CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

Statistical Review and Evaluation

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SDN #	20
eCTD SN #	0020
Received/Communication Date	August 7, 2020
Drug	Remdesivir
Indication	Treatment of COVID-19 in hospitalized patients
Sponsor	Gilead Sciences
Statistical Reviewer	Daniel Rubin, PhD
Medical Reviewer	Kirk Chan-Tack, MD
Project Manager	Christine Kim, PharmD
Biometrics Division	Division of Biometrics IV
Medical Division	Division of Antivirals (DAV)

1. Summary

This addendum to the statistical review of remdesivir discusses results from the SOLIDARITY treatment trial[1] conducted by the World Health Organization. The previously submitted statistical review briefly noted that this trial was meant to conclusively determine whether remdesivir provides a mortality benefit. The study was not discussed in any further detail because results were not yet known.

At the time of this writing the results are available[2] from a preprint. However, no additional materials or datasets have been reviewed.

The SOLIDARITY trial was a randomized, open label, multinational, large simple trial. The active treatments were remdesivir (intravenously administered at 200 mg on the first day and then 100 mg for the next 9 days), hydroxychloroquine, lopinavir-ritonavir, and interferon beta-1a. The hydroxychloroquine and lopinavir-ritonavir groups were previously dropped from the trial for futility due in part from results found in other clinical trials of these agents. When a patient was eligible for one or more active treatments that were locally available, he or she was randomized with equal probability to these groups or to an open-label standard of care control group. Results discussed in this review restrict to those participants concurrently randomized to remdesivir versus standard of care. This approach was considered statistically valid and yielded the same information for the (remdesivir – control) comparisons as a 1:1 randomization trial.

[1] https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments. Accessed October 20, 2020.
[2] https://www.medrxiv.org/content/10.1101/2020.10.15.20209817v1. Accessed October 20, 2020.

The SOLIDARITY trial had a large sample size with 5451 patients randomized to remdesivir or the concurrent control group. This was a pragmatic trial in which study procedures and data collection were minimized and patients were managed according to local standards. This form of design is meant to facilitate enrollment and generalize to real world settings.

Baseline factors were well balanced between treatment groups. Approximately 35%, 45%, and 19% of patients were respectively <50, 50-69, and ≥70 years of age. Over 70% of patients had been hospitalized for under 2 days at the baseline visit, but it is unclear to how long patients had been symptomatic before treatment initiation. Over 60% of enrollment occurred in Asia or Africa with remaining enrollment roughly evenly split between Latin America and Europe. The study population was 62% male, 25% of patients had a history of diabetes, and 21% of patients had a history of heart disease. In terms of baseline respiratory support, approximately 28%, 63%, and 8% of subjects were respectively not receiving supplemental oxygen, receiving non-ventilatory oxygen support, and already ventilated.

The primary endpoint was in-hospital mortality. The understanding of this reviewer is that follow-up was not attempted for post-discharge deaths but that such events would be counted in the primary analysis if they were recorded.

One potential issue with an in-hospital mortality endpoint is that in theory it could be misleading if discharge times systematically differ between groups and there is appreciable post-discharge death. Representatives from the study team claimed at an October 10, 2020 teleconference with the Agency that post-discharge deaths were likely rare because discharge was prompted by improved patient status.

Results for in-hospital mortality were as follows.[3]

- Remdesivir: 301/2743 (11.0%)
- Local standard of care control group: 303/2708 (11.2%)
- (Remdesivir – control) risk difference: -0.2% (95% CI: -1.9% to 1.5%)

Hence, this trial did not detect a mortality benefit for remdesivir. Furthermore, the lower limit of the confidence interval for the risk difference ruled out any mortality advantage of more than 2% on the absolute difference scale.

The previous statistical review had stated that "There is remaining uncertainty regarding whether remdesivir reduces all-cause mortality." While numerical results in ACTT-1 were suggestive of a mortality benefit (particularly for the subgroup with non-ventilatory oxygen requirements) this larger trial was unable to confirm this hypothesis.

The ACTT-1 primary endpoint of time to recovery was largely driven by hospital discharges. In contrast to ACTT-1 the SOLIDARITY trial did not detect a remdesivir

[3] The confidence interval for the risk difference was computed by this reviewer as the authors had presented results in terms of a stratified relative risk. This analysis considers in-hospital mortality as a binary endpoint and does not attempt to account for censoring.

benefit on time to discharge. It also did not detect a benefit for an endpoint defined as the composite of mortality or progression to ventilation (for those not already ventilated at baseline).

The main question under consideration in this addendum is whether the SOLIDARITY results should alter the statement in the previous statistical review that "Overall, this application provides statistically reliable evidence that remdesivir is effective for the treatment of COVID-19 in hospitalized patients."

Collective results from the two trials are consistent with remdesivir having a neutral or small impact on all-cause mortality. While ACTT-1 results were suggestive of improved mortality there remained residual statistical uncertainty, and the most straightforward interpretation of the two trials is that they have now ruled out a large mortality benefit. In terms of treatment effects on non-mortality endpoints, it is considered unlikely that differences between ACTT-1 and SOLIDARITY represented only random variation. The SOLIDARITY authors have noted that chance baseline imbalances in the two trials led to remdesivir groups having disproportionately fewer ventilated patients than the control group in ACTT-1 and more ventilated patients than the control group in SOLIDARITY. However, is unlikely that this chance variation alone was responsible for the ACTT-1 finding of strong statistical evidence for a treatment effect on the primary endpoint of time of recovery, which was driven by results in patients who were not ventilated at baseline. Likewise, ACTT-1 provided strong evidence for an effect on the key secondary endpoint of the Day 15 ordinal scale using a proportional odds analysis, which represented a general shift to improved oxygen support levels at this timepoint. Rather than chance variation, the most straightforward interpretation of the two large trials is that there were heterogeneous treatment effects on non-mortality endpoints. This heterogeneity may have been influenced by the fact that ACTT-1 was double blind while SOLIDARITY was open label as well as other differences in the designs and background conditions. Consequently, the thinking of this reviewer is that SOLIDARITY results do not refute the treatment effects on the primary and key secondary endpoint in ACTT-1.

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US Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

NDA NO.:	214787
SERIAL NO.:	
DATE RECEIVED BY OB:	June 1, 2020
DRUG NAME:	Remdesivir
SPONSOR:	Gilead Sciences
INDICATION:	Treatment of COVID-19
DOSAGE FORM:	lyophilized powder; Solution
STRENGTHS:	lyophilized powder:100 mg and 150 mg; Solution: 5mg/mL
REVIEW FINISHED DATE:	October 14, 2020
CMC STATISTICAL REVIEWER:	Yu-Ting Weng, Ph.D
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1. Executive Summary

The purpose of this review is to evaluate the applicant's proposals of the 12-month shelf life for Remdesivir (GS-5734TM) injection solution dosage form under long-term stability condition (5±3°C) and the (b) (4) month shelf life for Remdesivir (GS-5734TM) injection lyophilized dosage form under long-term condition (30°C/75%RH).

The analysis results are summarized by site as follows.

1) Gilead San Dimas Site

5 mg/ml solution dosage form

According to the ICH Q1E guidance [1], no extrapolation for the shelf life from the observed time is allowed because the accelerated data of assay and total degradation product content from two batches (004549 and 005796) has a significant trend within six months. Thus, we considered the shelf life of 12 months based on two batches (004549 and 005796) with 12-month stability data and Batch 005866 with 9-month stability data for this specific submission although the ICH Q1E guidance required at least three batches with 12-month stability data to support the shelf life of 12 months.

The 12-month stability data of assay, total degradation product content, (b) (4) pH, (b) (4) from two batches (004549 and 005796) under the long-term stability condition support the 12-month shelf life for Remdesivir (GS-5734TM) injection.

Some stability attributes (assay, total degradation product content, (b) (4), pH, (b) (4) (b) (4)) with a trend are summarized in Table 1 and Figures 6 to 20 in the Appendix. For (b) (4) we did not conduct statistical analysis if these values in most of the batches are not detectable. Based on the statistical poolablility test of orientation variable, data from two orientations (inverted and upright) are pooled together.

2) Gilead La Verne Site

5 mg/ml solution dosage form

According to the ICH Q1E guidance, no extrapolation for the shelf life from the observed time is allowed because the accelerated data of assay and total degradation product content from four batches (020985, 020953, 020954, and 020955) has a significant trend within six months.

These four batches (020985, 020953, 020954, and 020955) were not included in the analysis since the stability data has only three to six months under long-term stability condition. According to the ICH Q1A guidance [2], the applicant has provided a post-approval commitment to continue the long-term stability studies through the proposed shelf life and the accelerated studies for 3 months for further evaluation.

Table 1: Reviewer's Summarized Stability Analyses Results for Remdesivir (GS-5734TM) Injection Solution Dosage based on Three-Batch Long-term Stability Data at Gilead San Dimas Site

Variable	Batch No	Figure No*	At 12 months		Acceptance Criterion	Site	Is 12 Month Shelf Life Supported
			95% LCL	95% UCL			
Assay	004549	6	(b) (4)		(b) (4)%	Gilead San Dimas	Yes
	005796	7					
	005866	8					
Total degradation	004549	9			NMT (b) (4)%		
	005796	10					
	005866	11					
(b) (4)	004549	12			NMT (b) (4)%		
	005796	13					
	005866	14					
pH	004549	15			(b)		
	005796	16					
	005866	17					
(b) (4)	005866	18			NMT (b) (4)%		
(b) (4)	005796	19			NMT %		
	005866	20					

NA: not available
*Figure No: The corresponding figure in the Appendix to show the stability data trend

3) (b) (4) Site

a. 100 mg lyophilized dosage form

The ICH Q1E guidance required a batch with at least (b) (4) month data to support (b) (4) month shelf life, so we considered the shelf life of 30 months based on three batches (Batch EW1802A1, EW1803A1 and EW1804A1) with 18-month stability data in the analysis for this specific submission. In addition, we recommend the applicant changing the shelf life from (b) (4) months to 30 months and the IR has been sent to the applicant on October 14, 2020.

Some stability attributes (assay, pH, total degradation product content, (b) (4) (b) (4)) with a trend are summarized in Table 2 and Figures 21-23, 25-26, 28-30, 32-34, and 36-38 in the Appendix. For total degradation product content, we did not conduct statistical analyses for Batch EW1803A1 since there is no trend in the data. For (b) (4) (b) (4) we did not conduct statistical analyses for all batches since their values are not detectable.

The 18-month stability data of assay, total degradation product content, (b) (4) pH, (b) (4) from these three batches under the long-term stability condition support the 30-month shelf life for Remdesivir (GS-5734TM) injection. We noticed that, for Batch EW1803A1, the 95% CL of pH at 30 months is smaller than but close to the corresponding acceptance criterion.

b. 150 mg lyophilized dosage form

The 48-month stability data of assay, pH, total degradation product content, (b) (4) (b) (4) from Batch EW1602A1 under the long-

term stability condition support the 30-month shelf life for Remdesivir (GS-5734TM) injection.

Some stability attributes (assay, pH, total degradation product content, (b) (4) (b) (4)) with a trend are summarized in Table 2 and Figures 24, 27, 31, 35, and 39 in the Appendix. For (b) (4), we did not conduct statistical analyses for Batch EW1602A1 since their value are not detectable.

Table 2: Reviewer's Summarized Stability Analyses Results for Remdesivir (GS-5734TM) Injection Lyophilized Dosage based on Four-Batch Long-term Stability Data at (b) (4) Site

Variable	Batch No	Figure No*	At 30 months		Acceptance Criterion	Site	Is 30 Month Shelf Life Supported
			95% LCL	95% UCL			
Assay	EW1802A1	21	(b) (4)		(b) (4)%	(b) (4)	Yes
	EW1803A1	22					
	EW1804A1	23					
	EW1602A1	24					
Total degradation	EW1802A1	25			NMT (b) (4)%		
	EW1804A1	26					
	EW1602A1	27					
(b) (4)	EW1802A1	28			NMT (b) (4)%		
	EW1803A1	29					
	EW1804A1	30					
	EW1602A1	31					
pH	EW1802A1	32			(b) (4)		
	EW1803A1	33					
	EW1804A1	34					
	EW1602A1	35					
(b) (4)	EW1802A1	36			NMT (b) (4)%		
	EW1803A1	37					
	EW1804A1	38					
	EW1602A1	39					

NA: not available
*Figure No: The corresponding figure in the Appendix to show the stability data trend

4) (b) (4) Site

a. 100 mg lyophilized dosage form

The ICH Q1E guidance required a batch with at least (b) (4) month data to support (b) (4) month shelf life, but Batch EW1805A1 has only 12-month stability data, so we considered the shelf life of 30 months to be consistent with the analysis at the (b) (4) site.

Although the ICH Q1E guidance required a batch with at least 18-month data to support 30-month shelf life, Batch EW1805A1 with 12-month stability data was included in the analysis for this specific submission. The other five batches (EW2019A1, EW2020A1, EW2021A1, D20PV141, and D20PV142) were not included in the analysis since the stability data has only zero month under long-term stability condition.

Some stability attributes (assay, pH, (b) (4)) with a trend are summarized in Table 3 and Figures 40, 43, 45, and 47 in the Appendix. For total degradation product content, we did not conduct statistical analyses for Batch EW1805A1 since there is no trend in the data. For (b) (4) we did not conduct statistical analyses for Batch EW1805A1 since their value are not detectable.

(b) (4)

b. 150 mg lyophilized dosage form

The 36-month stability data of assay, pH, total degradation product content, (b) (4), (b) (4) from Batch EW1603A1 under the long-term stability condition support the 30-month shelf life for Remdesivir (GS-5734TM) injection.

Some stability attributes (assay, pH, total degradation product content, (b) (4) (b) (4)) with a trend are summarized in Table 3 and Figures 41, 42, 44, 46, and 48 in the Appendix. For (b) (4) we did not conduct statistical analyses for Batch EW1603A1 since their value are not detectable.

We also noticed that there might be a shift of the assay value between the (b) (4) site and the (b) (4) site. More details are provided in Section 3.

Table 3: Reviewer's Summarized Stability Analyses Results for Remdesivir (GS-5734TM) Injection Lyophilized Dosage based on Two-Batch Long-term Stability Data at (b) (4) Site

Variable	Batch No	Figure No*	At 30 months		Acceptance Criterion	Site	Is 30 Month Shelf Life Supported
			95% LCL	95% UCL			
Assay	EW1805A1	40	(b) (4)		(b) (4)%	(b) (4)	Yes
	EW1603A1	41					
Total degradation	EW1603A1	42			NMT (b) (4)%		
(b) (4)	EW1805A1	43			NMT (b) (4)%		
	EW1603A1	44					
pH	EW1805A1	45			(b) (4)		
	EW1603A1	46					
(b) (4)	EW1805A1	47			NMT (b) (4)%		
	EW1603A1	48					

NA: not available
*Figure No: The corresponding figure in the Appendix to show the stability data trend

5) (b) (4) site

100 mg lyophilized dosage form

Five batches (EW2014A1, EW2016A1, EW2018A1, AN7049B, and AN7050C) were not included in the analysis since the stability data has only zero to three months under long-term stability condition.

Since the applicant did not provide at least three batches covering the proposed the proposed shelf life, according to the ICH Q1A guidance, the applicant has provided a post-approval commitment to continue the long-term stability studies through the proposed shelf life and the accelerated studies for 6 months for further evaluation.

6) (b) (4) site

100 mg lyophilized dosage form

Three batches (00001, 00003, and 00004) were not included in the analysis since the stability data has only zero month under long-term stability condition.

Since the applicant did not provide at least three batches covering the proposed shelf life, according to the ICH Q1A guidance, the applicant has provided a post-approval commitment to continue the long-term stability studies through the proposed shelf life and the accelerated studies for 6 months for further evaluation.

7) (b) (4) site

100 mg lyophilized dosage form

Six batches (2041087.1, 2041088.1, 2009106.1, 2009107.1, 1010131.1, and 1010132.1) were not included in the analysis since the stability data has only zero month under long-term stability condition.

Since the applicant did not provide at least three batches covering the proposed the proposed shelf life, according to the ICH Q1A guidance, the applicant has provided a post-approval commitment to continue the long-term stability studies through the proposed shelf life and the accelerated studies for 6 months for further evaluation.

8) (b) (4) site

100 mg lyophilized dosage form

Three batches (200553F, 200613F, and 200653F) were not included in the analysis since the stability data has only zero month under long-term stability condition.

Since the applicant did not provide at least three batches covering the proposed the proposed shelf life, according to the ICH Q1A guidance, the applicant has provided a post-approval commitment to continue the long-term stability studies through the proposed shelf life and the accelerated studies for 6 months for further evaluation.

We also recommend the applicant providing additional batches with more months in the future submission for further evaluation.

2. Purpose of the Review

Gilead Sciences (applicant) proposed a shelf life of 12 months for Remdesivir (GS-5734^{TM}) injection, 5 mg/mL (solution dosage form), under long-term stability condition (5±3°C) and a shelf life of (b) (4) months for Remdesivir (GS-5734^{TM}) injection, 100 mg (lyophilized dosage form), under long-term stability condition (30°C/75%RH). To support these two proposals, the applicant analyzed the stability data from Gilead San Dimas Site, (b) (4) site, and (b) (4) site. The applicant also provided the stability data with zero to six months from Gilead La Verne Site, (b) (4) site, (b) (4) Site, (b) (4) Site, and (b) (4) Site.

On June 1, 2020, Office of Product Quality (OPQ) requested the CMC statistical team in Office of Biostatistics (OB) to evaluate the applicant's proposals of the (b) (4)-month shelf life for Remdesivir (GS-5734^{TM}) injection solution dosage form under long-term stability condition (5±3°C) and the (b) (4)-month shelf life for Remdesivir (GS-5734^{TM}) injection lyophilized dosage form under long-term stability condition (30°C/75%RH).

The OPQ CMC reviewer has the following question in the consultation request.

Question: From the statistical standpoint, does the applicant's statistical analysis of the stability data adequately support the proposals of the (b)(4)-month shelf life for Remdesivir (GS-5734™) injection solution dosage form under long-term stability condition (5±3°C) and the (b)(4)-month shelf life for Remdesivir (GS-5734™) injection lyophilized dosage form under long-term stability condition (30°C/75%RH)?

The CMC statistical reviewer carefully reviewed the provided data analyses in the submission and found the applicant provided the stability data for three batches in the solution dosage form from Gilead San Dimas site with the pdf format. Two of the three batches have twelve-month data and the other has nine-month data.

On June 10, 2020, the FDA sent the applicant the first Information Request (IR). The request is described below.

Request: In the files titled "stability data-xxx-5c-stats", the applicant provided the individual lot data and statistical analysis in PDF format for three primary batches: 004549, 005796, 005866. However, a file in Excel format is preferred for further statistical analyses. Provide all available stability data of the four stability attributes (assay, total degradation product content, (b)(4), (b)(4)) for drug product at both inverted and upright positions in excel format.

On June 23, 2020, the applicant provided the following data with the excel format.

1) Two batches with twelve-month data and one batch with nine-month data for four stability attributes (assay, total degradation product content, (b)(4)) in both inverted and upright positions.

Then, the CMC statistical reviewer found the applicant confirmed that (b)(4) (b)(4) are monitored as unspecified degradation products in both the solution and lyophilized dosage forms without providing stability data.

On June 30, 2020, the FDA sent the applicant the second IR. The request is described below.

Request: In the response to request for information dated June 23, 2020, the applicant confirmed that (b)(4) are monitored as unspecified degradation products in both solution and lyophilized products. Provide all available stability data of the seven stability attributes (assay, total degradation product content, (b)(4)-(b)(4)) of drug product at both inverted and upright positions in excel format.

On July 24, 2020, the applicant provided the following data with the excel format.

1) For the solution dosage form, two batches with twelve-month data, one batch with nine-month data for eight stability attributes (assay, pH, total degradation product content, (b)(4) (b)(4)) in both inverted and upright positions. In addition, one batch with three-month data and three batches with one-month data for eight stability attributes (assay, pH, total degradation product content, (b)(4) (b)(4)) in the inverted position.
2) For the lyophilized dosage form, one batch with forty-eight-month data from (b)(4) site (150 mg), one batch with thirty-six-month data from (b)(4) site (150 mg), one batch with eighteen-month data from (b)(4) site (100 mg), two batches with twelve-month data from

(b) (4) site (100 mg), and one batch with twelve-month data from (b) (4) site (100 mg) for seven stability attributes (assay, total degradation product content, (b) (4) (b) (4)).

In the teleconference dated October 1, 2020, the FDA requested more data for solution and lyophilized dosage forms. In addition, on October 6, 2020, the FDA sent the applicant the third IR. The request is described below.

Request: The applicant have submitted only 12-month of long-term stability data for two batches and 9-month of long-term data for one batch of remdesivir injection, 5 mg/mL, to support the proposed shelf life of remdesivir injection, 5 mg/mL. Remdesivir injection failed to meet the acceptance criteria (b) (4) (b) (4) (b) (4) So, we are unable to grant the shelf life for the drug product (b) (4). Given the stability concerns for remdesivir injection, please commit (b) (4) (b) (4) by means of a CBE-30 Supplement rather than by means of the Annual Report. Please acknowledge this statement.

On October 8, 2020, the applicant agreed the 12-month shelf life for Remdesivir (GS-5734™) injection solution dosage form and provided the following data with the pdf format.

1) For the solution dosage form, one batch (020985) with six-month data for eight stability attributes (assay, pH, total degradation product content, (b) (4) (b) (4)) in the inverted position.
2) For the lyophilized dosage form, 100 mg, three batches with eighteen-month data from (b) (4) site, three batches with three-month data from (b) (4) site, 19 batches with zero-month data from (b) (4) site, (b) (4) site, (b) (4) site, (b) (4) site, and (b) (4) site for eight stability attributes (assay, pH, total degradation product content, (b) (4) (b) (4)).

On October 7, 2020, the FDA sent the applicant the PostMarketing Commitments (PMCs). The PMCs are described below.

a) (b) (4) site
   i) Provide three-month long-term and accelerated stability data for three batches (EW2019A1, EW2020A1, EW2021A1) of remdesivir for injection, 100 mg, manufactured on the (b) (4) line.
   ii) Provide three-month long term and accelerated stability data for two batches (D20PV141 and D20PV142) of remdesivir for injection, manufactured on the (b) (4) line.

b) (b) (4) site
   i) Provide three-month long term and accelerated stability data for two batches (AN7049B, AN7050C) of remdesivir for injection, 100 mg, manufactured using the line (b) (4)
   ii) Provide six-month long term and accelerated stability data for three batches (EW2014A1, EW2016A1, EW2018A1) of remdesivir for injection, 100 mg, manufactured at the line (b) (4) of (b) (4) site, to

support the stoppers from (b) (4)

c) (b) (4) site
   i) The release data of two batches manufactured on each of lines (b) (4) (2041087.1, 2041088.1), (b) (4) (2009106.1, 2009107.1), and (b) (4) (2010131.1, 2010132.1) at (b) (4) is provided. Submit three- month long-term and accelerated stability data of these batches of remdesivir for injection.

d) (b) (4) site
   i) Submit three-month long term and accelerated stability data for 3 batches (200553F, 200613F and 200653F) of remdesivir for injection.

On October 13, 2020, the applicant agreed all above PMCs.

In addition, in the email dated September 2, 2020, the CMC reviewer, Dr. Shalini Anand, confirmed that the stability batches of remdesivir lyophilized formulation 100 mg and 150 mg strengths were packaged using the same stoppers (b) (4) Thus, stability data from 150 mg dosage strength can be used to support shelf life of the 100 mg dosage strength.

This review will evaluate the applicant's two proposals. The executive summary and conclusion are summarized in Section 1 and Section 5, respectively. The applicant's analyses and our comments for the applicant's analyses are provided in Section 3. Our independent analyses are provided in Section 4. Figures to show the stability data trend are provided in the Appendix.

2.1 Data Analyzed and Sources

Data for solution dosage form, lyophilized dosage 100 mg and 150 mg form are summarized in Table 4, Table 5 and Table 6, respectively.

Table 4: Stability Data Summary for Solution Dosage Form

Lot Number	Mfg Site	Date of Manufacture	Batch Size (kg)	Storage Condition	Study Duration (Months)	Available Data (Months)
5 mg/mL[a]						
004549	Gilead San Dimas	May 2015	(b) (4)	5 ℃	12	12
				25 ℃/60% RH	6	6
005796	Gilead San Dimas	Jan 2016		5 ℃	12	12
				25 ℃/60% RH	6	6
005866	Gilead San Dimas	Jan 2016		5 ℃	9	9
020985	Gilead La Verne	Feb 2020		5 ℃	24	6
				25 ℃/60% RH	3	3
020953	Gilead La Verne	March 2020		5 ℃	24	3
				25 ℃/60% RH	3	3
020954	Gilead La Verne	March 2020		5 ℃	24	3
				25 ℃/60% RH	3	3
020955	Gilead La Verne	March 2020		5 ℃	24	3
				25 ℃/60% RH	3	3

a. Vials stored in the upright and inverted orientation at long-term and accelerated stability conditions, except for lot 020985 which is store inverted only.

Table 5: Stability Data Summary for Lyophilized Dosage Form 100mg

Lot Number	Mfg Site	Date of Manufacture	Batch Size (kg)	Storage Condition	Study Duration (Months)[a]	Available Data (Months)
EW1802A1	(b) (4)	Sep 2018	(b) (4)	30 °C/75% RH	36	18
				40 °C/75% RH	6	6
EW1803A1		Sep 2018		30 °C/75% RH	36	18
				40 °C/75% RH	6	6
EW1804A1		Oct 2018		30 °C/75% RH	36	18
				40 °C/75% RH	6	6
EW1805A1		Nov 2018		30 °C/75% RH	36	12
				40 °C/75% RH	6	6
EW2019A1		Apr 2020		30 °C/75% RH	36	0
				40 °C/75% RH	6	1
EW2020A1		May 2020		30 °C/75% RH	36	0
				40 °C/75% RH	6	1
EW2021A1		May 2020		30 °C/75% RH	36	0
				40 °C/75% RH	6	1
D20PV141		Aug 2020		30 °C/75% RH	36	0
				40 °C/75% RH	6	1
D20PV142		Aug 2020		30 °C/75% RH	36	0
				40 °C/75% RH	6	1
EW2014A1		Apr 2020		30 °C/75% RH	36	3
				40 °C/75% RH	6	3
EW2016A1		Apr 2020		30 °C/75% RH	36	3
				40 °C/75% RH	6	3
EW2018A1		Apr 2020		30 °C/75% RH	36	3
				40 °C/75% RH	6	3
AN7049B		Jul 2020		30 °C/75% RH	36	0
				40 °C/75% RH	6	0
AN7050C		Jul 2020		30 °C/75% RH	36	0
				40 °C/75% RH	6	0
00001		Jul 2020		30 °C/75% RH	36	0
				40 °C/75% RH	6	0
00003		Jul 2020		30 °C/75% RH	36	0
				40 °C/75% RH	6	0
00004		Jul 2020		30 °C/75% RH	36	0
				40 °C/75% RH	6	0
2041087.1		Aug 2020		30 °C/75% RH	36	0
				40 °C/75% RH	6	0
2041088.1		Aug 2020		30 °C/75% RH	36	0
				40 °C/75% RH	6	0
2009106.1		Jul 2020		30 °C/75% RH	36	0
				40 °C/75% RH	6	0
2009107.1		Jul 2020		30 °C/75% RH	36	0
				40 °C/75% RH	6	0
1010131.1[b]		Jul 2020		30 °C/75% RH	36	0
				40 °C/75% RH	6	0

1010132.1[b]	(b) (4)	Jul 2020	(b) (4)	30 °C/75% RH	36	0
				40 °C/75% RH	6	0
200553F		Aug 2020		30 °C/75% RH	36	0
				40 °C/75% RH	6	0
200613F		Aug 2020		30 °C/75% RH	36	0
				40 °C/75% RH	6	0
200653F		Aug 2020		30 °C/75% RH	36	0
				40 °C/75% RH	6	0

(b) (4)

Table 6: Stability Data Summary for Lyophilized Dosage Form 150mg

Lot Number	Mfg Site	Date of Manufacture	Batch Size (kg)	Storage Condition	Study Duration (Months)[a]	Available Data (Months)
EW1602A1	(b) (4)	Apr 2016	(b) (4)	30 °C/75% RH	48	48
				40 °C/75% RH	6	6
EW1603A1	(b) (4)	Dec 2016	(b) (4)	30 °C/75% RH	36	36
				40 °C/75% RH	6	6

(b) (4)

2.2 Proposed Acceptance Criterion

For the solution dosage form during shelf-life:
The assay acceptance criterion is (b) (4) (%).
The total degradation product content acceptance criterion is not more than (NMT) (b) (4)(%).
The (b) (4) acceptance criterion is NMT (b) (4)(%).
The (b) (4) acceptance criterion is NMT (%).
The unspecified degradation product acceptance criterion is NMT (b) (4)(%)
The pH acceptance criterion is (b) (4)

For the lyophilized dosage form during shelf-life:
The assay acceptance criterion is (b) (4) (%).
The total degradation product content acceptance criterion is not more than (NMT) (b) (4)(%).
The (b) (4) acceptance criterion is NMT (b) (4)(%).
The (b) (4) acceptance criterion is NMT (%).
The unspecified degradation product acceptance criterion is NMT (b) (4) %)
The pH acceptance criterion is (b) (4)

3. Applicant's Analyses and FDA Statistical Reviewer's Comments

For the solution dosage form, the applicant did not conduct the statistical analysis on the stability data from three batches at the Gilead San Dimas site since a significant change is observed in the accelerated stability results for assay and degradation product between three and six months. Two of the three batches have twelve-month data and the other has nine-month data. The rest four batches with the stability data less than six months from the Gilead La Verne site were not included in the analysis.

Reviewer comments: Since there is a significant trend for assay and degradation product between three and six months in the accelerated stability results at the Gilead San Dimas site, the applicant agreed to change the proposed shelf life from (b)(4) months to 12 months. For Gilead La Verne Site, since the applicant did not provide at least three batches covering the proposed the proposed shelf life, according to the ICH Q1A guidance [2], the applicant (b)(4) (b)(4)

For the lyophilized dosage form, the applicant provided the stability data from 28 batches at six sites: one batch with forty-eight-month data from the (b)(4) site, one batch with thirty-six-month data from the (b)(4) site, three batches with eighteen-month data from the (b)(4) site, one batch with twelve-month data from the (b)(4) site, three batches with three-month data from the (b)(4) site, and 19 batches with zero-month data from (b)(4) site, (b)(4) site, (b)(4) site, (b)(4) site, and (b)(4) site. The applicant showed that the stability of the 100 mg and 150 mg product was comparable. (b)(4) (b)(4) In addition, the applicant did not conduct the statistical analysis for any QA.

Reviewer comments: According to the ICH Q1E Guidance [1], the proposed shelf life can be up to twice as long as, but should not be more than 12 months beyond, the period covered by long-term stability data. Thus, at least (b)(4) month data will be required to support the proposed (b)(4)-month shelf life for the lyophilized dosage form. Since the stability data from 100 mg product has only 12-18 months and the applicant provided the stability data from 150 mg product with at least 36 months, the applicant justified the stability of the 100 mg and 150 mg product was comparable first. However, with limited stability data from 100 mg product, it is hard to decide whether the stability of the 100 mg and 150 mg product was comparable from the statistical standpoint so we asked the reviewed chemist, Dr. Anand, and Dr. Anand has confirmed that the stability of the 100 mg and 150 mg product was comparable. Thus, stability data from 150 mg product can be used to support shelf life of the 100 mg product. In addition, it might be better to conduct the statistical analysis for the lyophilized dosage form although the proposed shelf life is less or equal to the month of the observed stability data from 150 mg product and there is small trend in the observed data. Furthermore, since the applicant has at least three batches with 18-month stability data from the (b)(4) site, we recommend the applicant changing the shelf life from (b)(4) months to 30 months if the statistical analysis of the extrapolation can be supported. For the (b)(4) site, according to the ICH Q1A guidance, the applicant has provided a post-approval commitment to continue the long-term stability studies through the proposed shelf life and the accelerated studies for 6 months for further evaluation. For the (b)(4) site, the (b)(4) site, the (b)(4) site, and the (b)(4) site, according to the ICH Q1A guidance, the applicant has provided a post-approval commitment to continue the long-term stability studies through the proposed shelf life and the accelerated studies for 6 months for further evaluation. In Figure 1, we also noticed that there might be a shift of the assay value between the (b)(4) site (EW1602A1 and EW1802-4A1) and the (b)(4) site (EW1603A1 and EW1805A1) although the number of batches is limited.

Figure 1: Assay of Remdesivir for injection lyophilized dosage form 30°C/75%RH

In our independent statistical analysis, for both dosage forms, since there are not at least three batches from the same manufacturing sites with sufficient stability data, we will analyze the long-term stability data by site and by batch.

4. Statistical Reviewer's Statistical Analysis

For the solution dosage form, we analyzed the stability data of eight stability attributes (assay, pH, total degradation product content, (b) (4) (b) (4)) from all available batches with sufficient stability data. For the lyophilized dosage form, we analyzed the stability data of eight stability attributes (assay, pH, total degradation product content, (b) (4)) from all available batches with sufficient stability data. We analyzed the long-term stability data by site and by batch.

4.1 Gilead San Dimas Site

5 mg/ml solution dosage form

According to the ICH Q1E guidance [1], no extrapolation for the shelf life from the observed time is allowed because the accelerated data of assay and total degradation product content from two batches (004549 and 005796) has a significant trend within six months as shown in Figure 2 and Figure 3. We only plotted the accelerated data of assay and total degradation product content in the inverted position. The accelerated data in the upright position has a similar trend. Thus, we will use statistical analysis to support the proposed shelf life of 12 months from the observed time.

Although the ICH Q1E guidance required three batches with 12-month data to support 12-month shelf life if refrigerated, two batches (004549 and 005796) with 12-month stability data and Batch 005866 with 9-month stability data were included in the analysis for this specific submission.

Some stability attributes (assay, total degradation product content, (b) (4) pH, (b) (4) (b) (4)) are analyzed and summarized in Table 7. Stability trends of six stability attributes for three long-term stability batches are shown in Figures 6 to 20 in the Appendix. The position effect is not significant, so it is not included in the model. The 95% CL of the corresponding stability attributes at 12 months is smaller than the corresponding acceptance criterion.

For (b) (4) we did not conduct statistical analysis if these values in any batch are not detectable.

