Alternative Pricing Models for Remdesivir and Other Potential Treatments for COVID-19

UPDATED REPORT

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Updates Since Last Version

We first highlight the updates made to this report compared to the version of this report that was previously posted on June 24th, 2020.

ICER-COVID Model 1: Remdesivir Cost Recovery

- No method updates.

ICER-COVID Model 2: Remdesivir Cost-Effectiveness Analysis

- Generated incremental cost-effectiveness ratios given the announcement from the manufacturer of remdesivir that included a price per vial for remdesivir ($520 per vial for private payers and $390 per vial for select government-sponsored payers). In these analyses, we assume the private payer price given the government-sponsored price is only for those government payers who directly purchase remdesivir from the manufacturer, which represents a minority of government-sponsored payers in the United States.
- Updated the standard of care in the base-case to include dexamethasone for patients with severe and critical COVID-19 in alignment with the World Health Organization's updated clinical care guidance. In alignment with this clinical care guidance, we assume the use of dexamethasone as standard of care for individuals in the moderate to severe population with an ordinal score of 5 or higher from ACTT-1. We used newly available peer-reviewed data from the RECOVERY trial to adjust the standard of care mortality and progression to ventilation from ACTT-1 to include dexamethasone as part of standard of care.
- Updated the base-case analysis to not include a survival benefit associated with remdesivir given newly available meta-analysis findings published by the SOLIDARITY trial consortium.
- Provided cost-effectiveness estimates and price benchmarks for a moderate to severe population separately from a mild population given the expanded population included in the formal FDA approval and newly available evidence specifically for the mild population that shows a differing effect between the two populations.
- Used newly published final results from ACTT-1 that suggested a benefit from remdesivir of reducing the progression to high-flow oxygen, noninvasive ventilation, mechanical ventilation, and ECMO, as well as small updates to other model inputs previously published in the preliminary results of ACTT-1, for the moderate to severe population.
- Updated the model structure to account for the four ordinal scores defined based on respiratory support needed (ordinal scores 4 through 7) and updated the model programming to allow for differences between baseline (i.e. ordinal score prior to receipt of remdesivir treatment) ordinal score and highest ever ordinal score.
- Fit functional forms to age- and sex-adjusted mortality, age-adjusted utility, and age-adjusted health care costs to allow for more precision estimating these elements in the Markov model.

ICER-COVID Model 1: Remdesivir Cost Recovery

The cost recovery methods have not been updated since the June 24th, 2020 version of this report.

Objective

The objective of this updated analysis was to provide estimates for the pricing of remdesivir in the treatment of COVID-19 that would represent a "cost recovery" approach. In this updated analysis, we present two cost recovery pricing estimates: 1) a price per treatment course that covers the minimal costs of production of the treatment; and 2) a price per treatment course that covers the cost of production plus the projected short-term spending by the manufacturer for clinical research directly related to the use of remdesivir for COVID-19.

Methods

The conceptual elements of the ICER model for a cost recovery pricing estimate include: 1) the marginal cost of producing the next course of remdesivir therapy; 2) research and development costs provided by the manufacturer; 3) and research and development costs provided by the federal government. The cost recovery pricing estimates do not include the remdesivir administration-related costs.

For remdesivir, we continue to use as one part of our estimate the analysis on the cost of producing the next course of therapy from an article by Hill et all in the Journal of Virus Eradication (2020). Their methods sought to determine the "minimum" costs of production by calculating the cost of active pharmaceutical ingredients, which is combined with costs of excipients, formulation, packaging and a small profit margin. Their analysis calculated a total cost of producing the "final finished product" of $9.32 US for a 10-day course of treatment. We rounded that amount up to $10 for a 10-day course. If a 5-day course of treatment becomes a recommended course of therapy, then the marginal cost would accordingly shrink to $5. In addition to this estimate we are now citing the pricing announced by three early generic producers of remdesivir in Bangladesh and India. Beximco, a Bangladeshi company, has announced a price range for patients treated in that country that translates into approximately $590-$710 for a 10-day treatment course. The company is planning to discount its product to the Bangladesh government while charging higher prices to private clinics in the country, so its announced price may represent a higher margin over cost of production in order to recoup the costs of donated or discounted doses. The two India-based companies, Hetero and Cipla, plan to launch their offerings for use in India at prices that would translate into costs between $390-$780 for a 10-day course of treatment. Given the $10 estimate from Hill et al, and the new information on early generic pricing in developing countries, we have chosen in this update to frame the cost recovery pricing for remdesivir as a range between $10 and a rough mid-point generic pricing figure of $600 per 10-day course.

Our updated report includes an estimate of federal investment in the earlier phases of research on remdesivir. For this purpose we used an analysis performed by Knowledge Ecology International that has been referenced by Public Citizen and Congressional leaders. Importantly, while this estimate includes figures from early research efforts on remdesivir, it does not include consideration of federal spending on trials such as ACTT-1 and other ongoing trials specific to COVID-19.

The extent to which drug maker expenditures on research and development should be considered as an empirical element in considerations of pricing for new treatments is disputed. As we noted in our initial report, we believe there are important reasons to assume that sunk research and development costs should not be used to help justify the price of new drugs. For remdesivir, this perspective is strengthened by the fact that it was previously developed as part of a suite of agents for potential use in chronic Hepatitis C. Given that the manufacturer successfully launched other drugs for Hepatitis C, it seems reasonable that any sunk costs for research and development have already been recouped in the successful market experience of the manufacturer's other treatments in that area.

