Should Remdesivir Be Used for the Treatment of Patients With COVID-19? Rapid, Living Practice Points From the American College of Physicians (Version 1)

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**KEY QUESTION 1**
What are the effectiveness and harms of remdesivir in patients with coronavirus disease 2019 (COVID-19)?

**KEY QUESTION 2**
Do effectiveness and harms vary by symptom duration, disease severity, and treatment duration?

**BACKGROUND**
Remdesivir, a broad-spectrum antiviral agent administered intravenously, was developed and studied as a potential treatment for Ebola virus disease and Marburg virus infection (1–3). In vitro and in vivo preclinical studies found antiviral activity for remdesivir against corona-like viruses, including Middle East respiratory syndrome coronavirus (4–6), severe acute respiratory syndrome coronavirus (SARS-CoV-1) (5), the circulating human coronaviruses HCoV-OC43 and HCoV-229E (7), and SARS-CoV-2 (8). Currently, the effectiveness of remdesivir is being tested as a treatment for patients infected with SARS-CoV-2 (COVID-19) and has been authorized for emergency use for treating COVID-19, by the U.S. Food and Drug Administration (9) in the United States, and in other countries (10–13).

The American College of Physicians (ACP) Scientific Medical Policy Committee (SMPC) based these rapid and living practice points (Table 1) on a systematic evidence review conducted by the U.S. Department of Veterans Affairs (VA) Evidence Synthesis Program in Minneapolis, Minnesota (14) (Appendix, available at Annals.org). This version of the practice points, based on a search completed on 3 June 2020 and updated through 31 August 2020, was approved by the ACP’s Executive Committee of Board of Regents on behalf of the Board of Regents on 14 August 2020 and submitted to Annals of Internal Medicine on 13 August 2020. Because many studies are planned or under way, literature surveillance is ongoing, with updates currently planned for every 2 months through December 2021. The target audience for these practice points includes clinicians and the public. The target patient population includes all nonpregnant patients with COVID-19.

Critical and important outcomes were determined by the evidence review team in collaboration with methodological and content experts. The magnitude of the effect (such as little or no, slight, modest, or large) for critical outcomes was defined as follows: little or no effect refers to a change of <10% in an outcome; slight effect refers to a change of 10% to 50% in an outcome; modest effect refers to a change of >50% but ≤200% in an outcome; large effect refers to a change of >200% in an outcome.

Table 1. Practice Points

| **Use remdesivir** for 5 days as a treatment for patients with moderate† COVID-19 |
| **Use remdesivir** for 5 days as a treatment for patients with severe† COVID-19 who do not require mechanical ventilation or extracorporeal membrane oxygenation (ECMO). |
| Consider extending the use of remdesivir* to 10 days in patients with severe† COVID-19 requiring mechanical ventilation or ECMO within a 5-day course. |

**COVID-19 = coronavirus disease 2019.**

*Remdesivir is not recommended for patients with an alveolar-arterial oxygen gradient ≥25 mm Hg or an estimated glomerular filtration rate <60 mL/min/1.73 m² (see further details in Table 3).†Within the evidence reviewed, severe COVID-19 is defined as hospitalized patients meeting ≥1 of the following criteria: radiographic infiltrates on imaging or clinical assessment, an oxygen saturation level ≤94% on room air, tachypnea (respiratory rate >24 breaths per minute without supplemental oxygen), or the need for supplemental oxygen or mechanical ventilation; moderate COVID-19 is defined as hospitalized patients with radiographic evidence of pulmonary infiltrates and oxygen saturation >94% on room air; and mild COVID-19 was not defined (14).
and important outcomes was determined by applying thresholds prespecified by the evidence review team (Table 2). Table 3 presents clinical considerations, the Figure and Tables 4 and 5 summarize current evidence, and Table 6 identifies additional evidence gaps. Appendix Tables 1 and 2 (available at Annals.org) present the data estimates supporting the practice points.

**Rationale**

**Use of Remdesivir in Patients With Moderate COVID-19**

Table 4 summarizes the current evidence on the use of remdesivir in patients with moderate COVID-19.

Overall, the current evidence points toward a net benefit for remdesivir in patients with moderate COVID-19 and suggests that a shorter treatment period (5 days) is as effective as a longer one (10 days), with no increase in harms (16). Low-certainty evidence shows that the 5-day course may be superior for mortality, recovery, and clinical improvement; however, low-certainty evidence also shows improvement for several outcomes when comparing the 10-day course to placebo. Thus, the SMPC believes that it is reasonable to consider extending treatment to 10 days for patients whose condition does not improve during the initial 5 days. Because the overall certainty of evidence is low across the comparisons, the SMPC has flagged course duration as a particular area of interest for further discussion and close monitoring.

Evidence from 1 randomized controlled trial (RCT) (16) compared a 5- or 10-day course of remdesivir with standard care, although “standard care” was not defined. Among outcomes rated as critical, remdesivir (5- or 10-day course) may reduce mortality slightly and result in slightly fewer serious adverse events compared with standard care (low certainty). Evidence also showed a modest increase in recovery and clinical improvement with a 5-day course, and slight increases in recovery and clinical improvement with a 10-day course, compared with standard care (low certainty). A

| Outcome | Little/No Effect | Small Effect $\dagger$ | Modest Effect $\ddagger$ | Large Effect $§$ |
|---------|------------------|------------------------|------------------------|-----------------|
| Critical outcomes | | | | |
| All-cause mortality, % | <1 | 1 to 2.9 | 3 to 4.9 | ≥5 |
| Recovery, % | <2 | 2 to 4.9 | 5 to 9.9 | ≥10 |
| Length of stay, d | <1 | ≥1 to 2 | NA | ≥3 |
| Serious adverse event, % | <1 | 1 to 4.9 | 5 to 9.9 | ≥10 |
| Important outcomes | | | | |
| Time to recovery, d | <1 | ≥1 to 2 | NA | ≥3 |
| Clinical improvement, % | <2 | 2 to 4.9 | 5 to 9.9 | ≥10 |
| Time to clinical improvement, d | <1 | ≥1 to 2 | >2 to <3 | ≥3 |
| Mechanical ventilation or ECMO, % | <1 | 1 to 4.9 | 5 to 9.9 | ≥10 |
| Nonserious/any adverse event, % | <2 | 2 to 4.9 | 5 to 19.9 | ≥20 |

ECMO = extracorporeal membrane oxygenation; NA = not applicable.
* Measured as absolute risk difference (when not otherwise specified).
† Described as “Slight increase or decrease.”
‡ Described as “Moderate increase or decrease.”
§ Described as “Large increase or decrease.”
5-day course may also reduce time to recovery slightly (low certainty), but evidence is insufficient to make any conclusions about a 10-day course. Both courses of remdesivir (5- and 10-day) may slightly reduce the need for invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) (low certainty). However, the occurrence of any adverse events may increase with a 5-day course (slight effect) and with a 10-day course (modest effect) compared with standard care (low certainty).