Figure 2: Assay versus time trend for all batches at Gilead San Dimas Site at 25°C

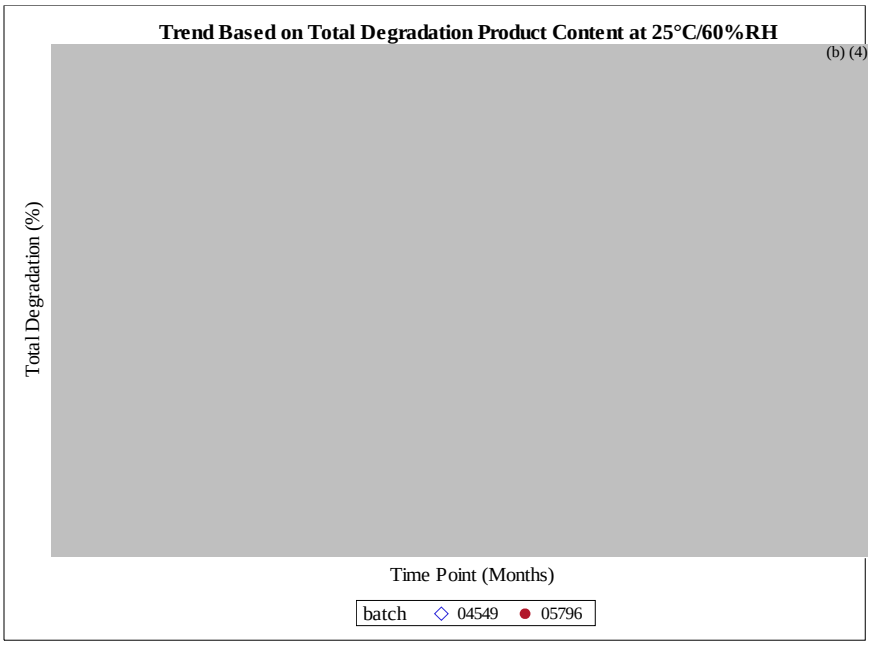

Figure 3: Total degradation product content versus time trend for all batches at Gilead San Dimas Site at 25°C

Table 7: Predicted Value and the Corresponding 95% Confidence Limit at 12 months for Remdesivir (GS-5734™) Injection Solution Dosage at Gilead Sand Dimas Site based on Three-Batch Long-term Stability Data

Variable	Batch No	Figure No*	Storage, Months	Time, Months	Predicted Value	At 12 months		Acceptance Criterion
						95% LCL	95% UCL	
Assay	004549	6	12	12	(b) (4)			(b) (4)%
	005796	7	12	12				
	005866	8	9	12				
Total degradation	004549	9	12	12				NMT (b) (4)%
	005796	10	12	12				
	005866	11	9	12				
(b) (4)	004549	12	12	12				NMT (b) (4)%
	005796	13	12	12				
	005866	14	9	12				
pH	004549	15	12	12				(b)
	005796	16	12	12				
	005866	17	9	12				
(b) (4)	005866	18	9	12				NMT (b) (4)%
(b) (4)	005796	19	12	12				NMT %
	005866	20	9	12				

NA: not available
*Figure No: The corresponding figure in the Appendix to show the stability data trend

4.2 Gilead La Verne Site

5 mg/ml solution dosage form

Four batches (020985, 020953, 020954, and 020955) were not included in the analysis since the stability data has only three to six months under long-term stability condition. In Figure 4 and Figure 5, we also show that the accelerated data of assay and total degradation product content from two batches (004549 and 005796) has a significant trend within six months.

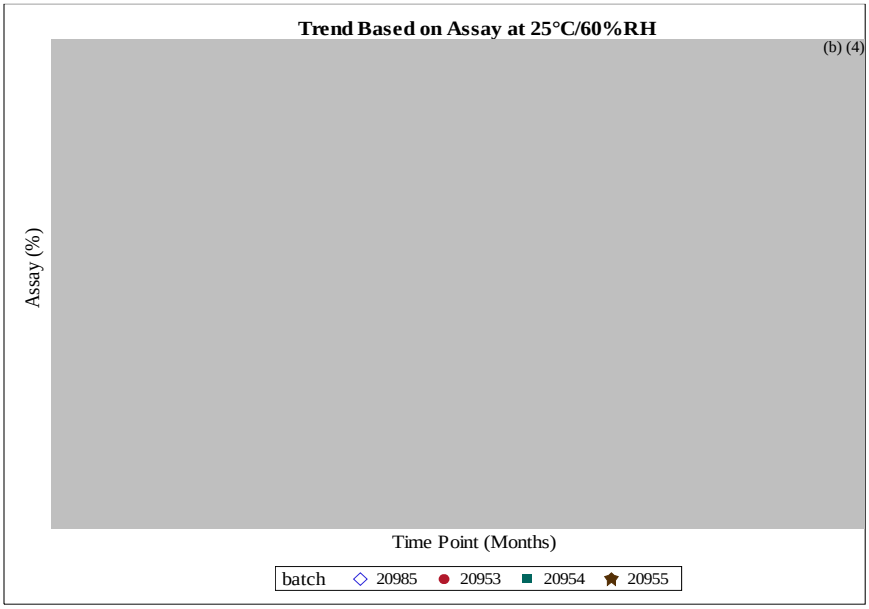

Figure 4: Assay versus time trend for all batches at Gilead La Verne Site at 25°C

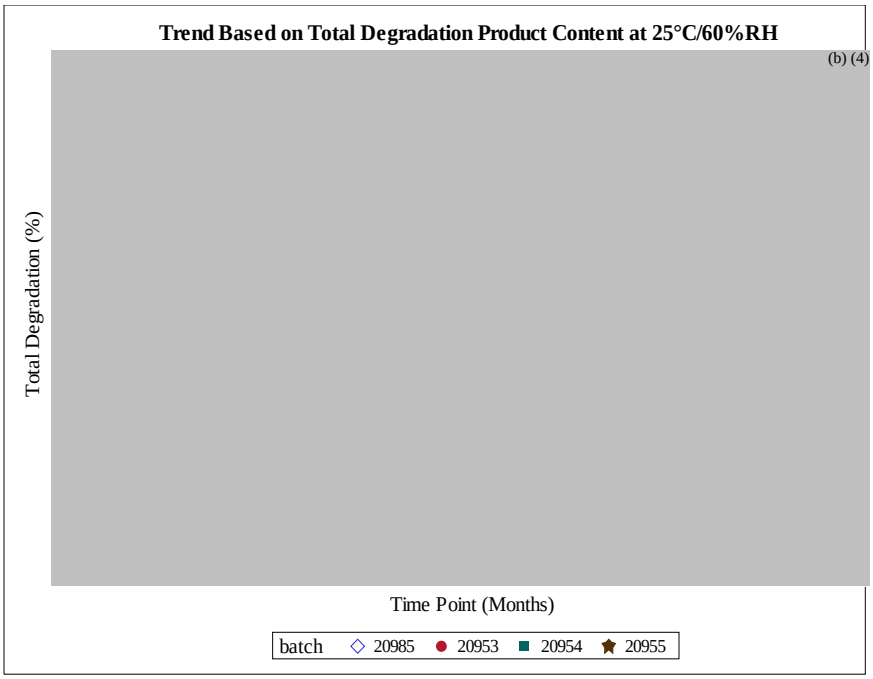

Figure 5: Total degradation product content versus time trend for all batches at Gilead La Verne Site at 25°C

4.3 (b) (4) Site

a. 100 mg lyophilized dosage form

Three batches (EW1802A1, EW1803A1 and EW1804A1) with 18-month stability data were included in the analysis. The ICH Q1E guidance required a batch with at least (b) (4) month data to support (b) (4) month shelf life, so we considered the shelf life of 30 months based on these three batches in the analysis for this specific submission.

Some stability attributes (assay, pH, total degradation product content, (b) (4) (b) (4)) are analyzed and summarized in Table 8. Stability trends of five stability attributes for three long-term stability batches are shown in Figures 21-23, 25-26, 28-30, 32-34, and 36-38 in the Appendix. The 95% CL of the corresponding stability attributes at 30 months is smaller than the corresponding acceptance criterion.

For total degradation product content, we did not conduct statistical analyses for Batch EW1803A1 since there is no trend in the data. For (b) (4) we did not conduct statistical analyses for all batches since their value are not detectable.

b. 150 mg lyophilized dosage form

Batch EW1602A1 with 48-month stability data was included in the analysis.

Some stability attributes (assay, pH, total degradation product content, (b) (4) (b) (4)) are analyzed and summarized in Table 7. Stability trends of five stability attributes for three long-term stability batches are shown in Figures 24, 27, 31, 35, and 39 in the Appendix. The 95% CL of the corresponding stability attributes at 30 months is smaller than the corresponding acceptance criterion.

For (b) (4) we did not conduct statistical analyses for all batches since their value are not detectable.

Table 8: Predicted Value and the Corresponding 95% Confidence Limit at 30 months for Remdesivir (GS-5734™) Injection Lyophilized Dosage at (b) (4) Site based on Four-Batch Long-term Stability Data

Variable	Batch No	Figure No*	Storage, Months	Time, Months	Predicted Value	At 30 months		Acceptance Criterion
						95% LCL	95% UCL	
Assay	EW1802A1	21	18	30	(b) (4)			(b) (4) %
	EW1803A1	22	18	30				
	EW1804A1	23	18	30				
	EW1602A1	24	48	30				
Total degradation	EW1802A1	25	18	30				NMT (b) (4) %
	EW1804A1	26	18	30				
	EW1602A1	27	48	30				
(b) (4)	EW1802A1	28	18	30				NMT (b) (4) %
	EW1803A1	29	18	30				
	EW1804A1	30	18	30				
	EW1602A1	31	48	30				
pH	EW1802A1	32	18	30				(b) (4)
	EW1803A1	33	18	30				
	EW1804A1	34	18	30				
	EW1602A1	35	48	30				
(b) (4)	EW1802A1	36	18	30				NMT (b) (4) %
	EW1803A1	37	18	30				
	EW1804A1	38	18	30				
	EW1602A1	39	48	30				

NA: not available
*Figure No: The corresponding figure in the Appendix to show the stability data trend

4.4 (b) (4) Site

a. 100 mg lyophilized dosage form

Batch EW1805A1 with 12-month stability data was included in the analysis for this special submission. Since the ICH Q1E guidance required a batch with at least (b) (4) month data to support (b) (4) month shelf life, we considered the shelf life of 30 months to be consistent with the analysis at the (b) (4) site.

Some stability attributes (assay, pH, (b) (4)) are analyzed and summarized in Table 9. Stability trends of four stability attributes for this long-term stability batch is shown in Figures 40, 43, 45, and 47 in the Appendix. The 95% CL of the corresponding stability attributes at 30 months is smaller than the corresponding acceptance criterion.

For total degradation product content, we did not conduct statistical analyses for Batch EW1805A1 since there is no trend in the data. For (b) (4) we did not conduct statistical analyses for Batch EW1805A1 since their value are not detectable.

b. 150 mg lyophilized dosage form

Batch EW1603A1 with 36-month stability data was included in the analysis.

Some stability attributes (assay, pH, total degradation product content, (b) (4) (b) (4)) are analyzed and summarized in Table 8. Stability trends of five stability attributes for this long-term stability batch are shown in Figures 41, 42, 44, 46, and 48 in the Appendix. The 95% CL of the corresponding stability attributes at 30 months is smaller than the corresponding acceptance criterion.

For (b) (4) we did not conduct statistical analyses for Batch EW1603A1 since their value are not detectable.

Table 9: Predicted Value and the Corresponding 95% Confidence Limit at 30 months for Remdesivir (GS-5734™) Injection Lyophilized Dosage at (b) (4) Site based on Two-Batch Long-term Stability Data

Variable	Batch No	Figure No*	Storage, Months	Time, Months	Predicted Value	At 36 months		Acceptance Criterion
						95% LCL	95% UCL	
Assay	EW1805A1	40	12	30	(b) (4)			(b) (4) %
	EW1603A1	41	36	30				
Total degradation	EW1603A1	42	36	30				NMT (b) %
(b) (4)	EW1805A1	43	12	30				NMT (b) (4) %
	EW1603A1	44	36	30				
pH	EW1805A1	45	12	30				(b)
	EW1603A1	46	36	30				
(b) (4)	EW1805A1	47	12	30				NMT (b) (4) %
	EW1603A1	48	36	30				

NA: not available
*Figure No: The corresponding figure in the Appendix to show the stability data trend

4.5 (b) (4) Site

100 mg lyophilized dosage form

Five batches (EW2014A1, EW2016A1, EW2018A1, AN7049B, and AN7050C) were not included in the analysis since the stability data has only zero to three months under long-term stability condition.

4.6 (b) (4) Site

100 mg lyophilized dosage form

Three batches (00001, 00003, and 00004) were not included in the analysis since the stability data has only zero month under long-term stability condition.

4.7 (b) (4) Site

100 mg lyophilized dosage form

Six batches (2041087.1, 2041088.1, 2009106.1, 2009107.1, 1010131.1, and 1010132.1) were not included in the analysis since the stability data has only zero to three months under long-term stability condition.

4.8 (b) (4) Site

100 mg lyophilized dosage form

Three batches (200553F, 200613F, and 200653F) were not included in the analysis since the stability data has only zero months under long-term stability condition.

5. Conclusions and Recommendations

We concluded the analysis results by site as follows.

Gilead San Dimas Site

5 mg/ml solution dosage form

According to the ICH Q1E guidance [1], no extrapolation for the shelf life from the observed time is allowed because the accelerated data of assay and total degradation product content from two batches (004549 and 005796) has a significant trend within six months. Thus, we will use statistical analysis to support the proposed shelf life of 12 months from the observed time.

Although the ICH Q1E guidance required three batches with 12-month data to support 12-month shelf life, two batches (004549 and 005796) with 12-month stability data and Batch 005866 with 9-month stability data was included in the analysis for this specific submission.

The 12-month stability data of assay, pH, total degradation product content, (b) (4) pH, (b) (4) from two batches (004549 and 005796) under the long-term stability condition support the 12-month shelf life for Remdesivir (GS-5734TM) injection.

Gilead La Verne Site

5 mg/ml solution dosage form

According to the ICH Q1E guidance, no extrapolation for the shelf life from the observed time is allowed because the accelerated data of assay and total degradation product content from four batches (020985, 020953, 020954, and 020955) has a significant trend within six months.

These four batches (020985, 020953, 020954, and 020955) were not included in the analysis since the stability data has only three to six months under long-term stability condition. Since the applicant did not provide at least three batches covering the proposed the proposed shelf life, according to the ICH Q1A guidance [2], the applicant has provided a post-approval commitment to continue the long-term stability studies through the proposed shelf life and the accelerated studies for 6 months for further evaluation.

(b) (4) **Site**

100 mg lyophilized dosage form

The ICH Q1E guidance required a batch with at least (b) (4) month data to support (b) (4) month shelf life, so we considered the shelf life of 30 months based on three batches (Batch EW1802A1, EW1803A1 and EW1804A1) with 18-month stability data in the analysis for this specific submission. In addition, we recommend the applicant changing the shelf life from (b) (4) months to 30 months and the IR has been sent to the applicant on October 14, 2020.

The 18-month stability data of assay, total degradation product content, (b) (4) pH, (b) (4) (b) (4) from these three batches under the long-term stability condition support the 30-month shelf life for Remdesivir (GS-5734TM) injection. We noticed that, for Batch EW1803A1, the 95% CL of pH at 30 months is smaller than but close to the corresponding acceptance criterion.

150 mg lyophilized dosage form

The 48-month stability data of assay, total degradation product content, (b) (4) pH, (b) (4) (b) (4) from Batch EW1602A1 under the long-term stability condition support the 30-month shelf life for Remdesivir (GS-5734TM) injection.

(b) (4) Site

100 mg lyophilized dosage form

The ICH Q1E guidance required a batch with at least (b) (4) month data to support (b) (4) month shelf life, so we considered the shelf life of 30 months to be consistent with the analysis at the (b) (4) site.

(b) (4)

150 mg lyophilized dosage form

The 36-month stability data of assay, total degradation product content, (b) (4) pH, (b) (4) (b) (4) from Batch EW1603A1 under the long-term stability condition support the 30-month shelf life for Remdesivir (GS-5734TM) injection.

We also noticed that there might be a shift of the assay value between the (b) (4) site and the (b) (4) site. More details are provided in Section 3.

(b) (4) site

100 mg lyophilized dosage form

Three batches (EW2014A1, EW2016A1, EW2018A1) were not included in the analysis since the stability data has only zero to three months under long-term stability condition. Since the applicant did not provide at least three batches covering the proposed the proposed shelf life, according to the ICH Q1A guidance, the applicant has provided a post-approval commitment to continue the long-term stability studies through the proposed shelf life and the accelerated studies for 6 months for further evaluation.

(b) (4) site

100 mg lyophilized dosage form

Three batches (00001, 00003, and 000041) were not included in the analysis since the stability data has only zero month under long-term stability condition. Since the applicant did not provide at least three batches covering the proposed the proposed shelf life, according to the ICH Q1A guidance, the applicant has provided a post-approval commitment to continue the long-term stability studies through the proposed shelf life and the accelerated studies for 6 months for further evaluation.

(b) (4) site

100 mg lyophilized dosage form

Six batches (2041087.1, 2041088.1, 2009106.1, 2009107.1, 1010131.1, and 1010132.1) were not included in the analysis since the stability data has only zero month under long-term stability

condition. Since the applicant did not provide at least three batches covering the proposed the proposed shelf life, according to the ICH Q1A guidance, the applicant has provided a post-approval commitment to continue the long-term stability studies through the proposed shelf life and the accelerated studies for 6 months for further evaluation.

(b) (4) **site**

100 mg lyophilized dosage form

Three batches (200553F, 200613F, and 200653F) were not included in the analysis since the stability data has only zero month under long-term stability condition. Since the applicant did not provide at least three batches covering the proposed the proposed shelf life, according to the ICH Q1A guidance, the applicant has provided a post-approval commitment to continue the long-term stability studies through the proposed shelf life and the accelerated studies for 6 months for further evaluation.

We also recommend the applicant providing additional batches with more months in the future submission for further evaluation.

6. References

[1] ICH HARMONISED TRIPARTITE GUIDELINE EVALUATION FOR STABILITY DATA Q1E

[2] ICH HARMONISED TRIPARTITE GUIDELINE EVALUATION FOR STABILITY DATA Q1A

7. Appendix

In the Appendix, we provided the stability plots of six stability attributes (assay, total degradation product content, (b) (4) pH, (b) (4)) for Remdesivir (GS-5734^{TM}) injection solution dosage at the Gilead San Dimas Site under long-term stability conditions of 5±3°C. We also provided the stability plots of five stability attributes (assay, total degradation product content, (b) (4) pH, and (b) (4)) for Remdesivir (GS-5734^{TM}) injection lyophilized dosage at the (b) (4) Site and the (b) (4) site under long-term stability conditions of 30°C/75%RH.

Please note, in all stability plots, the dots are the observed stability data, the fitted line is the predicted mean value obtained via linear regression, and the solid line are the 95% CL of the mean value. The straight lines are the acceptance criteria.

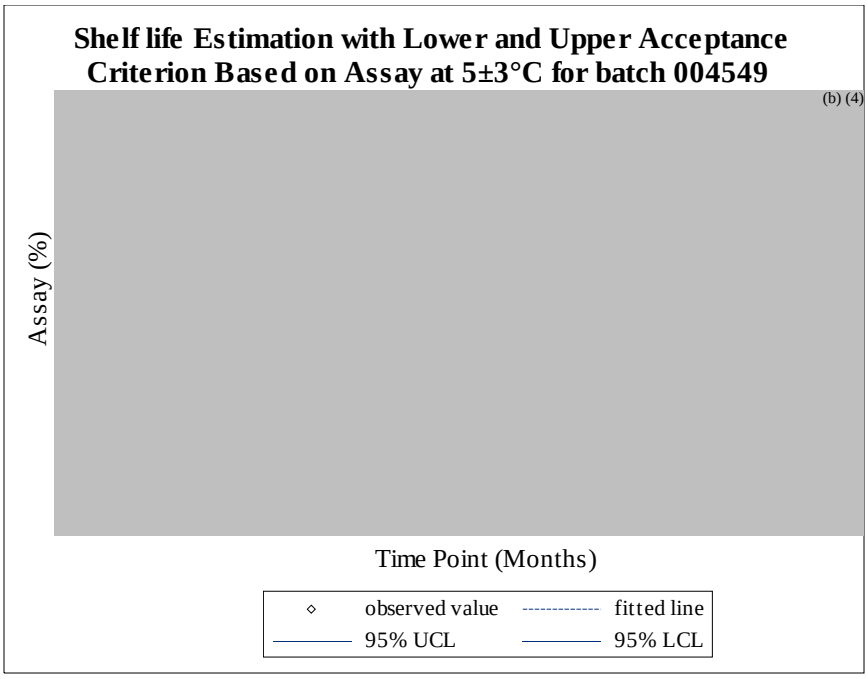

Figure 6: Assay versus time trend for Batch 004549 at 5±3°C

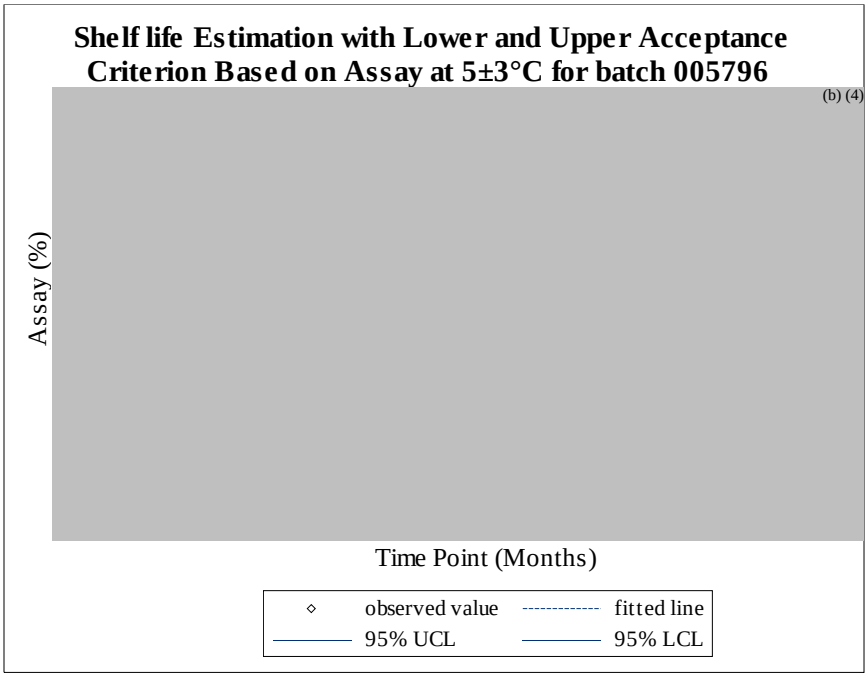

Figure 7: Assay versus time trend for Batch 005796 at 5±3°C

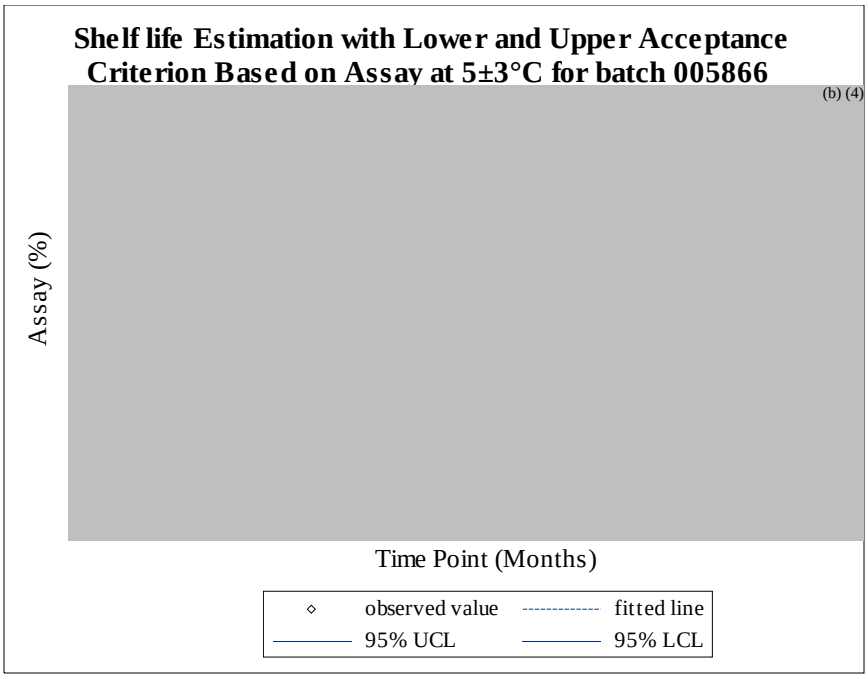

Figure 8: Assay versus time trend for Batch 005796 at 5±3°C

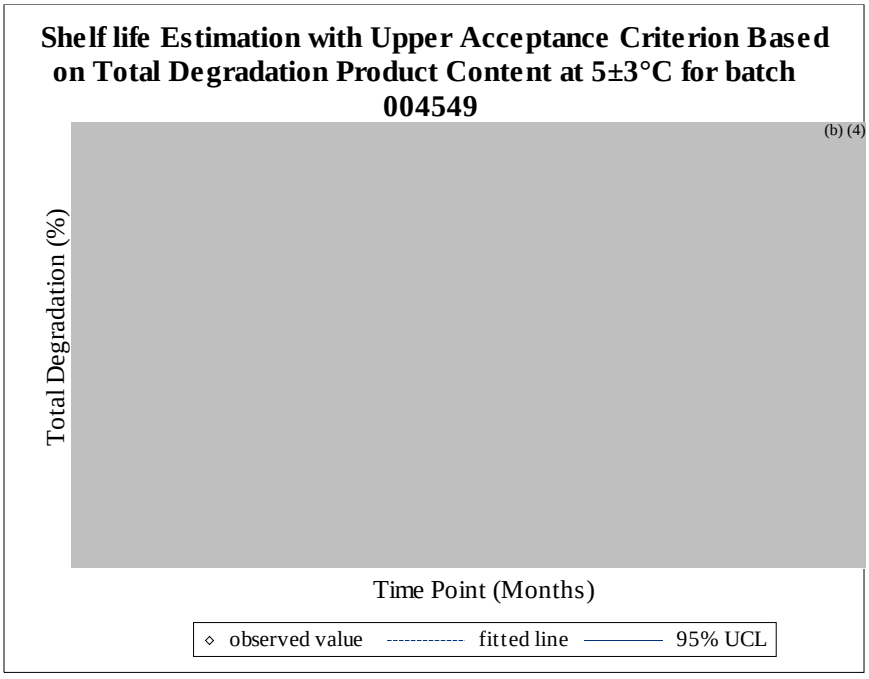

Figure 9: Total degradation product content versus time trend for Batch 004549 at 5±3°C

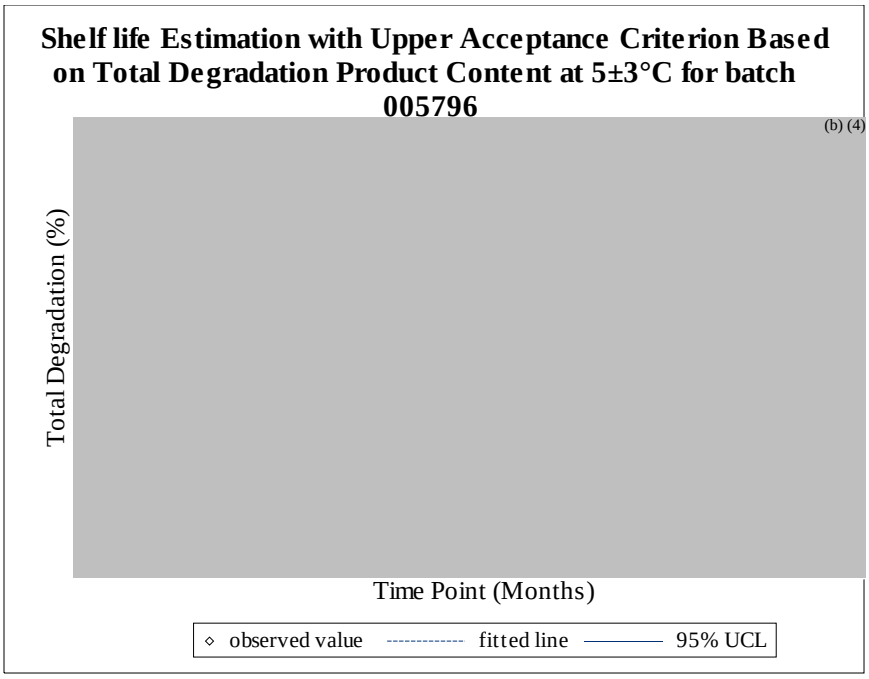

Figure 10: Total degradation product content versus time trend for Batch 005796 at 5±3°C

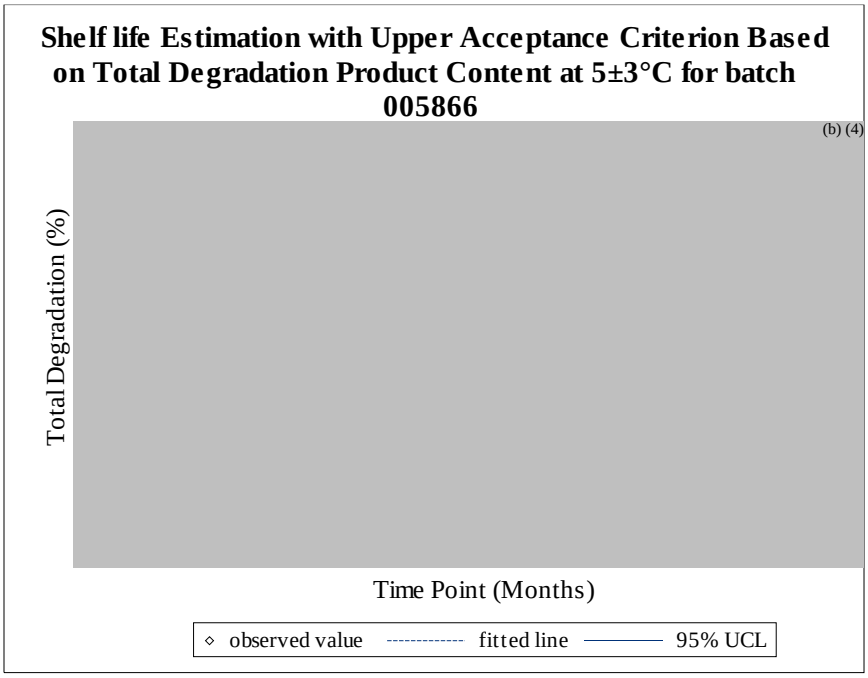

Figure 11: Total degradation product content versus time trend for Batch 005866 at 5±3°C