However, we believe that many policymakers will find it reasonable to include new research costs for studies directly related to evaluating the use of remdesivir for COVID-19 when calculating a cost recovery price benchmark. Therefore, in our updated analysis we have now added a pricing benchmark for cost recovery that includes projected spending by the sponsor (Gilead) for research directly related to understanding the risks and benefits of remdesivir for patients with COVID-19. We used public statements by Gilead for the purposes of estimating that they will spend approximately $1 billion in research on remdesivir in 2020 for this purpose.

In order to estimate the price that would recover these anticipated costs of research and development on remdesivir for COVID-19, it is necessary to choose the time course over which those costs must be recouped and a figure for the number of treatment courses that will be sold. There is great uncertainty about the time course and the scale of utilization of remdesivir, and market analysts have therefore projected a wide range of estimates for its uptake. Based on statements from Gilead, we have assumed at this stage that approximately 1 million treatment courses will be available and sold within the first year, and that the $1 billion cost should be recovered over this number of treated patients. Using these assumptions, the cost recovery pricing for remdesivir would need to include $1,000 for each course of treatment sold.

This second cost recovery pricing estimate is obviously very sensitive not only to the amount that Gilead actually spends on research and development, but on how many treatment courses are sold, and over what time course the costs are recouped. One possible policy approach to implementing a cost recovery pricing model would be to have a two-phase pricing model in which recovery of the costs for research and development is guaranteed within a short amount of time, resulting in a higher per-treatment price, followed by a reduction in price afterward to a level closer to the marginal cost of production.

Table 1 summarizes the key elements and findings of our updated cost recovery pricing model results. What remains unchanged is the need for policymakers and the public to debate whether these or other pricing paradigms are most appropriate if the goal is to create the right policy platform, for today and the future, to achieve rapid development and distribution of affordable treatments for a global pandemic.

Results

Table 1. Cost Recovery Model Results

Minimal Marginal Cost*	Manufacturer R&D Costs	Public Investment in R&D Costs	Total Cost Recovery Pricing Options
$5-$600	Prior to COVID-19: *No data available*	Prior to COVID-19: $70 million	Option 1. Minimal marginal cost only: **$5-$600**
	Directly related to COVID-19: **$1 billion** projected by Gilead for 2020	Directly related to COVID-19: *No data available*	Option 2. Minimal marginal cost and 2020 projected manufacturer R&D costs: **$1,005-$1,600**[¥]

***Per 5- or 10-day course of treatment*

[¥] *Assuming all costs recovered over 1 million patients receiving a 5- or 10-day treatment course*

ICER-COVID Model 2: Remdesivir Cost-Effectiveness Analysis

Objective

The objective of this updated analysis was to estimate the cost-effectiveness and corresponding cost-effectiveness price benchmarks of remdesivir plus standard of care versus standard of care alone for hospitalized patients with COVID-19, with results presented separately for 1) a moderate to severe hospitalized population, and 2) a mild hospitalized population.

Methods

We used a decision analytic model, populated by clinical evidence from ACTT-1, NCT04292730, RECOVERY, SOLIDARITY, and other sources, to estimate the costs, quality-adjusted life years (QALYs), and equal value of life-years gained (evLYGs) through hospital recovery or death. Without current evidence on the composition of COVID hospitalizations based on severity prior to receipt of treatment, we present estimates separately for the mild population and the moderate to severe population to reflect the differing effect of remdesivir in each population. We estimated the lifetime costs and outcomes of remdesivir and standard of care by assigning age-based average survival, utility, and health care costs for all those who recovered from the COVID-19 hospital event in a Markov Model. Consistent with prior ICER reviews, we generated evLYGs by assigning an average US general population utility of 0.851 to any observed life extensions within the Markov Model. We took the perspective of the healthcare system in which third-party insurers reimbursed hospitalizations through bundled payments. Costs and outcomes were discounted at 3% per year. Health system capacity measures, healthcare personnel impacts, and impacts beyond that of the health system were not included in this analysis.

Model inputs are detailed in Appendix Table 1 and provide a comprehensive description of evidence used to inform the model and other assumptions inherent to the model. The manufacturer of remdesivir announced a price of remdesivir of $520 per vial for private payers and $390 per vial for government-sponsored payers. Based on the FDA package insert, after a loading dose of 2 vials on day 1 of treatment, patients that do not require invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) are recommended to receive 1 vial per day for an additional 4 days following the loading dose (i.e. 5 days and 6 vials total for patients not requiring invasive mechanical ventilation and/or ECMO). Patients that require invasive mechanical ventilation and/or ECMO are recommended to receive 1 vial per day for an additional 9 days following the loading dose (i.e. 10 days and 11 vials total for patients requiring invasive mechanical ventilation and/or ECMO).

In the moderate to severe population, we assumed population characteristics consistent with ACTT-1. Namely, at randomization, 41% of patients received invasive mechanical ventilation and/or ECMO as their highest level of respiratory support and would thus have received 11 vials of remdesivir. The remaining 59% of patients were assumed to receive 6 vials total of remdesivir with the majority of these patients requiring either low-flow or high-flow oxygen prior to receiving remdesivir. Using these percentages and accounting for discontinuation reported in ACTT-1, the average treatment course consisted of 7.7 vials per patient, equating to an average treatment course price of $3,990 for the private payer. In the mild population, we assumed population characteristics similar to NCT04292730. Specifically, we defined the mild population as not requiring respiratory support (e.g. low- or high-flow oxygen, noninvasive ventilation, mechanical ventilation, ECMO) prior to receipt of remdesivir. Therefore, we assumed 0% of mild patients received invasive mechanical ventilation and/or ECMO and

100% received 6 vials total of remdesivir. Accounting for discontinuation reported in NCT04292730, the average mild treatment course consisted of 5.3 vials, equating to an average mild treatment course price of $2,750 for the private payer.