Evidence comparing a 5- versus 10-day course of remdesivir (16) showed that a 5-day course may reduce mortality slightly and may increase recovery (modest effect) and clinical improvement (slight effect) compared with a 10-day course (low certainty). However, evidence showed little to no difference between the 2 courses in reducing the need for invasive mechanical ventilation or ECMO (low certainty), and evidence is insufficient to show a difference in time to recovery. Evidence for potential harms showed that a 5-day course may result in fewer adverse events (any) compared with a 10-day course (modest effect), although the shorter course may not result in fewer serious adverse events (low certainty).

No evidence was found for any effect on other critical outcomes (hospital length of stay) or important outcomes (time to clinical improvement, nonserious adverse events) with either course in patients with moderate COVID-19. No evidence was identified as to whether outcomes vary by symptom duration in patients with moderate COVID-19.

Use of Remdesivir in Patients With Severe COVID-19

Table 5 summarizes the current evidence on the use of remdesivir in patients with severe COVID-19 (15, 17, 18).

Overall, the current evidence points toward a net benefit for a 10-day course of remdesivir in patients with severe COVID-19 (including those requiring mechanical ventilation or ECMO at baseline) compared with placebo (15, 18). No evidence was found comparing a 5-day course of remdesivir with placebo or standard care in patients with severe COVID-19. In the absence of this direct evidence, the SMPC looked at the indirect evidence that a 5-day course is as effective as a 10-day course of remdesivir with the same, or probably fewer, potential harms in patients with severe COVID-19 not requiring mechanical ventilation or ECMO at baseline (17). In addition, the compliance data showed that a 10-day course (10 doses) was used in 40.8% of patients with severe COVID-19 (including those requiring mechanical ventilation or ECMO at baseline), and 38.1% received fewer than 10 doses because they recovered and were discharged from the hospital (15). However, for a subgroup of patients with severe COVID-19 receiving mechanical ventilation or ECMO at day 5, extending treat-
### Table 4. Evidence Summary for Patients With Moderate* COVID-19: What Information Does the Evidence Provide?

| Outcome                               | Study Design (Patients, n) | Evidence                                                                 | Certainty of Evidence† |
|---------------------------------------|---------------------------|--------------------------------------------------------------------------|------------------------|
| **Remdesivir (5-d Course) vs. Placebo/Standard Care in Patients With Moderate* COVID-19** |                           |                                                                         |                        |
| Critical outcomes                     |                           |                                                                         |                        |
| Mortality                             | 1 RCT (391)               | Remdesivir (5-d course) may reduce mortality slightly compared with standard care (16) | Low                    |
| Recovery‡                             | 1 RCT (391)               | Remdesivir (5-d course) may result in a modest increase in recovery compared with standard care (16) | Low                    |
| Hospital length of stay               | NA                        | No evidence                                                              | No evidence            |
| Serious adverse events§                | 1 RCT (391)               | Remdesivir (5-d course) may reduce serious adverse events slightly compared with standard care (16) | Low                    |
| Important outcomes                    |                           |                                                                         |                        |
| Time to recovery‡                     | 1 RCT (391)               | Remdesivir (5-d course) may reduce time to recovery slightly compared with standard care (16) | Low                    |
| Clinical improvement‖                 | 1 RCT (391)               | Remdesivir (5-d course) may result in a modest increase in clinical improvement compared with standard care (16) | Low                    |
| Time to clinical improvement‖         | NA                        | No evidence                                                              | No evidence            |
| Invasive mechanical ventilation/ECMO  | 1 RCT (391)               | Remdesivir (5-d course) may reduce the need for invasive mechanical ventilation or ECMO slightly compared with standard care (16) | Low                    |
| Nonserious adverse events§             | NA                        | No evidence                                                              | No evidence            |
| Any adverse events§                   | 1 RCT (391)               | Remdesivir (5-d course) may increase adverse events slightly compared with standard care (16) | Low                    |
| **Remdesivir (10-d Course) vs. Placebo/Standard Care in Patients With Moderate* COVID-19** |                           |                                                                         |                        |
| Critical outcomes                     |                           |                                                                         |                        |
| Mortality                             | 1 RCT (393)               | Remdesivir (10-d course) may reduce mortality slightly compared with standard care (16) | Low                    |
| Recovery‡                             | 1 RCT (393)               | Remdesivir (10-d course) may increase recovery slightly compared with standard care (16) | Low                    |
| Hospital length of stay               | NA                        | No evidence                                                              | No evidence            |
| Serious adverse events§                | 1 RCT (393)               | Remdesivir (10-d course) may reduce serious adverse events slightly compared with standard care (16) | Low                    |
| Important outcomes                    |                           |                                                                         |                        |
| Time to recovery‡                     | 1 RCT (393)               | Very uncertain about the effect of remdesivir (10-d course) compared with standard care on time to recovery (16) | Insufficient           |
| Clinical improvement‖                 | 1 RCT (393)               | Remdesivir (10-d course) may increase clinical improvement slightly compared with standard care (16) | Low                    |
| Time to clinical improvement‖         | NA                        | No evidence                                                              | No evidence            |
| Invasive mechanical ventilation/ECMO  | 1 RCT (393)               | Remdesivir (10-d course) may reduce the need for invasive mechanical ventilation or ECMO slightly compared with standard care (16) | Low                    |
| Nonserious adverse events§             | NA                        | No evidence                                                              | No evidence            |
| Any adverse events§                   | 1 RCT (393)               | Remdesivir (10-d course) may result in a modest increase in adverse events compared with standard care (16) | Low                    |
| **Remdesivir (5-d Course) vs. Remdesivir (10-d Course) in Patients With Moderate* COVID-19** |                           |                                                                         |                        |
| Critical outcomes                     |                           |                                                                         |                        |
| Mortality                             | 1 RCT (384)               | Remdesivir 5-d course may reduce mortality slightly compared with remdesivir 10-d course (16) | Low                    |
| Recovery‡                             | 1 RCT (384)               | Remdesivir 5-d course may result in a modest increase in recovery compared with remdesivir 10-d course (16) | Low                    |
| Hospital length of stay               | NA                        | No evidence                                                              | No evidence            |
| Serious adverse events§                | 1 RCT (384)               | Remdesivir 5-d course may not reduce serious adverse effects compared with remdesivir 10-d course (16) | Low                    |
| Important outcomes                    |                           |                                                                         |                        |
| Time to recovery‡                     | NA                        | Very uncertain about the effect of remdesivir 5-d course compared with remdesivir 10-d course on time to recovery (16) | Insufficient           |
| Clinical improvement‖                 | 1 RCT (384)               | Remdesivir 5-d course may increase clinical improvement slightly compared with remdesivir 10-d course (16) | Low                    |
| Time to clinical improvement‖         | NA                        | No evidence                                                              | No evidence            |