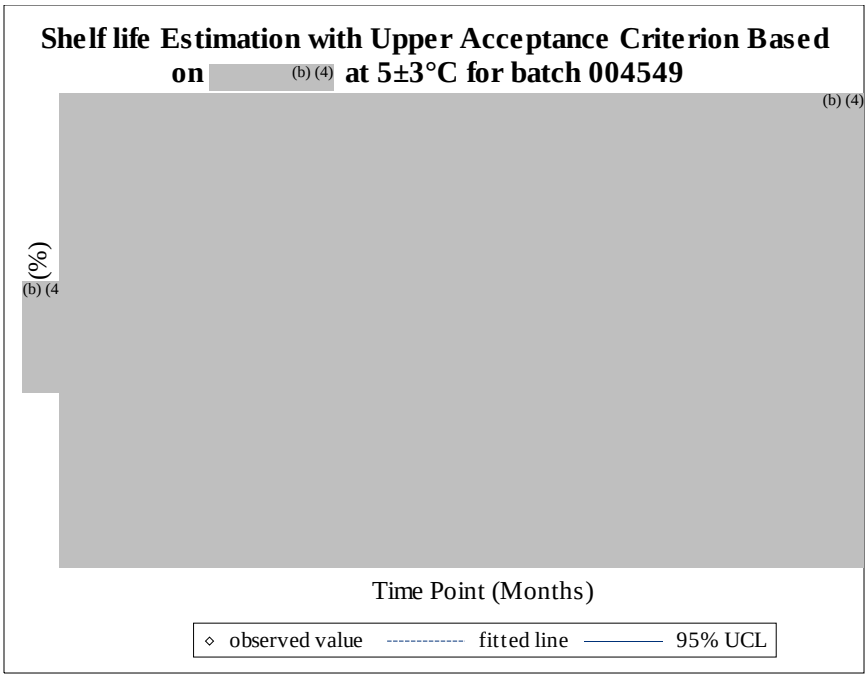

Figure 12: (b) (4) versus time trend for Batch 004549 at 5±3°C

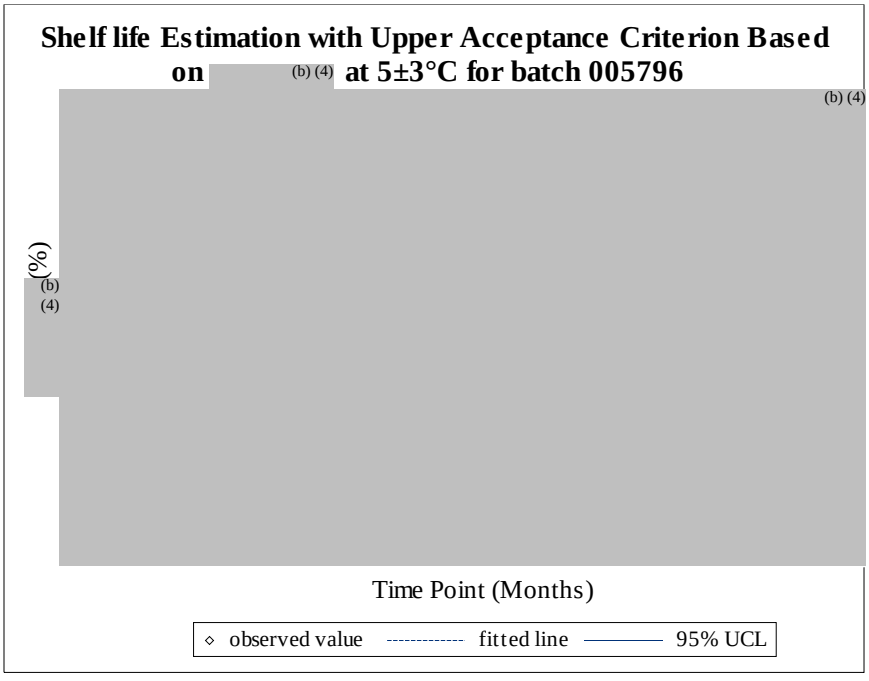

Figure 13: (b) (4) versus time trend for Batch 005796 at 5±3°C

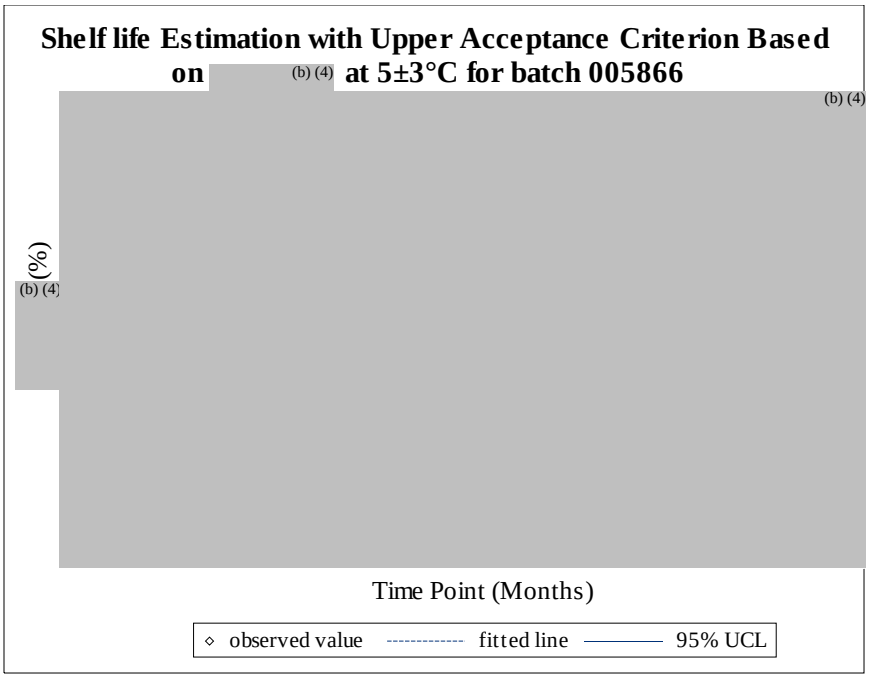

Figure 14: (b) (4) versus time trend for Batch 005866 at 5±3°C

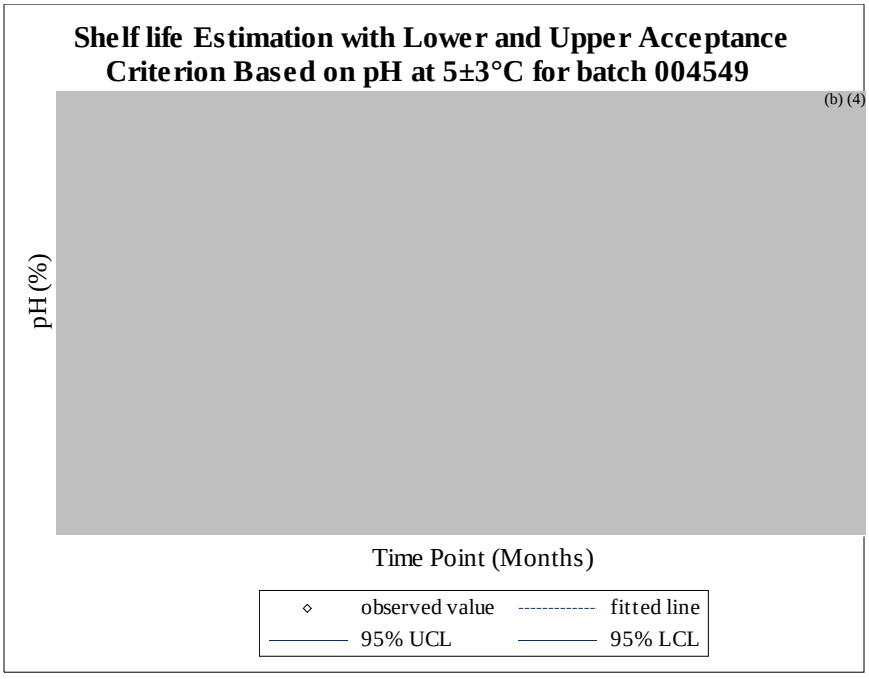

Figure 15: pH versus time trend for Batch 004549 at 5±3°C

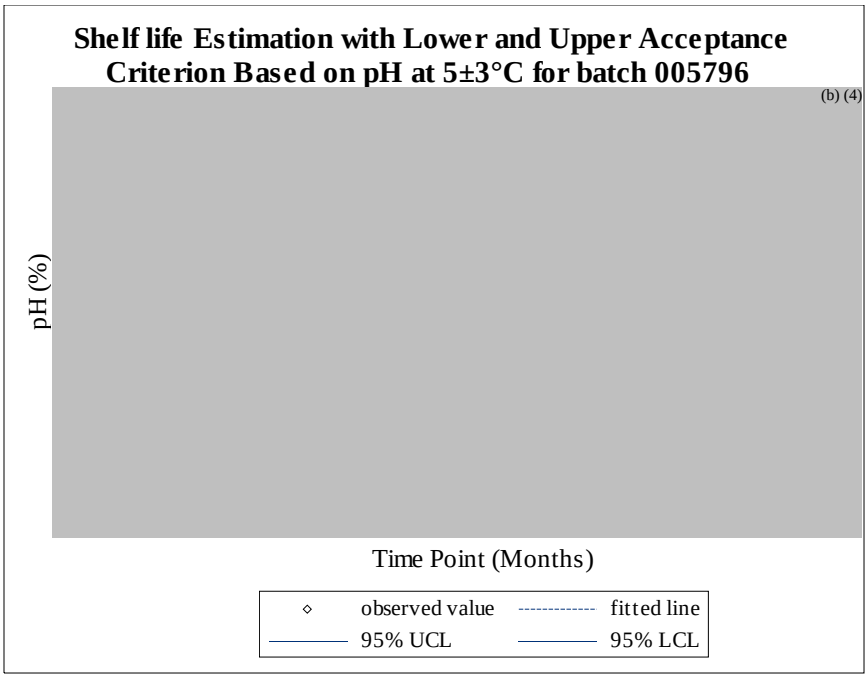

Figure 16: pH versus time trend for Batch 005796 at 5±3°C

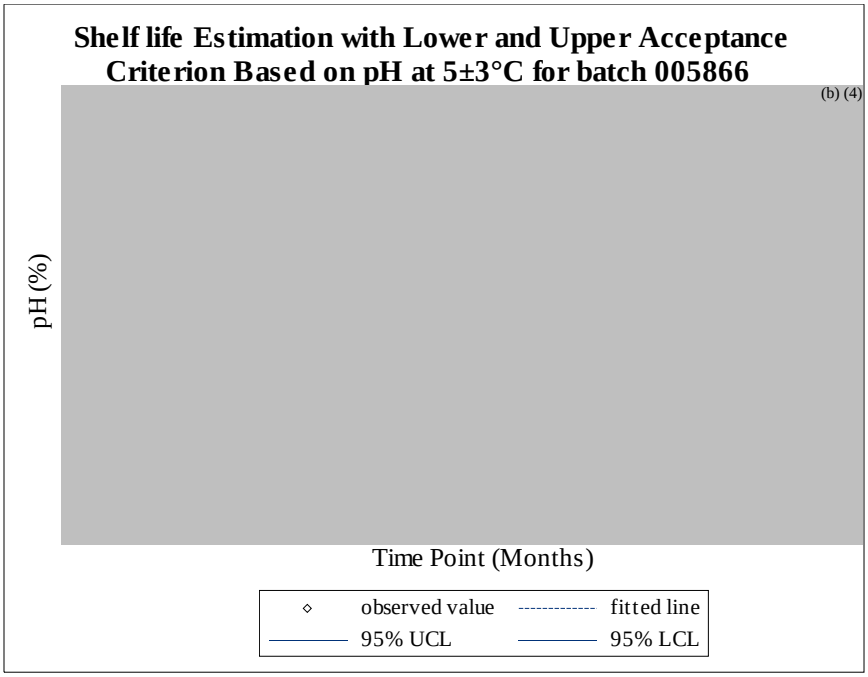

Figure 17: pH versus time trend for Batch 005866 at 5±3°C

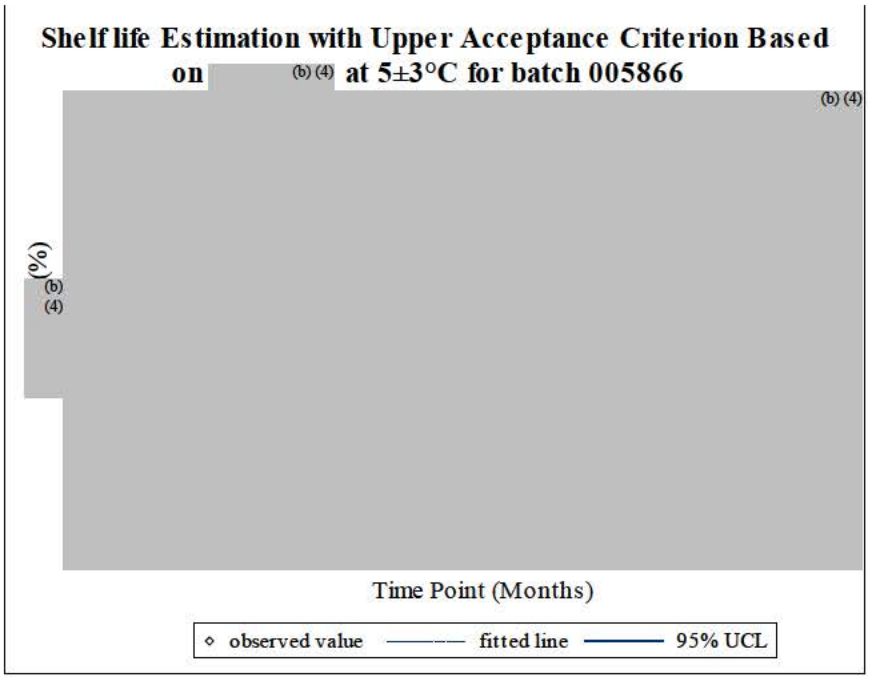

Figure 18: (b) (4) versus time trend for Batch 005866 at 5±3°C

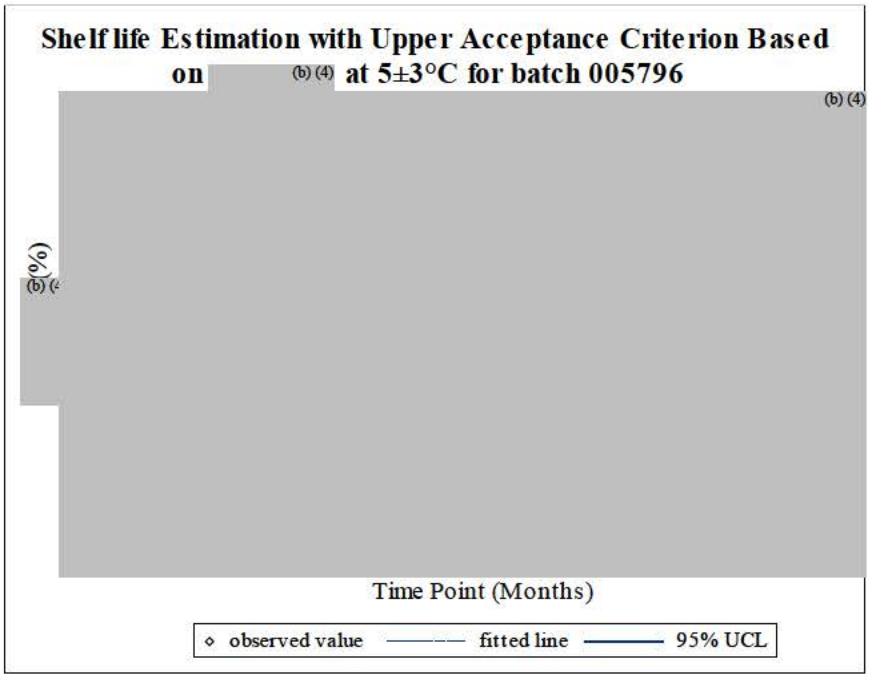

Figure 19: (b) (4) versus time trend for Batch 005796 at 5±3°C

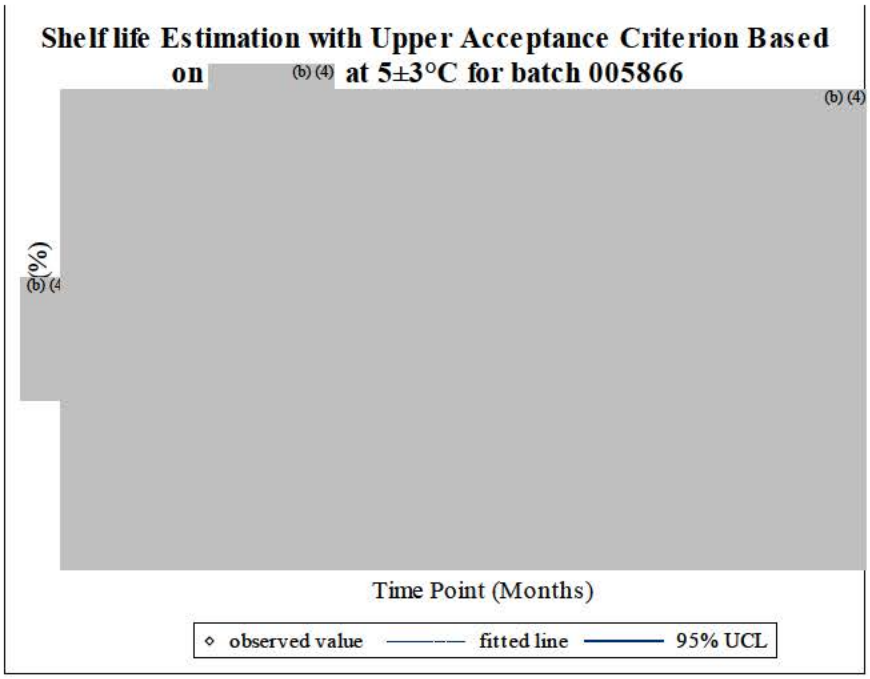

Figure 20: (b) (4) versus time trend for Batch 005866 at 5±3°C

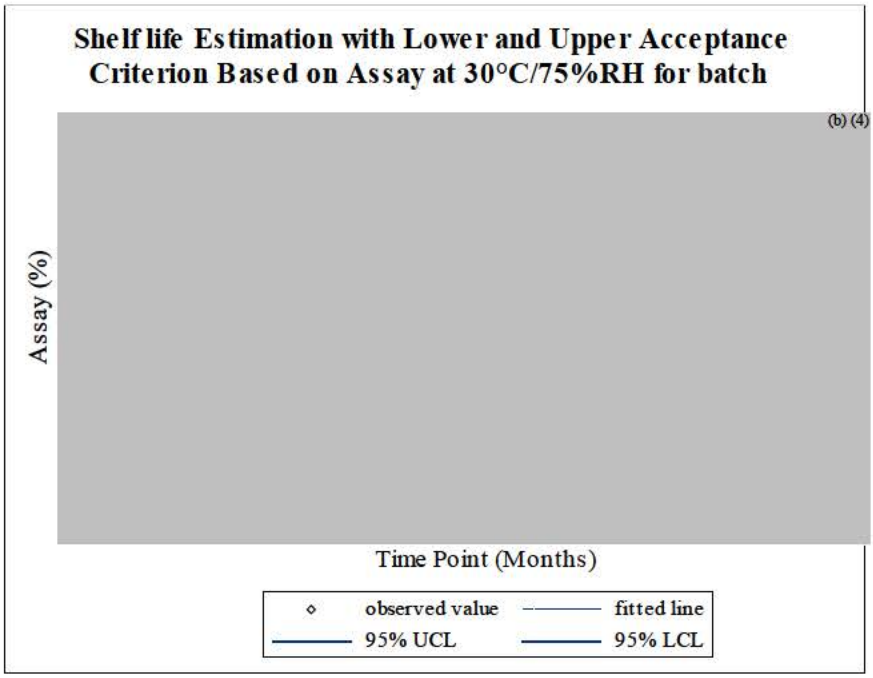

Figure 21: Assay versus time trend for Batch EW1802A1 at 30°C/75%RH

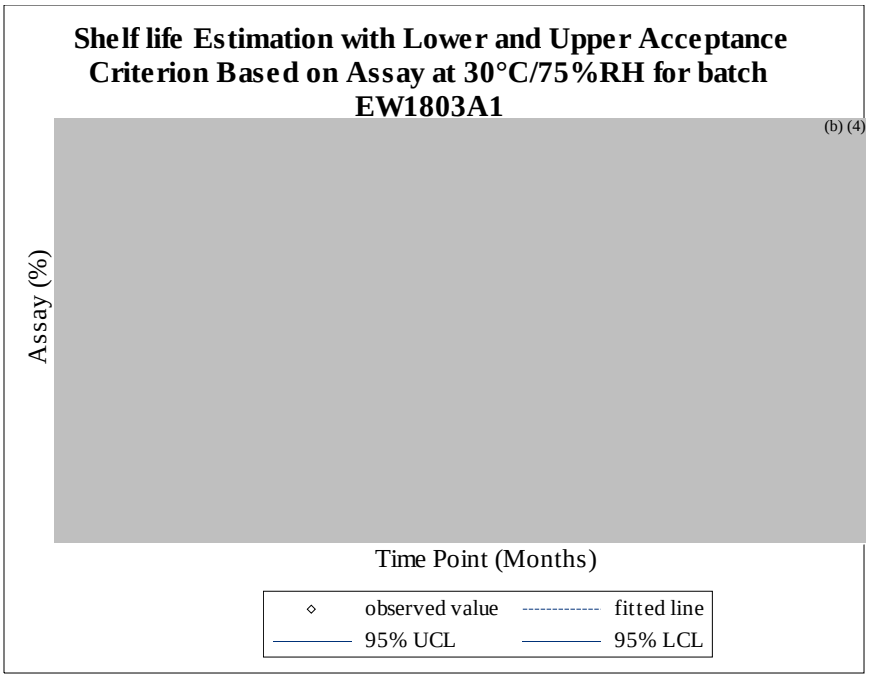

Figure 22: Assay versus time trend for Batch EW1803A1 at 30°C/75%RH

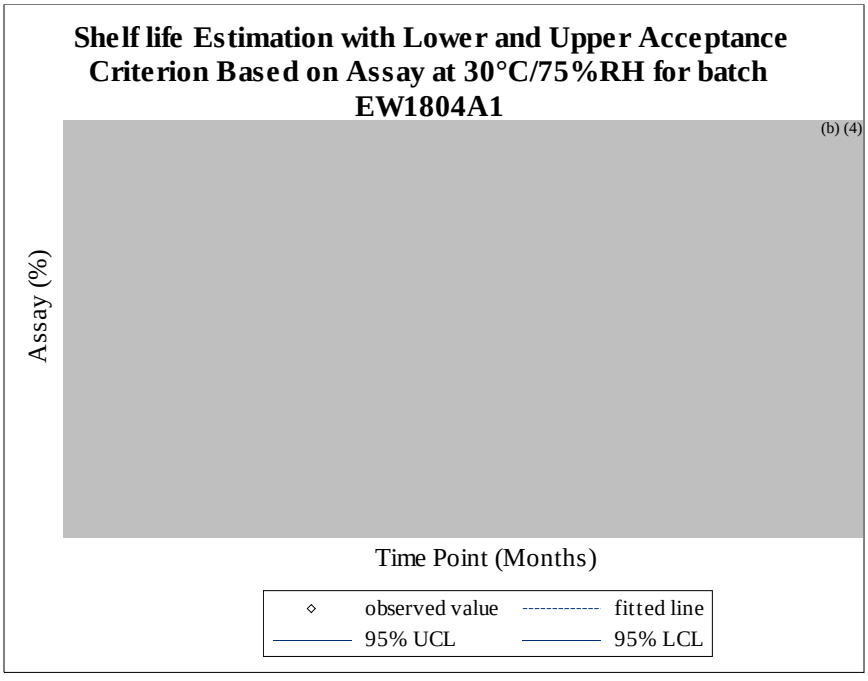

Figure 23: Assay versus time trend for Batch EW1804A1 at 30°C/75%RH

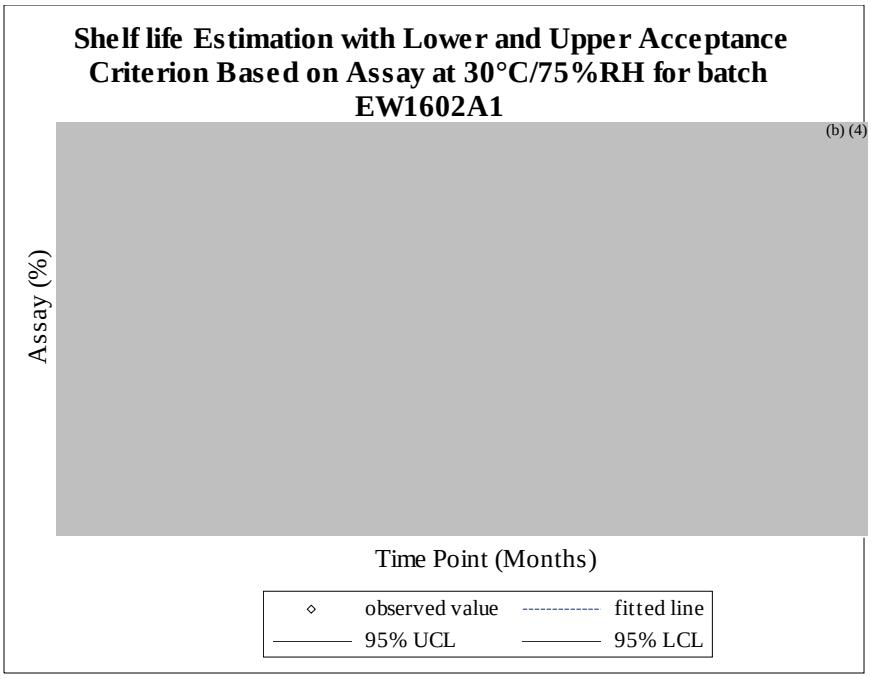

Figure 24: Assay versus time trend for Batch EW1602A1 at 30°C/75%RH

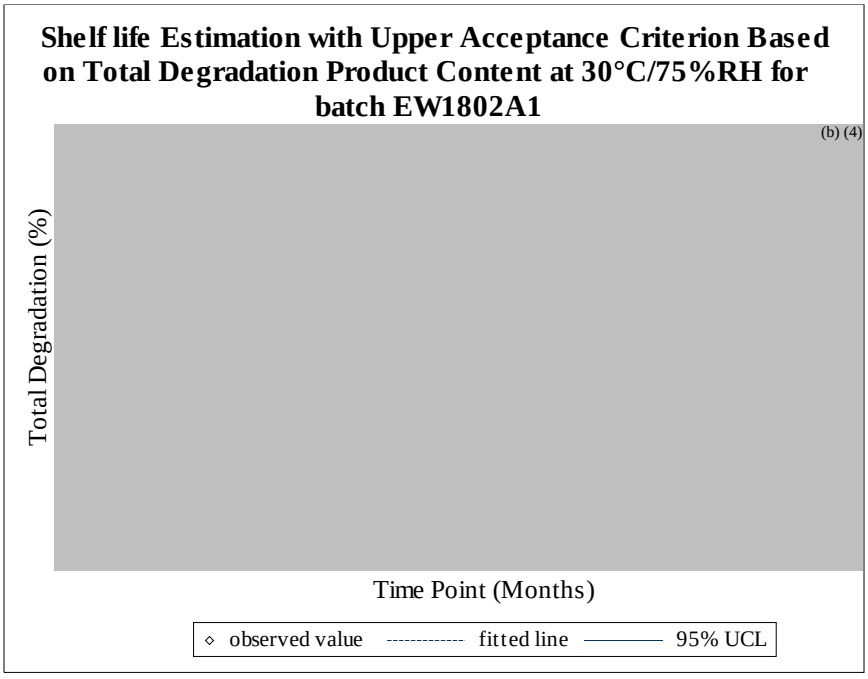

Figure 25: Total degradation product content versus time trend for Batch EW1802A1 at 30°C/75%RH

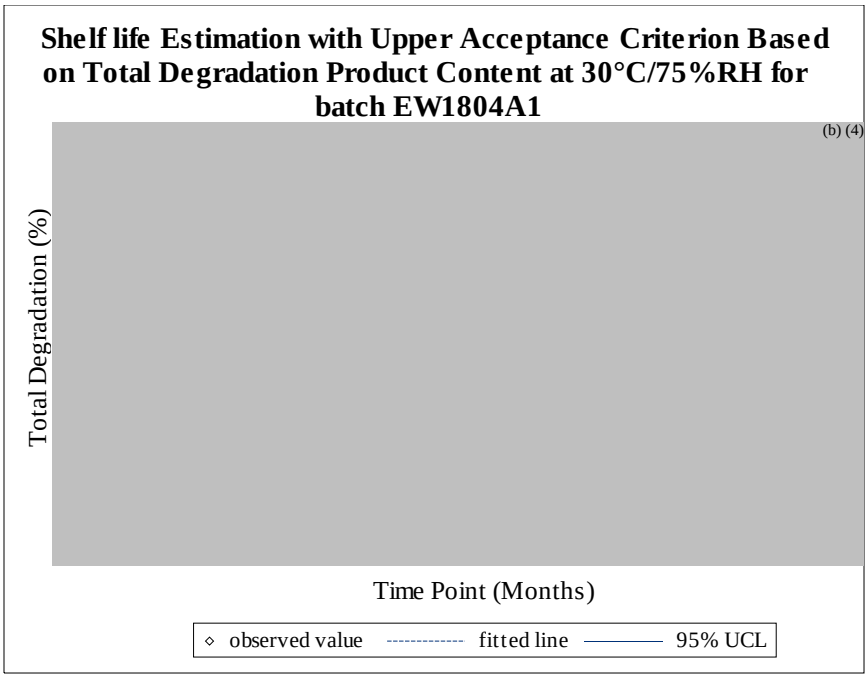

Figure 26: Total degradation product content versus time trend for Batch EW1804A1 at 30°C/75%RH

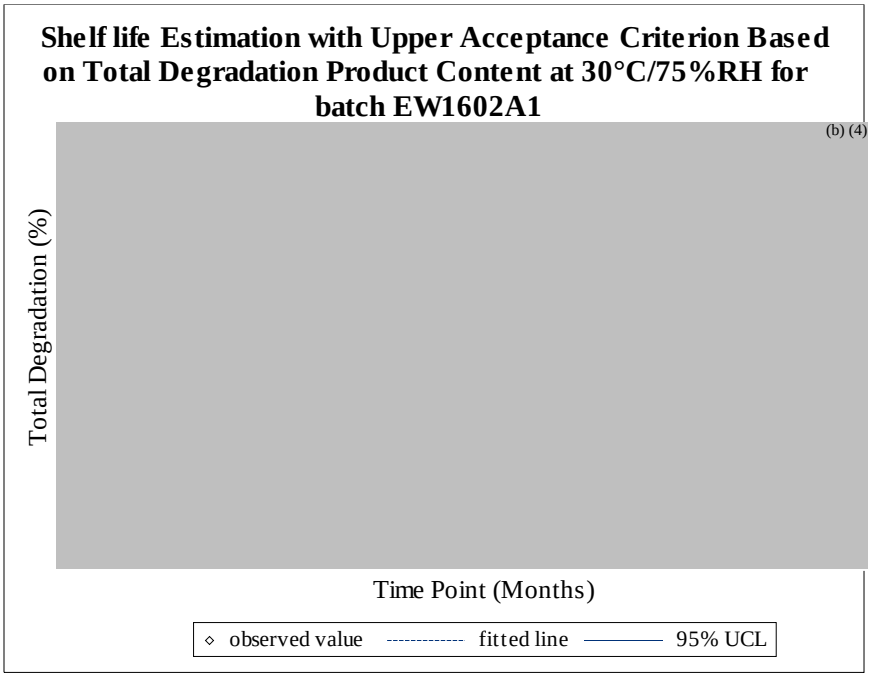

Figure 27: Total degradation product content versus time trend for Batch EW1602A1 at 30°C/75%RH