Due to the updated World Health Organization clinical care guidance for COVID-19, we now include dexamethasone within standard of care in our base-case analysis (this was a scenario analysis in the prior version of this report) for individuals in the moderate to severe population with an ordinal score of 5 or higher. We used the survival benefit associated with dexamethasone (for ordinal scores 5 and greater) to decrease the standard of care mortality observed in ACTT-1 to compare remdesivir plus an updated standard of care (including dexamethasone for ordinal scores 5 or greater) versus an updated standard of care alone (including dexamethasone for original scores 5 or greater). We also reduced the percent of the moderate to severe population eligible to progress to mechanical ventilation and/or ECMO by the effectiveness of dexamethasone on reducing such progression. In the mild population, dexamethasone was not included as part of standard of care to further align with the World Health Organization clinical care guidance.

Additional data on remdesivir's effect on mortality have been published or made available in pre-publication form since our last posting. The SOLIDARITY trial consortium reported findings from a meta-analysis of the available remdesivir evidence on mortality. Neither the hazard ratio of death across all populations, nor the hazard ratios of death stratified by lower risk and higher risk populations achieved statistical significance.

Results from the SOLIDARITY trial itself are major contributors to the meta-analysis. There are concerns about these results as SOLIDARITY has limitations: it has not yet been published in a peer-reviewed journal and there are aspects of the trial that need to be clarified; it was an open-label study; no diagnostic confirmation of infection was required, the timing of symptom duration before treatment initiation is unknown, as are the types of supportive care provided. In addition, multiple therapies studied in SOLIDARITY had trends toward increasing mortality, which is unexpected.

Despite these concerns, the size of the SOLIDARITY trial and the consistent failure of remdesivir to show statistically significant survival benefits across other trials lends weight to its conclusions and that of the meta-analysis conducted as part of the data release. After extensive consideration of all the data and discussion with external experts and the manufacturer, we feel that the most reasonable current interpretation of the existing data, in its totality, is to assume that remdesivir does not provide a significant survival benefit. Importantly, this assumption also must be reconsidered as data emerge from additional trials or further analyses from existing trials. But as a consequence of our updated assessment of the evidence, our base-case estimates have changed and now do not include an assumption of a survival benefit associated with remdesivir. We report estimates assuming a survival benefit among remdesivir-treated patients in a scenario analysis.

For the scenario analysis with assumed survival benefit, we used a hazard ratio of 0.91 in the moderate to severe population, which equated to the point estimate for the hazard ratio of death across the total population reported in the meta-analysis conducted by the SOLIDARITY trial consortium. The meta-analysis reported estimates stratified by ventilation status (no ventilation versus ventilation); however, that stratification did not correspond with our population definitions of mild versus moderate to severe. As previously defined, the ACTT-1 population is aligned with our definition of moderate to severe. We consider the ACTT-1 population to be more policy relevant for US clinicians or other decision makers

compared to focusing on the more severe criterion of ventilation prior to receipt of remdesivir. Therefore, we did not use the point estimate reported for the ventilated population of 1.16 given our moderate to severe population also included individuals not ventilated. Similarly, we did not use the point estimate reported for the non-ventilated population of 0.80 given our moderate to severe population also included individuals who were ventilated. The total point estimate of 0.91 represented a blend that was more representative of the population included in our moderate to severe population. We chose the total population point estimate from this meta-analysis conducted by the SOLIDARITY trial consortium as our evidence source for the survival benefit in the moderate to severe population rather than the point estimate from ACTT-1 because the meta-analysis included additional evidence and was within the confidence interval reported by ACTT-1 (95% confidence interval: 0.52, 1.03)

For the scenario analysis with assumed survival benefit in the mild population, we also used evidence from the meta-analysis conducted by the SOLIDARITY trial consortium. The hazard ratio of death used for this population was 0.804, which we calculated as a weighted average of the sub-groups from three studies (SOLIDARITY: no O_2, ACTT-1: no O_2, and NCT04292730: no O_2) that included this mild population per our definition. This point estimate of 0.804 was very similar to the point estimate reported by the SOLIDARITY trial consortium for the non-ventilated population. We chose the point estimate of 0.804 rather than the point estimate from NCT04292730 to include the largest sample size across studies and this point estimate across all three studies was within the confidence interval reported by NCT04292730 (95% confidence interval: 0.09, 2.80).

Although our base case now features no assumption of survival benefit from remdesivir, it does include new assumptions of an impact on third-party payer hospital payment based on newly published final results from ACTT-1. This new evidence suggests a benefit of remdesivir in reducing the progression of patients to requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation, and ECMO. This benefit was not described in the preliminary report of ACTT-1. To account for this new evidence, we updated the model programming to allow for differences between ordinal score prior to receipt of treatment and highest ever ordinal score. This reduction in the progression to higher levels of care results in cost offsets in healthcare utilization associated with remdesivir use because our base-case analysis assumed a bundled hospital payment that is based on the highest level of care.