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COVID-19 = coronavirus disease 2019; ECMO = extracorporeal membrane oxygenation; NA = not applicable; RCT = randomized controlled trial.

* Within the evidence reviewed, severe COVID-19 is defined as hospitalized patients meeting ≥1 of the following criteria: radiographic infiltrates on imaging, an oxygen saturation level ≤94% on room air, tachypnea (respiratory rate >24 breaths per minute without supplemental oxygen), or need for supplemental oxygen or mechanical ventilation; moderate COVID-19 is defined as hospitalized patients with radiographic infiltrates and oxygen saturation >94% on room air; and mild COVID-19 was not defined (14).

† Certainty of evidence: insufficient, confidence is inadequate to assess the likelihood of benefit (benefit minus harm) of an intervention or its impact on a health outcome; low, confidence in the effect is limited because the true effect may be substantially different from the estimated effect; moderate, confidence in the effect is moderate because the true effect is probably close to the estimated effect, but a sizable possibility exists that it is substantially different; high, confidence that the true effect is close to the estimated effect.

‡ Recovery is defined as discharge from the hospital or hospitalization for infection control purposes only in 1 RCT (15, 18) and discharge from the hospital or hospitalized but not requiring supplemental oxygen or ongoing medical care in 3 RCTs (17).

§ Serious adverse events reported in studies included in the evidence review (15–17) were acute coronary syndrome, acute kidney injury, acute respiratory distress syndrome, acute respiratory failure, increased aminotransferase levels, atrial fibrillation, bronchitis, cardiac arrest, cardiopulmonary failure, increased D-dimer, deep venous thrombosis, diabetic ketoacidosis, dyspnea, endotracheal intubation, decreased glomerular filtration rate, hemorrhage of lower digestive tract, hypotension, hypoxia, ileus, lung abscess, mechanical ventilation, multiple organ dysfunction syndrome, respiratory distress, respiratory failure, pneumothorax, pulmonary embolism, pulmonary failure, recurrence of COVID-19, septic shock, sepsis, shock, tachycardia, thrombocytopenia, and viral pneumonia. Nonserious adverse events reported in studies included in the evidence review (16) were acidosis, acute kidney injury, alkalosis, increased aspartate aminotransferase, anemia, atrial fibrillation, decreased blood albumin, increased blood bilirubin, increased blood glucose, increased blood creatinine, deep venous thrombosis, delirium, dyspnea, decreased glomerular filtration rate, decreased hemoglobin, hyperglycemia, hypotension, hypoalbuminemia, hypoxia, decreased lymphocyte count, lymphopenia, pneumonia, increased prothrombin time, pyrexia, respiratory distress, increased aminotransferase levels, and decreased urine creatinine clearance. Any adverse events reported in studies included in the evidence review (15, 17) were acute kidney injury, acute respiratory failure, increased alanine aminotransferase, anemia, increased aspartate aminotransferase, increased blood glucose, increased blood lipids, increased blood urea nitrogen, constipation, hyperlipidemia, hypoalbuminemia, hypokalemia, hypotension, insomnia, nausea, increased neutrophil count, rash, respiratory failure, increased serum potassium, reduced serum sodium, thrombocytopenia, increased total bilirubin, vomiting, and increased leukocyte count.

$ Clinical improvement is defined as a 2-point reduction in patients’ hospitalization status on a 6-point ordinal scale (1 = live discharge to 6 = death) or live discharge from the hospital, whichever came first (18), and as an improvement of at least 2 points from baseline on a 7-point ordinal scale (1 = death to 7 = discharged from hospital) (17).

Use of Remdesivir to Treat COVID-19

Table 4—Continued

| Outcome                               | Study Design (Patients, n) | Evidence                          | Certainty of Evidence† |
|---------------------------------------|---------------------------|----------------------------------|------------------------|
| Invasive mechanical ventilation/ECMO  | 1 RCT (384)               | Remdesivir 5-d course may not reduce the need for invasive mechanical ventilation or ECMO compared with remdesivir 10-d course (16) | Low                    |
| Nonserious adverse events§            | NA                        | No evidence                       | No evidence            |
| Any adverse events§                   | 1 RCT (384)               | Remdesivir 5-d course may result in a modest reduction in adverse events compared with remdesivir 10-d course (16) | Low                    |

For a 10-day course of remdesivir compared with placebo, the outcomes of mortality (18), time to recovery (15), and time to clinical improvement (18) did not vary by symptom duration (≤10 days vs. >10 days), and time to recovery also did not vary by baseline oxygenation or ventilation requirements (15). No evidence was found on whether other outcomes vary by symptom duration.

Evidence from 1 RCT (17) that compared a 5-day course with a 10-day course of remdesivir showed that the 5-day course may reduce mortality slightly versus the 10-day course in patients with severe COVID-19 who did not require mechanical ventilation or ECMO at baseline (17). However, a post hoc analysis suggested that a 5- versus a 10-day course might result in a large increase in mortality among the most critical patients of those with severe COVID-19 (those receiving mechanical ventilation or ECMO at day 5) (17). Treatment beyond 5 days did not improve mortality among patients who were receiving noninvasive positive pressure ventilation or high-flow oxygen, those receiving low-flow oxygen, or those breathing ambient air. This finding suggests that extending treatment to 10 days for patients receiving mechanical ventilation or ECMO at day 5 may be beneficial (17). Compared with a 10-day course, a 5-day course shows a modest increase in recovery, a slight decrease in the time to recovery, and a modest reduction in the need for mechanical ventilation or ECMO (low certainty). Evidence for potential harms showed that a 5-day course of remdesivir results in fewer serious adverse events (large effect, low certainty) and a fewer number of any adverse events (slight effect, low certainty) compared with a 10-day course.