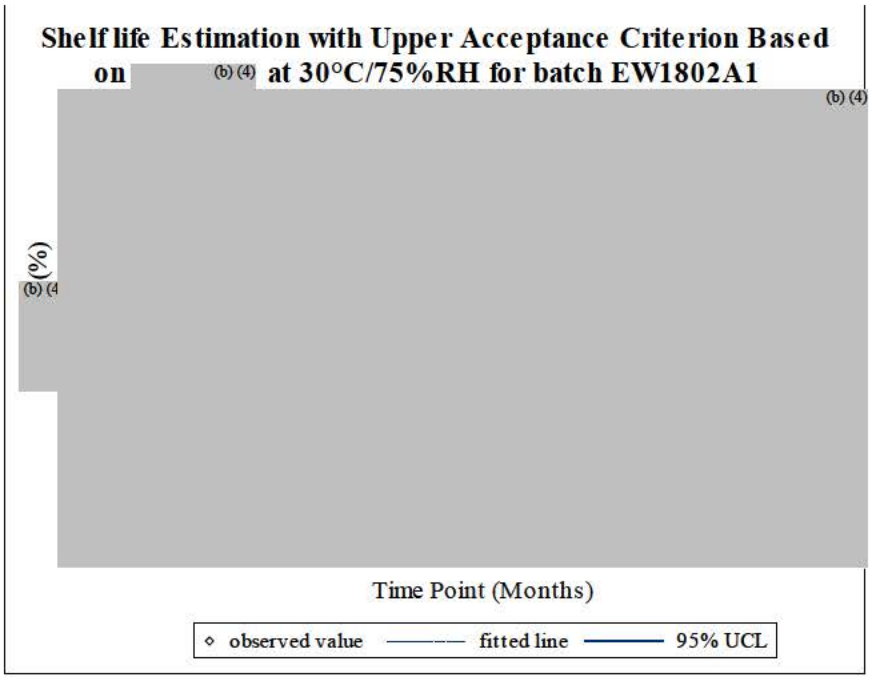

Figure 28: (b) (4) versus time trend for Batch EW1802A1 at 30°C/75%RH

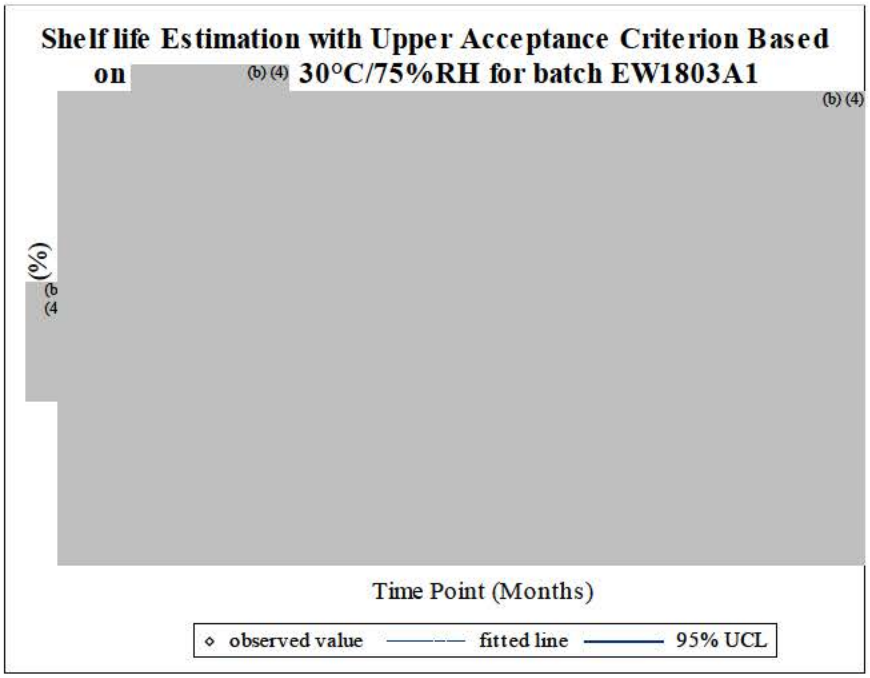

Figure 29: (b) (4) versus time trend for Batch EW1803A1 at 30°C/75%RH

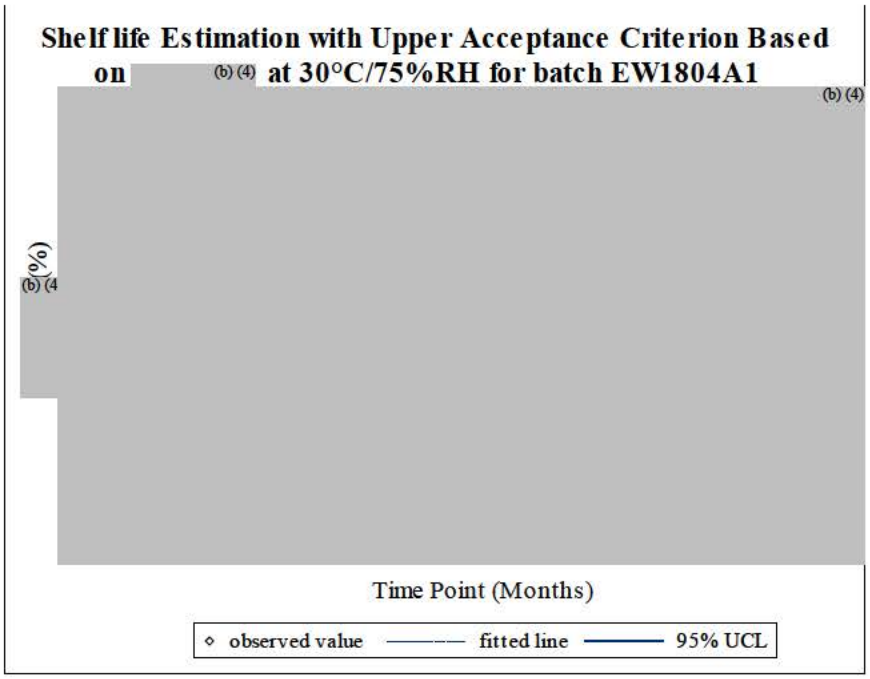

Figure 30: (b) (4) versus time trend for Batch EW1804A1 at 30°C/75%RH

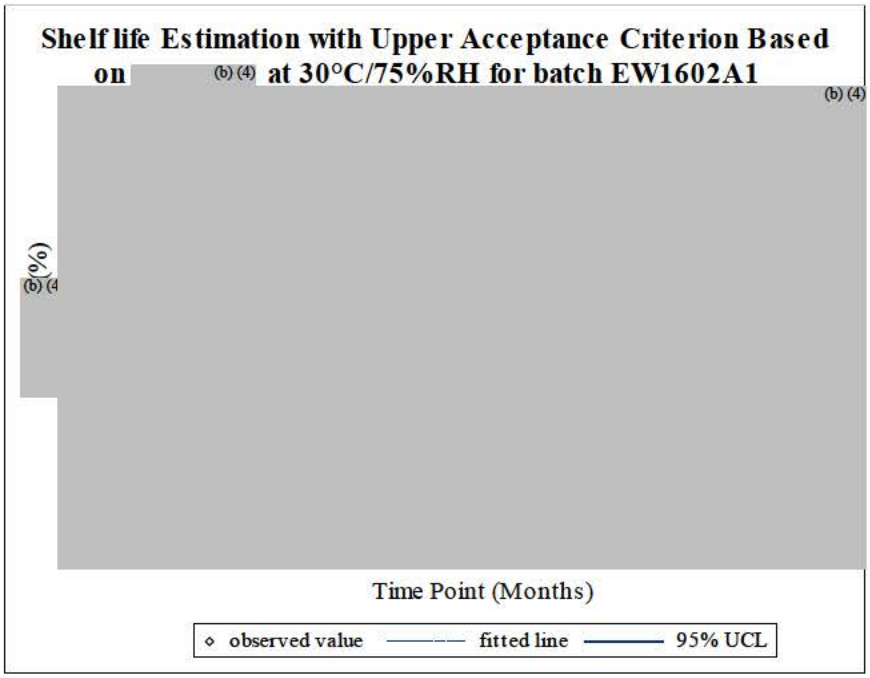

Figure 31: (b) (4) versus time trend for Batch EW1602A1 at 30°C/75%RH

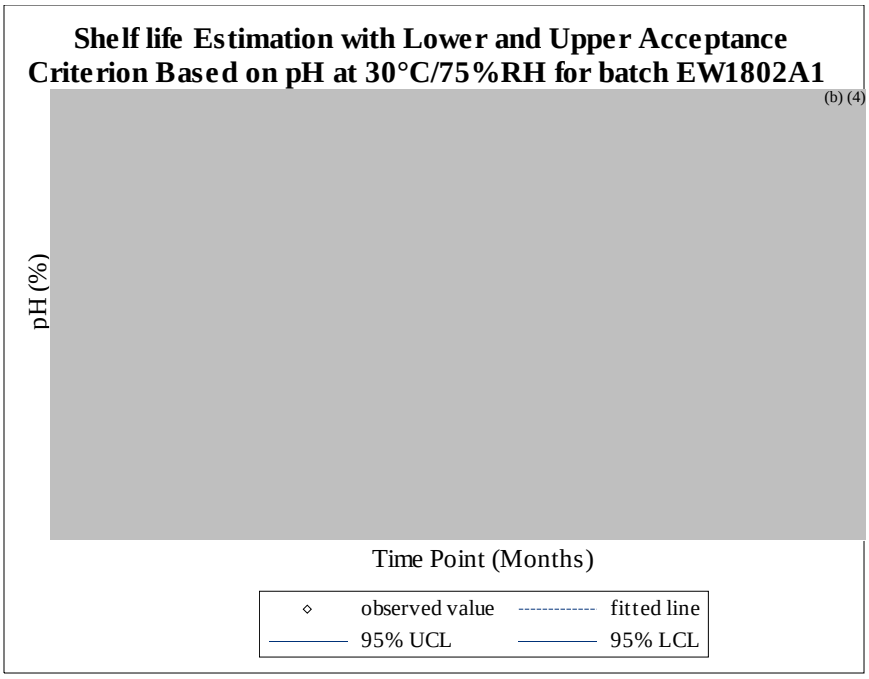

Figure 32: pH versus time trend for Batch EW1802A1 at 30°C/75%RH

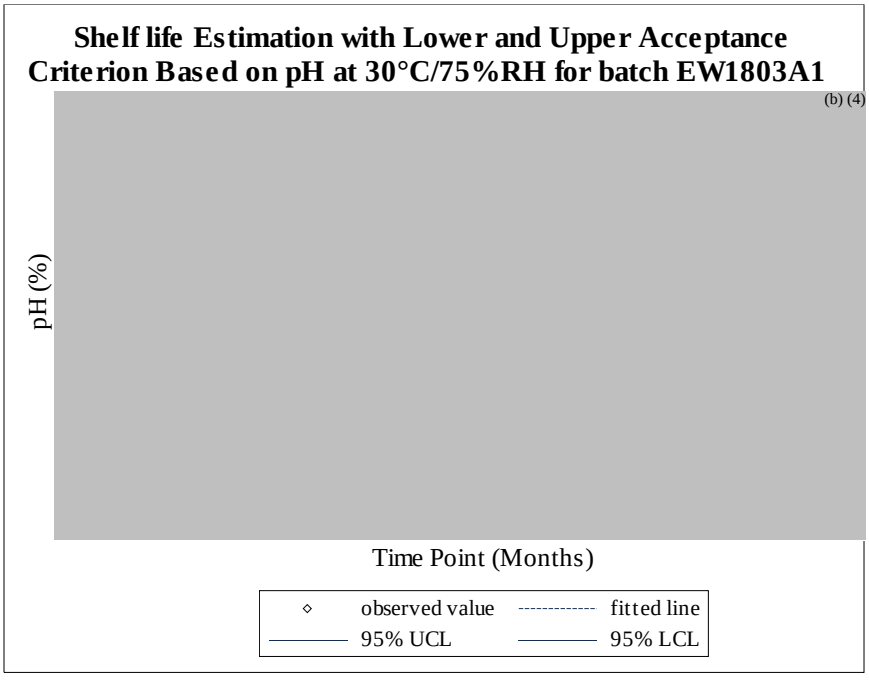

Figure 33: pH versus time trend for Batch EW1803A1 at 30°C/75%RH

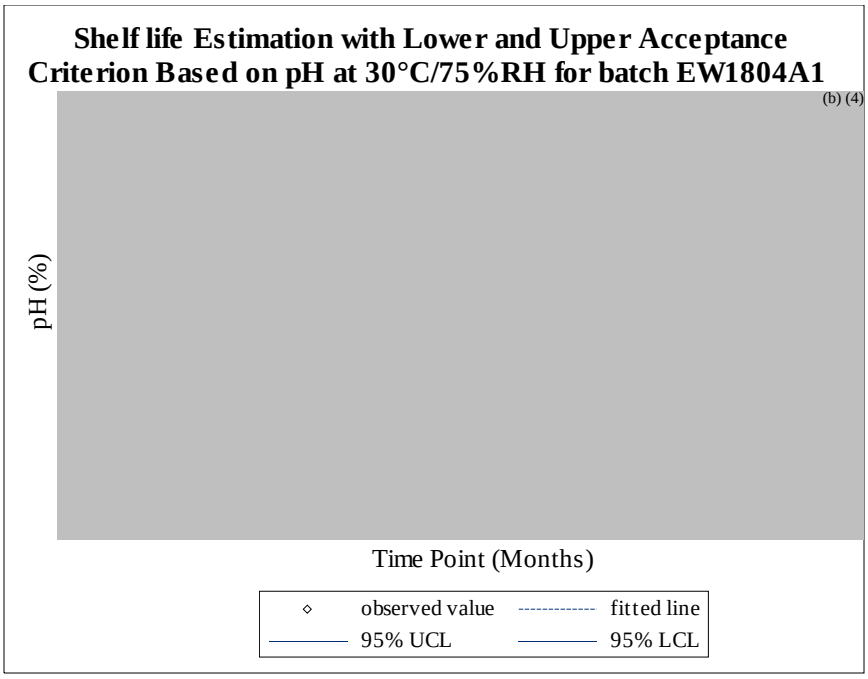

Figure 34: pH versus time trend for Batch EW1804A1 at 30°C/75%RH

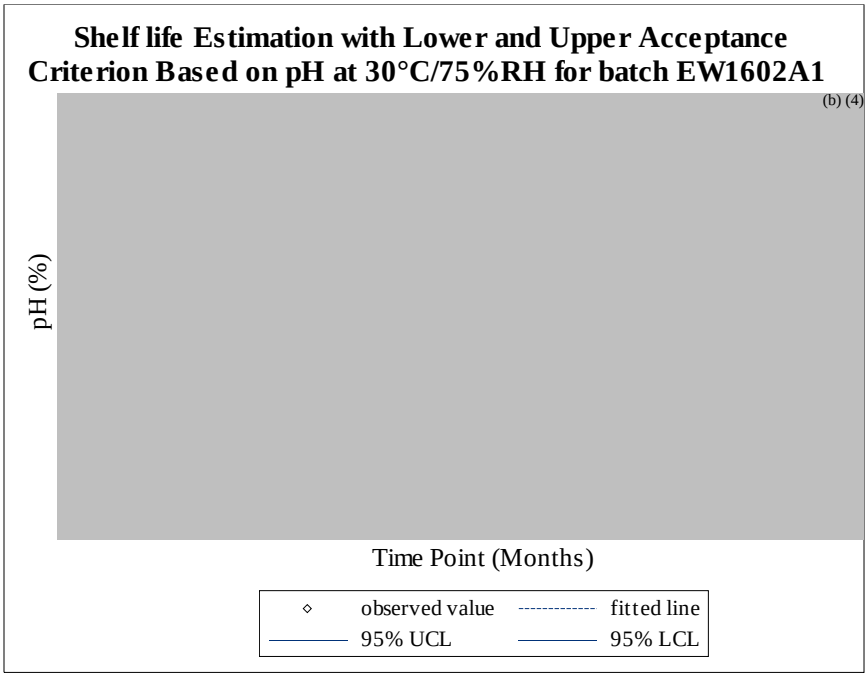

Figure 35: pH versus time trend for Batch EW1602A1 at 30°C/75%RH

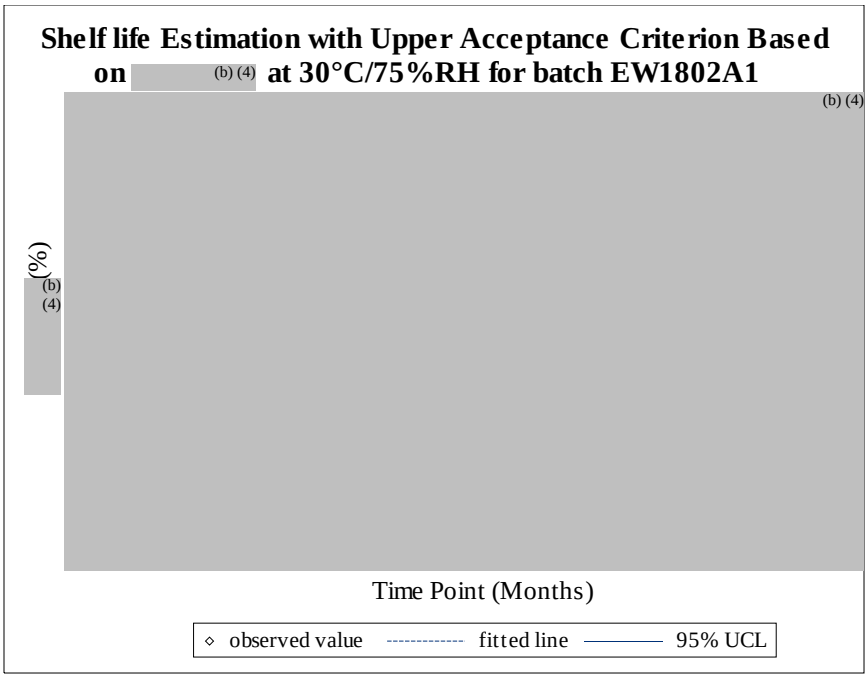

Figure 36: (b) (4) versus time trend for Batch EW1802A1 at 30°C/75%RH

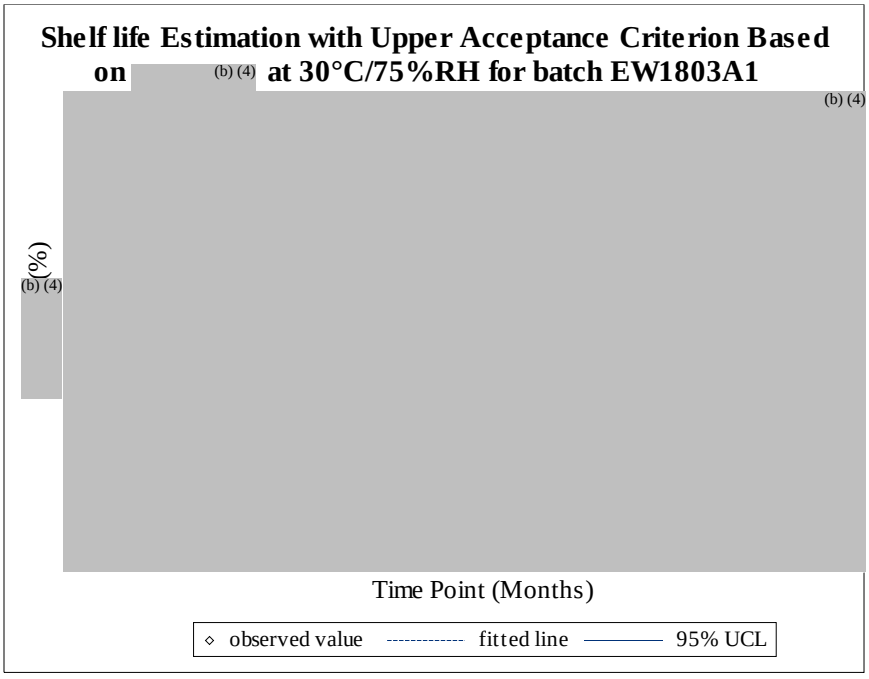

Figure 37: (b) (4) versus time trend for Batch EW1803A1 at 30°C/75%RH

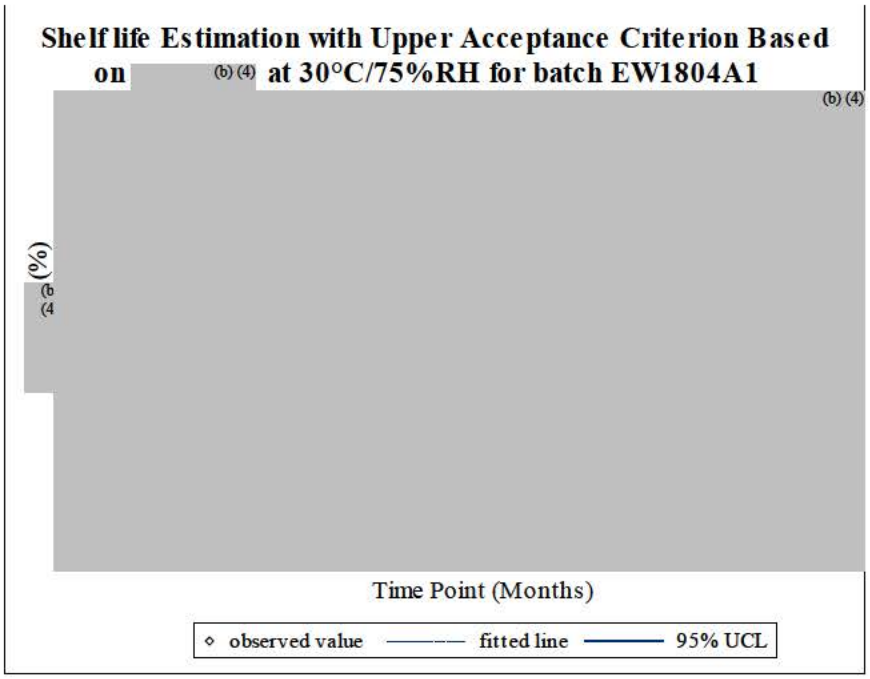

Figure 38: (b) (4) versus time trend for Batch EW1804A1 at 30°C/75%RH

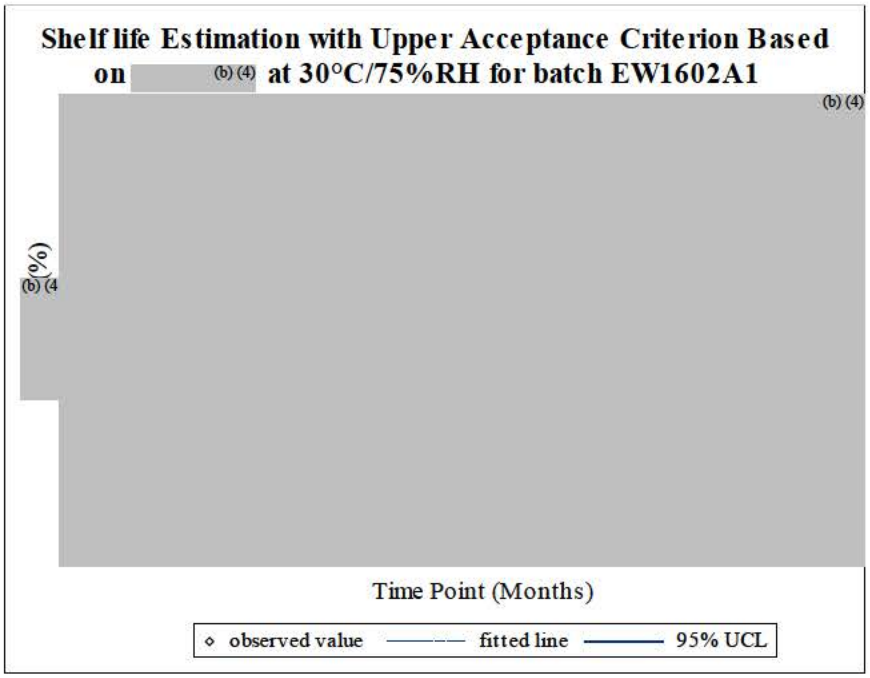

Figure 39: (b) (4) versus time trend for Batch EW1602A1 at 30°C/75%RH

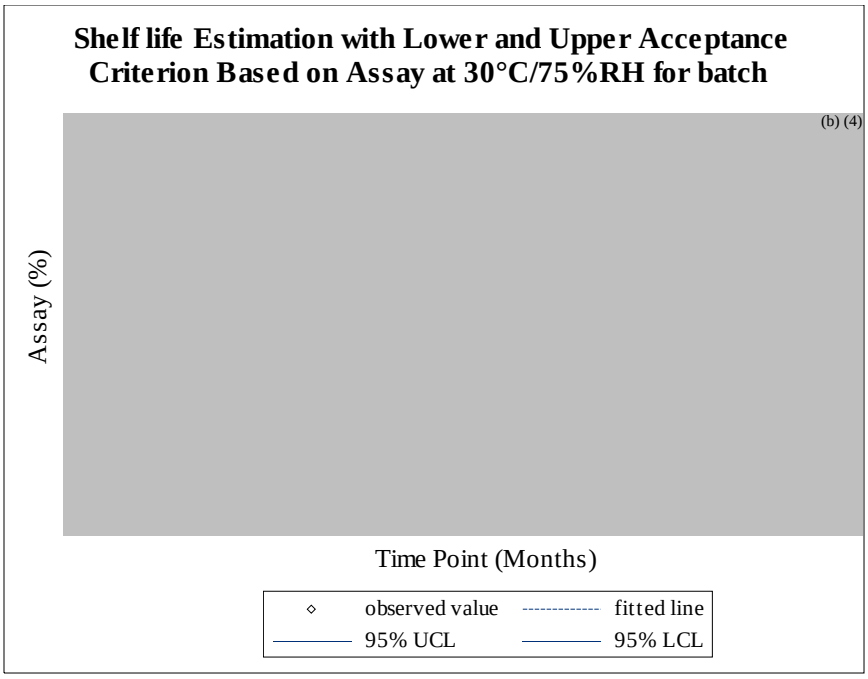

Figure 40: Assay versus time trend for Batch EW1805A1 at 30°C/75%RH

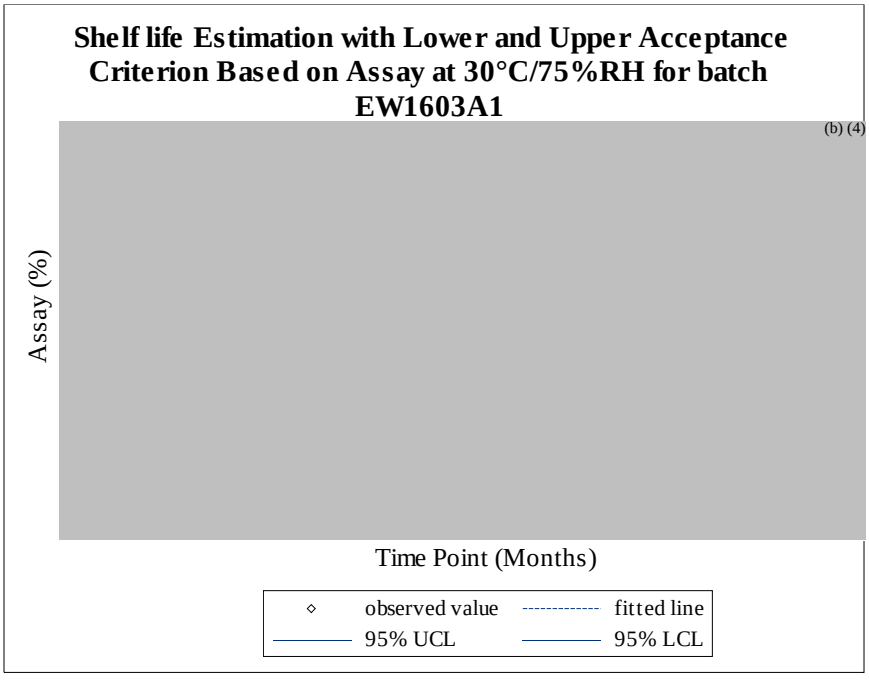

Figure 41: Assay versus time trend for Batch EW1603A1 at 30°C/75%RH

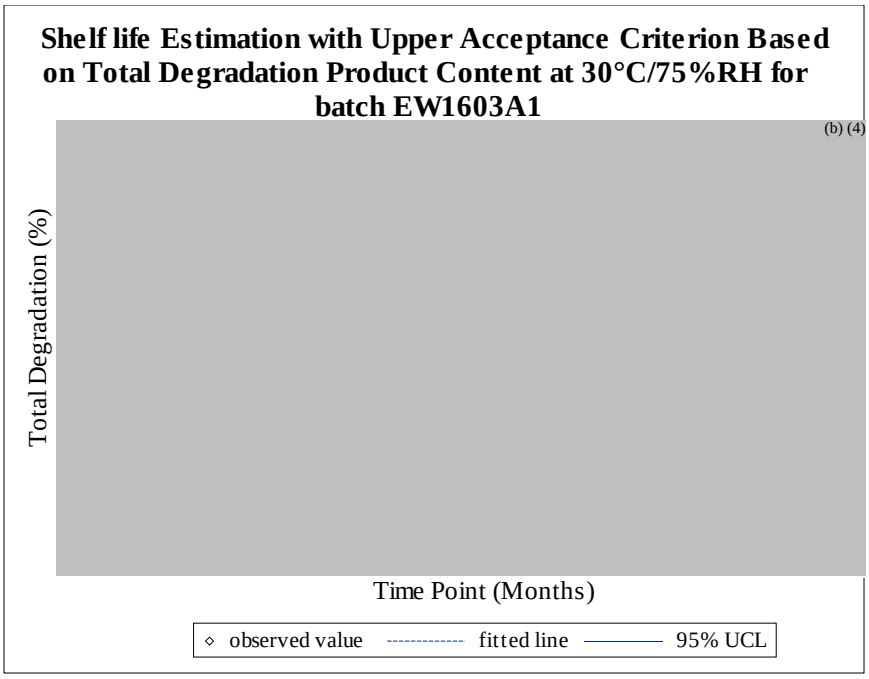

Figure 42: Total degradation product content versus time trend for Batch EW1603A1 at 30°C/75%RH

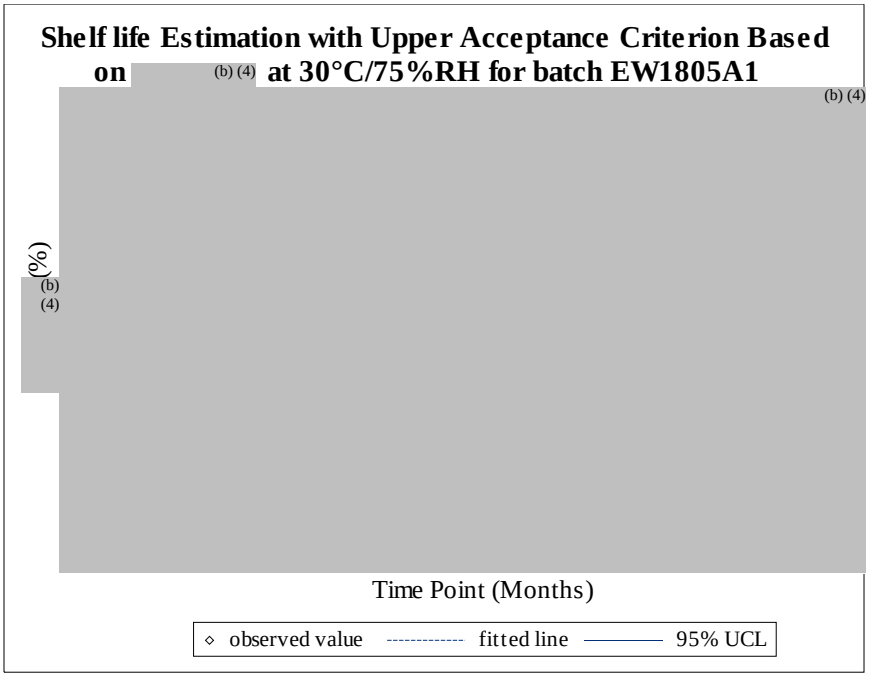

Figure 43: (b) (4) versus time trend for Batch EW1805A1 at 30°C/75%RH

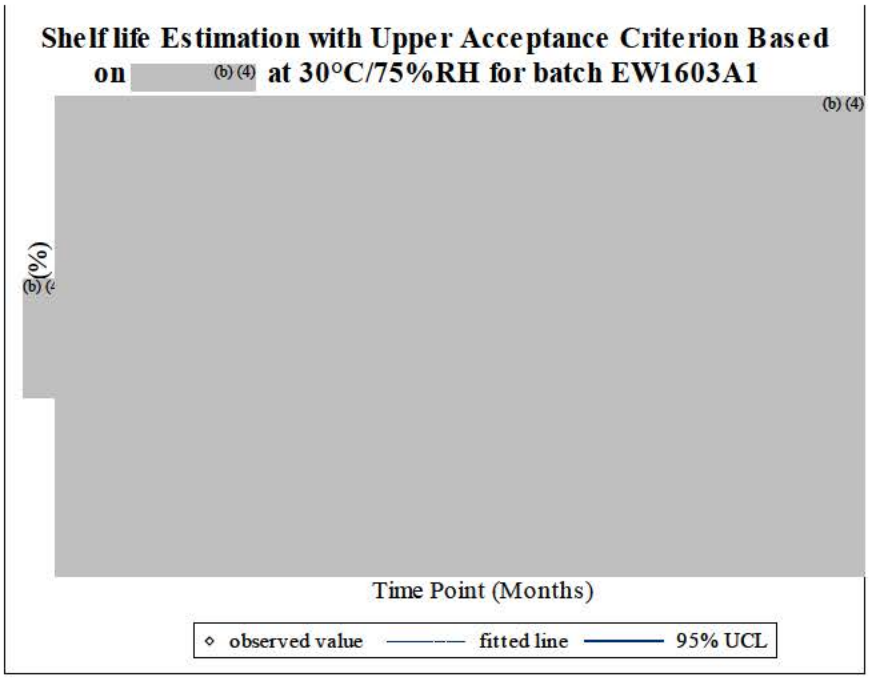

Figure 44: (b) (4) versus time trend for Batch EW1603A1 at 30°C/75%RH

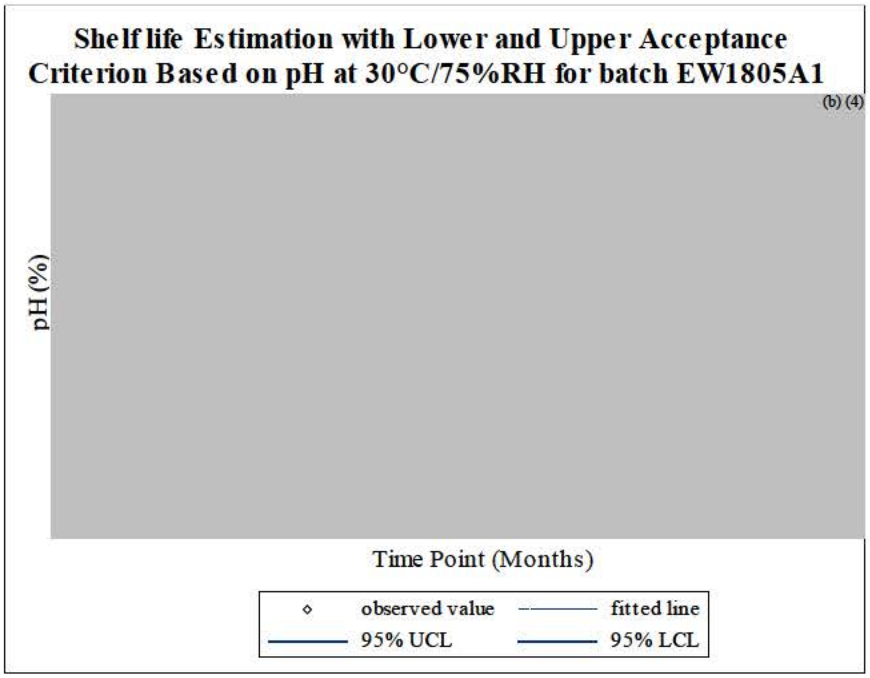

Figure 45: pH versus time trend for Batch EW1805A1 at 30°C/75%RH

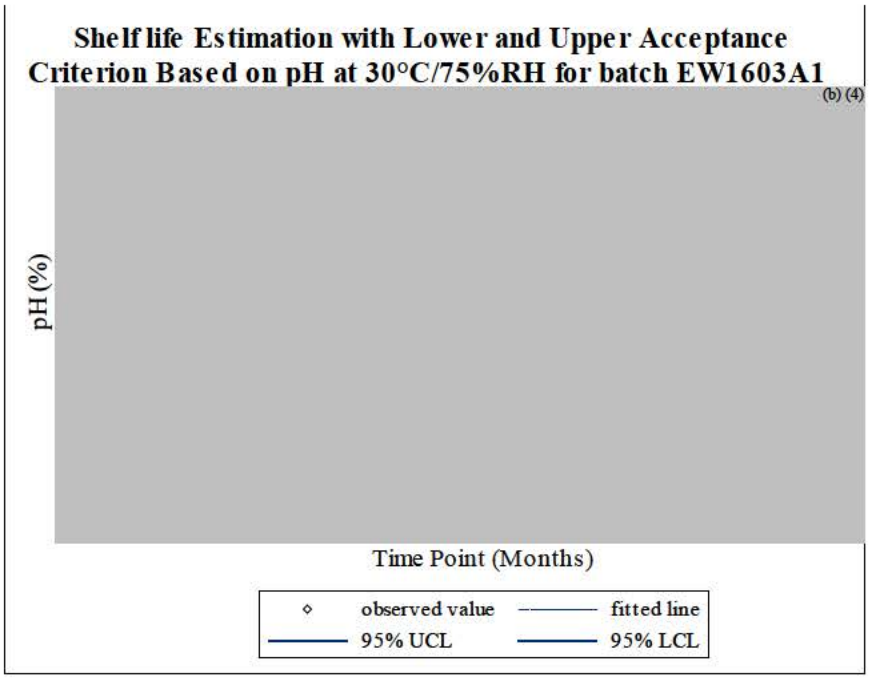

Figure 46: pH versus time trend for Batch EW1603A1 at 30°C/75%RH

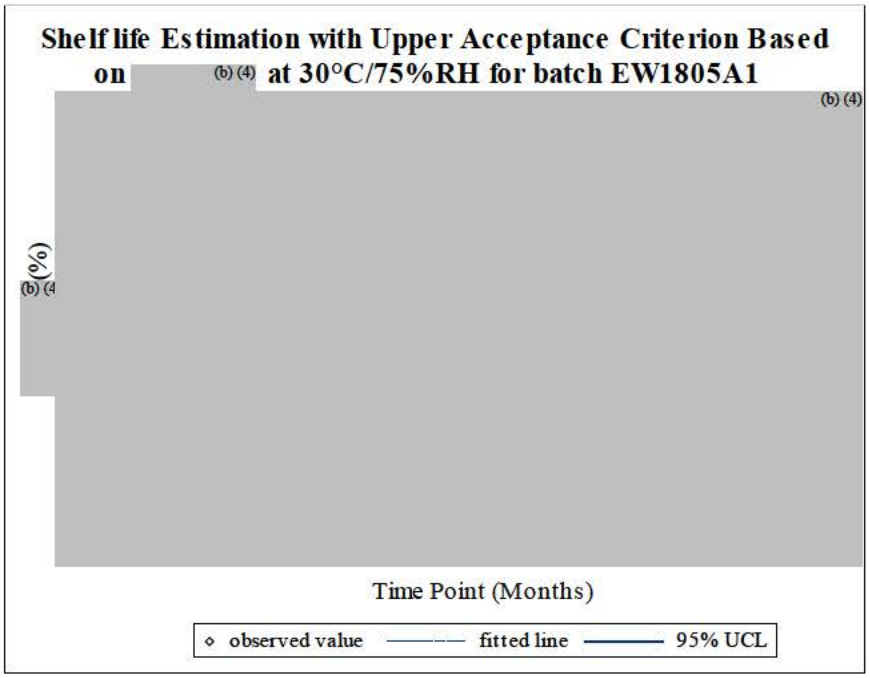

Figure 47: (b) (4) versus time trend for Batch EW1805A1 at 30°C/75%RH

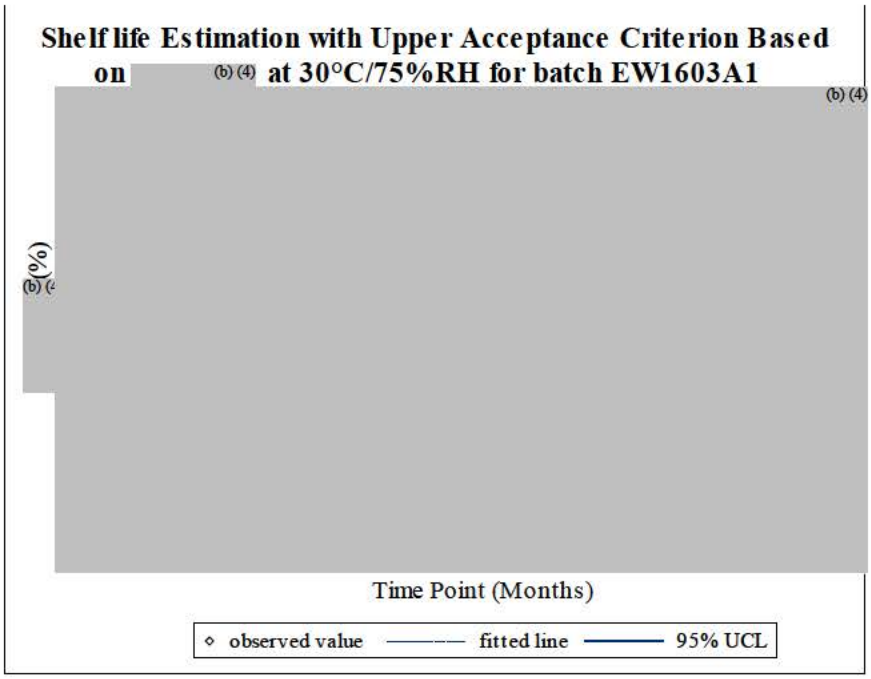

Figure 48: (b) (4) versus time trend for Batch EW1603A1 at 30°C/75%RH

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/s/

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10/14/2020 09:36:16 PM

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 214787
Drug Name:	Remdesivir
Indication(s):	Treatment of COVID-19
Applicant:	Gilead Sciences, Inc.
Date(s):	Stamp date: August 7, 2020
Review Priority:	Priority review
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Daniel Rubin, PhD
Concurring Reviewers:	Statistical team leader: Thamban Valappil, PhD
	Division Director: Dionne Price, PhD
Statistical analyst:	Bryant Chen, MS
Medical Division:	Division of Antiviral Products
Clinical Team:	Clinical reviewer: Kirk Chan-Tack, MD
Project Manager:	Christine Kim, PharmD

Table of Contents

1. EXECUTIVE SUMMARY

In this submission, the applicant Gilead Sciences seeks to provide evidence that remdesivir is safe and effective for the treatment of COVID-19 disease.