We also included two supporting scenarios with the following assumptions:

1. Evaluation of remdesivir using evidence solely from the SOLIDARITY trial: This scenario assumed no effect of remdesivir on time to recovery, mortality, or length of stay as compared to standard of care. This scenario analysis is not our base-case given the limitations of the SOLIDARITY trial described above, and the fact that our base-case evidence on the impact of treatment on time to improvement, reduction in length of stay, and reduction in progression to ventilation came from a high-quality trial in the US health care system.
2. Hospitalization reimbursed as per diem: This scenario assumed that hospital payments were not bundled into a per hospital stay cost as is typical of most payers in the United States, but rather, are monetized based on per diem estimates to allow for cost savings for reduced hospital days. This scenario calculates the average hospital price per day needed to offset the price of remdesivir. This scenario is not our base-case given this reimbursement structure is not typical in the United States.

Updated Results

Table 1 reports the incremental cost-effectiveness ratios for remdesivir plus standard of care versus standard of care alone for our base-case analysis that does not assume a survival benefit and includes dexamethasone in the moderate to severe population for ordinal score 5 or higher. Remdesivir is associated with increases in total health system costs due to the acquisition cost of remdesivir despite including cost offsets associated with fewer people progressing to higher levels of respiratory support. Remdesivir is also associated with increases in QALYs. These differences between remdesivir and standard of care generate an incremental cost-effectiveness ratio of $298,160 in the moderate to severe population and $1,847,400 in the mild population.

Table 1. Incremental cost-effectiveness ratios for remdesivir plus standard of care as compared to standard of care alone, assuming no survival benefit

Moderate to Severe Hospitalized Population (ACTT-1)	Total Health System Costs	Life Years	QALYs	evLYG	Incremental Cost-Effectiveness Ratio ($/QALY)	Incremental Cost-Effectiveness Ratio ($/evLYG)
Remdesivir* plus Standard of Care	$313,450	15.164	12.189	12.189	**$298,160**	**$298,160**
Standard of Care (dexamethasone for ordinal scores 5 and higher)	$311,620	15.164	12.182	12.182		
Incremental	$1,830	0.000	0.006	0.006		
Mild Hospitalized Population (NCT04292730)	**Total Health System Costs^**	**Life Years**	**QALYs**	**evLYG**	**Incremental Cost-Effectiveness Ratio ($/QALY)**	**Incremental Cost-Effectiveness Ratio ($/evLYG)**
Remdesivir¥ plus Standard of Care	$318,380	16.997	13.704	13.704	**$1,847,400**	**$1,847,400**
Standard of Care (no dexamethasone)	$315,630	16.997	13.703	13.703		
Incremental	$2,750	0.000	0.001	0.001		

evLYG=equal value of life years gained
QALY=quality-adjusted life year
The estimates reported in the table are rounded and will not perfectly equate to the incremental cost-effectiveness ratios calculated in the righthand side of this table.
**Average price for a remdesivir treatment course in the moderate to severe population was $3,990.*
¥Average price for a remdesivir treatment course in the mild population was $2,750.

The average remdesivir treatment course price to meet commonly used cost-effectiveness benchmarks is provided in Table 2.

Table 2. Cost-effectiveness price benchmarks for the average treatment course of remdesivir, assuming no survival benefit[†]

Benchmark Threshold	Moderate to Severe Hospitalized Population* (ACTT-1)	Mild Hospitalized Population[¥] (NCT04292730)
$50,000 per QALY and per evLYG	**$2,470**	**$70**
$100,000 per QALY and per evLYG	$2,770	$150
$150,000 per QALY and per evLYG	$3,080	$220

evLYG=equal value of life years gained
QALY=quality-adjusted life year
Prices are rounded to the nearest ten.
**Average price for a remdesivir treatment course in the moderate to severe population was $3,990.*
[¥]*Average price for a remdesivir treatment course in the mild population was $2,750.*
[†]*Price benchmarks are the same regardless of QALY or evLYG outcome due to no survival benefit.*

In public health emergencies, cost-effectiveness analysis thresholds are often scaled downward, and we feel the pricing estimate related to the threshold of $50,000 per incremental quality-adjusted life year (and equal value of a life-year gained) remains the most policy-relevant consideration. At that threshold, the updated ICER-COVID analysis suggests a base-case price of approximately $2,470 per treatment course for a moderate to severe patient and $70 per treatment course for a mild patient. The estimates for the moderate to severe population are higher than our no survival benefit estimates reported in our previous posting. This is due to the newly available evidence that suggests cost offsets for remdesivir by way of reducing progression to higher levels of respiratory support. Further evidence-based revisions may increase or decrease the cost-effectiveness price benchmark.

As a scenario analysis, we assumed a survival benefit with remdesivir, consistent with point estimates from a meta-analysis reported from the SOLIDARITY trial. In this scenario analysis, remdesivir extends life and improves quality of life versus standard of care. Table 3 presents the cost-effectiveness price benchmarks for the average treatment course of remdesivir assuming a survival benefit. When remdesivir is used in the moderate to severe population, its price is likely aligned with value if a survival benefit exists. In the mild population, discounts on the remdesivir price would be needed for the $50,000 per QALY/evLYG benchmark even if there were a survival benefit.

Table 3. Cost-effectiveness price benchmarks for the average treatment course of remdesivir, assuming the point estimate for survival benefit calculated in a meta-analysis reported from the SOLIDARITY trial[†]

Benchmark Threshold	Moderate to Severe Hospitalized Population* (ACTT-1)	Mild Hospitalized Population[¥] (NCT04292730)
$50,000 per QALY and per evLYG	**$3,980-$4,140**	**$690-$760**
$100,000 per QALY and per evLYG	$8,750-$9,080	$2,620-$2,740
$150,000 per QALY and per evLYG	$13,520-$14,020	$4,540-$4,720

evLYG=equal value of life years gained
QALY=quality-adjusted life year
**Average price for a remdesivir treatment course in the moderate to severe population was $3,990.*
[¥]*Average price for a remdesivir treatment course in the mild population was $2,750.*

†*For all cost-effectiveness price benchmarks that include a range, the lower value was derived from QALYs and the higher value was derived from evLYGs.*

If evidence solely from SOLIDARITY were used to inform our model, remdesivir would have zero value in either population, given SOLIDARITY suggested no difference in mortality or progression to higher levels of care.