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### Table 5. Evidence Summary for Patients With Severe* COVID-19: What Information Does the Evidence Provide?

| Outcome | Study Design (Patients, n) | Evidence | Certainty of Evidence† |
|---------|---------------------------|----------|------------------------|
| **Remdesivir (5-d Course) vs. Placebo/Standard Care in Patients With Severe* COVID-19** | | | |
| **Critical outcomes** | | | |
| Mortality | 2 RCTs (1300) | Remdesivir (10-d course) may reduce mortality slightly compared with placebo (15, 18)‡ | Low |
| Recovery|| 2 RCTs (1300) | Remdesivir (10-d course) probably results in a large increase in recovery compared with placebo (15, 18)‡ | Moderate |
| Hospital length of stay | 1 RCT (237) | Remdesivir (10-d course) may not reduce hospital length of stay compared with placebo (15, 18)‡ | Low |
| Serious adverse events¶ | 2 RCTs (1300) | Remdesivir (10-d course) probably results in a modest reduction in serious adverse events compared with placebo (15, 18)‡ | Moderate |
| **Important outcomes** | | | |
| Time to recovery|| 1 RCT (1063) | Remdesivir (10-d course) may result in a large reduction in time to recovery compared with placebo (15)‡ | Low |
| Clinical improvement** | 1 RCT (237) | Remdesivir (10-d course) may result in a modest increase in clinical improvement compared with placebo (15) | Low |
| Time to clinical improvement** | 1 RCT (237) | Remdesivir (10-d course) may reduce time to clinical improvement slightly compared with placebo (15) | Low |
| Invasive mechanical ventilation/ECMO | 2 RCTs (1300) | Remdesivir (10-d course) may reduce the need for mechanical ventilation or ECMO slightly compared with placebo (15, 18)‡ | Low |
| Nonserious adverse events¶ | 1 RCT (1063) | Remdesivir (10-d course) may reduce nonserious adverse events slightly compared with placebo (15) | Low |
| Any adverse events¶ | 1 RCT (237) | Very uncertain about the effect of remdesivir (10-d course) compared with placebo on adverse events (18) | Insufficient |

| **Remdesivir (5-d Course) vs. Remdesivir (10-d Course) in Patients With Severe* COVID-19** | | | |
| **Critical outcomes** | | | |
| Mortality | 1 RCT (397) | Remdesivir 5-d course may reduce mortality slightly compared with remdesivir 10-d course (17)‡‡ | Low |
| Recovery|| 1 RCT (397) | Remdesivir 5-d course may result in a modest increase in recovery compared with remdesivir 10-d course (17)‡‡ | Low |
| Hospital length of stay | NA | No evidence | No evidence |
| Serious adverse events¶ | 1 RCT (397) | Remdesivir 5-d course may result in a large reduction in serious adverse events compared with remdesivir 10-d course (17)‡‡ | Low |
| **Important outcomes** | | | |
| Time to recovery|| 1 RCT (397) | Remdesivir 5-d course may reduce time to recovery slightly compared with remdesivir 10-d course (17)‡‡ | Low |
| Clinical improvement** | 1 RCT (397) | Remdesivir 5-d course may result in a modest increase in clinical improvement compared with remdesivir 10-d course (17)‡‡ | Low |
| Time to clinical improvement** | NA | No evidence | No evidence |
| Invasive mechanical ventilation/ECMO | 1 RCT (397) | Remdesivir 5-d course may result in a modest reduction in the need for mechanical ventilation or ECMO compared with remdesivir 10-d course (17)‡‡ | Low |
| Nonserious adverse events¶ | NA | No evidence | No evidence |
| Any adverse events¶ | 1 RCT (397) | Remdesivir 5-d course may reduce adverse events slightly compared with remdesivir 10-d course (17)‡‡ | Low |

*Continued on following page*
Table 5—Continued

COVID-19 = coronavirus disease 2019; ECMO = extracorporeal membrane oxygenation; NA = not applicable; RCT = randomized controlled trial.

* Within the evidence reviewed, severe COVID-19 is defined as hospitalized patients meeting ≥1 of the following criteria: radiographic infiltrates on imaging, an oxygen saturation level ≤94% on room air, tachypnea (respiratory rate >24 breaths per minute without supplemental oxygen), or the need for supplemental oxygen or mechanical ventilation; moderate COVID-19 is defined as hospitalized patients with radiographic infiltrates and oxygen saturation >94% on room air; and mild COVID-19 was not defined (14).

† † Certainty of evidence: insufficient, confidence is inadequate to assess the likelihood of benefit (benefit minus harm) of an intervention or its impact on a health outcome; low, confidence in the effect is limited because the true effect may be substantially different from the estimated effect; moderate, confidence in the effect is moderate because the true effect is probably close to the estimated effect, but a sizable possibility exists that it is substantially different; high, confidence that the true effect is close to the estimated effect.

‡ Most (88.7%) of the participants enrolled in 1 RCT (15, 18) had severe disease, so this study is analyzed as being representative of patients with severe disease.

§ Determined from a subgroup analysis; the certainty of evidence was not assessed for this comparison.

¶ Recovery is defined as discharge from the hospital or hospitalization for infection control purposes only in 1 RCT (15, 18) and as discharge from the hospital or hospitalized but not requiring supplemental oxygen or ongoing medical care in 3 RCTs (17, 18).

