818 (91.1%) for study 5807 were from the US.

| Country      | Remdesivir cohort (study 5773) | Non-remdesivir cohort (study 5807) |
|--------------|--------------------------------|-----------------------------------|
|              | Total weighted sample size | Weighted recovery rate (%) | Total weighted sample size | Weighted recovery rate (%) |
| USA          | 286                           | 75                                 | 745                        | 60                          |
| Germany      | 1                              | 100                                | 0                          | NA                          |
| Spain        | 15                             | 61                                 | 0                          | NA                          |
| UK           | 0                              | NA                                 | 58                         | 52                          |
| Hong Kong    | 2                              | 76                                 | 0                          | NA                          |
| Korea        | 5                              | 49                                 | 7                          | 0                           |
| Singapore    | 3                              | 76                                 | 8                          | 71                          |
| Taiwan       | 1                              | 100                                | 0                          | NA                          |
| **Total**    | **312**                        | **74**                             | **818**                    | **59**                      |

Numbers and percentages may not add up due to rounding
References

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   https://www.nice.org.uk/Media/Default/About/what-we-do/Scientific-advice/COVID-19-scientific-
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2. WHO. WHO R&D blueprint COVID-19 therapeutic trial synopsis. Available at: 
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