Three randomized trials were considered in this review. The Adaptive COVID-19 Treatment Trial (ACTT-1) compared remdesivir versus placebo in hospitalized patients with mild-to-moderate or severe disease, GS-US-540-5773 compared a 5 day remdesivir duration versus a 10 day duration in hospitalized patients with severe disease, and GS-US-540-5774 compared a 5 day remdesivir duration, a 10 day remdesivir duration, and open-label standard of care in hospitalized patients with moderate disease.

ACTT-1 was a large, double-blind, multicenter, multinational trial comparing 541 patients randomized to remdesivir for 10 days versus 521 patients randomized to the placebo control group. The trial included 105 patients in a stratum with mild-to-moderate disease and 957 patients in a stratum with severe disease. The primary efficacy endpoint was time to clinical recovery through Day 29. Recovery was defined by either discharge from the hospital without limitations on activities, discharge from the hospital with limitations on activities and/or requiring home oxygen, or hospitalization without requiring supplemental oxygen and no longer requiring ongoing medical care. Time to recovery was significantly faster in the remdesivir group than the placebo group (recovery rate ratio 1.29; 95% CI: 1.12 to 1.49; $p<0.001$). There were several complexities to the time to recovery primary analysis related to the handling of deaths in the analysis, the handling of relapses or readmissions following discharge, and a change in the primary endpoint during the trial. However, results also strongly favored remdesivir for a key secondary efficacy endpoint based on analysis of an ordinal scale at Day 15, which was less affected by these issues and had been the originally specified primary endpoint. This study was considered an adequate and well-controlled trial that provided statistically reliable evidence of efficacy. There was remaining uncertainty regarding the treatment effect on all-cause mortality, and the degree of efficacy in subpopulations with baseline requirements for high-flow oxygen, ventilation, or ECMO.

GS-US-540-5773 was an open-label trial in patients with severe COVID-19 and did not have a placebo or standard or care control group. This study compared 200 patients randomized to a 5 day remdesivir duration versus 197 patients randomized to a 10 day remdesivir duration. There were chance baseline imbalances such that patients in the 10 day group required higher levels of oxygen support. The primary efficacy analysis was based on a Day 14 ordinal scale analyzed using a proportional odds model. Results for the primary analysis numerically favored the 5 day group but did not conclusively demonstrate that this shorter duration was sufficient or insufficient (odds ratio 0.74; 95% CI: 0.50 to 1.10; $p=0.136$). However, this trial was limited by potential open-label effects, a high degree of imputed data for the primary endpoint, and receipt of the statistical analysis plan after release of results.

GS-US-540-5774 was an open-label trial in patients with moderate COVID-19 that compared 191 patients randomized to the 5 day remdesivir group, 193 patients

randomized to the 10 day remdesivir group, and 200 patients randomized to the standard of care group. The primary analysis was based on a Day 11 ordinal scale analyzed using a proportional odds model. In this analysis, the 5 day remdesivir group was statistically superior to the standard of care group (odds ratio 1.65; 95% CI: 1.09 to 2.48; p = 0.017) but the efficacy comparison between the 10 day remdesivir group and standard of care group was inconclusive (odds ratio 1.31; 95% CI: 0.88 to 1.95; p = 0.182). This trial was limited by potential open-label effects on the primary endpoint, the degree of imputed data for primary endpoint following discharge, and receipt of the statistical analysis plan and corresponding method multiplicity control after release of topline results. However, the trial provided supportive evidence to buttress the ACTT-1 results for patients with moderate disease and provided support for the shorter 5 day remdesivir duration.

The table below summarizes primary efficacy analysis results in the three reviewed trials. Overall, this application provides statistically reliable evidence that remdesivir is effective for the treatment of COVID-19 in hospitalized patients. However, there remains statistical uncertainty regarding efficacy within subgroups defined by baseline severity, whether remdesivir provides a mortality benefit, and the optimal duration of remdesivir.

Table 1: Primary efficacy analyses of reviewed trials

Trial	Comparison	Primary endpoint	Result
ACTT-1	RDV 10 days (N = 541) versus Placebo (N = 521)	Time to clinical recovery	Recovery rate ratio = 1.29 (favored RDV 10 days) 95% CI: 1.12 to 1.49 p-value: <0.001
GS-US-540-5773	RDV 5 days (N = 200) versus RDV 10 days (N = 197	Day 14 ordinal scale	Odds ratio = 0.74 (favored RDV 5 days) 95% CI: 0.50 to 1.10 p-value: 0.136
GS-US-540-5774	RDV 5 days (N = 191) versus SOC (N = 200)	Day 11 ordinal scale	Odds ratio = 1.65 (favored RDV 5 days) 95% CI: 1.09 to 2.48 p-value: 0.017
GS-US-540-5774	RDV 10 days (N = 193) versus SOC (N = 200)	Day 11 ordinal scale	Odds ratio = 1.31 (favored RDV 10 days) 95% CI: 0.88 to 1.95 p-value: 0.182

Abbreviations: RDV = remdesivir; SOC = standard of care; CI = confidence interval.
Notes: The recovery rate ratio is based on a proportional hazards model and the odds ratios are based on proportional odds models.
Source: ACTT-1 Final Clinical Study Report (Table 14), GS-US-540-5773 Interim Clinical Study Report (Tables 11, 12), GS-US-540-5774 Interim Clinical Study Report (Tables 10, 12), and statistical reviewer.

2. INTRODUCTION

2.1 Overview

Coronavirus disease 2019 (COVID-19) is an infectious respiratory disease caused by the SARS-CoV-2 coronavirus, which was first identified in late 2019. COVID-19 was declared a public health emergency by the US Department of Health and Human Services on January 31, 2020 and at the present time continues to spread globally through person-to-person transmission and cause substantial mortality and morbidity. A range of symptoms often including cough and fever can occur in the days or weeks following exposure. In a subset of patients, the disease can progress in severity and lead to shortness of breath, hospitalization, requirements for oxygen support, and death. At the time of this writing, there are no FDA-approved therapeutics or vaccines for the treatment or prevention of COVID-19.

Remdesivir is a broad-spectrum antiviral drug developed by the applicant Gilead Sciences. The applicant began clinical development for COVID-19 due to *in vitro* data showing that remdesivir reduced SARS-CoV-2 replication by inhibiting RNA polymerase activity. Remdesivir is not currently FDA-approved for any indication but was previously assessed in a clinical trial comparing treatments for Ebola Virus Disease.

On May 1, 2020, the FDA issued an emergency use authorization (EUA) for remdesivir for the treatment of suspected or confirmed severe COVID-19. The EUA was based in part on clinical data that will be discussed in this review.

In the current NDA, the statistical review will focus on randomized clinical trials listed in the table below. The three trials reviewed were assessed individually rather than through a meta-analysis due to differences in designs and objectives. The main source of evidence was the ACTT-1 trial. This was a randomized, double-blind, placebo-controlled trial in hospitalized patients with either mild-to-moderate or severe disease. The trial was considered an adequate and well-controlled study used to provide substantial evidence of safety and efficacy. Study GS-US-540-5773 was a randomized, open-label trial comparing 5 day and 10 day durations of remdesivir for treatment of severe COVID-19. This trial did not have a placebo or standard of care control group but provided evidence to inform the duration of remdesivir. Study GS-US-540-5774 was a randomized, open-label trial comparing a 5 day remdesivir group, a 10 day remdesivir group, and a standard of care control group for the treatment of moderate COVID-19. This trial supplemented the ACTT-1 information regarding treatment of moderate disease and provided additional data concerning remdesivir durations.

Datasets were not available for an additional published trial that will be more briefly summarized in this review [Wang et al., 2020, *The Lancet*, https://doi.org/10.1016/S0140-6736(20)31022-9].

Finally, at the time of this writing a large multi-arm randomized trial[1] comparing remdesivir and standard of care groups is ongoing and is meant to conclusively determine whether remdesivir provides a mortality benefit. This trial is not considered in the review because results are not yet available.

Table 2: List of studies reviewed

Name	Clinicaltrials.gov identifier	Design	Study population	Treatment groups and sample sizes
ACTT-1	NCT04280705	• Randomized • Double-blind • Placebo-controlled	Moderate and severe COVID-19	Remdesivir 10 days: N = 541 Placebo: N = 521
GS-US-540-5773	NCT04292899	• Randomized • Open-label • Active-controlled	Severe COVID-19	Remdesivir 5 days: N = 200 Remdesivir 10 days: N = 197
GS-US-540-5774	NCT04292730	• Randomized • Open-label • Standard of care controlled	Moderate COVID-19	Remdesivir 5 days: N = 191 Remdesivir 10 days: N = 193 Standard of care: N = 200

2.2 Data Sources

Data sources reviewed included clinical study reports, protocols, statistical analysis plans, case report forms, and patient level datasets. Datasets for the three trials listed in the above table were provided in SDTM and ADaM formats.

For the ACTT-1 trial, preliminary datasets based on an April 28, 2020 cutoff are available at the following link in the CDER Electronic Document Room:
\\CDSESUB1\evsprod\NDA214787\0009\m5\datasets\co-us-540-5776
Final datasets for ACTT-1 can be found at
\\CDSESUB1\evsprod\IND147771\0098\m5\datasets\20-0006 or
\\cdsesub1\evsprod\NDA214787\0020\m5\datasets\co-us-540-5776
Datasets for Studies GS-US-540-5773 and GS-US-540-5774 are located at
\\cdsesub1\evsprod\NDA214787\0009\m5\datasets\gs-us-540-5773
and
\\cdsesub1\evsprod\NDA214787\0011\m5\datasets\gs-us-540-5774

[1] https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments. Accessed August 31, 2020.

3. STATISTICAL EVALUATION

3.1 ACTT-1

3.1.1 Data and Analysis Quality (ACTT-1)

Two different groups of datasets for ACTT-1 were submitted corresponding to an April 28, 2020 preliminary data cut and to final datasets. The use of different data cuts will be discussed later in this review. The preliminary and final datasets related to the same patients, but the final datasets contained information through a longer follow-up period. The structure of the preliminary and final datasets was similar but not identical, and some modification of code was needed to handle different naming conventions. In addition, data cleaning resulted in minor differences in values between the preliminary and final datasets and also between the preliminary datasets that were submitted and results previously published for this data cut.[2] The datasets were relatively straightforward to use, and it was possible to largely reproduce the applicant's results. Randomization in this trial was stratified by disease severity (mild-moderate versus severe), which will be subsequently discussed. There were some differences between the "randomized" strata used in real time and the "actual" strata classified based on the study team's blinded review of baseline data. Classifications were changed for 70 patients. The impact of this change will be described, and it did not affect the interpretation of results. Some results for analyses based on proportional odds models and proportional hazards models in this review differ from the applicant's reported result in the second decimal, but this did not impact any qualitative conclusions.

There are currently no inspection results or irregularities in the datasets leading to concerns regarding the integrity and accuracy of submitted data.

A protocol and statistical analysis plan had been submitted prior to unblinding of comparative results using the April 28, 2020 preliminary data cut. The applicant's reporting for this trial was largely consistent with prespecified analyses. The statistical analysis plan was amended after unblinding prior to submission of the final datasets, but changes in the amended analyses were considered relatively minor.

3.1.2 Study Design and Endpoints (ACTT-1)

The Adaptive Covid-19 Treatment Trial (ACCT-1) was sponsored by the National Institute of Allergy and Infectious Disease (NIAID) of the National Institutes of Health. The study randomized a total of 1062 patients in a 1:1 ratio to remdesivir or placebo groups. Randomization was stratified by baseline severity (mild-to-moderate versus severe) and by study site using a blocked variable scheme. The first patient was randomized on February 21, 2020, the last patient was randomized on April 20, 2020, and the trial results were unblinded due to efficacy conclusions following a data and safety

[2] Biegel JH et al. Remdesivir for the treatment of COVID-19 – preliminary report. New England Journal of Medicine. Published May 22, 2020. DOI: 10.1056/NEJMoa2007764

monitoring board (DSMB) meeting on April 27, 2020. The clinicaltrials.gov identifier for this study was NCT04280705.

Remdesivir was administered intravenously once daily for 10 days, using a 200 mg loading dose on Day 1 followed by 100 mg on Days 2-10. The sponsor stated that the placebo was identical in physical appearance to the active formulation and contained the same inactive ingredients.

The trial used the following inclusion criteria:
1. Admitted to a hospital with symptoms suggestive of COVID-19 infection.
2. Subject (or legally authorized representative) provides informed consent prior to initiation of any study procedures.
3. Subject (or legally authorized representative) understands and agrees to comply with planned study procedures.
4. Male or non-pregnant female adult ≥18 years of age at time of enrollment.
5. Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay in any specimen, as documented by either of the following:
   - PCR positive in sample collected < 72 hours prior to randomization; OR
   - PCR positive in sample collected ≥72 hours prior to randomization, documented inability to obtain a repeat sample (e.g. due to lack of testing supplies, limited testing capacity, results taking > 24 hours, etc.). AND progressive disease suggestive of ongoing SARS-CoV-2 infection.
6. Illness of any duration, and at least one of the following:
   - Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
   - SpO2 ≤94% on room air, OR
   - Requiring supplemental oxygen, OR
   - Requiring mechanical ventilation.
7. Women of childbearing potential must agree to either abstinence or use at least one primary form of contraception not including hormonal contraception from the time of screening through Day 29.
8. Agrees to not participate in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 through Day 29.

Exclusion criteria were as follows:
1. ALT/AST >5 times the upper limit of normal.
2. Estimated glomerular filtration rate (eGFR) <30 mL/min (including patients receiving hemodialysis or hemofiltration).
3. Pregnancy or breast feeding.
4. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours.
5. Allergy to any study medication.

Patients were classified at baseline as having either severe disease or mild-moderate disease as follows:

- Severe disease: requiring mechanical ventilation, requiring oxygen, a SpO2 ≤94% on room air, or tachypnea (respiratory rate ≥24 breaths/min).
- Mild-moderate disease: SpO2 >94% and respiratory rate <24 breaths/min without supplemental oxygen.

The protocol allowed inclusion of patients who had received prior therapy for COVID-19, but this therapy was to be stopped upon enrollment unless needed for another medical condition.

Study procedures included measurement vital signs, clinical data collection, adverse event evaluation, and safety laboratory assessments. Different procedures were to be performed at various timepoints during study visits at baseline, during the treatment period (up to 10 days or until discharge), and on Day 15±2, Day 22±3, and Day 29±3.

The following 8-point ordinal scale was used to define outcomes in this trial, and was measured daily.
1. Not hospitalized, no limitations on activities;
2. Not hospitalized, limitation on activities and/or requiring home oxygen;
3. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care. This would include those kept in hospital for quarantine/infection control, awaiting bed in rehabilitation facility or homecare, etc.
4. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);
5. Hospitalized, requiring supplemental oxygen;
6. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
7. Hospitalized, on invasive mechanical ventilation or ECMO;
8. Death.

Originally the trial had used a 7-point scale, but category 3 was added for patients who were hospitalized only for isolation purposes. This change in the scale did not impact interpretability because it was made independently of comparative data by treatment group, and relatively few patients wound up having outcomes in this category.

The prespecified primary efficacy endpoint in this trial was time to recovery through the Day 29 visit, defined as the time to reach one of the best three categories in this scale. Patients who died before achieving recovery were censored in the analysis at Day 29.

A prespecified key secondary analysis was to examine the above ordinal scale at Day 15. This was the original primary analysis, but was changed without access to unblinded comparative data based on NIAID simulations suggesting the time to recovery endpoint may have better power.

Additional secondary efficacy endpoints prespecified in the protocol or statistical analysis plan included:
- Time to discharge or a NEWS score ≤2
- Days of oxygenation

- Incidence of new oxygen use
- Days of non-invasive ventilation/high-flow oxygen
- Incidence of non-invasive ventilation/high-flow oxygen
- Days of mechanical ventilation/ECMO
- Incidence of mechanical ventilation/ECMO
- Days of hospitalization,
- 14-day all-cause mortality
- 28-day all-cause mortality

3.1.3 Statistical Methodologies (ACTT-1)

The primary analysis population was the intent-to-treat (ITT) population, defined as all randomized patients. Additional analysis populations included the modified intent-to-treat (MITT) population that excluded patients found to be ineligible at baseline and the safety population comprised of all patients who received any infusion of study drug.

The analysis of the time to recovery primary endpoint was to be based on a log-rank test, stratified by baseline severity (mild-moderate versus severe). In addition an estimate, confidence interval, and p-value for the recovery rate ratio were to be based on a proportional hazards model. Here the "recovery rate ratio" was defined identically to a hazard ratio but with different nomenclature to reflect that recovery was a favorable event rather than an unfavorable event. Results were also to be shown for Kaplan-Meier curves and median recovery times for both the remdesivir and placebo groups.

For the key secondary endpoint of the Day 15 ordinal scale, the analysis was to be conducted using a proportional odds model that included terms for treatment and baseline disease severity (mild-to-moderate versus severe). As noted above, this was the original primary endpoint. The endpoint was changed while the study was ongoing but remained blinded, and this did not lead to problematic statistical properties because the modification was made independently of comparative data from the trial.

The sample size calculation was based on the number of events for the time-to-recovery primary endpoint. Thus, this was an event-driven trial that did not have a fixed preplanned number of patients. The planned sample size was 400 recovery events. This was designed to achieve 85% power assuming a recovery rate ratio of 1.35 between the remdesivir and placebo groups under a proportional hazards assumption and a standard two-sided $\alpha = 0.05$ significance level.

The trial was monitored by a DSMB. The protocol allowed for early efficacy stopping using O'Brien-Fleming boundaries after reaching 33% and 67% of the planned number of recoveries. The DSMB was to consider recommending futility stopping if conditional power (under the original trial assumptions) was less than 20%. There was an inconsistency between the protocol and statistical analysis plan that specified interim efficacy analysis after reaching 50% of the planned number of recoveries.

The first DSMB meeting was planned for April 27, 2020. Due to extremely rapid enrollment, the number of recoveries had already exceeded the planned final number of 400 recoveries. Therefore, no interim adjustments to 95% confidence levels were applied for this DSMB analysis. The DSMB concluded that remdesivir was effective and recommended releasing results, which were disseminated in a preliminary publication.[2] After the DSMB recommended disseminating results, the trial allowed patients to have treatment status unblinded and for patients in the placebo group to receive remdesivir.

This review initially describes results for an April 28, 2020 data cut in which there were 607 recoveries. This was the designated data cut for the sponsor's preliminary report and termed the "early analysis set" by the sponsor.

Follow-up through Day 29 was not yet complete at the time of the April 28, 2020 data cut. As the primary efficacy analysis was a time-to-event analysis, this administrative censoring could be naturally handled for the time-to-recovery endpoint. However, the protocol and statistical analysis plan did not describe in detail how this censoring was to be handled for other endpoints such as the Day 15 ordinal scale. Hence, the final data cut based on observing patients through the complete 29-day follow-up period may provide more reliable secondary analyses.

3.1.4 Patient Disposition, Demographic and Baseline Characteristics (ACTT-1)

The table below summarize patient disposition. A total of 1062 patients were randomized to remdesivir or placebo groups in a 1:1 ratio and >98% of randomized subjects were treated. Although patients were randomized to 10 days of study drug, less than half of patients in each group completed all 10 doses. The most common reason for early treatment discontinuation was achieving clinical recovery.

Table 3: ACTT-1 disposition

		RDV 10 days	Placebo
		n	n
Randomized		541	521
Treatment receipt status	Received treatment	531	517
	Did not receive treatment	10	4
Study completion status	Completed study (including death or recovery)	517	508
	Discontinued study	14	9
Reason for study discontinuation	SAE or AE other than death	4	0
	Transferred to another hospital	1	1
	Voluntary withdrawal by subject	6	5

	Voluntary withdrawal by subject and transition to comfort care	3	2
	Withdrawal by investigator	0	1
Completed all 10 doses of treatment		208	226
Discontinued treatment		323	291
Reason for treatment discontinuation	Recovery	223	158
	Death	15	19
	Intermittent missed doses	18	26
	SAE or AE other than death	52	70
	Withdrawal by investigator	4	1
	Voluntary withdrawal by subject	6	8
	Voluntary withdrawal by subject and transition to comfort care	4	6
	Transferred to another hospital	1	1
	Became ineligible after enrollment	0	1
	Protocol deviation	0	1

Abbreviations: RDV = remdesivir.
Source: ACTT-1 Final Clinical Study Report (Figure 2).

The next table summarizes baseline demographics, which were generally balanced between treatment groups. Over a third of patients were at least 65 years old, around two thirds of patients were male, the majority of patients were White, and slightly less than 80% of patients were enrolled in the United States.

Table 4: ACTT-1 demographics (ITT population)

		RDV 10 days (N = 541)	Placebo (N = 521)
Demographic category	Characteristic	n (%)	n (%)
Age (years)	<40	59 (10.9)	60 (11.5)

	40-64	295 (54.5)	264 (50.7)
	≥65	187 (34.6)	197 (37.8)
Sex	Male	352 (65.1)	332 (63.7)
	Female	189 (34.9)	189 (36.3)
Race	White	279 (51.6)	287 (55.1)
	Black or African American	109 (20.1)	117 (22.5)
	Asian	79 (14.6)	56 (10.7)
	Other or not reported	74 (13.7)	61 (11.7)
Ethnicity	Hispanic or Latino	134 (24.8)	116 (22.3)
	Not Hispanic or Latino	382 (70.6)	373 (71.6)
	Other or not reported	25 (4.6)	32 (6.1)
Country	United States	427 (78.9)	410 (78.7)
	Great Britain	25 (4.6)	21 (4)
	Denmark	22 (4.1)	21 (4)
	Spain	16 (3)	12 (2.3)
	Greece	10 (1.8)	12 (2.3)
	South Korea	9 (1.7)	12 (2.3)
	Singapore	9 (1.7)	7 (1.3)
	Japan	8 (1.5)	7 (1.3)
	Germany	7 (1.3)	6 (1.2)
	North Macedonia	4 (0.7)	7 (1.3)
	Mexico	4 (0.7)	6 (1.2)

Abbreviations: ITT = intent-to-treat; RDV = remdesivir.
Source: ACTT-1 Final Clinical Study Report (Table 8) and statistical reviewer.

Additional baseline characteristics are summarized in the following table. Slightly over 10% of patients had a baseline score for the NIAID ordinal scale of 4 (hospitalized without requiring supplemental oxygen). The most common baseline score for the scale was 5 (hospitalized with supplemental oxygen but without needing ventilation), and approximately 40% of patients were in this category. Slightly under 20% of patients in each treatment group were in category 6 (hospitalized and requiring noninvasive ventilation or high-flow oxygen). There was some degree of random imbalance in the proportion of patients in category 7 (hospitalized with invasive mechanical ventilation or ECMO), as 24% of remdesivir patients were in this most severe category compared to 30% in the placebo group. Almost half of patients in the trial were enrolled 10 or more days after their first onset of symptoms. The table also displays that patients in this trial had a high degree of comorbidities such as hypertension, obesity, and diabetes.

Table 5: ACTT-1 baseline characteristics (ITT population)

		RDV 10 days (N = 541)	Placebo (N = 521)
Baseline category	Characteristic	n (%)	n (%)

Disease severity stratum	Mild-to-moderate disease	55 (10.2)	50 (9.6)
	Severe disease	486 (89.8)	471 (90.4)
Ordinal scale score	4. Hospitalized - not requiring supplemental oxygen - requiring ongoing medical care	75 (13.9)	63 (12.1)
	5. Hospitalized - requiring supplemental oxygen	232 (42.9)	203 (39)
	6. Hospitalized - on noninvasive ventilation or high-flow oxygen	95 (17.6)	98 (18.8)
	7. Hospitalized - on invasive mechanical ventilation or ECMO	131 (24.2)	154 (29.6)
Days from symptom onset to enrollment	≤6	158 (29.2)	124 (23.8)
	7-9	148 (27.4)	152 (29.2)
	10-12	113 (20.9)	108 (20.7)
	≥13	121 (22.4)	135 (25.9)
Comorbidities	Hypertension	269 (49.7)	264 (50.7)
	Type 2 diabetes	164 (30.3)	158 (30.3)
	Obesity	242 (44.7)	234 (44.9)
	Asthma	63 (11.6)	57 (10.9)
	Immunodeficiency	32 (5.9)	41 (7.9)
	Cancer	43 (7.9)	37 (7.1)

Abbreviations: ITT = intent-to-treat; RDV = remdesivir; ECMO = extracorporeal membrane oxygenation.
Notes: Patients with missing baseline comorbidity data are included in denominators when calculating percentages.
Source: ACTT-1 Final Clinical Study Report (Table 9) and statistical reviewer.

3.1.5 Results and Conclusions (ACTT-1)

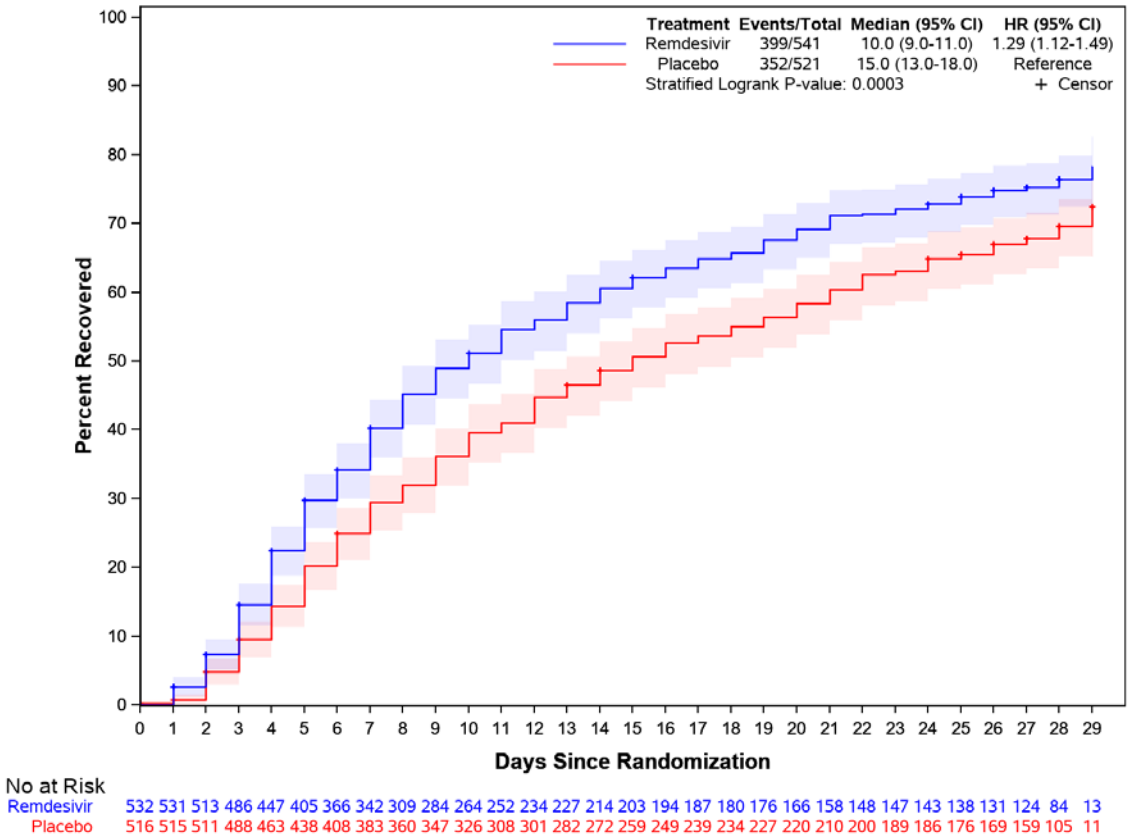
3.1.5.1 Time to recovery (ACTT-1)

Because this was an event driven trial, results for the primary efficacy analysis of time to recovery are first reported using the April 28, 2020 data cutoff following the DSMB meeting held after reaching the target number of events. In the intent to treat population of all randomized patients, time to recovery was significantly faster in the remdesivir group than in the placebo control group. Median days to recovery were 10 for the

remdesivir group compared with 14 in the placebo group. The recovery rate ratio was 1.31 with a confidence interval from 1.12 to 1.53 ($p<0.001$).

While the time to recovery assessment based on April 28, 2020 data cutoff was considered the primary analysis, a limitation was that many patients were still undergoing follow-up. Therefore, the analyses in this review instead display results using the final datasets corresponding to follow-up through the Day 29±3 visit. The figure and table below repeat the analysis of the primary endpoint using these more complete data. While the number of recoveries increased in each treatment group, the recovery rate ratio of 1.29 was similar to that seen with the earlier data cut, and results continued to show significantly faster recovery times in the remdesivir group compared with the placebo group.

Figure 1: ACTT-1 results for the primary analysis of time to recovery (ITT population)



Abbreviations: ITT = intent-to-treat; CI = confidence interval; HR = recovery rate ratio.
Notes: The plot is based on a Kaplan-Meier analysis. The recovery rate ratio is based on a proportional hazards model that stratifies for baseline disease severity (mild-to-moderate versus severe). A recovery rate ratio <1 favors placebo and a recovery rate ratio >1 favors remdesivir.
Source: Analytics and informatics reviewer and ACTT-1 Final Clinical Study Report (Table 14 and Figure 3).

Table 6: ACTT-1 Kaplan-Meier results for time to recovery (ITT population)

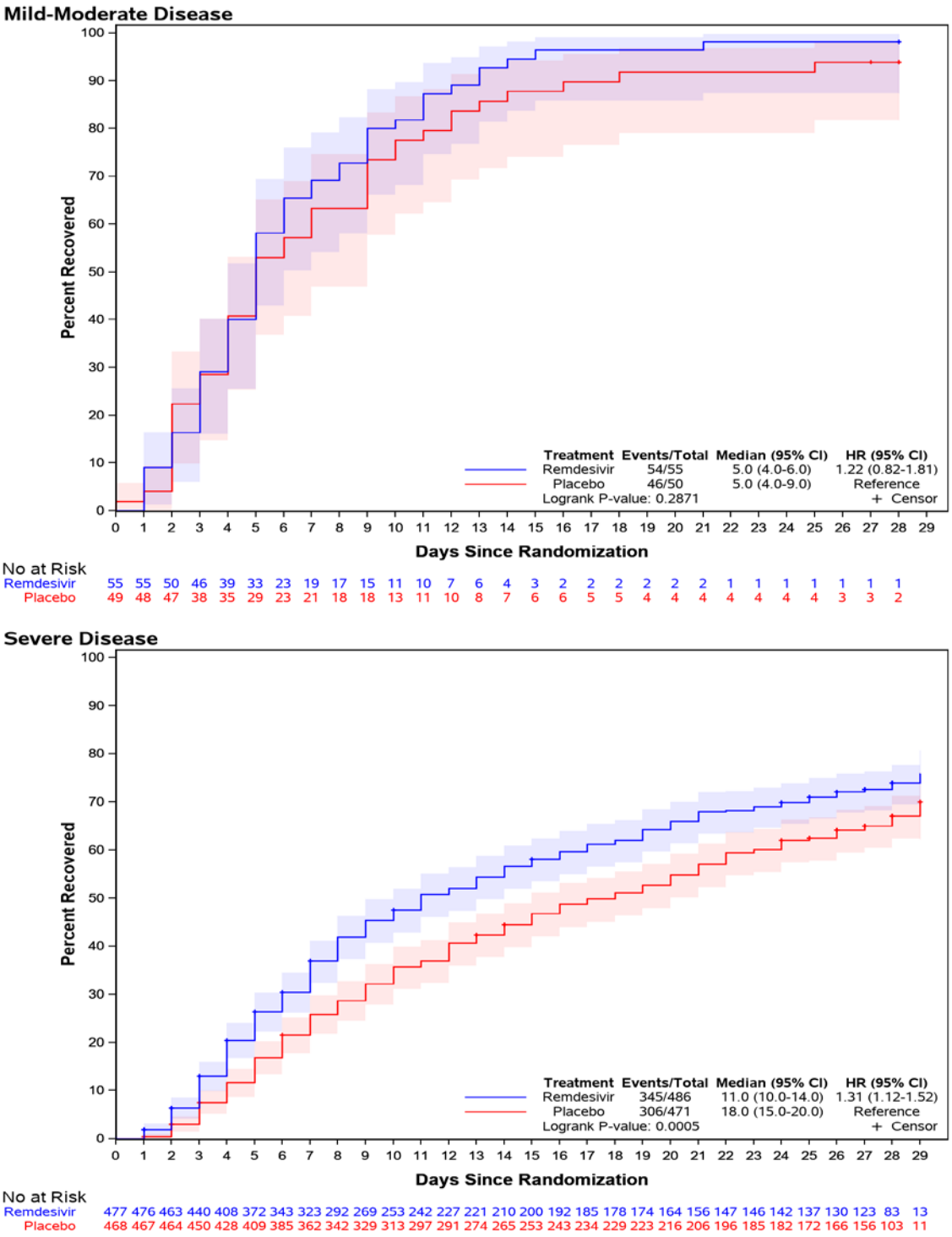
Day	Censored	Recovery for RDV 10 days (n = 541)	Recovery for placebo (n = 521)	Difference	95% CI
7	30/1062 (2.8%)	40.3%	29.5%	10.8%	5.1% to 16.6%
14	33/1062 (3.1%)	60.6%	48.7%	11.9%	5.9% to 18%
21	36/1062 (3.4%)	71.1%	60.4%	10.8%	5% to 16.6%
28	137/1062 (12.9%)	76.5%	69.6%	6.8%	1.3% to 12.4%

Abbreviations: ITT = intent-to-treat; RDV = remdesivir; CI = confidence interval.
Source: Statistical reviewer.