†‡ Serious adverse events reported in studies included in the evidence review (15-17) were acute coronary syndrome, acute kidney injury, acute respiratory distress syndrome, acute respiratory failure, increased aminotransferase levels, atrial fibrillation, bronchitis, cardiac arrest, cardiopulmonary failure, increased D-dimer, deep venous thrombosis, diabetic ketoacidosis, dyspnea, endotracheal intubation, decreased glomerular filtration rate, hemorrhage of lower digestive tract, hypotension, hypoxia, ileus, lung abscess, mechanical ventilation, multiple organ dysfunction syndrome, respiratory distress, respiratory failure, pneumothorax, pulmonary embolism, pulmonary failure, recurrence of COVID-19, septic shock, sepsis, shock, tachycardia, thrombocytopenia, and viral pneumonia. Nonserious adverse events reported in studies included in the evidence review (16) were acidosis, acute kidney injury, alkalosis, increased aspartate aminotransferase, anemia, atrial fibrillation, decreased blood albumin, increased blood bilirubin, increased blood glucose, increased blood creatinine, deep venous thrombosis, delirium, dyspnea, decreased glomerular filtration rate, decreased hemoglobin, hyperglycemia, hypotension, hyperbilirubinemia, hypoxia, decreased lymphocyte count, lymphopenia, pneumonia, increased prothrombin time, pyrexia, respiratory distress, increased aminotransferase levels, and decreased urine creatinine clearance. Any adverse events reported in studies included in the evidence review (15, 17) were acute kidney injury, acute respiratory failure, increased alanine aminotransferase, anemia, increased aspartate aminotransferase, increased blood glucose, increased blood lipids, increased blood urea nitrogen, constellation, hyperlipidemia, hyperbilirubinemia, hypokalemia, hypotension, insomnia, nausea, increased neutrophil count, rash, respiratory failure, increased serum potassium, reduced serum sodium, thrombocytopenia, increased total bilirubin, vomiting, and increased leukocyte count.

** Clinical improvement is defined as a 2-point reduction in patients’ hospitalization status on a 6-point ordinal scale (1 = live discharge to 6 = death) or live discharge from the hospital, whichever came first (18), and as an improvement of at least 2 points from baseline on a 7-point ordinal scale (1 = death to 7 = discharged from hospital) (17).

‡‡ Patients requiring mechanical ventilation or ECMO were excluded from 1 RCT (17), so despite a few patients (3.3%) developing a requirement for invasive mechanical ventilation between screening and the beginning of the treatment, this study is analyzed as being representative of patients with severe disease not requiring mechanical ventilation or ECMO at baseline.

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Note: The Practice Points are developed by the SMPC of the ACP. The Practice Points are “guides” only and may not apply to all patients and all clinical situations. All Practice Points are considered automatically withdrawn or invalid 5 years after publication, or once an update has been issued.

Financial Statement: Financial support for the development of the Practice Points comes exclusively from the ACP operating budget.

Disclosures: All financial and intellectual disclosures of interest were declared and potential conflicts were discussed and managed. Dr. Obley participated in discussion of the practice points but was recused from authorship and voting due to a moderate-level conflict of interest (author of supporting systematic review). A record of disclosures of interest and management of conflicts of is kept for each SMPC meeting and conference call and can be viewed at https://www.acponline.org/about-acp/who-we-are/leadership/boards-committees-councils/scientific-medical-policy-committee/disclosure-of-interests-and-conflict-of-interest-management-summary-for-scientific-medical-policy. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M20-5831.

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Ann Intern Med. 2021;174:229-236. doi:10.7326/M20-5831

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**APPENDIX: PRACTICE POINTS DEVELOPMENT PROCESS**

The SMPC, in collaboration with staff from ACP’s Department of Clinical Policy, developed these practice points on the basis of a rapid and living systematic evidence review conducted by the VA Evidence Synthesis Program, Minneapolis, Minnesota (14). The SMPC comprises 11 internal medicine physicians representing various clinical areas of expertise and 1 public (nonclinician) member, and includes members with expertise in epidemiology, evidence synthesis, health policy, and guideline development. In addition to contributing clinical, scientific, and methodological expertise, Clinical Policy staff provided administrative support and liaised among the SMPC, the evidence review funding entity and evidence team, and the journal. Clinical Policy staff and the SMPC reviewed and prioritized potential topic suggestions from ACP members, SMPC members, and ACP governance. A committee subgroup, including the SMPC chair, worked with staff to draft the key questions and led the development of the practice points. Clinical Policy staff worked with the subgroup and an independent evidence review team to refine the key questions and determine appropriate evidence synthesis methods for each key question. Via conference calls and e-mail, Clinical Policy staff worked with the committee subgroup to draft the practice points on the basis of the results of the rapid and living systematic evidence review. The full SMPC reviewed and approved the final practice points. Before journal submission, ACP’s Executive Committee of the Board of Regents also reviewed and approved the practice points on behalf of the ACP Board of Regents. The evidence review team will continually update the evidence review. The ACP will update the practice points based on the evidence review by using the same process as the first version described above. Updates are currently planned for every 2 months through December 2021. The SMPC will continuously assess the priority of the topic and the overall state of evidence, including the anticipated rate of new evidence, and may choose to modify the update intervals accordingly (any modifications will be described in an Update Alert).
## Appendix Table 1. Estimates: Patients With Moderate* COVID-19†