Last, if hospitalizations were paid for on a per diem basis and length of stay reductions are consistent with the ACTT-1 evidence, the average cost of a hospital day would need to be approximately $800 or more for the price of remdesivir to be offset in the moderate to severe population. Evidence does not suggest a length of stay reduction in the mild population and thus no cost offsets associated with remdesivir in the mild population would be expected.

Discussion

We will be continuing to monitor for new data on remdesivir and other emerging treatments for COVID-19, and we will perform further updates to our model as needed. In particular, there remains important uncertainty around the following elements that have a substantial impact on estimates of cost-effectiveness:

- The clinical outcomes associated with remdesivir when used in addition to and in comparison with dexamethasone.
    - The base-case model assumes only a reduction in standard of care mortality and a reduction in the percent eligible to progress to mechanical ventilation and/or ECMO from ACTT-1 based on dexamethasone effectiveness reported in the RECOVERY trial. There is no head-to-head evidence comparing remdesivir to dexamethasone. We acknowledge there was a small proportion of patients in ACTT-1 that received dexamethasone (~20%); however, given updated guidelines by the WHO, we anticipate this number would be closer to 90% of the ACTT-1 population. Thus, we made adjustments to the ACTT-1 standard of care evidence.
- Composition of COVID hospitalizations by severity.
    - We are not aware of a recent and generalizable source related to the percent of hospitalizations that are considered mild and the percent that are considered moderate to severe. Therefore, we present our cost-effectiveness findings for each population separately rather than attempt to blend them.
- Remdesivir effectiveness by different levels of severity.
    - The population characteristics used to inform our moderate to severe population were based on ACTT-1, although a very small proportion of the ACTT-1 population would be considered mild by our definition. Similarly, the population characteristics used to inform our mild population were based on NCT04292730, although a very small proportion of the NCT04292730 population would be considered moderate to severe by our definition. We do not think this small overlap biases our results given the overwhelming majority of the population from each evidence source aligning with our definitions. The appendix in ACTT-1 provided separate estimates based on population severity for some efficacy metrics and the estimates presented for the severe population were representative of the estimates of the overall ACTT-1 population.

Evidence could be further stratified into additional severity categories, although that likely does not reflect clinical practice given the reality that remdesivir is not only used in one category of severity or one ordinal score.

- COVID-19 hospital stay payments for different insurers. These reimbursed amounts vary by level of care as well as hospitalization stay duration.
    - The base-case model assumed variation in reimbursed amounts due to the highest level of care but no variation in reimbursed amounts due to potential differences in hospital length of stay.
- Differences in average costs or health decrements after recovering from COVID-19 as compared to the general US age- and sex-matched population.
    - The base-case model assumed no added costs or health decrements after recovering from COVID-19 as compared to the general US age- and gender-matched population.
- Comparative evidence on other relevant COVID-19 therapies alongside a rapidly changing standard of care.

APPENDIX

CEA Model Settings:

- Perspective: Health System
- Time Horizon: Lifetime
- Outcomes: Incremental costs, incremental QALYs, incremental evLYG
- Structure: Markov model (health states of alive and dead) with 1-month cycle length
    - Cycle 1 of the Markov model was calculated using COVID-19-specific evidence for mortality, utility, and cost and corresponded to the COVID-19 hospitalization assessment period.
    - Cycles 2 through the end of the time horizon used general population estimates for mortality, utility, and cost; future healthcare costs were capped to not exceed $50,000 per QALY gained
- Population: hospitalized patients with COVID-19, stratified between mild and moderate to severe
- Discount rate of 3% for costs and outcomes

CEA Model Assumptions:

- For all those who recover in either arm, we assigned probabilities of death, quality of life, and healthcare costs reflective of the general population
    - Fit an exponential distribution to estimate future related and unrelated healthcare costs based on average age-adjusted healthcare costs
    - Fit a linear distribution to estimate future quality of life based on age-adjusted utility estimates
        - To estimate evLYGs, a utility value of 0.851 was assigned to life extension (incremental life years) for each Markov model cycle
    - Fit a fifth order polynomial to estimate future mortality based on all-cause age- and sex-adjusted mortality
- Death prior to discharge occurred at the halfway point of the duration of the tree (at day 15 within the first 30 days)
- Treatment costs for remdesivir are in addition to a bundled hospital payment. We assumed no cost or disutility for potential adverse events separate from the cost and disutility of the admission.