The difference in recovery rates was apparent throughout the follow-up period, such as at the Day 7, Day 14, Day 21, and Day 28 timepoints displayed in the above table. Because censoring of time to recovery was minimal at earlier times, censored data did not impact the conclusion that recovery occurred faster in the remdesivir group.

As the primary analysis was stratified by disease severity, the figures below display time to recovery results separately in the two mild-to-moderate and severe disease strata. Patients with mild-to-moderate disease had a median time to recovery of 5 days in each group, and recovery times did not significantly differ. However, this stratum of 105 patients represented only 10% of patients. Results in the complementary stratum with severe disease at baseline mirrored the overall results and favored remdesivir.

Figure 2: ACTT-1 analysis of time to recovery by baseline disease severity strata (ITT population)



Abbreviations: ITT = intent-to-treat; CI = confidence interval; HR = recovery rate ratio.
Notes: The plots are based on Kaplan-Meier analyses. The recovery rate ratios are based on proportional hazards models that do not adjust or stratify by baseline covariates. A recovery rate ratio <1 favors placebo and a recovery rate ratio >1 favors remdesivir.
Source: Analytics and informatics reviewer.

These analyses and other analyses in this review are based on the "actual" baseline strata defined after blinded correction of "randomized" strata decisions made by investigators in real time to stratify the randomization. The actual and randomized strata differed for 70 (5%) patients. The table below summarizes sample sizes for the two strata definitions. The actual strata were considered a more accurate reflection of patient status at baseline and were used by the NIAID study team to report prespecified analyses. Results for the time to recovery primary endpoint were virtually unchanged when stratifying the proportional hazards model for randomized strata rather than actual strata [not shown]. However, the applicant's final study report generally presented analyses stratified by randomized severity strata, which led to minor discrepancies with numbers in this review.

Table 7: ACTT-1 actual and randomized baseline disease severity strata (ITT population)

		RDV 10 days (N = 541)	Placebo (N = 521)
Actual baseline severity stratum	Mild-to-moderate	55 (10.2)	50 (9.6)
	Severe	486 (89.8)	471 (90.4)
Randomized baseline severity stratum	Mild-to-moderate	82 (15.2)	77 (14.8)
	Severe	459 (84.8)	444 (85.2)

Abbreviations: ITT = intent-to-treat; RDV = remdesivir.
Source: Statistical reviewer.

As the mild-to-moderate stratum was relatively small, the next set of tables provide a more granular summary of time to recovery results by baseline severity. These results can be summarized as follows:

- In patients with a baseline ordinal scale score of 4 (Hospitalized – not requiring supplemental oxygen – requiring ongoing medical care), the recovery rate ratio estimate was similar to that in the overall ITT population. However, due to the small sample size the confidence interval showed that there remained uncertainty regarding whether remdesivir hastened recovery. Note that this subgroup had slightly more subjects than the mild-to-moderate disease severity stratum because these two subsets were not defined in an identical manner.
- In patients with a baseline ordinal scale score of 5 (Hospitalized - requiring supplemental oxygen) remdesivir was associated with a faster time to recovery than placebo.
- In patients with baseline ordinal scale scores of 6 or 7 (patients on high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or ECMO), the numerical trends for time to recovery were similar between remdesivir and placebo. However, the trial was not powered for analyses of these subgroups, and confidence intervals reflected substantial uncertainty regarding benefit in these groups. It generally took much longer for patients in these subgroups to meet recovery criteria than for patients in other subgroups.

Table 8: ACTT-1 time to recovery results in the subgroup with baseline ordinal score of 4 = Hospitalized - not requiring supplemental oxygen - requiring ongoing medical care (ITT population)

	RDV 10 days (N = 75)	Placebo (N = 63)
Number of recoveries	73	58
Median days (95% CI)	5 (4 to 6)	6 (4 to 9)
Recovery rate ratio (95% CI)	1.32 (0.93 to 1.87)	

Abbreviations: ITT = intent-to-treat; RDV = remdesivir; CI = confidence interval;
Notes: The recovery rate ratio is based on a proportional hazards model that does not adjust or stratify by baseline covariates. A recovery rate ratio <1 favors placebo and a recovery rate ratio >1 favors remdesivir.
Source: Statistical reviewer.

Table 9: ACTT-1 time to recovery results in the subgroup with baseline ordinal score of 5 = Hospitalized - requiring supplemental oxygen (ITT population)

	RDV 10 days (N = 232)	Placebo (N = 203)
Number of recoveries	206	156
Median days (95% CI)	7 (6 to 8)	9 (7 to 11)
Recovery rate ratio (95% CI)	1.47 (1.19 to 1.81)	

Abbreviations: ITT = intent-to-treat; RDV = remdesivir; CI = confidence interval;
Notes: The recovery rate ratio is based on a proportional hazards model that does not adjust or stratify baseline covariates. A recovery rate ratio <1 favors placebo and a recovery rate ratio >1 favors remdesivir.
Source: Statistical reviewer.

Table 10: ACTT-1 time to recovery results in the subgroup with baseline ordinal score of 6 = Hospitalized - on noninvasive ventilation or high-flow oxygen (ITT population)

	RDV 10 days (N = 95)	Placebo (N = 98)
Number of recoveries	57	61
Median days (95% CI)	15 (11 to 28)	19.5 (15 to 27)
Recovery rate ratio (95% CI)	1.09 (0.76 to 1.57)	

Abbreviations: ITT = intent-to-treat; RDV = remdesivir; CI = confidence interval;
Notes: The recovery rate ratio is based on a proportional hazards model that does not adjust or stratify by baseline covariates. A recovery rate ratio <1 favors placebo and a recovery rate ratio >1 favors remdesivir.
Source: Statistical reviewer.

Table 11: ACTT-1 time to recovery results in the subgroup with baseline ordinal score of 7 = Hospitalized - on invasive mechanical ventilation or ECMO (ITT population)

	RDV 10 days (N = 131)	Placebo (N = 154)
Number of recoveries	63	77
Median days (95% CI)	29 (25 to ∞)	28 (24 to ∞)
Recovery rate ratio (95% CI)	0.98 (0.7 to 1.36)	

Abbreviations: ITT = intent-to-treat; RDV = remdesivir; CI = confidence interval; ECMO = extracorporeal membrane oxygenation.
Notes: The recovery rate ratio is based on a proportional hazards model that does not adjust or stratify by baseline covariates. A recovery rate ratio <1 favors placebo and a recovery rate ratio >1 favors remdesivir.
Source: Statistical reviewer.

While results for the time to recovery primary endpoint provided evidence for a treatment effect of remdesivir, there were several issues impacting the interpretability of this endpoint. First, it was unclear whether a reduction in days to recovery was the most clinically meaningful outcome in a disease setting with high mortality and irreversible morbidity. Second, time to recovery was impacted by the competing risk of death. As noted above, patients who died before Day 29 were censored at this timepoint. This was equivalent to imputing an infinite recovery time in the analysis of time to recovery through Day 29, and thus appeared reasonable. Third, the time to recovery endpoint did not take into account negative clinical events that occurred after meeting recovery criteria, and some COVID-19 patients relapsed or failed to achieve complete resolution and return to normal status after discharge.

To address the issues with post-recovery events, the tables below summarize hospital readmissions after recovery and an analysis in which patients with readmission are considered to have not recovered through the Day 29 visit. Readmission rates (under 5% per group) were relatively low in this trial. However, readmission rates were higher in the subset of patients who were immunocompromised at baseline. When imputing an infinite recovery time for patients with readmissions, results for the recovery endpoint were similar to the primary analysis. This suggested that readmissions did not greatly impact the interpretability of the primary efficacy results. This trial was not able to assess longer term disability from COVID-19 beyond the Day 29 visit.

Table 12: ACTT-1 rates of readmission after recovery (ITT population)

	RDV 10 days	Placebo
Overall ITT	26/541 (4.8%)	15/521 (2.9%)
Immunodeficiency	8/32 (25%)	4/41 (9.8%)
No immunodeficiency	18/509 (3.5%)	11/480 (2.3%)

Abbreviations: RDV = remdesivir.
Source: Statistical reviewer.

Table 13: ACTT-1 analysis of time to recovery through the Day 29 visit when imputing an infinite recovery time for patients with readmissions (ITT population)

	RDV 10 days (N = 541)	Placebo (N = 521)
Number of recoveries	373	337
Median days (95% CI)	11 (10 to 14)	16 (14 to 20)
Recovery rate ratio (95% CI)	1.22 (1.05 to 1.41)	

Abbreviations: ITT = intent-to-treat; RDV = remdesivir; CI = confidence interval.

Notes: The recovery rate ratio is based on a proportional hazards model that stratifies for baseline disease severity (mild-to-moderate versus severe). A recovery rate ratio <1 favors placebo and a recovery rate ratio >1 favors remdesivir.
Source: Statistical reviewer.

3.1.5.2 Day 15 ordinal scale (ACTT-1)

The key secondary endpoint based on the ordinal scale at Day 15 was considered an important efficacy outcome. As previously discussed, this had been the original primary endpoint of the trial. Results from the proportional odds model strongly favored remdesivir for this endpoint, as shown in the table below. Hence, the modification to the primary endpoint did not impact efficacy conclusions. The odds ratio from this analysis represented an overall favorable shift in the distribution of ordinal scale categories between the treatment groups. This was apparent at both the top and bottom ends of the scale, as remdesivir was associated with greater rates of discharge and lower rates of death, invasive mechanical ventilation, or ECMO.

Table 14: ACTT-1 key secondary analysis of the Day 15 ordinal scale results (ITT population)

	RDV 10 days (N = 541)	Placebo (N = 521)
Ordinal scale score	n (%)	n (%)
1. Not hospitalized - no limitations on activities	157 (29)	115 (22.1)
2. Not hospitalized - limitations on activities and/or requiring home oxygen	117 (21.6)	102 (19.6)
3. Hospitalized - not requiring supplemental oxygen or ongoing medical care	14 (2.6)	8 (1.5)
4. Hospitalized - not requiring supplemental oxygen - requiring ongoing medical care	38 (7)	33 (6.3)
5. Hospitalized - requiring supplemental oxygen	58 (10.7)	60 (11.5)
6. Hospitalized - on noninvasive ventilation or high-flow oxygen	28 (5.2)	24 (4.6)
7. Hospitalized - on invasive mechanical ventilation or ECMO	95 (17.6)	121 (23.2)
8. Death	34 (6.3)	58 (11.1)
Odds ratio (95% CI)	1.54 (1.25 to 1.91)	

p-value	<0.001	

Abbreviations: ITT = intent-to-treat; RDV = remdesivir; CI = confidence interval;
Notes: The Odds ratio is based on a proportional odds model that adjusts for baseline disease severity (mild-to-moderate versus severe). An odds ratio <1 favors placebo and an odds ratio >1 favors remdesivir.
Source: Statistical reviewer.

The subsequent tables display results for the Day 15 ordinal scale by baseline severity. Numerical results favored remdesivir compared with placebo in all baseline subgroups considered, but the strongest evidence for a remdesivir treatment effect was in the subgroup with baseline ordinal scale score of 5 (hospitalized, requiring supplemental oxygen, but not requiring high-flow oxygen, ventilation, or ECMO).

Table 15: ACTT-1 Day 15 ordinal scale results in the subgroup with baseline ordinal score of 4 = Hospitalized - not requiring supplemental oxygen - requiring ongoing medical care (ITT population)

	RDV 10 days (N = 75)	Placebo (N = 63)
Ordinal scale score	n (%)	n (%)
1. Not hospitalized - no limitations on activities	38 (50.7)	28 (44.4)
2.	20 (26.7)	15 (23.8)
3.	8 (10.7)	4 (6.3)
4.	3 (4)	7 (11.1)
5.	3 (4)	5 (7.9)
6.	1 (1.3)	0 (0)
7.	1 (1.3)	3 (4.8)
8. Death	1 (1.3)	1 (1.6)
Odds ratio (95% CI)	1.46 (0.78 to 2.72)	

Abbreviations: ITT = intent-to-treat; RDV = remdesivir; CI = confidence interval;
Notes: The Odds ratio is based on a proportional odds model that does not adjust for baseline covariates. An odds ratio <1 favors placebo and an odds ratio >1 favors remdesivir.
Source: Statistical reviewer.

Table 16: ACTT-1 Day 15 ordinal scale results in the subgroup with baseline ordinal score of 5 = Hospitalized - requiring supplemental oxygen (ITT population)

	RDV 10 days (N = 232)	Placebo (N = 203)
Ordinal scale score	n (%)	n (%)
1. Not hospitalized - no limitations on activities	90 (38.8)	62 (30.5)
2.	70 (30.2)	58 (28.6)
3.	6 (2.6)	4 (2)
4.	17 (7.3)	13 (6.4)
5.	25 (10.8)	18 (8.9)
6.	5 (2.2)	7 (3.4)

7.	13 (5.6)	21 (10.3)
8. Death	6 (2.6)	20 (9.9)
Odds ratio (95% CI)	1.64 (1.17 to 2.31)	

Abbreviations: ITT = intent-to-treat; RDV = remdesivir; CI = confidence interval;
Notes: The Odds ratio is based on a proportional odds model that does not adjust for baseline covariates. An odds ratio <1 placebo and an odds ratio >1 favors remdesivir.
Source: Statistical reviewer.

Table 17: ACTT-1 Day 15 ordinal scale results in the subgroup with baseline ordinal score of 6 = Hospitalized - on noninvasive ventilation or high-flow oxygen (ITT population)

	RDV 10 days (N = 95)	Placebo (N = 98)
Ordinal scale score	n (%)	n (%)
1. Not hospitalized - no limitations on activities	18 (18.9)	14 (14.3)
2.	22 (23.2)	19 (19.4)
3.	0 (0)	0 (0)
4.	12 (12.6)	4 (4.1)
5.	2 (2.1)	14 (14.3)
6.	12 (12.6)	11 (11.2)
7.	16 (16.8)	20 (20.4)
8. Death	13 (13.7)	16 (16.3)
Odds ratio (95% CI)	1.4 (0.85 to 2.3)	

Abbreviations: ITT = intent-to-treat; RDV = remdesivir; CI = confidence interval;
Notes: The Odds ratio is based on a proportional odds model that does not adjust for baseline covariates. An odds ratio <1 favors placebo and an odds ratio >1 favors remdesivir.
Source: Statistical reviewer.

Table 18: ACTT-1 Day 15 ordinal scale results in the subgroup with baseline ordinal score of 7 = Hospitalized - on invasive mechanical ventilation or ECMO (ITT population)

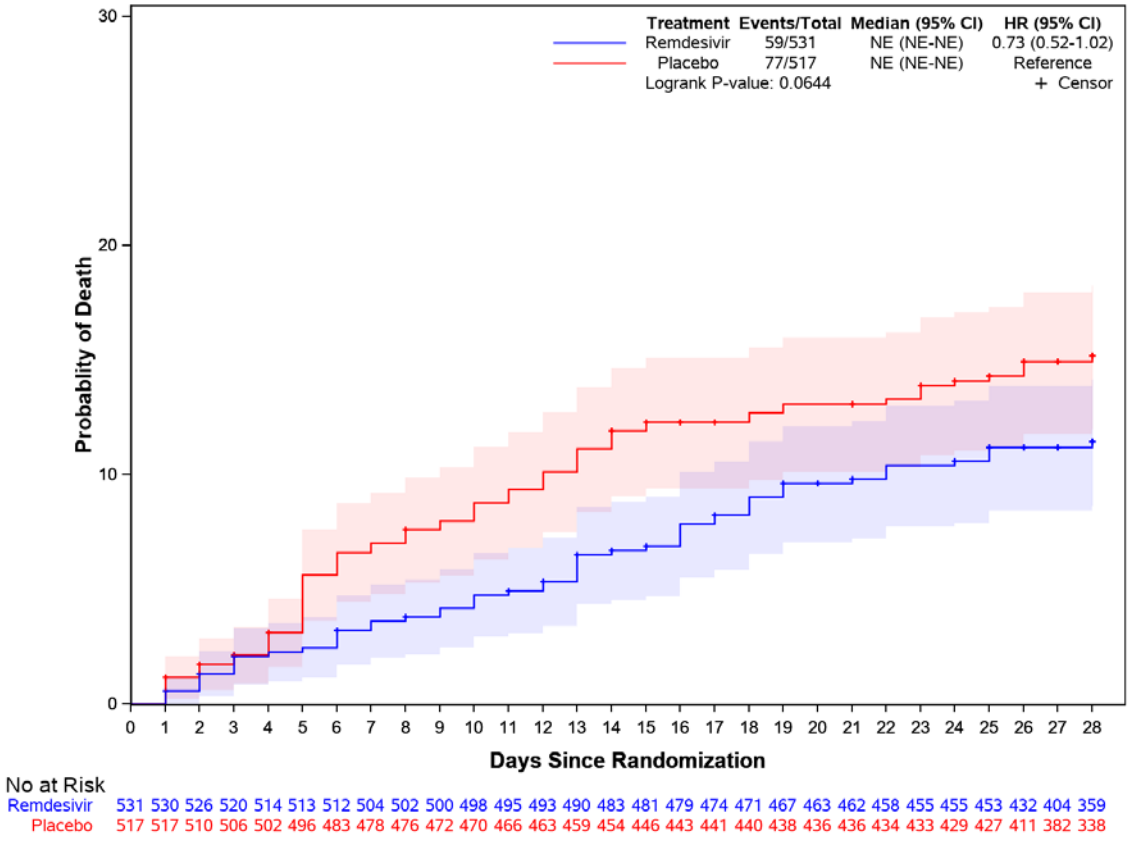
	RDV 10 days (N = 131)	Placebo (N = 154)
Ordinal scale score	n (%)	n (%)
1. Not hospitalized - no limitations on activities	11 (8.4)	11 (7.1)
2.	5 (3.8)	10 (6.5)
3.	0 (0)	0 (0)
4.	6 (4.6)	9 (5.8)
5.	28 (21.4)	23 (14.9)
6.	10 (7.6)	6 (3.9)
7.	57 (43.5)	74 (48.1)
8. Death	14 (10.7)	21 (13.6)
Odds ratio (95% CI)	1.22 (0.79 to 1.86)	

Abbreviations: ITT = intent-to-treat; RDV = remdesivir; CI = confidence interval; ECMO = extracorporeal membrane oxygenation.
Notes: The Odds ratio is based on a proportional odds model that does not adjust for baseline covariates. An odds ratio <1 favors placebo and an odds ratio >1 favors remdesivir.
Source: Statistical reviewer.

3.1.5.3 All-cause mortality (ACTT-1)

All-cause mortality was also an important efficacy outcome in this trial due to its predominant clinical importance. The figure and table below summarize results. The estimated mortality rate was numerically lower for remdesivir than placebo in the overall ITT population, with the p-value near the boundary of a nominally statistically significant mortality benefit.

Figure 3: ACTT-1 analysis of all-cause mortality (ITT population)



Abbreviations: ITT = intent-to-treat; CI = confidence interval; HR = hazard ratio.
Notes: The plot is based on a Kaplan-Meier analysis. The hazard ratio is based on a proportional hazards model that does not adjust or stratify by baseline covariates. A hazard ratio <1 favors remdesivir and a hazard ratio >1 favors placebo.
Source: Analytics and informatics reviewer.

Table 19: ACTT-1 Kaplan-Meier results for time to death (ITT population)

Day	Censored	Mortality for RDV 10 days	Mortality for placebo	Difference	95% CI

		(N = 541)	(N = 521)		
7	29/1062 (2.7%)	3.6%	7%	-3.4%	-6.1% to -0.7%
14	34/1062 (3.2%)	6.7%	11.9%	-5.2%	-8.7% to -1.7%
21	47/1062 (4.4%)	9.8%	13.1%	-3.3%	-7.2% to 0.6%
28	231/1062 (21.8%)	11.4%	15.2%	-3.7%	-7.9% to 0.4%

Abbreviations: ITT = intent-to-treat; RDV = remdesivir; CI = confidence interval.
Source: Statistical reviewer.

The next set of tables display mortality results in subgroups defined by baseline disease severity. There were very few deaths in either treatment group for patients who did not require supplemental oxygen at baseline. Mortality results were most favorable to remdesivir in the subgroup that required supplemental oxygen, but not high-flow oxygen, ventilation, or ECMO. There were no numerical trends toward mortality benefit in subgroups with baseline ordinal scores of 6 or 7 corresponding to more severe illness.

Table 20: ACTT-1 Day 28 all-cause mortality results in the subgroup with baseline ordinal score of 4 = Hospitalized - not requiring supplemental oxygen - requiring ongoing medical care (ITT population)

	RDV 10 days (N = 75)	Placebo (N = 63)
Number of deaths	3	3
Kaplan-Meier estimate	4.1%	4.8%
Hazard ratio (95% CI)	0.82 (0.17 to 4.07)	

Abbreviations: ITT = intent-to-treat; RDV = remdesivir; CI = confidence interval;
Notes: The hazard ratio is based on a proportional hazards model that does not adjust for baseline covariates. A hazard ratio <1 favors remdesivir and a hazard ratio >1 favors placebo.
Source: Statistical reviewer.

Table 21: ACTT-1 Day 28 all-cause mortality results in the subgroup with baseline ordinal score of 5 = Hospitalized - requiring supplemental oxygen (ITT population)

	RDV 10 days (N = 232)	Placebo (N = 203)
Number of deaths	9	25
Kaplan-Meier estimate	4%	12.7%
Hazard ratio (95% CI)	0.3 (0.14 to 0.64)	

Abbreviations: ITT = intent-to-treat; RDV = remdesivir; CI = confidence interval;
Notes: The hazard ratio is based on a proportional hazards model that does not adjust for baseline covariates. A hazard ratio <1 favors remdesivir and a hazard ratio >1 favors placebo.
Source: Statistical reviewer.

Table 22: ACTT-1 Day 28 all-cause mortality results in the subgroup with baseline ordinal score of 6 = Hospitalized - on noninvasive ventilation or high-flow oxygen (ITT population)

	RDV 10 days (N = 95)	Placebo (N = 98)
Number of deaths	19	20
Kaplan-Meier estimate	21.2%	20.4%
Hazard ratio (95% CI)	1.02 (0.54 to 1.91)	

Abbreviations: ITT = intent-to-treat; RDV = remdesivir; CI = confidence interval;
Notes: The hazard ratio is based on a proportional hazards model that does not adjust for baseline covariates. A hazard ratio <1 favors remdesivir and a hazard ratio >1 favors placebo.
Source: Statistical reviewer.

Table 23: ACTT-1 Day 28 all-cause mortality results in the subgroup with baseline ordinal score of 7 = Hospitalized - on invasive mechanical ventilation or ECMO (ITT population)

	RDV 10 days (N = 131)	Placebo (N = 154)
Number of deaths	28	29
Kaplan-Meier estimate	21.9%	19.3%
Hazard ratio (95% CI)	1.13 (0.67 to 1.9)	

Abbreviations: ITT = intent-to-treat; RDV = remdesivir; CI = confidence interval; ECMO = extracorporeal membrane oxygenation.
Notes: The hazard ratio is based on a proportional hazards model that does not adjust for baseline covariates. A hazard ratio <1 favors remdesivir and a hazard ratio >1 favors placebo.
Source: Statistical reviewer.

Another issue potentially affecting the mortality analyses concerned patient unblinding and crossover. After release of preliminary topline results based on the April 28, 2020 data cut, the trial allowed all patients to have treatment assignment unblinded and receive remdesivir. This occurred for 26/521 (5%) patients in the placebo group. A limitation of such crossover is that it can reduce the power for detecting a treatment benefit, although the study team considered it an ethical necessity. The tables below show Day 28 all-cause mortality by unblinding and crossover status and also an exploratory analysis of all-cause mortality at Day 12. The exploratory analysis was conducted because crossover had less impact at this early timepoint, as the first unblinding occurred at Day 13. The exploratory results were suggestive of a mortality benefit.

Table 24: ACTT-1 Day 28 all-cause mortality by treatment unblinding and treatment group crossover (ITT population)

	RDV 10 days (N = 541)	Placebo (N = 521)
Remained blinded	57/524 (10.9%)	74/485 (15.3%)
Unblinded with no crossover to the other treatment group	2/17 (11.8%)	0/10 (0%)
Unblinded with crossover to the other treatment group	0/0	3/26 (11.5%)

Abbreviations: ITT = intent-to-treat; RDV = remdesivir.
Source: Statistical reviewer.

Table 25: ACTT-1 all-cause mortality through Day 12, which was the last study day before any unblinding or crossover (ITT population)

	RDV 10 days (N = 541)	Placebo (N = 521)
Number of deaths	28	52
Kaplan-Meier estimate	5.3%	10.1%
Hazard ratio (95% CI)	0.51 (0.32 to 0.81)	

Abbreviations: ITT = intent-to-treat; RDV = remdesivir; CI = confidence interval.
Notes: The hazard ratio is based on a proportional hazards model that does not adjust for baseline covariates. A hazard ratio <1 favors remdesivir and a hazard ratio >1 favors placebo.
Source: Statistical reviewer.

3.1.5.4 Conclusions (ACTT-1)

Overall, this randomized trial was considered an adequate and well-controlled study. Two main strengths of the study was its large sample size of >1000 randomized patients and its double-blinding using a placebo control. The statistical analysis was considered appropriate, including reporting of results from the April 28, 2020 data cutoff in this event driven trial, prespecification of the analysis prior to review of unblinded comparative data, and handling of deaths in the primary analysis of the time to recovery endpoint. Results for this primary endpoint and key secondary endpoint based on the Day 15 ordinal scale strongly favored remdesivir compared with placebo. These results together provided substantial evidence for the efficacy of remdesivir.

There were several outstanding questions remaining after completion of this trial. One question concerned whether remdesivir provides a mortality benefit. Although numerical trends favored remdesivir for this endpoint of ultimate importance, there was residual statistical uncertainty. The trial also only evaluated a 10 day remdesivir regimen, and thus could only provide evidence for this assigned duration of therapy. Finally, results in this trial by baseline severity were inconclusive regarding remdesivir benefit in patients with more moderate disease who did not require oxygen supplementation, although estimated treatment effects in this subgroup generally mirrored the overall results. Results were also inconclusive in patients requiring high flow oxygen, ventilation, or ECMO at baseline. However, the trial was not powered for these subgroup analyses.

3.2 GS-US-540-5773

3.2.1 Data and Analysis Quality (GS-US-540-5773)

The submitted SDTM and ADaM datasets were relatively straightforward to use for Study GS-US-540-5773. In particular, it was possible to reproduce the applicant's analyses to sufficient precision such that conclusions were unaffected. At the time of this writing, there are no site inspection results or irregularities challenging the integrity or accuracy of the submitted data. As will be discussed in more detail below, the applicant's statistical analysis plan was not submitted until after release of topline results. However, the applicant's reported analyses were broadly consistent with the protocol.

3.2.2 Study Design and Endpoints (GS-US-540-5773)

Study GS-US-540-5773 was a randomized, open-label, multicenter, multinational trial comparing the following treatments for severe COVID-19:

- Remdesivir for 5 days.
- Remdesivir for 10 days.

Remdesivir was administered intravenously at 200 mg on the first day of treatment, and at 100 mg daily on subsequent days.

This trial was sponsored by the applicant Gilead Sciences. A total of 402 hospitalized patients were randomized in a 1:1 ratio to the 5-day and 10-day remdesivir groups. Randomization was not stratified by any baseline factors. Patients were enrolled between March 6, 2020 and March 26, 2020. The clinicaltrials.gov identifier for this trial was NCT04292899. The trial had an extension phase termed Part B that will not be discussed in this review.

The following inclusion criteria were required for enrollment.
1. Willing and able to provide written informed consent (patients ≥18 years of age) or assent (patients ≥12 and <18 years of age, where locally and nationally approved) prior to performing study procedures. For patients ≥12 and <18 years of age, a parent or legal guardian willing and able to provide written informed consent prior to performing study procedures.
2. Aged ≥18 years (at all sites), or aged ≥12 and <18 years of age weighing ≥ 40 kg (where permitted according to local law and approved nationally and by the relevant institutional review board [IRB] or independent ethics committee [IEC]).
3. SARS-CoV-2 infection confirmed by PCR test ≤4 days before randomization.
4. Currently hospitalized.
5. SpO_2 ≤94% on room air or requiring supplemental oxygen at screening.
6. Radiographic evidence of pulmonary infiltrates.
7. Men and women of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception.

The requirement for SpO_2 ≤94% on room air or requirement for supplemental oxygen was used to ensure this trial restricted to severe disease rather than moderate disease.

Exclusion criteria were as follows:
1. Participation in any other clinical trial of an experimental treatment for COVID-19.
2. Concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 <24 hours prior to study drug dosing.
3. Evidence of multiorgan failure.
4. Mechanically ventilated (including V-V ECMO) ≥ 5 days, or any duration of V-A ECMO.
5. ALT or AST >5 x ULN.
6. Creatinine clearance <50 mL/min using the Cockcroft-Gault formula for patients ≥18 years of age and Schwartz Formula for patients <18 years of age.
7. Positive pregnancy test.

8. Breastfeeding woman.
9. Known hypersensitivity to the study drug, the metabolites, or formulation excipient.

Study procedures performed daily from Days 2-14 or until discharge included vital signs, a symptom-directed physical exam, respiratory status (e.g., oxygen supplementation), and review of adverse events and concomitant medications. Safety laboratory tests (white blood cell count, hemoglobin and/or hematocrit, platelets, creatinine and creatinine clearance, glucose, total bilirubin, ALT, AST) were performed on Days 3, 5, 8, 10, and 14 or until discharge. The final study visit was on Day 28 (± 5 days). This could be completed in person or by telephone if the patient had been discharged. If conducted remotely this visit would only assess survival status, hospitalization, oxygen support status, adverse events, concomitant medications.

The following 7-point ordinal scale was recorded at baseline, from Days 2-14 or until discharge, and at Day 28. If assessed multiple times during a day, the worst score for that day was used. Note that this scale was similar but not identical to that used in ACTT-1.
1. Death.
2. Hospitalized, on invasive mechanical ventilation or ECMO.
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices.
4. Hospitalized, requiring low flow supplemental oxygen.
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise).
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration).
7. Not hospitalized.

The primary efficacy endpoint was the ordinal scale score at Day 14. The primary endpoint was modified during the trial. Originally, it was defined as the proportion of patients in each group with normalization of fever and oxygen saturation through Day 14 [criteria for normalization: T <36.6 C armpit, <37.2 C oral, <37.8 C rectal; and $Sp0_2$ >94%, sustained for at least 24 hours]. Although the sponsor has stated that the decision to change the primary endpoint was made before any patients were enrolled, the protocol amendment was implemented while the study was ongoing. The only secondary endpoint described in the protocol was the proportion of patients with treatment emergent adverse events.

3.2.3 Statistical Methodologies (GS-US-540-5773)

The primary analysis population in this trial was the full analysis set, defined as all randomized patients who received any dose of remdesivir. The primary analysis of the Day 14 ordinal endpoint was based on a proportional odds model. The model was to include treatment and adjustment for the baseline ordinal score. The percentage of patients in each category of the scale was also to be summarized by treatment group.

The open-label design and primary endpoint choice may have favored the 5-day regimen compared with the 10-day regimen. Patients in the latter group may have had a lower

chance of achieving discharge (the best category in the ordinal scale) between Day 6 and Day 10 because they were still assigned to receive intravenous therapy.

There was an issue with prespecification in this trial, as the statistical analysis plan was not provided to the FDA until after release of topline results. Specifically, the adjustment for baseline ordinal score in the proportional odds model was not included in the protocol or documented with FDA prior to dissemination of results.

Missing data for the ordinal score primary endpoint were to be imputed using the last known value. Discharge and death were considered absorbing states (with death superseding discharge). Due to this imputation, it is possible that the primary endpoint analysis misclassified some patients who were discharged and subsequently relapsed to a worse category in the ordinal scale by Day 14.

The planned sample size was 400 total patients. This was designed to detect an odds ratio of 1.75 representing improved outcomes for the 10-day regimen. There was an independent data monitoring committee for this trial, but formal interim analyses were not planned or conducted before all subjects had recorded values for the Day 14 primary endpoint or were lost to follow-up.

3.2.4 Patient Disposition, Demographic and Baseline Characteristics (GS-US-540-5773)

The tables below display the disposition of patients in this trial. The full analysis set of randomized and treated patients contained 197 patients in the remdesivir 10 day group, 200 patients in the remdesivir 5 day group, and excluded almost no randomized patients. Almost all patients in the remdesivir 5 day group were treated for ≤5 days as assigned. In the remdesivir 10 day group, slightly under half of patients were treated for the full 10 days, and the main reason for early treatment discontinuation was hospital discharge.

Table 26: GS-US-540-5773 screening, randomization, and treatment

Screened	N = 407	
Randomized	RDV 5 days (N = 201)	RDV 10 days (N = 200)
Full analysis set (randomized and treated)	RDV 5 days (N = 200)	RDV 10 days (N = 197)

Abbreviations: RDV = remdesivir.
Source: GS-US-540-5773 Interim Clinical Study Report (Table 6).

Table 27: GS-US-540-5773 disposition (full analysis set)

		RDV 5 days (N = 200)	RDV 10 days (N = 197)
		n (%)	n (%)
Completed study		168 (84)	164 (83.2)
Discontinued study		32 (16)	33 (16.8)
Reason for study discontinuation	Adverse Event	2 (1)	1 (0.5)
	Death	21 (10.5)	28 (14.2)

	Investigator's Discretion	0 (0)	0 (0)
	Lost to Follow-Up	8 (4)	4 (2)
	Protocol Violation	0 (0)	0 (0)
	Withdrew Consent	1 (0.5)	0 (0)
Completed treatment		172 (86)	86 (43.7)
Discontinued treatment		28 (14)	111 (56.3)
Reason for treatment discontinuation	Adverse Event	9 (4.5)	22 (11.2)
	Death	0 (0)	12 (6.1)
	Hospital Discharge	16 (8)	67 (34)
	Investigator's Discretion	0 (0)	5 (2.5)
	Protocol Violation	1 (0.5)	1 (0.5)
	Subject Decision	2 (1)	4 (2)
	Subject Never Dosed with Study Drug	0 (0)	0 (0)
Days of treatment	1	2 (1)	4 (2)
	2	6 (3)	9 (4.6)
	3	8 (4)	11 (5.6)
	4	11 (5.5)	10 (5.1)
	5	171 (85.5)	19 (9.6)
	6	2 (1)	11 (5.6)
	7	0 (0)	17 (8.6)
	8	0 (0)	16 (8.1)
	9	0 (0)	13 (6.6)
	10	0 (0)	85 (43.1)
	11	0 (0)	0 (0)
	12	0 (0)	1 (0.5)
	13	0 (0)	0 (0)
	14	0 (0)	1 (0.5)

Abbreviations: RDV = remdesivir.
Source: GS-US-540-5773 Interim Clinical Study Report (Table 6) and statistical reviewer.