| Outcome | Study Design (Patients, n) | Evidence | Certainty of Evidence‡ |
|---------|----------------------------|----------|------------------------|
| **Critical outcomes** | | | |
| Mortality (FU: 11 d) | 1 RCT (391) | Remdesivir 5-d course, 0% (0/191), vs. standard care, 2% (4/200); ARD, −2.0% (CI, −4.2% to −0.2%) (16) | Low |
| Recovery§ (FU: 11 d) | 1 RCT (391) | Remdesivir 5-d course, 73.8% (141/191), vs. standard care, 64% (128/200); ARD, 9.8% (CI, 0.7% to 18.9%) (16) | Low |
| Hospital length of stay | NA | No evidence | NA |
| Serious adverse events|| | | |
| Any adverse events|| | | |
| **Important outcomes** | | | |
| Time to recovery§ (FU: 11 d) | 1 RCT (391) | Remdesivir 5-d course, median 6 d (IQR, 5 to 10 d), vs. standard care, median 7 d (IQR, 4 to 15 d); HR, 1.18 (CI, 0.96 to 1.45) (16) | Low |
| Clinical improvement¶ (FU: 11 d) | 1 RCT (391) | Remdesivir 5-d course, 70.2% (134/191), vs. standard care, 60.5% (121/200); ARD, 9.7% (CI, 0.3% to 19%) (16) | Low |
| Time to clinical improvement¶ | NA | No evidence | NA |
| Invasive mechanical ventilation/ECMO (FU: 11 d) | 1 RCT (391) | Remdesivir 5-d course, 0% (0/191), vs. standard care, 2.0% (4/200); ARD, −2.0% (CI, −4.2% to −0.2%) (16) | Low |
| Nonserious adverse events|| | | |
| Any adverse events|| | | |
| **Remdesivir (10-d Course) vs. Placebo/Standard Care in Patients with Moderate* COVID-19** | | | |
| Mortality (FU: 11 d) | 1 RCT (393) | Remdesivir 10-d course, 1.0% (2/193), vs. standard care, 2.0% (4/200); ARD, −1.0% (CI, −3.4% to 1.4%) (16) | Low |
| Recovery§ (FU: 11 d) | 1 RCT (393) | Remdesivir 10-d course, 68.4% (132/193), vs. standard care, 64% (128/200); ARD, 4.4% (CI, −4.9% to 13.7%) (16) | Low |
| Hospital length of stay | NA | No evidence | NA |
| Serious adverse events|| | | |
| Any adverse events|| | | |
| **Important outcomes** | | | |
| Time to recovery§ (FU: 11 d) | 1 RCT (393) | Remdesivir 10-d course, median 8 d (IQR, 4 to 13 d), vs. standard care, median 7 d (IQR, 4 to 15 d); HR, 1.11 (CI, 0.90 to 1.37) (16) | Insufficient |
| Clinical improvement¶ (FU: 11 d) | 1 RCT (393) | Remdesivir 10-d course, 65.3% (126/193), vs. standard care, 60.5% (121/200); ARD, 4.8% (CI, −4.8% to 14.3%) (16) | Low |
| Time to clinical improvement¶ | NA | No evidence | NA |
| Invasive mechanical ventilation/ECMO (FU: 11 d) | 1 RCT (393) | Remdesivir 10-d course, 0.5% (1/193), vs. standard care, 2.0% (4/200); ARD, −1.5% (CI, −3.7% to 0.7%) (16) | Low |
| Nonserious adverse events|| | | |
| Any adverse events|| | | |
| **Remdesivir (5-d Course) vs. Remdesivir (10-d Course) in Patients with Moderate* COVID-19** | | | |
| Mortality (FU: 11 d) | 1 RCT (384) | Remdesivir 5-d course, 0% (0/191), vs. remdesivir, 10-d course, 1.0% (2/193); ARD, −1.0% (CI, −2.8% to 0.7%) (16) | Low |
| Recovery§ (FU: 11 d) | 1 RCT (384) | Remdesivir 5-d course, 73.8% (141/191), vs. remdesivir, 10-d course, 68.4% (132/193); ARD, 5.4% (CI, −3.6% to 14.5%) (16) | Low |
| Hospital length of stay | NA | No evidence | NA |
| Serious adverse events|| | | |
| Any adverse events|| | | |

*Note: Estimates for patients with moderate COVID-19 based on evidence from randomized controlled trials (RCTs). Evidence certainty levels: Low = insufficient evidence, Insufficient = low certainty.

†Moderate COVID-19 includes patients with symptoms and signs of COVID-19 consistent with pneumonia on radiographic imaging and no clinical findings consistent with severe COVID-19.

‡Evidence certainty levels: Low = insufficient evidence, Insufficient = low certainty.
### Appendix Table I—Continued

| Outcome | Study Design (Patients, n) | Evidence | Certainty of Evidence‡ |
|---------|---------------------------|----------|-------------------------|
| **Important outcomes** | | | |
| Time to recovery§ (FU: 11 d) | 1 RCT (384) | Remdesivir 5-d course, median 6 d (IQR, 5 to 10 d), vs. remdesivir 10-d course, median 8 d (IQR, 4 to 13 d); HR not reported (16) | Insufficient |
| Clinical improvement¶ (FU: 11 d) | 1 RCT (384) | Remdesivir 5-d course, 70.2% (134/191), vs. remdesivir 10-d course, 65.3% (126/193); ARD, 4.9% (CI, −4.5% to 14.2%) (16) | Low |
| Time to clinical improvement¶ | NA | No evidence | NA |
| Invasive mechanical ventilation/ECMO | 1 RCT (384) | Remdesivir 5-d course, 0% (0/191), vs. remdesivir 10-d course, 0.5% (1/193); ARD, −0.5% (CI, −1.9% to 0.9%) (16) | Low |
| Nonserious adverse events| NA | No evidence | NA |
| Any adverse event¶ (FU: 11 d) | 1 RCT (384) | Remdesivir 5-d course, 51.3% (98/191), vs. remdesivir 10-d course, 58.5% (113/193); ARD, −7.2% (CI, −17.2% to 2.7%) (16) | Low |

ARD = absolute risk difference; COVID-19 = coronavirus disease 2019; ECMO = extracorporeal membrane oxygenation; FU = follow-up; HR = hazard ratio; IQR = interquartile range; NA = not applicable; RCT = randomized controlled trial.

* Within the evidence reviewed, severe COVID-19 is defined as hospitalized patients meeting ≥1 of the following criteria: radiographic infiltrates on imaging, an oxygen saturation level ≤94% on room air, tachypnea (respiratory rate >24 breaths per minute without supplemental oxygen), or the need for supplemental oxygen or mechanical ventilation; moderate COVID-19 is defined as hospitalized patients with radiographic infiltrates and oxygen saturation >94% on room air; and mild COVID-19 was not defined (14).

† Statistically significant findings are in boldface.

‡ Certainty of evidence: insufficient, confidence is inadequate to assess the likelihood of benefit (benefit minus harm) of an intervention or its impact on a health outcome; low, confidence in the effect is limited because the true effect may be substantially different from the estimated effect; moderate, confidence in the effect is moderate because the true effect is probably close to the estimated effect, but a sizable possibility exists that it is substantially different; high, confidence that the true effect is close to the estimated effect.

§ Recovery is defined as discharge from the hospital or hospitalization for infection control purposes only in 1 RCT (15, 18) and as discharge from the hospital or hospitalized but not requiring supplemental oxygen or ongoing medical care in 3 RCTs (17, 18).