Appendix Table 1. Model Inputs

	Value	Source	Notes
Model Wide Inputs, Moderate to Severe Population			
Percent not requiring supplemental oxygen at baseline	13.1%	ACTT-1	Table 1, ordinal score 4 (138/1051)
Percent requiring supplemental oxygen at baseline	41.4%	ACTT-1	Table 1, ordinal score 5 (435/1051)
Percent not requiring noninvasive ventilation or high-flow oxygen at baseline	18.4%	ACTT-1	Table 1, ordinal score 6 (193/1051)
Percent not requiring mechanical ventilation or ECMO at baseline	27.1%	ACTT-1	Table 1, ordinal score 7 (285/1051)
Disutility of COVID symptoms	-0.19	Assumption & Smith & Roberts, 2002	For duration of time to recovery
Disutility of COVID hospitalization with or without supplemental oxygen	-0.30	Assumption & Barbut et al., 2019	For duration of time to recovery; additive onto disutility of COVID symptoms
Disutility of COVID hospitalization requiring noninvasive ventilation or high-flow oxygen	-0.50	Barbut et al., 2019	For duration of time to recovery; additive onto disutility of COVID symptoms
Disutility of COVID hospitalization requiring mechanical ventilation or ECMO	-0.60	Barbut et al., 2019	For duration of time to recovery; additive onto disutility of COVID symptoms
Bundled payment for COVID hospitalization with or without supplemental oxygen	$12,692	Rae et al., 2020	Median total cost for larger employer plans for Pneumonia inpatient stay; similar to other reported estimates (Bartsch et al. and Cohen et al.)

Bundled payment for COVID hospitalization requiring noninvasive ventilation or high-flow oxygen	$34,223	Rae et al., 2020	Median total cost for larger employer plans for Respiratory system diagnosis with ventilator support for less than 96 hours; similar to other reported estimates (Bartsch et al. and Cohen et al.)
Bundled payment for COVID hospitalization requiring mechanical ventilation or ECMO	$61,169	Rae et al., 2020	Average of the median total cost for larger employer plans for Respiratory system diagnosis with ventilator support for less than 96 hours and for 96 hours or more; similar to other reported estimates (Bartsch et al. and Cohen et al.)
Average age of population at hospital admission	58.9	ACTT-1	
Average age of population that died during hospitalization	71.6	US epidemiological evidence adjusted to ACTT-1 population	Adjustment for trial population was conducted to estimate average age at death given average age at hospitalization was less than average age of hospitalization in CDC estimates
Age-based utility	Alpha = 0.9442 Beta = -0.0027	Sullivan & Ghushchyan, 2006	We fit a linear function (y=alpha+beta*(age)) to age-adjusted utility for the US adult population to smooth utility by age and allow for more precision on utility; starting age of distribution was 18 years

Age-based future healthcare costs	Alpha = 4,045.2 Beta = 0.0285	Health expenditures by age and gender	We fit an exponential function (y=alpha*e^(beta*age)) for age-adjusted health care costs for the US adult population to smooth costs by age and allow for more precision on costs; starting age of distribution was 18 years
Age-based mortality	Intercept = $-3*10^{-5}$ 1st order = $5*10^{-5}$ 2nd order = $-8*10^{-6}$ 3rd order = $4*10^{-7}$ 4th order = $-8*10^{-9}$ 5th order = $6*10^{-11}$	All-cause age- and sex-adjusted mortality	We fit a 5th order polynomial (y=intercept +1st order*age+ 2nd order*age^2 + 3rd order*age^3 + 4th order*age^4 + 5th order*age^5) to age- and sex-adjusted mortality for the US adult population to smooth mortality by age and allow for more precision on mortality; starting age of distribution was 18 years
Average general US population utility	0.851	Pickard AS et al., 2019	For generating evLYG outputs
Standard of Care-Specific Inputs, Moderate to Severe Population			

Probability of COVID-19 death if not requiring supplemental oxygen at baseline	4.9%	ACTT-1 and RECOVERY	Mortality probability for ordinal score 4 at baseline over the entire ACTT-1 study period was 4.8%. Mortality probability was then multiplied by an adjustment factor so the sum product of the mortality from the four ordinal scores equated to 15.2%, which was the overall standard of care mortality reported in ACTT-1. Dexamethasone was not used in this sub-population as per the WHO clinical care guidance, so no adjustments for dexamethasone use were included.

Probability of COVID-19 death if requiring supplemental oxygen at baseline	10.6%	ACTT-1 and RECOVERY	Mortality probability for ordinal score 5 at baseline over the entire ACTT-1 study period was 12.7%. Mortality probability was then multiplied by an adjustment factor so the sum product of the mortality from the four ordinal scores equated to 15.2%, which was the overall standard of care mortality reported in the trial. To adjust the mortality given dexamethasone was used in the standard of care, the mortality was multiplied by the dexamethasone mortality rate ratio for individuals on oxygen without invasive mechanical ventilation (0.82).

Probability of COVID-19 death if requiring noninvasive ventilation or high-flow oxygen at baseline	17.1%	ACTT-1 and RECOVERY	Mortality probability for ordinal score 6 at baseline over the entire ACTT-1 study period was 20.4%. Mortality probability was then multiplied by an adjustment factor so the sum product of the mortality from the four ordinal scores equated to 15.2%, which was the overall standard of care mortality reported in the trial. To adjust the mortality given dexamethasone was used in the standard of care, the mortality was multiplied by the dexamethasone mortality rate ratio for individuals on oxygen without invasive mechanical ventilation (0.82).