As shown in the baseline demographics table below, slightly under half of patients were at least 65 years old, around two thirds of patients were male, and approximately 70% of patients were White. Over half of patients were enrolled in the United States, while approximately 20% of patients were enrolled in Italy and approximately 15% patients were enrolled in Spain.

Table 28: GS-US-540-5773 demographics (full analysis set)

		RDV 5 days (N = 200)	RDV 10 days (N = 197)
Demographic category	Characteristic	n (%)	n (%)

Age (years)	<40	23 (11.5)	18 (9.1)
	40-64	93 (46.5)	95 (48.2)
	≥65	84 (42)	84 (42.6)
Sex	Male	120 (60)	133 (67.5)
	Female	80 (40)	64 (32.5)
Race	White	142 (71)	134 (68)
	Black or African American	21 (10.5)	23 (11.7)
	Asian	20 (10)	25 (12.7)
	Other or not reported	17 (8.5)	15 (7.6)
Ethnicity	Hispanic or Latino	47 (23.5)	38 (19.3)
	Not Hispanic or Latino	152 (76)	150 (76.1)
	Other or not reported	1 (0.5)	9 (4.6)
Country	United States	118 (59)	111 (56.3)
	Italy	39 (19.5)	38 (19.3)
	Spain	31 (15.5)	30 (15.2)
	South Korea	6 (3)	6 (3)
	Singapore	1 (0.5)	8 (4.1)
	Germany	3 (1.5)	1 (0.5)
	Hong Kong	2 (1)	2 (1)
	Taiwan	0 (0)	1 (0.5)

Abbreviations: RDV = remdesivir.
Source: GS-US-540-5773 Interim Clinical Study Report (Table 8) and statistical reviewer.

The following table summarizes additional baseline characteristics. The groups were imbalanced to some degree in terms of baseline values of the ordinal scale. Approximately 11% of patients in the remdesivir 10 day group were in category 5 (hospitalized without supplemental oxygen) compared with 17% in the remdesivir 5 day group, while approximately 35% of patients in the 10 day group were in categories 2 or 3 (noninvasive ventilation, high-flow oxygen, invasive ventilation, or ECMO) compared with 26.5% of patients in the 5 day group. Overall, the 10 day group required a higher degree of oxygen support at baseline than the 5 day group. Note that although the trial had exclusion criteria pertaining to mechanical ventilation, some patients could progress to invasive ventilation or ECMO between screening and the first dose of study drug and were counted in this category of the table. Patients in this trial had a high level of comorbidities such as hypertension and obesity. Slightly under half of patients in each treatment group received their first dose of remdesivir 10 or more days after the onset of symptoms.

Table 29: GS-US-540-5773 baseline characteristics (full analysis set)

		RDV 5 days (N = 200)	RDV 10 days (N = 197)
Baseline category	Characteristic	n (%)	n (%)

Ordinal scale score	2. Hospitalized with invasive mechanical ventilation or ECMO	4 (2)	9 (4.6)
	3. Hospitalized with noninvasive ventilation or high-flow oxygen	49 (24.5)	59 (29.9)
	4. Hospitalized with low-flow supplemental oxygen	113 (56.5)	108 (54.8)
	5. Hospitalized without supplemental oxygen but requiring ongoing medical care	34 (17)	21 (10.7)
Days from symptom onset to first dose	≤6	52 (26)	45 (22.8)
	7-9	62 (31)	62 (31.5)
	10-12	48 (24)	51 (25.9)
	≥13	36 (18)	36 (18.3)
Comorbidities	Hypertension	101 (50.5)	98 (49.7)
	Hyperglycemia	92 (46)	96 (48.7)
	Obesity	83 (41.5)	80 (40.6)
	Asthma	37 (18.5)	28 (14.2)
	Immunodeficiency	2 (1)	1 (0.5)
	Cancer	27 (13.5)	18 (9.1)

Abbreviations: RDV = remdesivir; ECMO = extracorporeal membrane oxygenation.
Source: GS-US-540-5773 Interim Clinical Study Report (Table 9) and statistical reviewer. The applicant's comorbidity datasets are located in the Electronic Document Room at \\CDSESUB1\evsprod\NDA214787\0033\m5\datasets\gs-us-540-5773\analysis\adam\datasets

3.2.5 Results and Conclusions (GS-US-540-5773)

3.2.5.1 Ordinal scale endpoint (GS-US-540-5773)

The table below displays results for the primary endpoint based on the Day 14 ordinal scale in the full analysis set. The odds ratio between the 5 day and 10 day remdesivir groups was not statistically significant but numerically favored the 5 day group. At the upper end of the scale, rates of discharge were higher for the 5 day group (60.0%) than the 10 day group (52.3%), while rates for the worst two categories (death, invasive ventilation, or ECMO) were lower for the 5 day group (16.5%) than the 10 day group (27.4%).

Table 30: GS-US-540-5773 primary analysis of the Day 14 ordinal scale results (full analysis set)

	RDV 5 days (N = 200)	RDV 10 days (N = 197)
Ordinal scale score	n (%)	n (%)
1. Death	16 (8)	21 (10.7)
2. Hospitalized with invasive mechanical ventilation or ECMO	17 (8.5)	33 (16.8)
3. Hospitalized with noninvasive ventilation or high-flow oxygen	8 (4)	10 (5.1)
4. Hospitalized with low-flow supplemental oxygen	19 (9.5)	15 (7.6)
5. Hospitalized without supplemental oxygen but requiring ongoing medical care	12 (6)	12 (6.1)
6. Hospitalized without supplemental oxygen or ongoing medical care	8 (4)	3 (1.5)
7. Not hospitalized	120 (60)	103 (52.3)
Odds ratio (95% CI)	0.74 (0.5 to 1.1)	
p-value	0.136	

Abbreviations: RDV = remdesivir; ECMO = extracorporeal membrane oxygenation; CI = confidence interval.
Notes: The odds ratio and p-value are based on a proportional odds model that adjusts for the baseline ordinal scale score. An odds ratio <1 favors the 5 day group and an odds ratio >1 favors the 10 day group.
Source: GS-US-540-5773 Interim Clinical Study Report (Tables 11, 12) and statistical reviewer.

The odds ratio was almost identical when excluding patients who were enrolled before FDA receipt of the previously discussed protocol amendment that modified the primary endpoint, as shown in the table below. Thus, the primary endpoint change in this trial did not impact conclusions.

Table 31: GS-US-540-5773 Day 14 ordinal scale results for patients enrolled after March 17, 2020 when the protocol amendment changing the primary endpoint was received (full analysis set)

	RDV 5 days (N = 166)	RDV 10 days (N = 164)
Ordinal scale score	n (%)	n (%)
1. Death	14 (8.4)	17 (10.4)
2.	17 (10.2)	28 (17.1)
3.	7 (4.2)	9 (5.5)
4.	16 (9.6)	13 (7.9)

5.	8 (4.8)	11 (6.7)
6.	8 (4.8)	2 (1.2)
7. Not hospitalized	96 (57.8)	84 (51.2)
Odds ratio (95% CI)	0.77 (0.5 to 1.17)	
p-value	0.221	

Abbreviations: RDV = remdesivir;; CI = confidence interval.
Notes: The odds ratio and p-value are based on a proportional odds model that adjusts for the baseline ordinal scale score. An odds ratio <1 favors the 5 day group and an odds ratio >1 favors the 10 day group.
Source: Statistical reviewer.

Unfortunately, it was not possible to discern whether these efficacy results were impacted by open-label bias. The main issue was that (as previously noted) virtually all subjects in the 5 day group received ≤5 days of therapy, and thereafter could be discharged. Almost half of patients in the 10 day received the full 10 days of therapy, and thus may have been more likely to remain hospitalized to complete the assigned therapy. It is unknown whether the difference in windows for discharge may have impacted the Day 14 ordinal scale results.

Another issue with the primary endpoint concerned imputed data. As previously discussed, patients who were discharged before Day 14 had the top ordinal scale score of 7 imputed. The table below shows that there were high rates of imputed data. It was not possible to assess from the datasets whether recording deteriorations in patient status between the time of discharge and Day 14 would have changed results.

Table 32: GS-US-540-5773 imputations for the Day 14 ordinal scale primary endpoint (full analysis set)

	RDV 5 days (N = 200)	RDV 10 days (N = 197)
No imputation	74 (37)	86 (43.7)
'Not hospitalized' carried forward	118 (59)	101 (51.3)
Last observation carried forward	8 (4)	10 (5.1)

Abbreviations: RDV = remdesivir.
Notes: Deaths occurring at or before Day 14 are counted as “no imputation.”
Source: Statistical reviewer.

The following two tables apply two modifications to the primary efficacy analysis. First, note that the statistical analysis plan specified that the primary analysis should be adjusted for the baseline ordinal score in the proportional odds model. However, as previously noted the statistical analysis plan was not received until after release of topline results, and there appeared to be a chance baseline imbalance in which sicker patients were randomized to the 10 day group. To consider the impact of adjustment, the table below presents results for an unadjusted proportional odds analysis. In this analysis the 5 day group was associated with improved outcomes compared with the 10 day group. A Wilcoxon test also was conducted because this method did not require invoking the

proportional odds assumption. The p-values were similar for this test and the unadjusted proportional odds model. Overall, the adjusted and unadjusted analyses suggested that chance baseline imbalances may have impacted comparisons between the randomized groups to the detriment of the 10 day arm.

Table 33: GS-US-540-5773 unadjusted proportional odds model analysis comparing RDV 5 days versus RDV 10 days for the Day 14 ordinal scale results (full analysis set)

	RDV 5 days (N = 200)	RDV 10 days (N = 197)
Odds ratio (95% CI)	0.67 (0.46 to 0.98)	
p-value	0.0365	

Abbreviations: RDV = remdesivir; CI = confidence interval.
Notes: The Odds ratio and p-value are based on a proportional odds model that does not adjusted for baseline covariates. An odds ratio <1 favors the 5 day group and an odds ratio >1 favors the 10 day group.
Source: Statistical reviewer.

Table 34: GS-US-540-5773 Wilcoxon rank test comparing RDV 5 days versus RDV 10 days for the Day 14 ordinal scale results (full analysis set)

	RDV 5 days (N = 200)	RDV 10 days (N = 197)
p-value	0.0372	

Abbreviations: RDV = remdesivir.
Notes: The p-value is two-sided.
Source: GS-US-540-774 Interim Clinical Study Report (Table 12).

The subsequent tables display results for the Day 14 ordinal scale primary endpoint in subgroups defined by baseline values of the ordinal scale. The proportional odds models were not adjusted because the restriction to these subgroups already was considered to control for baseline severity. There were no subgroups in which results convincingly pointed to the need for the longer 10 day treatment course.

Table 35: GS-US-540-5773 Day 14 ordinal scale results in the subgroup with baseline ordinal score of 3 = Hospitalized with noninvasive ventilation or high-flow oxygen (full analysis set)

	RDV 5 days (N = 49)	RDV 10 days (N = 59)
Ordinal scale score	n (%)	n (%)
1. Death	8 (16.3)	13 (22)
2.	6 (12.2)	19 (32.2)
3.	7 (14.3)	6 (10.2)
4.	7 (14.3)	5 (8.5)
5.	1 (2)	2 (3.4)
6.	1 (2)	0 (0)
7. Not hospitalized	19 (38.8)	14 (23.7)
Odds ratio (95% CI)	0.46 (0.23 to 0.91)	

Abbreviations: RDV = remdesivir; CI = confidence interval.

Notes: The Odds ratios and p-value are based on a proportional odds model that is not adjusted for baseline covariates. An odds ratio <1 favors the 5 day group and an odds ratio >1 favors the 10 day group.
Source: Statistical reviewer.

Table 36: GS-US-540-5773 Day 14 ordinal scale results in the subgroup with baseline ordinal score of 4 = Hospitalized with low-flow supplemental oxygen (full analysis set)

	RDV 5 days (N = 113)	RDV 10 days (N = 108)
Ordinal scale score	n (%)	n (%)
1. Death	5 (4.4)	2 (1.9)
2.	9 (8)	9 (8.3)
3.	1 (0.9)	3 (2.8)
4.	9 (8)	10 (9.3)
5.	11 (9.7)	7 (6.5)
6.	5 (4.4)	2 (1.9)
7. Not hospitalized	73 (64.6)	75 (69.4)
Odds ratio (95% CI)	1.19 (0.69 to 2.06)	

Abbreviations: RDV = remdesivir; CI = confidence interval.
Notes: The Odds ratios and p-value are based on a proportional odds model that is not adjusted for baseline covariates. An odds ratio <1 favors the 5 day group and an odds ratio >1 favors the 10 day group.
Source: Statistical reviewer.

Table 37: GS-US-540-5773 Day 14 ordinal scale results in the subgroup with baseline ordinal score of 5 = Hospitalized without supplemental oxygen but requiring ongoing medical care (full analysis set)

	RDV 5 days (N = 34)	RDV 10 days (N = 21)
Ordinal scale score	n (%)	n (%)
1. Death	2 (5.9)	2 (9.5)
2.	0 (0)	1 (4.8)
3.	0 (0)	1 (4.8)
4.	2 (5.9)	0 (0)
5.	0 (0)	3 (14.3)
6.	2 (5.9)	1 (4.8)
7. Not hospitalized	28 (82.4)	13 (61.9)
Odds ratio (95% CI)	0.35 (0.1 to 1.21)	

Abbreviations: RDV = remdesivir; CI = confidence interval.
Notes: The Odds ratios and p-value are based on a proportional odds model that is not adjusted for baseline covariates. An odds ratio <1 favors the 5 day group and an odds ratio >1 favors the 10 day group.
Source: Statistical reviewer.

One potential issue with the primary endpoint in this trial concerned the timepoint. There was some degree of arbitrariness is specifying the timepoint, and it was unclear whether a

Day 14 endpoint ensured sufficient capture of clinical events important to patients. Consequently, the following table displays results for the ordinal endpoint at the later timepoint of Day 28. The adjusted proportional odds model yielded numerically better results for the 5 day group than the 10 day group. Thus, this later timepoint analysis did not suggest that the 5 day duration led to a falloff in efficacy for longer term outcomes.

Table 38: GS-US-540-5773 Day 28 ordinal scale results (full analysis set)

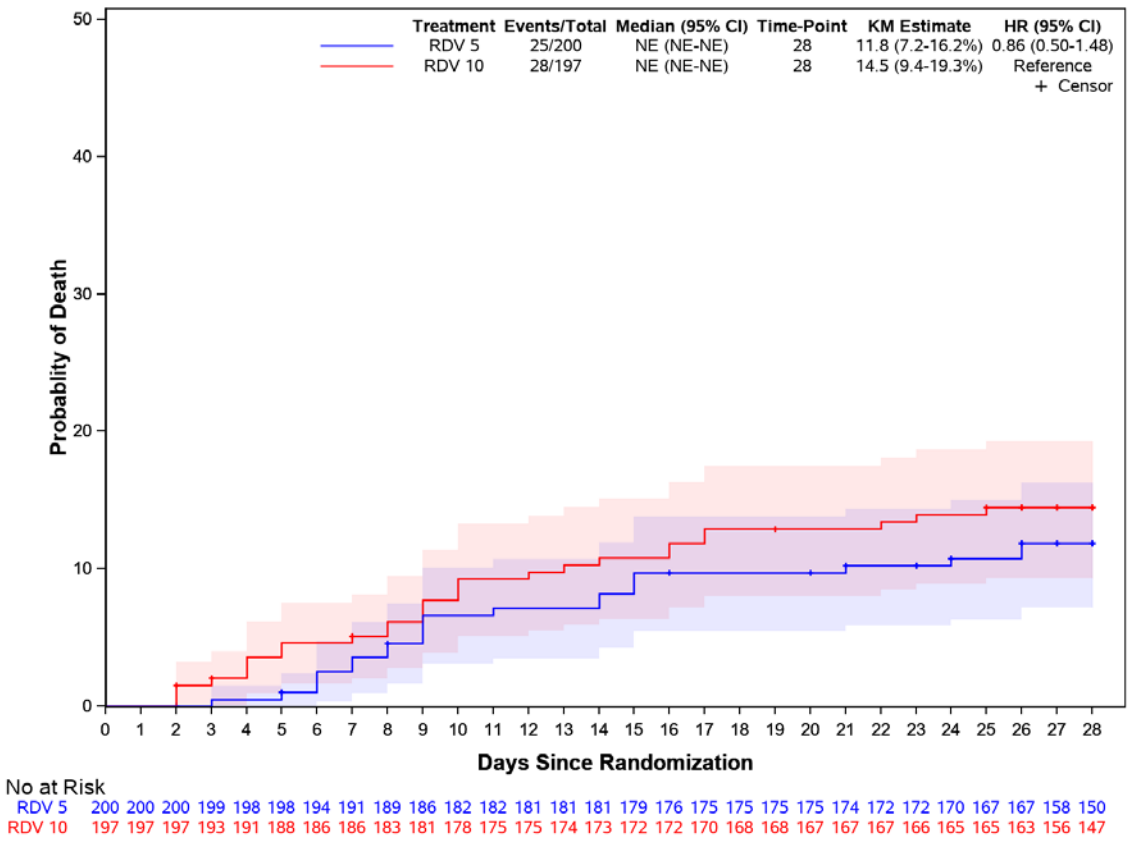
	RDV 5 days (N = 200)	RDV 10 days (N = 197)
Ordinal scale score	n (%)	n (%)
1. Death	23 (11.5)	28 (14.2)
2.	6 (3)	17 (8.6)
3.	3 (1.5)	6 (3)
4.	3 (1.5)	9 (4.6)
5.	12 (6)	8 (4.1)
6.	2 (1)	2 (1)
7. Not hospitalized	151 (75.5)	127 (64.5)
Odds ratio (95% CI)	0.69 (0.44 to 1.1)	
p-value	0.118	

Abbreviations: RDV = remdesivir; CI = confidence interval.
Notes: The odds ratio and p-value are based on a proportional odds model that adjusts for the baseline ordinal scale score. An odds ratio <1 favors the 5 day group and an odds ratio >1 favors the 10 day group.
Source: Statistical reviewer.

3.2.5.2 All-cause mortality (GS-US-540-5773)

The next figure and table present Kaplan-Meier results for all-cause mortality. In addition to representing the most clinically meaningful outcome, it is likely that mortality was less affected by the potential open-label issues that were noted for ordinal scale outcome. The table restricts to results at Day 5, Day 14, Day 28. In particular, Day 5 is displayed because interventions should have been identical at this timepoint in both arms of this trial comparing 5 and 10 day durations, yet results significantly favored the 5 day group. Hence, mortality results in the overall full analysis set were likely impacted by the previously discussed baseline imbalances.

Figure 4: GS-US-540-5773 analysis of all-cause mortality (full analysis set)



Abbreviations: RDV = remdesivir; CI = confidence interval; HR = hazard ratio.
Notes: The plot is based on a Kaplan-Meier analysis. The hazard ratio is based on a proportional hazards model that does not adjust or stratify by baseline covariates. A hazard ratio <1 favors the remdesivir 5 day group and a hazard ratio >1 favors the remdesivir 10 day group.
Source: Analytics and informatics reviewer.

Table 39: GS-US-540-5773 Kaplan-Meier analysis of all-cause mortality at Day 5, Day 14, and Day 28 (full analysis set)

Day	Censored	Mortality for RDV 5 days (N = 200)	Mortality for RDV 10 days (N = 197)	Difference	95% CI
5	3/397 (0.8%)	1%	4.6%	-3.6%	-6.8% to -0.3%
14	9/397 (2.3%)	8.2%	10.8%	-2.6%	-8.5% to 3.2%
28	49/397 (12.3%)	11.8%	14.5%	-2.6%	-9.3% to 4.1%

Abbreviations: RDV = remdesivir; CI = confidence interval.
Source: Statistical reviewer.

To address this issue, the following tables summarize mortality in baseline subgroups defined by disease severity. However, due to small sample sizes in these subgroups and

corresponding wide confidence intervals, it was not possible to determine if there was a mortality difference between the remdesivir duration arms within severity subsets.

Table 40: GS-US-540-5773 all-cause mortality results through Day 28 in the subgroup with baseline ordinal score of 3 = Hospitalized with noninvasive ventilation or high-flow oxygen (full analysis set)

	RDV 5 days (N = 49)	RDV 10 days (N = 59)
Number of deaths	14	18
Kaplan-Meier estimate	28.8%	30.8%
Hazard ratio (95% CI)	1.13 (0.56 to 2.27)	

Abbreviations: RDV = remdesivir; CI = confidence interval.
Notes: The hazard ratio is based on a proportional hazards model that does not adjust for baseline covariates. A hazard ratio <1 favors the 10 day group and a hazard ratio >1 favors the 5 day group.
Source: Statistical reviewer.

Table 41: GS-US-540-5773 all-cause mortality results through Day 28 in the subgroup with baseline ordinal score of 4 = Hospitalized with low-flow supplemental oxygen (full analysis set)

	RDV 5 days (N = 113)	RDV 10 days (N = 108)
Number of deaths	6	3
Kaplan-Meier estimate	5.5%	2.8%
Hazard ratio (95% CI)	0.51 (0.13 to 2.03)	

Abbreviations: RDV = remdesivir; CI = confidence interval.
Notes: The hazard ratio is based on a proportional hazards model that does not adjust for baseline covariates. A hazard ratio <1 favors the 10 day group and a hazard ratio >1 favors the 5 day group.
Source: Statistical reviewer.

Table 42: GS-US-540-5773 all-cause mortality results through Day 28 in the subgroup with baseline ordinal score of 5 = Hospitalized without supplemental oxygen but requiring ongoing medical care (full analysis set)

	RDV 5 days (N = 34)	RDV 10 days (N = 21)
Number of deaths	2	3
Kaplan-Meier estimate	6.1%	14.3%
Hazard ratio (95% CI)	2.31 (0.39 to 13.8)	

Abbreviations: RDV = remdesivir; CI = confidence interval.
Notes: The hazard ratio is based on a proportional hazards model that does not adjust for baseline covariates. A hazard ratio <1 favors the 10 day group and a hazard ratio >1 favors the 5 day group.
Source: Statistical reviewer.

3.2.5.3 Conclusions (GS-US-540-5773)

Study GS-US-540-5773 provided data supporting the use of a 5 day duration for remdesivir for the treatment of severe COVID-19 disease. The main limitations of this study were the lack of a placebo or standard of care control group, possible open-label bias for the primary analysis due to the fact that the 5 day group had greater opportunities for achieving discharge after completing assigned therapy, imputations needed for the primary endpoint after discharge, baseline imbalances in which patients in the 10 day had more severe disease, and receipt of the statistical analysis plan and method of covariate adjustment after release of topline results. Furthermore, this trial was not designed for formal noninferiority assessments to rule out acceptable losses of efficacy for the 5 day group, and determination of an appropriate noninferiority margin would be challenging in this setting. In spite of these limitations, the primary efficacy analysis based on an adjusted proportional odds model for the Day 14 ordinal scale, the Day 28 ordinal scale results, and all-cause mortality results were consistent with the 5 day treatment course being of sufficient duration.

3.3 GS-US-540-5774

3.3.1 Data and Analysis Quality (GS-US-540-5774)

The datasets for Study GS-US-540-5774 in patients with moderate COVID-19 were structured very similarly to those for Study GS-US-540-5773 in patients with severe disease. It was relatively straightforward to reproduce the applicant's reported results to sufficient precision using these datasets. There are currently no site inspection results or other findings questioning the integrity or accuracy of submitted data for this trial. The applicant's reporting of results was largely consistent with the protocol and statistical analysis plan, but as in GS-US-540-5773 the statistical analysis plan was not submitted until after release of topline results. Additional comments regarding prespecification will be provided below.

3.3.2 Study Design and Endpoints (GS-US-540-5774)

Study GS-US-540-5774 was a randomized, open-label, multicenter, multinational trial comparing the following three regimens for the treatment of hospitalized patients with moderate COVID-19.

- Remdesivir for 5 days.
- Remdesivir for 10 days.
- Open-label standard of care.

Remdesivir was intravenously administered once a day at a dose of 200 mg on the first day of therapy and 100 mg on subsequent days.

This Gilead-sponsored trial randomized approximately 600 participants in a 1:1:1 ratio to the three treatment groups. No stratification factors were used in the randomization. The clinicaltrials.gov identifier for this trial was NCT04292730. This review does not discuss the trial's non-randomized extension phase that was termed Part B.

Inclusion criteria were as follows:

1. Willing and able to provide written informed consent (participants ≥ 18 years of age) or assent (participants ≥12 and <18 years of age) prior to performing study procedures. For participants ≥12 and <18 years of age, a parent or legal guardian willing and able to provide written informed consent prior to performing study procedures.
2. Aged ≥18 years (at all sites), or aged ≥12 and <18 years of age weighing ≥40 kg (where permitted according to local law and approved nationally and by the relevant institutional review board [IRB] or independent ethics committee [IEC]).
3. SARS-CoV-2 infection confirmed by PCR ≤ 4 days before randomization.
4. Currently hospitalized and requiring medical care for COVID-19
5. SpO_2 >94% on room air at screening.
6. Radiographic evidence of pulmonary infiltrates.
7. Men and women of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception.

The requirement for SpO_2 >94% on room air at screening was the main restriction differentiating this moderate study from a severe COVID-19 study.

The following exclusion criteria were used in the trial:
1. Participation in any other clinical trial of an experimental agent treatment for COVID-19.
2. Concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 <24 hours prior to study drug dosing.
3. Requiring mechanical ventilation at screening.
4. ALT or AST > 5 x ULN.
5. Creatinine clearance <50 mL/min using the Cockcroft-Gault formula for participants ≥18 years of age, Cockcroft and Schwartz Formula for participants <18 years of age.
6. Positive pregnancy test.
7. Breastfeeding woman.
8. Known hypersensitivity to the study drug, the metabolites, or formulation excipient.

Study procedures performed daily from Days 2-14 or until discharge included vital signs, a symptom-directed physical exam, respiratory status (e.g., oxygen supplementation), and review of adverse events and concomitant medications. Safety laboratory tests (white blood cell count, hemoglobin and/or hematocrit, platelets, creatinine and creatinine clearance, glucose, total bilirubin, ALT, AST) were performed on Days 3, 5, 8, 10, and 14 or until discharge. The final study visit was on Day 28 (± 5 days). This could be completed in person or by telephone if the participant had been discharged. If conducted remotely this visit would only assess survival status, hospitalization, oxygen support status, adverse events, concomitant medications.

The following 7-point ordinal scale was recorded at baseline, from Days 2-14 or until discharge, and at Day 28. If assessed multiple times during a day, the worst score for that day was used. This was identical to the scale used in GS-US-540-5773 for severe disease, and slightly differed from the ordinal scale used in ACTT-1.
1. Death.
2. Hospitalized, on invasive mechanical ventilation or ECMO.

3. Hospitalized, on non-invasive ventilation or high flow oxygen devices.
4. Hospitalized, requiring low flow supplemental oxygen.
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise).
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration).
7. Not hospitalized.

The primary efficacy endpoint was the ordinal scale score at Day 11. The analysis of this scale will be discussed in the next subsection.

The primary endpoint was modified during the trial. In the original protocol the primary endpoint was based on the proportion of participants in each group with normalization of fever and respiratory rate through Day 10 [criteria for normalization: T <36.6 C armpit, <37.2 C oral, <37.8 C rectal; and respiratory rate of <24 breaths per minute, for at least 24 hours]. However, at the time of the protocol amendment only 1 participant had been enrolled, so the endpoint change was considered immaterial.

The only secondary endpoint described in the protocol was the proportion of participants with treatment emergent adverse events.

3.3.3 Statistical Methodologies (GS-US-540-5774)

The primary efficacy analysis population was the full analysis set. This was defined as all randomized participants, but excluding participants randomized to one of the two remdesivir groups who did not receive any study drug.

As this was an open-label design, exclusions of randomized participants in theory had the potential to introduce confounding, as they only applied to the remdesivir groups and not to the standard of care control group.

The primary analysis of the Day 11 ordinal scale was based on a proportional odds model. Each remdesivir treatment group was to be separately compared with the standard of care group using a proportional odds analysis. The model was to only include a treatment term and did not adjust for baseline variables such as the baseline ordinal score. The number and percentage of participants in each category of the scale was also to be summarized by treatment group.

The primary endpoint and open-label design may have favored the 5-day remdesivir regimen compared with the 10-day remdesivir regimen. In particular, participants in the 10-day group may have had a lower chance of achieving discharge between Day 6 and Day 10 because they were still assigned to receive intravenous therapy.

Missing data for the ordinal score primary endpoint were to be imputed using the last known value. Discharge and death were considered absorbing states (with death superseding discharge).

The statistical analysis plan specified that a Bonferroni correction would be used to control multiplicity due to this trial having two active treatment groups. Thus, the two superiority hypothesis (5-day remdesivir versus standard of care; 10-day remdesivir versus standard of care) would each be tested a two-sided $\alpha = 0.025$ significance level. There were no formal direct comparisons between the 10-day and 5-day remdesivir groups.

One issue in this trial related to prespecification. Specifically, the statistical analysis plan was not submitted to FDA until after submission of topline results. The preceding protocol did not discuss the specific multiplicity correction that would be applied for the primary analyses.

The planned sample size for this trial was 600 total participants (200 per group). This was meant to achieve at least 85% power for detecting an odds ratio of 1.8 for the 10-day remdesivir versus standard of care comparison, and also an odds ratio of 1.8 for the 5-day remdesivir versus standard of care comparison. The sponsor's sample size calculation did not consider the Bonferroni adjustment noted above. There was an independent data monitoring committee, but it did not conduct any formal interim analyses before all patients had recorded values for the Day 11 primary endpoint.

3.3.4 Patient Disposition, Demographic and Baseline Characteristics (GS-US-540-5774)

Patient disposition is summarized in the two tables below. One issue in this open-label trial was that randomized patients were only excluded from the full analysis set in the remdesivir treatment groups rather than the standard of care control group. This was because only patients randomized to remdesivir could be excluded due to failing to receive study drug. However, the number of such exclusions was relatively small. Over 90% of patients in each group completed study assessments, with the most common reason for study discontinuation being loss to follow-up. The assigned treatment course was completed by approximately 76% of patients in the remdesivir 5 day treatment group but only 38% of patients in the remdesivir 10 day group. The most common reason for early treatment discontinuation was hospital discharge, and almost half of patients randomized to the remdesivir 10 day group actually received 5 or fewer days of therapy.

Table 43: GS-US-540-5774 screening, randomization, and treatment

Screened	N = 612		
Randomized	RDV 5 days (N = 199)	RDV 10 days (N = 197)	SOC (N = 200)
Full analysis set (randomized and treated)	RDV 5 days (N = 191)	RDV 10 days (N = 193)	SOC (N = 200)

Abbreviations: RDV = remdesivir; SOC = standard of care.
Source: GS-US-540-5774 Interim Clinical Study Report (Table 5).

Table 44: GS-US-540-5774 disposition (full analysis set)

		RDV 5 days (N = 191)	RDV 10 days (N = 193)	SOC (N = 200)
		n (%)	n (%)	n (%)
Completed study		179 (93.7)	176 (91.2)	178 (89)
Discontinued study		12 (6.3)	17 (8.8)	22 (11)
Reason for study discontinuation	Death	2 (1)	2 (1)	4 (2)
	Investigator's Discretion	0 (0)	0 (0)	0 (0)
	Lost to Follow-Up	8 (4.2)	12 (6.2)	12 (6)
	Non-Compliance with Study Drug	0 (0)	1 (0.5)	0 (0)
	Protocol Violation	0 (0)	0 (0)	1 (0.5)
	Withdrew Consent	2 (1)	2 (1)	5 (2.5)
Completed treatment		145 (75.9)	73 (37.8)	200 (100)
Discontinued treatment		46 (24.1)	120 (62.2)	0 (0)
Reason for study drug discontinuation	Adverse Event	4 (2.1)	8 (4.1)	0 (0)
	Death	0 (0)	1 (0.5)	0 (0)
	Hospital Discharge	35 (18.3)	98 (50.8)	0 (0)
	Investigator's Discretion	1 (0.5)	4 (2.1)	0 (0)
	Lost to Follow-Up	1 (0.5)	0 (0)	0 (0)
	Non-Compliance with Study Drug	0 (0)	1 (0.5)	0 (0)
	Protocol Violation	0 (0)	2 (1)	0 (0)
	Subject Decision	5 (2.6)	6 (3.1)	0 (0)
	Subject Never Dosed with Study Drug	0 (0)	0 (0)	0 (0)
Days of study drug	1	7 (3.7)	8 (4.1)	0 (0)
	2	11 (5.8)	18 (9.3)	0 (0)

	3	18 (9.4)	26 (13.5)	0 (0)
	4	10 (5.2)	20 (10.4)	0 (0)
	5	143 (74.9)	18 (9.3)	0 (0)
	6	1 (0.5)	10 (5.2)	0 (0)
	7	1 (0.5)	10 (5.2)	0 (0)
	8	0 (0)	7 (3.6)	0 (0)
	9	0 (0)	3 (1.6)	0 (0)
	10	0 (0)	73 (37.8)	0 (0)

Abbreviations: RDV = remdesivir; SOC = standard of care.
Source: GS-US-540-5774 Interim Clinical Study Report (Table 5) and statistical reviewer.

The next table summarizes baseline demographics, which appeared relatively balanced between treatment groups. Over a quarter of patients were 65 years or older. The study population was majority male, majority White, and was largely enrolled from the United States, Spain, and Italy.