¶ Serious adverse events reported in studies included in the evidence review (15-17) were acute coronary syndrome, acute kidney injury, acute respiratory distress syndrome, acute respiratory failure, increased aminotransferase levels, atrial fibrillation, bronchitis, cardiac arrest, cardiopulmonary failure, increased D-dimer, deep venous thrombosis, diabetic ketoacidosis, dyspnea, endotracheal intubation, decreased glomerular filtration rate, hemorrhage of lower digestive tract, hypotension, hypoxia, ileus, lung abscess, mechanical ventilation, multiple organ dysfunction syndrome, respiratory distress, respiratory failure, pneumothorax, pulmonary embolism, pulmonary failure, recurrence of COVID-19, septic shock, sepsis, shock, tachycardia, thrombocytopenia, and viral pneumonia. Nonserious adverse events reported in studies included in the evidence review (16) were acidosis, acute kidney injury, alkalosis, increased aspartate aminotransferase, anemia, atrial fibrillation, decreased blood albumin, increased blood bilirubin, increased blood glucose, increased blood creatinine, deep venous thrombosis, delirium, dyspnea, decreased glomerular filtration rate, decreased hemoglobin, hyperglycemia, hypertension, hyperalbuminemia, hypotension, hypoxia, decreased lymphocyte count, lymphopenia, pneumonia, increased prothrombin time, pyrexia, respiratory distress, increased aminotransferase levels, and decreased urine creatinine clearance. Any adverse events reported in studies included in the evidence review (15, 17) were acute kidney injury, acute respiratory failure, increased alanine aminotransferase, anemia, increased aspartate aminotransferase, increased blood glucose, increased blood lipids, increased blood urea nitrogen, constipation, hyperlipidemia, hyperalbuminemia, hypokalemia, hypertension, insomnia, nausea, increased neutrophil count, rash, respiratory failure, increased serum potassium, reduced serum sodium, thrombocytopenia, increased total bilirubin, vomiting, and increased leukocyte count.

¶¶ Clinical improvement is defined as a 2-point reduction in patients’ hospitalization status on a 6-point ordinal scale (1 = live discharge to 6 = death) or live discharge from the hospital, whichever came first (18), and as an improvement of at least 2 points from baseline on a 7-point ordinal scale (1 = death to 7 = discharged from hospital) (17).
### Appendix Table 2. Estimates: Patients With Severe* COVID-19†

| Outcome | Study Design | Evidence | Certainty of Evidence‡ |
|---------|--------------|-----------|-------------------------|
| No evidence | | | |
| **Critical outcomes** | | | |
| Mortality (FU: range, 14–28 d) | 2 RCTs (1300) | Remdesivir 10-d course, 5.9% (32/538), vs. placebo, 10.4% (54/521); ARD, −4.4% (95% CI, −7.7% to −1.1%) measured at 14 d (15)§ | Low |
| Remdesivir 10-d course, 13.9% (22/158), vs. placebo, 12.8% (10/78); ARD, 1.1% (CI, −8.1% to 10.3%) measured at 28 d (18) | | |
| Note: The effect of remdesivir (10-d course) by symptom duration[18]: • ≤10 d of symptoms: remdesivir, 11% (8/71), vs. placebo, 15% (7/47); ARD, −3.6% (CI, −16.2% to 9.9%) | | |
| • >10 d of symptoms: remdesivir, 14% (12/84), vs. placebo, 10%, ARD, 4.6% (CI, −8.2% to 17.4%) | | |
| | | | |
| Recovery¶ (FU: range, 28–29 d) | 2 RCTs (1300) | Remdesivir 10-d course, 62.1% (334/538), vs. placebo, 52.4% (273/521); ARD, 9.7% (CI, 3.7% to 15.6%) measured at 29 d (15)§ | Moderate |
| Remdesivir 10-d course, 70.7% (106/150), vs. placebo, 63.6% (49/77); ARD, 7.0% (CI, −6.0% to 20.0%) measured at 28 d (18) | | |
| Hospital length of stay (FU: 28 d) | 1 RCT (237) | Remdesivir 10-d course, median 25 d (IQR, 16 to 38 d), vs. placebo, median 24 d (IQR, 18 to 36 d); MD, 0 d (CI, −4.0 to 4.0 d) | Low |
| Serious adverse events** (FU: range, 28–29 d) | 1 RCT (1063) | Remdesivir 10-d course, 8.2% (13/158), vs. placebo, 12.8% (10/78); ARD, −4.6% (CI, −13.2% to 4.0%) measured at 28 d (15)§ | Moderate |
| Nonserious adverse events** (FU: 29 d) | 1 RCT (1063) | Remdesivir 10-d course, 28.8% (156/541), vs. placebo, 33.0% (172/522); ARD, −4.1% (CI, −9.7% to 1.4%) (15)§ | Low |
| Any adverse events** (FU: 28 d) | 1 RCT (237) | Remdesivir 10-d course, 65.8% (102/155), vs. placebo, 64.1% (50/78); ARD, 1.7% (CI, −11.3% to 14.7%) (18) | Insufficient |
| **Important outcomes** | | | |
| Time to recovery¶ (FU: 29 d) | 1 RCT (1063) | Remdesivir 10-d course, median 11 d (IQR, 9 to 12 d), vs. placebo, median 15 d (IQR, 13 to 19 d); P < 0.001 (15)§ | Low |
| Note: The effect of remdesivir (10-d course) by symptom duration[15]§: • ≤10 d of symptoms: rate ratio, 1.28 (CI, 1.05 to 1.57) | | |
| • >10 d of symptoms: rate ratio, 1.31 (CI, 1.12 to 1.54) | | |
| Clinical improvement†† (FU: 28 d) | 1 RCT(237) | Remdesivir 10-d course, 65.2% (103/158), vs. placebo, 57.7% (45/78); ARD, 7.5% (CI, −5.7% to 20.7%) (18) | Low |
| Time to clinical Improvement¶†† (FU: 28 d) | 1 RCT(237) | Remdesivir 10-d course, median 21 d (IQR, 13 to 28 d), vs. placebo, median 23 d (IQR, 18 to 36 d); HR, 1.23 (CI, 0.87 to 1.75) (18) | Low |
| Invasive mechanical ventilation/ECMO (FU: 28 d) | 2 RCTs (1300) | Remdesivir 10-d course, 13.8% (60/434), vs. placebo, 17.6% (72/410); ARD, −3.7% (CI, −8.6% to 1.2%) measured at 15 d (15)§ | Low |
| Remdesivir 10-d course, 8.2% (13/158), vs. placebo, 12.8% (10/78); ARD, −4.6% (CI, −13.2% to 4.0%) (18) | | |
| Nonserious adverse events** (FU: 29 d) | 1 RCT (1063) | Remdesivir 10-d course, 28.8% (156/541), vs. placebo, 33.0% (172/522); ARD, −4.1% (CI, −9.7% to 1.4%) (15)§ | Low |
| Any adverse events** (FU: 28 d) | 1 RCT (237) | Remdesivir 10-d course, 65.8% (102/155), vs. placebo, 64.1% (50/78); ARD, 1.7% (CI, −11.3% to 14.7%) (18) | Insufficient |