Probability of COVID-19 death if requiring mechanical ventilation or ECMO at baseline	12.6%	ACTT-1 and RECOVERY	Mortality probability for ordinal score 7 at baseline over the entire ACTT-1 study period was 19.3%. Mortality probability was then multiplied by an adjustment factor so the sum product of the mortality from the four ordinal scores equated to 15.2%, which was the overall standard of care mortality reported in the trial. To adjust the mortality given dexamethasone was used in the standard of care, the mortality was multiplied by the dexamethasone mortality rate ratio for individuals on invasive mechanical ventilation (0.64).
Time to recovery (days) given no supplemental oxygen at baseline	5.7	ACTT-1	Table 2, ordinal score 4 multiplied by an adjustment factor so the sum product of the four ordinal scores equated to 15, which was the overall time to recovery reported in the trial
Time to recovery (days) given supplemental oxygen at baseline	8.6	ACTT-1	Table 2, ordinal score 5 multiplied by an adjustment factor so the sum product of the four ordinal scores equated to 15, which was the overall time to recovery reported in the trial

Time to recovery (days) given noninvasive ventilation or high-flow oxygen at baseline	19.0	ACTT-1	Table 2, ordinal score 6 multiplied by an adjustment factor so the sum product of the four ordinal scores equated to 15, which was the overall time to recovery reported in the trial
Time to recovery (days) given mechanical ventilation or ECMO at baseline	26.6	ACTT-1	Table 2, ordinal score 7 multiplied by an adjustment factor so the sum product of the four ordinal scores equated to 15, which was the overall time to recovery reported in the trial
Percent never requiring supplemental oxygen	6.8%	ACTT-1	Table S3
Percent requiring supplemental oxygen as highest level of respiratory support	28.7%	ACTT-1	Table S3
Percent requiring noninvasive ventilation or high-flow oxygen as highest level of respiratory support	19.0%	ACTT-1	Table S3
Percent requiring mechanical ventilation or ECMO as highest level of respiratory support	45.5%	ACTT-1	Table S3
Treatment course price for standard of care	$14.87	Redbook	Wholesale Acquisition Cost (WAC) for a 10-day course of once-daily dexamethasone (6mg tablet); given to ordinal score 5 or higher in both treatment arms
Duration of hospitalization	17 days	ACTT-1	Only used in scenario analysis that examined if hospitalizations were reimbursed per day
Remdesivir-Specific Inputs, Moderate to Severe Population			

Adjusted mortality hazard ratio	No Survival Benefit: 1.0 Survival Benefit: 0.91	SOLIDARITY	Applied to mortality from standard of care; 0.91 hazard ratio is estimated from the meta-analysis reported in Figure 4
Adjusted rate ratio for time to recovery	1.26	ACTT-1	Applied to standard-of-care overall time to recovery to estimate remdesivir overall time to recovery
Time to recovery (days) given no supplemental oxygen at baseline	3.7	ACTT-1	Table 2, ordinal score 4 multiplied by an adjustment factor so the sum product of the four ordinal scores equated to 11.9, which was the overall time to recovery for standard of care divided by the adjusted overall rate ratio (15/1.26)
Time to recovery (days) given supplemental oxygen at baseline	5.2	ACTT-1	Table 2, ordinal score 5 multiplied by an adjustment factor so the sum product of the four ordinal scores equated to 11.9, which was the overall time to recovery for standard of care divided by the adjusted overall rate ratio (15/1.26)
Time to recovery (days) given noninvasive ventilation or high-flow oxygen at baseline	11.1	ACTT-1	Table 2, ordinal score 6 multiplied by an adjustment factor so the sum product of the four ordinal scores equated to 11.9, which was the overall time to recovery for standard of care divided by the adjusted overall rate ratio (15/1.26)

Time to recovery (days) given mechanical ventilation or ECMO at baseline	26.6	ACTT-1	Equivalent to standard of care time to recovery for ordinal score 7 given a rate ratio not greater than 1
Probability of discontinuing remdesivir treatment	9.8%	ACTT-1	(52/531), converted to %
Percent of treatment regimen completed given discontinuation	50%	Gilead active arm study	
Percent never requiring supplemental oxygen	7.1%	ACTT-1	The standard of care percent plus the percent of individuals who did not progress to noninvasive ventilation, high-flow oxygen, mechanical ventilation, or ECMO given remdesivir treatment based on transitions reported in Table 2 of ACTT-1
Percent requiring supplemental oxygen as highest level of respiratory support	33.2%	ACTT-1	The standard of care percent plus the percent of individuals who did not progress to noninvasive ventilation, high-flow oxygen, mechanical ventilation, or ECMO given remdesivir treatment based on transitions reported in Table 2 of ACTT-1

Percent requiring noninvasive ventilation or high-flow oxygen as highest level of respiratory support	18.4%	ACTT-1	Reduced probability of progression to noninvasive ventilation or high-flow oxygen from a lower ordinal score by 7% (ACTT-1), plus the percent of individuals who did not progress to mechanical ventilation or ECMO given remdesivir treatment based on transitions reported in Table 2 of ACTT-1
Percent requiring mechanical ventilation or ECMO as highest level of respiratory support	41.3%	ACTT-1 and RECOVERY	Reduced probability of progression to mechanical ventilation from a non-mechanically ventilated state by 10% (ACTT-1) after reducing the individuals eligible for progression to a non-mechanically ventilated state by the benefits reported for dexamethasone using a risk ratio of 0.77 (RECOVERY). The difference in percent of the cohort at this ordinal score between the intervention and standard of care arms was allocated to the three lower ordinal scores based on transitions reported in table 2 of ACTT-1