Table 45: GS-US-540-5774 demographics (full analysis set)

		RDV 5 days (N = 191)	RDV 10 days (N = 193)	SOC (N = 200)
Demographic category	Characteristic	n (%)	n (%)	n (%)
Age (years)	<40	24 (12.6)	31 (16.1)	37 (18.5)
	40-64	118 (61.8)	110 (57)	105 (52.5)
	≥65	49 (25.7)	52 (26.9)	58 (29)
Sex	Male	114 (59.7)	118 (61.1)	125 (62.5)
	Female	77 (40.3)	75 (38.9)	75 (37.5)
Race	White	109 (57.1)	107 (55.4)	112 (56)
	Black or African American	35 (18.3)	37 (19.2)	27 (13.5)
	Asian	34 (17.8)	31 (16.1)	37 (18.5)
	Other or not reported	13 (6.8)	18 (9.3)	24 (12)
Ethnicity	Hispanic or Latino	25 (13.1)	42 (21.8)	34 (17)
	Not Hispanic or Latino	162 (84.8)	144 (74.6)	152 (76)
	Other or not reported	4 (2.1)	7 (3.6)	13 (6.5)
Country	United States	76 (39.8)	99 (51.3)	85 (42.5)
	Spain	37 (19.4)	28 (14.5)	31 (15.5)
	Italy	30 (15.7)	23 (11.9)	26 (13)
	Great Britain	7 (3.7)	9 (4.7)	17 (8.5)
	Hong Kong	9 (4.7)	11 (5.7)	7 (3.5)
	Germany	8 (4.2)	6 (3.1)	8 (4)
	South Korea	7 (3.7)	4 (2.1)	10 (5)

	Singapore	3 (1.6)	6 (3.1)	9 (4.5)
	Switzerland	4 (2.1)	5 (2.6)	6 (3)
	Taiwan	5 (2.6)	1 (0.5)	0 (0)
	Netherlands	3 (1.6)	0 (0)	1 (0.5)
	France	2 (1)	1 (0.5)	0 (0)

Abbreviations: RDV = remdesivir; SOC = standard of care.
Source: GS-US-540-5774 Interim Clinical Study Report (Table 7) and statistical reviewer.

The subsequent table displays additional baseline characteristics. At least 80% of patients in each treatment group had an ordinal score of 5 at baseline (hospitalized, not requiring supplemental oxygen). However, despite the design of this trial to examine moderate COVID-19 more than 10% of patients in each group had an ordinal score of 4 (hospitalized, requiring low flow supplemental oxygen), which was consistent with more severe disease.

Table 46: GS-US-540-5774 baseline characteristics (full analysis set)

		RDV 5 days (N = 191)	RDV 10 days (N = 193)	SOC (N = 200)
Baseline category	Characteristic	n (%)	n (%)	n (%)
Ordinal scale score	3. Hospitalized with noninvasive ventilation or high-flow oxygen	2 (1)	1 (0.5)	2 (1)
	4. Hospitalized with low-flow supplemental oxygen	29 (15.2)	23 (11.9)	36 (18)
	5. Hospitalized without supplemental oxygen but requiring ongoing medical care	160 (83.8)	163 (84.5)	160 (80)
	6. Hospitalized without supplemental oxygen or ongoing medical care	0 (0)	6 (3.1)	2 (1)
Days from symptom onset to first dose	≤6	73 (38.2)	80 (41.5)	54 (27)
	7-9	53 (27.7)	49 (25.4)	63 (31.5)
	10-12	34 (17.8)	31 (16.1)	43 (21.5)
	≥13	31 (16.2)	29 (15)	37 (18.5)
Comorbidities	Hypertension	82 (42.9)	85 (44)	81 (40.5)
	Hyperglycemia	71 (37.2)	85 (44)	76 (38)

	Obesity	53 (27.7)	59 (30.6)	55 (27.5)
	Asthma	22 (11.5)	31 (16.1)	28 (14)
	Immunodeficiency	7 (3.7)	6 (3.1)	2 (1)
	Cancer	36 (18.8)	26 (13.5)	33 (16.5)

Abbreviations: RDV = remdesivir; SOC = standard of care.
Source: GS-US-540-5774 Interim Clinical Study Report (Tables 8 and 15.8.3.3) and statistical reviewer. The applicant's comorbidity datasets are located in the Electronic Document Room at \\CDSESUB1\evsprod\NDA214787\0033\m5\datasets\gs-us-540-5774\analysis\adam\datasets

3.3.5 Results and Conclusions (GS-US-540-5774)

3.3.5.1 Ordinal scale endpoint (GS-US-540-5774)

Results for the primary efficacy analysis of the Day 11 ordinal endpoint in the full analysis set are shown below. The proportional odds model analysis showed that the remdesivir 5 day group was associated with more favorable outcomes than the standard of care control group. At the upper end of the ordinal scale, rates of discharge by Day 11were higher for the 5 day remdesivir group than the standard of care group, while for the lower two categories of the scale the rates of death, invasive mechanical ventilation, or ECMO at Day 11 were lower for the remdesivir 5 day group than the standard of care group. The remdesivir 10 day group also had numerically superior results compared with the standard of care group, but the proportional odds model analysis did not statistically rule out a lack of benefit.

Table 47: GS-US-540-5774 primary analysis of the Day 11 ordinal scale results (full analysis set)

	RDV 5 days (N = 191)	RDV 10 days (N = 193)	SOC (N = 200)
Ordinal scale score	n (%)	n (%)	n (%)
1. Death	0 (0)	2 (1)	4 (2)
2. Hospitalized with invasive mechanical ventilation or ECMO	0 (0)	1 (0.5)	4 (2)
3. Hospitalized with noninvasive ventilation or high-flow oxygen	5 (2.6)	0 (0)	7 (3.5)
4. Hospitalized with low-flow supplemental oxygen	7 (3.7)	12 (6.2)	11 (5.5)
5. Hospitalized without supplemental oxygen but	38 (19.9)	44 (22.8)	46 (23)

requiring ongoing medical care			
6. Hospitalized without supplemental oxygen or ongoing medical care	7 (3.7)	9 (4.7)	8 (4)
7. Not hospitalized	134 (70.2)	125 (64.8)	120 (60)
Odds ratio (95% CI) versus SOC	1.65 (1.09 to 2.48)	1.31 (0.88 to 1.95)	
p-value	0.017	0.182	

Abbreviations: RDV = remdesivir; SOC = standard of care; ECMO = extracorporeal membrane oxygenation; CI = confidence interval.
Notes: Odds ratios and p-values are based on proportional odds models that are not adjusted for baseline covariates. An odds ratio <1 favors SOC and an odds ratio >1 favors remdesivir.
Source: GS-US-540-5774 Interim Clinical Study Report (Tables 10, 12) and statistical reviewer.

The table below shows imputations used for the primary endpoint. Because discharge was carried forward to the best outcome for the ordinal scale for a majority of patients in each treatment group, the endpoint did not incorporate any worsening in condition between discharge and Day 11.

Table 48: GS-US-540-5774 imputations for the Day 11 ordinal scale primary endpoint (full analysis set)

	RDV 5 days (N = 191)	RDV 10 days (N = 193)	SOC (N = 200)
No imputation	48 (25.1)	59 (30.6)	61 (30.5)
'Not hospitalized' carried forward	134 (70.2)	125 (64.8)	120 (60)
Last observation carried forward	9 (4.7)	9 (4.7)	19 (9.5)

Abbreviations: RDV = remdesivir; SOC = standard of care.
Notes: Deaths occurring at or before Day 11 are counted as “no imputation.”
Source: Statistical reviewer.

It is possible that open-label issues influenced the differences seen between the remdesivir 5 day group and remdesivir 10 day group. As previously discussed, virtually all patients in the 5 day group received ≤5 days of therapy, while over a third of patients in the 10 day group received the full 10 days of therapy. Hence, patients in the 5 day group may have had greater opportunities for discharge following treatment completion.

It was unclear whether open-label bias affected differences between the remdesivir groups and standard of care group. As the standard of care group did not require any hospital length of stay solely to complete therapy, this reviewer expected any open-label bias to favor standard of care. However, the directionality of any open-label effects could not be determined from the data.

The statistical analysis plan had specified use of a Bonferroni correction in the primary analysis to adjust for multiple comparisons due to this trial evaluating two active treatment arms. Even with this correction, the remdesivir 5 day group was statistically superior to the standard of care group. However, the statistical analysis plan was not received until after release of topline results. Although the Bonferroni method is often considered conservative, results would not have been significant using other methods of multiplicity control (e.g., hierarchical testing of the 10 day group before the 5 day group).

Outcomes were not available for patients who were randomized but not included in the full analysis set because they did not receive study drug. As previously noted, by design such exclusions only applied to the remdesivir groups and not the standard of care group, and led to 12 randomized patients being excluded from efficacy analyses. If imputing a value of 5 (i.e., hospitalized without supplemental oxygen but requiring ongoing medical care) or worse for the primary endpoint, results would no longer have shown statistically significant benefit for either remdesivir group compared with standard of care (not shown). Hence, efficacy conclusions from this trial depend in part on assuming that exclusion from the full analysis set was not associated with poor clinical outcomes.

The subsequent two tables display results for additional modifications of the primary analysis. The first shows results from a proportional odds model adjusted for the baseline value of the ordinal scale. This was consistent with the primary analysis in GS-US-540-5773 and was conducted to examine the impact of analytic choices because the statistical analysis plan was not received until after topline results had been reported. Adjustment for baseline scores appeared to have minimal impact on results. The second table displays results from Wilcoxon rests comparing each remdesivir group to the standard of care group. These tests did not depend on the proportional odds assumption, but yielded very similar p-values to the proportional odds model analyses.

Table 49: GS-US-540-5774 adjusted proportional odds model analyses comparing RDV 5 days versus SOC and RDV 10 days versus SOC for the Day 11 ordinal scale results (full analysis set)

	RDV 5 days (N = 191)	RDV 10 days (N = 193)	SOC (N = 200)
Odds ratio (95% CI)	1.69 (1.12 to 2.55)	1.3 (0.87 to 1.94)	
p-value	0.013	0.206	

Abbreviations: RDV = remdesivir; SOC = standard of care; CI = confidence interval.
Notes: Odds ratios and p-values are based on proportional odds models that are adjusted for the baseline ordinal scale score. An odds ratio <1 favors SOC and an odds ratio >1 favors remdesivir.
Source: Statistical reviewer.

Table 50: GS-US-540-5774 Wilcoxon rank tests comparing RDV 5 days versus SOC and RDV 10 days versus SOC for the Day 11 ordinal scale results (full analysis set)

	RDV 5 days (N = 191)	RDV 10 days (N = 193)	SOC (N = 200)
p-value	0.017	0.183	

Abbreviations: RDV = remdesivir; SOC = standard of care.
Notes: p-values are two-sided.

Source: GS-US-540-5774 Interim Clinical Study Report (Table 12).

One issue with the interpretation of efficacy results in this trial is that it was by design a study of moderate COVID-19 but included a nontrivial fraction of patients (15%) who required some degree of oxygen supplementation at baseline. If efficacy was driven by results in these patients, this trial would provide less compelling supportive evidence for remdesivir as a treatment of moderate disease. However, subgroup results by baseline severity in the tables below show that the remdesivir 5 day group appeared more effective than the standard of care group even when restricting to the moderate disease patients who required medical care without oxygen supplementation.

Table 51: GS-US-540-5774 Day 11 ordinal scale results in the subgroup with baseline ordinal score of 4 = Hospitalized with low-flow supplemental oxygen (full analysis set)

	RDV 5 days (N = 29)	RDV 10 days (N = 23)	SOC (N = 36)
Ordinal scale score	n (%)	n (%)	n (%)
1. Death	0 (0)	0 (0)	4 (11.1)
2.	0 (0)	0 (0)	3 (8.3)
3.	0 (0)	0 (0)	2 (5.6)
4.	4 (13.8)	4 (17.4)	3 (8.3)
5.	5 (17.2)	2 (8.7)	4 (11.1)
6.	0 (0)	1 (4.3)	1 (2.8)
7. Not hospitalized	20 (69)	16 (69.6)	19 (52.8)
Odds ratio (95% CI) versus SOC	2.47 (0.91 to 6.64)	2.48 (0.85 to 7.2)	

Abbreviations: RDV = remdesivir; SOC = standard of care; CI = confidence interval.
Notes: Odds ratios and p-values are based on proportional odds models that are not adjusted for baseline covariates. An odds ratio <1 favors SOC and an odds ratio >1 favors remdesivir.
Source: Statistical reviewer.

Table 52: GS-US-540-5774 Day 11 ordinal scale results in the subgroup with baseline ordinal score of 5 = Hospitalized without supplemental oxygen but requiring ongoing medical care (full analysis set)

	RDV 5 days (N = 160)	RDV 10 days (N = 163)	SOC (N = 160)
Ordinal scale score	n (%)	n (%)	n (%)
1. Death	0 (0)	2 (1.2)	0 (0)
2.	0 (0)	1 (0.6)	1 (0.6)
3.	3 (1.9)	0 (0)	4 (2.5)
4.	3 (1.9)	7 (4.3)	8 (5)
5.	33 (20.6)	40 (24.5)	42 (26.2)
6.	7 (4.4)	6 (3.7)	7 (4.4)
7. Not hospitalized	114 (71.2)	107 (65.6)	98 (61.2)
Odds ratio (95% CI) versus SOC	1.62 (1.02 to 2.56)	1.21 (0.78 to 1.89)	

Abbreviations: RDV = remdesivir; SOC = standard of care; CI = confidence interval.
Notes: Odds ratios and p-values are based on proportional odds models that are not adjusted for baseline covariates. An odds ratio <1 favors SOC and an odds ratio >1 favors remdesivir.
Source: Statistical reviewer.

The protocol and statistical analysis plan for this trial did not specify secondary efficacy endpoints. However, the ordinal scale results at Day 28 are shown below. Both remdesivir groups yielded favorable results compared with standard of care. These results also provided some evidence against the previously discussed possibility of an open-label bias favoring the remdesivir 5 day group compared to the 10 day group, as rates for each ordinal category appeared similar between these two arms.

Table 53: GS-US-540-5774 Day 28 ordinal scale results (full analysis set)

	RDV 5 days (N = 191)	RDV 10 days (N = 193)	SOC (N = 200)
Ordinal scale score	n (%)	n (%)	n (%)
1. Death	2 (1)	3 (1.6)	4 (2)
2.	0 (0)	1 (0.5)	4 (2)
3.	1 (0.5)	1 (0.5)	0 (0)
4.	4 (2.1)	0 (0)	5 (2.5)
5.	9 (4.7)	10 (5.2)	17 (8.5)
6.	5 (2.6)	4 (2.1)	4 (2)
7. Not hospitalized	170 (89)	174 (90.2)	166 (83)
Odds ratio (95% CI) versus SOC	1.69 (0.94 to 3.03)	1.9 (1.05 to 3.46)	
p-value	0.0778	0.0352	

Abbreviations: RDV = remdesivir; SOC = standard of care; CI = confidence interval.
Notes: Odds ratios and p-values are based on proportional odds models that are not adjusted for baseline covariates. An odds ratio <1 favors SOC and an odds ratio >1 favors remdesivir.
Source: Statistical reviewer.

3.3.5.2 All-cause mortality (GS-US-540-5774)

Deaths were uncommon in this trial of moderate disease. As shown in the table below 2% or fewer patient died in each treatment group. Thus, this trial did not allow assessment of treatment effects on mortality outcomes.

Table 54: GS-US-570-5774 Day 28 all-cause mortality (full analysis set)

RDV 5 days (N = 191)	RDV 10 days (N = 193)	SOC (N = 200)
n (%)	n (%)	n (%)
2 (1)	3 (1.6)	4 (2)

Abbreviations: RDV = remdesivir; SOC = standard of care.
Notes: No deaths were recorded in the trial after Day 28.
Source: Statistical reviewer.

3.3.5.3 Conclusions (GS-US-540-5774)

This trial provided supportive evidence for (i) the efficacy of remdesivir for the treatment of patients with moderate COVID-19, who made up a relatively small proportion of ACTT-1; (ii) use of a 5 day remdesivir duration. However, potential limitations of this trial included the previously discussed issues related to prespecification of the statistical analysis, exclusions from the full analysis set differentially affecting remdesivir groups, the possibility of open-label biases favoring the shorter remdesivir duration, and imputations of discharge outcomes for the primary endpoint.

3.4 Wang et al. (2020)

An additional randomized, placebo-controlled trial of remdesivir has been published [Wang et al., 2020, *The Lancet*, https://doi.org/10.1016/S0140-6736(20)31022-9]. Patient-level data have not been submitted or reviewed for this study, but this section will briefly summarize the published results.

This double-blind trial randomized patients in a 2:1 ratio to receive remdesivir or placebo for 10 days. Remdesivir was administered intravenously at a dose of 200 mg on Day 1 followed by 100 mg on Days 2-10 in single daily infusions. A total of 237 patients out of the planned 453 patients were enrolled in China prior to study termination on April 1, 2020. The study was terminated due to operational futility as the epidemic had largely ended in China. The clinicaltrials.gov identifier for this trial was NCT04257656.

Inclusion criteria specified that patients were to be males and non-pregnant female patients aged ≥18 years who were RT-PCR positive for SARS-CoV-2, had pneumonia confirmed by chest imaging, had SpO2 ≤94% on room air or PaO2/FiO2 ratio ≤300mgHg, and were within 12 days of illness onset. Exclusion criteria disallowed pregnancy or breast-feeding; hepatic cirrhosis or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevated over 5 times the ULN; known severe renal impairment (estimated eGFR< 30 mL/min/1.73m^2), or having received continuous renal replacement therapy (CRRT), hemodialysis or peritoneal dialysis; or possibility of transfer to a non-study hospital within 72 hours.

Among 255 patients who were screened, 237 patients were eligible, consented and were randomized, of whom 1 withdrew. 158 patients were then assigned to receive remdesivir and 78 to placebo. In the remdesivir group, 155 (98%) received remdesivir, and placebo was given to all patients in the control group. The median age of study patients was 65 years (interquartile range [IQR], 56 to 71 years) and 140 (59%) were males. The most common comorbidity was hypertension (43%), followed by diabetes (24%) and coronary heart disease (7%). Most patients (82% in the remdesivir and 83% in the control group) were hospitalized with oxygen therapy at baseline, but without requiring high flow or noninvasive ventilation. The median days from illness onset to randomization was 10 days (IQR 9 to 12 days), and there were more patients (60%) in the control group than in the remdesivir group (46%) who had been symptomatic for 10 days or less at the time of randomization.

The efficacy analyses were conducted in an intention-to-treat population of all randomized patients.

The primary endpoint was the time to clinical improvement. This was defined as a decline in 2 points (on a 6-point ordinal scale) or discharge. The 6-point scale included
6. Death;
5. Hospitalized for ECMO and/or mechanical ventilation;
4. Hospitalized for noninvasive ventilation and/or high flow oxygen therapy:
3. Hospitalized for oxygen therapy (but not requiring high flow or noninvasive ventilation);
2. Hospitalization but not requiring oxygen therapy:
1. Discharged or having reached discharge criteria (defined as clinical recovery, i.e., normalization of pyrexia, respiratory rate [<24/minute], and SpO2 [>94% on room air], and relief of cough, all maintained for at least 72 hours).

In the primary efficacy analysis, the median time to clinical improvement was 21 days for remdesivir versus 23 days for placebo. The hazard ratio (on a scale with values greater than 1 favoring remdesivir) was 1.23, with a 95% confidence interval from 0.87 to 1.75, and a two-sided p-value of 0.24 from a log-rank test. At Day 28, the proportions of patients with at least a 2-point improvement on the ordinal scale were 103/158 (65.2%) for remdesivir versus 45/78 (57.7%) for placebo, with a 7.5% difference in rates, and a 95% confidence interval for the difference from -5.7% to 20.7%. These primary efficacy results represented a numerical trend in favor of remdesivir that did not reach conventional levels of statistical significance.

Day 28 all-cause mortality rates were similar in the two treatment groups. Mortality rates were 22/158 (13.9%) for the remdesivir group versus 10/78 (12.8%) for the placebo group, with a difference in mortality rates of 1.1% and a 95% confidence interval for the difference from -8.1% to 10.3%.

The table below displays results for the ordinal scale at Day 28. The odds ratio estimated from a proportional odds model (on a scale with values greater than 1 favoring remdesivir) was 1.15, with a 95% confidence interval from 0.67 to 1.96.

Table 55: Results for the 6-point ordinal scale at Day 28 (Wang et al. 2020)

Ordinal scale categories	RDV 10 days (n = 158)	Placebo (n = 78)
1 = discharged alive	92 (58.2)	45 (57.7)
2	14 (8.9)	4 (5.1)
3	18 (11.4)	13 (16.7)
4	2 (1.3)	2 (2.6)
5	2 (1.3)	3 (3.8)
6 = death	22 (13.9)	10 (12.8)
Missing	8 (5.1)	1 (1.3)

Source: Wang et al. (2020), Table 3.

Rates of viral clearance appeared similar between remdesivir and placebo in this trial, and viral load decreased similarly in both groups through Day 28.

Rates of adverse events were also similar between treatment groups, with at least 1 adverse reported for 66% of remdesivir patients and 64% of placebo patients. However, study drug discontinuation due to adverse events or serious adverse was more common for the remdesivir group (12% versus 5%), including 5% in the remdesivir group with respiratory failure or ARDS.

Overall, this trial was much smaller than ACTT-1. Consequently, there was a higher degree of uncertainty in estimating treatment effects. Nevertheless, the point estimate for the remdesivir treatment effect was consistent with results from the adequate and well-controlled ACTT-1 using a similar time to improvement endpoint for the primary analysis. Thus, this trial was not considered to have provided discordant findings.

3.5 Evaluation of Safety

Evaluation of safety for this application is deferred to the clinical reviewer Kirk Chan-Tack, MD.

4. FINDINGS IN SPECIAL SUBGROUP/POPULATIONS

This section discusses subgroup results from ACTT-1, GS-US-540-5773, and GS-US-540-5774. Subgroup analyses in these trials were generally exploratory due to the relatively small sample sizes within subsets and the lack of multiplicity control.

4.1 Gender, Race, Age, and Geographic Region

The table below displays ACTT-1 subgroup results for the primary endpoint of time to recovery, key secondary endpoint of the Day 15 ordinal score, and for Day 28 all-cause mortality. Results generally favored remdesivir compared with placebo across the demographic subgroups considered.

Table 56: ACTT-1 time to recovery results, Day 15 ordinal scale results, and Day 28 all-cause mortality results by baseline subgroup (ITT population)

		Number of subjects	Recovery rate ratio (95% CI)	Odds ratio for Day 15 ordinal scale (95% CI)	Hazard ratio for all-cause mortality (95% CI)
Age (years)	<40	119	2 (1.31 to 3.03)	2.79 (1.43 to 5.42)	0.66 (0.11 to 3.95)
	40-64	559	1.2 (0.99 to 1.45)	1.33 (0.99 to 1.79)	0.63 (0.36 to 1.12)
	≥65	384	1.3 (1 to 1.68)	1.51 (1.06 to 2.15)	0.84 (0.54 to 1.29)
Sex	Male	684	1.31	1.49	0.74

			(1.1 to 1.57)	(1.14 to 1.94)	(0.49 to 1.12)
	Female	378	1.32 (1.04 to 1.67)	1.62 (1.13 to 2.31)	0.7 (0.39 to 1.26)
Race	White	566	1.3 (1.07 to 1.59)	1.57 (1.17 to 2.11)	0.68 (0.42 to 1.11)
	Black or African American	226	1.26 (0.92 to 1.73)	1.19 (0.75 to 1.88)	1.05 (0.53 to 2.08)
	Asian	135	1.08 (0.73 to 1.59)	1.11 (0.61 to 2.03)	0.86 (0.32 to 2.32)
Ethnicity	Hispanic or Latino	250	1.28 (0.94 to 1.74)	1.6 (1.02 to 2.5)	0.52 (0.24 to 1.09)
	Not Hispanic or Latino	755	1.32 (1.11 to 1.56)	1.49 (1.16 to 1.92)	0.82 (0.54 to 1.22)
Country	US site	837	1.31 (1.11 to 1.54)	1.6 (1.26 to 2.04)	0.69 (0.47 to 1)
	Non-US site	225	1.33 (0.98 to 1.8)	1.33 (0.83 to 2.11)	0.91 (0.42 to 2)
Days from symptom onset to enrollment	<10	582	1.33 (1.1 to 1.62)	1.67 (1.25 to 2.23)	0.7 (0.45 to 1.09)
	≥10	477	1.3 (1.05 to 1.61)	1.39 (1.01 to 1.91)	0.74 (0.43 to 1.26)

Abbreviations: ITT = intent-to-treat; RDV = remdesivir; CI = confidence interval.
Notes: Recovery rate ratios and hazard ratios are estimated from proportional hazards models, and odds ratios are estimated from proportional odds models. None of the models adjust or stratify by baseline covariates. Recovery rate ratios and odds ratios >1 and hazard ratios <1 favor remdesivir.
Source: Statistical reviewer.

In the Gilead severe trial GS-US-540-5773, subgroup results are displayed in the table below for the Day 14 ordinal scale primary endpoint and all-cause mortality. No demographic subgroups were identified in which evidence convincingly pointed to the need for the longer 10 day duration of remdesivir.

Table 57: GS-US-540-5773 Day 14 ordinal scale results and Day 28 all-cause mortality results by baseline subgroup (full analysis set)

		Number of subjects	Odds ratio for Day 14 ordinal scale (95% CI)	Hazard ratio for time to death (95% CI)
Age (years)	<40	41	1.14 (0.22 to 5.86)	N/A
	40-64	188	0.97 (0.54 to 1.72)	0.99 (0.35 to 2.83)
	≥65	168	0.45 (0.26 to 0.79)	1.24 (0.66 to 2.34)

Sex	Male	253	0.81 (0.51 to 1.28)	0.89 (0.48 to 1.66)
	Female	144	0.5 (0.26 to 0.97)	2.19 (0.71 to 6.71)
Race	White	276	0.62 (0.4 to 0.98)	1.31 (0.71 to 2.4)
	Black or African American	44	1.47 (0.39 to 5.52)	1.94 (0.18 to 21.4)
	Asian	45	0.78 (0.26 to 2.34)	0.27 (0.028 to 2.59)
Ethnicity	Hispanic or Latino	85	1.07 (0.47 to 2.42)	0.89 (0.2 to 4)
	Not Hispanic or Latino	302	0.57 (0.37 to 0.89)	1.34 (0.74 to 2.42)
Country	US site	229	0.66 (0.38 to 1.13)	1.47 (0.7 to 3.11)
	Non-US site	168	0.7 (0.4 to 1.2)	0.87 (0.4 to 1.91)
Days from symptom onset to enrollment	<10	221	0.67 (0.4 to 1.14)	1.11 (0.53 to 2.34)
	≥10	171	0.72 (0.41 to 1.26)	0.97 (0.42 to 2.23)

Abbreviations: RDV = remdesivir; CI = confidence interval.
Notes: The Odds ratios are based on a proportional odds models that do not adjust for baseline covariates. The hazard ratios are based on proportional hazards models that do not adjust for baseline covariates. Odds ratio <1 and hazard ratios >1 favor the 5 day group. Values are listed as "N/A" when fits fail to converge.
Source: Statistical reviewer.

The subsequent table displays results for the Day 11 ordinal scale primary endpoint by demographic subgroup in the Gilead moderate trial GS-US-540-5774. In every subgroup considered for these comparisons, the estimated odds ratio from a proportional odds model numerically favored the remdesivir 5 day group compared with the standard of care control group.

Table 58: GS-US-540-5774 Day 11 ordinal scale results by subgroup (full analysis set)

		Number of subjects	Odds ratio for RDV 5 days versus SOC	Odds ratio for RDV 10 days versus SOC
Age (years)	<40	92	2.09 (0.69 to 6.39)	1.68 (0.61 to 4.69)
	40-64	333	1.58 (0.87 to 2.84)	1.03 (0.59 to 1.81)
	≥65	159	1.65	1.59

			(0.81 to 3.37)	(0.78 to 3.22)
Sex	Male	357	1.59 (0.95 to 2.66)	1.45 (0.88 to 2.41)
	Female	227	1.73 (0.87 to 3.41)	1.11 (0.58 to 2.12)
Race	White	328	1.51 (0.88 to 2.58)	1.61 (0.93 to 2.78)
	Black or African American	99	7.81 (0.85 to 71.4)	0.96 (0.27 to 3.42)
	Asian	102	1.62 (0.66 to 3.93)	0.61 (0.24 to 1.55)
Ethnicity	Hispanic or Latino	101	1.1 (0.34 to 3.56)	1.34 (0.47 to 3.82)
	Not Hispanic or Latino	458	1.83 (1.17 to 2.88)	1.33 (0.85 to 2.08)
Country	US site	260	2.69 (1 to 7.27)	0.94 (0.46 to 1.95)
Country	Non-US site	324	1.67 (1.02 to 2.73)	1.41 (0.85 to 2.36)
Days from symptom onset to first dose	<10	372	1.47 (0.89 to 2.45)	1.63 (0.98 to 2.71)
Days from symptom onset to first dose	≥10	205	2.01 (0.98 to 4.15)	0.96 (0.49 to 1.85)

Abbreviations: RDV = remdesivir; SOC = standard of care; CI = confidence interval.
Notes: Odds ratios and p-values are based on proportional odds models that are not adjusted for baseline covariates. An odds ratio <1 favors SOC and an odds ratio >1 favors remdesivir.
Source: Statistical reviewer.

4.2 Other Special/Subgroup Populations

Subgroup results by baseline severity were previously discussed in Section 3 in the summaries of individual trials.

The tables in the preceding subsection display results for subgroups defined by the time from symptom onset to baseline (<10 days versus ≥10 days). The trial results did not provide evidence for an interaction in which treatment effects differed between patients starting therapy at earlier or later times following symptoms. However, the trials reviewed were not designed or powered to make such assessments, and could not rule out differential efficacy according to earlier or later initiation of therapy.

Subgroup analyses by study site are not shown. ACTT-1, GS-US-540-5773, and GS-US-540-5774 each enrolled patients at >50 sites, and no study sites had sufficiently large enrollment to impact generalizability.

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

This review evaluated whether remdesivir was effective for the treatment of COVID-19 based on the three studies in hospitalized patients: ACTT-1, GS-US-540-5773, and GS-US-540-5774. In considering the data from the three trials, each served a different purpose. ACCT-1 was an adequate and well-controlled trial capable of providing substantial evidence of efficacy. GS-US-540-5773 was designed to inform the remdesivir duration for treatment of severe disease. GS-US-540-4774 provided supportive evidence for comparisons between remdesivir groups and a standard of care control, buttressed ACTT-1 data on patients with moderate disease, and informed the recommended duration for remdesivir. Due to the differences in objectives and designs, the three trials were analyzed individually rather than assessed through meta-analysis.

The results of ACTT-1 provided statistically reliable evidence of a treatment effect for remdesivir compared with placebo for the primary analysis of time recovery through the Day 29 visit. In the overall ITT population, recovery rates were significantly faster in the remdesivir group than the placebo group. Results also strongly favored remdesivir for the key secondary endpoint based on a Day 15 ordinal scale. As this was the trial's original primary endpoint, efficacy conclusions were robust to the midstream endpoint change in this study. The Day 15 ordinal endpoint also was less susceptible to certain analytic complexities than the time to recovery endpoint, such as the appropriate handling of deaths and readmissions. Numerical trends in this trial for all-cause mortality favored remdesivir, but there remained uncertainty surrounding whether the drug provided a mortality benefit. Post-hoc subgroup analyses by baseline severity of primary and secondary endpoints also revealed uncertainty with respect to the degree of efficacy in patients with moderate disease who did not require supplemental oxygen, and in patients with severe or critical disease requiring ventilation.

In GS-US-540-5773 comparing 5 and 10 day remdesivir durations for the treatment of severe COVID-19, the main limitation was the lack of a placebo or standard of care control group. For the primary endpoint based on a Day 14 ordinal scale, the estimated treatment effect favored the 5 day group but did not reach statistically significant superiority. However, interpretability was limited by potential open-label effects on the Day 14 ordinal scale primary endpoint, because patients in the 5 day group may have had greater opportunities to achieve the discharge category of the scale by requiring less time to complete assigned therapy. Interpretability was further limited due to the high degree of imputed data for the primary endpoint, baseline imbalances that appeared to favor the 5 day remdesivir group, and receipt of the statistical analysis plan after release of topline results.

GS-US-540-5774 compared a 5 day remdesivir group, 10 day remdesivir group, and a standard of care group for the treatment of moderate COVID-19. The 5 day remdesivir group was statistically superior to the standard of care control group in the primary

analysis of the ordinal scale at Day 11. The comparison of the 10 day remdesivir group to the standard of care group was inconclusive. Receipt of the statistical analysis plan after release of topline results partially limited interpretability of efficacy conclusions, because the 5 day group was significantly superior to the standard of care group using the specified Bonferroni multiplicity adjustment, but would not have been superior using other reasonable methods of multiplicity control such as hierarchical testing. Another limitation of this trial included possible open-label effects on the ordinal endpoint, because patients in the three treatment groups may have had systematically different opportunities to meet discharge criteria due to different times required to complete assigned therapies. In addition, there was substantial imputed data for the ordinal endpoint and systematically greater exclusions from the full analysis set in the remdesivir groups than the standard of care group. Despite the fact that this trial was meant to evaluate treatment regimens for moderate disease, the study population included a nontrivial proportion of patients with baseline oxygen requirements. However, efficacy results were similar when excluding these more severe patients.

5.2 Conclusions and Recommendations

Conclusions and recommendations are summarized as follows:

- This application has provided statistical evidence that remdesivir is effective for the treatment of COVID-19 and reduces the time required to achieve clinical recovery, as defined in the ACTT-1 trial.
- The strongest evidence for a treatment effect is in patients who are hospitalized with supplemental oxygen requirements, but do not require high-flow oxygen, mechanical ventilation, or ECMO.
- There is remaining uncertainty regarding efficacy in the subpopulation severe enough to require high-flow oxygen, mechanical ventilation, or ECMO.
- There is remaining uncertainty regarding whether remdesivir reduces all-cause mortality.
- There is remaining uncertainty regarding the optimal duration of remdesivir, but the preponderance of evidence supports a 5 day treatment course being sufficient for the groups in which it was evaluated.
- None of the trials considered in this review assessed outcomes beyond approximately 4 weeks after the start of treatment. Thus, there is remaining uncertainty regarding how remdesivir impacts longer term complications associated with COVID-19.

5.3 Labeling Recommendations

Two potential labeling issues concern the following issues:

- The scope of the indication and the presentation of results by baseline severity in the Clinical Studies section.
- The recommended duration of therapy.

Due to the potential impact of chance and random high effects on subgroup analyses, it is recommended that the label describe the composition of the study populations in the

reviewed trials but emphasize the prespecified overall analyses rather than post-hoc analyses of subgroups defined by baseline severity.

Concerning the duration of remdesivir, only a 10 day remdesivir duration was assessed in ACTT-1, although many patients did not complete the full treatment course due to improvement in clinical status. GS-US-540-5773 and GS-US-540-5774 each compared 5 day and 10 day remdesivir durations. Neither study conclusively demonstrated that the longer duration was necessary or that the shorter duration was sufficient. In both studies the 5 day group had numerically favorable outcomes compared with the 10 day group for the primary endpoint, although these findings were limited by possible open-label effects and residual uncertainty. Collective evidence from the three trials reviewed does not support a rigid treatment duration recommendation. Considering potential uncertainties, it is instead recommended that the label allow a flexible 5 to 10 day range for the duration of remdesivir.

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