Continued on following page
### Appendix Table 2—Continued

| Outcome | Study Design (Patients, n) | Evidence | Certainty of Evidence‡ |
|---------|--------------------------|----------|------------------------|
| **Important outcomes** | | | |
| Time to recovery¶ (FU: 14 d) | 1 RCT(397) Remdesivir 5-d course, median 10 d (IQR, 6 to 18 d), vs. remdesivir 10-d course, median 11 d (IQR, 7 d to not estimable); HR, 0.81 (CI, 0.64 to 1.04) (17)‡‡ | Low |
| Clinical improvement†† (FU: 14 d) | 1 RCT(397) Remdesivir 5-d course, 64.5% (129/200), vs. remdesivir 10-d course, 54.3% (107/197); baseline-adjusted ARD, 6.5% (CI, −2.8% to 15.7%) (17)‡‡ | Low |
| Time to clinical improvement†† | NA No evidence | No evidence |
| Invasive mechanical ventilation/ECMO (FU: 14 d) | 1 RCT (397) Remdesivir 5-d course, 8.0% (16/200), vs. remdesivir 10-d course, 16.8% (33/197); ARD, −8.8% (CI, −15.2% to −2.3%) (17)‡‡ | Low |
| Nonserious adverse events** (FU: 14 d) | NA No evidence | No evidence |
| Any adverse events** | 1 RCT (397) Remdesivir 5-d course, 70.5% (141/200), vs. remdesivir 10-d course, 73.6% (145/197); ARD, −3.1% (CI, −11.9% to 5.7%) (17)‡‡ | Low |

ARD = absolute risk difference; COVID-19 = coronavirus disease 2019; ECMO = extracorporeal membrane oxygenation; FU = follow-up; HR = hazard ratio; IQR = interquartile range; MD = mean difference; NA = not applicable; RCT = randomized controlled trial.

* Within the evidence reviewed, severe COVID-19 is defined as hospitalized patients meeting ≥1 of the following criteria: radiographic infiltrates on imaging, an oxygen saturation level ≤94% on room air, tachypnea (respiratory rate >24 breaths per minute without supplemental oxygen), or the need for supplemental oxygen or mechanical ventilation; moderate COVID-19 is defined as hospitalized patients with radiographic infiltrates and oxygen saturation >94% on room air; and mild COVID-19 was not defined (14).

† Statistically significant findings are in bold.

‡ Certainty of evidence: insufficient, confidence is inadequate to assess the likelihood of benefit (benefit minus harm) of an intervention or its impact on a health outcome; low, confidence in the effect is limited because the true effect may be substantially different from the estimated effect; moderate, confidence in the effect is moderate because the true effect is probably close to the estimated effect, but a sizable possibility exists that it is substantially different; high, confidence that the true effect is close to the estimated effect.

§ Most of the participants (88.7%) enrolled in 1 RCT (15, 18) had severe disease, so this study is analyzed as being representative of patients with severe disease.

¶ The certainty of evidence was not assessed for this comparison determined from a subgroup analysis.

†† Recovery is defined as discharge from the hospital or hospitalization for infection control purposes only in 1 RCT (15, 18) and as discharge from the hospital or hospitalized but not requiring supplemental oxygen or ongoing medical care in 3 RCTs (17, 18).

** Serious adverse events reported in studies included in the evidence review (15-17) were acute coronary syndrome, acute kidney injury, acute respiratory distress syndrome, acute respiratory failure, increased amino transferase levels, atrial fibrillation, bronchitis, cardiac arrest, cardiopulmonary failure, increased D-dimer, deep venous thrombosis, diabetic ketoacidosis, dyspnea, endotracheal intubation, decreased glomerular filtration rate, hemorrhage of lower digestive tract, hypotension, hypoxia, ileus, lung abscess, mechanical ventilation, multiple organ dysfunction syndrome, respiratory distress, respiratory failure, pneumothorax, pulmonary embolism, pulmonary failure, recurrence of COVID-19, septic shock, sepsis, shock, tachycardia, thrombocytopenia, and viral pneumonia. Nonserious adverse events reported in studies included in the evidence review (16) were acidosis, acute kidney injury, alkalosis, increased aspartate amino transferase, anemia, atrial fibrillation, decreased blood albumin, increased blood bilirubin, increased blood glucose, increased blood creatinine, deep venous thrombosis, delirium, dyspnea, decreased glomerular filtration rate, decreased hemoglobin, hyperglycemia, hypertension, hypoalbuminemia, hypotension, hypoxia, decreased lymphocyte count, lymphopenia, pneumonia, increased prothrombin time, pyrexia, respiratory distress, increased amino transferase levels, and decreased urine creatinine clearance. Any adverse events reported in studies included in the evidence review (15, 17) were acute kidney injury, acute respiratory failure, increased alanine amino transferase, anemia, increased aspartate amino transferase, increased blood glucose, increased blood lipids, increased blood urea nitrogen, constipation, hyperlipidemia, hypoalbuminemia, hypokalemia, hypotension, insomnia, nausea, increased neutrophil count, rash, respiratory failure, increased serum potassium, reduced serum sodium, thrombocytopenia, increased total bilirubin, vomiting, and increased leukocyte count.

†† Clinical improvement is defined as a 2-point reduction in patients’ hospitalization status on a 6-point ordinal scale (1 = live discharge to 6 = death) or live discharge from the hospital, whichever came first (18), and as an improvement of at least 2 points from baseline on a 7-point ordinal scale (1 = death to 7 = discharged from hospital) (17).

‡‡ Patients requiring mechanical ventilation or ECMO were excluded from 1 RCT (17), so despite a few patients (3.3%) developing a requirement for invasive mechanical ventilation between screening and the beginning of the treatment, this study is analyzed as being representative of patients with severe disease not requiring mechanical ventilation or ECMO at baseline.