Price per vial	$520/vial for private payers	Gilead press release	Assumed pricing based on private payers in the analysis given the government-sponsored price is only for those government payers who directly purchase remdesivir from the manufacturer, which represents a minority of government-sponsored payers in the United States. Patients not receiving mechanical ventilation or ECMO received 6 vials; patients receiving mechanical ventilation or ECMP received 11 vials based on FDA package insert
Absolute difference in duration of hospitalization with use of remdesivir	-5 days	ACTT-1	Only used in scenario analysis that examined if hospitalizations were reimbursed per day
Model Wide Inputs, Mild Population (all other model-wide inputs same as moderate to severe population)			
Percent not requiring supplemental oxygen at baseline	82.3%	NCT04292730	Table 1 (ordinal scores 5 and 6) for 5-day remdesivir and standard of care
Percent requiring supplemental oxygen at baseline	16.6%	NCT04292730	Table 1 (ordinal score 4) for 5-day remdesivir and standard of care
Percent not requiring noninvasive ventilation or high-flow oxygen at baseline	1%	NCT04292730	Table 1 (ordinal score 3) for 5-day remdesivir and standard of care
Percent not requiring mechanical ventilation or ECMO at baseline	0%	NCT04292730	Table 1 (ordinal score 2) for 5-day remdesivir and standard of care
Average age of population at hospital admission	57	NCT04292730	
Standard of Care-Specific Inputs, Mild Population (all other model-wide inputs same as moderate to severe population)			

Probability of COVID-19 death if not requiring supplemental oxygen at baseline	1.7%	NCT04292730, ACTT-1, and SOLIDARITY	Calibrated the moderate/severe value so the overall mortality for standard of care was 2.2%, which was the average mortality observed among the three published studies examining this mild population
Probability of COVID-19 death if requiring supplemental oxygen at baseline	4.5%	NCT04292730, ACTT-1, and SOLIDARITY	Calibrated the moderate/severe value so the overall mortality for standard of care was 2.2%, which was the average mortality observed among the three published studies examining this mild population
Probability of COVID-19 death if requiring noninvasive ventilation or high-flow oxygen at baseline	7.2%	NCT04292730, ACTT-1, and SOLIDARITY	Calibrated the moderate/severe value so the overall mortality for standard of care was 2.2%, which was the average mortality observed among the three published studies examining this mild population
Probability of COVID-19 death if requiring mechanical ventilation or ECMO at baseline	6.8%	NCT04292730, ACTT-1, and SOLIDARITY	Calibrated the moderate/severe value so the overall mortality for standard of care was 2.2%, which was the average mortality observed among the three published studies examining this mild population
Time to recovery (days) given no supplemental oxygen at baseline	6.3	NCT04292730 and ACTT-1	Calibrated the moderate/severe value so the overall time to recovery for standard of care was 7 days, which was the recovery reported in the study.

Time to recovery (days) given supplemental oxygen at baseline	9.5		Calibrated the moderate/severe value so the overall time to recovery for standard of care was 7 days, which was the recovery reported in the study.
Time to recovery (days) given noninvasive ventilation or high-flow oxygen at baseline	21.1	NCT04292730 and ACTT-1	Calibrated the moderate/severe value so the overall time to recovery for standard of care was 7 days, which was the recovery reported in the study.
Time to recovery (days) given mechanical ventilation or ECMO at baseline	29.5	NCT04292730 and ACTT-1	Calibrated the moderate/severe value so the overall time to recovery for standard of care was 7 days, which was the recovery reported in the study.
Highest level of respiratory support received	Same as baseline values	NCT04292730	No evidence to suggest differences in progression to higher levels of respiratory support between remdesivir and standard of care in the mild population
Treatment course price for standard of care	$0		Corticosteroids are not currently recommended for use in the mild population, thus no dexamethasone is assumed for the mild population
Duration of hospitalization	7 days	NCT04292730	Assumed equivalent to time to recovery; Only used in scenario analysis that examined if hospitalizations were reimbursed per day
Remdesivir-Specific Inputs, Mild Population (all other model-wide inputs same as moderate to severe population)			

Rate ratio for time to recovery	1.18	NCT04292730	Appendix eTable 3; Applied to standard-of-care overall time to recovery to estimate remdesivir overall time to recovery
Time to recovery (days) given no supplemental oxygen at baseline	5.4	NCT04292730 and ACTT-1	Calibrated the moderate/severe value so the overall time to recovery for remdesivir was 5.9 days, which was the recovery for standard of care (7 days) divided by the rate ratio for time to recovery (1.18).
Time to recovery (days) given supplemental oxygen at baseline	7.6	NCT04292730 and ACTT-1	Calibrated the moderate/severe value so the overall time to recovery for remdesivir was 5.9 days, which was the recovery for standard of care (7 days) divided by the rate ratio for time to recovery (1.18).
Time to recovery (days) given noninvasive ventilation or high-flow oxygen at baseline	16.3	NCT04292730 and ACTT-1	Calibrated the moderate/severe value so the overall time to recovery for remdesivir was 5.9 days, which was the recovery for standard of care (7 days) divided by the rate ratio for time to recovery (1.18).
Time to recovery (days) given mechanical ventilation or ECMO at baseline	29.5	NCT04292730 and ACTT-1	Equivalent to standard of care time to recovery
Adjusted mortality hazard ratio	No Survival Benefit: 1.0 Survival Benefit: 0.80	NCT04292730, ACTT-1, and SOLIDARITY	0.80 was the average hazard ratio observed among the three published studies examining this mild population
Probability of stopping treatment early	24%	NCT04292730	Figure 1

Highest level of respiratory support received	Same as baseline values	NCT04292730	No evidence to suggest differences in progression to higher levels of respiratory support between remdesivir and standard of care in the mild population
Absolute difference in duration of hospitalization with use of remdesivir	0 days	NCT04292730 and Assumption	No evidence suggested reductions in length of stay when remdesivir was used in the mild population; Only used in scenario analysis that examined if hospitalizations were reimbursed per day